

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

ref. 1, continuation ref. 2 Zastrozhin et al. Impact of polymor- phism of CYP2D6 on equilibrium concentration of duloxetine in patients suffering from major depres- sive disorder.	3	activity. They indicate t elevated levels of C-re- limit of normal), resultir		nhenotype of por	r CVD1A2	lizer CYP1A2 phe-			
Zastrozhin et al. Impact of polymor- phism of CYP2D6 on equilibrium concentration of duloxetine in patients suffering from major depres- sive disorder.	3	elevated levels of C-re- limit of normal), resulting 118 patients were treat	drug monitoring data indicated a phenotype of poor CYP1A2 lizer CYP1A2 phe activity. They indicate that this might be due to the slightly notype has to be						
Zastrozhin et al. Impact of polymor- phism of CYP2D6 on equilibrium concentration of duloxetine in patients suffering from major depres- sive disorder.	3	118 patients were treat	elevated levels of C-reactive protein (2.2-2.4 times the upper						
Zastrozhin et al. Impact of polymor- phism of CYP2D6 on equilibrium concentration of duloxetine in patients suffering from major depres- sive disorder.	3		limit of normal), resulting from a vaginal mycosis.118 patients were treated with duloxetine (mean dose 104Authors' conclusion						
Impact of polymor- phism of CYP2D6 on equilibrium concentration of duloxetine in patients suffering from major depres- sive disorder.		Ingraay) ior a period of	118 patients were treated with duloxetine (mean dose 104						
phism of CYP2D6 on equilibrium concentration of duloxetine in patients suffering from major depres- sive disorder.		Duloxetine effectivenes	'The effect of gene- tic polymorphism of						
concentration of duloxetine in patients suffering from major depres- sive disorder.		Anxiety and Depressio	the CYP2D6 gene						
duloxetine in patients suffering from major depres- sive disorder.		Rating Scale, Adverse	on the efficacy and						
patients suffering from major depres- sive disorder.		Side- Effect Rating Sca Therapeutic drug moni	safety profiles of duloxetine was						
sive disorder.		of treatment.	demonstrated in a						
		Other psychotropic me	group of 118 pa-						
Psychopharmacol		mentioned whether not CYP2D6 is excluded.	tients with recurrent depressive disor-						
Bull		abuse, but were currer				der.'			
2020;50:47-57.		The Benjamin-Hochbe	rg test was	s used to adjust f	or multiple				
PMID: 32733111.		comparisons.							
		Genotyping:							
		- 95x NM							
		- 23x IM							
		Results:							
		Results compared to	NM:						
				IM	value				
				4.44.(0)	for NM				
		median Hospital Anxiety and Depres-	week 4 week 8	x 1.14 (S) NS	22.0 16.0				
		sion Scale score	Week o		10.0				
		median Hamilton	week 4	NS	14.0				
		Depression Rating Scale score	week 8x 1.22 (S)9.0For both IM and NM, the median						
	Hamilton D								
			Madian daga						
		median UKU Side-							
		Effect Rating Scale			3.0	concentration			
		score		× 1 70 (0)	0.770	compared to NM:			
				x 1.79 (S)		IWI: 179%			
		IT THA CONCENTRATION OF C							
		tine	f + 4	- in Alexandre (* 1	a what is t				
		tine Note: Genotyping was			ortant				
		tine Note: Genotyping was variant allele in this Ru	ssian pop	ulation.					
