CYP2C19: mirtazapine 3506 to 3508

IM = intermediate metaboliser (*1/*2, *1/*3, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), NM = normal metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), UM = ultrarapid metaboliser (*17/*17) (elevated CYP2C19 enzyme activity).

Brief summary and justification of choices:
Mirtazapine is converted by CYP2D6 and CYP1A2 to inactive hydroxy metabolites. Mirtazapine is also converted by CYP3A4 to the pharmacologically active N-demethyl metabolite and inactive N-oxide metabolites.
None of the available publications (a study with 171 patients with the number of intermediate, poor, and ultrarapid metabolisers not mentioned (Scherf-Clavel 2022), a study with 49 patients among whom 10 intermediate metabolisers (Grasmäder 2004), and a case report with 1 poor metaboliser (Johnson 2006)) found an effect of the CYP2C19 phenotype on metabolism, adverse effects or effectiveness of mirtazapine. The KNMP Pharmacogenetics Working Group concluded that there is no evidence for a gene-drug interaction (no/no-interactions).
You can find an overview of the observed kinetic and clinical effects per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below uses the KNMP nomenclature for NM, PM, IM and UM. As a result, the definitions of NM, PM, IM and UM in the table below can differ from the definitions used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Scherf-Clavel M et al. Effects of pharmacokinetic gene variation on therapeutic drug levels and anti-depressant treatment response. Pharmacopsychiatry 2022 Jul 15. Online ahead of print. PMID: 35839823.	**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 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. Comedication with CYP2C19 inhibitors was excluded, but smoking was not. 34% of the patients was smoker. Results were not corrected for smoking status. The authors do not indicate whether the difference	Authors' conclusion: 'Dose-corrected concentrations of quetiapine and mirtazapine were not associated with the examined diplotypes/phenotypes. ….. Pk gene variation did not affect treatment response.'

<table>
<tr><td>ref. 1, continuation</td><td>PM: AA
IM: AA
UM: AA</td><td>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 (*1/*1 and *1/*17), IM, PM and UM is not mentioned.

Results:<table><tr><td colspan="2">Results for PM versus IM versus *1/*1 versus *1/*17 versus UM:</td></tr><tr><td>clinical improvement (percentual reduction in $HAMD_{21}$ score)</td><td>NS

(There was a trend for an association before Bonferroni-correction (p = 0.059, NS))</td></tr><tr><td>% of patients with remission</td><td>NS</td></tr><tr><td>dose-corrected concentration of mirtazapine</td><td>NS</td></tr></table>
Note: Genotyping was for *2 and *17. These are the most important gene variants in this German population.</td><td></td></tr>
<tr><td>ref. 2
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.</td><td>1

PM: AA</td><td>A 50-year-old woman who previously had to discontinue venlafaxine, amitriptyline and escitalopram monotherapies due to side effects was found to be CYP2C19 *2/*2 and CYP2D6 *4/*4. She was started on mirtazapine 45 mg/day without sedation occurring.</td><td>Authors’ conclusion:
“The patient seemed to respond well to mirtazapine, a drug that does not depend extensively on CYP 2D6 or CYP 2C19 for its metabolism.”</td></tr>
<tr><td>ref. 3
Grasmäder K et al.
Population pharmacokinetic analysis of mirtazapine.
Eur J Clin Pharmacol 2004;60:473-80.</td><td>3

IM: AA</td><td>65 patients, including 49 genotyped (39x *1/*1, 10x *1/*2), were treated with mirtazapine. Mirtazapine trough concentrations were measured on a weekly basis after attaining steady state. 20% of the trough concentrations measured were found in users of relevant co-medication (16% CYP2C19 substrates and 4% CYP2C19 inhibitors). The number of patients with co-medication was too small to investigate the relevance of the effect on mirtazapine clearance.
A multiple linear regression analysis did not identify the CYP2C19 genotype as a possible relevant factor in the clearance of mirtazapine. Addition of the CYP2C19 genotype to a population pharmacokinetic model for mirtazapine clearance did not improve the prediction of plasma concentrations.

NOTE: only the predominant null allele *2 was genotyped.</td><td>Authors’ conclusion:
“The clearance of CYP2D6 intermediate metabolisers was reduced by 26% compared with normal metabolisers. No other factor significa ntly influenced the clearance of these patients.”
“The following covariates were included in the clearance mixed-effects specification to model interindividual variability: … CYP2C19 genotype and co-medication with sub-</td></tr>
</table>

ref. 3, continuation			strates of CYP-2C19 …. ."

