Review

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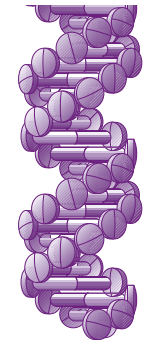
Pharmacogenomics



Atomoxetine pharmacogenetics: associations with pharmacokinetics, treatment response and tolerability

Atomoxetine is indicated for the treatment of attention deficit hyperactivity disorder and is predominantly metabolized by the CYP2D6 enzyme. Differences in pharmacokinetic parameters as well as clinical treatment outcomes across *CYP2D6* genotype groups have resulted in dosing recommendations within the product label, but clinical studies supporting the use of genotype guided dosing are currently lacking. Furthermore, pharmacokinetic and clinical studies have primarily focused on extensive as compared with poor metabolizers, with little information known about other metabolizer categories as well as genes involved in the pharmacodynamics of atomoxetine. This review describes the pharmacogenetic associations with atomoxetine pharmacokinetics, treatment response and tolerability with considerations for the clinical utility of this information.

Keywords: ADHD • atomoxetine • CYP2D6 • pharmacogenetics

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Background

Atomoxetine was approved in 2002 for the treatment of attention-deficit hyperactivity disorder (ADHD) in adults and children under the brand name Strattera™ [1]. As a novel nonstimulant option for the treatment of ADHD, atomoxetine became the third most prescribed ADHD medication in children less than 18 (behind methylphenidate and amphetamine/dextroamphetamine) between 2002 and 2004. The initial surge in utilization was followed by a decline in prescribing between 2004 and 2010 [2], despite an increasing prevalence of ADHD. While it is difficult to identify the exact reasons for this decline, it has been suggested that it may have been due to a perceived lack of efficacy among clinicians [3]. Additionally, prescription rates may have been affected by a Public Health Advisory issued in September of 2005 by the US FDA entitled 'Suicidal Thinking in Children and Adolescents Being Treated with Strattera (Atomoxetine)', although Du *et al.* note that prescription rates began to decline prior to this [4].

Approximately 9% of all children between 6 and 17 years of age in the US have received a diagnosis of ADHD at one point in time [5]. Additionally, the overall prevalence of ADHD in children reportedly increased by 33% (from 5.69 to 7.57%) from 1997–1999 to 2006–2008 [6], while the prevalence in adults is reported to be approximately 4.4% [7]. Stimulant medications such as methylphenidate and amphetamine/dextroamphetamine are commonly utilized first-line agents for the treatment of ADHD. However, in one 5-year prospective study only half of patients remained on methylphenidate after 1 year, potentially due to tolerability issues related to side effects [8]. This, coupled with concerns for abuse/serious adverse events with stimulants, makes a nonstimulant medication such as atomoxetine an attractive alternative treatment option.

Atomoxetine is unique in that it is a nonstimulant therapeutic option for ADHD, with a primary pharmacodynamic mechanism of action involving the selective inhibition of the presynaptic norepinephrine transporter [9,10]. The onset of action of atomoxetine is somewhat delayed as compared with stimulant medications, possibly due to neuroadaptive changes on noradrenergic receptors fol-

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lowing repeated administration [11], and typically takes 2–3 weeks for an initial response [12]. Although long-term studies reveal that atomoxetine is generally effective in approximately 75% of patients [13], extensive metabolism by the highly variable CYP2D6 drug-metabolizing enzyme leads to considerable variability in exposure at standard dosing recommendations. There is variability of CYP2D6 activity observed in different ethnic groups [14], and the pharmacokinetic parameters of atomoxetine vary significantly depending upon an individual's *CYP2D6* genotype.

