CYP2D6: paroxetine 1563/1564/1565

AUC = area under the concentration-time curve, Cl_{or} = oral clearance, Css = steady state plasma concentration, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metaboliser (gene dose 0.5-1) (reduced CYP2D6 enzyme activity), MADRS = Montgomery-Åsberg Depression Rating Scale, NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, $t_{1/2}$ = half-life, SmPC = summary of product characteristics, UM = ultra-rapid metaboliser (gene dose ≥ 3) (increased CYP2D6 enzyme activity), V_m = maximum elimination rate.

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:
CYP2D6 converts paroxetine to inactive metabolites. Paroxetine is a strong inhibitor of CYP2D6. As a result, the effect of CYP2D6 on the pharmacokinetics of paroxetine is greater for a single dose than for the repeated doses used in practice (the difference between EM and PM is reduced by a factor 3.5). There is no obvious relationship between the plasma concentration and the effect of paroxetine.

IM and PM: The dose-corrected plasma concentration is increased for IM and PM. However, there is no effect on side effects or efficacy. Therefore, NO action is required for this gene-drug interaction (guideline without therapeutic recommendations).

UM: For 71% of the UMs where the plasma concentration was determined (n=7), this value was below the detection limit following standard doses of paroxetine. There was no therapeutic efficacy in 100% of the UMs for who the therapeutic efficacy was determined (n=6). As a precaution, we recommend selecting an alternative (guideline with therapeutic recommendations).

You can find a detailed overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions on 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 Dutch Pharmacogenetics Working Group considers genotyping before starting paroxetine to be potentially beneficial for drug efficacy. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the Dutch 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 paroxetine 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 Summary of Product Characteristics (SmPC) of paroxetine does not mention a CYP2D6 genotype or phenotype and does not recommend pre-emptive genotyping. 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 or a recommendation to genotype).

The table below uses the KNMP nomenclature for EM, PM, IM and UM. As a result, the definitions of EM, 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 Janssen PK et al. Nonresponders to daily paroxetine and another SSRI in men with lifelong premature ejaculation: a pharmacokinetic dose-escalation study for a rare phenomenon. Korean J Urol 2014;55:599-607. PubMed PMID: 25237462.	3 IM: AA	13 men with lifelong premature ejaculation, of which 5 did not respond to paroxetine and another SSRI and 1 did not respond to paroxetine, received paroxetine for 12 weeks (10 mg/day in weeks 1-4, 20 mg/day in weeks 5-8 and 30 mg/day in weeks 9-12). Co-medication was excluded. Genotyping: - 11x EM - 2x IM Results: IM versus EM: - no difference in intra-vaginal ejaculation latency time (NS) - higher plasma concentration with use of 30 mg/day (NS; significance could not be determined due to low number of patients) With each of the doses, there was no difference in the plasma concentration of paroxetine between responders (increase in the intra-vaginal ejaculation latency time by a factor 2 or more) and non-responders. NOTE: Genotyping was performed for *3, *4, *6 and gene duplication.	Authors' conclusion: 'We did find that serum concentrations of paroxetine were higher in two men with the Cyp2D6*3 and *4 variations, respectively. However, because there is no relation between the serum paroxetine concentration and the intravaginal ejaculatory latency time, this genotype for paroxetine metabolism is not relevant for paroxetine-induced ejaculation delay in the current study.'
ref. 2 Saruwatari J et al. Possible impact of the CYP2D6*10 polymorphism on the nonlinear pharmacokinetic parameter estimates of paroxetine in Japanese patients with major depressive disorders. Pharmgenomics Pers Med 2014;7:121-7. Pubmed PMID: 24868171.	4 IM+EM : A	15 patients were treated with paroxetine (20 mg/day during week 1, 40 mg/day during weeks 2-6, dose adjustment based on side effects) for at least 2 weeks. Relevant co-medication was excluded. Blood was collected 10-20 hours after the last dose (mean 13.5 hours). Carriers of the *10 allele were significantly younger than non-carriers (36.5 and 62.5 years respectively). Genotyping: - 11x *10 (2x *2/*10, 2x *10/*39, 6x *10/*10, 1x *5/*10) - 4x no *10 (2x *39/*39, 2x *5/*39) *10 versus (no *10): - decrease in the dose-corrected plasma concentration determined using multiple linear regression (S) NOTE: The abovementioned contradicts the trend found with multiple linear regression for a decrease in the maximum conversion rate V_{max} (NS). - no significant difference in plasma concentrations for patients who were treated with the same dose (20, 30 or 40 mg/day) Age was not included in the linear regression. However, age had no effect on V_{max}, either in *10 or in (no *10). NOTE: genotyping was performed for *2, *4, *5, *10, *18, *39 and *41. These are the most common variant alleles in this Japanese population group.	Authors' conclusion: 'This is the first study to demonstrate that CYP2D6 *10 polymorphism could affect the nonlinear pharmacokinetic parameter estimates of paroxetine in Asian populations.'
ref. 3 Murata Y et al.	3	A total of 27 patients were treated with paroxetine, of which 4 patients developed hypersomnia. Only	Authors' conclusion:

