CYP2D6: imipramine 2391-2393

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, C_{ss} = plasma concentration in steady state, CTCAE = common terminology criteria for adverse events, DI = desipramine, HI = 2-hydroxy imipramine, I = imipramine, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, TCA = tricyclic antidepressant, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 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:
Imipramine and the active metabolite desipramine are primarily converted by CYP2D6 to inactive hydroxy metabolites.
Genetic variants in CYP2D6 can result in a decreased CYP2D6 enzyme activity (intermediate metabolisers (IM)), an absent CYP2D6 enzyme activity (poor metabolisers (PM)) or an increased CYP2D6 enzyme activity (ultra-rapid metabolisers (UM)).
Kinetic studies showed differences in imipramine + desipramine exposure for patients with CYP2D6 gene variants (Schenk 2008, Koyama 1994, Sindrup 1990 and Brosen 1986). A case report suggests an increased risk for toxic plasma concentrations and adverse events in PM (Balant-Gorgia 1989). A study showed a stronger increase in the electrical single pain detection threshold for IM compared to NM, but no difference in 10 other experimental pain thresholds (Schliessbach 2018). Vos 2023 did not find CYP2D6 and CYP2C19 genotype-guided therapy in 3 patients to decrease the time to therapeutic plasma concentration. However, in this study, the mean plasma concentration of imipramine + desipramine in NM on normal dose (175 mg/day) was subtherapeutic, suggesting that the chosen normal dose and the genotype-guided doses calculated from it were actually too low. Because imipramine has a narrow therapeutic range, changes in exposure are likely to have therapeutic consequences. For these reasons, the KNMP Pharmacogenetics Working Group decides that a gene-drug interaction is present and that dose adjustments are required for PM, IM and UM (yes/yes-interactions).
Justification of recommendations per CYP2D6 phenotype
Dose adjustments have been calculated on the basis of the AUC or C_{ss} for imipramine + desipramine.

PM: The weighted mean of the calculated dose adjustment – based on a total of 16 PM from 3 studies (Schenk 2008, Koyama 1994, and Brosen 1986) – is a dose reduction to 31% of the normal dose (21%-37%; median 24%). This was rounded off to 30% to be more achievable in clinical practice. The plasma concentration or efficacy and adverse events should be monitored in order to set the maintenance dose.

IM: The weighted mean of the calculated dose adjustment – based on a total of 71 IM from 2 studies (Vos 2023 and Schenk 2008) – is a dose reduction to 67% of the normal dose (41%-68%; median 55%). This was rounded off to 70% to be more achievable in clinical practice.
The plasma concentration or efficacy and adverse events should be monitored in order to set the maintenance dose.

UM: The calculated dose adjustment – based on one study with 11 UM (Schenk 2008) – is a dose increase to 170% of the normal dose. The plasma concentration or efficacy and adverse events should be monitored in order to set the maintenance dose.
An alternative can be selected as a precaution due to the absence of knowledge about the effects of high concentrations of the possible cardiotoxic hydroxy metabolites.

Note: The kinetics of imipramine and the metabolite desipramine are non-linear at a therapeutic dose, due to saturation of the metabolism via CYP2D6. Therefore, dose adjustments that are calculated based on linearity of the kinetics can be too high.
You can find an overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background

information 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 imipramine to be potentially beneficial for the prevention of side effects. 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 severe clinical effects were observed in users of imipramine with a variant phenotype. The maximum severity code was C corresponding to CTCAE grade 2. 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 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 American Summary of Product Characteristics (SmPC) of imipramine mentions the CYP2D6 PM phenotype, but the Dutch SmPC (SmPC Imipramine HCl CF 31-8-2021) does not. 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 (Dutch) SmPC).

