CYP2D6: mirtazapine 2001/2002/2003

Cl_{or} = oral clearance, C_{ss} = steady state concentration, HAMD = Hamilton Rating Scale for Depression, 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, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 enzyme activity)

Brief summary and justification of choices:
Mirtazapine is converted by CYP3A4 to the metabolite N-desmethylmirtazapine, which has a pharmacological activity that is 3-6% that of mirtazapine. Mirtazapine is mainly converted by CYP2D6 and CYP1A2 to inactive hydroxy metabolites. This conversion primarily involves the S(+)-enantiomer. Both enantiomers play a role in the side effect "sedation", only the R(-)-enantiomer plays a role in the effects on blood pressure and heart rate. The S(+)-enantiomer is probably more therapeutically effective than the R(-)-enantiomer.

IM: Two studies from the same group, one with 38 IM and one with 28 IM showed an increase in side effects and either a reduced or a better (or faster) effectiveness (Zastrozhin 2020 and Zastrozhin 2019). However, Zastrozhin 2020 did not find significant differences in plasma concentrations and dose-corrected plasma concentrations of mirtazapine between NM and IM, making it very unlikely that the observed (small and/or inconsistent) differences in clinical outcomes were due to CYP2D6 gene variants.. In addition, Zastrozhin 2019 only determined effects during treatment initiation (until day 16) and the patient group was not representative for patients normally treated with mirtazapine. The patients in Zastrozhin 2019 had mild depression (Hamilton Rating Scale score < 15) combined with alcohol use disorder. Because of this, the KNMP Pharmacogenetics Working Group decided that there is no evidence that the IM phenotype results in clinical effects after the treatment initiation phase and in patients with major depression. IM has been shown to increase S(+)-mirtazapine, but not R(-)-mirtazapine (Hayashi 2015, Lind 2009 and Brockmöller 2007). For these reasons, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction, but that adjustment of therapy is not required.

PM: A study with 3 PM and single dose administration found a longer duration of the adverse event "dry mouth" for PM (Kirchheiner 2004). However, 2 case reports and a study with 1 PM found no side effects for PM on mirtazapine (Johnson 2006, Stephan 2006, and Grasmäder 2004). In addition, Murphy 2003 did not find an increase in side effects for 27x PM+IM. A study involving a very low dose of S-mirtazapine found an effect on the ability to drive for 7 PM, but not for IM+NM+UM (Ramaekers 2011). However, in therapeutic doses, mirtazapine does have a severe negative effect on the ability to drive, also for non-PM. So, there is insufficient evidence for a clinical effect for PM patients. For this reason, the KNMP Pharmacogenetics Working Group decided that adjustment of therapy is not required for PM either.

UM: No clinical effects were found for UM.

Based on the data above, the KNMP Pharmacogenetics Working Group concluded that there is a gene drug interaction (due to the effect on S(+)-mirtazapine pharmacokinetics (Hayashi 2015, Lind 2009 and Brockmöller 2007)), but that therapy adjustments are not required (yes/no-interactions).
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.

The table below follows the KNMP definitions for NM, PM, IM and UM. Therefore, the definitions of NM, PM, IM and UM used in the table below may differ from the definition used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Scherf-Clavel M et al. Effects of pharmacokinetic gene variation on therapeutic drug levels and	**3**	171 patients from two cohorts (107 and 64 patients from each of the cohorts) were treated with mirtazapine (final dose 7.5-120 mg/day (mean 45 mg/day)). The cohort from which 107 patients were derived included patients with unipolar depression. Therapeutic drug monitoring was performed according to the doctor's choice and not per protocol and used to adjust the dose. Patients were analysed after 6 weeks of treatment. The other cohort included patients with at least a moderate depressive	Authors' conclusion: 'Dose-corrected concentrations of quetiapine and mirtazapine were not associated with the examined diplotypes/

<table>
<tr>
<td>anti-depressant treatment response. Pharmacopsychiatry 2022 Jul 15. Online ahead of print. PMID: 35839823.

ref. 1, continuation</td>
<td>PM: AA
IM: AA
UM: AA</td>
<td>period (Hamilton Depression Rating Scale-21 ($HAMD_{21}$) > 14). Therapeutic drug monitoring was performed in week 3, 5, and 7 of treatment and used to adjust the dose. Patients were analysed after 7 weeks of treatment.
49% of patients were responders (31% in the cohort from which the 107 patients were derived and 77% in the other cohort). Treatment response was defined as ≥ 50% reduction in $HAMD_{21}$-score. 31% of patients showed remission (19% in the cohort from which the 107 patients were derived and 52% in the other cohort).
Change of antidepressant due to adverse drug reactions was assessed in the cohort from which 107 patients were derived (not observed, but data missing in 64% of patients). Adverse drug reactions were assessed in the other cohort (1 mild and 1 medium adverse drug reaction were observed),
Clinical improvement was measured as the percentual reduction in the $HAMD_{21}$-score. Remission was defined as a $HAMD_{21}$-score ≤ 7.
Trough serum concentrations in steady state were determined.
Dimensional outliers (≥ 4 SD from the mean) from the (dose-corrected) serum concentration were set as missing data.
Relevant comedication was not excluded, but the dose-corrected concentration and clinical improvement were also determined in a post-hoc, explorative analysis excluding patients using CYP2D6 inhibitors. 34% of the patients was smoker. Results were not corrected for smoking status. The authors do not indicate whether the difference in response and remission between the two cohorts is significant and do not correct for the cohort from which the patient was derived.
P-values were Bonferroni-corrected for the total number of genes (7) and the total number of drugs (4) investigated. As a result p ≤ 0.001 was considered significant.

