# Clinical Pharmacogenetics Implementation Consortium Guideline for Cytochrome P450 (*CYP*)*2D6* Genotype and Atomoxetine Therapy

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**Atomoxetine is a nonstimulant medication used to treat attention-deficit/hyperactivity disorder (ADHD). Cytochrome P450 (*CYP*)*2D6* polymorphisms influence the metabolism of atomoxetine thereby affecting drug efficacy and safety. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for atomoxetine based on *CYP*2D6 genotype (updates at www.cpicpgx.org).**

The purpose of this guideline is to provide information to allow the interpretation of clinical CYP2D6 genotype tests so that the results can be used to guide the use of atomoxetine. Detailed guidelines for prescribing of atomoxetine as well as analyses of cost effectiveness are beyond the scope of this document. The Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines are periodically updated at https://cpicpgx.org/guidelines and http://www.pharmgkb.org.

## FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2D6* genotype and atomoxetine use was conducted (details in **Supplement**).

## GENE: *CYP2D6*

*CYP2D6* is highly polymorphic with over 100 known allelic variants and subvariants identified (www.PharmVar.org; *CYP2D6* Allele Definition Table[1,2]). *CYP2D6* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups, and significant differences in allele frequencies have been observed (*CYP2D6* Allele Frequency Table[1,2]). The most commonly reported alleles are categorized into functional groups as follows: normal function (e.g., *CYP2D6*1*, **2*, and **35*), decreased function (e.g., *CYP2D6*9*, **10*, **17*, **29*, and **41*), and no function (e.g., *CYP2D6*3–*6*).[3,4] Because *CYP2D6* is subject to deletions and gene duplications or multiplications, many clinical laboratories also report copy number variations. *CYP2D6*5* represents a gene deletion (no function allele) whereas gene duplications and multiplications are denoted by "*xN*" (e.g., *CYP2D6*1xN* with *xN* representing the number of *CYP2D6* gene copies). Alleles carrying two or more normal function gene copies are categorized as alleles with increased function.

The combination of alleles is used to determine a patient's diplotype. Each functional group is assigned an activity value ranging from 0–1 (e.g., 0 for no, 0.5 for decreased, and 1.0 for normal function).[4] If an allele contains multiple copies of a functional gene, the value is multiplied by the number of copies present. Thus, the *CYP2D6* activity score (AS) is the sum of the values assigned to each allele, which typically range from 0–3.0 but may exceed 3.0 in rare cases.[4]

The CYP2D6 AS can be translated into a standardized phenotype classification system (*CYP2D6* Allele Definition Table[1,2]): patients with an AS of 0 are poor metabolizers (PMs), those with a score of 0.5 are considered intermediate metabolizers (IMs), those with a score of 1.0–2.0 represent normal metabolizers (NMs), and patients with a score > 2 are classified as ultrarapid metabolizers (UMs). However, diplotypes with an AS of 1.0 give rise to less activity toward certain drugs, including tamoxifen and atomoxetine compared with those with an AS of 1.5 or 2.0; therefore, patients with an AS of 1.0 may be classified as IMs by some reference laboratories. Thus, for this guideline, an AS of 1.0 is classified as a CYP2D6 NM or IM (**Table 1**). This is in contrast to the classification used in some previous guidelines[5,6] but similar to the recently published guideline on *CYP2D6* and tamoxifen.[7] Note that genotypes with an AS of 1 are classified as NMs in the *CYP2D6* Genotype-to-Phenotype Table[1], and CPIC will update the CPIC website and this table if needed. Efforts to standardize *CYP2D6* genotype-to-phenotype translation system are ongoing. Currently, a *CYP2D6* Genotype-to-Phenotype

