CYP2D6: clomipramine 2373-2375

AUC = area under the concentration-time curve, C = clomipramine, C_{ss} = plasma concentration in steady state, Cl_{or} = oral clearance, CTCAE = common terminology criteria for adverse events, DC = desmethylclomipramine, FIBSER = Frequency, Intensity, and Burden of Side Effects Rating scale, HAMD-17 = 17-item Hamilton Rating Scale for Depression, HC = 8-hydroxyclomipramine, HDC = 8-hydroxydesmethylclomipramine, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), MR = metabolic ratio, 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, 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:
Clomipramine and the active metabolite desmethylclomipramine are primarily converted by CYP2D6 to inactive hydroxy metabolites. Clomipramine is mainly converted by CYP2C19, and to a lesser extent by CYP1A2 and CYP-3A4, to desmethylclomipramine. The active metabolite desmethylclomipramine lacks serotonin re-uptake activity and does not appear to contribute to the treatment of obsessive compulsive disorder and other anxiety disorders.
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)).
Two kinetic studies showed significant differences in clomipramine exposure for PM (De Vos 2011 and Nielsen 1994) and one study found a numerically increase in the percentage of patients with adverse events for IM compared to NM (Vandel 2004). In addition, 3 case-reports suggest an increased risk for adverse events and supratherapeutic plasma concentrations in PM and/or IM (de Jong 2018, Stephan 2006, Balant-Gorgia 1989) and 2 case-reports suggest an increased risk for inefficacy and subtherapeutic plasma concentrations in UM (Baumann 1998 and Bertilsson 1993). Vos 2023 did not find genotype-guided therapy in 19 patients to decrease the time to therapeutic plasma concentration. However, in this study, the mean plasma concentration of clomipramine + desmethylclomipramine in NM on normal dose (125 mg/day) was subtherapeutic, suggesting that the chosen normal dose and the genotype-guided doses calculated from it were actually too low. Because clomipramine 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 choices per CYP2D6 phenotype
Dose adjustments are calculated based on clomipramine + desmethylclomipramine, because the sum of these concentrations determines the toxicity. This sum also determines the effectiveness in the case of depression, whilst clomipramine alone determines the effectiveness in the case of anxiety disorders.
Depression:
PM: The weighted mean of the calculated dose adjustment – based on a total of 13 PM from 5 studies (Vos 2023, De Vos 2011, Danish University Antidepressant Group 1999, Nielsen 1992, and Ballant-Gorgia 1987) – is a dose reduction to 49% of the normal dose (33%-53%; median 46%). This was rounded off to 50% to be more achievable in clinical practice.
IM: The weighted mean of the calculated dose adjustment – based on a total of 65 IM from 2 studies (Vos 2023 and De Vos 2011) – is a dose reduction to 72% of the normal dose (68%-100%; median 84%). This was rounded off to 70% to be more achievable in clinical practice.
UM: The calculated dose adjustment – based on one study with 3 UM – is an increase of the dose to 150%. As there is a theoretically increased risk of cardiotoxic side effects, an alternative can be chosen instead. There is one case where a dose increase to 300 mg/day (120% of the maximum dose) was implemented without resulting in any problems, but in the case of cardiotoxicity it is the long-term effects in particular that are of concern.
Anxiety disorders:
PM: The dose reduction for the prevention of toxicity is greater than the dose reduction required to achieve the

correct therapeutic concentration. In order to achieve the therapeutic concentration, the weighted mean of the calculated dose adjustment (based on clomipramine) is a dose reduction to 90% of the normal dose (35%-152%; mean 91%) (based on a total of 24 PM from 5 studies (De Vos 2011, Danish University Antidepressant Group 1999, Nielsen 1994, Nielsen 1992, and Ballant-Gorgia 1987)). This means that it is probably not possible to reduce the dose such that toxicity is avoided (dose reduction by 50%), while the effectiveness is retained (dose reduction not larger than 10%). This is why an alternative is recommended as a second option.