Genotyping:
The number of NM, IM, PM and UM+gene dose 2.5 is not mentioned.

Results:
<table>
<tr><td colspan="2">Results for PM versus IM versus NM versus UM+gene dose 2.5:</td></tr>
<tr><td rowspan="2">clinical improvement (percentual reduction in $HAMD_{21}$ score)</td><td>NS

(The association was S before Bonferroni-correction.)</td></tr>
<tr><td>Results were similar after exclusion of patients using CYP2D6 inhibitors.</td></tr>
<tr><td>% of patients with remission</td><td>NS</td></tr>
<tr><td rowspan="2">dose-corrected concentration of mirtazapine</td><td>NS</td></tr>
<tr><td>The association was also NS after exclusion of patients using CYP2D6 inhibitors.</td></tr>
</table>

Note: Genotyping was for *2 through *6, *9, *10, *41, and gene multiplication. These are the most important gene variants in this German population.</td>
<td>phenotypes. ….. Pk gene variation did not affect treatment response.’</td>
</tr>
<tr>
<td>ref. 2
Milosavljevic F et al. Association of CYP2C19 and CYP2D6 poor and intermediate metabolizer status with antidepressant and antipsycho-</td>
<td>4</td>
<td>Meta-analysis of 4 studies with a total of 144 participants (patients or healthy volunteers), including a total of 125 NM (gene dose 2) and 19 PM. Studies showing a critical risk of bias were not excluded from the meta-analysis. Of the 4 included studies, 1 had a serious risk of bias according to the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool (showing a serious risk of bias in 1 of the 7 assessed domains and a moderate risk in another domain), and the other 3 had a moderate risk of bias (showing a moderate risk of bias in 2-3 of the 7 assessed domains).
Of the 4 studies included in the meta-analysis, 3 were included in this risk analysis separately (Jacquenoud Sirot 2012, Lind 2009, and</td>
<td>Authors’ conclusion:
‘Exposure differences were also observed for clozapine, quetiapine fumarate, amitriptyline hydrochloride, mirtazapine, nortriptyline hydro-</td>
</tr>
</table>

<table>
<tr>
<td>tic exposure: a systematic review and meta-analysis. JAMA Psychiatry 2021;78:270-80.
PMID: 33237321.

ref. 2, continuation</td>
<td>PM: A</td>
<td>Kirchheiner 2004).
Meta-analyses were performed with a fixed-effects model, but prospective registration of the protocol was not mentioned. In addition, a fixed-effects model should only been applied in case of absence of heterogeneity between the studies and so, this statistical method should only be chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias analysis was assessed by Egger test and funnel plot. However, publication bias could not be assessed reliably owing to the insufficient number of included studies (< 10).

Results:
<table>
<tr><td>Mirtazapine exposure for PM compared to NM (gene dose 2):</td></tr>
<tr><td>x 1.39 (S) in a fixed-effects model and
x 1.42 (S) in a random-effects model</td></tr>
<tr><td>Heterogeneity between the studies was significant and moderate.</td></tr>
<tr><td>Results were similar after exclusion of the study with a serious risk of bias (x 1.40 (S) in a fixed-effects model; heterogeneity between the studies was significant and moderate).</td></tr>
<tr><td>There were no indications for publication bias.</td></tr>
</table>
</td>
<td>chloride, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, and venlafaxine hydrochloride; however, these differences were marginal, ambiguous, or based on less than 3 independent studies.’</td>
</tr>
<tr>
<td>ref. 3
Zastrozhin MS et al.
The Influence of concentration of microRNA hsa-miR-370-3p and CYP2D6*4 on equilibrium concentration of mirtazapine in patients with major depressive disorder. Psychopharmacol Bull 2020;50:58-75.
PMID: 32733112.</td>
<td>3</td>
<td>192 patients were treated with mirtazapine (mean dose 37.4 mg/day) for a period of 8 weeks.
Mirtazapine effectiveness was evaluated with the Hamilton Depression Rating Scale and the Hospital Anxiety and Depression Scale, Adverse events were evaluated with the UKU Side- Effect Rating Scale (UKU).
Therapeutic drug monitoring was performed in the 8th week of treatment.
Other psychotropic medication is excluded, but it is not mentioned whether non-psychotropic comedication affecting CYP2D6 is excluded. All patients had a history of alcohol abuse, but were currently abstinent.
The Benjamin-Hochberg test was used to adjust for multiple comparisons.