While atomoxetine is generally considered safe and tolerable in both poor and extensive metabolizers [15], it was included in a 2014 special report on children by the Institute for Safe Medication Practices as the 12th most frequent suspected drug in serious adverse drug events reported in normal medication use between 2008 and 2012 [16]. Specifically, suicidal ideation and chest pain were the two most frequently reported serious adverse drug events noted for atomoxetine. Additionally, the product labeling notes several adverse drug events that occur either twice as often or significantly more frequently in CYP2D6-poor versus extensive metabolizers, most commonly reported being insomnia, decrease in weight, constipation and depression [1].

Metabolic pathway of atomoxetine

Atomoxetine is the active parent compound and undergoes extensive metabolism in the liver. The primary metabolic pathway, mediated by CYP2D6, results in oxidative metabolism of atomoxetine leading to the formation of an active metabolite, 4-hydroxyatomoxetine (Figure 1); however, this active metabolite circulates in very low concentrations and is rapidly glucuronidated to the inactive 4-hydroxyatomoxetine glucuronide metabolite [17]. Although this pathway is predominant in both poor and extensive metabolizers of CYP2D6, additional CYP enzymes such as CYP2C19, CYP3A4, CYP1A2, CYP2A6 and CYP2E1 have also been shown to have the capacity to biotransform atomoxetine to 4-hydroxyatomoxetine when CYP2D6 is not expressed [18], and is an additional area of potential variability warranting further investigation. To a lesser extent, atomoxetine is also metabolized by CYP2C19 to the inactive N-desmethylatomoxetine; which presumably is also cleared by CYP2D6 in the formation of N-desmethyl-4-hydroxyatomoxetine glucuronide. As a result, CYP2D6-poor metabolizers experience increased concentrations of N-desmethylatomoxetine as compared with extensive metabolizers [18].

Cytochrome p450 2D6

CYP2D6 is involved in the metabolism of approximately 25% of the currently available medications to patients [19], including antipsychotics, antidepressants and β-blockers, among others. The *CYP2D6* gene is highly polymorphic, resulting in genetically influenced variability in the metabolic activity of this enzyme. The *CYP2D6* gene, located on chromosome 22, contains well over 100 single-nucleotide variations (SNVs) identified across various ethnic groups [20], and genotyping has become the most common method for predicting an individual's phenotype [21]. Although there is no current ubiquitously accepted standard for grouping individuals based on *CYP2D6* genotypes, the most common nomenclature classifies individuals as ultra-rapid metabolizers (functional copy number duplications), extensive metabolizers (individuals with two 'wild-type' alleles), intermediate metabolizers (individuals with one reduced and one loss of function allele) and poor metabolizers (those with two loss of function alleles) [22]. Assessing and classifying CYP2D6 metabolizer status based on genotyping technologies is complex due to the diversity of the types of genetic variants observed in this gene [14]. The aforementioned SNVs can result in either decreased activity or complete loss of function and are located throughout the gene as well as regulatory regions. The sequence of *CYP2D6* and surrounding regions predisposes this area for misalignment and unequal crossing-over in meiosis resulting in gene duplications, deletions, as well as gene fusion with other neighboring genes. Individuals with multiple copies of functional *CYP2D6* alleles have greater CYP2D6 enzyme activity as compared with those homozygous for the wild type allele.

One strategy for making sense of multiple sources of variability in CYP2D6 and the resulting functional consequences has been the development of 'activity scores' (ASs) for specific *CYP2D6* alleles. In this paradigm, a fully function allele is assigned a score of 1, a decreased function a score of 0.5 and a loss of function allele as 0 [14]. Thus, someone with an AS of 2 would be considered an extensive metabolizer, while an AS of 0 would infer poor metabolizer status. Despite these attempts to group individuals, inconsistencies remain in how to classify someone with a CYP2D6 AS less than 2 but more than 0 (i.e., individuals with one or more reduced function allele) [21]. Adding to this complexity, genotyping platforms that do not sequence the gene can vary considerably to the extent of which they investigate for polymorphisms, and when no polymorphism is detected (potentially due to not testing for it) a default wild-type allele is assigned. While pharmacogenetic information regarding *CYP2D6* is included in the product label of several medications, few of them contain specific dosing recommendations [23].

