CYP2D6: duloxetine 1673/1674/1675

IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated CYP2D6 enzyme activity)

Brief summary and justification of choices:
Duloxetine is metabolised to inactive metabolites, primarily by CYP1A2 and to a lesser extent by CYP2D6.
A study with 23 patients with genetically reduced CYP2D6 enzyme activity (intermediate metabolisers (IM)) found a lower duloxetine exposure in these patients than in patients with genetically normal CYP2D6 enzyme activity (normal metabolisers (NM)) (Zastrozhin 2020). However, a larger study in paediatric patients with 30 IM and 21 patients with genetically absent CYP2D6 enzyme activity (poor metabolisers (PM)) did not find duloxetine clearance to differ from NM (Lobo 2014). Another study with 8 IM did not find a significantly lower clearance for these patients either (Tianmei 2007). In a PM with a very high duloxetine concentrations, inhibition of CYP1A2 by inflammation might (partially or fully) be the cause of this high concentration (Kuzin 2020). The KNMP Pharmacogenetics Working Group indicates that convincing evidence for a significant kinetic effect in patients with a variant CYP2D6 phenotype is lacking.
In addition, convincing evidence for a clinical effect is also lacking. The evidence in Zastrozhin 2020 for an effect on duloxetine response and adverse events was inconsistent. For adverse events, the difference was only significant in week 8 and not in week 4. Regarding depression symptom scores, the difference was only significant in week 4 for one of the scales and only in week 8 for the other scale. In addition, the observed difference was small and unlikely to be clinically significant. In two cases in which adverse events occurred in IM, there were also other risk factors that could explain these adverse events (a CYP1A2 polymorphism, high age and female gender could have contributed to the occurrence of the syndrome of inadequate secretion of anti-diuretic hormone in the first case and co-medication with trazodone, ondansetron and fentanyl could have contributed to serotonin syndrome in the second case) (Kamei 2015 and Beatty 2013). Despite very high duloxetine plasma concentration in the case described by Kuzin 2020, adverse events were lacking.
For these reasons, the KNMP Pharmacogenetics Working Group concludes that there is insufficient evidence for a gene-drug interaction and thus for a need to adjust the treatment (no/no-interactions).
You can find an overview of the observed kinetic and clinical consequences per phenotype in the background information text of the phenotype-drug combination 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 follows the KNMP definition for NM, PM, IM and UM, unless stated otherwise. The definition of NM, PM, IM and UM used in the table below may therefore differ from the definition used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Kuzin M et al. The role of the poor metabolizer genotype CYP2D6 and CYP1A2 phenotype in the pharmacokinetics of duloxetine and venlafaxine-a case report. Basic Clin Pharmacol Toxicol 2020;127:354-7. PMID: 32365274.	2	A 32-year-old woman developed duloxetine trough plasma concentrations in the toxic range (mean of two measurements 1.5 times the minimum concentration to be considered toxic of 240 ng/ml) on duloxetine 60 mg/day. The woman did not show any signs or symptoms of a serotonin syndrome or any other adverse drug reaction with a normal electrocardiogram and electroencephalogram. A dose decrease to 30 mg/day resulted in plasma concentrations below the toxic concentration, but still above the therapeutic range of 30-120 ng/ml (mean of two measurements 7 and 9 days after dose reduction 1.3 times the upper limit of the therapeutic range). Duloxetine was discontinued due to insufficient clinical response. The woman did not use any comedication and did not smoke.	Authors' conclusion: 'The extraordinarily high duloxetine levels and not measurable ODV level may be seen in the light of a decreased CYP1A2 activity due to elevated (>5 mg/L) levels of CRP or due to the CYP-2D6 PM activity as duloxetine is at least metabolized via 2D6 to a minor extent. As a further explanation, a poor metabo-
	PM: A	The woman was found to have the genotypes CYP2D6 *4/*4 and CYP2C19 *1/*2. The authors indicate that therapeutic	

<table>
<tr><td>ref. 1, continuation</td><td></td><td>drug monitoring data indicated a phenotype of poor CYP1A2 activity. They indicate that this might be due to the slightly elevated levels of C-reactive protein (2.2-2.4 times the upper limit of normal), resulting from a vaginal mycosis.</td><td>lizer CYP1A2 phenotype has to be considered as well.’</td></tr>
<tr><td>ref. 2
Zastrozhin et al. Impact of polymorphism of CYP2D6 on equilibrium concentration of duloxetine in patients suffering from major depressive disorder. Psychopharmacol Bull 2020;50:47-57. PMID: 32733111.</td><td>3