Genotyping:
- 154x NM
- 38x IM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td></td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="3">median Hamilton Depression Rating Scale score</td><td>week 4</td><td>x 1.12 (S)</td><td>13.0</td></tr>
<tr><td>week 8</td><td>x 1.20 (S)</td><td>10.0</td></tr>
<tr><td colspan="3">For both IM and NM, the median Hamilton Depression Rating Scale score in week 1 was 22.0, indicating a decrease during treatment with 54.5% for NM and with 45.5% for IM, with the final difference in score between NM and IM being only 9% of the score observed in week 1. Because response is usually defined as a decrease ≥ 50%, it is questionable whether this small difference is clinically relevant.</td></tr>
<tr><td rowspan="3">median Hospital Anxiety and Depression Scale score</td><td>week 4</td><td>x 1.11 (S)</td><td>22.0</td></tr>
<tr><td>week 8</td><td>x 1.20 (S)</td><td>15.0</td></tr>
<tr><td colspan="3">The median Hospital Anxiety and Depression Scale score in week 1 was 37.0 and 36.0 for NM and IM, respectively,,indicating a decrease during treatment with 59% for NM and with 50% for IM, with the final diffe-</td></tr>
</table>
</td>
<td>Authors’ conclusion:
‘The effect of genetic polymorphism of the CYP2D6 gene on the efficacy and safety profiles of mirtazapine was demonstrated in a group of 192 patients with recurrent depressive disorder.’</td>
</tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td>IM: B</td><td>
<table>
<tr><td></td><td colspan="3">rence in score between NM and IM being only 8% of the score observed in week 1. it is questionable whether this small difference is clinically relevant.</td></tr>
<tr><td rowspan="2">median UKU Side-Effect Rating Scale score</td><td>week 4</td><td>NS</td><td>3.0</td></tr>
<tr><td>week 8</td><td>x 1.33 (S)</td><td>3.0</td></tr>
<tr><td colspan="2">median dose-corrected plasma concentration of mirtazapine</td><td>x 1.26 (NS)</td><td>0.23 ng/ml per mg</td></tr>
<tr><td colspan="2">median plasma concentration of mirtazapine</td><td>NS</td><td>9.60 ng/ml</td></tr>
</table>
Note: Genotyping was for *4. This is the most important variant allele in this Russian population.
Genotype distribution was in Hardy-Weinberg equilibrium.</td><td>Median dose-corrected plasma concentration of mirtazapine compared to NM:
IM: 126%</td></tr>
<tr><td>ref. 4
Zastrozhin MS et al.
Effects of CYP-2D6 activity on the efficacy and safety of mirtazapine in patients with depressive disorders and comorbid alcohol use disorder.
Can J Physiol Pharmacol 2019;97:781-5.
PubMed PMID: 31100205.

ref. 4, continuation</td><td>3

IM: AA#

IM: C</td><td>109 patients with depressive disorder and comorbid alcohol use disorder were treated with mirtazapine for 16 days. The median mirtazapine dose was 30 mg/day.
Depression and addiction symptoms were rated with the following scales: Penn Alcohol Craving Scale, Visual Analogue Scale, Clinical Global Impression, Hospital Anxiety and Depression Scale, and Hamilton Rating Scale for Depression. Higher scores on these scales indicate greater addiction or depression. Adverse events were rated with The UKU Side Effects Rating Scale.
Psychotropic medication other than mirtazapine was excluded, with the exception of phenazepam for the treatment of alcohol withdrawal syndrome. Co-medication with effect on CYP2D6 activity was not excluded.

Genotyping:
- 81x NM
- 28x IM

Results:
<table>
<tr><td colspan="4">Median scores on addiction, depression and adverse event rating scales for IM compared to NM:</td></tr>
<tr><td></td><td></td><td></td><td>value for NM</td></tr>
<tr><td rowspan="3">Penn Alcohol Craving Scale</td><td>day 1</td><td>NS</td><td>7.0</td></tr>
<tr><td>day 9</td><td>x 0.50 (S)</td><td>4.0</td></tr>
<tr><td>day 16</td><td>x 0.50 (S)</td><td>2.0</td></tr>
<tr><td rowspan="3">Visual Analogue Scale</td><td>day 1</td><td>NS</td><td>30.0</td></tr>
<tr><td>day 9</td><td>x 0.65 (S)</td><td>17.0</td></tr>
<tr><td>day 16</td><td>x 0.41 (S)</td><td>11.0</td></tr>
<tr><td rowspan="3">Clinical Global Impression</td><td>day 1</td><td>NS</td><td>3.0</td></tr>
<tr><td>day 9</td><td>x 0.50 (S)</td><td>2.0</td></tr>
<tr><td>day 16</td><td>x 0 (S)</td><td>1.0</td></tr>
<tr><td rowspan="3">Hospital Anxiety and Depression Scale</td><td>day 1</td><td>NS</td><td>22.0</td></tr>
<tr><td>day 9</td><td>x 0.63 (S)</td><td>12.0</td></tr>
<tr><td>day 16</td><td>x 0.50 (S)</td><td>8.0</td></tr>
<tr><td rowspan="3">Hamilton Rating Scale for Depression</td><td>day 1</td><td>NS</td><td>13.0</td></tr>
<tr><td>day 9</td><td>x 0.57 (S)</td><td>7.0</td></tr>
<tr><td>day 16</td><td>x 0.30 (S)</td><td>5.0</td></tr>
<tr><td rowspan="3">UKU Side Effects Rating Scale</td><td>day 1</td><td>NS</td><td>1.0</td></tr>
<tr><td>day 9</td><td>x 1.33 (S)</td><td>3.0</td></tr>
<tr><td>day 16</td><td>x 1.42 (S)</td><td>6.0</td></tr>
</table>
NOTE: Genotyping was performed for *4. This is the most important gene variant in this Russian population.</td><td>Authors' conclusion:
''This study demonstrated that an increased CYP2D6 activity reduces the efficacy of treatment with mirtazapine.''</td></tr>
<tr><td>ref. 5
Hayashi Y et al.
Factors affec-</td><td>4</td><td>66 patients were treated with mirtazapine (mean dose 20.4 mg/day; range: 3.75-45 mg/day (0.065-1.10 mg/kg per day)). Steady-state plasma concentrations were determined 10-15 hours after dosing.</td><td>Authors' conclusion:
''Homozygous</td></tr>
</table>