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**Table 1 Assignment of likely CYP2D6 phenotypes based on diplotypes**

| Likely phenotype[b] | AS | Genotypes[a] | Examples of *CYP2D6* diplotypes |
|---|---|---|---|
| CYP2D6 ultrarapid metabolizer | > 2 | An individual carrying duplications of functional alleles | **1/*1xN, *1/*2xN, *2/*2xN*[c] |
| CYP2D6 normal metabolizer | 1.5–2.0 | An individual carrying two 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)[d] | 1.0 | An individual carrying two decreased function alleles or one normal function and one no function allele. *An AS of 1.0 is associated with decreased atomoxetine metabolism compared with those with an AS of 1.5 or 2* | **1/*4, *1/*5, *41/*41, *10/*10* |
| CYP2D6 intermediate metabolizer | 0.5 | An individual carrying one decreased function and one no function allele | **4/*10, *4/*41, *5/*9* |
| CYP2D6 poor metabolizer | 0 | An individual carrying only no functional alleles | **3/*4, *4/*4, *5/*5, *5/*6* |

AS, activity score; CYP, cytochrome P450.
[a]Assignment of allele function and citations for allele function can be found https://www.pharmgkb.org/page/cyp2d6RefMaterials (*CYP2D6* Allele Definition Table and *CYP2D6* Allele Functionality Table[1,2]). For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the *CYP2D6* Genotype to Phenotype Table[1,2]. Note that genotypes with an AS of 1 are classified as normal metabolizers in the online *CYP2D6* genotype to phenotype table. [b]See the *CYP2D6* Frequency Table for race-specific allele and phenotype frequencies or see Gaedigk *et al.*[1,2,37] [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]Patients with an AS 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. The Clinical Pharmacogenetic Implementation Consortium (CPIC) will update the CPIC website accordingly (*CYP2D6* Genotype to Phenotype Table[1,38]).

Working Group is also reviewing the classification of the decreased function *CYP2D6*10* allele (discussions regarding the accuracy of *CYP2D6*10* classification using a value of 0.5 for AS calculation have been ongoing for years[7]). This allele seems to convey a reduction in activity across many substrates, which led to a special recommendation for *CYP2D6*10*-containing diplotypes for tamoxifen and for atomoxetine (**Table 2**).

Of importance, reference laboratories providing clinical *CYP2D6* genotyping may use varying methods to assign phenotypes. Therefore, it is advisable to note a patient's *CYP2D6* diplotype and to calculate the AS before making therapeutic decisions about atomoxetine therapy. See the CYP2D6 Diplotype-to-Phenotype Table for a comprehensive translation of diplotype to phenotype.[1,2]

### Genetic test interpretation

Clinical laboratories rarely sequence through the *CYP2D6* gene or interrogate every known variant position. Instead, they typically test for variants that are used to determine common allele haplotypes using the star-allele (*) nomenclature system. Allele definitions are maintained by the Pharmacogene Variation Consortium (www.PharmVar.org). The CYP2D6 Allele Definition Table and CYP2D6 Allele Functionality Table and tables found on the PharmGKB website contain a list of *CYP2D6* alleles,[1,2] the specific combination of variants that can be used to determine the allele, functional status, and frequency across major ethnic populations as reported in the literature.

Genetic test results are reported as diplotypes or the combination of the maternal and paternal alleles (e.g., *CYP2D6*1/*2*). Phenotypes are assigned based on the reported *CYP2D6* diplotype, as summarized in **Table 1** and in the CYP2D6 Dipl Table.

The limitations of genetic testing as described here include: (i) rare variants are often not detected, (ii) known star alleles (*), which are not tested by a specific laboratory will not be reported, and instead, the patient will be reported as a **1*, and (iii) most tests are not designed to detect unknown or *de novo* variants. **Supplemental Material** (Genetic Test Interpretation Section) contains additional information regarding *CYP2D6* genetic test interpretation and phenotype assignment.

### Available genetic test options

See **Supplemental Material** and the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options.

### Incidental findings

Currently, there are no diseases or conditions that have been consistently linked to variation in the *CYP2D6* gene independent of drug metabolism and response.

