

# CYP2C19: amitriptyline

6944-6946

AUC = area under the plasma concentration-time curve, AUC = AUC $_{0^{-\infty}}$  = AUC extrapolated to infinity, AUC $_{0^{-48h}}$  = AUC during the first 48 hours after medicine intake, Clor = oral clearance, Css = steady-state concentration, IM = intermediate metaboliser (\*1/\*2, \*1/\*3, \*2/\*17, \*3/\*17) (reduced CYP2C19 enzyme activity), MR = metabolic ratio, NM = normal metaboliser (\*1/\*1, \*1/\*17) (normal CYP2C19 enzyme activity), NS = non-significant, PM = poor metaboliser (\*2/\*2, \*2/\*3, \*3/\*3) (absent CYP2C19 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, TCA = tricyclic antidepressant, UM = ultra-rapid metaboliser (\*17/\*17) (elevated CYP2C19 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:

Amitriptyline is mainly converted by CYP2C19-mediated N-demethylation to the active metabolite nortriptyline. Both amitriptyline and nortriptyline are metabolised by CYP2D6 to 10-hydroxy metabolites, predominantly E-10-hydroxy metabolites. Amitriptyline is approximately three times as potent as E-10-OH-amitriptyline. Nortriptyline is approximately twice as potent as E-10-OH-nortriptyline.

N-oxidation and N-glucuronidation of amitriptyline also take place. Nortriptyline is converted by CYP2D6 and CYP-2C19 to the inactive metabolite didesmethylamitriptyline (desmethylnortriptyline).

The therapeutic range of amitriptyline is a sum concentration of amitriptyline and nortriptyline of 100-300 ng/ml and values higher than 400 ng/ml are considered to be toxic. An upper limit is indicated for the therapeutic range of nortriptyline (50-150 ng/ml), but not for the therapeutic range of amitriptyline (> 50 ng/ml).

Genetic variants in CYP2C19 can result in a reduced CYP2C19 enzyme activity (intermediate metabolisers (IM)), an absent CYP2C19 enzyme activity (poor metabolisers (PM)) or an elevated CYP2C19 enzyme activity (ultra-rapid metabolisers (UM)).

IM and PM: All but one of the 11 studies including kinetics showed that a genetically reduced CYP2C19 enzyme activity (IM and PM) increased the amitriptyline/nortriptyline ratio by decreasing the nortriptyline exposure while not affecting or slightly increasing the amitriptyline exposure (Mifsud Buhagiar 2022, Zhou 2021, Matthaei 2021, Ryu 2017, De Vos 2011, van der Weide 2005, Steimer 2005, Steimer 2004, Jiang 2002, and Shimoda 2002; no significant effect found in Scherf-Clavel 2022). However, IM and PM hardly influenced the sum concentration of amitriptyline+nortriptyline, that determines efficacy and side effects (Scherf-Clavel 2022, Mifsud Buhagiar 2022, Zhou 2021, Matthaei 2021, Ryu 2017, De Vos 2011, Steimer 2005, Steimer 2004, Jiang 2002, and Shimoda 2002). Compared to NM, the sum exposure increased with a weighted mean of 15% for IM and a weighted mean of 12% for PM (based on 102 IM and 24 PM from 5 studies (Zhou 2021, De Vos 2011, Steimer 2004, Jiang 2002, and Shimoda 2002)). Accordingly, the four studies investigating response (Scherf-Clavel 2022, Zhou 2021, Atasayar 2016, and Steimer 2005) and the four studies investigating adverse drug reactions (Richards-Belle 2023, Matthaei 2021, Ryu 2017, and Steimer 2005), did not find a significant effect of IM and/or PM compared to NM. The only study investigating adverse drug reactions other than lipid levels in patients analysed only 1 PM (Steimer 2005). However, for 18 IM + 1 PM, this study showed a trend for a decrease in adverse drug reactions compared to NM, making it unlikely that a significant increase in adverse drug reactions due to a amitriptyline/nortriptyline imbalance would have been found for PM if more PM would have been studied. The KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction for IM and PM, but adjustment of therapy is not required (yes/no-interactions).

UM: The only study including UM and investigating effectiveness found no effect of the CYP2C19 phenotype on the clinical improvement and the percentage of patients with remission of depression (Scherf-Clavel 2022). Of the two studies investigating adverse events, one did not find an effect of the CYP2C19 phenotype on the intensity of fatigue after a single dose in healthy volunteers (Matthaei 2021). The other did not find an effect of UM on lipid levels during amitriptyline therapy (Richards-Belle 2023). Of the 3 studies including kinetics, De Vos 2011 (8 UM) showed the percentage of patients with supratherapeutic plasma concentrations (nortriptyline > 150 ng/ml) to be significantly higher for UM compared to \*1/\*1 if only CYP2D6 NM were analysed. However, the nortriptyline plasma concentration did not differ significantly between UM and \*1/\*1 in this study (respectively 83 and 71 ng/ml). In Scherf-Clavel 2022, the metabolic ratio nortriptyline/amitriptyline differed significantly between the CYP2C19

phenotypes before, but not after Bonferroni-correction. After a single dose in healthy volunteers, the AUC<sub>0-48h</sub> of nortriptyline was associated with the CYP2C19 phenotype, being lowest in PM and highest in UM (Matthaei 2021). The only UM in this study was also CYP2D6 IM, probably exaggerating the difference between this UM and NM. The only of the 3 studies investigating a possible association of the CYP2C19 phenotype with the exposure of amitriptyline+nortriptyline did not find a significant effect (Scherf-Clavel 2022). The dose-corrected amitriptyline+nortriptyline concentration could be calculated for 5 UM in De Vos 2011. This sum concentration was 78% of that for NM. A dose increase of 29% would be required to correct for this decrease. However, the upper limit of the nortriptyline therapeutic range (150 ng/ml) is considerably lower than that of the amitriptyline+nortriptyline therapeutic range (300 ng/ml). This means that at higher nortriptyline/amitriptyline ratios as occur in UM, the upper limit of the nortriptyline therapeutic range might be reached at lower doses than the upper limit of the amitriptyline+nortriptyline therapeutic range, making it uncertain whether recommendation of a dose increase would improve or worsen the therapy. The KNMP Pharmacogenetics Working Group concluded that there is a genedrug interaction, but that there is insufficient evidence to recommend adjustment of therapy for UM (yes/no-interaction).

You can find a detailed overview of the observed kinetic and clinical effects per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background text via your pharmacy or physician electronic decision support system.