Severe sleepiness and excess sleep duration induced by paroxetine treatment is a benefit-ceal pharmacological effect, not an adverse reaction. J Affect Disord 2013;150:1209-12. PubMed PMID: 23809402. **ref. 3, continuation**	IM: AA	co-medication with tandospirone, benzodiazepines and zolpidem or zopiclon was permitted. Genotyping: - 5x gene dose 2 (*1/*1, *1/*2 or *2/*2) - 13x gene dose 1-1.5 (*1/*5, *2/*5, *1/*10 or *2/*10) - 9x gene dose 0.5-1 (*5/10 or *10/*10) Gene dose 0.5-1 versus gene dose 1-1.5 versus gene dose 2: - no difference in the percentage of patients with hypersomnia NOTE: genotyping was performed for *2, *5 and *10. These are the most common variant alleles in this Japanese population group.	'No significant association was found between the "hypersomnia" and the genetic polymorphisms studied.'
ref. 4 Murata Y et al. Effects of the serotonin 1A, 2A, 2C, 3A, and 3B and serotonin transporter gene polymorphisms on the occurrence of paroxetine discontinuation syndrome. J Clin Psychopharmacol 2010;30:11-7. Pubmed PMID: 20075642.	3 IM: AA	A total of 56 patients were treated with paroxetine 10-60 mg/day (mean maintenance dose 28.8 mg/day) for 23 weeks or longer, with gradual reduction (n=33) or sudden termination of the treatment (n=23). Co-medication with the serotonin-1A-receptor antagonist tandospirone, benzodiazepines, zolpidem, zopiclon or non-psychotropic drugs was not excluded. Plasma concentrations were determined for patients for whom the dose had remained unchanged for at least 2 weeks. Genotyping: - 23x gene dose 2 (17x *1/*1, 5x *1/*2, 1x *2/*2) - 23x gene dose 1-1.5 (18x *1/*10, 2x *2/*10, 2x *1/*5, 1x *2/*5) - 10x gene dose 0.5-1 (7x *10/*10, 3x *5/*10) Gene dose 0.5-1 versus gene dose 1-1.5 versus gene dose 2: - no difference in the occurrence of withdrawal symptoms after discontinuation or dose reduction of paroxetine (NS) - no difference in the plasma concentration (not corrected for dose) of paroxetine (NS) NOTE: The study did not indicate which alleles were genotyped. However, the most common variant alleles in this Japanese population group were genotyped (*2, *5 and *10).	Authors' conclusion: 'No significant differences between the groups with and without paroxetine discontinuation syndrome were found in the 3 subgroups according to the number of functional alleles of the CYP2D6 gene polymorphisms. …. The mean plasma levels of paroxetine were 187.7, 156.7, and 92.7 ng/mL in the subgroups with genotypes of 2 functional alleles, one functional allele and no functional alleles of the CYP2D6 gene polymorphisms, respectively, and there were no significant differences in the 3 subgroups according to the number of functional alleles of the CYP2D6 gene polymorphisms.'
ref. 5 Ververs FF et al. Effect of cytochrome P450 2D6 genotype on maternal paroxetine plasma concentrations during pregnancy. Clin Pharmacokinet 2009;48:677-83. PubMed PMID: 19743889.	4	A total of 74 pregnant women were treated with paroxetine 10-40 mg/day. Relevant co-medication was not excluded, but had no effect on the plasma concentration in the pharmacokinetic model. Plasma concentrations of paroxetine were determined at 3 time points during the pregnancy (in week 16-20, week 27-31 and week 36-40). Dose correction was performed by converting the plasma concentrations to a dose of 20 mg/day. All the kinetic results mentioned in the study were obtained from the pharmacokinetic model. Genotyping: - 43x EM (30x *1/*1, 2x *1/*9, 2x *1/*10 and 9x *1/*41) - 1x UM (*1/*1xn) - 25x IM (19x *1/*4, 3x *1/*5, 1x *1/*6, 1x *4/*41 and 1x *9/*9) - 5x PM (4x *4/*4 and 1x *3/*4)	Authors' conclusion: 'Differences in CYP2D6 genotype may have divergent effects on maternal plasma paroxetine concentrations during pregnancy, with therapeutic consequences. Accumulation of paroxetine in a considerable group of pregnant women will lead to unintended increased exposure of paroxetine to the unborn child. Knowledge about a patient's CYP2D6 genotype is indispensable when prescribing paroxetine in pregnancy.'

