CYP2D6: fluoxetine 5996/5997/5998

C_{ss} = steady-state plasma concentration, EM = extensive metabolizer (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metabolizer (gene dose 0.5-1) (decreased CYP2D6 enzyme activity), MR = metabolic ratio, NS = not significant, PM = poor metabolizer (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, UM = ultrarapid metabolizer (gene dose ≥ 3) (enhanced 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:
Fluoxetine is predominantly metabolized by CYP2D6 into the active metabolite norfluoxetine (N-demethylfluoxetine). While S- and R-fluoxetine are approximately equipotent, S-norfluoxetine is approximately 20 times as potent as R-norfluoxetine. Fluoxetine is a potent inhibitor of CYP2D6. Because fluoxetine inhibits its own metabolism, its kinetics are not linear at therapeutic doses.
Studies found an effect of CYP2D6 genotype on the ratio fluoxetine/norfluoxetine. However, there was no effect on the sum of the plasma concentrations of the active substances (fluoxetine + norfluoxetine or fluoxetine + S-norfluoxetine). Accordingly, studies found no effect of CYP2D6 activity on either response (3 studies) or side effects (2 studies). One case report reported an adverse outcome for a PM, but it is not clear whether and to what extent the absent CYP2D6 activity contributed to this adverse outcome.
Thus, although there is a gene-drug interaction, this does not lead to a change in clinical effects and the need for adjustment of therapy for any of the CYP2D6 genotypes (yes/no-interactions).
You can find an overview of the clinical and kinetic effects per phenotype in the background information text of the corresponding phenotype-drug interaction on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

In the table below the definitions of EM, PM, IM and UM according to the KNMP are used. As a result, the definitions of EM, PM, IM and UM in the table below might differ from the definitions used by the authors of the article.

Source	Code	Effect	Comments
ref. 1 Gassó P et al. Effect of CYP2D6, CYP2C9 and ABCB1 genotypes on fluoxetine plasma concentrations and clinical improvement in children and adolescent patients. Pharmacogenomics J 2014;14:457-62. PubMed PMID: 24663076.	4	83 children aged between 10 and 17 years with major depression disorder (68.7%), obsessive-compulsive disorder or generalized anxiety disorder were treated with fluoxetine (mean final dosage 25.2 mg/day) for a period of 12 weeks. Relevant comedication was not excluded, but comedication was distributed equally among the CYP2D6 genotype groups and there was no association between plasma concentrations and comedication. Genotyping: - 53x EM - 26x IM - 1x PM - 3x UM Results: IM+PM versus EM versus UM: No difference in response for: - the whole group (NS) - the patients with the ABCB1 2677T allele that results in higher clinical improvements (NS)	Author's conclusion: 'Our results confirm the influence of CYP-2D6 genetic variants in fluoxetine pharmacokinetics and provide evidence for the potential effect of the ABCB1 genotype on the clinical improvement in children and adolescent patients treated with fluoxetine.'

<table>
<tr>
<td>ref. 1, continuation</td>
<td>IM+PM: A

UM: A</td>
<td>
<table>
<tr><td colspan="3">Median dose-corrected plasma concentration of the active moiety (fluoxetine + S-norfluoxetine) after 12 weeks in comparison with EM (11.7 nmol/l.mg):</td></tr>
<tr><td>IM + PM</td><td>UM</td><td></td></tr>
<tr><td>x1,07</td><td>x1,14</td><td>NS for the trend IM+PM versus EM versus UM</td></tr>
<tr><td colspan="3">The ratio fluoxetine/S-norfluoxetine decreased with increasing CYP2D6 gene dose (S for the trend IM+PM versus EM versus UM), indicating a CYP2D6-fluoxetine interaction.</td></tr>
<tr><td colspan="3">Similar results were obtained after 8 weeks.</td></tr>
</table>

NB: Alleles *3-*6 and gene multiplication were assessed.
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<td></td>
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<tr>
<td>ref. 2
Brandl EJ et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant 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>66 patients with obsessive-compulsive disorder were treated with a moderate to high dose of fluoxetine for more than 10 weeks. The evaluation of response was performed retrospectively in a structured patient interview. Patients rated as minimally improved on a scale adapted from the CGI-improvement scale were included in the nonresponder group. Patients having only mild side effects were considered to be without significant side effects. Relevant comedication was not excluded.