The table below follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore 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 patients with major depressive disorder: a randomized clinical trial. JAMA Netw Open 2023;6:e2312443. PMID: 37155164.	4	3 unipolar nonpsychotic major depressive disorder patients received at least one dose of CYP2D6 and CYP2C19 genotype-guided imipramine treatment and 3 patients received at least one dose of not genotype-guided imipramine treatment. Plasma concentrations and genotypes were reported for 2 patients in the genotype-guided arm and 3 patients in the not genotype-guided arm. The dosing recommendation in the not genotype guided treatment arm was 175 mg/day. The dosing recommendations in the genotype-guided treatment arm were according to the 2022 KNMP Pharmacogenetics Working Group guidelines except for patients having both the CYP2C19 PM phenotype and a variant CYP2D6 phenotype receiving nortriptyline instead of imipramine with both dose adaptations and being randomised to the nortriptyline arm of the study: 175 mg/day (100%) for CYP2D6 NM, 125 mg/day (70%) for CYP2D6 IM, 50 mg/day (30%) for CYP2D6 PM, 300 mg/day (170%) for CYP2D6 UM, 175 mg/day (100%) for CYP2C19 NM, IM and UM, and 125 mg/day (70%) for CYP2C19 PM. 96.4% of patients initiated treatment with the recommended dose and all patients attained the recommended dose within the first week of treatment. Steady state plasma concentrations were determined (i.e., after 7 days without dose adjustment). In cases of subtherapeutic or supratherapeutic plasma concentrations, dose adjustments were made based on linear kinetics until a therapeutic drug concentration was reached. Follow-up was for 7 weeks. In both treatment arms, therapeutic drug monitoring was weekly, which is more often than usual (in clinical practice, it takes several weeks until plasma concentrations are measured). Comedication affecting imipramine pharmacokinetics	Authors' conclusion: 'In this randomized clinical trial, pharmacogenetics-informed treatment resulted in faster attainment of therapeutic TCA concentrations. No effect was observed for imipramine.'

ref. 1, continuation

Genotype-guided versus not genotype-guided treatment: AA

(e.g. CYP2D6 inhibitors) and psychotropic comedication other than a benzodiazepine in a dose equivalent up to 4 mg lorazepam per day were excluded.
Based on the assumption that 50% of the not genotpe-guided group would reach a therapeutic plasma concentration within 4 weeks and that 50% of the genotype-guided group would reach a therapeutic concentration within 2 weeks, a power of 80% was calculated to require a sample size of 44 patients per treatment arm. Based on the mean reduction of adverse event scores reported previously, a power of 80% was calculated to require a sample size of 63 patients per treatment arm.

Genotyping CYP2D6:

Genotype-guided arm	Not genotype-guided arm
- 1x NM (CYP2C19 PM)	- 2x NM (CYP2C19 NM)
- 1x IM (CYP2C19 NM)	- 1x IM (CYP2C19 NM)

Results:

Results for genotype-guided treatment compared to not genotype-guided treatment:			
time to therapeutic plasma concentration		NS	
plasma concentration imipramine + desipramine	NM	x 1.18 (NS)	77.0 ng/ml
	IM	x 0.35 (NS) The plasma concentration was therapeutic (150-300 ng/ ml) on the not genotype-guided dose and subtherapeutic on the genotype-guided dose.	186.0 ng/ml
	Note: On the not-genotype guided dose, the mean plasma concentration was subtherapeutic (<150 ng/ml) in NM and therapeutic in IM (150-300 ng/ ml). This indicates that genotype-guided treatment, i.e. adjusting the dose such that the plasma concentration will be equal to that in NM is predicted to decrease the percentage of IM having a therapeutic plasma concentration on the recommended dose.		

Results compared to NM (significance not determined):		
	IM	value for NM
plasma concentration of imipramine + desipramine at a dose of 175 mg/day	x 2.42 (NS)	77.0 ng/ml
plasma concentration of imipramine + desipramine at the genotype-guided dose	x 0.73 (NS)	91.0 ng/ml

plasma concentration of imipramine + desipramine versus NM:
IM: 242%

<table>
<tr><td>ref. 1, continuation</td><td></td><td>Note: Genotyping was for *1 through *11, *15, *17, *29, *35, *41, and gene duplication. These are the most important gene variants in this Dutch population.</td><td></td></tr>
<tr><td>ref. 2
Schliessbach J et al. Effect of single-dose imipramine on chronic low-back and experimental pain. A randomized controlled trial. PLoS One 2018;13:e0195776. PubMed PMID: 29742109.</td><td>3