ref. 5, continuation	IM+PM : A	IM+PM versus EM+UM: - no increase versus an increase by 0.08 points per week of pregnancy in the score on the Edinburgh Postnatal Depression Scale (EPDS) - no difference in prevalence of EPDS scores higher than 12 (indicative of depression) (NS) - increase by 0.82 µg/L versus a decrease by 0.3 µg/L per week of pregnancy in the dose-corrected C_{ss} of paroxetine (S) Raw data demonstrate a greater effect for PM than IM (significant increase in the plasma concentration for 2 PMs, but no increase over the entire period for 13 IMs.) NOTE: genotyping was performed for *3 to *6, *9, *10 and *41. These are the most common variant alleles in this Dutch population group.	
ref. 6 Van Nieuwerburgh FC et al. Response to serotonin reuptake inhibitors in OCD is not influenced by common CYP2D6 polymorphisms. Int J Psychiatry Clin Pract 2009;13:345-348. Pubmed PMID: 20174590.	4 IM+ PM: A	A total of 35 patients with obsessive compulsive disorder received paroxetine for 12 weeks. The paroxetine dose was gradually increased to 60 mg/day according to a set schedule. Relevant co-medication was excluded. Genotyping: - 18x gene dose 2 (EM) - 17x gene dose 0-1.5 (PM+IM+EM) Gene dose 0-1.5 versus gene dose 2: - no difference in response (NS) - increase in the plasma concentration by 42% (from 125 to 177 ng/mL) (S) Gene dose 0-1 versus gene dose 2: - no difference in response (NS) - increase in the plasma concentration (S) NOTE: genotyping was performed for *4, *6, *10 and *41. These are the most common variant alleles in this Dutch population group.	Authors' conclusion: 'Our results show that the investigated CYP2D6 polymorphisms are not a decisive factor in the response to paroxetine and venlafaxine treatment in OCD in spite of their highly significant effect on the blood levels of these medicines.'
ref. 7 Gex-Fabry M et al. CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. Ther Drug Monit 2008;30:474-82.	4 PM: AA IM: AA	A total of 71 patients, 42x EM, 22x IM (13x *1/*4, 8x *1/*5, 1x *1/*6), 2x PM (1x *4/*4, 1x *4/*6), 4x UM (*1/*xN), 1x *4/*xN), paroxetine 20 mg/day for 2 weeks, followed by 20-30 mg/day, only co-medication with clorazepic acid and zolpidem was allowed. Persistent response was defined as a persistent improvement in the score on the MADRS by 50%; early persistent improvement as a persistent improvement on the MADRS by 20% from week 2. PM versus EM: - increase in median C_{ss} at a dose of 20 mg/day from 22 to 28 ng/mL (NS by 27%). - decrease in the prevalence of persistent response from 43.2% to 0% (NS by 100%). - increase in the prevalence of early persistent improvement from 40.5% to 50.0% (NS by 23%). IM versus EM: - increase in median C_{ss} at a dose of 20 mg/day from 22 to 27 ng/mL (NS by 23%). - a multi-variable pharmacokinetic model predicted a 1.3x higher C_{ss} in EMs than in IMs, but the contribution of the CYP2D6 phenotype did not achieve significance (NS). - decrease in the prevalence of persistent	Authors' conclusion: 'Sex and CYP2D6 heterozygous versus homozygous EM phenotype only allowed explaining a modest fraction of paroxetine large pharmacokinetic variability.' C_{ss} at a dose of 20 mg/day versus EM: PM: 127% IM: 123% UM: <9%