Risk group	--

Comments:

- The article of Zastrozhin 2021 (Zastrozhin MS et al. Impact of the omics-based biomarkers on the mirtazapine's steady-state concentration, efficacy and safety in patients with affective disorders comorbid with alcohol use disorder. Psychopharmacol Bull 2021;51:31-42. PMID: 34092821) was not included in the risk analysis, because it was unclear whether the right data were reported. The article reported that no patient was found to be *2/*2 or *3/*3, but did report outcome data for these genotypes. In addition, the table with outcome data only contains a heading Concentration of fluvoxamine, but not a heading Concentration of mirtazapine. Finally, the article indicated the alleles with the highest frequency to be the minor alleles instead of the major alleles and reported a mean dose of 45 mg/week, which is an unlikely dosing schedule for mirtazapine.
- Possible relationship between CYP2C19 polymorphisms and depression:
  - Jukić MM et al. Elevated CYP2C19 expression is associated with depressive symptoms and hippocampal homeostasis impairment. Mol Psychiatry 2017;22:1155-1163. PubMed PMID: 27895323.
    This publication is from the same group as Sim 2010.
    In a cohort of 3849 urban African-Americans of low economic status, the 123 CYP2C19*2/*2 subjects had a decrease in major depressive disorder prevalence compared to the other subjects with at least one active CYP-2C19 allele (23% versus 32%) (S). In addition, there was a trend for a lower Beck's Depression Inventory (BDI) score in the CYP2C19*2/*2 subjects compared to the other subjects (p = 0.074). However, the lifetime stress exposure was much larger in the African-American cohort compared with the previously analysed Swedish cohort (Sim 2010), thereby increasing the BDI score variability. After the most traumatized subjects (perceived stress scale score at higher quartile and above) were exempted from the analysis to better match the two samples, the BDI score reduction was significant (effect size = - 2.05 (-24.61%)) (S).
    In order to test whether the CYP2C19 genotype influences suicidality in patients with major depressive disorder, CYP2C19 genotype was tested as a predictor for suicide intent in 209 Western European suicide attempters with major depressive disorder. As there were only two CYP2C19*2/*2 allele carriers in the cohort, it was not possible to test whether this genotype affects Beck's suicide intent scale-objective circumstances (SIS-OS) score. However, in a complementary exploratory analysis, the SIS-OS score seemed to vary between different CYP2C19 genotypes with a decrease for *2/*2 versus *1/*1 versus *1/*2 versus *2/*17 versus *17/*17 versus *1/*17. Further analysis showed that SIS-OS score was not significantly affected by the presence of the CYP2C19*2 allele, whereas it was significantly increased in CYP2C19*17 allele carriers (119 versus 90 subjects, effect size = +1.36 (+25.69%)) (S). Since the score was lower for the 8 patients with genotype *17/*17 compared to the patients with genotype *1/*17, this significant effect seemed to be mainly driven by the *1/*17 genotype. The classification of the suicide attempters to severe (SIS-OS score at higher quartile and above) and non-severe, yielded a higher frequency of patients with *17 allele among severe suicide attempters (S).
    The authors conclude that the CYP2C19*2/*2 genotype associates with a phenotype more resilient to major depressive disorder and that the CYP2C19*17 allele may be a risk allele for suicidality in major depressive disorder. They indicate that a major limitation of the suicidality study is the absence of information regarding the individuals' drug treatment and their drug plasma levels. Therefore, it was not possible to determine whether the observed relationship was caused by endogenous or drug-metabolic CYP2C19-mediated effects.
  - Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 2013;18:497-511. PubMed PMID: 22472876.
    A mega-analysis of genome-wide association studies found no significant association between the risk of depression and CYP2C19.
  - Sim SC et al. Association between CYP2C19 polymorphism and depressive symptoms. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:1160-6.
    In a group of 1472 Europeans older than 44 years (1017x NM (637x *1/*1, 380x *1/*17), 375x IM (290x *1/*2, 85x *2/*17), 35x PM (*2/*2), 45x UM), significantly lower depressive symptoms (measured on the Center of Epidemiologic Studies Depression (CES-D) scale) were found among PM patients than among *1/*1. There was only a difference among people younger than 73 years and among men. The effect size was in the same order of magnitude as that observed between non-users and users of antidepressants. The authors stated that CYP2C19 polymorphisms may have an effect on depressive symptoms in adult Europeans.

Date of literature search: 19 September 2022.

Phenotype	Code	Gene-drug interaction	Action	Date

KNMP Pharmacogenetics Working Group decision	PM	3 AA	no	no	14 November 2022
	IM	3 AA	no	no	
	UM	3 AA	no	no	

Mechanism:
Mirtazapine is converted by CYP2D6 and CYP1A2 to inactive hydroxy metabolites. Mirtazapine is also converted by CYP3A4 to the pharmacologically active N-demethyl metabolite and inactive N-oxide metabolites.