ref. 3	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c	ssian pop was in Har italopram	ulation. <u>dy-Weinberg equ</u> or escitalopram p	ilibrium. reviously	Authors' conclusion:			
Ahmed AT et al.	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c failed, were treated wit	ssian pop was in Har italopram h duloxetii	ulation. dy-Weinberg equ or escitalopram p ne for a period of	ilibrium. reviously 8 weeks.	'We found no signi-			
Ahmed AT et al. Pharmacokinetic-	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c failed, were treated wit Duloxetine dose was ti	ssian pop vas in Har italopram h duloxetii trated and	ulation. <u>dy-Weinberg equ</u> or escitalopram p ne for a period of maximum dose y	ilibrium. reviously 8 weeks. was				
Ahmed AT et al.	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c failed, were treated wit Duloxetine dose was ti reached at week 4. 29	ssian pop was in Har italopram h duloxetii trated and additional	ulation. dy-Weinberg equ or escitalopram p ne for a period of maximum dose y patients also con	ilibrium. reviously 8 weeks. was npleted 8	'We found no signi- ficant difference in duloxetine remission rates by CYP2D6			
Ahmed AT et al. Pharmacokinetic- pharmacodynamic interaction associa- ted with venlafaxine-	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c failed, were treated wit Duloxetine dose was ti reached at week 4. 29 weeks of duloxetine tre discontinued duloxetine	ssian pop was in Har italopram h duloxetin trated and additional eatment, w e prematu	ulation. dy-Weinberg equ or escitalopram p ne for a period of maximum dose patients also con thile 21 additional rely because of ir	ilibrium. reviously 8 weeks. was npleted 8 patients neffective-	'We found no signi- ficant difference in duloxetine remission rates by CYP2D6 metabolism pheno-			
Ahmed AT et al. Pharmacokinetic- pharmacodynamic interaction associa- ted with venlafaxine- XR remission in	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c failed, were treated wit Duloxetine dose was ti reached at week 4. 29 weeks of duloxetine tre discontinued duloxetine ness or adverse events	ssian pop was in Har italopram h duloxetii trated and additional eatment, w e prematu s. It was n	ulation. dy-Weinberg equ or escitalopram p ne for a period of maximum dose y patients also con hile 21 additional rely because of ir ot investigated wh	ilibrium. reviously 8 weeks. was npleted 8 patients neffective- nether the	'We found no signi- ficant difference in duloxetine remission rates by CYP2D6			
Ahmed AT et al. Pharmacokinetic- pharmacodynamic interaction associa- ted with venlafaxine- XR remission in patients with major	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c failed, were treated wit Duloxetine dose was ti reached at week 4. 29 weeks of duloxetine tre discontinued duloxetine ness or adverse events completers and drop-o	ssian pop was in Har italopram h duloxetii trated and additional eatment, w e prematu s. It was n	ulation. dy-Weinberg equ or escitalopram p ne for a period of maximum dose y patients also con hile 21 additional rely because of ir ot investigated wh	ilibrium. reviously 8 weeks. was npleted 8 patients neffective- nether the	'We found no signi- ficant difference in duloxetine remission rates by CYP2D6 metabolism pheno-			
Ahmed AT et al. Pharmacokinetic- pharmacodynamic interaction associa- ted with venlafaxine- XR remission in	3	tine Note: Genotyping was variant allele in this Ru Genotype distribution v 28 patients, in whom c failed, were treated wit Duloxetine dose was ti reached at week 4. 29 weeks of duloxetine tre discontinued duloxetine ness or adverse events completers and drop-o distribution.	ssian pop was in Har italopram h duloxetii trated and additional eatment, w e prematu s. It was n uts differe	ulation. <u>dy-Weinberg equ</u> or escitalopram p ne for a period of maximum dose y patients also con hile 21 additional rely because of ir ot investigated wh d in CYP2D6 phe	ilibrium. reviously 8 weeks. was npleted 8 patients neffective- nether the enotype	'We found no signi- ficant difference in duloxetine remission rates by CYP2D6 metabolism pheno-			
	IM: B	scorex 1.79 (S)0.776ma concentration of duloxe- tineng/mlper mgNote: Genotyping was for *4. This is the most important variant allele in this Russian population. Genotype distribution was in Hardy-Weinberg equilibrium.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 ineffective- ness or adverse events. It was not investigated whether the completers and drop-outs differed in CYP2D6 phenotype							

treatment failure. J Affect Disord 2019;246:62-8. PMID: 30578947. <b>ref. 3, continuation</b>		score ≤ 5. The ma Significance was c and OR was calcu versus NM+IM ver It is not mentioned ded. Genotyping: - 25x NM+gene dos - 1x PM+gene dos - 2x UM Results: Results compare				
	PM+IM: AA UM: AA	% of patients with remission	NS for PM+ge 0.5 versus NM versus UM		dose 1 24%	
		Note: Genotyping *41, and gene dup gene variants in th	lication, These is White popula	are the most im tion.	portant	
<b>ref. 4</b> Kamei S et al. Rapid onset of syndrome of inap- propriate antidiuretic hormone secretion induced by duloxe- tine in an elderly type 2 diabetic patient with painful diabetic neuropathy. J Diabetes Investig 2015;6:343-5. PubMed PMID: 25969720.	1 IM: D	An 80-year-old Jap decreased appetite 20 mg/day for diab Following hospitali her serum sodium tration were at 879 The serum concer times the upper lin other possible cau duloxetine-induced anti-diuretic hormo after withdrawal of leave the hospital woman's genotype CYP1A2 *1/*1C (II	Authors' conclusion: 'These phenotypes indicate the interme- diate metabolizer of duloxetine. We fai- led to evaluate the patient's serum con- centration of duloxe- tine, but we assume that this was one of the reasons why duloxetine induced the syndrome of inappropriate anti- diuretic hormone secretion, although its precise associa- tion remains unknown.'			