ref. 7, continuation	UM: A	response from 43.2% to 15.8% (NS by 63%). - increase in the prevalence of early persistent improvement from 40.5% to 47.4% (NS by 17%). - IM versus EM was not a significant predictor of persistent response in a multi-variable pharmacodynamic model in which the plasma concentration of paroxetine was included as an independent variable (NS). UM versus EM: - decrease in median C_{ss} at a dose of 20 mg/day from 22 to <2 ng/mL (S by > 91%). (For 3 of the 4 UM, the C_{ss} was below the detection limit (2 ng/mL) and this value was assumed as the concentration). - decrease in the prevalence of persistent response from 43.2% to 0% (NS by 100%). - decrease in the prevalence of early persistent improvement from 40.5% to 25% (NS by 38%). The pharmacokinetics of paroxetine are non-linear: an increase in the dose of 20 mg/day by a factor 1.5 results in an increase in the paroxetine concentration by a factor 1.9.	
ref. 8 Kuhn UD et al. Reboxetine and cytochrome P450--comparison with paroxetine treatment in humans. Int J Clin Pharmacol Ther 2007;45:36-46.	3 PM: AA IM: A	A total of 25 healthy volunteers, 18x EM (*1/*1 or *1/*41), 6x IM (*1/*4), 1x PM (*4/*4), paroxetine 30 mg/day for 11 days, no co-medication. PM versus EM: - increase in the trough concentration from 27.4 to 56.0 ng/mL (NS by 104%). - increase in the $AUC_{9\text{-}24\ h}$ from 424 to 954 ng.h/mL (NS by 125%). - decrease in the percentage of patients with plasma concentrations below the detection limit (10 ng/mL) from 22% to 0% (NS by 100%). IM versus EM: - increase in the trough concentration from 27.4 to 42.0 ng/mL (S by 53%). - increase in the $AUC_{9\text{-}24\ h}$ from 424 to 618 ng.h/mL (NS by 46%). - decrease in the percentage of patients with plasma concentrations below the detection limit (10 ng/mL) from 22% to 0% (NS by 100%).	Authors' conclusion: 'Paroxetine concentrations showed some dependence on CYP2D6.' $AUC_{9\text{-}24\ h}$ versus EM: PM: 225% IM: 146%
ref. 9 Sugai T et al. The effect of 5-hydroxytryptamine 3A and 3B receptor genes on nausea induced by paroxetine. Pharmacogenomics J 2006;6:351-6.	3 IM: AA	A total of 78 patients, 51x gene dose 2 (*1/*1), 12x gene dose 1-1.5 (11x *1/*10, 1x *1/*5), 15x gene dose 1 (12x *10/*10, 3x *5/*10), paroxetine dose based on clinical effect (10-40 mg/day; mean 22.2 mg/day), co-medication not reported. gene dose 1 versus gene dose 1-1.5 versus gene dose 2: - no significant difference in daily dose or C_{ss} (both NS). - no significant difference in the percentage of patients with nausea or in the severity of the nausea (both NS). IM (*10/*10 + *5/*10 + *1/*5) versus EM (*1/*1 + *1/*10): - no significant difference in the percentage of patients with nausea (NS).	Authors' conclusion: 'The CYP2D6 gene polymorphism had no significant effect on the incidence of nausea.'
ref. 10 Findling RL et al.	4	A total of 53 patients aged 7-17 years, 3x gene dose 0 (PM), 3x gene dose 0.5-0.75, 16x gene	Authors' conclusion:

Multiple dose pharmacokinetics of paroxetine in children and adolescents with major depressive disorder or obsessive-compulsive disorder. Neuropsychopharmacology 2006;31:1274-85. **ref. 10, continuation**	PM: A IM: A UM: A	dose 1-1.25, 10x gene dose 1.5, 21x gene dose ≥ 1.75, paroxetine 10 mg/day for 2 weeks, followed by 20 mg/day in weeks 3 and 4 and 40 mg/day in weeks 5 and 6, no relevant co-medication. - regression analysis revealed that Cl_{or} is strongly dependent on paroxetine dose, CYP2D6 gene dose and body weight (S). - the body weight-corrected Cl_{or} increased with the gene dose and this effect was strongest for low paroxetine doses. - none of the 3 patients who discontinued the study prematurely due to side effects was a PM. - 1 of the 3 PM had the highest $AUC_{0\text{-}24\ h}$ for his age group, the other 2 had values close to those of the EM.	'Stepwise regression analysis indicated that both oral clearance and volume of distribution were highly dependent on paroxetine dose, cytochrome P4502D6 genotype, and weight ($p<0.0001$).'
ref. 11 Feng Y et al. Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling. Br J Clin Pharmacol 2006;61:558-69.	3 PM: A IM: A UM: A	A total of 68 patients aged ≥ 69 years, 1x PM, 26x gene dose 0.5-1.5 (IM+EM), 36x gene dose 2 (EM), 5x UM, maintenance therapy with paroxetine 10-40 mg/day, relevant co-medication not excluded. PM versus IM+EM versus EM versus UM: - CYP2D6 phenotype was the variable that yielded the greatest improvement in a model for V_m (S). - the V_m that was calculated from the final model: 125 versus 182 versus 454 versus 3670 µg/h.	Authors' conclusion: 'The data indicate that female and male subjects with different CYP2D6 polymorphisms have different elimination rates and therefore may need to be dosed differently based on metabolizer genotype.'
ref. 12 Ueda M et al. The impact of CYP2D6 genotypes on the plasma concentration of paroxetine in Japanese psychiatric patients. Prog Neuro-psychopharmacol Biol Psychiatry 2006;30:486-91.	4 IM: AA	A total of 55 patients, 17x gene dose 2, 26x gene dose 0.5-1.5 (19x *1/*10, 4x *2/*10, 1x *1/*41, 1x *1/*5, 1x *2/*5), 12x gene dose 1 (*10/*10 or *10/*41), paroxetine 10-40 mg/day (mean 24 mg/day), no relevant co-medication. gene dose 1 versus gene dose 1-1.5: - **decrease** in $C_{ss}{}^b$ from 243.6 to 76.7 ng.kg/mL.mg for patients who used paroxetine 30 mg/day (S by 68%). - no significant change in $C_{ss}{}^b$ for paroxetine 10, 20 or 40 mg/day (NS). gene dose 1-1.5 versus gene dose 2: - increase in $C_{ss}{}^b$ from 150.9 to 243.6 ng.kg/mL.mg for patients who used paroxetine 30 mg/day (S by 61%). - no significant change in $C_{ss}{}^b$ for paroxetine 10, 20 or 40 mg/day (NS). gene dose 1 versus gene dose 2: - **decrease** in $C_{ss}{}^b$ from 150.9 to 76.7 ng.kg/mL.mg for patients who used paroxetine 30 mg/day (NS by 49%). - no significant change in $C_{ss}{}^b$ for paroxetine 10, 20 or 40 mg/day (NS). The authors indicate that *10 is inhibited to a lesser extent by paroxetine than *1.	Authors' conclusion: 'The present results suggest that having one non-functional allele is the marker for high plasma concentration of PAX when relatively high daily dose of PAX is administered.' $C_{ss}{}^b$ versus EM: IM: 51-100%
ref. 13 Güzey C et al. Low serum concentrations of paroxetine in CYP2D6 ultrarapid metabolizers. J Clin Psychopharmacol 2006;26:211-2.	2 UM: C	2 patients with a lack of response to paroxetine and very low C_{ss} were found to be UM. - A woman on paroxetine 30 mg/day had a C_{ss} of 24-37 nmol/L. This is approximately 25% of the median C_{ss} for this dose (n=159). - A man on paroxetine 20 mg/day had an undetectable C_{ss} (<5 nmol/L), and for 40, 60 and 75 mg/day the C_{ss} was 14, 35 and 56 nmol/L respectively. This is approximately 10% of the median C_{ss} for these doses	Authors' conclusion: 'The 2 cases in this report suggest that defining a subject as an ultrarapid metabolizer by genotyping might be of value to predict nonresponse to a standard dose of paroxetine.'