CYP2D6 influence on atomoxetine pharmacokinetics

Variation in atomoxetine half-life was first described in a pharmacokinetic study by Farid *et al.* in 1985 in drug development studies, initially with thoughts that it may be a candidate for a new antidepressant [24]. Two distinct groups were observed in healthy volunteers, in which the average atomoxetine half-life was 4.5 h in one group, and 19 h in another (Figure 2). After Ring *et al.* described the involvement of CYP2D6 via human liver microsomes as the primary human enzyme responsible for the formation of atomoxetine's active metabolite in 2002 [18], a formal pharmacokinetic study was completed in adult volunteers. This pharmacokinetic study in adults investigated multiple daily doses and revealed rapid absorption [17]. These individuals also experienced an area under the curve (AUC) approximately 10-times greater if they were CYP2D6-poor metabolizers as compared with extensive metabolizers. Poor metabolizers also had an extended half-life nearly fourfold as long (Figure 2), a significantly increased maximum concentration (C_{max}), and a clearance 1/10th that of extensive metabolizers. Given the short half-life in extensive metabolizers, minimal accumulation of atomoxetine was observed [17].

While these previous studies focused exclusively on poor and extensive metabolizers, an additional pharmacokinetic study in Chinese adults examined the effect of the CYP2D6*10 allele (an allele with reduced function common in Asian populations) on atomoxetine [25]. For both single and multiple dosing pharmacokinetics the individuals homozygous for the *10 allele (and thus a CYP2D6 AS of 1) experienced AUCs approximately 2.2-fold higher and C_{max} approximately 1.5-fold higher as compared with extensive metabolizers. Similarly, Matsui *et al.* also studied the impact of the *10 allele on atomoxetine disposition in Japanese men, grouping individuals as *10/*10 (AS = 1), *1/*10 or *2/10 (AS = 1.5) and *1/*1 or *1/*2 (AS = 2) [26]. This pharmacokinetic study revealed very similar results for the *10/*10 group (approximately 2.10-fold increase as compared with the *1/*1 or *1/*2 group), while the *1/*10 or *2/*10 groups experienced an increased AUC of 1.79-fold as compared with the extensive metabolizer group.

Similar pharmacokinetic studies have been conducted in children with normal CYP2D6 activity as compared with those having various levels of reduced activity. Included in clinical studies, children categorized as poor metabolizers had a ninefold lower clearance [27] and peak concentrations fivefold greater as compared with extensive metabolizers [28]. An additional pharmacokinetic study of atomoxetine utilized comparable weight-based dosing (0.5 mg/kg) while stratifying children by their CYP2D6 AS. This revealed that those with a CYP2D6 AS of 0 (poor metabolizers) experienced dose-corrected AUC values 2.5-, 8.5- and 10.8-fold higher than children with ASs of 0.5, 1 and 2, suggesting similar profiles for the 0/0.5 and 1/2 AS groups. It also showed 25.8-fold variation in dose-corrected AUC across the entire study population [29].

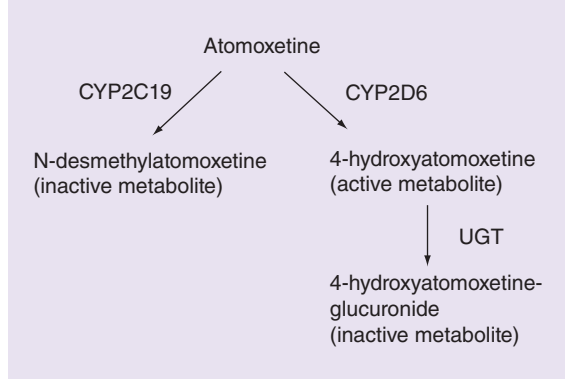

Figure 1. Atomoxetine metabolic pathway.