IM: AA#</td><td>In a cross-over study, 46 patients with chronic low-back pain were subjected to experimental pain after a single dose of either imipramine 75 mg or tolteridine 1 mg (active placebo). Tolteridine lacks anti-nociceptive effects, but mimics some of the sedative side effects of imipramine such as blurred vision, drowsiness and sleepiness. The patients had chronic low-back pain of at least 3 months duration and a pain intensity at rest ≥ 3 on a 10-point rating scale.
Experimental pain tests were performed before and one and two hours after drug administration. All tests were performed at the more painful body side. Pressure pain detection and tolerance thresholds were measured at the second toe. Detection thresholds for electrical single pain and repeated pain (with 5 stimuli at 2 Hz inducing temporal summation) were measured in the innervation area of the sural nerve. After hand immersion in ice water, the time until cold pain reached an intensity of 7 on a 10-point rating scale was measured. Heat pain detection and tolerance thresholds and cold pain detection threshold were measured at the leg and forearm. The heat stimulus was limited to a maximum of 50.5°C. Cold pain detection threshold was dichotomized into patients with a threshold of 0°C (cold pain detection threshold at 0°C) and patients with a threshold above 0°C. For all tests, triplicate measurements were recorded.
Co-medication with antidepressants, opioids or anticonvulsants and intake of centrally active substances (including drug or alcohol abuse) were excluded. Analgesic medication had to be stopped one week before the first experiment. Only acetaminophen or ibuprofen were allowed as rescue medication until 24 hours before the experiments. Co-medication with CYP2D6 inhibitors or inducers was not excluded.

Genotyping:
- 26x NM
- 20x IM

Results:
<table>
<tr><td colspan="4">Imipramine/tolteridine ratio compared to NM:</td></tr>
<tr><td colspan="2"></td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="3">electrical single pain detection threshold</td><td>1 hr</td><td>x 1.17</td><td>1.03</td></tr>
<tr><td>2 hr</td><td>x 1.16</td><td>0.99</td></tr>
<tr><td></td><td>S for both time points combined</td><td></td></tr>
<tr><td rowspan="2">electrical repeated pain detection threshold</td><td>1 hr</td><td rowspan="2">trend for an increase for both time points combined (NS, p = 0.079)</td><td>0.97</td></tr>
<tr><td>2 hr</td><td>0.95</td></tr>
<tr><td rowspan="2">pressure pain detection threshold</td><td>1 hr</td><td rowspan="2">trend for an increase for both time points combined (NS, p = 0.054)</td><td>0.99</td></tr>
<tr><td>2 hr</td><td>0.96</td></tr>
<tr><td>pressure pain tole-</td><td>1 hr</td><td>NS for both time</td><td>0.98</td></tr>
</table>
</td><td>Author’s conclusion: ”Anti-nociceptive effects as assessed by quantitative sensory tests may depend on CYP2D6 genotype, indicating that metabolizer status should be accounted for when future studies with tricyclic antidepressants are undertaken.”</td></tr>
</table>

