# CYP2D6: Atomoxetine

AUC: 'area under the concentration-time curve', AUEC: 'area under the time-effect curve', BID: twice a day, 95%CI: 95% confidence interval, DBP: diastolic blood pressure, EM: extensive metabolizer, 4-HA: 4-hydroxyatomoxetine, IM: intermediate metabolizer, MR: metabolic ratio, N-DA = N-desmethylatomoxetine, NS: not statistically significant, PM: poor metabolizer, QTc-interval: Heart rate corrected QT interval, S: statistically significant, SBP: systolic blood pressure, t1/2: half life, UM: ultrarapid metabolizer.

| Reference | Level of evidence | Clinical relevance | Effect | Remarks |
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| **ref. 1**<br>Ramoz N et al.<br>A Haplotype of the Norepinephrine Transporter (Net) Gene Slc6a2 is Associated with Clinical Response to Atomoxetine in Attention-Deficit Hyperactivity Disorder (ADHD).<br>Neuropsychopharmacology 2009;34:2135-42.<br><br>PMID: 19387424 | 3 | PM: AA | 265 children with ADHD, 9x PM, 246x EM[#] (genotyped for *3-*8). Atomoxetine 0.5-1.8 mg/kg per day for 6 weeks. Concomitant medication not reported.<br><br>Compared to EM[#]:<br><br>PM:<br>- No difference in response (NS) defined as a minimum decrease of 25% in ADHD Rating Scale IV-Parent Version and a Clinical Global Impression-Severity (CGI-S) score less than or equal to 2 at week 6. | Conclusion authors:<br>'Interindividual response was independent of the genetic variants of CYP2D6. The lack of effect of CYP2D6 metabolism status seen in this study may be due to small sample size as this has been previously shown in a larger population including some patients from this genetic cohort (Michelson et al, 2007).' |
| **ref. 2**<br>Trzepacz PT et al.<br>CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD.<br>Eur Neuropsycho | 3 | PM: A | 1365 children with ADHD, 87x PM, 1239x EM[#] (genotyped for *3-*8). Atomoxetine for 10 weeks. Patients were assessed weekly and doses titrated for efficacy and tolerability at the discretion of investigators. Initial dose 0.5 mg/kg per dag. Maximum dose 1.8 mg/kg per day. Concomitant medications allowed with the exclusion of medications for other psychiatric conditions.<br><br>Compared to EM[#]: | Conclusion authors:<br>'Results suggest genotyping is unnecessary during routine clinical management, because investigators were able to dose atomoxetine to comparable efficacy and safety levels in EMs and PMs without knowledge of genotype metabolizer status.' |

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| pharmacol 2008;18:79-86.<br><br>PMID: 17698328 | | | PM:<br>- Mean modal dose decreased from 1.26 mg/kg/day to 1.14 mg/kg/day (S)<br>- Mean final dose decreased from 1.50 mg/kg/day to 1.35 mg/kg/day (S)<br>- No increase in response rate (≥ 25% reduction in ADHD symptoms) with 81.6% and 84.9% for EMs and PMs respectively (NS)<br>- No larger decrease in ADHD symptoms with 52% and 59% for EMs and PMs respectively (NS)<br>- Larger decrease in inattention score with 49% and 57% for EMs and PMs respectively (S)<br>- No effect on incidence of treatment-emergent adverse events (including decreased appetite) with 57.5% and 54% for EMs and PMs respectively (NS)<br>- No differences between groups for discontinuation due to any adverse event with 2.4% and 5.8% for EMs and PMs respectively (NS)<br>- No effect on height, DBP, SBP, QTc-interval.<br>- Weight loss increased from a 1.0% weight increase to a 2.5% decrease (S)<br>- Smaller increase in mean pulse rate with 8.5% and 13.4% for EMs and PMs respectively (S)<br>- Predicted AUC at t=8-10 weeks increased from approximately 3 to 25 µg.hour/ml (729%) | |
| **ref. 3**<br>Cui YM et al. Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 allele.<br>Br J Clin Pharmacol 2007;64:445-9. | 4 | IM: A | 16 healthy subjects, 7x IM (*10/*10), 9x EM (*1/*1 of *1/*10) (genotyped for *2-*11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *36, *40, *4). Atomoxetine 40 mg/day for 3 days followed by 80 mg/day for 7 days. No relevant concomitant medication.<br><br>Compared to EM:<br><br>IM:<br>- AUC0-24h increased from 4427 to 9693 h/ng per ml (S, by 119%) | Conclusion authors:<br>'Whilst the number of homozygous CYP2D6*10 subjects was too small to support definitive conclusions, higher average drug exposures in this group did not appear to result in differences in safety or tolerability.'<br><br>AUC atomoxetine compared to EM: |

