KNMP

CYP2D6: sertraline

3512 to 3514

AUC = area under the concentration-time curve, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metaboliser (gene dose 0.5-1) (reduced CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), $t_{1/2}$ = half-life, S = significant, UM = ultra-rapid metaboliser (gene dose ≥ 3) (increased CYP2D6 enzyme activity).

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Sertraline is mainly converted by CYP2C19 to the active metabolite desmethylsertraline. Although desmethylsertraline has antidepressant activity, the activity is low and not clinically relevant at the standard sertraline dose. There is no evidence to support a CYP2D6-sertraline interaction (no/no-interactions).
Four studies did not find a difference in the pharmacokinetics, efficacy and/or side effects of sertraline for patients with a genetically altered CYP2D6 enzyme activity (poor metabolisers (PM), intermediate metabolisers (IM) and/or ultra-rapid metabolisers (UM)) compared to patients with a normal CYP2D6 enzyme activity (extensive metabolisers (EM)).
You can find a detailed overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below uses the KNMP nomenclature for EM, PM, IM and UM. As a result, the definitions of EM, PM, IM and UM in the table below can differ from the definitions used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Saiz-Rodríguez M et al.
Effect of polymorphisms on the pharmacokinetics, pharmacodynamics and safety of sertraline in healthy volunteers.
Basic Clin Pharmacol Toxicol 2018;122:501-511.
PubMed PMID: 29136336.</td><td>3

PM: AA</td><td>45 healthy volunteers received a single dose of sertraline 100 mg on two separate occasions.
Adverse drug reactions were defined as adverse events that were definitely, probably or possibly caused by sertraline.
No severe adverse events occurred. 73.9% of the volunteers experienced at least one adverse drug reaction. The most frequent were insomnia (43.5%), nausea/vomiting (34.8%) and headache (30.4%).
Co-medication and smoking were excluded.

Genotyping:
- 28x EM
- 13x IM
- 3x PM
- 1x UM

Results:
<table><tr><td colspan="3">Results for PM versus IM versus EM versus UM:</td></tr><tr><td></td><td></td><td>value for EM</td></tr><tr><td>% of patients with</td><td>NS</td><td>82.8%</td></tr></table></td><td>Authors’ conclusion:
“No significant effect was found for polymorphisms in CYP2C9, CYP2D6 and ABCB1 on sertraline pharmacokinetics.”</td></tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td>IM: AA
UM: AA</td>
<td>
<table>
<tr><td>at least 1 adverse drug reaction</td><td></td><td></td></tr>
<tr><td>AUC sertraline</td><td>NS</td><td>866.0 ng/hr.ml</td></tr>
</table>

NOTE: Genotyping was for *3, *4, *5 and gene multiplication. These are the most important gene variants in this Spanish population.

NOTE 2: The authors do not provide the definitions of the CYP2D6 phenotypes mentioned in the article. They refer to an article defining gene dose 1 as slow EM. As a consequence, a guess had to be made regarding these definitions.
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<td></td>
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<tr>
<td>ref. 2
AlOlaby RR et al. Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome. Brain Dev 2017;39:483-492. PubMed PMID: 28242040.</td>
<td>3

IM+PM: AA</td>
<td>In a double blind clinical trial, 25 children with fragile X syndrome, 2 to 6 years of age, receiving sertraline were compared to 26 children receiving placebo. Sertraline was administered in liquid form in a dose of 2.5 mg/day for patients aged 2 or 3 years and 5.0 mg/day for patients aged 4 years to 5 years and 8 months. The duration of the clinical trial was 6 months.
Fragile X syndrome is characterised by an altered brain development resulting in significant behavioural, cognitive, and emotional problems. Deficits in serotonin synthesis in young children resulting in impaired synaptogenesis and postnatal brain development, are believed to play a role in disease development.
Primary outcome measures were the Mullen Scales of Early Learning (MSEL) expressive language raw score and expressive language standard score, and the Clinical Global Impression Scale-Improvement (CGI-I). The CGI-I is a 7-point scale varying from 1 = very much improved since the initiation of treatment to 7 = very much worse since the initiation of treatment.
Associations with CYP2D6 genotype were investigated by regression analysis with genotype, treatment, genotype by treatment interaction, baseline score (baseline score for severity for CGI), molecular category (fragile X syndrome caused by full mutation versus mosaic), and gender.
Relevant co-medication was not excluded. In addition, most but not all children also received a non-pharmacological intervention.

Genotyping:
sertraline group
- 17x EM
- 8x IM+PM (2x IM, 6x PM)

placebo group
- 21x EM
- 5x IM+PM (4x IM, 1x PM)

Results:
<table>
<tr><td colspan="2">Efficacy results for IM+PM versus EM:</td></tr>
<tr><td>CGI-I</td><td>NS</td></tr>
<tr><td>Sensory Processing Measure – Preschool Home Form – social participation raw</td><td>A significant difference between sertraline and placebo, while there was not a significant difference for EM.