<table>
<tr><td>ref. 2, continuation</td><td></td><td>
<table>
<tr><td>rance threshold</td><td>2 hr</td><td>points combined</td><td>1.04</td></tr>
<tr><td rowspan="2">time until cold pain reaches intensity 7 on a 10-point scale</td><td>1 hr</td><td>NS for both time points combined</td><td>1.05</td></tr>
<tr><td>2 hr</td><td></td><td>1.03</td></tr>
<tr><td rowspan="2">heat pain detection threshold (leg)</td><td>1 hr</td><td>NS</td><td>0.77</td></tr>
<tr><td>2 hr</td><td>NS</td><td>1.95</td></tr>
<tr><td rowspan="2">heat pain detection threshold (arm)</td><td>1 hr</td><td>NS</td><td>0.85</td></tr>
<tr><td>2 hr</td><td>NS</td><td>0.94</td></tr>
<tr><td rowspan="2">heat pain tolerance threshold (leg)</td><td>1 hr</td><td>NS</td><td>0.77</td></tr>
<tr><td>2 hr</td><td>NS</td><td>1.04</td></tr>
<tr><td rowspan="2">heat pain tolerance threshold (arm)</td><td>1 hr</td><td>NS</td><td>1.35</td></tr>
<tr><td>2 hr</td><td>NS</td><td>1.08</td></tr>
<tr><td rowspan="2">cold pain detection threshold (leg) at 0°C</td><td>1 hr</td><td>NS</td><td>1.08</td></tr>
<tr><td>2 hr</td><td>NS</td><td>1.06</td></tr>
<tr><td rowspan="2">cold pain detection threshold (arm) at 0°C</td><td>1 hr</td><td>NS</td><td>0.90</td></tr>
<tr><td>2 hr</td><td>NS</td><td>1.53</td></tr>
</table>

NB: Genotyping was for *3-*6, *8, *10, *41 and gene multiplication. These are the most important gene variants in this Swiss population. *3, *6 and *8 were not detected in this patient group. 3 PM and 1 UM were excluded from the study.
</td><td></td></tr>
<tr><td>ref. 3
Schenk PW et al.
Association of graded allele-specific changes in CYP2D6 function with imipramine dose requirement in a large group of depressed patients.
Mol Psychiatry 2008;13:597-605.</td><td>4

PM: A
IM: A

UM: A</td><td>The gene dose was determined in a retrospective study of 181 patients (10x 0; 15x 0.5; 55x 1; 28x 1.5; 62x 2; 11x >2) on imipramine 40-900 mg/day. Relevant co-medication was excluded. The dose of imipramine was based on a target value of 200-300 µg/mL for Css I+DI.

Css I+DI / dose varies significantly per gene dose:
0: 2.84x10^{-3}/L
0.5: 1.91x10^{-3}/L
1: 1.43x10^{-3}/L
1.5: 1.21x10^{-3}/L
2: 0.96x10^{-3}/L
>2: 0.61x10^{-3}/L

The calculated imipramine dose for a Css I+DI of 250 µg/mL differs significantly per gene dose:
0: 131 mg/day
0.5: 155 mg/day
1: 217 mg/day
1.5: 245 mg/day
2: 326 mg/day
>2: 509 mg/day

NOTE: The actual mean dose for gene dose >2 was 309 mg/day. Therefore, there is little experience with the use of very high doses for UM.</td><td>Authors' conclusion: 'Faster dose adjustment may lead to a reduced number of adverse drug reactions and faster recovery and, therefore, shortened hospitalization. Based on our present data we would thus recommend our protocol for CYP2D6 genotyping before the start of IMI pharmacotherapy.'

Css[a] I + DI versus NM (gene doses 1.5 and 2):
PM (gene dose 0): 274%
IM (0.5 and 1): 148%
UM (>2): 59%</td></tr>
<tr><td>ref. 4
Koyama E et al.
Metabolic disposition of imipramine in oriental subjects: relation to metoprolol alpha-hydroxylation and S-mephenytoin 4'-hydroxylation phenotypes.
J Pharmacol Exp Ther 1994;271:860-7.</td><td>3

PM: A</td><td>A total of eleven (11) healthy volunteers (7x NM, 4x PM (phenotyping with metoprolol), all CYP2C19 NM) received a single dose of imipramine 25 mg.

PM versus NM:
- AUC I+DI increased from 327 to 1383 ng/mL per hour (S by 323%).