ref. 13, continuation		(n=578, 470 and 154 respectively for the doses 20, 40 and 60 mg/day).	Css t.o.v. EM: UM: approx. 10-25%
ref. 14 Sawamura K et al. Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine. Eur J Clin Pharmacol 2004;60:553-7.	4 IM: A PM: AA	A total of 73 patients, 16x *1/*1, 9x *1/*2, 2x *2/*2, 22x *1/*10, 6x *2/*10, 1x *1/*5, 13x *10/*10, 1x *5/*5, 3x *5/*10, paroxetine 10-40 mg/day, no relevant co-medication; - 1 or 2x *10: increase in C_{ss} versus *1/*1+*1/*2+*2/*2 from 2.99 to 7.30 ng/mL (S by 144%) for dose 10 mg/day. No difference for higher doses of paroxetine. - 1 or 2x *5: non-significant increase in Css.	Authors' conclusion: 'There was a significant effect of the CYP2D6*10 allele on plasma paroxetine concentration at low doses, although clinical implication of this effect is not clear.'
ref. 15 Charlier C et al. Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. Ther Drug Monit 2003;25:738-42.	4 PM: A UM: AA	A total of 37 patients, 30x EM, 6x PM (2x *4/*5, 1x *3/*4, 3x *4/*4), 1x UM (*2/*2xN), paroxetine 20 mg/day, no relevant co-medication; - PM: increase in Css versus EM from 20.97 to 72.50 µg/mL (S by 246%). - UM: C_{ss} paroxetine is below the detection limit.	C_{ss} versus EM: PM: 346%
ref. 16 Murphy G et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830-5.	4 PM+IM : AA	A total of 120 patients, 15x PM-IM (no functional allele, 0-2 alleles with reduced functionality), 105x EM-UM (0-1 duplication *1 or *2), paroxetine 20-40 mg/day, CYP2D6 inhibitors and substrates as co-medication; *kinetic endpoint* C_{ss} paroxetine does not differ between the groups PM+IM and EM+UM. *clinical endpoint* Required dose, efficacy, side effects, patient compliance or discontinuation of therapy did not differ between the PM + IM group and the EM + UM group. NOTE: co-medication does not influence the genotype effect on the endpoint "side effects".	Authors' conclusion: 'We found no evidence that dosages of these medications should be adjusted for CYP2D6 poor and intermediate metabolizers.'
ref. 17 Ozdemir V et al. Paroxetine steady-state plasma concentration in relation to CYP2D6 genotype in extensive metabolizers. J Clin Psychopharmacol 1999;19:472-5.	3 IM: AA	17 healthy study subjects, 10x EM (*1/*1), 7x IM (*1/*3 or *1/*4 or *1/*5), paroxetine 20 mg/day, no relevant co-medication allowed; - IM: increase in C_{ss} paroxetine versus EM from 43 to 85 nM (NS by 98%).	C_{ss} versus EM: IM: 198%
ref. 18 Sindrup SH et al. Pharmacokinetics of the selective serotonin reuptake inhibitor paroxetine: nonlinearity and relation to the sparteine oxidation polymorphism. Clin Pharmacol Ther 1992;51:288-95.	4 PM: AA	16 patients, 13x EM#, 3x PM (phenotyped with sparteine), paroxetine 10-40 mg/day for PM and 10-70 mg/day for EM, no CYP2D6 inhibitors as co-medication; - PM: increase in C_{ss} paroxetine versus EM, for 10 mg/day from 22.3 to 115.0 nM (NS by 416%), for 20 mg/day from 77.7 to 234.3 nM (NS by 201%) and for 30 mg/day from 142.7 to 475.0 nM (NS by 233%). NOTE: genotype not known. Phenotyping can only distinguish between PM and the other phenotypes, so EM# is equal to IM, EM and UM.	Authors' conclusion: 'The findings show that paroxetine in extensive metabolizers is metabolized in parallel by the saturable CYP2D6 and alternative, low affinity enzymes' C_{ss} versus EM+IM+UM at a dose of 20 mg/day: PM: 302%
ref. 19 Sindrup SH et al. The relationship between paroxetine and the sparteine oxidation	4 PM: A	17 healthy study subjects, 9x EM#, 8x PM (phenotyped using sparteine), paroxetine 30 mg/day, no co-medication; - PM: increase in AUC versus EM from 2550 to 4410 nM·hour (S by 73%), increase in C_{ss} from	Authors' conclusion: 'Therefore the impact of sparteine phenotype on paroxetine kinetics does not appear to be of major