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

Source	Code	Effect					Comments
ref. 1 Richards-Belle A et al. Associations of antidepressants and antipsychotics with lipid parameters: Do CYP2C19/CYP2D6 genes play a role? A UK population-based study. J Psychopharmacol 2023;37:396-407. PMID: 36772859.	PM: AA IM: AA UM: AA	Database-derived of analysed. Relevant comedical cholesterol-lowering sis only roughly adjustence of strong/rice or absence of chanalysis was by line cholesterol-lowering group (categorical) inhibitors (binary). Bonferroni-correctic performed, but not analysed. As a resusingificant.  Genotyping: - 5155x NM (3162x - 2519x IM - 366x UM  Results: Results compared total cholesterol LDL-cholesterol HDL-cholesterol	tion (CYF) g medicat usted for moderate nolesterol- ear regres g medicat and use of the number of th	22C19 inhi cion) was r this co-me CYP2C19 -lowering r ssion, adju- cion (binary of strong/n total number amber of ge 13 (0.05/4)  993x *1/*1	bitors and not excludedication (a) inhibitors medication (b), genetic moderate (c) oer of outcenes and (d) was constant.	inducers and ed and analy-presence or and presen- age, sex, ancestry CYP2C19 comes (4) was medications sidered  UM NS NS S before but NS after Bonferronicorrection	Authors' conclusion: 'We did not find evidence for a role of CYP2C19 or CYP2D6 metabolic phenotypes on lipid parameters in other medications studied.'
		triglycerides	NS	NS	NS		
		Note: In this study, higher total choleste and lower HDL-cho	amitriptyl erol, LDL	ine users v	were foun ol, and trig	d to have plycerides,	

ref. 1. continuation	<u> </u>			
Ter. 1, continuation		Note: Genotyping was with	n an Affymetrix array, so for many	
			iding the most important gene vari-	
ref. 2 Scherf-Clavel M et al. Effects of pharmacokinetic gene variation on therapeutic drug levels and antidepressant treatment response. Pharmacopsychiatry 2022;55:246-54. PMID: 35839823.	3	gene polymorphisms, incluants in this British population 109 patients from two cohors of the cohorts) were treated 340 mg/day (mean143 mg). The cohort from which 62 patients with at least a morphisms performent and used to adjust the after 7 weeks of treatment. The other cohort included Therapeutic drug monitoring doctor's choice and not performed octor's choice and not perform the 62 patients were analysed 50% of patients were deschort). Treatment responsin HDRS21-score. 23% of patients were deschort from which the first the other cohort). Adverse drug reactions were observed and patients were deschorted from the HDRS21-score. HDRS21-score ≤ 7.  Trough serum concentration in the HDRS21-score. HDRS21-score ≤ 7.  Trough serum concentration in the HDRS21-score on ortriptyline/amitriptyline were described by the cohort from the coho	ading the most important gene varion.  Ports (62 and 47 patients from each d with amitriptyline (final dose 25-/day)).  patients were derived, included derate depressive period (Hamilton 21 (HDRS <sub>21</sub> ) > 14). Therapeutic rmed in week 3, 5, and 7 of treatne dose. Patients were analysed according to the reprotocol and used to adjust the redefined and 38% in the other seed after 6 weeks of treatment. Onders (59% in the cohort from acceptation and as ≥ 50% reduction attents showed remission (30% in 62 patients were derived and 15% are assessed in the cohort from rived (4 mild and 4 medium adverse wed), change of anti-depressant due was assessed in the other cohort measured as the percentual reduction and in steady state were determined as a consinusted as the percentual reduction and in steady state were determined as a consinusted as the percentual reduction and metabolic ratio are set as missing data. The ether the difference in response two cohorts is significant and do from which the patient was derived. Corrected for the total number of mother of drugs (4 for concentrations investigated. As a result p ≤ 0.001	Authors' conclusion: 'As only CYP2D6 seems to clinically affect total drug concentration, the present data support previous studies showing that compared to CYP2D6, CYP-2C19 had less influence on total amitriptyline clearance.'
			∕I and UM is not mentioned.	
		Results for PM versus IM versus UM:	versus *1/*1 versus *1/*17	
		clinical improvement (percentual reduction in HDRS <sub>21</sub> score)	NS	
	PM: AA	% of patients with remission	NS	
	IM: AA UM: AA	dose-corrected concentration of amitriptyline+nortriptyline	NS	
		metabolic ratio nortrip- tyline/amitriptyline	S before, but NS after Bonfer- roni-correction	

ref. 2, continuation	T	Note: Constyping was with Ag	jena's PGx 74 v1.0 assay, so for	
Ter. 2, Continuation		,, ,	cluding the most important gene	
		variants in this German popula		
ref. 3	3	33 patients were treated with a		Authors' conclu-
Mifsud Buhagiar L et	_		5 mg/day) divided over 1, 2 or 4	sion:
al.		doses.	og, aay, aaca e.e, = e	'CYP2C19 meta-
The interplay		Steady-state serum concentra	tions were measured 11-18	bolizer status
between pharmaco-			m concentrations were calcula-	explained inter-
genetics, concomi-			concentrations, using the calcu-	patient variation in
tant drugs and blood			(ke). Trough serum concentra-	nortriptyline to
levels of amitripty-			losing schedule to allow interpa-	amitriptyline con-
line and its main		tient comparisons.		centration ratio.'
metabolites.		CYP2C19 inhibitors and induc		
Per Med			ormed with a parsimonious gene-	
2022;19:113-23.			etabolic ratio nortriptyline/amitrip-	
PMID: 35118877.		tyline and the dose-corrected	_	
			ormed with a parsimonious logis-	
		tic regression model for the me		
			elow, within or above the expec-	
		ted range.		
		Canatamina		
		Genotyping: - 24x *1/*1		
		- 5x *1/*17		
		- 4x IM		
		- 4X		
		Results:		
		Results for IM versus *1/*1 ver	ersus *1/*17:	
		measured concentration of	NS	
		amitriptyline+nortriptyline		
		being below, within or		
		above the expected range		
		dose-corrected concen-	NS	
		tration of amitriptyline dose-corrected concen-	NS	
		tration of nortriptyline	INS	
		dose-corrected concen-	NS	
		tration of amitriptyline+		
		nortriptyline		
	IM: A	metabolic ratio nortrip-	S, with the ratio increasing	
		tyline/amitriptyline	in the order IM, *1/*1,	
			*1/*17	
			CYP2C19 genotype was	
			the parameter with the	
			main effect on the metabo-	
			lic ratio.	
		Note: Genetyping was for *2 th	nrough *10, and *17. These are	
		the most important gene varia	•	
ref. 4	3		ninant irritable bowel syndrome	Authors' conclu-
Zhou WC et al.		were treated with amitriptyline		sion:
Role of serum ami-			tions were measured after over-	'Nortriptyline
triptyline concentra-		night fasting.		serum concentra-
tion and CYP2C19			essed with the Adequate Relief	tion but not
polymorphism in			enced adequate symptom relief	CYP2C19 poly-
predicting the res-		for at least 50% of the treatme	morphism may be	
ponse to low-dose		responders.	correlated with	
amitriptyline in irrita-		CYP2C19 inhibitors and induc	ers were not excluded.	the clinical effica-
ble bowel syndrome.		Ganatynina:		cy of amitriptyline for treating
Dig Liver Dis		Genotyping: - 33x NM		diarrhea-dominant
2021;53:1422-7.		- 44x IM		irritable bowel
	<u> </u>	- <del>                                   </del>		

