CYP2D6: flupentixol 1532/1533/1534

IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 enzyme activity)

Justification of choices:
The enzymes involved in flupentixol metabolism are unknown. It was believed that CYP2D6 plays an important role. However, Waade 2021 showed that CYP2D6 phenotype does not affect flupentixol exposure, making involvement of CYP2D6 in flupentixol metabolism unlikely. For this reason, the KNMP Pharmacogenetics Working Group decided that there is no CYP2D6-flupentixol interaction, and thus no reason to recommend dose adjustment or selection of an alternative in patients with a CYP2D6 IM, PM or UM phenotype (no/no-interactions).
The available kinetic data per phenotype are provided in the background information text of the phenotype-drug combinations in the KNMP Kennisbank. You may also have access to this background text via your pharmacy or physician electronic decision support system.

The table below follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore 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
Waade RB et al. Impact of CYP-2D6 on serum concentrations of flupentixol, haloperidol, perphenazine and zuclopenthixol.
Br J Clin Pharmacol 2021;87:2228-35.
PMID: 33118660.</td>
<td>4

PM: AA
IM: AA</td>
<td>53 patients were treated with oral flupentixol. Therapeutic drug monitoring was routinely done. The mean number of measurements per patient was 2.4 for NM, 1.9 for IM and 2.0 for PM. Genotyping was performed either before or after treatment start. Due to the small number, UMs were not included. Trough serum concentrations were determined (10 to 26 hours after dosing). Only measured serum concentrations within the lower and upper limits of quantification were included. Measurements were also excluded if the requisition forms (lacking for approximately 11% of measurements) provided information on possible noncompliance, or on concomitant use of CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers.

Genotyping:
- 28x NM
- 21x IM
- 4x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>dose-corrected trough concentration</td><td>x 0.99 (NS)</td><td>x 0.88 (NS)</td><td>2.18 nmol/L. mg</td></tr>
<tr><td>trough concentration</td><td>NS</td><td>trend for a decrease (p = 0.089) (NS)</td><td>8.52 nmol/L</td></tr>
<tr><td>daily dose</td><td>NS</td><td>NS</td><td>4.08 mg</td></tr>
</table>
NOTE: Genotyping was performed for *3-*6, *9, *10, *41, and gene multiplication. These are the most important gene variants in this Norwegian population.
Patients with multiplied, functional alleles were excluded from the study due to few samples.</td>
<td>Authors' conclusion: 'This study shows that CYP2D6 is important for the metabolism of perphenazine and zuclopenthixol, but not for haloperidol and flupentixol.'</td>
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</table>

Risk group	--

Comments:
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Date of literature search: 28 July 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 AA	no	no	13 September 2021
	IM	4 AA	no	no	
	UM	--	no	no	

Mechanism:
The enzymes involved in flupentixol metabolism are unknown. It was believed that CYP2D6 played an important role. However, a study showed that CYP2D6 phenotype does not affect flupentixol exposure in patients, making involvement of CYP2D6 in flupentixol metabolism unlikely.