IM: B</td><td>118 patients were treated with duloxetine (mean dose 104 mg/day) for a period of 8 weeks.
Duloxetine effectiveness was evaluated with the Hospital Anxiety and Depression Scale and the Hamilton Depression Rating Scale, Adverse events were evaluated with the UKU Side- Effect Rating Scale (UKU).
Therapeutic drug monitoring was performed in the 8th week of treatment.
Other psychotropic medication is excluded, but it is not mentioned whether non-psychotropic comedication affecting CYP2D6 is excluded. All patients had a history of alcohol abuse, but were currently abstinent.
The Benjamin-Hochberg test was used to adjust for multiple comparisons.

Genotyping:
- 95x NM
- 23x IM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td></td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="2">median Hospital Anxiety and Depression Scale score</td><td>week 4</td><td>x 1.14 (S)</td><td>22.0</td></tr>
<tr><td>week 8</td><td>NS</td><td>16.0</td></tr>
<tr><td rowspan="3">median Hamilton Depression Rating Scale score</td><td>week 4</td><td>NS</td><td>14.0</td></tr>
<tr><td>week 8</td><td>x 1.22 (S)</td><td>9.0</td></tr>
<tr><td colspan="3">For both IM and NM, the median Hamilton Depression Rating Scale score in week 1 was 22.0, indicating a decrease during treatment with 59% for NM and with 50% for IM. Because response is usually defined as a decrease ≥ 50%, the difference between NM and IM is unlikely to be clinically relevant.</td></tr>
<tr><td rowspan="2">median UKU Side-Effect Rating Scale score</td><td>week 4</td><td>NS</td><td>3.0</td></tr>
<tr><td>week 8</td><td>x 1.33 (S)</td><td>3.0</td></tr>
<tr><td colspan="2">median dose-corrected plasma concentration of duloxetine</td><td>x 1.79 (S)</td><td>0.776 ng/ml per mg</td></tr>
</table>
Note: Genotyping was for *4. This is the most important variant allele in this Russian population.
Genotype distribution was in Hardy-Weinberg equilibrium.</td><td>Authors’ conclusion: ‘The effect of genetic polymorphism of the CYP2D6 gene on the efficacy and safety profiles of duloxetine was demonstrated in a group of 118 patients with recurrent depressive disorder.’

Median dose-corrected trough concentration compared to NM:
IM: 179%</td></tr>
<tr><td>ref. 3
Ahmed AT et al. Pharmacokinetic-pharmacodynamic interaction associated with venlafaxine-XR remission in patients with major depressive disorder with history of citalopram / escitalopram</td><td>3</td><td>28 patients, in whom citalopram or escitalopram previously failed, were treated with duloxetine for a period of 8 weeks. Duloxetine dose was titrated and maximum dose was reached at week 4. 29 additional patients also completed 8 weeks of duloxetine treatment, while 21 additional patients discontinued duloxetine prematurely because of ineffectiveness or adverse events. It was not investigated whether the completers and drop-outs differed in CYP2D6 phenotype distribution.
Remission was defined as a 16-item Quick Inventory of Depressive Symptomatology Clinician-rated (QIDS-C_{16})</td><td>Authors’ conclusion: ‘We found no significant difference in duloxetine remission rates by CYP2D6 metabolism phenotype.’</td></tr>
</table>

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<tr>
<td>treatment failure.
J Affect Disord 2019;246:62-8.
PMID: 30578947.

ref. 3, continuation</td>
<td>PM+IM: AA
UM: AA</td>
<td>score ≤ 5. The maximum score on the QIDS-C_{16} is 27. Significance was determined with a linear regression model and OR was calculated assuming a linear effect for PM versus NM+IM versus UM.
It is not mentioned whether relevant comedication is excluded.

