CYP2C19: doxepine 6941-6943

AUC = area under the plasma concentration-time curve, Cl_{or} = oral clearance, C_{ss} = 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:
Doxepin is converted by CYP2C19, CYP1A2 and CYP3A4 to the active metabolite N-desmethyldoxepin (nordoxepin). Doxepin and the active metabolite N-methyldoxepin (nordoxepin) are primarily converted by CYP2D6 to inactive hydroxy metabolites.
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)).
PM and IM phenotypes affected doxepin clearance (Kirchheiner 2002). However, they did not affect the AUC of doxepin + nordoxepin, that determines efficacy and side effects. For this reason, the KNMP Pharmacogenetics Working Group decided that there is a gene-drug interaction, but no therapy adjustment is required (yes/no-interactions).
You can find a detailed overview of the observed kinetic 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.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Kirchheiner J et al. Contributions of CYP2D6, CYP2C9 and CYP2C19 to the biotransformation of E- and Z-doxepin in healthy volunteers. Pharmacogenetics 2002;12:571-80. PubMed PMID: 12360109.</td>
<td>3</td>
<td>22 healthy volunteers, selected for their genotype, received a single dose of doxepin 75 mg. The volunteers were CYP2D6 NM and CYP2C9 NM.
It was not mentioned that relevant comedication was excluded, but diseases, drug abuse and alcohol dependence were excluded. In addition, the volunteers were asked not to drink caffeine-containing beverages and to refrain from grapefruits for at least 3 days before and 1 day after taking doxepin.
The sample size was chosen to be sufficient to detect a difference of at least 30% in trough concentrations between the PM and the NM group using population variability data from the study of Burrows 1978 with a power of 80% and a type-I-error of 5%.

Genotyping:
- 8x NM
- 7x IM
- 7x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value</td></tr>
</table>
</td>
<td>Authors’ conclusion:
“CYP2C19 was involved in Z-doxepin metabolism with 2.5-fold differences in oral clearances (73 l h^{-1} in CYP2C19 PMs compared with 191 l h^{-1} in EMs).”

AUC doxepin + nordoxepin</td>
</tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td>PM: A
IM: A</td><td>
<table>
<tr><td></td><td></td><td></td><td>for NM</td></tr>
<tr><td rowspan="2">median AUC of doxepin+nordoxepin</td><td>x 1.00</td><td>x 0.90</td><td>1.43 pmol.h/ml</td></tr>
<tr><td colspan="2">NS for PM versus IM versus NM</td></tr>
<tr><td rowspan="4">median weight-corrected doxepin clearance</td><td>x 0.45</td><td>x 0.87</td><td>6.2 L/h.kg</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td colspan="2">CYP2C19 genotype had only a minor effect on E-doxepin clearance (with the clearance in PM being 83% of the clearance in NM), but in pharmacokinetic modelling a minor improvement was obtained by considering the CYP2C19 genotypes (S).</td></tr>
<tr><td colspan="2">CYP2C19 genotype had a stronger effect on Z-doxepin clearance (with the clearance in PM being 38% of the clearance in NM), but there was only a trend for significance in a population pharmacokinetic analysis (p = 0.06; NS), probably due to the large variation within the CYP2C19 PM group.</td></tr>
<tr><td>median $AUC_{0\text{-}48h}$ of nordoxepin</td><td colspan="2">NS for PM versus IM versus NM</td><td>1.28 pmol.h/ml</td></tr>
</table>

NOTE: Pharmaceutical doxepin is a mixture of 15% Z-doxepin and 85% E-doxepin.

NOTE: Genotyping was performed for *2. Next to *17, this is the most important gene variant in this German population.
</td><td>versus NM:
PM: 100%
IM: 90%</td></tr>
<tr><td>ref. 2
SmPC Silenor (doxepin) 29-10-20, USA.</td><td>0

PM: AA</td><td colspan="2"><u>Clinical pharmacology</u>:
Poor Metabolizers of CYPs
Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.</td><td></td></tr>
</table>

Risk group	-

Comments:

- <u>Possible relationship between CYP2C19 polymorphisms and depression</u>:
  - 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 uses amitriptyline as a representative TCA for this guideline. CPIC states that the results of the amitriptyline studies may apply to other TCAs because these drugs have comparable pharmacokinetic properties (the reviews Rudorfer MV et al. Metabolism of tricyclic antidepressants. Cell Mol Neurobiol 1999;19:373-409 and 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, extrapolated dose adjustments based on metaboliser status are similar across the tricyclic class (Stingl 2013). However, CPIC also states that the average extent of first-pass metabolism of TCAs is approximately 50%, although the average first-pass metabolism of doxepin may be closer to 70% (Rudorfer 1999).
For amitriptyline, CPIC states that the usual 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 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. Despite this, CPIC states that extrapolated pharmacokinetic data suggest that CYP2C19 *1/*17 or UM may need a dose increase. In addition, CPIC indicates that the CYP2C19*17 allele was associated with higher nortriptyline plasma concentrations, possibly increasing the risk of adverse events. 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. 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.

Because the TCAs have comparable pharmacokinetic properties, CPIC states that it may be reasonable to extrapolate the amitriptyline guideline to other TCAs, including doxepin, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.
Thus, the therapeutic recommendations for doxepin are identical to the therapeutic recommendations for amitriptyline with only the classification of the recommendations adapted to the fewer supporting clinical and pharmacokinetic data:

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

[a] Dosing recommendations only apply to higher initial doses of TCAs 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 the TCA. 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 guidelines 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 TCA therapy for neuropathic pain.
[b] Because the tricyclics have comparable pharmacokinetic properties, it may be reasonable to apply these amitriptyline recommendations to other tricyclics, including doxepin, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.
[c] 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.
[d] 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.
[e] 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.
[f] Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.

As evidence linking CYP2C19 genotype with doxepin phenotype, CPIC mentions Kirchheiner 2002 and Härtter 2002. Kirchheiner 2002 is included in our risk analysis, Härtter 2002 is not because it is an in-vitro study. CPIC indicates that Kirchheiner 2002 provides a moderate level of evidence for a significant correlation between the number of CYP2C19 no function alleles (*2) and oral clearance of doxepin. In addition, Härtter 2002 provides a moderate level of evidence that CYP2C19 contributes to the N-demethylation of doxepin.
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 5-1-2024, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search: 21 December 2023.

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

Mechanism:

Doxepin is converted by CYP2C19, CYP1A2 and CYP3A4 to the active metabolite N-desmethyldoxepin (nordoxepin). Doxepin and nordoxepin are primarily converted by CYP2D6 to inactive hydroxy metabolites.
The therapeutic range is 100-250 ng/ml for the sum of doxepin and nordoxepin and values higher than 400 ng/ml are considered to be toxic. The therapeutic range of doxepin is considered to be 50-150 ng/ml and of nordoxepin 50-100 ng/ml.