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| PMID: 17610534 | | | - Clor decreased from 0.29 to 0.13 l/hour per kg (S, by 55%)<br>- t1/2 increased from 3.74 to 5.17 hour (S, by 38%)<br>- The effects on AUC0-24h, Clor, and t1/2 following single and multiple doses were similar (S, by 121%, 55%, 62% respectively)<br>- No difference in frequency, severity and type of adverse events reported. Most common adverse events were dizziness, nausea and upper abdominal pain. All adverse events were of mild severity and had resolved by the time of study completion. | IM: 219% |
| **ref. 4**<br>Michelson D et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD.<br>J Am Acad Child Adolesc Psychiatry 2007;46:242-51.<br><br>PMID: 17242628 | 3 | | 589 children with ADHD, 559x EM[#] (genotyped for *3-*8), who participated in in 4 registration trials. Atomoxetine for 6-8 weeks.<br>Dose was titrated for efficacy and tolerability. Maximum dose 1.8 mg/kg per day. Only concomitant psychotropic medications were excluded. The assessment of efficacy included 2 open label studies. Safety and tolerability were assessed in pooled data from 3524 children, 237x PM, 3017x EM[#]. In one safety study, fluoxetine 20 mg/day was coadministered with atomoxetine to 141 patients. In this study, patients (n=46) who had peak plasma atomoxetine concentrations that exceeded a threshold value (2 SDs below the mean peak plasma atomoxetine concentration for a genotypic PM taking the same dose of atomoxetine as measured in previous pharmacokinetic studies) were considered to have a PM phenotype. These patients were included as PM patients in the safety analyses. A secondary analysis of the data excluding these 46 patients did not change the results.<br><br>Compared to EM[#]:<br><br>PM:<br>- Mean final dose decreased from 1.37 to 1.28 mg/kg/day (NS, by 7%). 2 open-label studies; mean final dose decreased from 1.5 to 1.33 mg/kg/day (S, by 11%). | Conclusion authors:<br>'These results suggest that CYP2D6 poor metabolizers taking atomoxetine in doses up to 1.8 mg/kg/day are likely to have greater efficacy, greater increases in cardiovascular tone, and some differences in tolerability compared with CYP2D6 extensive metabolizers taking similar doses.' |