PMID: 33753003.		- 7x PM				syndrome, and		
						such a response		
ref. 4, continuation		Results:	<u> </u>			may occur at the		
		Results compared to NM		IM	value	upper nortriptyline threshold of 2.91		
			PM	IIVI	for NM	ng/ml.'		
		% of patients with	N	IS	33.33	,		
		treatment response	•		%			
		concentration of ami-	NS	NS	5.84			
		triptyline	NS for PM	versus IM	ng/ml			
			versus NM					
	PM: A	concentration of nortrip-	x 0.59 (S)	x 0.81 (S)	4.70			
	IM: A	tyline	4.00	4.07	ng/ml			
		concentration of ami-	x 1.02	x 1.07 e not deter-	10.54			
		triptyline + nortriptyline	mined.	e not deter-	ng/ml			
		dose-corrected concen-	NS	NS	0.38			
		tration of amitriptyline		M versus IM	ng/ml			
			versus NM		per mg			
			(NS)	,		Dose-corrected		
		dose-corrected concen-	x 0.50	x 0.87	0.38	serum concentra-		
		tration of nortriptyline	(S)	(NS)	ng/ml	tion of amitripty-		
			S for PM ve	ersus IM	per mg	line+nortriptyline		
		dose-corrected concen-	versus NM x 1.07	x 1.29	0.76	versus NM: PM: 107%		
		tration of amitriptyline+	Significance		ng/ml	IM: 129%		
		nortriptyline	mined.	o not deter	per mg			
		dose- and weight-	NS	NS	0.0079			
		corrected concen-	NS for PM	versus IM	ng/ml			
		tration of amitriptyline	versus NM		per			
					mg/kg			
		dose- and weight-	x 0.54	x 0.85	0.0071			
		corrected concen- tration of nortriptyline	(S) S for PM ve	(NS)	ng/ml per			
		l transfrontional profile	versus NM	JIGUG IIVI	mg/kg			
		dose- and weight-	x 1.05	x 1.27	0.0150			
		corrected concen-	Significance	e not deter-	ng/ml			
		tration of amitriptyline+	mined.		per "			
		nortriptyline			mg/kg			
		Note: In this study, a corre						
		nortriptyline serum concer						
		mean nortriptyline serum o						
		was higher than the propo						
		the mean nortriptyline seru	um concentra	tion in PM wa	as slightly			
		lower (2.78 ng/ml).n bm						
		Note: Genotyping was by	sequencing (	so for all gen	e variants			
		However, only *2 and *3, t						
		this Chinese population, w	•	_				
ref. 5	3	35 healthy volunteers, seld	ected for their	r organic cati	on trans-	Authors' conclu-		
Matthaei J et al.		porter 1 (OCT1) genotype	, received a s	single dose of	f 25 mg	sion:		
Effects of genetic		amitriptyline.	'The pharmacoki-					
polymorphism in		Participants reported adversacles. No serious advers		netics of amitrip- tyline and nortrip-				
CYP2D6, CYP2C19,		was the only statistically s		tyline are strongly				
and the organic cation transporter		Relevant comedication wa				dependent on the		
OCT1 on amitripty-		not be determined for nort				CYP2C19 and		
line pharmacokine-		nortriptyline concentration				CYP2D6 geno- types.'		
tics in healthy volun-		the last measurement at 4	st measurement at 48 hours after amitriptyline intake.					
teers and depres-		Because this underestima						
sive disorder		nortriptyline for PM and IM	1, the results	of this study	cannot be			
	<u> </u>	I				<u> </u>		

		1					T-
patients.		used for dose ca	alculations.	In addition,	the only UI	M was also	
Front Pharmacol		CYP2D6 IM.					
2021;12:688950.		Multiple linear re				x, age, body	
PMID: 34093211.		mass index, and	l glomerula	r filtration ra	ate.		
ref. 5, continuation		Genotyping:					
		- 1x UM					
		- 26x NM					
		- 7x IM					
		- 1x PM					
		Results:	14 5154				
		Results compa			LINA	Lyalya	
			PM	IM	UM	value for	
						NM	
		intensity of	Independ	dent of CYP	2C19	INIVI	
		fatigue	genotype		2010		
		AUC <sub>0-∞</sub>		M versus *1	/*2 versus	210.3	
		amitriptyline		ersus *1/*1 v		μg.h/L	
			*1/*17 ve	rsus UM			
				inear regres			
				at the CYP2			
				did not pre			
		ALIC	AUC <sub>0-∞</sub> a	mitriptyline. M versus *1	/**	171.6	
		AUC <sub>0-48h</sub> amitriptyline		ersus *1/*1 v		μg.h/L	
			*1/*17 ve		reisus	μg.ι/∟	
	PM: A	AUC <sub>0-48h</sub>	x 0.38	x 0.81	x 2.71	104.7	
	IM: A	nortriptyline		versus *1/*		μg.h/L	
	UM: A			ersus *1/*1 v			
			*1/*17 ve				
			Multiple I	inear regres	ssion con-	1	
				e CYP2C19			
				independen			
				48h nortriptyl		0=0	
		AUC <sub>0-48h</sub>	x 0.97	x 1.04	x 1.74	276.3	
		amitriptyline+ nortriptyline	Significal	nce not dete	erminea.	μg.h/L	
		Hortiptyline					
		Note: AUCs did	not differ h	etween diff	erent OCT1	genotypes	
		1.0.0.7.000 ala		coon and	J. J. N. J. J. I	300t, poo.	
		Note: The CYP2	2C19 UM w	as CYP2D6	IM, which	probably	
		contributed to th	e high nort		·		
		line AUCs in this	s patient.				
					<del>-</del> .		
		Note: Genotypin	•				
rof 6	2	important gene					Author's sonal:
ref. 6 Ryu S et al.	3	24 healthy volun					Author's conclusion:
A study on CYP-		investigators we					"The extent of N-
2C19 and CYP2D6		The subjects rat					demethylation of
polymorphic effects		gue scales befor					amitriptyline signi-
on pharmacokine-		hours after dosir					ficantly decreased
tics and pharmaco-		siness or a change in blood pressure.					in subjects carry-
dynamics of amitrip-		Eight adverse events occurred in the 24 volunteers, of which					ing two nonfunc- tional alleles of
tyline in healthy			were considered amitriptyline-related (1x dry eyes, 2x				
Koreans.		headache, 1x he	ead heavin	ess). All eve	ents were m	ild and fully	CYP2C19 The
Clin Transl Sci		recovered.	and amalda	a wara aval	udod		gene variations of
2017;10:93-101. PubMed PMID:		Co-medication a	ıııu smokin	y were excl	uued.		CYP2C19 and CYP2D6 did not
28296334.		Genotyping:					change the phar-
20230JJ4.	L	Lochotyping.					Tonange the bilat-