### Other considerations

CYP2D6 is the primary enzyme responsible for the metabolism of many other commonly used medications. It is important to note that variation in CYP2D6 may have implications for other therapies that are beyond the scope of this guideline. CPIC guidelines exist for other drugs metabolized by CYP2D6.[3,6-9]

## DRUGS: ATOMOXETINE

### Background

Based on a parent-reported survey in 2016, an estimated 6.1 million children (9%) between the ages of 2 and 17 years received a diagnosis of ADHD.[10] Although not a first-line agent for the treatment of ADHD, atomoxetine was the first nonstimulant medication approved in the United States to treat ADHD in 2002. Originally developed in the 1980s to treat adult depression, but only approved for the treatment of ADHD, atomoxetine is a selective norepinephrine reuptake inhibitor.[11] A surge in atomoxetine prescriptions occurred following its approval, peaking

**Table 2 Dosing recommendations for atomoxetine based on *CYP2D6* genotype for children**

| Phenotype | AS | Implication | Therapeutic recommendation | Classification of recommendation[a] |
|---|---|---|---|---|
| CYP2D6 ultrarapid metabolizer | > 2 | 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 (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.[b,c] | Moderate |
| CYP2D6 normal metabolizer | 1.5–2.0 | Normal metabolizers of atomoxetine have a lower likelihood of response as compared to 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 (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.[b,c] | Moderate |
| CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[d] | 1.0 (no **10* allele present) | Possibly higher atomoxetine concentrations as compared to normal metabolizers but questionable clinical significance. Normal metabolizers with AS of 1 may be at an increased risk of increased discontinuation as compared to 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 (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.[b,c] | Moderate |
| CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[d] | 1.0 (**10* present) | Decreased metabolism of atomoxetine and higher atomoxetine concentrations as compared with normal metabolizers. Individuals with AS of 1.0 with *CYP2D6*10* may be at an increased risk of increased 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 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. | Moderate |
| CYP2D6 intermediate metabolizer | 0.5 | 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 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. | Moderate |
| CYP2D6 poor metabolizer | 0 | Significantly decreased metabolism of atomoxetine may result in higher concentrations as compared to 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 to 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 |

ADHD, attention-deficit/hyperactivity disorder; AS, activity score; CYP, cytochrome P450.
[a]Rating scheme described in the **Supplement**. [b]Therapeutic range of 200–1000 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 compared to non-poor metabolizers and may be related to the higher plasma concentrations 1–1.5 hours after dosing in poor metabolizers compared with non-poor metabolizers administered a similar dose. Furthermore, modest improvement in response, defined as reduction in ADHD-rating scale (RS), is observed at peak concentrations > 400 ng/mL. [d]The Clinical Pharmacogenetic Implementation Consortium (CPIC) has general classified patients with AS of 1 as “NM.” However, in the case of atomoxetine, prescribing recommendations for those with an AS of 1.0 are allele-dependent, based on the presence of the *CYP2D6*10* allele.

in 2004 when it was the third most commonly prescribed medication for ADHD after methylphenidate and amphetamine/dextroamphetamine; however, following 2004, prescriptions gradually decreased to around 2 million per year in 2010.[12] Unlike stimulants, atomoxetine has a delayed onset to clinical effect and typically takes 2–4 weeks for full impact on symptoms to be observed.[13]

Atomoxetine is an active parent compound and is metabolized by CYP2D6 to an active metabolite, 4-OH-atomoxetine; however, this metabolite is rapidly glucuronidated to the inactive 4-OH-atomoxetine-*O*-glucuronide, and the unconjugated metabolite circulates at concentrations ~ 100-fold lower than the parent compound.[14,15] To a lesser extent, atomoxetine is also metabolized by CYP2C19 to N-desmethylatomoxetine, which is subsequently metabolized via CYP2D6 to *N*-desmethyl-4-hydroxyatomoxetine (**Figure 1**).

The recommended initial daily dose of atomoxetine is 0.5 mg/kg in children and adolescents up to 70 kg with a target and maximum dose of 1.2 mg/kg/day and 1.4 mg/kg/day, respectively. In children and adolescents over 70 kg and adults, the initial daily dose of atomoxetine is 40 mg/day, with a target and maximum daily dose of 80 mg/day and 100 mg/day, respectively (according to the product labeling). In patients taking a CYP2D6 inhibitor or those who are known to be CYP2D6 PMs, the product labeling currently recommends starting therapy at the usual daily dose and increasing to the recommended target doses if the drug is well tolerated and symptoms fail to improve after 4 weeks.