<b>ref. 5</b> Lobo ED et al. Pharmacokinetics of orally administered duloxetine in chil- dren and adoles- cents with major depressive disorder. Clin Pharmacokinet 2014;53:731-40. PubMed PMID: 24989060.	3 PM: AA IM: AA	428 paediatric patients (7-18 years) were treated with dulo- xetine 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: <u>"PM" versus "IM" versus "NM":</u> oral clearance no difference (NS) NOTE: The analysed CYP2D6 alleles and the translation of				Authors' conclusion: 'Patient characteris- tics such as age, sex, BMI, serum creatinine, CYP2D6 predicted pheno- type, and menarche status did not have a statistically signi- ficant effect on any of the duloxetine pharmacokinetic parameters.'
	genotype to phenotype were not described. When calcula- ting the number of patients with a genotype other than NM and PM, it was assumed that UM was not determined.					

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ref. 6 Beatty NC et al. Pharmacogenetic workup of periope- rative 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 dulo- xetine 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 appea- red to aggravate the confusion and muscle rigidity. There- fore, 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 cyto- chrome P4502D6 genetic test result suggested a poten- tial alteration in metabolism. For this patient, who was taking combination antidepressant medications and receiving common perioperative medi- cines, additive pharmacodynamic effects converged with a pharmacoge- netic predisposition, resulting in seroto- nin 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 admi- nistration 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 pharma- cokinetics between CYP2D6 intermedi- ate metabolizers and CYP2D6 normal metabolisers sho- wed that duloxetine exposure was slight- ly higher (16%) in CYP2D6 interme- diate metabolisers than in CYP2D6 normal metaboli- sers. However, this magnitude of differ- rence is not clinically meaningful.' Oral clearance compared to NM: IM: 87%
<b>ref. 8</b> Chan C et al. Duloxetine pharma- cokinetics are simi- lar in Japanese and Caucasian subjects. Br J Clin Pharmacol 2007;63:310-4. PubMed PMID: 17380590.	3 PM: AA	<ul> <li>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).</li> <li>Genotyping: <ul> <li>administration of a</li> <li>administration of multiple</li> <li>single dose:</li> <li>doses:</li> <li>- 38x (NM + genotype</li> <li>- 25x (NM + genotype</li> <li>1/0)</li> <li>- 6x IM</li> <li>- 6x IM</li> <li>- 6x IM</li> <li>- 4x PM</li> <li>- 1x UM</li> </ul> </li> <li>Results:</li> <li>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.</li> <li>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</li> </ul>	Authors' conclusion: 'The high duloxetine concentrations observed in normal metabolizers sug- gests that exposure cannot be predicted by knowledge of CYP2D6 metaboli- zer status alone, and other factors, such as the degree of expression of CYP1A2 activity, appear to affect duloxetine pharma- cokinetics 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 alle- les 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	0	The pharmacokinetics of duloxetine in patients who are poor	
SmPC Cymbalta		metabolisers with regards to CYP2D6, were not examined	
(duloxetine) 30-03-	PM: AA		
16.		trations 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	PM	3 AA	no	no	14 November 2022
Working Group decision	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).