CYP2C19: clomipramine 6958-6960

AUC = area under the plasma concentration-time curve, clomi = clomipramine, Cl_{or} = oral clearance, C_{ss} = steady-state concentration, desmethylclomi = N-desmethylclomipramine, 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:
Clomipramine is mainly converted by CYP2C19, and to a lesser extent by CYP1A2 and CYP3A4, to the active metabolite desmethylclomipramine. Desmethylclomipramine lacks serotonin re-uptake activity and does not appear to contribute to the treatment of obsessive compulsive disorder and other anxiety disorders.Clomipramine and the active metabolite desmethylclomipramine are primarily converted by CYP2D6 to inactive hydroxy metabolites.
For depression, the therapeutic range is 200-400 ng/ml for the sum of clomipramine and desmethylclomipramine and values higher than 600 ng/ml are considered to be toxic. The therapeutic range of clomipramine is considered to be higher than 50 ng/ml and of desmethylclomipramine higher than 100 ng/ml.
For anxiety disorders, the therapeutic clomipramine plasmaconcentration is approximately 100 ng/ml in combination with a desmethylclomipramine plasma concentration below 200 ng/ml.
For obsessive compulsive disorder, the therapeutic range is a clomipramine plasmaconcentration higher than 200 ng/ml in combination with a desmethylclomipramine plasma concentration as low as possible.
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)).
The primary effects found for all phenotypes were effects on clomipramine exposure (De Vos 2011, Yokono 2001, and Nielsen 1994). The effects on clomipramine+ desmethylclomipramine AUC and C_{ss}, which determines the therapeutic effectiveness for depression and the side effects, were smaller and there was no evidence of significance (Vos 2023, De Vos 2011, Yokono 2001, and Nielsen 1994). None of the four studies investigated effectiveness and/or side effects. Based on the pharmacokinetic effect, the KNMP Pharmacogenetics Working Group decided that there is a gene-drug interaction. De Vos 2011 found an increase in the percentage of patients with subtherapeutic clomipramine concentrations for 10 UM compared to NM. Because also the expected higher desmethylclomipramine/clomipramine ratio in UM would decrease the chance of effectiveness for anxiety disorders and obsessive compulsive disorder, the KNMP Pharmacogenetics Working Group decided to recommend therapy adjustment in these cases (yes/yes-interaction). For PM and IM, the clomipramine exposure increased (Yokono 2001 and Nielsen 1994). However, the increase in the plasma concentration of clomipramine+desmethylclomipramine was small and significance was not shown (Vos 2023, De Vos 2011, Yokono 2001 and Nielsen 1994). In addition, no increase in the percentage of patients with supratherapeutic plasmaconcentrations (clomipramine+desmethylclomipramine > 400 ng/ml) was observed for 53 IM and 5 PM (De Vos 2011). Because the combination of higher clomipramine plasma concentrations without a marked increase in clomipramine+desmethylclomipramine plasma concentrations is expected to increase the chance of effectiveness in anxiety disorders and obsessive compulsive disorder without increasing the risk of adverse events, the KNMP Pharmacogenetics Working Group decided that no therapy adjustment is needed for IM and PM (yes/no-interactions).
A detailed justification of choices – including the justification of the recommendation for UM - is given below.

UM: De Vos 2011 found for 10 UM an increase in the percentage of patients with subtherapeutic clomipramine concentrations, but did not find a decrease in clomipramine/desmethylclomipramine ratio in these patients. In addition, they did not find a significant decrease in dose-corrected clomipramine plasma concentrations in 4 UM. However, significant differences in demethylation ratios for PM in all three studies confirm CYP2C19 to play an important role in demethylation of clomipramine. For this reason, the KNMP Pharmacogenetics Working Group considered the amount of evidence to be sufficient for a yes/yes-interaction.
Because the expected low clomipramine/desmethylclomipramine ratio in UM cannot be improved by dose

adjustment, the KNMP Pharmacogenetics Working Group decided to recommend an alternative drug for the indications anxiety disorders and obsessive compulsive disorder. Fluoxetine, fluvoxamine and paroxetine are not metabolised by CYP2C19.
The estimated dose-corrected plasma concentration of clomipramine+desmethylclomipramine for 4 UM was 90% of that in NM (De Vos 2011). This small effect argues against an important effect of the UM phenotype on effectiveness for the indication depression. Thus, the KNMP Pharmacogenetics Working Group decided that no therapy adjustment is required if clomipramine is used for this indication.