In registry clinical trials for the efficacy and safety of atomoxetine, separation from placebo was, on average, observed after 1–2 weeks of treatment.[13] Incremental increases in response may occur for up to 24 weeks or longer. Pharmacokinetic studies highlight that doses producing atomoxetine peak concentrations > 200 ng/mL 1–4 hours after dosing may increase the likelihood of response.[16] Common dose-related side effects from atomoxetine occurring more frequently in CYP2D6 PMs compared to non-PMs in children or adults include dry mouth, blurred vision, sleep disturbances, decreased weight or appetite, constipation, depression, tremor, feeling jittery, excoriation, dry eye or conjunctivitis, syncope, urinary retention, sexual dysfunction, hyperhidrosis, peripheral coldness, and elevated blood pressure.[16]

### Linking genetic variability to variability in drug-related phenotypes

**Atomoxetine pharmacokinetics.** A strong association exists between *CYP2D6* genotype and atomoxetine pharmacokinetic variability (see **Table S1**). Atomoxetine is considered a CYP2D6 "sensitive substrate" by the US Food and Drug Administration (FDA) for evaluating drug–drug interactions. As such, *CYP2D6* genetic variation has a profound effect on atomoxetine pharmacokinetics.[17] The range of values observed

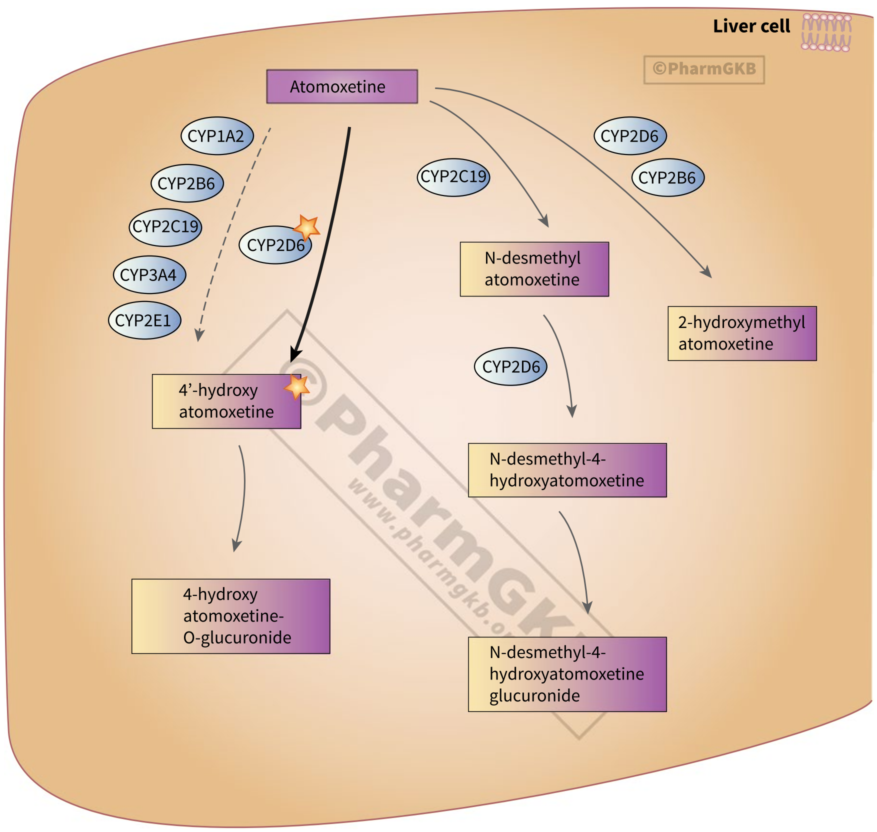


**Figure 1** Atomoxetine pathway, pharmacokinetics. Data observed from ref. 36. Image reproduced and is licensed under CC BY-SA 4.0 from PharmGKB. CYP, cytochrome P450.