While available pharmacokinetic studies have focused primarily on the differences between poor, intermediate and extensive metabolizers, little is published on the pharmacokinetic parameters of individuals with *CYP2D6* duplication of functional alleles, or ultrarapid metabolizers. Given the linear pharmacokinetics described in adults, it is likely that these individuals experience lower overall maximum concentrations and total exposure as compared with extensive metabolizers, and thus may require a dose higher than what is currently recommended [30].

Specific drug–drug interactions have also been described in individuals who are taking a potent CYP2D6 inhibitor resulting in phenoconversion most notably with paroxetine. This effect essentially converts an extensive or intermediate CYP2D6 metabolizer into a poor metabolizer for the duration they are on that medication, regardless of their genotype. A pharmacokinetic study was conducted in volunteers known to be CYP2D6-extensive metabolizers receiving atomoxetine alone as well as atomoxetine with paroxetine. This study showed that these individuals exhibited a profile similar to CYP2D6-poor metabolizers when given paroxetine concomitantly, with an increase in N-desmethylatomoxetine and a decrease in 4-hydroxyatomoxetine levels [31]. Paulzen *et al.* report utilizing low-dose paroxetine (10 mg/day) in order to elevate atomoxetine levels in a 38-year-old male with ADHD and a previous diagnosis of major depressive disorder. Initially started on 40 mg/day of atomoxetine, he was eventually increased to 30 mg three-times daily, resulting in improved psychomotor restlessness but no affect on alertness or con-

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centration. After having three atomoxetine levels drawn at 30, 120 and 240 min, the patient had repeat atomoxetine samples drawn after 14 days of starting paroxetine. When taken with paroxetine, atomoxetine levels were more than twofold greater after 30 min (242 vs 538 ng/ml), threefold greater after 120 min (760 vs 250 ng/ml) and 4.5-fold greater after 240 min (506 vs 111 ng/ml) [32]. This patient reported better attentiveness while receiving concomitant paroxetine therapy, suggesting increased plasma concentrations may be effective in some patients.

Atomoxetine pharmacodynamics

Atomoxetine is a potent and highly selective inhibitor of the norepinephrine transporter on presynaptic neurons, resulting in an increase in norepinephrine availability at postsynaptic terminals. Efficacy for the treatment of ADHD is thought to be a result of this activity due to the importance of the noradrenergic system in sustained attention, learning and memory [33]. Additionally, depletion of norepinephrine has been shown to lead to increased distractibility in animal studies [34]. The areas of the brain most associated with ADHD are the prefrontal cortex, caudate and cerebellum [35,36], in which norepinephrine and dopamine play essential roles in attention, learning and memory processes. Although the pharmacodynamic mechanism of atomoxetine is as a selective norepinephrine reuptake inhibitor, it may also increase dopamine release in prefrontal cortex [37,38]. The dopaminergic effects of atomoxetine may be region specific as evidenced by other investigations that have not found such relationships in the striatum or nucleus accumbens [38].

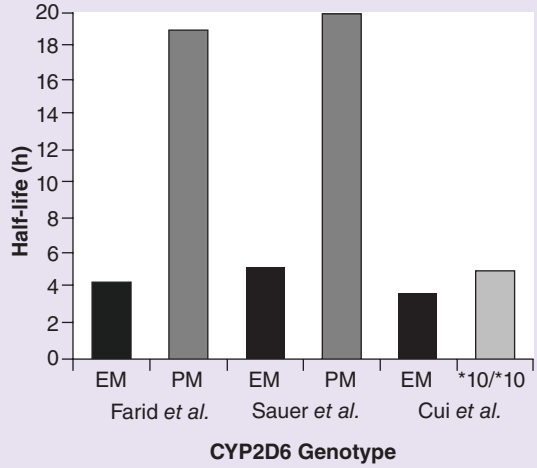

Figure 2. Half-life differences between extensive, intermediate (*10/*10) and poor metabolizers.
EM: Extensive metabolizer; PM: Poor metabolizer; *10 allele: Reduced activity.