ref. 6, continuation		- 8x NM				macodynamic
ren o, commutation		- 8X INIVI - 10X IM				macodynamic effect."
		- 6x PM				Onoot.
		Results:				
		Results compared to	NM+IM or NN	Л:		
		•	PM	IM	value for	
					NM+IM or	
					NM	
		dry mouth	no differenc			
		dan constant and	groups (NS			
		drowsiness	no differenc		no signi- ficant in-	
			groups (NS	)	crease	
		increase in pulse	no differenc	ce between	Grease	
		rate	groups (NS			
		change in blood	no differenc		no signi-	
		pressure	groups (NS	)	ficant	
				ı	change	
	PM: A	AUC amitriptyline	x 1.78 (S)		NM+IM:	
		(in ng.h/ml) AUC nortriptyline	V 0 E4 (C)		268.26 NM+IM:	
		(in ng.h/ml)	x 0.54 (S)		234.03	
		AUC amitriptyline +	x 1.20		NM+IM:	
		AUC nortriptyline	(NS (sig-		502.28	
		(in ng.h/ml)	nificance			
			not deter-			
			mined))			
	IM: AA	AUC ratio amitripty-	x 4.03	x 1.58	NM:	
		line/nortriptyline	(S)	(NS)	0.85	
		NB: Genotyping was fo	or *2 *2 and *	17 Thoso o	ro the most	
		important gene variant				
		patients had *17.	3 111 1113 11010	an population	i. None of the	
ref. 7	3	152 migraine patients	received amit	riptyline prop	hylaxis for a	Author's conclu-
Atasayar G et al.		minimum of 2 months.				sion:
Association of		effective dose and the		•		"There were no
MDR1, CYP2D6,		mum effective dose ac				significant correla-
and CYP2C19 gene		effects. Only patients r				tions between the
polymorphisms with prophylactic		prophylaxis and indicate evaluated.	ung no misse	u amımpıyım	e doses were	treatment responses to amitripty-
migraine treatment		Treatment response w	as defined as	a decrease	in the head-	line, propranolol,
response.		ache frequency during				and valproic acid
J Neurol Sci		44% of patients respon				and the MDR1,
2016;366:149-154.		Relevant co-medicatio	n was not exc	cluded.		CYP2D6 and
PubMed PMID:		0				CYP2C19 gene
27288795.		Genotyping: - 121x NM				polymorphisms."
		- 12 IX INIVI - 31x IM				
		JIX IIVI				
		Results:				
		Percentage of respon	ders compar	ed to NM (44	<b>!</b> %	
		responders):		•		
	IM: AA	IM NS				
			***			
		NB: Genotyping was for				
		important gene variant patients had *3 or *4.				
ref. 8	3	Routine therapeutic dr	ua monitorina	was nerform	ned for 150	Authors' conclu-
De Vos A et al.		patients on amitriptylin	-	•		sion:
Association between		post-medication. The a				'This study con-
CYP2C19*17 and		patients. The dose var				firms the increa-
metabolism of		•				sed activity of the

amitriptyline, citalo-		ge of 108 mg/day.						CYP2C19*17			
pram and clomipra-			Relevant co-medication was not excluded.								
mine in Dutch hospi-											
talized patients.		Genotyping							bolism of drugs		
Pharmacogenomics			- 105x NM (60x *1/*1, 45x *1/*17) (59 with known dose)								
J			- 8x UM (5 with known dose)								
2011;11:359-67.		- 32x IM (21	x *1/*2,	11x *2/*1	7) (19 wi	th knowr	n dose)		2C19, including		
PubMed PMID:		- 5x PM (3 v	vith know	n dose)					amitriptyline and		
20531370.									citalopram. Howe-		
		Results:							ver, the clinical		
ref. 8, continuation		Results co	mpared t	to *1/*1 ( *1/*2	or NM):	*1/			relevance of CYP-		
			PM	value	2C19*17 is proba-						
					*17	*17		for	bly limited for		
								*1/*1	amitriptyline,		
								(or	citalopram, and		
								NM)	clomipramine.'		
		dose-cor-	x 1.36	x 1.18	x 1.00	x 0.73	x 0.55	1.1			
		rected	(NS)	(NS)	(NS)	(NS)	(NS)		=		
	IM: AA	C <sub>ss</sub> ami-	x 1.57		.31		x 0.63	NM:			
		triptyline	(NS)	(N	IS)		(NS)	0.95			
		(ng/ml									
		per mg)	0.4.4	4 04	4 04	4.00	0.04	4 4	4		
	PM: A	metabo-	x 3.14	x 1.21	x 1.21	x 1.00	x 0.64	1.4			
		lic ratio	(S)	(NS)	(NS)	(NS)	(NS)	4.0			
		(ami/nor-				were an		1.6			
		triptyline)				icant for					
						(x 2.31 (	1	NIN 4.	_		
			x 3.14		.21		x 0.64	NM:			
		% with	(S) NS		IS)	NC	(NS)	1.40			
		subthera-	for	NS for	NS for	NS for	NS for	30%			
		peutic	each	each	each	each	each				
		C <sub>ss</sub>	CYP-	CYP-	CYP-	CYP-	CYP-				
		(ami+nor	2D6	2D6	2D6	2D6	2D6				
		< 100	phe-	phe-	phe-	phe-	phe-				
		ng/ml)	noty-	noty-	noty-	noty-	noty-				
		,	pe	pe	pe	pe	pe				
	UM: A	% with	NS	NS	NS	NS	increa	0%	=		
	OWI. A	suprathe-	for	for	for	for	se (S				
		rapeutic	each	each	each	each	for				
		Css	CYP-	CYP-	CYP-	CYP-	CYP-				
		(nortrip-	2D6	2D6	2D6	2D6	2D6				
		tyline	phe-	phe-	phe-	phe-	NM,				
		> 150	noty-	noty-	noty-	noty-	NS				
		ng/ml)	pe	pe	pe	pe	for				
			'			-	CYP-				
							2D6				
							IM				
							and				
							PM)		_		
		dose	NS	NS	NS	NS	NS	101			
		(mg/day) There were also no significant differen-									
		ces after stratification for CYP2D6 phenotype (NM, PM, IM and UM) (NS).									
		-							4		
		C <sub>ss</sub> ami-	x 1.84	NS	NS	NS	NS	77			
		triptyline	(S)								
		(ng/ml)	NC	NC	NC	NC	NC	74	-		
		C <sub>ss</sub> nor-	NS	NS	NS	NS	NS	71			
		triptyline									
		(ng/ml) C <sub>ss</sub>	NS	NS	NS	NS	NS	148	-		
		ami+nor-	INO	INO	INO	INO	INO	140	Estimated alasma		
		triptyline							Estimated plasma concentration of		
	]	Прини	<u>I</u>	I	I	<u>I</u>	<u>I</u>	1	CONCENTIALION OF		