for atomoxetine exposure, most often reported as either the area under the drug plasma concentration-time curve (AUC) or the maximum concentration ($C_{max}$), is substantial. Atomoxetine exposure (AUC) is, *on average*, 10-fold higher in CYP2D6 PMs compared to non-PMs.[14–16,18,19] However, the comparison of group mean values obscures the full range of exposures that may be present in a population. For example, a *CYP2D6* genotype-stratified single-dose pharmacokinetic study ($n$ = 23 children) observed a 30-fold range in AUC when dosed using the FDA-recommended initial dose of 0.5 mg/kg. Decreasing atomoxetine exposure was associated with genotype (i.e., increasing CYP2D6 AS).[15] It should be noted that in early *in vivo* drug development studies, the depth of genotyping only differentiated between CYP2D6 PMs and non-PMs. Subsequent studies that performed more comprehensive genotyping suggest that CYP2D6 IMs (e.g., a CYP2D6 AS of 0.5) have pharmacokinetic profiles that differ from both PMs and NMs.[15]

*Ex vivo* studies evaluating metabolic capacity in human liver microsomes that have been genotyped for *CYP2D6* provide evidence that increased exposure is due to reduced metabolic capacity in both IMs and PMs.[11,20,21] The most studied decreased function *CYP2D6* allele in the context of atomoxetine is the *CYP2D6*10* variant. Individuals with two *CYP2D6*10* alleles had higher atomoxetine exposure (5-fold higher peak concentration) when compared with individuals with at least one normal function allele.[22–24] Individuals heterozygous for **10* and one fully functional *CYP2D6* allele had higher atomoxetine exposure compared with individuals carrying two fully functioning alleles.

**Atomoxetine response/toxicity.** The likelihood of favorable treatment response and side effects are both reported to be higher in CYP2D6 PMs compared to non-PMs, which is likely due to increased exposure to the parent drug in the PMs. The extent of improvement in ADHD symptoms (i.e., mean change in ADHD symptom rating scale scores), was greater in PMs compared to non-PMs, whereas CYP2D6 non-PMs were also more likely to discontinue atomoxetine therapy due to inefficacy as compared with CYP2D6 PMs.[16] Current evidence is limited to comparisons between CYP2D6 PMs and non-PMs; thus, there is no evidence correlating efficacy and/or drug discontinuation with other CYP2D6 phenotype classes. Higher exposures to atomoxetine may also partially explain a greater percentage of side effects in CYP2D6 PMs, such as increases in heart rate and diastolic blood pressure, when compared with non-PMs.[16,19,25] However, in a retrospective study that evaluated atomoxetine response in participants enrolled from six atomoxetine randomized controlled trials ($n$ = 618), beneficial response was noted in 47% of patients, 13% of patients were determined to have minimal response, and 40% had no response.[26] These data suggest at least two distinct atomoxetine response groups within the observed population. Additionally, it can also be inferred that *CYP2D6* genotype alone does not account for the atomoxetine response distribution described in the above investigation, given that CYP2D6 PMs frequency is ~ 5–10% of the population (CYP2D6 Frequency Table[2]).

The most well-studied pharmacokinetic parameter for atomoxetine relates plasma drug concentrations that approximate the $C_{max}$ of the parent compound to reduction of ADHD symptoms.[16] Given this evidence, the therapeutic recommendation for each CYP2D6 phenotype class also includes guidance for plasma drug concentration testing, as a means to estimate atomoxetine exposure (i.e., exposure check). These target reference values are from the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology and are meant to guide the clinician in the event that patient response to atomoxetine is inadequate.[27] Included with these guidelines is a plasma concentration (henceforth described as an "exposure check") performed post–drug administration, which is included to rule out inadequate systemic exposure as a cause of nonresponse in individuals with a CYP2D6 AS of 1 or more. This CPIC guideline also includes a grading system to evaluate the strength of evidence between various *CYP2D6* genotype-predicted phenotypes and the corresponding therapeutic recommendation. Data from both *in vitro* and *in vivo* studies (**Table S1**), as well as consensus recommendations, were used in formulating the guidance in **Table 2**.