IM: Based on three studies with a total of 54 IM with known dose, the weighted mean of the dose-corrected plasma concentration of clomipramine+desmethylclomipramine was calculated to be 115% of that in NM (93-117%; median 114%) (Vos 2023, De Vos 2011, and Yokono 2001). This small effect and the lack of a difference in the percentage of patients with supratherapeutic plasma concentration of clomipramine+desmethylclomipramine for 53 IM compared to NM (De Vos 2011) argue against an important effect of the IM phenotype on adverse events and on effectiveness for the indication depression. As already indicated, the effect of the IM phenotype on clomipramine plasma concentration is expected to improve effectiveness for the indications anxiety disorders and obsessive compulsive disorder.

PM: Based on two studies with a total of 10 PM with known dose, the weighted mean of the dose-corrected plasma concentration of clomipramine+desmethylclomipramine was calculated to be 130% of that in NM (118-136%; median 127%) (De Vos 2011 and Yokono 2001). This percentage was reduced to 113% (111-118%; median 115%) if the metabolic ratios of all 11 PM were included in the calculation. In addition, a third study showed similar clomipramine+desmethylclomipramine AUC in PM and non-PM after single dosing in healthy volunteers (Nielsen 1994; study with 6 PM). This relatively small and uncertain effect and the lack of a difference in the percentage of patients with supratherapeutic plasma concentration of clomipramine+desmethylclomipramine for 5 PM compared to NM (De Vos 2011) argue against an important effect of the PM phenotype on adverse events and on effectiveness for the indication depression. As already indicated, the effect of the PM phenotype on clomipramine plasma concentration is expected to improve effectiveness for the indications anxiety disorders and obsessive compulsive disorder. For this reason, the KNMP Pharmacogenetics Working Group considered the evidence to be insufficient to recommend a therapy adjustment.

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.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting clomipramine to be potentially beneficial in patients with anxiety disorders and obsessive compulsive disorder. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 0 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):
No reports of a clinical effect in users of clomipramine with a variant phenotype were available. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for association with clinical effects with a severity code ≥ D corresponding to CTCAE grade ≥ 3).
The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).
The Summary of Product Characteristics (SmPC) Clomipramine HCl Mylan 13-2-2023 does not mention a CYP2C19 genotype or phenotype. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).

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 Vos CF et al. Effectiveness of genotype-specific tricyclic antidepressant dosing in	4	16 unipolar nonpsychotic major depressive disorder patients were treated with clomipramine 125 mg/day. Steady state plasma concentrations were determined (i.e., after 7 days without dose adjustment). The patient group was enriched in patients with a variant CYP2D6 phenotype, because 65% of CYP2D6 NM were not included.	

<table>
<tr>
<td>patients with major depressive disorder: a randomized clinical trial.
JAMA Netw Open 2023;6:e2312443.
PMID: 37155164.

ref. 1, continuation</td>
<td>IM: AA</td>
<td>Comedication affecting clomipramine pharmacokinetics (e.g. CYP2D6 inhibitors) and psychotropic comedication other than a benzodiazepine in a dose equivalent up to 4 mg lorazepam per day were excluded.

Genotyping:
- 14x NM
- 2x IM

Results:
<table>
<tr><td colspan="3">Result for IM compared to NM:</td></tr>
<tr><td></td><td></td><td>value for NM</td></tr>
<tr><td>plasma concentration of clomipramine + desmethylclomipramine</td><td>x 0.93 (significance not determined)</td><td>196.6 ng/ml</td></tr>
</table>
Note: Genotyping was for *1, *3 and *17. These are the most important gene variants in this Dutch population.</td>
<td>Plasma concentration of clomipramine + desmethylclomipramine versus NM:
IM: 93%</td>
</tr>
<tr>
<td>ref. 2
De Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J
2011;11:359-67.
PubMed PMID: 20531370.</td>
<td>3

IM: AA

PM: A

UM: A</td>
<td>Routine therapeutic drug monitoring was performed for 244 patients on clomipramine. Blood samples were drawn 12-16 h post-medication. The clomipramine dose was known in 151 patients. The dose varied from 25-300 mg/day, with an average of 115 mg/day.
Relevant co-medication was not excluded.
The mean age of UMs was significantly lower compared with the other genotype groups, while decreased age was associated with decreased dose-corrected steady state plasma concentration of clomipramine, decreased metabolic ratio and increased daily dose.