<table>
<tr>
<td>ting steady-state plasma concentrations of enantiomeric mirtazapine and its desmethylated metabolites in Japanese psychiatric patients. Pharmacopsychiatry 2015;48:279-85.
PubMed PMID: 26595747.

ref. 5, continuation</td>
<td>IM: A</td>
<td>CYP enzyme inhibitors and inducers were excluded. 15 patients were smokers.

Genotyping:
- 17x gene dose 2 (no *10 alleles; NM)
- 35x gene dose 1.25 (one *10 allele; NM)
- 14x gene dose 0.5 (two *10 alleles; IM)

Results:
<table>
<tr><td colspan="4">Dose- and bodyweight-corrected plasma concentrations (in ng/mL per mg/kg) compared to gene dose 2:</td></tr>
<tr><td></td><td>gene dose 0.5</td><td>gene dose 1.25</td><td>value for gene dose 2</td></tr>
<tr><td rowspan="2">S(+)-mirtazapine</td><td>x 1.84 (S)</td><td>x 1.12 (NS)</td><td>17.9</td></tr>
<tr><td colspan="3">S for (gene dose 0.5) versus (gene dose 1.25) versus (gene dose 2)
Multiple regression analysis showed the number of *10 alleles to be an independent predictor for the dose-corrected S(+)-mirtazapine plasma concentration.
The number of CYP2D6 *10 alleles determined 7.8% of the variability in dose-corrected plasma concentration of S(+)-mirtazapine.</td></tr>
<tr><td rowspan="2">R(-)-mirtazapine</td><td>x 1.35 (NS)</td><td>x 0.99 (NS)</td><td>36.2</td></tr>
<tr><td colspan="3">NS for (gene dose 0.5) versus (gene dose 1.25) versus (gene dose 2)</td></tr>
<tr><td rowspan="2">S(+)-desmethylmirtazapine</td><td>x 1.89 (NS)</td><td>x 1.56 (NS)</td><td>6.2</td></tr>
<tr><td colspan="3">NS for (gene dose 0.5) versus (gene dose 1.25) versus (gene dose 2)</td></tr>
<tr><td rowspan="2">R(-)-desmethylmirtazapine</td><td>x 1.26 (NS)</td><td>x 1.08 (NS)</td><td>46.3</td></tr>
<tr><td colspan="3">NS for (gene dose 0.5) versus (gene dose 1.25) versus (gene dose 2)</td></tr>
<tr><td rowspan="2">ratio S(+)-mirtazapine/R(-)-mirtazapine</td><td>x 1.38 (NS)</td><td>x 1.04 (NS)</td><td>0.55</td></tr>
<tr><td colspan="3">NS for (gene dose 0.5) versus (gene dose 1.25) versus (gene dose 2)</td></tr>
</table>

NOTE: Genotyping was performed for *2, *5 and *10. These are the most important gene variants in this Japanese population. Patients with a *5-allele were excluded from the study.</td>
<td>CYP2D6 *10 alleles and smoking have a significant impact on the metabolism of S-(+)-mirtazapine in Japanese patients.''

Dose-corrected plasma concentration of mirtazapine compared to gene dose 2:
IM: 151%</td>
</tr>
<tr>
<td>ref. 6
Okubo M et al. Effects of cytochrome P450 2D6 and 3A5 genotypes and possible co-administered medicines on the metabolic clearance of antidepressant mirtazapine in Japanese patients. Biochem Pharmacol 2015;93:104-9.
PubMed PMID: 25475885.</td>
<td>3

IM: A</td>
<td>14 patients were treated with mirtazapine.
Relevant co-medication was not excluded. 2 patients were smokers (one NM (<10 cigarettes per day) and one IM (>20 cigarettes per day)).