### Therapeutic recommendations

**Tables 2 and 3** 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 and 1,000 ng/mL are generally considered to be "therapeutic;"[16,28] 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.[29] 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 2 and 3** propose that prescribers consider measuring peak concentrations 1–2 hours after dosing in known CYP2D6 UMs, NMs, and IMs with high activity (AS 1.0 without a *CYP2D6*10* allele), 2–4 hours after dosing in CYP2D6 IMs with low activity (AS 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.[30] As discussed above, CYP2D6 non-PMs have a lower likelihood of treatment response as compared with CYP2D6 PMs.[16] Thus, for CYP2D6 UMs and NMs, recommendations are to initiate standard atomoxetine dosing (see **Tables 2 and 3** for pediatric and adult dosing, respectively), and if no clinical response is observed after 2 weeks, consider obtaining a peak plasma concentration 1–2 hours after dose administration. If the peak concentration is < 200 ng/mL, consider increasing the dose proportionally to

**Table 3 Dosing recommendations for atomoxetine based on *CYP2D6* genotype for adults**

| Phenotype | AS | Implication | Therapeutic recommendation | Classification of recommendation[a] |
|---|---|---|---|---|
| CYP2D6 ultrarapid metabolizer | > 2 | 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 (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.[b,c] Dosages > 100 mg/day may be needed to achieve target concentrations.[d] | Moderate |
| CYP2D6 normal metabolizer | 1.5–2.0 | 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 to 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 (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.[b,c] Dosages > 100 mg/day may be needed to achieve target concentrations.[d] | Moderate |
| CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[e] | 1.0 (**10* allele not present) | Possibly higher atomoxetine concentrations as compared with normal metabolizers but questionable clinical significance. Normal metabolizers may be at an increased risk of increased discontinuation 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 (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL.[b,c] Dosages > 100 mg/day may be needed to achieve target concentrations.[d] | Moderate |
| CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[e] | 1.0 (**10* allele present) | Decreased metabolism of atomoxetine higher atomoxetine concentrations as compared with normal metabolizers. Individuals with AS of 1.0 with *CYP2D6*10* may be at an increased risk of increased 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 hours 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 |
| CYP2D6 intermediate metabolizer | 0.5 | 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 hours 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 |
| CYP2D6 poor metabolizer | 0 | Significantly decreased metabolism of atomoxetine may result in higher concentrations as compared to 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 to 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 hours 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 |

ADHD, attention-deficit/hyperactivity disorder; AS, activity score; CYP, cytochrome P450.
[a]Rating scheme described in the **Supplement**. [b]Therapeutic range of 200–1,000 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 compared with non-poor metabolizers and may be related to the higher plasma concentrations 1–1.5 hours after dosing in poor metabolizers compared with non-poor metabolizers administered a similar dose. Furthermore, modest improvement in response, defined as reduction in ADHD-rating scale (RS), is observed at peak concentrations > 400 ng/mL. [d]Doses above 120 mg/day have not been evaluated. [e]The Clinical Pharmacogenetic Implementation Consortium (CPIC) has general classified patients with an AS of 1 as "NM." However, in the case of atomoxetine, prescribing recommendations for those with an AS of 1.0 are allele-dependent, based on the presence of the *CYP2D6*10* allele.

approach 400 ng/mL.[16] 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. Although CYP2D6 NMs with an AS of 1 (without the presence of the *CYP2D6*10* allele) have higher atomoxetine plasma concentrations compared with 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 an 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.[16,19,25] However, these individuals may also have greater improvement of ADHD symptoms and lower dose requirements as compared with non-PMs. Therefore, the recommendation for these phenotype groups is to initiate with a standard starting dose (see **Tables 2 and 3** 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 2–4 hours after dosing. If response is inadequate and side effects are not present, consider adjusting the dose proportionally to approach 400 ng/mL.

### Recommendations for incidental findings

Not applicable.

### Other considerations

In addition to *CYP2D6*, variation in atomoxetine response has also been examined with its pharmacodynamic target, the norepinephrine transporter, SLC6A2. Ramoz *et al.*[31] describes significant associations between 20 single-nucleotide polymorphisms within *SLC6A2* and responders as compared with nonresponders of atomoxetine. If other studies replicated this finding, future guidelines may consider incorporating this result in its recommendations.