NOTE: genotype unknown</td><td>AUC I + DI versus NM:
PM: 423%</td></tr>
</table>

ref. 5 Sindrup SH et al. Nonlinear kinetics of imipramine in low and medium plasma level ranges. Ther Drug Monit 1990;12:445-9.	4 PM: A UM: A IM: A	19 diabetics with neuropathy, 1x "rapid NM" (MR of sparteine 0.14), 15x NM (MR of sparteine 0.18-3.5), 1x "slow NM" (MR of sparteine 6.4), 2x PM (MR of sparteine > 20), no relevant co-medication; Required dose for Css I+DI 300-500 nM: - PM: 20-25 mg/day for therapeutic concentration - rapid NM: 350 mg/day - slow NM: 50 mg/day NOTE: genotype unknown	
ref. 6 Balant-Gorgia AE et al. High blood concentrations of imipramine or clomipramine and therapeutic failure: a case report study using drug monitoring data. Ther Drug Monit 1989;11:415-20.	2 PM: C	8 patients, 4 received imipramine. 3 of them received a CYP2D6 inhibitor as co-medication (thioridazine and levomepromazine), therefore not described here. - patient 1: received imipramine 150 mg/day, no improvement of depression, did experience side effects and orthostatic hypotension. The patient was found to be a PM. Css imipramine = 125 ng/mL and Css DI 1730 ng/mL, Css I+DI = 1855 ng/mL. The side effects disappeared following the re-start of the therapy with imipramine 25 mg/day. Css I+DI = 160 ng/mL. NOTE: genotype unknown	
ref. 7 Brosen K et al. Imipramine demethylation and hydroxylation: impact of the sparteine oxidation phenotype. Clin Pharmacol Ther 1986;40:543-9.	3 PM: A IM: AA	18 healthy volunteers, 6x "rapid NM" (MR of sparteine 0.22-0.33), 6x "slow NM" (MR of sparteine 0.72-0.99), 6x PM (MR of sparteine 62-179), no co-medication, a single dose of 100 mg imipramine; - PM: decrease in Cl_{or} imipramine versus "rapid NM" from 2.55 to 1.35 L/min (S by 47%), increase in t½ from 16 to 23 hours. Increase in AUC ratio DI/I from 0.89 to 6.8 (S by 664%), no OH metabolite detectable. - "slow NM": decrease in Cl_{or} imipramine versus "rapid NM" from 2.55 to 2.28 L/min (NS by 11%), t½ unchanged. Increase in AUC ratio DI/I from 0.89 to 1.6 (NS by 80%), decrease in AUC ration HI/I from 0.40 to 0.23 (S by 43%). NOTE: PM homozygote recessive, genotype of other volunteers unknown	
ref. 8 Brosen K et al. Steady-state concentrations of imipramine and its metabolites in relation to the sparteine/ debrisoquine polymorphism. Eur J Clin Pharmacol 1986;30:679-84.	4 (2) PM: A	35 patients, 33x NM, 2x PM, no relevant co-medication, with imipramine dose 100 mg/day; - PM: increase in C_{ss} imipramine versus NM from 169 to 378.5 nM (NS by 124%), increase in C_{ss} desipramine from 212 to 1434.5 nM (NS by 578%). Sum concentration I+DI was elevated by 376%. C_{ss} ratio HI/I and HDI/DI both decreased, from 0.25 to 0.055 and from 0.57 to 0.065 respectively (NS by 78% and 86% respectively). With dose based on Css I+DI = 700-900 nM: - PM: 1x 50 mg/day, other patient did not want to go lower than 100 mg/day, despite toxic concentrations. - NM: 50-400 mg/day NOTE: genotype unknown	Authors' conclusion: 'We therefore conclude that the sparteine/debrisoquine polymorphism is an important determinant of therapeutic outcome and toxicity during treatment with standard doses of imipramine' Css I+DI versus NM: PM: 476%
ref. 9 SmPC Tofranil-PM	0	<u>Drug interactions</u>: *Drugs metabolized by P450 2D6*	

(imipramine) 28-07-14, USA. **ref. 9, continuation**	PM: A	The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).	

[a]: corrected for dose.
NOTE: Phenotyping usually does not distinguish between IM, NM and UM. Therefore, in these studies, NM is usually equal to IM+NM+UM.