Genotyping:
- 9x NM (2x gene dose 2, 7x gene dose 1.5)
- 5x IM (1x gene dose 1, 3x gene dose 0.5, 1x gene dose 0.25)

Results:
<table>
<tr><td colspan="2">Dose corrected trough plasma concentration of mirtazapine compared to NM (approximately 0.9 ng/ml per mg):</td></tr>
<tr><td>IM</td><td>approximately x 2.44 (S)</td></tr>
</table>

NOTE: Genotyping was performed for *2, *5 and *10. These are the most important gene variants in this Japanese population.v</td>
<td>Authors' conclusion:
'These results suggested that mirtazapine metabolic clearance could be variously influenced by the CYP-2D6 and CYP-3A5 genotypes and coadministered drugs in clinical patients.''

Dose-corrected plasma concentration of mirtazapine compared to NM:
IM: approx. 244%</td>
</tr>
</table>

<table>
<tr>
<td>ref. 7
Jaquenoud Sirot E et al. Multicenter study on the clinical effectiveness, pharmacokinetics, and pharmacogenetics of mirtazapine in depression. J Clin Psychopharmacol 2012;32:622-9. PubMed PMID: 22926595.</td>
<td>3

IM: A
PM: A
UM: A</td>
<td>41 patients were treated with mirtazapine for 8 weeks. The mirtazapine dose was 30 mg/day on days 1-14 and 30-45 mg/day on days 15-56. The dose could be adapted on days 15, 28, and 42. Deviations from the dosing schedule, such as dose reductions below 30 mg/d or at other time points, were allowed only in case of intolerable adverse events.
Depression symptoms were measured with the 17-item Hamilton Depression rating scale (HAMD). HAMD total score significantly decreased from 24.8 at baseline to 9.8 at the end of this study, and the response rate (≥ 50% decrease in the score on the HAMD) was 81%. No serious adverse drug reactions were reported during the study.
Stable benzodiazepine treatment (with a maximum of 30% change in dose during the study), and zopiclone, zolpidem or chloral hydrate for night-time sedation were not excluded, but other psychotropic and sedative drugs, antiepileptic drugs and thyroid hormones were excluded. Co-medication with effect on mirtazapine metabolism was not excluded. 38% of patients was smoker.

Genotyping:
-22x NM
-13x IM
-3x PM
-3x UM

Results:
<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM</td></tr>
<tr><td>score on the Hamilton Depression scale</td><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr>
<tr><td>change in score on the Hamilton Depression scale</td><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr>
<tr><td rowspan="2">R-mirtazapine plasma concentration on day 14 (ng/ml)</td><td>x 1.01</td><td>x 1.00</td><td>x 0.88</td><td>22.5</td></tr>
<tr><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr>
<tr><td rowspan="4">S-mirtazapine plasma concentration on day 14 (ng/ml)</td><td>x 2.17</td><td>x 1.55</td><td>x 1.38</td><td>6.5</td></tr>
<tr><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr>
<tr><td colspan="4">S for PM versus IM versus NM versus UM in non-smokers, but not in smokers</td></tr>
<tr><td colspan="4">S-mirtazapine/R-mirtazapine was S for PM versus IM versus NM versus UM in all patients and in non-smokers, but not in smokers.</td></tr>
<tr><td rowspan="2">R-mirtazapine + S-mirtazapine plasma concentration on day 14 (ng/ml)</td><td>x 1.30</td><td>x 1.15</td><td>x 1.02</td><td>28.3</td></tr>
<tr><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr>
<tr><td rowspan="2">R-desmethylmirtazapine plasma concentration on day 14 (ng/ml)</td><td>x 1.55</td><td>x 1.17</td><td>x 1.48</td><td>16.7</td></tr>
<tr><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr>
<tr><td rowspan="4">S-desmethylmirtazapine plasma concentration on day 14 (ng/ml)</td><td>x 2.24</td><td>x 1.71</td><td>x 1.24</td><td>2.1</td></tr>
<tr><td colspan="4">Trend for an association (p = 0.09) (NS).</td></tr>
<tr><td colspan="4">S for PM versus IM versus NM versus UM in non-smokers, but not in smokers</td></tr>
<tr><td colspan="4">S for PM versus IM versus NM versus UM on day 28, 42 and 56 (dose-corrected plasma concentrations).</td></tr>
<tr><td rowspan="2">R-8-hydroxymirtazapine plasma concentration on day 14 (ng/ml)</td><td>-</td><td>x 0.42</td><td>x 0.35</td><td>2.6</td></tr>
<tr><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr>
</table>
</td>
<td>Authors' conclusion:
'Only in nonsmokers, plasma levels of S(+)-enantiomer of mirtazapine and metabolites depended on the CYP2D6 genotype. Therefore, high CYP1A2 activity seen in smokers seems to mask the influence of the CYP-2D6 genotype.''