Individuals taking atomoxetine along with a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, and paroxetine) may experience higher than expected concentrations based on their *CYP2D6* genotype through a process known as phenoconversion. This has been described for paroxetine and fluoxetine in non-PM metabolizers taking atomoxetine.[32–34] For the duration of the phenoconversion (for fluoxetine it may last up to 2–3 months after fluoxetine discontinuation in average patients and longer in some individuals[35]), the individual phenotypically resembles a CYP2D6 PM regardless of genotype.

**Implementation resources for this guideline.** The guideline supplement contains resources that can be used within electronic health records to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support section in the supplement). Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems, workflow diagrams, a table that translates genotype test results into a predicted phenotype with genetic test interpretation, and an example text for documentation in the electronic health records and point-of-care alerts.

## POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of using an individual's *CYP2D6* genotype to guide atomoxetine dosing is that clinicians can be alerted to individuals who are more likely to fail treatment at standard dosing (e.g., NMs or UMs) or be at an increased risk of adverse effects (e.g., PMs). The FDA recommends atomoxetine doses up to 100 mg/day in adults or 1.2 mg/kg/day in children. This guideline proposes that CYP2D6 UMs (AS > 2 and 1–2% of US patients) and NMs (AS 1–2 and 77–92% of US patients) may need higher than FDA-recommended doses to achieve concentrations associated with clinical response, based on low atomoxetine peak concentrations (< 200 ng/mL). It is estimated that up to one of three of US patients may be in this category of needing higher than recommended doses,[30] but the exact prevalence needs to be established by future clinical studies. A potential risk of testing is the misinterpretation of genetic test results, as rare or novel variants are typically not interrogated. If an individual carries a rare variant, the actual phenotype may differ from the phenotype predicted by the genotypes included on a specific laboratory test. An individual's intrinsic CYP2D6 activity may also be impacted by other factors, including epigenetics, diet, comorbidities, or comedications. Any of these factors, including the comedication with a CYP2D6 inhibitor, would be reflected through atomoxetine therapeutic drug monitoring. Although *CYP2D6* genotyping is usually reliable when performed in qualified laboratories, the possibility for error in genotyping, contamination, or mislabeling of the sample remains.

## CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Rare *CYP2D6* variants may not be included in the genotype testing used by some laboratories, and patients with rare variants may be assigned a "wild-type" (*CYP2D6*1*) genotype by default. Thus, there is a small risk that an assigned "wild-type" allele could potentially harbor a no or decreased function variant. Furthermore, it is important that the genetic testing platform includes testing for gene copy number to identify CYP2D6 ultrarapid metabolizers or gene deletions that may decrease CYP2D6 AS. Caution should be used regarding molecular diagnostics of *CYP2D6* gene copy number variation because commercially available genotyping results may differ between diagnostic laboratories depending on assay design. Like all diagnostic tests, *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient. Furthermore, there are several other factors that cause potential uncertainty in the genotyping results and phenotype predictions. These are discussed in detail in the **Supplemental Material** online.

In this guideline, we propose that exposure be assessed to guide subsequent dosing decisions when the desired clinical response has not been achieved, but we also recognize that this recommendation has limitations: available exposure-response data from clinical trials are derived from concentrations drawn 60–90 minutes after dosing; although this measure may not be the best predictor of response, the relationship between other exposure measures, such as trough concentration at steady state, steady-state AUC, unbound atomoxetine concentrations, or total active compounds (unbound atomoxetine + unbound 4-OH aglycone), has not been evaluated.

**SUPPORTING INFORMATION**

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

**Supplementary Material S1.** Methods.
**Supplementary Material S2.** Implementation Tables.

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**CONFLICT OF INTEREST**

The authors declared no competing interests for this work.

**DISCLAIMER**

The CPIC guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. The CPIC assumes no responsibility for any injury to persons or damage to property related to any use of the CPIC's guidelines, or for any errors or omissions.

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