CYP2D6: Clozapine


<table>
<thead>
<tr>
<th>Reference</th>
<th>Level of evidence</th>
<th>Clinical relevance</th>
<th>Effect</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ref. 1</td>
<td>4</td>
<td>IM + PM: AA</td>
<td>17 patients, 1x PM, 5x IM, 11x EM. Clozapine 100-600 mg/day. 6 smokers, no relevant concomitant medication. Compared to EM: IM+ PM: - No effect on the clozapine and N-desethylclozapine concentration-to-dose ratios - No effect on the Css ratio clozapine/N-desethylclozapine. No significant differences in the clozapine and N-desethylclozapine concentration-to-dose ratios were observed between smokers and non-smokers. Note: *3-6 (the major non functional alleles in caucasians) and gene duplications were assessed.</td>
<td>Conclusion authors: ‘Clozapine and N-desethylclozapine C/D ratios were not related to the CYP2D6 genotype.’</td>
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<tr>
<td>ref. 2</td>
<td>4</td>
<td>PM: AA, IM: AA, UM: AA</td>
<td>34 patients, 1x PM, 8x IM (1 active allele), 22x EM (2 active alleles), 1x UM (3 active alleles). Clozapine was started at 25 mg/day with dose increments of 25–50 mg every 3–4 days in 2-3 daily doses. Mean final dose was 320 mg/day. No concomitant medication. Subgroup analyses for smokers and non-smokers. Compared to EM: PM: - Css* clozapine increased from 0.8 to 1.0 ng/ml/mg (NS,</td>
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| PMID: 11041319 | by 25%). IM: 
- C\textsubscript{ss}\textsuperscript{a} clozapine decreased from 0.8 to 0.6 ng/ml/mg (NS, by 25%). UM: 
- C\textsubscript{ss}\textsuperscript{a} clozapine decreased from 0.8 to 0.6 ng/ml/mg (NS, by 25%). There was no correlation between CYP2D6 genotype and clozapine-response. Note: Allele screening was performed for UM alleles *1×2 and *2×2, PM alleles *3, *4, *4×2, *5, *6, *7, *8, *11, *12, *14, and IM alleles *2, *9, *10, and *17. |
| ref. 3 | Dettling M et al. Clozapine-induced agranulocytosis and hereditary polymorphisms of clozapine metabolizing enzymes: no association with myeloperoxidase and cytochrome P4502D6. Pharmacopsychiatry 2000;33:218-20. PMID: 11147929 | 3 | PM: AA UM: AA | 108 patients, 31 with clozapine-induced agranulocytosis, 1x PM, 8x IM, 21x EM, 1x UM (3 active alleles) and 77 controls (4x PM, 22x IM, 48x EM, 3x UM. Clozapine 220-260 mg/day. No concomitant medication. The distribution of PM and UM was equal among patients with agranulocytosis and controls. There was no association of agranulocytosis CYP2D6 genotype. Note: 
- Only 1 PM and 1 UM among the cases. 
- Agranulocytosis is a multifactorial process 
- Allele screening was performed for *3- *6, *8, *14. *1 = active allele. |
| ref. 4 | Arranz MJ et al. Cytochrome P4502D6 genotype does not determine response | 3 | PM: AA | 123 patients, 8x PM (1x *3/*3, 7x *4/*4), 115x EM + IM (3x wt/*3, 35x wt/*4, 77x wt/wt). Clozapine 125-600 mg/day. Concomitant medication and smoking status not reported. |
To clozapine. 
PMID: 7640149

Compared to EM#: 
PM: 
- AUC decreased from 943 to 785 nM.hour (NS, by 17%) 
Note: 
- Genotype not reported. Phenotyping usually does not separate the IM and groups. EM# therefore represents the combined results of IM+EM. 
- The used dose is very low, especially for healthy subjects. | Conclusion authors: 'Although the power of the present study is low, our results suggest that the overall pharmacokinetics of clozapine in vivo are not influenced significantly by polymorphic variation in CYP2D6 hydroxylase activities.' 
AUC clozapine compared to EM + IM: 
PM: 120%. |

a adjusted for dose

**Remarks**
Date literature search: 12 February 2009

- The active metabolite desmethylclomipramine lacks serotonin-reuptake-activity and does not contribute to the treatment of obsessive-compulsive disorder or anxiety.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Code</th>
<th>Gene-Drug Interaction</th>
<th>Action Required</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision DPWG</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PM</td>
<td>4 AA</td>
<td>No</td>
<td>No</td>
<td>26 May 2009</td>
</tr>
<tr>
<td>IM</td>
<td>4 AA</td>
<td>No</td>
<td>No</td>
<td></td>
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</table>
Considerations
None of the retrieved studies reports an association between the CYP2D6 genotype and clozapine response or clozapine toxicity. Also no statistically significant associations between pharmacokinetic parameters of clozapine and CYP2D6 genotype are reported. Therefore no action (e.g. dose adjustment or selection of alternative drug) is required.

Mechanism
Clozapine is mainly metabolized by CYP1A2 to the active metabolite N-desmethyloclozapine (norclozapine). Other enzymes involved in clozapine metabolism are CYP3A4 and possibly CYP2C19 and CYP2C9.