Linear regression showed a trend for association of the CYP2D6 phenotype with the social participation raw</td></tr>
</table>
</td>
<td>Authors’ conclusion: “Polymorphisms in the MAOA, Cytochrome P450 2C19 and 2D6, and in the 5-HTTLPR gene showed a significant correlation with some of the secondary measures included in this study. This study shows that polymorphisms of genes involved in the serotonergic pathway could play a potential role in predicting response to sertraline treatment in young children with fragile X syndrome.”</td>
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</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td></td>
<td>
<table>
<tr><td>score</td><td>score (p = 0.07) (NS).</td></tr>
<tr><td colspan="2">No association with the CYP2D6 phenotype was found for the following response para-meters:
- MSEL expressive language raw score
- MSEL composite score
- MSEL receptive language raw score
- MSEL visual reception raw score
- MSEL fine motor raw score
- MSEL visual reception age equivalent score
- MSEL fine motor age equivalent score
- MSEL cognitive T score (cognitive standard score)</td></tr>
</table>

NOTE 1: Genotyping was for *2-*11, *15, *17, *29, *35 and *41. Apart from gene multiplication, these are the most important gene variants in this population from the USA.

NOTE 2: The authors do not provide the definitions of the CYP2D6 phenotypes mentioned in the article. As a consequence, a guess had to be made regarding these definitions.
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<tr>
<td>ref. 3
Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antide-pressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81. PubMed PMID: 23545896.</td>
<td>3

PM: AA
IM: AA
UM: AA</td>
<td>64 patients with obsessive-compulsive disorder (OCD) were treated with sertraline at a dose of 100 mg/day or higher for more than 10 weeks. Response and side effects were assessed by patient interviews some time after treatment discontinuation. Response was measu-red using an OCD-adjusted Clinical Global Impression Scale-Improvement (CGI-I). Patients who showed a minimal improvement on this scale were included in the group of the non-responders. Patients with mild side effects were included in the group without significant side effects.
Relevant co-medication was not excluded.

Genotyping (calculated on the basis of the percentage distribution):
- 55x EM+gene dose 1/0 (36x EM, 19x gene dose 1/0)
- 5x IM (2-3x gene dose 0.5/0, 2-3x gene dose 0.5/0.5)
- 1x PM
- 3x UM

Results:
<table>
<tr><td colspan="2">Results for PM versus IM versus (EM+gene dose 1/0) versus UM:</td></tr>
<tr><td rowspan="2">response</td><td>NS</td></tr>
<tr><td>There was also no association for:
- (PM+IM+UM) versus (EM+gene dose 1/0) (NS)
- (gene dose ≥ 3.0) versus (gene dose 2.5) versus (gene dose 2) versus (gene dose 1.5) versus (gene dose 1) versus (gene dose 0.5) versus (gene dose 0) (NS)</td></tr>
<tr><td rowspan="2">side effects</td><td>NS</td></tr>
<tr><td>There was also no association for (PM+IM+UM) versus (EM+gene dose 1/0) (NS).</td></tr>
</table>

NOTE: Genotyping was for *3-*5, *10, *17, *41 and gene multiplication. These are the most important gene vari-ants in this Canadian population.</td>
<td>Authors' conclusion: "There was no signi-ficant effect of CYP-2D6 metabolizer status on treatment response to any of the drugs studied. … There was no signi-ficant association of CYP2D6 and CYP-2C19 metabolizer status with side effects to any of the drugs included in the study."</td>
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</table>

ref. 4 Hamelin BA et al. The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. Clin Pharmacol Ther 1996;60:512-21.	3 PM: AA	20 healthy volunteers (phenotyped, 10x EM#, 10x PM) received a single dose of 50 mg sertraline. Co-medication was excluded. PM versus EM#: - no difference in AUC and $t_{1/2}$ of sertraline NOTE: genotype unknown	Authors' conclusion: "We observed no effect of CYP2D6 activity in vivo on sertraline or desmethylsertraline pharmacokinetics."

#: Phenotyping did not distinguish between IM, EM and UM. EM# is therefore equal to IM+EM+UM.

Risk group	-

Comments:

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Date of literature search: 12 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetic Working Group decision	PM	3 AA	No	No	14 May 2018
	IM	3 AA	No	No	
	UM	3 AA	No	No	

Mechanism:

Sertraline is mainly converted by CYP2C19 to the active metabolite desmethylsertraline. Although desmethylsertraline has antidepressant activity, the activity is low and not clinically relevant at the standard sertraline dose. For this reason, most Dutch hospitals use only the sertraline concentration for therapeutic drug monitoring (therapeutic range: 50-300 µg/L) (http://tdm-monografie.org/monografie/ssri-selectieve-serotonine-heropnameremmers). However, some hospitals use the sum of the sertraline and desmethylsertraline concentrations for therapeutic drug monitoring (therapeutic range: 50-250 µg/L).