IM: The dose reduction for the prevention of toxicity is equal to the dose reduction required to achieve the correct therapeutic concentration. In order to achieve the therapeutic concentration, the calculated dose adjustment (based on clomipramine) is a dose reduction to 67% of the normal dose (based on one study with 56 IM (De Vos 2011)). The calculated dose adjustment is therefore a dose reduction to 67-72% of the normal dose. This was rounded off to 70% to be more achievable in clinical practice.

UM: The dose increase required to achieve the correct therapeutic concentration is equal to the permitted dose increase in relation to toxicity. In order to achieve the therapeutic concentration, the weighted mean of the calculated dose adjustment (based on clomipramine) is a dose increase to 150% of the normal dose (133%-200%; median 167%) (based on a total of 4 UM from 2 studies (De Vos 2011 and Bertilsson 1993)). As there is a theoretically increased risk of cardiotoxic side effects, an alternative can be chosen instead. A dose of 300 mg/day (120% of the maximum dose of 250 mg/day) was implemented without resulting in any problems (Bertilsson 1993), but in the case of cardiotoxicity it is the long-term effects in particular that are of concern.

Note: Clomipramine has been shown to exhibit a nonlinear pharmacokinetic profile (Balant-Gorgia AE et al. Clinical pharmacokinetics of clomipramine. Clin Pharmacokinet 1991;20:447-62). Indeed, the SmPC of clomipramine mentions clomipramine to inhibit CYP2D6 and therefore its own metabolism. For this reason, 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 clomipramine to be potentially beneficial for the prevention of side effects and for drug efficacy. 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 clomipramine 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 clomipramine mentions the CYP2D6 PM phenotype, but the Dutch SmPC (SmPC Clomipramine HCl Mylan 13-2-2023) 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.	4	19 unipolar nonpsychotic major depressive disorder patients received at least one dose of CYP2D6 genotype-guided clomipramine treatment and 19 patients received at least one dose of not genotype-guided clomipramine treatment. Plasma concentrations and genotypes were reported for 17 patients in each arm. The dosing recommendation in the not genotype guided treatment arm was 125 mg/day. The dosing recommendations in the genotype-guided treatment arm were according to the 2022 KNMP Pharmacogenetics Working Group guidelines: 125 mg/day (100%) for NM, 85 mg/day (70%) for IM, 60 mg/	Authors' conclusion: 'In this randomized clinical trial, pharmacogenetics-informed treatment resulted in faster attainment of therapeutic TCA concentrations. No effect was observed for clomipramine.'

<table>
<tr>
<td>PMID: 37155164.

ref. 1, continuation</td>
<td>Genotype-guided versus not genotype-guided treatment: AA</td>
<td>day (50%) for PM, and 187.5 mg/day (150%) for UM. 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. Both groups were enriched in patients with a variant phenotype, because 65% of NM were not included in one of these treatment arms, but in a reference group. 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).
17-item Hamilton Rating Scale for Depression (HAMD-17) scores (score range 0-52, with higher scores indicating greater depression severity) were used to measure severity of depressive symptoms. Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scores (score range of each of the 3 items 0-6, with higher scores indicating more severe interference with activities) were used to measure severity (intensity) of adverse events. The interaction between treatment group and time for both depression severity and severity of adverse effects was examined.
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.
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:
Genotype-guided arm
- 4x NM
- 10x IM
- 2x PM
- 1x UM