ref. 8, continuation		(ng/ml)							amitriptyline+nor-
		dose-	x 0.98	x 1.09	x 0.93	x 0.73	x 0.67	1.89	triptyline versus
		corrected	(NS)	(NS)	(NS)	(NS)	(NS)		NM:
		C <sub>ss</sub> ami-	x 1.13	x 1			x 0.78	NM:	PM: 113% IM: 121%
		triptyline +nortrip-	(NS)	(1)	IS)		(NS)	1.63	UM: 78%
		tyline,							OW. 1070
		calcula-							
		ted from							
		the mean							
		values							
		for cor-							
		rected Css ami-							
		triptyline							
		and the							
		metabo-							
		lic ratio							
		(ng/ml							
		per mg)							-
		NOTE T							
		NOTE: The							
		and dose water					_		
		tration value					ecieu cc	nicen-	
		tration value	decida	SCG WILIT	norcasci	u uoses.			
		NOTE: Gen	otyping v	was for *2	2 and *17	7. These	are the r	nost	
		important ge							
ref. 9	4	69 patients						serum	Authors' conclu-
van der Weide J et		trough conc				•			sion:
al.		therapeutic	-	-					'According to
Metabolic ratios of psychotropics as		patients trea				•			these data, correlations exist
indication of cyto-		for which an							between the
chrome P450 2D6/		and DNA we probably are						ol .	log(MR) of venla-
2C19 genotype.		Co-medicati						indu-	faxine, amitripty-
Ther Drug Monit		cers was ex		011 201			11 2010	iiidd	line, and risperi-
2005;27:478-83.									done and the
PubMed PMID: 16044105.		Genotyping:							genotype of the
10044105.		- 52x NM							CYP enzymes involved in their
		- 15x IM							metabolism.'
		- 2x PM							
		Results:							
		Results co	mpared	to NM:					
				PM		IM	V	alue	
								or NM	
	PM: A	metabolic i		x 4.0 (S	) :	x 1.6 (S)	1	.0	
	IM: A	amitrityline	/nor-						
		triptyline							
		NOTE: Gen	otypina	was for *1	) These	is the mo	nst impo	rtant	
		gene varian				is the HIC	or impul	will	
ref. 10	3					e depres	sive disc	rder	Authors' conclu-
Steimer W et al.		49 patients with at least medium-grade depressive disorder were treated amitriptyline for a period of 3 weeks. The amitrip-							sion:
Amitriptyline or not,		tyline dose was increased over the first 2 days and was then							'Combined phar-
that is the question:									macogenetic tes-
pharmacogenetic		dose was lowered at the treating psychiatrist's discretion, who was blinded for genotype and trough concentrations (75							
testing of CYP2D6 and CYP2C19		was billiaca for generype and trough concentrations (70							
identifies patients		111g/ddy, 11 = 1, 100 111g/ddy, 11 = 0, 120 111g/ddy, 11 = 1).							
with low or high risk		Steady state had been reached at day 7. Mean trough							
		concentrations of day 7 to day 21 were assessed. Depression   Side effects in							

for side effects in amitriptyline therapy. Clin Chem 2005;51:376-85. PubMed PMID: 15590749.

# ref. 10, continuation

was scored with the Hamilton Depression Scale (HAMD) and Clinical Global Impression Scale. Full response was defined as a value  $\leq 8$  and an improvement > 30% on the Hamilton Depression Scale (HAMD). Complete nonresponse was defined as a value  $\geq 16$  or an improvement < 30% on the HAMD. Side effects were scored with the Dosage Record and Treatment Emergent Symptoms Scale (DOTES). DOTES consist of 30 items each rated on a 3-points scale and is organised in five clusters. DOTES scores  $\geq 5$  corresponded with above-average side effects.

88% of patients used psychotropic co-medication. Co-medication interfering with CYP2D6 or CYP2C19 metabolism was not excluded, but avoided whenever possible. 6 patients used possible CYP2C19-relevant co-medication (citalopram, diazepam, omeprazole), 13 patients possible CYP2D6-relevant co-medication (flupentixol, haloperidol, metoprolol, risperidone, sertraline, venlafaxine, yohimbine).

## Genotyping:

- 30x NM (19x CYP2D6 NM, 11x CYP2D6 IM)
- 19x IM+PM (18x IM, 1x PM) (12x CYP2D6 NM, 6x CYP2D6 IM, 1x CYP2D6 UM)

#### Results:

Results compared	to NM:					
·	CYP2D6 phenotype	IM+PM	value for NM			
% of patients	NM+UM	NS	52.6%			
with full response	IM	NS	36.4%			
% of patients	NM+UM	NS	12.1%			
with complete nonresponse	IM	NS	36.4%			
% of patients with above-average side effects	all	NS	40.0%			
total side effect score	NM+UM	trend for a decrease (p = 0.098; NS)	2.95			
	IM	NS	6.64			
C., portriptyline	For (IM+PM/CYP2D6 NM+UM) versus (NM/CYP2D6 NM+UM) versus (IM+PM/CYP2D6 IM) versus (NM/CYP2D6 IM), the effect was significant for the total side effect score and for the scores on the clusters mental side effects, anti-cholinergic/gastrointestinal symptoms and cardiovascular symptoms. There was a trend for the cluster neuromuscular symptoms (p = 0.554) and no significance for the cluster other symptoms.					
C <sub>ss</sub> nortriptyline (ng/ml)	NM+UM	trend for a decrease (p = 0.071; NS)	65.0			
C amplifying trailing	IM	NS	108.4			
C <sub>ss</sub> amitriptyline	NM+UM	x 1.50 (S)	70.5			
(ng/ml)	IM	NS	93.5			
C <sub>ss</sub> amitriptyline+	NM+UM	x 1.15 (NS)	134.7			
nortriptyline (ng/ml)		x 1.00 (NS) was not determine is NM. There was				

rapy and could possibly be used to individualize antidepressive regimens and reduce treatment cost. .... The lowest risk was observed for carriers of two functional CYP2D6 alleles combined with only one functional CYP-2C19 allele. .... We found no correlations between drug concentrations or genotypes and therapeutic response.'

amitriptyline the-

IM+PM: A

	T	1		/ILA E /C: := :		T
ref. 10, continua- tion			ficant effect for UM) versus (NM)			
lion						
			versus (IM+ PM			
			(NM/CYP2D6 II			
			2D6 IM, the val IM+PM and NM			
			UM, the differen			
			and NM was re			
			not very likely to			
		amitriptyline/nor-		( 2.04 (S)	1.02	
		triptyline ratio		( 1.23 (NS)	0.81	
			Significance wa			
			IM+PM versus			
			ficant effect for			
			UM) versus (NN		,	
			versus (IM+ PM	,		
			(NM/CYP2D6 II	,		
			UM, the differer			
			and NM was ve			
			cant, because of	•		
			se in amitriptylii			
			the trend for a s			
			the nortriptyline			
			IM+PM compar			
			IM, the different			
			NM was unlikely			
			because both the			
			tyline concentration nortriptyline of			
			IM+PM compar			
			significant.	ed to Mivi were	TIOL	
			signincant.			
ref. 11	3	NOTE: Nortriptyline of but amitriptyline condinfluence on side effecton side effecton sides, than of the planitriptyline into nort nortriptyline concentratyline+nortriptyline concentratyline+nortriptyline+nowith therapeutic responder of the sides of th	centration did no ects of the pheno extyline and nortriphenotype of CYF criptyline, suggestation is due to it oncentration. Intriptyline concertonse.  I was for *2, *3 and patient group.	ot. However, the otype of CYP2E ptyline into inace P2C19, which costs that the effects effect on the other intration did not day. These are an population.	e stronger 06, which ctive meta- onverts ct of amitrip- correlate the most Only *2	Authors' conclu-
Steimer W et al.	3	mer 2005 were analy		ı ıne 45 panem	3 III 3181-	sion:
Allele-specific chan-		mor 2000 were arialy				'Eighteen CYP-
ge of concentration		Genotyping:				2C19 heterozy-
and functional gene		- 30x NM (19x CYP2	D6 NM. 11x CY	P2D6 IM)		gotes (*1/*2) had
dose for the predic-		- 18x IM (11x CYP2E			2D6 UM)	higher amitripty-
tion of steady-state		- 1x PM (CYP2D6 NI	·	,	- ···/	line and lower
serum concentra-		,	•			nortriptyline con-
tions of amitriptyline		Results:				centrations than
and nortriptyline in		Results compared t	o NM:			30 homozygotes
CYP2C19 and CYP-			PM	IM	value	(*1/*1)
2D6 extensive and					for NM	CYP2D6 but not
intermediate meta-		dose- and weight-	x 0.90 (NS)	x 1.06 (NS)	74.0	CYP2C19 corre-
bolizers.		corrected C <sub>ss</sub>		, ,	ng.kg/	lates with the sum
Clin Chem		amitriptyline+nor-			ml.mg	of both concentra-
2004;50:1623-33.		triptyline				tions used to
PubMed PMID:			·			guide amitriptyline