Clinical effects & comparisons with other ADHD medications

Atomoxetine as well as stimulants are often considered as drug treatments for ADHD [39], although stimulants are more commonly used or recommended first line in patients without contraindications [40]. Response rates to stimulants such as amphetamine derivatives and methylphenidate are estimated to be between 80 and 90% [41], with nearly 90% of patients responding clinically to one of these two treatment options [42]. Atomoxetine is generally considered second line to stimulants or as an alternative in patients with tic disorders, substance use concerns or other contraindications to stimulants, with response rates around 60% [40]. The clinical effects of stimulants are more immediately apparent while the onset of action for atomoxetine is generally delayed, although there appear to be some patients who are 'rapid' responders. As it pertains to the applicability of pharmacogenetic information, there appears to be greater variability in atomoxetine response than in stimulants. Understanding mechanisms subserving this variance may benefit from examining biological measures, such as genetic markers, in combination with clinical variables that have been linked to different response patterns.

Several factors influence the robustness of response to atomoxetine in registry trials, including ADHD subtype (combined subtype = greater response), prior stimulant use (prior use = less response) and CYP2D6-poor metabolizer status (more common in robust responders) [43]. The onset of clinical effect in randomized controlled trials (RCTs) separates from placebo at approximately 4 weeks for most patients, with improvements seen out to 12 weeks [44]. There are some indications that earlier response may be observed in some patients, as some treatment naive patients have shown clinical effects observable in the 3–4-week time frame. Additional reports corroborate these findings that there may be an early responder/robust responder group [45].

With a couple of exceptions, the effects of pharmacogenetic information has predominantly been assessed in study samples aggregated from registry or postmarketing trials of atomoxetine for the treatment of ADHD in younger patients. Most of these studies have focused on genetic variation in *CYP2D6*, although some pharmacodynamic candidate genes have been assessed. The largest pharmacogenetic analysis to date involved subjects who participated in efficacy and safety trials for atomoxetine [28]. In the study sample used to assess pharmacogenetic associations with treatment

response, 589 participants (30 of whom were identified as CYP2D6-poor metabolizers) were assessed for response over the course of 6–8 weeks of treatment. As titration and dosing schedules for these RCTs were largely standardized, doses at end point were comparable for poor and non-poor metabolizers. Average improvement as measured by ADHDRS-IV-Parent Interview scale was 14.1 ± 13.4 points vs 20.9 ± 15.2 points in non-poor and poor metabolizers, respectively. Response rates according to clinical global improvement (CGI) scores were 59.4 and 80% for the non-poor metabolizer and poor metabolizer groups, respectively [28]. A second analysis of 2–10-week data from two flexibly dosed open label registry studies of 1326 (n = 87 poor metabolizers) children and adolescents also found slight improvements on ADHDRS-IV inattention measures in poor metabolizers as compared with extensive metabolizers, but with similar response rates (81.6 vs 84.9%, respectively) as measured by at least a 25% improvement on this assessment [46]. Doses between poor and extensive metabolizers in these open label studies began to separate after approximately 3 weeks such that poor metabolizers received lower doses through the end of the studies. Although clinical care was done blind to CYP2D6 metabolizer status, the clinical presentation of poor metabolizers was such that clinicians selected lower doses for these patients even in the absence of knowledge regarding metabolizer status. Alternatively, a retrospective review of 100 children identified ten of whom either had a delay in response defined as beyond 9 weeks, or experienced an adverse effect such as gastrointestinal problems, sleep disorders, malaise, inactivity or mood instability. Of these, several were noted to have decreased CYP2D6 activity and responded well to a dose adjustment. From these results, ter Laak *et al.* concluded that knowledge of *CYP2D6* genotype prior to dosing may enhance a provider's ability to safely prescribe atomoxetine [47]. An additional investigation [48] incorporated CYP2D6 metabolizer status into pharmacogenetic analyses that primarily focused on pharmacodynamics targets of *SLC6A2*, *ADRA1A* and *ADRA2A* genotypes. These 6-week analyses of two child and adolescent cohorts originally investigated flexible dosing strategies and longer term treatment outcomes, although no effects of CYP2D6 metabolizer status on treatment response were observed.