Not genotype-guided arm
- 6x NM
- 9x IM
- 2x PM

Results:
<table>
<tr><td colspan="4">Results for genotype-guided treatment compared to not genotype-guided treatment:</td></tr>
<tr><td colspan="2"></td><td></td><td>value for not genotype-guided treatment</td></tr>
<tr><td rowspan="2">time to therapeutic plasma</td><td>mean</td><td>NS</td><td>25.8 days</td></tr>
<tr><td>median</td><td>NS</td><td>28 days</td></tr>
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ref. 1, continuation		concentration			
		depression severity (HAMD-17) score over time		NS	
		adverse event severity (FIBSER item 2 (Intensity)) score over time		NS (significance not mentioned for clomipramine, but difference between the genotype-guided and not genotype-guided) curves smaller than for depression severity)	
		plasma concentration clomipramine + desmethyl clomipramine	NM	x 0.91 (NS)	171.5 ng/ml
			PM	x 0.40 (NS) The plasma concentration was therapeutic (200-400 ng/ ml) on the not genotype-guided dose and subtherapeutic on the genotype-guided dose.	375,5 ng/ml
			IM	x 0.82 (NS) The plasma concentration was subtherapeutic (<200 ng/ ml) on both the not genotype-guided dose and genotype-guided dose.	172.0 ng/ml
			UM	The plasma concentration was supratherapeutic (487 ng/ml) on the genotype-guided dose.	
			Note: On the not-genotype guided dose, the mean plasma concentration was subtherapeutic (<200 ng/ml) in NM and IM, and therapeutic in PM (200-400 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 PM and IM having a therapeutic plasma concentration on the recommended dose.		

Results compared to NM (significance not determined):

	PM	IM	UM	value for NM
plasma concentration of clomipramine + desmethylclomipramine at a dose of 125 mg/day	x 2.19 (NS)	x 1.00 (NS)		171.5 ng/ml
plasma concentration of clomipramine + des-	x 0.98 (NS)	x 0.90 (NS)	x 3.13 (NS)	155.8 ng/ml

plasma concentration of clomipramine + desmethylclomipramine versus NM:
PM: 219%
IM: 100%

ref. 1, continuation		methylclomipramine at the genotype-guided dose 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.	
ref. 2 de Jong C et al. Clomipramine toxicity in a CYP 2D6 poor metabolizer patient who suddenly stopped smoking. J Clin Psychopharmacol 2018;38:389-391. PubMed PMID: 29894392.	1 PM: C	A 70-year-old woman with recurrent episodes of anxiety with obsessive-compulsive disorder and depression developed agitation and confusion during treatment with clomipramine 100 mg/day. The sum of the plasma concentrations of clomipramine and desmethylclomipramine was 1713 ng/ml (therapeutic range is 200-400 ng/ml, values higher than 600 ng/ml considered to be toxic). The patient was found to be PM for CYP2D6 (*4/*5) and NM for CYP2C19 (*1/*1). The patient used clomipramine for at least 10 years. Three and a half months before agitation and confusion occurred, the clomipramine dose was increased from 50 mg/day to 100 mg/day because of lack of effectiveness, and 2 weeks before agitation and confusion occurred, the patient suddenly stopped smoking. She used the strong CYP1A2 inhibitor fluvoxamine (100 mg/day) and the CYP2C19 inhibitor omeprazole, and had a total knee arthroplasty infection that might have contributed to agitation and confusion. 22 days after clomipramine was stopped, the sum plasma concentration was reduced to less than 600 ng/ml, with evident impovement of the patient's agitated and confused state. Note: Genotyping was for CYP2D6 *3-*6 and gene multiplication and for CYP2C19 *2, *3 and *17.	
ref. 3 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. PMID: 20531370.	3 PM: A IM: AA UM: AA	Routine therapeutic drug monitoring was performed on 244 patients being treated with clomipramine (134x NM (*1/*1), 87x IM (gene dose 1), 15x PM (gene dose 0), 8x UM (gene dose ≥ 3)). The clomipramine dose was known for 151 patients (85x NM, 56x IM, 7x PM, 3x UM). Relevant co-medication was not excluded. PM versus NM: - no significant difference in dose, C_{ss} C, and C_{ss} DC - no difference in the dose-corrected C_{ss} C (both 1.2 µg/L per mg/day) (NS) - decrease in the ratio of C_{ss} C/DC by 63% (from 1.6 to 0.6) (S) IM versus NM: - no significant difference in dose, C_{ss} C, C_{ss} DC and ratio C_{ss} C/DC - increase in the dose-corrected C_{ss} C by 50% (from 1.2 to 1.8 µg/L per mg/day) (NS) UM versus NM: - no significant difference in dose, C_{ss} C, C_{ss} DC and ratio C_{ss} C/DC - decrease in the dose-corrected C_{ss} C by 25% (from 1.2 to 0.9 µg/L per mg/day) (NS)	Authors' conclusion: "The involvement of CYP2D6 genotype in clomipramine degradation is not supported by the present data, but the data do support the indicated metabolism of N-desmethylclomipramine." C_{ss} C versus NM: PM: 100% IM: 150% UM: 75%
ref. 4 de Vos A et al. Association between CYP2C19*17 and	3 PM: AA	PM versus NM: - increase in the dose-corrected C_{ss} C+DC by 88% (from 2.25 to 4.22 µg/L per mg/day) (NS) IM versus NM:	C_{ss} C+DC versus

metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J 2011;11:359-67, personal communication.	IM: AA UM: AA	- increase in the dose-corrected C_{ss} C+DC by 48% (from 2.25 to 3.34 µg/L per mg/day) (NS) UM versus NM: - decrease in the dose-corrected C_{ss} C+DC by 33% (from 2.25 to 1.51 µg/L per mg/day) (NS)	NM: PM: 188% IM: 148% UM: 67%
ref. 5 Stephan PL et al. Adverse drug reactions following nonresponse in a depressed patient with CYP2D6 deficiency and low CYP 3A4/5 activity. Pharmacopsychiatry 2006;39:150-2.	2 PM: C	A 47-year-old man exhibited multiple side effect during treatment with clomipramine 225-300 mg/day and quetiapine 700 mg/day. Plasma concentrations of clomipramine and quetiapine were significantly elevated. C_{ss} C + DC was 1228 ng/mL (therapeutic range is 175-400 ng/mL). The patient was found to be PM for CYP2D6 (*4/*6), NM for CYP2C19 and had a low CYP3A4/5 activity. All side effects, except for the elevated liver enzymes, disappeared once clomipramine was reduced to 75 mg/day and quetiapine was stopped. C_{ss} C + DC decreased to 374 ng/mL.	
ref. 6 Vandel P et al. Clomipramine, fluoxetine and CYP2D6 metabolic capacity in depressed patients. Hum Psychopharmacol 2004;19:293-8.	3 IM: C	45 patients, 20x *1/*2, 25x *1/*4, clomipramine 100-150 mg/day for ≥ 3 weeks, co-medication with benzodiazepines; IM versus NM: increase in the percentage of patients with side effects from 30% to 56% (significance not calculated). The mean CYP2D6 activity was significantly lower in the group with side effects than in the group without side effects (ratio of dextrorphan/dextromethorphan in urine was 5.5 and 13.3 respectively).	
ref. 7 Yokono A et al. The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. Clin Psychopharmacol 2001;21:549-55.	4 IM: AA	51 patients, 8x *1/*1, 4x *1/*2, 1x *2/*2, 17x *1/*10, 9x *2/*10, 1x *1/*5, 2x *2/*5, 9x *10/*10, clomipramine 10-250 mg/day or 0.14-4.82 mg/kg/day, no relevant co-medication; - *10/*10: ratio C_{ss} DC/HDC is 1.72, non-significant difference versus NM (decrease by 11%). - 1 mutation (*5 or *10): ratio C_{ss} DC/HDC is 1.77, non-significant difference versus NM (decrease by 9%). - no mutation: ratio C_{ss} DC/HDC is 1.94. NOTE: for CYP2C19, 2 mutations result in a 1.7 increase in C_{ss} clomipramine and ratio C_{ss} C/DC versus no mutation.	Authors' conclusion: 'The genotyping of CYP2D6 is not useful for predicting the individual capacity to hydroxylate DC.'
ref. 8 Danish University Antidepressant Group. Clomipramine dose-effect study in patients with depression: clinical end points and pharmacokinetics. Clin Pharmacol Ther 1999;66:152-65.	4 PM: AA	109 patients, 97 NM, 12 PM (phenotyped with sparteine), clomipramine 25-200 mg/day, no relevant co-medication; PM versus NM: - 50 mg/day: - increase in C_{ss} C+DC from 2.6 to 4.5 nM[a] (NS by 73%) - decrease in C_{ss} C from 1.5 to 0.8 nM[a] (NS by 47%) - decrease in ratio HC/C from 0.8 to 0.7 (NS by 13%) and decrease in ratio HDC/DC from 0.6 to 0.2 (NS by 67%) - 75 mg/day: - increase in C_{ss} C+DC from 3.2 to 8.2 nM[a] (NS by 156%) - increase in C_{ss} C from 1.6 to 2.1 nM[a] (NS by 31%) - decrease in ratio HC/C from 0.7 to 0.3 (NS by 57%) and decrease in ratio HDC/DC from 0.6 to 0.1 (NS by 83%) - 125 mg/day:	Authors' conclusion: 'Dose-dependent kinetics and, to a lesser extent, genetic polymorphism (related to CYP2D6) are the major reasons for variability in kinetics.' C_{ss} C+DC versus NM at dose 125

