CYP2D6: quetiapine 2393/2394/2395

IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 enzyme activity)

Brief summary and justification of choices:
Quetiapine is mainly converted by CYP3A4 to the inactive metabolite quetiapine sulfoxide and to N-desalkylquetiapine (norquetiapine). N-desalkylquetiapine is active, but seems to have mainly anti-depressive activity. In addition, quetiapine and N-desalkylquetiapine are metabolised by CYP2D6 to a limited extent to active 7-hydroxymetabolites. Genetic variants of CYP2D6 can result in reduced or absent CYP2D6 activity (intermediate and poor metabolisers (IM and PM)) or increased CYP2D6 activity (ultra-rapid metabolisers (UM)).
A case report reported two IM patients with quetiapine-induced severe adverse events (Stäuble 2021; 2 IM with gene dose 1). However, in another case report, one even more deficient IM patient tolerated quetiapine well (Kato 2005; 1 IM with gene dose 0.25). In addition, one of the cases in Stäuble 2021 did not show recurrence of severe adverse events on a lower dose of quetiapine after addition of the strong CYP2D6 inhibitor bupropion, suggesting that the problem might not be CYP2D6-related. The patient developing the severe adverse event postural orthostatic tachycardia syndrome, had tachycardia before the start of quetiapine. This raises the question whether he might have had a tachycardia predisposition. Moreover, in a study with 87 IM, 20 PM and 9 UM patients, Bakken 2015 did not find a significant effect of CYP2D6 phenotype on the quetiapine plasma concentration. Results on the plasma concentration of N-desalkylquetiapine were contradictory in this study. Whereas a significant but small effect on the plasma concentration of N-desalkylquetiapine for IM and PM suggested an effect of CYP2D6 phenotype, the lack of a significant effect on the ratio N-desalkylquetiapine/quetiapine suggested the absence of an effect. Finally, due to the relatively high prevalence of the *1/*4 genotype and IM phenotype, the case report of Stäuble 2021 is too small to suggest a significant effect of IM phenotype on the risk of severe adverse events. The allele frequency of *4 is approximately 20% in Europe (18.4% in the Netherlands). Based on the frequencies of the most important CYP2D6 alleles in the Netherlands, the frequency of genotype *1/*4 is 22-23%. As a result, the chance of two randomly picked patients both having this phenotype is 4.94-5.03%, i.e. approximately the probability of 0.05 generally considered the upper border for significance. If also the second major IM group (genotype *1/*5 with the allele frequency of *5 in the Netherlands being 5%) is included in the calculation, the probability of two randomly picked patients being IM already increases to 0.080-0.086, so a value too high for significance. Because of the more than 8% chance of two randomly picked patients being both IM, a case report with 2 IM cases does not suggest a significant effect, For these reasons, the KNMP Pharmacogenetics Working Group decided that there is not enough evidence for a CYP2D6-quetiapine interaction, and thus no reason to recommend a dose adjustment or an alternative (no/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 definition for NM, PM, IM and UM, unless stated otherwise. The definition of NM, PM, IM and UM used in the table below may therefore differ from the definition used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Stäuble CK et al. Severe adverse drug reactions to quetiapine in two patients carrying CYP-2D6*4 variants: a case report. Int J Mol Sci 2021;22:6480.	1 IM: C	Two patients developed severe adverse drug reactions during treatment with quetiapine at doses of 300 and 400 mg/day, respectively. Both patients were CYP2D6 *1/*4. Measurement of quetiapine plasma concentrations was not performed. The only relevant CYP3A4 allele (*22) was not determined. A 63-year-old male with bipolar disorder was treated with agomelatin, vortioxetine, and quetiapine for an episode of moderate bipolar II depression. After quetiapine dose increase to 400 mg/day (an extended-release evening dose of 200 mg and a direct release night dose of 200 mg), the patient suddenly showed a strong sedation and severe movement disorders, which manifested as a persis-	Author's conclusion: "The herein reported cases could spark a discussion on the potential impact of a patient's pharmacogenetic predisposition in the treatment with quetiapine.