Genotyping (estimated based on the distribution in the total group (users of fluoxetine or other antidepressants)):
- 57x gene dose 1.5-2 and gene dose 1/0 (1 fully active and 1 inactive allele) (37x gene dose 1.5-2, 20x gene dose 1/0)
- 5-6x gene dose 0.5 and gene dose 0.5/0.5 (two alleles with reduced activity)
- 0-1x PM
- 2-3x UM

Results:
<table>
<tr><td>PM versus (gene dose 0.5 + gene dose 0.5/0.5) versus (gene dose 1.5-2 + gene dose 1/0) versus UM:</td></tr>
<tr><td>No difference in:
- treatment response (NS)
- side effects (NS)</td></tr>
</table>

<table>
<tr><td>(gene dose 1.5-2 + gene dose 1/0) versus the other genotypes:</td></tr>
<tr><td>- trend for a better treatment response (30% versus 0% responders) (NS, p = 0.056).
When different gene doses were compared to each other or low (< 1.0) to high (> 2.0) gene doses, no association was found (NS)
- no difference in side effects (NS)</td></tr>
</table>

NB: Alleles *3-*5, *10, *17, *41 and gene multiplication were assessed.
</td>
<td>Author’s conclusion: ‘There were nonsignificant trends for association of CYP2D6 metabolizer status with response to fluoxetine.’</td>
</tr>
<tr>
<td>ref. 3
Scordo MG et al. Influence of CYP2C9, 2C19 and 2D6 genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. Basic Clin Pharmacol Toxicol 2005;97:296-301.</td>
<td>4</td>
<td>78 patients were treated with fluoxetine 10-60 mg/day. Relevant comedication was excluded.

Genotyping:
- 49x EM
- 22x IM
- 1x PM
- 6x UM

Results:
<table>
<tr><td colspan="4">Median dose-corrected steady state plasma concentration of the active moiety (fluoxetine + S-norfluoxetine) in comparison with EM (26.9 nmol/l.mg):</td></tr>
<tr><td>PM</td><td>IM</td><td>UM</td><td></td></tr>
</table>
</td>
<td>Author’s conclusion: ‘No statistically significant relationship was identified between CYP2D6 or CYP2C19 genotypes and the dose normalised plasma concentrations of any of the enantiomers or the active moiety (i.e. the sum of S-fluoxetine, R-fluoxetine and S-norfluoxetine).’</td>
</tr>
</table>

PubMed PMID: 16236141. **ref. 3, continuation**	PM: AA UM: AA IM: A	x0.68 | x1.13 | x1.07 | NS for the trend IM versus EM versus UM The ratio S-fluoxetine/S-norfluoxetine decreased with increasing CYP2D6 gene dose (S for IM versus EM), indicating a CYP2D6-fluoxetine interaction. IM versus EM versus UM: - no difference in daily dose (NS) NB: Alleles *3-*6 and gene multiplication were assessed.	
ref. 4 LLerena A et al. Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. Eur J Clin Pharmacol 2004;59:869-73. PubMed PMID: 14726986.	4 PM: A IM: A UM: A	64 patients were treated with fluoxetine 10-60 mg/day. Relevant comedication was excluded. Genotyping: - 41x EM - 19x IM - 1x PM - 3x UM Results: Dose-corrected steady state plasma concentration (C_{ss}) of the active moiety (fluoxetine + norfluoxetine) in comparison with EM (30.3 nmol/l.mg) (calculated with the mean fluoxetine concentration and mean fluoxetine/ norfluoxetine ratio): PM | IM | UM | x0.81 | x1.18 | x1.24 | NS for the trend PM versus IM versus EM versus UM The ratio fluoxetine/norfluoxetine and C_{ss} fluoxetine decreased with increasing CYP2D6 gene dose (both S for PM versus IM versus EM versus UM), indicating a CYP2D6-fluoxetine interaction. NB: Alleles *3-*6 and gene duplication were assessed.	Author's conclusion: 'The dose-corrected plasma concentrations of fluoxetine were related to CYP-2D6 genotypes (number of active genes). The fluoxetine/norfluoxetine ratio also correlated with the number of active CYP2D6 genes.'
ref. 5 Roberts RL et al. No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. Hum Psychopharmacol 2004;19:17-23. PubMed PMID: 14716707.	4 PM: AA	65 patients were treated with fluoxetine 10-80 mg/day for 6 weeks (20 mg/day in week 1-3, then dose adjustment based on clinical response and side effects). Comedication was excluded. Genotyping: - 59x EM+IM - 6x PM Results: PM versus EM+IM: No difference in: - the percentage of patients with a side effect (NS) - the percentage of patients with a moderate/severe side effect (NS) - the percentage of patients that failed to complete the trial (NS) - the percentage of nonresponders (NS) NB: Alleles *2-*16, *19, *20 and gene duplication were assessed.	Author's conclusion: 'Our data strongly suggest that CYP-2D6 genotypic PMs receiving solely fluoxetine or nortriptyline are at no greater risk of adverse drug reactions than genotypic EM patients.'
ref. 6 Perucca E et al. Fluoxetine-induced movement disorders and deficient CYP2D6 enzyme activity. Mov Disord 1997;12:624-5. PubMed PMID: 9251094.	1 PM: B	A 74-year-old woman developed involuntary choreiform movements involving the tongue, lips and masticatory muscles after 7 months of treatment with fluoxetine 20 mg/day. Her trunk, upper limbs and, to a lesser extent, lower extremities were also affected. The movements disappeared after fluoxetine treatment was discontinued. A CYP2D6 phenotyping test showed a PM phenotype.	Author's conclusion: 'Therefore, our results provide direct experimental support to the suggestion that impaired CYP2D6 activity may play a significant role in the pathogenesis of rare adverse reactions to fluoxetine.'