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| | | PM: AA[#]<br><br>PM: B | Safety analysis group; Mean final dose decreased from 1.44 to 1.29 mg/kg/day (NS, by 10%)<br><br>- Response (>=25% decrease in ADHD symptom reduction from baseline) increased from 59.4% to 80% (S) (placebo: 32,1%). Open label studies, NS<br><br>- Larger decrease in ADHD symptoms with 35% and 54% for EMs and PMs respectively (S). Open label studies 52% and 59% respectively (S).<br>- Discontinuation due to lack of effect decreased from 26.0% to 17.3% (S, by 33%)<br>- Incidence of tremor increased from 1.1% to 5.1% (S, by 364%)<br>- Incidence of decreased appetite increased from 17% to 24.1% (S, by 42%)<br>- Incidence of abrasion increased from 2.2% to 5.1% (S, by 132%). Authors suggest this is not therapy related.<br>- Incidence of insomnia increased from 6.8% to 10.5% (S, by 54%)<br>- No effect on discontinuation due to adverse events with 5.8% and 8.9% for EMs and PMs respectively (NS)<br>- No difference in height, SBP, Qtc-interval<br>- Weight gain decreased from 6.4% to 4.2% (S, by 34%)<br>- Heart rate increased from +7.1% to +11.9% (S, by 67%). This might be clinically relevant for in patients with underlying cardiac diseases.<br>- DBP increased from +4.0% to +6.6% (S, by 64%)<br>- Mean peak atomoxetine concentrations at a dose of approximately 0.9 mg/kg/day increased from 167.1 to 850.6 ng/ml (NS, by 409%) | |
| **ref. 5**<br>Sauer JM et al. Disposition and metabolic fate of atomoxetine hydrochloride: the role | 3 | PM: AA | 7 healthy subjects, 3x PM, 4x EM[#] (genotyped for *3-*8, PM were compared to the other genotypes, phenotyping with dextromethorphan). Atomoxetine 20 mg BID for 6 days. Concomitant medication not reported. Statistical significance not reported. | AUC atomoxetine + 4-HA<br>Compared to EM[#]:<br><br>PM: 781% |

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| of CYP2D6 in human disposition and metabolism.<br>Drug Metab Dispos 2003;31:98-107.<br><br>PMID: 12485958 | | | Compared to EM[#]:<br>PM:<br>- AUC increased from 1.08 to 8.44 µg.hour/ml (by 681%)<br>- Css,max increased from 160 to 915 ng/ml (by 473%<br>- t½ increased from 5.34 to 20.0 hour<br>- Clor decreased from 0.737 to 0.0357 l/h/kg (by 95%).<br>- 4-HA concentration was below the limit of quantitation<br>- AUC N-DA increased from 0.0618 to 2.82 µg.hour/ml (by 4463%),<br>- Css,max N-DA increased from 7.02 to 259.22 ng/ml (3593%),<br>- t½ N-DA increased from 8.97 to 33.3 hr | |
| **ref. 6**<br>SPC Strattera (atomoxetinehydrochloride) 08-04-2009. | 1 | PM: B | Dose: Approximately 7% of the white population is of the CYP2D6 PM genotype. Compared to EMs, PMs have a higher exposure to atomoxetine. As a result, PMs have a higher risk for adverse events. Consider a lower initial dose and titration schedule for PMs. No data on study design.<br><br>Compared to EM:<br><br>PM:<br>*Pharmacokinetic effects:*<br>- Approximately 10 fold increase in AUC atomoxetine<br>- Approximately 5 fold increase in Css atomoxetine<br><br>*Clinical effects:*<br>Side effects reported for ≥2% of PM and more frequently in PM than for EM (S):<br>- Decreased appetite (24,1% vs. 17,0%)<br>- Insomnia, other sleeping problems (14.9% vs. 9.7%)<br>- Enuresis (3.0% vs. 1.2%)<br>- Depression, somnolence, severe depression, dysphoria (6.5% vs. 4.1%)<br>- Weight loss (7.3% vs. 4.4%)<br>- Constipation (6.8% vs. 4.3%)<br>- Tremor (4.5% vs. 0.9%) | |