15205367.	IM: A	dose- and weight-	NS	x 1.29 (S)	37.4	therapy.'
		corrected C <sub>ss</sub>		- (-)	ng.kg/	
ref. 11, continua-		amitriptyline			ml.mg	Dose- and weight-
tion		dose- and weight-	NS	trend for a	37.0	corrected concen-
		corrected Css		decrease (p	ng.kg/	tration of amitrip-
		nortriptyline		= 0.059; NS)	ml.mg	tyline+nortriptyline
			Multivariate li			versus NM:
			sion showed			PM: 90% IM: 106%
	PM: A		association o			11VI. 100%
			2C19 phenot	ype with cor- otyline concen-		
			tration (S).	ntylline concern-		
		amitriptyline/nor-	NS	x 1.61 (S)	0.93	
		triptyline ratio	1.10	X 1.01 (0)	0.00	
		p sys				
		NOTE: Genotyping v	was for *2, *3 ar	nd *4. These are	the most	
		important gene varia				
		was detected in this	patient group.		•	
ref. 12	4	50 patients were trea	ated with a stab	le dose of amitri	ptyline for	Authors' conclu-
Shimoda K et al.		at least 2 weeks. Do	ses ranged fron	n 25 to 225 mg/d	day (0.46-	sion:
The impact of CYP-		5.18 mg/kg body we	ight). Blood san	nples were draw	n 9.5-16	'The genotype of
2C19 and CYP2D6		hours after the even	ing dose.			CYP2C19 is one
genotypes on meta-		Neuroleptics and ba				of the important
bolism of amitripty-		affect amitriptyline m				determinants of
line in Japanese psychiatric patients.		ded. None of the pat	tients in the stud	dy took CYP-mo	dulating	the plasma con- centrations of
J Clin Psychophar-		agents.				amitriptyline and
macol		Multiple regression a				the capacity to
2002;22:371-8.		number of variant all	leles of CYP2C	19 and CYP2D6	•	desmethylate
PubMed PMID:		Construciona				amitriptyline.
12172336.		Genotyping: - 24x NM				Mother compound
		- 19x IM				amitriptyline is
		- 7x PM				shunted via
		1 X 1 W				hydroxylation
		Results:				pathways from
		Results compared	to NM:			amitriptyline to E- and Z-hydroxy-
			PM	IM	value	amitriptyline in the
					for NM	subjects with
	PM: A	dose- and	x 1.78 (S)	approximate-	36.0	homozygotes of
		weight-corrected		ly	ng/ml	mutated alleles of
		C <sub>ss</sub> amitriptyline		x 1.11 (NS)	per "	CYP2C19 in order
			Multiple regres		mg/kg	to compensate for
			showed the nu 2C19 variant a			the decreased
			significant pred			capacity to des-
			corrected C <sub>ss</sub> (			methylate amitrip-
			ber of CYP2C1			tyline.'
			les explained 1			
			variability in the	e logarithm of		
			the corrected (			
		dose- and	trend for an	NS	9.5	
		weight-corrected	increase (p =		ng/ml	
		C <sub>ss</sub> hydroxyami-	0.051; NS)		per "	
		triptyline	v 2 60 (C)	v 1 20 (C)	mg/kg	
	IM: A	metabolic ratio	x 2.68 (S)	x 1.39 (S)	1.27	
		(ami/nortriptyline)	Multiple regres showed the nu			
			2C19 variant a			
			significant pred			Estimated dose-
				(S). The num-		and weight-cor-
				19 variant alle-		rected concentra-
		1 1				

ref. 12, continua-			variability in the			line+nortriptyline versus NM:
		dose- and weight-corrected C <sub>ss</sub> amitriptyline+ nortriptyline, cal- culated from the mean values for C <sub>ss</sub> amitriptyline and the metabo- lic ratio	x 1.29 (NS)	approximate- ly x 0.97 (NS)	64.3 ng/ml per mg/kg	PM: 129% IM: 97%
		NOTE: Genotyping important gene varia	ants in this Japa	nese population		
ref. 13 Jiang ZP et al. The role of CYP- 2C19 in amitriptyline N-demethylation in Chinese subjects. Eur J Clin Pharma- col 2002;58:109-13. PubMed PMID: 12012142.	3	12 healthy volunteer single dose of amitrice Co-medication, smooth excluded.  Genotyping: - 4x NM - 2x IM - 6x PM  Results:	Authors' conclusion: 'The genetic defects of CYP2C19 have a significant effect on amitriptyline pharmacokinetics, and CYP2C19 plays an important role in N-demethyla-			
		Results compared	to NM:			tion of amitripty- line in vivo at a clinically thera-
			PM	IM	value for NM	
		AUC amitriptyline	x 1.07 (NS)	x 0.92 (NS)	2339 ng.h/ ml	peutic dose.'  AUC of amitripty-
	PM: A IM: AA	AUC amitriptyline	x 1.39 (S for PM versus NM+IM)	NS	1593 ng.h/ ml	line+nortriptyline versus NM: PM: 107%
		AUC nortriptyline	x 0.39 (S for PM versus NM+IM)	NS	746 ng.h/ ml	IM: 92%
		metabolic ratio (ami/nortriptyline)	x 3.51 (S for PM versus NM+IM)	NS	2.17	
		NOTE: Genotyping important gene varia				
ref. 14 SmPC Amitriptyline HCl Auro 24-01-22.	O PM: A	Dose: Known poor metabore These patients can amitriptyline and the reducing the initial discretions: The metabolism can (CYP2D6 and CYP2	have a higher ple active metaboli lose with 50%.	asma concentra ite nortriptyline.	Consider	

Risk group	-

### **Comments:**

<sup>-</sup> Articles reporting kinetic effects published after 2017 were only included if they compared the exposure of amitripty-line + nortriptyline in IM, PM or UM with that in NM. Articles investigating amitriptyline and nortriptyline concentrations in other media than plasma (like hair) or post-mortem and cases without clinical effects of the variant genotype were not included in the risk analysis. In addition, an article only modelling data from another article was not included. These articles do not contribute enough to the evidence.