polymorphism. Clin Pharmacol Ther 1992;51:278-87. **ref. 19, continuation**		81 to 151 nM (S by 86%), increase in t½ from 16 to 41 hours (S by 156%). NOTE: genotype not known. Phenotyping can only distinguish between PM and the other phenotypes, so EM# is equal to IM, EM and UM.	clinical importance because paroxetine is widely nontoxic and no concentration-effect relationship (efficacy or adverse events) has yet been established in paroxetine treatment of depression.' AUC versus EM+IM+UM: PM: 173%

[a] corrected for body weight.
[b] corrected for dose and body weight

Risk group	UM with CYP2D6 inducer

Comments: ===

- Kinetic articles with single dosing were not included for the period after 2014. As paroxetine is a strong inhibitor of CYP2D6, kinetic data for single use provide too little information about the kinetics of repeated doses. In addition, after 2016 only kinetic articles providing the AUC of C_{ss} of paroxetine per CYP2D6 phenotype were included.
- Zourková A et al. Links among paroxetine-induced sexual dysfunctions, gender, and CYP2D6 activity. J Sex Marital Ther 2007;33:343-55:
  One of the conclusions from this article is that the CYP2D6 genotype is a poor predictor of the CYP2D6 activity in long-term users of paroxetine (10-40 mg/day; average 23.2 mg/day). Of the 36 paroxetine users with genotype *1/*1 (screening for *3, *4, *5, *6 and gene duplication), 61% was phenotypically PM and only 39% was phenotypically EM# (EM+IM+UM) when phenotyping was performed using dextromethorphan. Of the 19 paroxetine users with gene dose 1 or 0, 74% was phenotypically PM and 26% was phenotypically EM#.
- Existing guidelines:
  Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther 2015;98: 127-34. PubMed PMID: 25974703.
  CPIC uses the same definition for PM as we do. However, CPIC uses different definitions for EM (gene dose 1-2), IM (gene dose 0.5) and UM (gene dose ≥ 2.5). The summary below uses the KNMP definitions for EM, PM, IM and UM.
  CPIC indicates that gene dose ≥ 2.5 results in low or undetectable plasma concentrations in comparison to gene dose 1-2 (Charlier 2003, Gex-Fabry 2008, Guzey 2006 and Lam 2002). Although the minimum therapeutic concentration of paroxetine has not been properly defined, low plasma concentrations can increase the risk of failure of the therapy. Therefore, for gene dose ≥ 2.5, the CPIC recommends considering an alternative SSRI that is not primarily metabolised by CYP2D6. CPIC indicates that there are insufficient data to calculate an initial dose for gene dose ≥ 2.5. CPIC classifies the recommendation for gene dose ≥ 2.5 as "strong".