Genotyping:
- 176x NM (109x *1/*1, 67x *1/*17) (117 with known dose)
- 10x UM (4 with known dose)
- 53x IM (37x *1/*2, 16x *2/*17) (27 with known dose)
- 5x PM (3 with known dose)

Results:
<table>
<tr><td colspan="7">Results compared to *1/*1 (or NM):</td></tr>
<tr><td></td><td>PM</td><td>*1/*2</td><td>*2/ *17</td><td>*1/ *17</td><td>UM</td><td>value for *1/*1 (or NM)</td></tr>
<tr><td rowspan="2">dose-corrected C_{ss} clomipramine (ng/ml per mg)</td><td>x 1.62 (NS)</td><td>x 1.23 (NS)</td><td>x 1.38 (NS)</td><td>x 1.15 (NS)</td><td>x 1.08 (NS)</td><td>1.3</td></tr>
<tr><td>x 1.52 (NS)</td><td colspan="3">x 1.20 (NS)</td><td>x 1.01 (NS)</td><td>NM: 1.38</td></tr>
<tr><td rowspan="2">metabolic ratio (clomi/ desmethylclomi)</td><td>x 1.79 (S)</td><td>x 1.07 (NS)</td><td>x 0.86 (NS)</td><td>x 0.79 (NS)</td><td>x 1.21 (NS)</td><td>1.4</td></tr>
<tr><td>x 1.94 (S)</td><td colspan="3">x 1.10 (NS)</td><td>x 1.32 (NS)</td><td>NM: 1.29</td></tr>
<tr><td>% with subtherapeutic C_{ss} (clomi < 50 ng/ml)</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>x 4.4 (S)</td><td>4.6%</td></tr>
</table>
</td>
<td>Authors' conclusion:
'No clear correlation was found between CYP-2C19 genotype and clomipramine metabolism.'

Trough plasma concentration of clomipramine versus NM:
PM: 152%
IM: 120%
UM: 101%</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td></td>
<td>
<table>
<tr><td>% with suprathe-rapeutic C_{ss} (clomi + desme-thylclomi > 400 ng/ml)</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>19%</td></tr>
<tr><td>dose (mg/day)</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>120</td></tr>
<tr><td>C_{ss} clomi-pramine (ng/ml)</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>145</td></tr>
<tr><td>C_{ss} des-methylclo-mipramine (ng/ml)</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td><td>157</td></tr>
<tr><td rowspan="2">dose-corrected C_{ss} clo-mipramine+des-methylclo-mipramine, cal-culated from the mean values for cor-rected C_{ss} clo-mipramine and the meta-bolic ra-tio (ng/ml per mg)</td><td>x 1.32 (NS)</td><td>x 1.20 (NS)</td><td>x 1.48 (NS)</td><td>x 1.28 (NS)</td><td>x 1.00 (NS)</td><td>2.23</td></tr>
<tr><td>x 1.18 (NS)</td><td colspan="2">x 1.14 (NS)</td><td></td><td>x 0.90 (NS)</td><td>NM: 2.48</td></tr>
</table>

NOTE: The relationship between clomipramine concentration and dose was non-linear; a trend was observed for higher levels with higher dose, whereas the dose-corrected concen-tration value decreased with increased doses.

NOTE: Genotyping was for *2 and *17. These are the most important gene variants in this Dutch population.
</td>
<td>Estimated plasma concentration of clomipramine+des methylclomipramine versus NM:
PM: 118%
IM: 114%
UM: 90%</td>
</tr>
<tr>
<td>ref. 3
Yokono A et al.
The effect of CYP-2C19 and CYP2D6 genotypes on the metabolism of clomi-pramine in Japa-nese psychiatric patients.
J Clin Psychophar-macol 2001;21:549-55.
PubMed PMID: 11763000.</td>
<td>4</td>
<td>51 patients were treated with a stable dose of clomipramine for at least 2 weeks. Doses ranged from 10 to 250 mg/day. Blood samples were drawn 8-17.5 hours after the evening dose.
Neuroleptics and barbiturates were excluded, because they affect clomipramine metabolism. Benzodiapines were not excluded. Patients did not have any general medical condi-tions.
Multiple regression analyses included age, gender, and the number of variant alleles of CYP2C19 and CYP2D6.