PMID: 34204223. **ref. 1, continuation**		tent tremor, while severe constipation was present at that time. Sedation and movement disorders disappeared after quetiapine dose reduction to 100-200 mg/day. Adverse events did not reappear after a change from vortioxetine to the strong CYP2D6 inhibitor bupropion. None of the other comedication of the patient is known to have an effect on CYP2D6 or CYP3A4. The patient had chronic renal insufficiency, but renal insufficiency is not known to affect quetiapine therapy. After a suicide attempt, a 29-year-old male was treated with lisinopril for arterial hypertension and tachycardia and with escitalopram and quetiapine for a moderate depressive episode. After 4 weeks, the lisinopril dose was increased from 7.5 mg/day to 10 mg/day, metoprolol was added, and the quetiapine dose was increased from 50 to 300 mg/day (an extended-release evening dose of 200 mg and a direct release night dose of 100 mg) over a period of 5 days. Upon reaching the maximum quetiapine dosage, the patient suddenly developed massive and continuous emesis and vertigo with an unsteady gait. He did not recover during the next two days. The patient was diagnosed with a postural orthostatic tachycardia syndrome (normotonic, heart rate > 100 bpm). First, quetiapine was slowly reduced and finally discontinued. Then, lisinopril was stopped as well, and metoprolol dose was increased from 25 to 75 mg/day, administered in two doses. Thereby, the aforementioned severe adverse drug reactions remitted. Escitalopram is a weak CYP2D6 inhibitor. Side effects including nausea and vertigo are also reported for metoprolol and lisinopril, and metoprolol clearance may as well be affected by alterations in CYP2D6 activity. However, after remission of the reported adverse events, the patient well tolerated an increase of metoprolol dosage from 25 to 75 mg daily. Note: CYP2D6 genotyping was for *3-*11, *17, *29, *41, and gene multiplication. These are the most important gene variants in Swiss patients.	However, further studies are warranted to promote the adoption of pharmacogenetic testing for the prevention of drug-induced toxicities associated with quetiapine.”
ref. 2 Xu Q et al. Association studies of genomic variants with treatment response to risperidone, clozapine, quetiapine and chlorpromazine in the Chinese Han population. Pharmacogenomics J 2016;16:357-65. PubMed PMID: 26282453.	4	294 patients were treated with quetiapine for 2 months. The initial quetiapine dose was 100-200 mg/day. This dose was gradually increased to 600-800 mg/day within the first week. After week 2, the dose was adjusted according to individual tolerance. Good response was defined as a ≥50% reduction of the score on the Positive and Negative Syndrome Scale (PANSS). Co-medication other than trihexyphenidyl for extrapyramidal side effects, clonazepam or lorazepam for insomnia and sennoside for constipation was excluded. Bonferroni correction was used to correct for multiple testing. A power calculation indicated that the study was sufficiently powered (at least 82.86%) to detect an association with most of the gene variants. The calculated power of 82.86% was based a risk allele frequency of 0.2, a dominant model (risk allele carriers compared to patients homozygous for the wild type allele), and a genotypic relative risk of 1.5 at a significance level of 0.05. A genotypic relative risk of 1.5 is small for drug response of schizophrenia as the genotypic relative risk of most gene variants were >1.5 in this study. Except for *4, the minor allele frequencies of the CYP2D6 gene variants determined in this study were >0.2. Genotyping: *4: - 265x *1/*1 - 16x *1/*4 - 1x *4/*4 *10: - 64x *1/*1 - 125x *1/*10 - 99x *10/*10 2851C>T (*2): - 205x CC - 73x CT - 27x TT 4181G>C (*2): - 169x GG - 98x GC - 27x CC	Author’s conclusion: ”Our study found that rs1135840 in CYP2D6 was associated with quetiapine response.”

<table>
<tr>
<td>ref. 2, continuation</td>
<td>PM: AA

IM: AA</td>
<td>Results:
% of good responders for homozygous variant versus heterozygous versus homozygous wildtype:
<table>
<tr><td></td><td></td><td>value for homozygous wildtype</td></tr>
<tr><td rowspan="2">*4</td><td>NS</td><td rowspan="2">70%</td></tr>
<tr><td>Results were also NS for *4 compared to *1.</td></tr>
<tr><td rowspan="2">*10</td><td>NS</td><td rowspan="2">77%</td></tr>
<tr><td>Results were also NS for *10 compared to *1.</td></tr>
<tr><td rowspan="2">2851C>T (*2)</td><td>NS</td><td rowspan="2">72%</td></tr>
<tr><td>Results were also NS for 2851T compared to 2851C.</td></tr>
<tr><td rowspan="2">4181G>C (*2)</td><td>trend for an increase with increasing numbers of variant alleles (p = 0.095) (NS)</td><td rowspan="2">65%</td></tr>
<tr><td>For 4181C compared to 4181G, OR was 1.60 (95% CI: 1.04-2.45) (S). but significance was lost after correction for multiple testing.</td></tr>
</table>
Note: Genotyping was for both gene variants in *2, and for *4 and *10. Except for *5, these are the most important gene variants in this Chinese population.</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Bakken GV et al.
Impact of genetic variability in CYP2D6, CYP3A5, and ABCB1 on serum concentrations of quetiapine and N-desalkylquetiapine in psychiatric patients.
Ther Drug Monit 2015;37:256-61.
PubMed PMID: 25254417.</td>
<td>3

PM: A
IM: A
UM: AA</td>
<td>287 patients were treated with quetiapine. Blood sampling was performed within 10-14 hours after the last dose.
Relevant co-medication was not excluded.
Results were corrected for significant covariates (sex for quetiapine and N-desalkylquetiapine, and time after last dose for quetiapine).
Sidak correction was used to adjust for multiple testing.