  CPIC indicates that PM results in a significantly higher exposure to gene dose 1-2 (Charlier 2003 and Sawa-mura 2004). This higher exposure can be a risk factor for side effects. In order to prevent possible side effects, the CPIC recommends considering an alternative SSRI that is not primarily metabolised by CYP2D6. If treatment with paroxetine is desired, the CPIC recommends a dose reduction by 50%. The percentage dose reduction is derived from percentage differences in oral clearance calculated/estimated by Stingl JC et al. Mol Psychiatry 2013;18:273-87. As therapeutic drug monitoring is not commonly performed for SSRIs, there are only limited data available about a linear or non-linear correlation between dose and plasma concentration of paroxetine and the correlation between the plasma concentration and therapeutic effect and side effects. Therefore, the CPIC classifies the strength of the recommendation for PM as "optional".
  According to CPIC, no action is required for gene dose 0.5. Although gene dose 0.5 probably results in a modest increase in exposure and an increased sensitivity to CYP2D6 inhibition, the existing evidence does not support adjustment of the therapy. CPIC classifies the recommendation to start the standard initial dose for gene dose 0.5 as "moderate". The reason for this is that the literature is difficult to assess, because of inconsistent categorisation of the genotypes into either the phenotype group IM or EM. However, CPIC classifies the recommendation to start the standard initial dose for gene dose 1-2 as "strong".
  The recommendations are as follows:
  - gene dose ≥ 2.5: consider an alternative that is not predominantly metabolised by CYP2D6.
  - IM (gene dose 0.5 or 1): no action required.

- PM: choose an alternative that is not predominantly metabolised by CYP2D6, or - if paroxetine is desired - consider decreasing the dose to 50% of the standard initial dose and adjust the dose based on effect.

On 9-4-2018, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of literature search: 6 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmaco-genetics Working Group decision	PM	4 A	yes	no	14 May 2018
	IM	4 A	yes	no	
	UM	4 C	yes	yes	

Mechanism:

Paroxetine is primarily metabolised by CYP2D6 to inactive metabolites. Paroxetine is a strong inhibitor of CYP2D6. As a result, the pharmacokinetics of paroxetine are non-linear (an increase in a dose of 20 mg/day by a factor 1.5 results in an increase in the paroxetine concentration by a factor 1.9) and the effect of CYP2D6 on the pharmaco-kinetics of paroxetine is greater for a single dose than for repeated doses (the difference between EM and PM is reduced by a factor 3.5).

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 genotype 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