Safety and tolerability based on CYP2D6 metabolizer status has also been assessed in two analyses [28,46]. The study samples for these two reports were n = 3254 (n = 237 poor metabolizers) [28] and n = 1326 (n = 87 poor metabolizers) [46], and notable for small but significant differences in side effect measures between poor metabolizer and non-poor metabolizer groups. Both studies identified that pulse rates increased in both extensive and poor metabolizers, but significantly greater increases were observed in poor metabolizers (mean ~10–11 bpm) as opposed to extensive metabolizers (~6–7 bpm). Small differences in weight/BMI profile were observed in both studies either indicating slightly more weight loss or slightly less weight gain in poor metabolizers as compared with non-poor metabolizers. Assessments of reported treatment-emergent effects were notable for decreased appetite being reported more often in poor metabolizers versus non-poor metabolizers (24.1 vs 17%) when all dosing groups were considered together [28]. The larger analysis of Michelson *et al.* additionally identified small but significantly greater increases in diastolic blood pressure in poor versus non-poor metabolizers.

Only limited data exist at this time investigating genes related to the pharmacodynamics of atomoxetine. Ramoz *et al.* identified a haplotype covering exons 4–9 of *SLC6A2* that was associated with an increased likelihood (OR = 1.83) of achieving at least a 25% improvement in ADHD ratings after 6 weeks of flexibly dosed atomoxetine in a combination of two studies totaling 265 participants [48]. A second study investigated 111 Chinese children and adolescents treated with atomoxetine for ADHD over the course of 8–12 weeks and examined pharmacogenetic associations between selected variants in *SLC6A2*, *ADRA1A* and *ADRA2A* [49]. They identified a single SNV in *SLC6A2* that was associated with the likelihood of achieving at least a 25% improvement in ADHD ratings. This SNV was also present in the haplotype found associated with response in the Ramoz *et al.* investigation [48].

Taken together with the previously described pharmacokinetic data, this information suggests that CYP2D6-poor metabolizers may exhibit a greater therapeutic benefit due to increased exposure to medication. Additionally, poor metabolizers may exhibit small but notable increases in some cardiovascular outcomes as well as decreased appetite. The magnitude of these effects appears to be less in open label investigations as compared with RCTs, suggesting that the clinical presentation in poor metabolizers is different enough that clinicians, at least as represented by those involved in the clinical investigations considered here, noted them to adjust dosing accordingly [46]. These results raise the ultimate question as to whether preemptive genotyping is necessary when clinicians adjust according to clinical response. Variations in genes associated with the pharmacodynamics of atomoxetine are largely understudied. Preliminary associations in regions of *SLAC6A2* appear consistent across two study samples of different ancestries, although the functional variant responsible for these findings is unclear as is the clinical applicability of this information.

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Application of clinical pharmacogenetic testing

In children, the product labeling states that atomoxetine should be initiated at 0.5 mg/kg/day and ultimately titrated to the target dose of 1.2 mg/kg/day, with a maximum daily dose of 1.4 mg/kg/day. In children and adults greater than 70 kg, the starting dose is 40 mg/day to be titrated up to 80 mg/day, with a maximum dose of 100 mg/day [1]. Alternatively, specific dosing recommendations exist within the product label based on known *CYP2D6* information, although there is no specific recommendation to obtain genotyping prior to or after initiating atomoxetine. Children identified as CYP2D6-poor metabolizers or taking a strong CYP2D6 inhibitor (specifically noted are paroxetine, fluoxetine and quinidine) are recommended to be initiated at the same starting dose of 0.5 mg/kg/day as those with normal CYP2D6 activity, only to be increased in total daily dose in the absence of serious adverse effects or a lack of therapeutic effect.