Genotyping:
- 171x NM
- 87x IM
- 20x PM
- 9x UM

Results:
<table>
<tr><td colspan="5">Dose-corrected trough concentrations 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>quetiapine</td><td>NS</td><td>NS</td><td>NS</td><td>approx. 0.5 nM/mg</td></tr>
<tr><td>N-desalkylquetiapine</td><td>x 1.3 (S)</td><td>x 1.2 (S)</td><td>x 1.1 (NS)</td><td>0.89 nM/mg</td></tr>
<tr><td>ratio N-desalkylquetiapine/ quetiapine</td><td>NS</td><td>NS</td><td>NS</td><td></td></tr>
</table>
Note: Genotyping was for *3 through *6 and gene duplication. These are the most important gene variants in this Norwegian population.</td>
<td>Author’s conclusion:
”Genetic variability in CYP2D6 contributes to the interindividual variability in steady-state serum concentrations of N-desalkylquetiapine. Although the metabolite exhibits relevant pharmacological activity, the quantitative effect of CYP2D6 genotype on serum concentration of N-desalkylquetiapine is probably of limited clinical relevance for quetiapine treatment.”</td>
</tr>
<tr>
<td>ref. 4
Khazaal Y et al.
Use of high doses of quetiapine in bipolar disorder episodes are not linked to high activity of cytochrome P450</td>
<td>3</td>
<td>21 patients were treated with quetiapine. 12 patients required a normal dose (100-800 mg/day, mean 433 mg/day, median 350 mg/day) and 9 patients required a high dose (1000-3000 mg/day, mean 1467 mg/day, median 1200 mg/day). Dose titration was based on effectiveness and tolerability.
Relevant co-medication was not excluded.

Genotyping:
- 19x (NM+IM+PM)
- 2x UM</td>
<td>Author’s conclusion:
”The use of high quetiapine dosage for the patients included in the present study cannot be explained by variations in</td>
</tr>
</table>

<table>
<tr><td>3A4 and/or cytochrome P4502D6. Psychiatr Q 2013;84:329-35.
PubMed PMID: 23230007.</td><td>UM: AA</td><td>Results:
<table><tr><td colspan="2">Chance of requiring a high dose compared to NM+IM+PM (high dose requirement in 42% of patients):</td></tr><tr><td>UM</td><td>NS</td></tr></table>
Note: Genotyping was for *3 through *6 and gene duplication. These are the most important gene variants in this Swiss population.</td><td>pharmacokinetics parameters such as a high activity of CYP3A4 and/ or of CYP2D6.”</td></tr>
<tr><td>ref. 5
Kato D et al. Delirium resolving upon switching from risperidone to quetiapine: implication of CYP2D6 genotype. Psychosomatics 2005;46:374-5.</td><td>1

IM: AA</td><td>A 74-year-old male with delirium was switched from risperidone to quetiapine 25 mg/day due to severe extrapyramidal symptoms. The man did not exhibit any side effects on quetiapine. The man was found to be CYP2D6 *5/*10.
The authors reported that quetiapine is primarily metabolised by CYP3A4.</td><td></td></tr>
</table>

Risk group	--

Comments:

- The article of Milosavljevic 2021 (Milosavljevic F et al. Association of CYP2C19 and CYP2D6 poor and intermediate metabolizer status with antidepressant and antipsychotic exposure: a systematic review and meta-analysis. JAMA Psychiatry 2021;78:270-80) was not included, because it does not contain a meta-analysis for CYP2D6 and quetiapine (only 1 study (Bakken 2015) included in the analysis).

Date of literature search: 31 July 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 A	no	no	13 September 2021
	IM	4 C	no	no	
	UM	3 AA	no	no	

Mechanism:

Quetiapine is mainly converted by CYP3A4 to the inactive metabolite quetiapine sulfoxide and to N-desalkylquetiapine (norquetiapine). N-desalkylquetiapine is active, but seems to have mainly anti-depressive activity. In addition, quetiapine and N-desalkylquetiapine are metabolised by CYP2D6 to a limited extent to active 7-hydroxymetabolites. The NVZA (Dutch association of hospital pharmacists) mentions the therapeutic range to be 50-500 ng/ml (131-1304 nmol/L) in general, however with large interindividual variation, and states that toxic concentrations are not known. The NVZA states that there is insufficient evidence to recommend an optimal trough plasma concentration of quetiapine, due to the weak relation between plasma concentration and clinical effect. It seems that in general a plasma concentration of 50-500 ng/ml belongs to a therapeutic dose of 200-800 mg quetiapine per day. However, higher concentrations have been measured in patients without toxic effects. Reference values for the active metabolite N-desalkylquetiapine are still scarce. Routine therapeutic drug monitoring is not recommended for quetiapine.
In literature, a therapeutic range of quetiapine of 100-500 ng/ml (261-1304 nmol/L) with toxic concentrations > 1,000 ng/ml (2607 nmol/L), and a therapeutic range of 100-250 ng/ml (339-846 nmol/L) for N-desalkylquetiapine is mentioned (Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62).