Plasma concentration of mirtazapine compared to NM:
IM:115%
PM:130%
UM:102%</td>
</tr>
</table>

ref. 7, continuation		<table><tr><td>S-8-hydroxymirtazapine plasma concentration on day 14 (ng/ml)</td><td>x 1.18</td><td>x 1.18</td><td>x 0.73</td><td>1.1</td></tr><tr><td colspan="4">NS for PM versus IM versus NM versus UM</td></tr></table> NOTE: In this study, there was no evidence for a significant plasma concentration-clinical effectiveness or plasma concentration-adverse effect relationship regarding any pharmacokinetic parameter, with the exception of a high probability of being a responder for patients with a plasma concentration of S-mirtazapine ≥ 5 ng/mL (probability of 77%). NOTE: Genotyping was performed for *3-*6 and gene duplication. These are the most important gene variants in this mixed Swiss/ French population. Further analyses identified a *16-allele in one PM (*5/*16).	
ref. 8 Ramaekers JG et al. Residual effects of esmirtazapine on actual driving performance: overall findings and an exploratory analysis into the role of CYP2D6 phenotype. Psychopharmacology 2011;215:321-32. PubMed PMID: 21246188.	3 PM: B	A total of 32 healthy volunteers in a cross-over study received S-mirtazapine 1.5 or 4.5 mg or placebo in the evening for 7 days. The deviation in distance from the side of the lane in a driving ability test was measured eleven hours after the first and last dose. Relevant co-medication was excluded. Phenotyping: 7x PM, 25x NM+IM+UM. PM versus NM+IM+UM: - increase in the percentage of volunteers who stopped prematurely due to mirtazapine-related adverse events (from 0% to 14%) (NS) - for both phenotypes, an effect on the ability to drive comparable to an alcohol concentration of 0.5 mg/mL cannot be ruled out following a single dose of 4.5 mg - for PM, an effect on the ability to drive comparable to an alcohol concentration of 0.5 mg/mL cannot be ruled out following a single dose of 1.5 mg or a repeated dose of 4.5 mg; this can be ruled out for NM+IM+UM - increase in the plasma concentration on day 8 by 80% (from 0.54 to 0.97 ng/mL) at a dose of 1.5 mg/day (NS) - increase in the plasma concentration on day 8 by 39% (from 1.52 to 2.12 ng/mL) at a dose of 4.5 mg/day (NS) NOTE: Genotype unknown. NOTE: The doses used (intended for insomnia) are much lower than the doses used for depression.	Authors' conclusion: "Exploratory analysis in a small group of poor CYP 2D6 metabolizers suggested that these subjects are more sensitive to the impairing effects of esmirtazapine on car driving." Plasma concentration of mirtazapine versus NM+IM+UM: PM: 139-180%
ref. 9 Borobia AM et al. Influence of sex and CYP2D6 genotype on mirtazapine disposition, evaluated in Spanish healthy volunteers. Pharmacol Res 2009;59:393-8. PubMed PMID: 19429471.	3 IM: A IM+PM: A	A total of 68 healthy volunteers received a single dose of mirtazapine 30 mg in both parts of a cross-over study (various, bio-equivalent formulations). Co-medication was excluded. Genotyping: - 34x NM (32x *1/*1, 1x (*1/*4)x2, 1x *1/*9) - 26x IM (24x gene dose 1 (18x *1/*4, 2x *1/*5, 4x *1/*6) and 2x gene dose 0.5 (1x *3/*9, 1x *4/*9)) - 7x PM (6x *4/*4, 1x *4/*6) - 1x UM ((*1/*1)x2) Gene dose 1 versus NM+UM: - AUC decreased by 16% (from 2176.86 to 1829.34 ng.hour/mL) (NS) - increase in the dose-corrected and weight-corrected AUC, predicted using a pharmacokinetic model, by 6.4% (from 1516.62 to 1613.63 ng.hour/mL) (S for the trend) (PM + gene dose 0.5) versus NM+UM: - AUC decreased by 25% (from 2176.86 to 1628.72 ng.hour/mL) (NS) - increase in the dose-corrected and weight-corrected AUC, predicted using a pharmacokinetic model, by 35% (from 1516.62 to 2049.28 ng.hour/mL) (S for the trend)	Authors' conclusion: "Both CYP2D6 genotype group and sex influence the disposition of mirtazapine in healthy volunteers." AUC mirtazapine versus NM: IM: 106%