Created by the Royal Dutch Pharmacist's Association, the Dutch Pharmacogenetics Working Group consists of scientists and clinicians aimed toward the development of pharmacogenetics-based recommendations. In regard to atomoxetine dosing, their therapeutic dose recommendation does not differ from what is currently in the product label. Specifically, they recommend the standard dose for CYP2D6-poor metabolizers, while being alert to adverse drug events with a dose increase likely unnecessary. For individuals categorized as intermediate or ultrarapid metabolizers no dosing recommendations exist, although they do note that reduced efficacy may occur in ultrarapid metabolizers and an alternate ADHD medication may be more appropriate [50]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides drug selection/dosing recommendations for clinicians when pharmacogenetic information is available [51]. Currently, there is no CPIC guideline for atomoxetine and CYP2D6. The considerable variability in exposure largely dependent upon an individual's *CYP2D6* genotype may represent a need for more detailed dosing recommendations than what is currently included in the product label.

Conclusion

Individual variation in CYP2D6 activity results in markedly different overall exposure profiles in patients taking atomoxetine. The clinical utility of this is unclear. However, there is compelling evidence that while CYP2D6-poor metabolizers may have a better response to atomoxetine, they may also experience a higher frequency of adverse events as compared to CYP2D6-extensive metabolizers. While it is likely that the overall clinical response to atomoxetine involves several genes, knowledge of an individual's *CYP2D6* genotype has the potential to improve the safety and efficacy of atomoxetine usage.

Future perspective

As broadly compared with methylphenidate and amphetamine alternatives in the treatment of ADHD, atomoxetine appears to exhibit greater variability in response. Atomoxetine also exhibits a delayed onset of clinical effect as compared with the more immediate effect of stimulant medications that are commonly used first line. However, there are clinical considerations that make atomoxetine (as a nonstimulant) of great interest in some patients. In this context pharmacogenetic applications may have a clinical role. Currently, it appears that genetic influences in drug metabolism through CYP2D6 have some implications for dose selection and potentially titration, but in the absence of this information clinicians appear to gradually reach these differences on their own. While the majority of clinical studies compared only CYP2D6-extensive metabolizers with -poor metabolizers, future considerations should be given for individuals who are CYP2D6-intermediate and -ultrarapid metabolizers. Whether proactively obtaining and applying this information improves the safety or symptom response profile is unknown and an area of needed research. This future research should also assess the cost–effectiveness of pharmacogenetic testing with atomoxetine, as these studies are currently lacking. Pharmacogenetic studies investigating pharmacodynamic genes have identified some consistency in signals associating SNVs or haplotypes in the norepinephrine transporter (*SLC6A2*) with clinical response; however, no studies to our knowledge have identified strong genetic associations with the different 'types' of responders (fast, robust, moderate, nonresponders, etc.), and this information might be very useful clinically. The product labeling for atomoxetine currently describes detailed dosing instructions for known CYP2D6-poor metabolizers, yet at this time this information is not used clinically due to uncertainties as to whether patients are better off after this information is applied as opposed to standard clinical practice.

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Executive summary

- Atomoxetine is a norepinephrine transporter inhibitor utilized as a second line agent in the treatment of attention-deficit hyperactivity disorder (ADHD).
- Atomoxetine appears to exhibit greater variability in treatment response than stimulant medications for the treatment of ADHD.
- CYP2D6 is the primary enzyme involved in the metabolism of atomoxetine, and poor or reduced metabolic activity significantly increases overall exposure to atomoxetine and its metabolites.
- Information regarding the effects of increased (ultrarapid) CYP2D6 metabolism or genetic variants in genes related to the pharmacodynamics of atomoxetine remain less studied at this time.
- Atomoxetine dosing strategies based on *CYP2D6* genotype may provide more comparable exposure in the general population, potentially leading to improved therapeutic outcomes.

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