ref. 7 SPC Prozac (fluoxetine), USA, 30-01-09.	0 PM: AA	Pharmacokinetics: When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same.	

Risk group	-

Comments:

- Only kinetic studies with multiple dosing and determination of the exposure of the active moiety (fluoxetine + norfluoxetine) were included in the risk analysis. The contribution of other studies to the evidence was too low. Because fluoxetine inhibits its own metabolism, single dose studies provide little information about the effect in normal therapy when multiple doses are given.
  A case report in which a 9-year-old boy died due to fluoxetine poisoning was not included, because the dose of 100 mg/day was 2.5 times the maximum dose of 40 mg/day in children (Sallee FR et al. Fluoxetine-related death in a child with cytochrome P-450 2D6 genetic deficiency. J Child Adolesc Psychopharmacol 2000;10:27-34. PubMed PMID: 10755579).
- Existing evidence review:
  Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther 2015;98: 127-34. PubMed PMID: 25974703.
  CPIC uses the same definition for PM as we do. However, CPIC uses another definition for EM (gene dose 1-2), IM (gene dose 0.5) en UM (gene dose ≥ 2.5). In the summary below, EM, PM, IM and UM are defined according to the KNMP.
  CPIC indicates that although PM possess significantly higher fluoxetine plasma concentrations than EM, the total sum of fluoxetine plus norfluoxetine concentrations may not vary significantly by CYP2D6 phenotypes. They state that few data are available describing how CYP2D6 phenotype status influences the total sum of fluoxetine plus norfluoxetine concentrations over time, or if an imbalance between fluoxetine and norfluoxetine concentrations caused by CYP2D6 phenotype status affects patient outcome or safety. Therefore, CPIC does not provide gene-based dosing recommendations for fluoxetine.
  However, CPIC states that it may be reasonable to monitor PM and patients with gene dose ≥ 2.5 more closely if they are prescribed fluoxetine or to select an alternative SSRI not extensively metabolized by CYP2D6 due to conflicting/inconclusive data describing how CYP2D6 status influences fluoxetine therapy. CPIC indicates that the prescribing information for fluoxetine states that caution is warranted in situations that may prolong QT such as “conditions that predispose to increased fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, or use of other highly protein-bound drugs).” However, this warning is not present in the SPC Prozac (fluoxetine), USA, 30-01-09.
  On 16-4-2018, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of the literature search: 9 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Working group decision	PM	4B	yes	no	14 May 2018
	IM	4A	yes	no	
	UM	4A	yes	no	

Mechanism:

Fluoxetine is predominantly metabolized by CYP2D6 into the active metabolite norfluoxetine (N-demethylfluoxetine). While S- and R-fluoxetine are approximately equipotent, S-norfluoxetine is approximately 20 times as potent as R-norfluoxetine. Fluoxetine is a potent inhibitor of CYP2D6. Because fluoxetine inhibits its own metabolism, its kinetics are not linear at therapeutic doses.
There is no clear plasma concentration-response and plasma concentration-adverse effect relationship.