Genotyping:
- 18x NM
- 25x IM</td>
<td>Authors' conclu-sion:
'These results suggest that genotyping CYP-2C19 is useful for grossly predic-ting the risk of getting high plas-ma concentra-tions of clomipra-mine and the low individual capacity to demethylate clomipramine</td>
</tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>PM: A
IM: A</td>
<td>- 8x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>dose- and weight corrected C_{ss} clomipramine</td><td>x 1.76 (S)
5 of the 8 PM had corrected C_{ss} close to or below the mean in NM</td><td>x 1.41 (S)</td><td>57.4 ng/ml per mg/kg</td></tr>
<tr><td></td><td colspan="2">Multiple regression analysis did not show a significant correlation between the number of CYP2C19 variant alleles and the corrected C_{ss} (NS).</td><td></td></tr>
<tr><td>metabolic ratio (clomi/desmethylclomi)</td><td>x 1.68 (S)
1 PM with a value of 9.61 was excluded from the calculation based on the Smirnov test for the extreme value</td><td>x 1.44 (S)</td><td>0.81</td></tr>
<tr><td></td><td colspan="2">Multiple regression analysis showed the number of CYP-2C19 variant alleles to be a significant predictor for the metabolic ratio (S). Age and the number of CYP2C19 variant alleles together explained 21% of the variability in the metabolic ratio.</td><td></td></tr>
<tr><td>dose- and weight-corrected C_{ss} clomipramine+desmethylclomipramine, calculated from the mean values for C_{ss} clomipramine and the metabolic ratio</td><td>x 1.36 (NS)
If the PM with the very high metabolic ratio would not have been excluded, this would have been x 1.11 (NS).</td><td>x 1.17 (NS)</td><td>128 ng/ml per mg/kg</td></tr>
</table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Japanese population.</td>
<td>because there is marked interindividual variability within each genotype.’

Plasma concentration of clomipramine versus NM:
PM: 176%
IM: 141%

Estimated plasma concentration of clomipramine+desmethylclomipramine versus NM:
IM: 117%
PM: 136%
(111% if also the metabolic ratio of the 8th patient was included in the calculation)</td>
</tr>
<tr>
<td>ref. 4
Nielsen KK et al. Single-dose kinetics of clomipramine: relationship to the sparteine and S-mephenytoin oxidation polymorphisms. Clin Pharmacol Ther 1994;55:518-27. PubMed PMID:</td>
<td>3</td>
<td>25 healthy volunteers selected for their CYP2C19 and CYP-2D6 phenotype received a single dose of 100 mg clomipramine.
All volunteers experienced in mild to moderate extent one or more side effects, such as nausea, sedation, dry mouth, dizziness, vertigo, headache, and loss of appetite. Nine volunteers vomited between 1 and 4 hours after drug intake, but there was no systematic difference in the clearance of clomipramine between those volunteers and those who did not vomit.
The demethylation index was defined as ($AUC_{0\text{-}48h}$ desmethyl-</td>
<td>Authors’ conclusion:
’Our data thus provide evidence that the 2- and 8-hydroxylation of clomipramine are catalyzed by CYP2D6 and that the N-demethylation is catalyzed</td>
</tr>
</table>

<table>
<tr>
<td>8181196.

ref. 4, continuation</td>
<td>PM: A</td>
<td>clomipramine + AUC_{0-48h} unconjugated 8-hydroxydesmethyl-clomipramine)/(AUC_{0-48h} clomipramine + AUC_{0-48h} unconjugated 8-hydroxyclomipramine).
Co-medication and alcohol were excluded.