ref. 9, continuation		NOTE: Genotyping was performed for *3 through *7, *9 and gene duplication.	
ref. 10 Lind AB et al. Steady-state concentrations of mirtazapine, N-desmethyl-mirtazapine, 8-hydroxy-mirtazapine and their enantiomers in relation to cytochrome P450 2D6 genotype, age and smoking behaviour. Clin Pharmacokinet 2009;48:63-70. PubMed PMID: 19071885.	4 IM: A PM: A UM: AA	A total of 95 patients were treated with mirtazapine 30 mg/day for 4 weeks, substrates and strong inhibitors of CYP2D6 as co-medication were excluded. Correction was performed for gender, age and smoking. Genotyping: - 56x NM (*1/*1) - 30x IM (4x *1/*3, 19x *1/*4, 5x *1/*5, 2x *1/*6) - 6x PM (3x *4/*4, 3x *4/*5) - 3x UM (*1/*1xN with N $\geq$ 2) IM versus NM: - increase in the median C_{ss} of mirtazapine by 3.3% (from 122 to 126 nmol/L) (NS) - increase in the median C_{ss} of S(+)-mirtazapine by 39% (from 28 to 39 nmol/L) (S) - decrease in the median C_{ss} of R(-)-mirtazapine by 1.1% (from 91 to 90 nmol/L) (NS) PM versus NM: - increase in the median C_{ss} of mirtazapine by 57% (from 122 to 192 nmol/L) (NS) - increase in the median C_{ss} of S(+)-mirtazapine by 111% (from 28 to 59 nmol/L) (S) - increase in the median C_{ss} of R(-)-mirtazapine by 9.9% (from 91 to 100 nmol/L) (NS) UM versus NM: - increase in the median C_{ss} of mirtazapine by 4.1% (from 122 to 127 nmol/L) (NS) - decrease in the median C_{ss} of S(+)-mirtazapine by 25% (from 28 to 21 nmol/L) (NS) - increase in the median C_{ss} of R(-)-mirtazapine by 16% (from 91 to 106 nmol/L) (NS) NOTE: Genotyping was performed for *3 through *6 and gene duplication.	Authors' conclusion: "This study is the first to show the impact of the CYP2D6 genotype on steady-state serum concentrations of the enantiomers of mirtazapine and its metabolites." Plasma concentration of mirtazapine versus NM: PM: 157% IM: 103% UM: 104%
ref. 11 Brockmöller J et al. Pharmacokinetics of mirtazapine: enantioselective effects of the CYP2D6 ultra rapid metabolizer genotype and correlation with adverse effects. Clin Pharmacol Ther 2007;81:699-707.	3 PM: A UM: A	The samples obtained in Kirchheiner, 2004 were analysed for enantioselective effects. S(+)-mirtazapine: - decrease in AUC from PM to NM to UM (17.7, 9.9 and 6.7 mg.min/L respectively) (S) - increase in Cl_{or} from PM to NM to UM (1.3, 2.3 and 3.4 L/min respectively) (S) - the clearance is higher than can be explained by the hepatic blood flow (1-1.6 L/min): therefore, a "first pass" effect occurs - plasma concentration correlates with sedation (S) R(-)-mirtazapine: - no decrease in AUC from PM to NM to UM (34.1, 29.4 and 30.3 mg.min/L respectively) (S) - no increase in Cl_{or} from PM to NM to UM (0.66, 0.77 and 0.74 L/min respectively) (S) - plasma concentration correlates with sedation and to a reduction in heart rate and blood pressure 4 hours after administration (S) Both enantiomers: - no difference in plasma concentrations of the desmethyl metabolite between PM, NM and UM	Authors' conclusion: "In ultrarapid metabolizers, one might consider administering higher doses to achieve equivalent sedative and antidepressive effects, but one encounters the dilemma that the cardiovascularly active R(-) enantiomer will not be equally ultrarapidly eliminated."

ref. 11, continuation		- plasma concentrations of the desmethyl metabolites were lower than those of the mother substance	
ref. 12 Johnson M et al. A poor metabolizer for cytochromes P450 2D6 and 2C19: a case report on antidepressant treatment. CNS Spectr 2006;11:757-60.	1 PM: AA	A female patient stopped taking venlafaxine, amitriptyline and escitalopram due to side effects. The patient was found to be CYP2D6 *4/*4 and CYP2C19 *2/*2. The patient's condition improved in the hospital, after the dose was set to mirtazapine 45 mg/day and hydroxyzine 50 mg/day. There was no follow-up after discharge and plasma concentrations were not determined.	
ref. 13 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: AA	A 47-year-old male exhibited multiple side effects during treatment with clomipramine and quetiapine. The patient was found to be a PM for CYP2D6 (*4/*6), NM for CYP2C19 and had a low CYP3A4/5 activity. The patient was previously treated with mirtazapine (for 4 weeks, maximum dose 60 mg/day). The patient exhibited no clinical response to mirtazapine, side effects that formed a reason to perform genotyping were only reported for clomipramine and quetiapine.	
ref. 14 Kirchheiner J et al. Impact of the CYP2D6 ultrarapid metabolizer genotype on mirtazapine pharmacokinetics and adverse events in healthy volunteers. J Clin Psychopharmacol 2004;24:647-52.	3 UM: A PM: B	A total of 25 healthy, male volunteers (12x NM (gene dose 2), 10x UM (gene dose 3), 3x PM (gene dose 0)) received a single dose of mirtazapine 45 mg. UM versus NM: - AUC mirtazapine decreased from 1.13 to 0.9 mg.hour/L (S by 20%). - Cl_{or} mirtazapine increased from 39.7 to 49.8 L/hour (S by 25%) PM versus NM: - AUC mirtazapine increased from 1.13 to 2.24 mg.hour/L (S by 98%) - Cl_{or} mirtazapine decreased from 39.7 to 20.1 L/hour (S by 49%) - 10 hours after administration, the PMs were still experiencing dry mouth, i.e. a longer period of side effects There was a significant correlation of the mirtazapine plasma concentration with reduced blood pressure, but not with heart rate or QT interval. All volunteers experienced significant sedation. The AUC of desmethylmirtazapine did not differ significantly between PM, NM and UM. Population pharmacokinetics analysis predicts that in carriers of 0, 1, 2 and 3 active CYP2D6 alleles, 0%, 25%, 39% and 55% of Cl_{or} mirtazapine is caused by CYP2D6. NOTE: Genotyping was performed for the alleles *3, *4, *5 and *6 and for gene duplication.	AUC mirtazapine versus NM: PM: 198% UM: 80%
ref. 15 Grasmäder K et al. Population pharmacokinetic analysis of mirtazapine.	3	Plasma concentrations were determined on a weekly basis in 49 patients (29x NM, 1x PM, 18x IM and 1x UM) on mirtazapine. A total of 22 patients received CYP2D6 substrates as co-medication, 10 patients received CYP2D6 inhibitors. A population pharmacokinetics model was constructed with the data. The PM and UM had no abnormal plasma concentrations (33 and 36 ng/mL respectively) and were added to the IMs and NMs respectively	Authors' conclusion: "The variability of mirtazapine plasma concentrations in clinical routine is caused