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| | | | - Sedation (3.9% vs. 2.1%)<br>- Abrasion (3.9% versus 1.7%)<br>- Early awaking (2.3% vs. 0.8%)<br>- Conjunctivitis (2.5% vs. 1.2%)<br>- Syncope (2.5% vs. 0.7%)<br>- Mydriasis (2.0% versus 0.6%)<br><br>A noteworthy finding that did not meet the above criteria is the increase number of patients with a generalized anxiety disorder (NS, 0.1% for EMs vs. 0.8% for PMs, respectively). Also an increased weight loss was reported in studies < 10 weeks (NS, 0.6 kg for EMs vs. 1.1 kg for PMs, respectively). | |
| **ref. 7**<br>Data on file, Lilly Research Laboratories. Atomoxetine – comparison of data of extensive metaboliser and poor metaboliser patients. | 0 | PM: B | <u>Dose titration:</u><br>1216 patiënten, 85x PM, 1131x EM, doses titrated for clinical response,<br><br>Compared to EM:<br><br>PM:<br>- Mean dose decreased from 1.30 to 1.24 mg/kg/day (NS)<br><br><u>Safety analyses:</u><br>3138 patients, 228x PM, 2910x EM. Subgroup treated > 6 months 90x PM, 1245x EM.<br>Side effects reported for ≥2% of PM and more frequently in PM than for EM (S):<br>- Decreased appetite, Insomnia, sedation, depression, tremor, early awaking, mydriasis, pruritus (S)<br>- For subgroup treated > 6 months: ‘chest discomfort’, laryngitis, vasovagal attack (S)<br><br>Repolarization, 100 patients:<br>- no significant association between Css atomoxetine and QTc-interval. | |

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| | | | Vital symptoms and weight:<br>- Larger increase in heart rate from +6.7 to + 10.3 bpm (S)<br>- Larger increase in SBP from +2.6 to +3.8 mmHg (NS)<br>- Smaller increase in DBP from + 4.3 to +2.7 mmHg (S)<br>- Weight -0.2 KG for PM vs. +1.1 kg for EM (S)<br>- For subgroup treated > 6 months: Larger increase in heart rate from +6.8 to + 11.1 bpm (S) and weight 0.7 KG for PM vs. +3.0 kg for EM (S)<br><br>Discontinuation of therapy:<br>- Rate of discontinuation due to side effects increased from 5% to 7.5% (NS). PMs experience significantly more constipation (S)<br>- The subgroup treated > 6 shows the opposite effect with a rate of discontinuation due to side effects of 0% for PMs and 1.6% for EMs (NS).<br>- Rate of discontinuation due to lack of efficacy decreased from 7.3% to 3.3%<br><br><u>Efficacy:</u><br>Placebo-controlled studies, 15x PM, 277x EM and 143x placebo;<br>- Decrease in ADHD-RS score larger for PMs than for EMs (-24.1 vs. -14.4, S)<br><br>Meta-analysis open-label trials, 86x PM, 1232x EM;<br>- Decrease in ADHD-RS score larger for PM than for EMs (-22.2 vs. -19.9, NS) | |
| **ref. 8**<br>USA full prescribing Information (accessed 4 Aug 2009, www.fda.gov, (Table of Valid Genomic Biomarkers in the Context of Approved | | | Concise report of results reported in ref 3. Concludes ‘‘routine laboratory tests are not required’ and the higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA’.<br><br>Dose adjustmens:<br>- “In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors or in patients who | |

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| Drug Labels) | | | are known to be CYP2D6 PMs, STRATTERA 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."<br><br>If the initial dose is not increased this is comparable to a decrease to 42% of the normal recommended dose.<br><br>- "In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, STRATTERA 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."<br><br>If the initial dose is not increased this is comparable to a decrease to 50% of the normal recommended dose. | |

EM#: All phenotypes other than PM. IM, EM and UM phenotypes are not separated by phenotyping. EM# therefore consists of IM+EM+UM.
AA#: There is a statistically significant difference between EM and PM. However, clinical response is better in PM than EM. Since the Clinical relevance score was developed to score negative clinical effects positive clinical effects are scored as AA#.