Risk group	IM with CYP2D6 inhibitor, UM with CYP2D6 inducer

Comments:

- 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 and October 2019 update on the CPIC site (modifications to CPIC’s prior system of genotype-phenotype translation, including downgrading the value assigned to the CYP2D6*10 allele for activity score calculation from 0.5 to 0.25 and changing the phenotype assignment for an activity score of 1 from normal metaboliser to intermediate metaboliser).
  CPIC uses the same definition for NM, IM and PM as we do. However, CPIC uses a different definition for UM (gene dose ≥ 2.5 instead of ≥ 2.75), because CPIC did not decide to include gene dose 2.5 in NM until most laboratories can determine which allele has been duplicated and therefore can distinguish between e.g. *1x2/*41 (gene dose 2.5) and *1/*41x2 (gene dose 2). The summary below uses the KNMP definition 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). CPIC also uses amitriptyline as a representative for imipramine, although literature suggests that the clearance of TCAs is mostly a linear process, but saturation of the hydroxylation pathway may occur at higher plasma concentrations for certain TCAs, including imipramine and desipramine (Rudorfer 1999 and Cooke RG et al. The nonlinear kinetics of desipramine and 2-hydroxydesipramine in plasma. Clin Pharmacol Ther 1984;36:343-9).
  For amitriptyline, CPIC states that the recommended starting dose does not need dose adjustment for NM. In addition, CPIC states that a 25% reduction of the recommended dose may be considered for patients with a CYP2D6 gene dose of 0.5. As a reference for this percentage reduction they mention the 2011 publication of our dosing recommendations in Clinical Pharmacology and Therapeutics. However, this dosing recommendation is primarily based on patients with gene dose 1. In addition, we changed the percentage reduction in 2011 from 25% to 40%, based on the switch from using the sum of the plasma concentrations of amitriptyline and nortriptyline to using the plasma concentration of nortriptyline for dose calculations. Because patients with a CYP2D6 activity score of 1.0 are inconsistently categorised as intermediate or normal metabolisers in the literature, making these studies difficult to evaluate, CPIC classified the strength of the recommendation for gene dose 0.5 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). After the October 2019 update, CPIC states that a 25% reduction of the recommended dose may also be considered for patients with a CYP2D6 gene dose of 1.
  CPIC states that CYP2D6 ultra-rapid metabolisers + gene dose 2.5 have a higher probability of failing amitriptyline pharmacotherapy due to subtherapeutic plasma concentrations, and alternate agents are preferred.
  CPIC states that, if amitriptyline is warranted, there are insufficient data in the literature to calculate a starting dose for a patient with CYP2D6 ultra-rapid metaboliser or gene dose 2.5 status, and therapeutic drug monitoring is strongly recommended.
  Based on a nortriptyline study, CPIC indicates that adverse effects are more likely in CYP2D6 poor metabolisers due to elevated tricyclic plasma concentrations; therefore, alternate agents are preferred. If a tricyclic is

warranted, CPIC recommends to consider a 50% reduction of the usual dose, and strongly recommends 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 imipramine, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.
Thus, the therapeutic recommendations for imipramine 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 imipramine for conditions requiring higher doses such as depression based on CYP2C19 phenotype[a,b]		
Phenotype	Therapeutic recommendation	Classification of recommendation
UM + gene dose 2.5	Avoid imipramine use due to potential lack of efficacy. Consider alternative drug not metabolised by CYP2D6. If imipramine is warranted, consider titrating to a higher target dose (compared to normal metabolisers).[c] Utilise therapeutic drug monitoring to guide dose adjustments.	Optional[e]
NM	Initiate therapy with recommended starting dose.[d]	Strong[f]
gene dose 1	Consider a 25% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Optional[e]
gene dose 0.5	Consider a 25% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Optional[e]
PM	Avoid imipramine use due to potential for side effects. Consider alternative drug not metabolised by CYP2D6. If imipramine is warranted, consider a 50% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Optional[e]

[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 recommends no dose modifications for PM or gene dose 0.5, because it is less likely that PM or gene dose 0.5 will experience adverse effects due to supra-therapeutic 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 UM+gene dose 2.5, CPIC recommends considering an alternative agent. Based on predicted and observed pharmacokinetic data in those with depression, CYP2D6 UM+gene dose 2.5 may be at an increased risk of failing TCA therapy for neuropathic pain due to lower than expected drug concentrations (Dworkin RH et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;13: 237-51).