Moreover, the kinetic meta-analysis of Milosavljevic 2021 was not included in the risk analysis, because the meta-analysis included only 1 study for PM (Jiang 2002) and 1 study for IM (Steimer 2004), so does not add to the summaries of these two articles in the risk analysis (Milosavljevic F et al. Association of CYP2C19 and CYP2D6 poor and intermediate metabolizer status with antidepressant and antipsychotic exposure: a systematic review and meta-analysis. JAMA Psychiatry 2021;78:270-80. PMID: 33237321.)

In addition, the case report of Muhn 2022 was not included in this risk analysis, because the patient used the CYP-2C19 inhibitor omeprazole and 3 other drugs against neuropathic pain (gabapentin, pregabalin, duloxetine) concomitantly and improved pain control was achieved despite discontinuing amitriptyline (Muhn S et al. Pharmacogenomics and drug-induced phenoconversion informed medication safety review in the management of pain control and quality of life: A case report. J Pers Med 2022;12:974. PMID: 35743759). Because improved pain control was mainly achieved by switching the opioid analgetic from tramadol to buprenorphine and not by optimising amitriptyline therapy, it is not known whether the IM phenotype of the patient contributed to the absence of adequate pain control by ami\triptyline.

- Possible relationship between CYP2C19 polymorphisms and depression:
- Jukić MM et al. Elevated CYP2C19 expression is associated with depressive symptoms and hippocampal homeostasis impairment. Mol Psychiatry 2017;22:1155-1163. PubMed PMID: 27895323. This publication is from the same group as Sim 2010.

In a cohort of 3849 urban African-Americans of low economic status, the 123 CYP2C19\*2/\*2 subjects had a decrease in major depressive disorder prevalence compared to the other subjects with at least one active CYP-2C19 allele (23% versus 32%) (S). In addition, there was a trend for a lower Beck's Depression Inventory (BDI) score in the CYP2C19\*2/\*2 subjects compared to the other subjects (p = 0.074). However, the lifetime stress exposure was much larger in the African-American cohort compared with the previously analysed Swedish cohort (Sim 2010), thereby increasing the BDI score variability. After the most traumatized subjects (perceived stress scale score at higher quartile and above) were exempted from the analysis to better match the two samples, the BDI score reduction was significant (effect size = - 2.05 (-24.61%)) (S).

In order to test whether the CYP2C19 genotype influences suicidality in patients with major depressive disorder, CYP2C19 genotype was tested as a predictor for suicide intent in 209 Western European suicide attempters with major depressive disorder. As there were only two CYP2C19\*2/\*2 allele carriers in the cohort, it was not possible to test whether this genotype affects Beck's suicide intent scale-objective circumstances (SIS-OS) score. However, in a complementary exploratory analysis, the SIS-OS score seemed to vary between different CYP2C19 genotypes with a decrease for \*2/\*2 versus \*1/\*1 versus \*1/\*2 versus \*2/\*17 versus \*17/\*17 versus \*1/\*17. Further analysis showed that SIS-OS score was not significantly affected by the presence of the CYP2C19\*2 allele, whereas it was significantly increased in CYP2C19\*17 allele carriers (119 versus 90 subjects, effect size = +1.36 (+25.69%)) (S). Since the score was lower for the 8 patients with genotype \*17/\*17 compared to the patients with genotype \*1/\*17, this significant effect seemed to be mainly driven by the \*1/\*17 genotype. The classification of the suicide attempters to severe (SIS-OS score at higher quartile and above) and non-severe, yielded a higher frequency of patients with \*17 allele among severe suicide attempters (S).

The authors conclude that the CYP2C19\*2/\*2 genotype associates with a phenotype more resilient to major depressive disorder and that the CYP2C19\*17 allele may be a risk allele for suicidality in major depressive disorder. They indicate that a major limitation of the suicidality study is the absence of information regarding the individuals' drug treatment and their drug plasma levels. Therefore, it was not possible to determine whether the observed relationship was caused by endogenous or drug-metabolic CYP2C19-mediated effects.

- Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 2013;18:497-511. PubMed PMID: 22472876.
   A mega-analysis of genome-wide association studies found no significant association between the risk of depression and CYP2C19.
- Sim SC et al. Association between CYP2C19 polymorphism and depressive symptoms. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:1160-6. In a group of 1472 Europeans older than 44 years (1017x NM (637x \*1/\*1, 380x \*1/\*17), 375x IM (290x \*1/\*2, 85x \*2/\*17), 35x PM (\*2/\*2), 45x UM), significantly lower depressive symptoms (measured on the Center of Epidemiologic Studies Depression (CES-D) scale) were found among PM patients than among \*1/\*1. There was only a difference among people younger than 73 years and among men. The effect size was in the same order of magnitude as that observed between non-users and users of antidepressants. The authors stated that CYP2C19 polymorphisms may have an effect on depressive symptoms in adult Europeans.
- Existing guideline:

Hicks JK et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017;102:37-44. PubMed PMID: 27997040.

CPIC uses the same definitions of IM, PM and UM as we do. CPIC assigns \*2/\*17 and \*3/\*17 to the IM phenotype, because the currently available evidence indicates that the CYP2C19\*17 increased function allele is unable to completely compensate for the CYP2C19 no function alleles, but indicates that this is a provisional classification, However, CPIC uses a different definition for NM (only \*1/\*1). CPIC created a new phenotype rapid metaboliser (RM) for \*1/\*17. CPIC also has nomenclature, but no recommendations for genotypes with very uncommon alleles with lower activity, e.g. \*9 and \*10. The summary below uses the KNMP definitions for NM, PM, IM and UM.

CPIC states that the usual amitriptyline starting dose may be used in CYP2C19 \*1/\*1 and IM. Although CYP2C19 IM would be expected to have a modest increase in the ratio of amitriptyline to nortriptyline plasma concentrations, the evidence does not indicate that CYP2C19 IM should receive an alternate dose. CPIC classifies this recommendation as strong (i.e. "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"). CPIC states that patients taking amitriptyline who are CYP2C19 \*1/\*17 or UM may be at risk for having low plasma concentrations and an imbalance between parent drug and metabolites causing treatment failure and/or adverse events. However, CPIC states that the CYP2C19\*17 allele did not alter the sum of amitriptyline plus nortriptyline plasma concentrations (De Vos 2011). Despite this, CPIC states that extrapolated pharmacokinetic data suggest that CYP2C19 \*1/\*17 or UM may need a dose increase (Stingl JC et al. Genetic variability of drug metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psychiatry 2013;18:273-87). In addition, CPIC indicates that the CYP2C19\*17 allele was associated with higher nortriptyline plasma concentrations, possibly increasing the risk of adverse events (De Vos 2011). However, nortriptyline is registered for use in depression and neuropathic pain itself. Therefore, it seems unlikely that an increased conversion of amitriptyline into nortriptyline would result in an increase in adverse events necessitating therapy adjustment. CPIC states that due to the need for further studies investigating the clinical importance of CYP2C19\*17 regarding TCA metabolism and the possibility of altered concentrations, they recommend considering an alternative TCA or other drug not affected by CYP2C19. Due to limited available data, this recommendation is classified as optional (i.e. the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action). CPIC states that if amitriptyline is administered to a CYP2C19 \*1/\*17 or UM, therapeutic drug monitoring is recommended.