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| Groups at risk | IMs prescribed a concomitant CYP2D6 inhibitor |

**Remarks**
Date literature search: 31 March 2007

- The data from ref 8. Are also used in the publication by Allen et al. (Biol Psychiatry 2002;51 [suppl8]: 37S) and a review by Wernicke et al. (J Clin Psychiatry 2002;63 Suppl 12:50-5). 67 PMs are compared to 1290 EMs prescribed ≥ 1.2 mg/kg/day atomoxetine. Compared to EM there is no difference in mean atomoxetine dose, QTc-interval, blood pressure, withdrawal due to adverse events, and adverse event rate (except headache). Compared to EMs there is a statistically significant increase in reduction of ADHD symptoms, weight, heart rate, and headache.

| | Phenotype | Code | Gene-Drug Interaction | Action Required | Date |
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| Decision DPWG | PM | 3 B | Yes | Yes | 12 November 2009 |
| | IM | 4 A | Yes | No | |
| | UM | -- | Yes | Yes | |

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| Action Pharmacy Technician | PM: The metabolism of atomoxetine by CYP2D6 is decreased due to a genetic polymorphism.<br>First prescription: Consult pharmacist<br>Subsequent prescription: Advise the patient to contact his physician if he experiences side effects (e.g. loss of appetite, nausea, vomiting, constipation, insomnia, disturbed sleeping pattern, irritability, agitation, mydriasis or itch) |
| | IM: -- |
| | UM: The metabolism of atomoxetine by CYP2D6 is increased due to a genetic polymorphism.<br>Consult pharmacist<br>First prescription: Consult pharmacist<br>Subsequent prescription: Advise the patient to contact his physician in case of lack of therapeutic effect. |
| Action Pharmacist, Physician | PM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is decreased. This might result in increased atomoxetine concentrations and decreased concentrations of the active metabolite. Start with the normal dose. A subsequent dose increase might not be necessary. Be alert to ADEs (e.g. loss of appetite, nausea, vomiting, constipation, insomnia, disturbed sleeping pattern, irritability, agitation, mydriasis or itch) |
| | IM: -- |
| | UM: As a result of a genetic polymorphism in the gene coding for CYP2D6, the metabolic capacity of this enzyme is increased. This might result in decreased atomoxetine concentrations and increased concentrations of the active metabolites.<br>There are insufficient data for UM to calculate a dose adjustment. Be alert to reduced efficacy or select an alternative drug that is less metabolized by CYP2D6 (e.g., methylphenidate, clonidine) |

**Considerations**

Atomoxetine plasmaconcentrations are significantly increased in PMs compared to EMs. This effect remains if the dose is titrated in response of efficacy and tolerability. However, the increased plasma concentrations do not result in an increased number of adverse events, possibly due to the large therapeutic window of atomoxetine. As a result, dose adjustments are not required for PM and IM.

PM: Different pharmacokinetic parameters compared to EM. As a result the incidence of adverse events (e.g. increased heart rate, diastolic blood pressure, insomnia, depression, tremor etc.) is increased. The USA drug label recommends to "initiate at 0.5 mg/kg day and 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" in children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors or in patients who are known to be CYP2D6 PMs.

IM: No differences in type, frequency or severity of adverse events have been reported for IMs. An AUC increase by a factor 2 has been reported. Due to the large therapeutic window of atomoxetine this does not seem to result in an increased frequency of adverse events.

UM: There are insufficient data for UM to calculate a dose adjustment. Be alert to reduced efficacy due to decreased atomoxetine plasma concentrations.

Alternative drugs that are less metabolized by CYP2D6 are methylphenidate and clonidine

**Mechanism**

Atomoxetine is mainly metabolized by CYP2D6 to 4-hydroxyatomoxetine. This metabolite is equipotent to the parent compound as a norepinephrine transporter inhibitor; however, it is present in low concentrations in plasma relative to the parent compound (about 1%). CYP2C19 and other isoenzymes atomoxetine is metabolized to the inactive N-desmethylatomoxetine. In EMs 5% of atomoxetine is metabolized to N-desmethylatomoxetine. In PMs 45% of atomoxetine is metabolized to N-desmethylatomoxetine.