[b] Because the tricyclics have comparable pharmacokinetic properties, it may be reasonable to apply these amitriptyline recommendations to other tricyclics, including imipramine, with the acknowledgment that there are fewer data supporting dose adjustments for these drugs than for amitriptyline.

[c] Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects.

[d] Patients may receive an initial low dose of imipramine, 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.

[e] 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.

[f] Strong indicates that "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."

As evidence linking CYP2D6 genotype with imipramine phenotype, CPIC mentions Schenk 2008, Bijl 2008, Chen 1996, Madsen 1996, Madsen 1995, Koyama 1994, Brosen 1991, Sindrup 1990, Balant-Gorgia 1989, and two times Brosen 1986. These studies, except for Bijl 2008, Chen 1996, Madsen 1996, Madsen 1995 and Brosen 1991 are included in our risk analysis. Bijl 2008 was not included in our risk analysis because only 29 of the 1198 patients in the study (among whom 807 TCA users) used imipramine, and results were not reported separately for imipramine. Chen 1996 was not included because only 5 of the 18 patients with adverse events on antidepressants (had) used imipramine, and results were not reported separately for imipramine. Madsen 1996 and Madsen 1995 were not included, because only metabolites in urine were determined, no plasma concentrations. Brosen 1991 was not included because it was an in vitro study. In addition to the studies considered by CPIC, our risk analysis includes the recent studies of Schliessbach 2018 and Vos 2023. CPIC indicates that the studies provide a high level of evidence for a decreased imipramine metabolism in PM compared to gene dose 1-2 (based on 7 studies including Madsen 1995 and Madsen 1996 for PM and on 1 study for UM+gene dose 2.5), for a correlation between the number/function of CYP2D6 variant alleles and metabolism of imipramine (Schenk 2018), and for a correlation of sparteine metabolism with imipramine metabolism (Madsen 1995). In addition, CPIC indicates that these studies provide a high level of evidence for the requirement of a lower dose of imipramine by PM as compared to gene dose 1-2 (3 studies, including Bijl 2008), for the requirement of a higher dose of imipramine by UM+gene dose 2.5 as compared to gene dose 1-2 (Schenk 2008), and for an association of CYP2D6 genotype with variations in dose requirement for imipramine (Schenk 2008). CPIC indicates that these studies provide a moderate level of evidence for an

increased risk for side effects in carriers of no function alleles compared to carriers of other alleles (3 studies, including Bijl 2008 and Chen 1996).
CPIC also provides therapeutic recommendations based on both CYP2D6 and CYP2C19 genotypes. For CYP2D6 UM+gene dose 2.5 and for CYP2D6 PM the therapeutic recommendations for the different CYP-2C19 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. Based on Steimer 2005, CPIC mentions that patients carrying at least one CYP2D6 no function allele and two CYP2C19 normal function alleles had an increased risk of experiencing side effects when administered amitriptyline. This would argue for a therapeutic recommendation also for patients with CYP2D6 gene dose 1, which is the predominant phenotype in this patient group.
On 18-12-2023, 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 Pharmacogenetic Working Group decision	PM	4 C	yes	yes	8 February 2024
	IM	4 A	yes	yes	
	UM	4 A	yes	yes	

Mechanism:
Imipramine and the active metabolite desipramine are primarily converted by CYP2D6 to inactive hydroxy metabolites. Imipramine is mainly converted by CYP2C19 to desipramine. The Z-hydroxymetabolites of amitriptyline and nortriptyline are known to be cardiotoxic. It cannot be excluded that the Z-hydroxymetabolites of imipramine and desipramine are also cardiotoxic.
The therapeutic effectiveness and side effects of imipramine are associated with the plasma concentration of the sum of imipramine and desipramine. The therapeutic range is 150-300 ng/ml and values above 500 ng/ml are considered to be toxic.

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