Eur J Clin Pharmacol 2004;60:473-80. **ref. 15, continuation**	IM: A	for the model construction. The resulting model predicts a 26.4% lower clearance for IMs than for NMs. The article did not contain any raw data. NOTE: Genotyping was performed for the alleles *2,*3, *4, *5, *6, *7, *8 and *9 and for gene duplication. In this study, the *9 allele was categorised with the null alleles.	to a relevant degree by CYP-2D6. This should be taken into account when a special clinical situation, such as co-morbidity and add-on medication, demands careful dosing of this drug."
ref. 16 Grasmäder K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.	3 PM: AA UM: AA	A total of 136 Caucasian patients on antidepressants, including 43 on mirtazapine (dose unknown) were genotyped. Of the 43 patients on mirtazapine, one was a PM and one was a UM, the other 41 were either IM or NM. Relevant co-medication was not excluded. The mean dose-corrected C_{ss} of mirtazapine was 0.82 ng/mL per mg of dosed doxepin. For the PM, the dose-corrected plasma concentration was 28% higher than the mean. The PM had no relevant side effects. For the UM, the dose-corrected plasma concentration was 4% higher than the mean. The UM did have relevant side effects.	Plasma concentration of mirtazapine versus NM (+ IM): PM: 128% UM: 104%
ref. 17 Murphy GM Jr et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry 2003;160:1830-5.	4 PM+IM: AA	Out of a total of 246 elderly patients, 121 patients (94x NM#+UM, 27x PM+IM) in a mirtazapine versus paroxetine trial received mirtazapine (15 mg/day for 2 weeks, followed by 30 mg/day for 2 weeks, followed by 30 or 45 mg/day for 4 weeks.) PM+IM compared to NM#+UM: - no significant difference in final dose (31.54 versus 31.22 mg/day) - no significant difference in plasma concentration on day 28 (39.84 versus 40.55 ng/mL) - slightly lower percentage of women (44.4 versus 52.1%) - no difference in three depression scores - lower score for the severity of side effects (NS; 38.36 versus 49.47) - lower percentage of patients who stopped treatment due to side effects (NS; 7.4 versus 18.1%) Analysis of variance demonstrated no significant interaction between co-medication and effects of the CYP2D6 genotype on the severity of side effects. NM#: In this study, gene dose 1 – 0 was considered as an NM instead of as an IM. The same results were obtained if gene dose 1 – 0 was considered as an IM instead of an NM.	Authors' conclusion: "CYP2D6 genotype did not predict treatment outcome."

Risk group	-

Comments:

- The study of Shinozaki 2019 (Shinozaki M et al. 8-Hydroxylation and glucuronidation of mirtazapine in Japanese psychiatric patients: significance of the glucuronidation pathway of 8-hydroxy-mirtazapine. Pharmacopsychiatry 2019;52:237-44. PubMed PMID: 31158907) was not included in the risk analysis, because 94% of the patients in this study was also included in Hayashi 2015 and Shinozaki 2019 only contains association analyses, no concentration values per genotype/phenotype.

Date of literature search: 1 September 2022.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4B	Yes	No	14 November 2022
	IM	4C	Yes	No	
	UM	4A	Yes	No	

Mechanism:
Mirtazapine is converted by CYP3A4 to the metabolite N-desmethylmirtazapine, which has a pharmacological activity that is 3-6% that of mirtazapine.
Mirtazapine is mainly converted by CYP2D6 and CYP1A2 to inactive hydroxy metabolites. This conversion primarily involves the S(+)-enantiomer.
Both enantiomers play a role in the side effect “sedation”, only the R(-)-enantiomer plays a role in the effects on blood pressure and heart rate. The S(+)-enantiomer is probably more therapeutically effective than the R(-)-enantiomer.