ref. 8, continuation		- increase in C_{ss} C+DC NM from 5.0 to 10.0 nM[a] (NS by 100%) - increase in C_{ss} C from 2.1 to 2.8 nM[a] (NS by 33%) - decrease in ratio HC/C from 0.6 to 0.4 (NS by 33%) and decrease in ratio HDC/DC from 0.6 to 0.2 (NS by 67%) - 200 mg/day: - increase in C_{ss} C+DC from 7.5 to 11.7 nM[a] (NS by 56%) - decrease in C_{ss} C from 3.2 to 2.1 nM[a] (NS by 34%) - no change in ratio HC/C, decrease in ratio HDC/DC from 0.3 to 0.1 (NS by 67%) Serum concentrations of C + DC exhibited a (weak) correlation with reduction in depression. Several blood pressure effects and typical side effects exhibited a statistically significant concentration-effect relationship. NOTE: genotype unknown	mg/day: PM: 200% C_{ss} C versus NM at dose 200 mg/day: PM: 76%
ref. 9 Baumann P et al. Ultrarapid metabolism of clomipramine in a therapy-resistant depressive patient, as confirmed by CYP2 D6 genotyping. Pharmacopsychiatry 1998;31:72.	2 UM: C	A 62-year-old patient did not respond to various antidepressants. He had unusually low concentrations of D + DC during treatment with clomipramine 150-225 mg/day. Following addition of the CYP1A2 inhibitor fluvoxamine 100 mg/day, which is primarily metabolised via CYP2D6, the clomipramine concentration increased by a factor of 5 and the patient exhibited a rapid and consistent clinical response. The patient was found to have a duplication of the CYP-2D6 gene.	
ref. 10 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.	3 PM: A	25 healthy subjects, 15x NM (for CYP2C19 5x PM), 10x PM (for CYP2C19 1x PM) phenotyped with sparteine, single dose of clomipramine 100 mg, no co-medication; PM versus NM: - decreased Cl_{or} from 98.6 to 65.2 L/hr (S by 34%) - increased t½ from 18.7 to 22.7 (NS by 21%) NOTE: genotype unknown	Cl_{or} clomipramine versus NM: PM: 76%
ref. 11 Bertilsson L et al. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. Lancet 1993;341:63.	2 UM: C	A patient with agoraphobia received clomipramine 150 mg/day. As there was no response, the dose was increased to 225 mg/day. The plasma concentrations were very low (150 nM clomipramine and desmethylclomipramine was below the detection limit of 100 nM). The patient was stabilised on clomipramine 300 mg/day.	maintenance dose versus normal dose (for anxiety disorder): UM: 200%
ref. 12 Tacke U et al. Debrisoquine hydroxylation phenotypes of patients with high versus low to normal serum antidepressant concentrations. J Clin Psychopharmacol 1992;12:262-7. PubMed PMID: 1527229.	1 PM: A	1 patient with a supratherapeutic clomipramine+desmethylclomipramine plasma concentration (3132 nM = 986 ng/ml) at a dose of 225 mg/day was compared to 1 sex-, age- and dose-matched control with a therapeutic clomipramine plasma concentration (1078 nM = 339 ng/ml). Phenotyping revealed that the case was PM and the control was not. Relevant comedication was not excluded. The PM patient used the CYP2D6 substrate haloperidol at the time of (desmethyl)clomipramine measurement and the CYP2D6 inhibitor thioridazine at the time of phenotyping. Due to the large difference in phenotyping results between PM and non-PM (with and without thioridazine), the authors	