Genotyping:
- 25x NM+gene dose 1
- 1x PM+gene dose 0.25-0.5
- 2x UM

Results:
<table>
<tr><td colspan="4">Results compared to NM+gene dose 1:</td></tr>
<tr><td></td><td>PM+gene dose 0.25-0.5</td><td>UM</td><td>value for NM+ gene dose 1</td></tr>
<tr><td>% of patients with remission</td><td colspan="2">NS for PM+gene dose 0.25-0.5 versus NM+gene dose 1 versus UM</td><td>24%</td></tr>
</table>
Note: Genotyping was for *2A, *3 through *6, *9, *10, *17, *41, and gene duplication, These are the most important gene variants in this White population.</td>
<td></td>
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<td>ref. 4
Kamei S et al. Rapid onset of syndrome of inappropriate antidiuretic hormone secretion induced by duloxetine in an elderly type 2 diabetic patient with painful diabetic neuropathy. J Diabetes Investig 2015;6:343-5.
PubMed PMID: 25969720.</td>
<td>1

IM: D</td>
<td>An 80-year-old Japanese woman developed nausea and decreased appetite in the morning after starting duloxetine 20 mg/day for diabetic peripheral neuropathic pain. Following hospitalisation, she was found to be drowsy and her serum sodium concentration and serum chloride concentration were at 87% of the lower limit of the normal values. The serum concentration of anti-diuretic hormone was 3.6 times the upper limit of the normal values. Having ruled out other possible causes of hyponatraemia, the diagnosis of duloxetine-induced syndrome of inadequate secretion of anti-diuretic hormone was made. Gradual recovery occurred after withdrawal of duloxetine and the patient was able to leave the hospital without any symptoms after 13 days. The woman’s genotype was found to be CYP2D6 *1/*5 (IM) and CYP1A2 *1/*1C (IM).</td>
<td>Authors’ conclusion: ‘These phenotypes indicate the intermediate metabolizer of duloxetine. We failed to evaluate the patient’s serum concentration of duloxetine, but we assume that this was one of the reasons why duloxetine induced the syndrome of inappropriate antidiuretic hormone secretion, although its precise association remains unknown.’</td>
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<tr>
<td>ref. 5
Lobo ED et al. Pharmacokinetics of orally administered duloxetine in children and adolescents with major depressive disorder. Clin Pharmacokinet 2014;53:731-40.
PubMed PMID: 24989060.</td>
<td>3

PM: AA
IM: AA</td>
<td>428 paediatric patients (7-18 years) were treated with duloxetine 20-120 mg/day. Smoking was not excluded.

Genotyping (calculated from the listed percentages for “NM” and “PM”):
- 377x “NM”
- 30x “IM”
- 21x “PM”

Results:
<table>
<tr><td colspan="2">“PM” versus “IM” versus “NM”:</td></tr>
<tr><td>oral clearance</td><td>no difference (NS)</td></tr>
</table>
NOTE: The analysed CYP2D6 alleles and the translation of genotype to phenotype were not described. When calculating the number of patients with a genotype other than NM and PM, it was assumed that UM was not determined.</td>
<td>Authors’ conclusion: ‘Patient characteristics such as age, sex, BMI, serum creatinine, CYP2D6 predicted phenotype, and menarche status did not have a statistically significant effect on any of the duloxetine pharmacokinetic parameters.’</td>
</tr>
</table>