Genotyping:
- 19x NM# (10 CYP2D6 NM# and 9 CYP2D6 PM)
- 6x PM (5 CYP2D6 NM# and 1 CYP2D6 PM)

Results:
<table>
<tr><td colspan="4">Results compared to NM#:</td></tr>
<tr><td></td><td>CYP2D6 pheno-type</td><td>PM</td><td>value for NM#</td></tr>
<tr><td rowspan="2">clomipramine clearance</td><td>NM#</td><td>x 0.60 (S for the median values)</td><td>114 L/h</td></tr>
<tr><td>PM</td><td>x 0.64</td><td>68 L/h</td></tr>
<tr><td rowspan="2">median demethylation index</td><td>NM#</td><td>x 0.14 (S)</td><td>0.42</td></tr>
<tr><td>PM</td><td>x 0.61</td><td>0.57</td></tr>
<tr><td rowspan="3">$AUC_{0-\infty}$ clomi-pramine+des methylclomi-pramine</td><td>NM#</td><td colspan="2">similar for PM and NM# (median for both approxima-tely 4 nmol.hr/ml)</td></tr>
<tr><td>PM</td><td colspan="2">higher value for PM (approxi-mately 30 nmol.hr/ml) than for NM# (median approxima-tely 17 nmol.hr/ml)</td></tr>
<tr><td colspan="3">Note: AUC0-∞ clomipramine+desmethyl-clomipramine is only depicted graphically in the article. No values are given.</td></tr>
</table>

NOTE: Patients were phenotyped with mephenytoin instead of genotyped. Phenotyping cannot distinguish between NM, IM and UM. For this reason NM# = NM+IM+UM.</td>
<td>in part by CYP-2C.’

Clearance of clomipramine versus NM#:
PM: 60%</td>
</tr>
</table>

Risk group	IM and PM with CYP2D6 PM or CYP2D6 inhibitors, UM with CYP2D6 UM, IM and PM with CYP2C19 inhibitors, UM with CYP2C19 inducers

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).
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 clomipramine, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.
Thus, the therapeutic recommendations for clomipramine 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 clomipramine for conditions requiring higher doses such as depression based on CYP2C19 phenotype[a,b]

Phenotype	Therapeutic recommendation	Classification of recommendation
UM	Avoid clomipramine 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 clomipramine is warranted, utilise therapeutic drug monitoring to guide dose adjustments.[f]	Optional[d,e]
*1/*17	Avoid clomipramine 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 clomipramine 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 clomipramine 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 clomipramine, 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 clomipramine, 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 clomipramine phenotype, CPIC mentions De Vos 2011, Yokono 2001 and Nielsen 1994. All three studies are included in our risk analysis. CPIC indicates that these studies provide a high level of evidence for a decreased clomipramine metabolism in PM and IM compared to *1/*1 (based on all three references for PM and on Yokono 2001 for IM). In addition, De Vos 2011 provides a moderate level of evidence for the absence of significant differences in clomipramine metabolism in IM and *1/*17 compared to *1/*1 and for a higher frequency of clomipramine concentrations below the therapeutic range in UM.
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 5-1-2023, 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	4 A	Yes	No	8 February 2024
	IM	4 A	Yes	No	
	UM	3 A	Yes	Yes	

Mechanism:
Clomipramine is mainly converted by CYP2C19, and to a lesser extent by CYP1A2 and CYP3A4, to the active metabolite desmethylclomipramine. Desmethylclomipramine lacks serotonin re-uptake activity and does not appear to contribute to the treatment of obsessive compulsive disorder and other anxiety disorders.Clomipramine and the active metabolite desmethylclomipramine are primarily converted by CYP2D6 to inactive hydroxy metabolites.
For depression, the therapeutic range is 200-400 ng/ml for the sum of clomipramine and desmethylclomipramine and values higher than 600 ng/ml are considered to be toxic. The therapeutic range of clomipramine is considered to be higher than 50 ng/ml and of desmethylclomipramine higher than 100 ng/ml.
For anxiety disorders, the therapeutic clomipramine plasmaconcentration is approximately 100 ng/ml in combination with a desmethylclomipramine plasma concentration below 200 ng/ml.
For obsessive compulsive disorder, the therapeutic range is a clomipramine plasmaconcentration higher than 200 ng/ml in combination with a desmethylclomipramine plasma concentration as low as possible.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	0+
Corresponding Clinical Implication Score:		Potentially beneficial