ref. 12, continuation		concluded that it is unlikely that comedication with thioridazine at the time of phenotyping could have resulted in misclassification of phenotypes. NOTE: genotype unknown. NOTE: Phenotyping revealed the control patient to have a higher CYP2D6 activity than 19 non-PM control patients used for other TCAs. This suggests the control patient to be either an NM with a higher than average CYP2D6 activity or an UM.	
ref. 13 Nielsen KK et al. Steady-state plasma levels of clomipramine and its metabolites: impact of the spartene/debrisoquine oxidation polymorphism. Danish University Antidepressant Group. Eur J Clin Pharmacol 1992;43:405-11.	4 PM: AA	36 patients, 35x NM, 1x PM (phenotyped with sparteine), clomipramine 75 mg twice daily, no relevant co-medication; PM versus NM: - increase in C_{ss} C+DC from 710 to 2120 nM (NS by 199%) - increase in C_{ss} C from 200 to 570 nM (NS by 185%) - no change in ratio C_{ss} C/DC - increase in ratio C/HC from 1.9 to 4.7 (NS by 147%) - increase in ratio DH/HDC from 1.6 to 7.1 (NS by 343%) - increase in ratio (C+DC)/(HC+HDC) from 1.7 to 6.1 (NS by 259%). NOTE: genotype unknown	Authors' conclusion: 'Phenotyping before treatment may be a valuable guideline for selecting the appropriate initial dose of clomipramine, which in PM should be only ¼ of that in NM.' C_{ss} C+DC versus NM: PM: 299% C_{ss} C versus NM: PM: 285%
ref. 14 Balant-Gorgia 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 IM: C PM: C	2 patients received clomipramine. - patient 1 received clomipramine 150 mg/day for 3 weeks: no improvement in symptoms of depression, but did experience side effects. C_{ss} C+DC is 1215 ng/mL, C_{ss} clomipramine is 235 ng/mL, C_{ss} DC is 980 ng/mL, found to be a slow metaboliser. - patient 2 received clomipramine 225 mg/day for 8 weeks: no improvement in symptoms, but did experience side effects. C_{ss} C+DC is 1120 ng/mL, C_{ss} clomipramine is 160 ng/mL, C_{ss} DC is 960 ng/mL, found to be a poor metaboliser. NOTE: genotype unknown	
ref. 15 Balant-Gorgia AE et al. High plasma concentrations of desmethylclomipramine after chronic administration of clomipramine to a poor metabolizer. Eur J Clin Pharmacol 1987;32:101-2.	2 PM: A	patient, PM, received clomipramine 100 mg/day; Two measurements: C_{ss} C+DC is 598 ng/mL and 558 ng/mL. Compared to the mean for the reference values in this laboratory (125-350 ng/mL), this is an increase by 135-152% (NS). The increase was primarily caused by an increase in DC. C_{ss} C is increased by 6-14% compared to the mean of the reference values (25-100 ng/mL) (NS). NOTE: genotype unknown	C_{ss} C+DC versus reference values: PM: 243% C_{ss} C versus reference values: PM: 110%.
ref. 16 SmPC Anafranil (clomipramine) 10-05-19, USA.	0 PM: A	Warning: *Drugs metabolized by P450 2D6* 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 increa-	

ref. 16, continuation		se in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).	