ref. 6 Beatty NC et al. Pharmacogenetic workup of perioperative serotonin syndrome. J Clin Anesth 2013;25:662-5. PubMed PMID: 24096103.	1 IM: B	A 47-year-old man, who was receiving treatment with duloxetine 120 mg/day, trazodone 100 mg/day and gabapentin, underwent general anaesthesia with fentanyl, midazolam, propofol, suxamethonium, desflurane and vecuronium. Towards the end of the procedure he received ketamine, ondansetron 4 mg, glycopyrronium and neostigmine. During waking, the patient had a systolic blood pressure of nearly 200 mmHg and a heart rate > 160 beats per minute. Following extubation, he also developed muscle rigidity over his entire body, locked jaw, tremor, confusion, agitation, ocular clonus and complained of pain. As these problems persisted, midazolam, esmolol and fentanyl 2x 50 µg were administered 20 minutes after extubation. Fentanyl appeared to aggravate the confusion and muscle rigidity. Therefore, lorazepam and hydromorphone were administered. The diagnosis of serotonin syndrome was made and he received an additional dose of hydromorphone. Gradual recovery occurred and the symptoms disappeared in the 24 hours after the surgery. The man's genotype was found to be CYP2D6 *2A/*4.	Authors' conclusion: 'A subsequent cytochrome P4502D6 genetic test result suggested a potential alteration in metabolism. For this patient, who was taking combination antidepressant medications and receiving common perioperative medicines, additive pharmacodynamic effects converged with a pharmacogenetic predisposition, resulting in serotonin syndrome.'
ref. 7 Tianmei S et al. Pharmacokinetics and tolerability of duloxetine following oral administration to healthy Chinese subjects. Clin Pharmacokinet 2007;46:767-75. PubMed PMID: 17713974.	3 IM: AA	20 healthy volunteers received duloxetine 60 mg 1x daily for 1 or 6 days. The oral clearance did not differ between administration of a single dose or multiple doses. Smoking was not excluded. Genotyping: - 12 NM - 8 IM Oral clearance compared to NM (86.2 L/hour): IM: x 0.87 (NS) NOTE 1: Alleles *2-*11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *36, *40 and *41 were genotyped. NOTE 2: The translation of genotype to phenotype was not described in detail. The authors did indicate that *10/*10 phenotype includes IM. *10 is the most important variant allele in this Chinese patient group.	Authors' conclusion: 'Comparison of duloxetine pharmacokinetics between CYP2D6 intermediate metabolizers and CYP2D6 normal metabolisers showed that duloxetine exposure was slightly higher (16%) in CYP2D6 intermediate metabolisers than in CYP2D6 normal metabolisers. However, this magnitude of difference is not clinically meaningful.' Oral clearance compared to NM: IM: 87%
ref. 8 Chan C et al. Duloxetine pharmacokinetics are similar in Japanese and Caucasian subjects. Br J Clin Pharmacol 2007;63:310-4. PubMed PMID: 17380590.	3 PM: AA	80 healthy volunteers received duloxetine 20, 40 or 60 mg single dose (n=48) or 20 or 40 mg 2x daily for 5 days (n = 32). Genotyping: administration of a single dose: - 38x (NM + genotype 1/0) - 6x IM - 4x PM administration of multiple doses: - 25x (NM + genotype 1/0) - 6x IM - 1x UM Results: - Following administration of a single dose, the exposure to duloxetine was 1-3x greater for 2 PMs than the average exposure for the non-PMs. For the other 2 PMs, the pharmacokinetics were comparable to the non-PMs. - For 2 volunteers in the group receiving 40 mg 2x daily, the exposure to duloxetine was 2-5x greater than the average exposure in this group. These two volunteers were found	Authors' conclusion: 'The high duloxetine concentrations observed in normal metabolizers suggests that exposure cannot be predicted by knowledge of CYP2D6 metabolizer status alone, and other factors, such as the degree of expression of CYP1A2 activity, appear to affect duloxetine pharmacokinetics more substantially.'

ref. 8, continuation		to be NM or genotype 1/0. NOTE: The specific alleles and the translation of genotype to phenotype was not described in detail. The genotyping assay manufactured by DNA Sciences Laboratories was used. This assay appears to detect at least *3, *4, *10 and gene duplication. These are the most important variant alleles in these groups, which both consisted of 50% Japanese and 50% Caucasian individuals. The authors defined IM as CYP2D6*10 genotype, which together with the reported frequency of 30% in the Japanese volunteers appears to indicate the genotype *10/*10 (*1/*10 is generally the most common genotype in Asian populations). IM was not found in the Caucasian volunteers, which must mean that *1/*3 and *1/*4 were considered as NM.	
ref. 9 SmPC Cymbalta (duloxetine) 30-03-16.	0 PM: AA	The pharmacokinetics of duloxetine in patients who are poor metabolisers with regards to CYP2D6, were not examined specifically. Limited data suggest that the plasma concentrations of duloxetine in these patients are higher.	

Risk group	--

Comments:

- For the period after 2015, case reports that did not check the duloxetine concentration were not included in the risk analysis, because they provide too little information about a possible causal involvement of the CYP2D6 phenotype.
- Metabolisation of duloxetine by CYP2D6 was demonstrated using CYP2D6 inhibitors (Skinner MH et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clin Pharmacol Ther 2003;73:170-7.) The referenced article demonstrates that the strong CYP2D6 inhibitor paroxetine increases the AUC of duloxetine by 59% in Asian volunteers (S). No increase in side effects was observed following addition of paroxetine. Duloxetine was given at a dose of 40 mg/day (50-67% of the standard maintenance dose).

Date of literature search: 29 August 2022.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	PM	3 AA	no	no	14 November 2022
	IM	3 D	no	no	
	UM	3 AA	no	no	

Mechanism:

Duloxetine is converted to inactive metabolites, primarily by CYP1A2 and to a lesser extent by CYP2D6.
Duloxetine is a moderate inhibitor of CYP2D6.
The NVZA does not indicate a therapeutic range for duloxetine, but in literature a therapeutic range of duloxetine of 30-120 ng/ml is mentioned with plasma concentrations > 240 ng/ml considered to be toxic (Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62).