CPIC states that CYP2C19 PM are expected to have a greater ratio of amitriptyline to nortriptyline plasma concentrations (Shimoda 2002). Although the total concentration of amitriptyline and nortriptyline may be unchanged for a CYP2C19 PM in certain instances, CPIC states that the elevated amitriptyline plasma concentrations may increase the chance of a patient experiencing side effects. CPIC recommends to consider a 50% reduction of the usual amitriptyline starting dose along with therapeutic drug monitoring (Stingl JC et al. Genetic variability of drug metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psychiatry 2013;18:273-87). Although CPIC indicates that there is limited evidence demonstrating that a serotonergic/noradrenergic imbalance (i.e. amitriptyline/nortriptyline imbalance) influences outcomes and that therapeutic drug monitoring is based on the total concentration of amitriptyline and nortriptyline, this recommendation is classified as moderate (i.e. "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects).

The therapeutic recommendations for amitriptyline are indicated below:

Dosing recomm	endations for amitriptyline for conditions requiring higher doses such as depre	ession based on
CYP2C19 phen	otype <sup>a</sup>	
Phenotype	Therapeutic recommendation	Classification of recommendation
UM	Avoid amitriptyline use due to potential for sub-optimal response <sup>e</sup> . Consider alternative drug not metabolised by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine.  If amitriptyline is warranted, utilise therapeutic drug monitoring to guide dose adjustments. <sup>b</sup>	Optional <sup>d</sup>
*1/*17	Avoid amitriptyline use due to potential for sub-optimal response <sup>e</sup> .  Consider alternative drug not metabolised by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine.  If amitriptyline is warranted, utilise therapeutic drug monitoring to guide dose adjustments. <sup>b</sup>	Optional <sup>d</sup>
*1/*1	Initiate therapy with recommended starting dose.c	Strong
IM	Initiate therapy with recommended starting dose.c	Strong
PM	Avoid amitriptyline use due to potential for sub-optimal response <sup>e</sup> . Consider alternative drug not metabolised by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine.  For amitriptyline, consider a 50% reduction of the recommended starting dose. <sup>c</sup> Utilise therapeutic drug monitoring to guide dose adjustments. <sup>b</sup>	Moderate

<sup>&</sup>lt;sup>a</sup> Dosing recommendations only apply to higher initial doses of amitriptyline for treatment of conditions such as depression. For conditions at which lower initial doses are used, such as neuropathic pain, CPIC does recommend no dose modifications for PM or IM, because it is less likely that PM or IM will experience adverse effects due to supratherapeutic plasma concentrations of amitriptyline (Halling J et al. The CYP2D6 polymorphism in relation to the metabolism of amitriptyline and nortriptyline in the Faroese population. Br J Clin Pharmacol 2008;65:134-8). However, CPIC indicates that these patients should be monitored closely for side effects. In addition, if larger doses of TCA are warranted, CPIC recommends following the gene-based dosing quidelines in the table above.

For \*1/\*17 and UM, CPIC recommends considering an alternative agent, because pharmacokinetic data predict these patients to be at risk of failing amitriptyline therapy for neuropathic pain.

- <sup>b</sup> Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.
- <sup>c</sup> Patients may receive an initial low dose of a TCA, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.
- <sup>d</sup> The classification optional indicates that the desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- <sup>e</sup> Although the total concentration of amitriptyline and nortriptyline may be unchanged for a CYP2C19 ultra-rapid or poor metaboliser in certain instances, an imbalance between serotonergic and noradrenergic affect could influence clinical response or toxicities. There is limited evidence demonstrating that a serotonergic/noradrenergic imbalance influences outcomes, thus contributing to the classification of recommendations as optional or moderate.

As evidence linking CYP2C19 genotype with amitriptyline phenotype, CPIC mentions De Vos 2011, Koski 2006, Steimer 2005, Van der Weide 2005, Grasmäder 2004, Steimer 2004, Jiang 2002, Shimoda 2002, and Breyer-Pfaff 1992. All of these studies except for Koski 2006, Grasmäder 2004 and Breyer-Pfaff 1992 are included in our risk analysis. Koski 2006 was not included in our risk analysis because it concerns a post-mortem study. Grasmäder 2004 was not included, because the only data provided for amitriptyline separately, concerned a case without clinical effects of the variant genotype. Breyer-Pfaff 1992 was not included in our risk analysis, because it concerned a case without clinical effects of the variant genotype. CPIC indicates that these studies provide a high level of evidence for a decreased amitriptyline metabolism in PM and IM compared to \*1/\*1 (based on 8 references including Koski 2006 and Grasmäder 2004 for PM, and on 6 references including Koski 2006 for IM). In addition, De Vos 2011 provides a moderate level of evidence for an increased amitriptyline metabolism in UM compared to \*1/\*1 and Breyer-Pfaff 1992 a moderate level of evidence for a correlation of mephenytoin metabolism with amitriptyline metabolism.

CPIC also took other gene-based dosing recommendations in consideration, including the 2008 and 2011 publications of our dosing recommendations in Clinical Pharmacology and Therapeutics.

CPIC also provides therapeutic recommendations based on both CYP2D6 and CYP2C19 genotypes. For CYP2D6 UM and for CYP2D6 PM the therapeutic recommendations for the different CYP2C19 phenotypes are similar, reflecting the stronger influence of the CYP2D6 phenotype compared to the CYP2C19 phenotype. CPIC indicates that further studies are needed to develop moderate or strong dosing recommendations for TCAs when considering combined CYP2D6/CYP2C19 phenotypes. At the moment, insufficient data are available.

On 14-12-2023, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search: 14 December 2023.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics	PM	4 A	Yes	No	8 February 2024
Working Group decision	IM	4 A	Yes	No	
	UM	3 A	Yes	No	

#### Mechanism:

Amitriptyline is mainly converted by CYP2C19-mediated N-demethylation to the active metabolite nortriptyline. Both amitriptyline and nortriptyline are metabolised by CYP2D6 to 10-hydroxy metabolites, predominantly E-10-hydroxy metabolites. Amitriptyline is approximately three times as potent as E-10-OH-amitriptyline. Nortriptyline is approximately twice as potent as E-10-OH-nortriptyline.

N-oxidation and N-glucuronidation of amitriptyline also take place. Nortriptyline is converted by CYP2D6 and CYP-2C19 to the inactive metabolite didesmethylamitriptyline (desmethylnortriptyline).

Study results show an association between the sum of the concentrations of amitriptyline and nortriptyline with the efficacy of the therapy. The therapeutic range is 100-300 ng/ml and values higher than 400 ng/ml are considered to be toxic. An upper limit is indicated for the therapeutic range of nortriptyline (50-150 ng/ml), but not for the therapeutic range of amitriptyline (> 50 ng/ml). The Z-hydroxy metabolites can cause cardiotoxicity and plasma concentrations of Z-hydroxy nortriptyline or Z-hydroxy amitriptyline higher than 40 ng/ml are considered to be toxic.