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

Risk group	IM with CYP2D6 inhibitor

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).
  For amitriptyline, CPIC states that the recommended starting dose of amitriptyline 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 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 + gene dose 2.5	Avoid clomipramine use due to potential lack of efficacy. Consider alternative drug not metabolised by CYP2D6.	Strong[e]

	If clomipramine is warranted, consider titrating to a higher target dose (compared to normal metabolisers).[c] Utilise therapeutic drug monitoring to guide dose adjustments.	
NM	Initiate therapy with recommended starting dose.[d]	Strong[e]
gene dose 1	Consider a 25% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Optional[f]
gene dose 0.5	Consider a 25% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Moderate[g]
PM	Avoid clomipramine use due to potential for side effects. Consider alternative drug not metabolised by CYP2D6. If clomipramine is warranted, consider a 50% reduction of recommended starting dose.[d] Utilise therapeutic drug monitoring to guide dose adjustments.[c]	Strong[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 IM 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 clomipramine, 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 clomipramine, 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] Strong indicates that “The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.”

[f] 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.

[g] Moderate indicates that “there is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

As evidence linking CYP2D6 genotype with clomipramine phenotype, CPIC mentions De Vos 2011, Bijl 2008, Stephan 2006, Vandel 2004, DUAG 1999, Baumann 1998, Chen 1996, Nielsen 1994, Bertilsson 1993, Nielsen 1992, Tacke 1992, Balant-Gorgia 1989 and Balant-Gorgia 1987. These studies, except for Bijl 2008 and Chen 1996, are included in our risk analysis. Bijl 2008 was not included in our risk analysis because only 79 of the 1198 patients in the study (among whom 807 TCA users) used clomipramine, and results were not reported separately for clomipramine. Chen 1996 was not included because only 1 of the 18 patients with adverse events on antidepressants used clomipramine, and results were not reported separately for clomipramine. In addition to the studies considered by CPIC, our risk analysis includes the small study of Yokono 2001 and the recent publications of De Jong 2018 and Vos 2023. CPIC indicates that the studies provide a high level of evidence for a decreased clomipramine metabolism in PM compared to gene dose 1-2 (7 studies). In addition, the studies provide a high level of evidence for an increased risk for side effects in carriers of CYP2D6 no function alleles compared to carriers of other alleles (5 references including Bijl 2008 and Chen 1996). CPIC indicates that these studies provide a moderate level of evidence for a decreased metabolism of clomipramine and a decrease in response in UM+gene dose 2.5 (based on 2 and 1 studies, respectively). Contrary to this, CPIC also indicates a moderate level of evidence for the absence of a correlation between significant differences in plasma concentrations of clomipramine and desmethylclomipramine and the number of variant CYP2D6 alleles (De Vos 2011). Finally, CPIC indicates that these studies provide a weak level of evidence for the requirement of a decreased dose by PM compared to gene dose 1-2 (Bijl 2008).

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 11-12-2023, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search: 7 December 2023.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 C	yes	yes	8 February 2024
	IM	4 C	yes	yes	
	UM	3 C	yes	yes	

Mechanism:
Clomipramine and the active metabolite desmethylclomipramine are primarily converted by CYP2D6 to inactive hydroxy metabolites. Clomipramine is mainly converted by CYP2C19, and to a lesser extent by CYP1A2 and CYP3A4, to desmethylclomipramine. The active metabolite desmethylclomipramine lacks serotonin re-uptake activity and does not appear to contribute to the treatment of obsessive compulsive disorder and other anxiety disorders. The Z-hydroxymetabolites of amitriptyline and nortriptyline are known to be cardiotoxic. It cannot be excluded that the Z-hydroxymetabolites of clomipramine and desmethylclomipramine are also cardiotoxic.
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