CYP2D6: risperidone 1535/1536/1537

AUC = area under the concentration-time curve, BMI = body-mass index, CI = confidence interval, Cl_{or} = oral clearance, C_{ss} = steady state plasma concentration, HR = 9-hydroxyrisperidone (paliperidone), 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, PANSS = positive and negative syndrome scale, PANSS-T = PANSS - total score, PANSS-P = PANSS - subscale for positive symptoms, PANSS-N = PANSS - subscale for negative symptoms, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), R = risperidone, QT_c interval = corrected QT interval, S = significant, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose $\geq$ 2.75) (increased CYP2D6 enzyme activity)

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Risperidone is converted by CYP2D6 to the active metabolite 9-hydroxyrisperidone (paliperidone). As a result, any effect of genetic variations in CYP2D6 activity is limited.
However, the by far largest study in the risk analysis (Jukic 2019) found an increased incidence of therapeutic failure (switching to another antipsychotic) for 35 patients with genetically determined increased CYP2D6 activity (ultrarapid metabolisers (UM)) and 90 patients with genetically determined absent CYP2D6 activity (poor metabolisers (PM)), but not for 91 patients with genetically determined decreased CYP2D6 activity (intermediate metabolisers (IM)). In the smaller studies, an increase in side effects or a decrease in effectiveness was not consistently found (see the summary per phenotype group below). So, no firm conclusion could be reached based on the smaller studies. For this reason, decisions on the need for therapy adjustment were based on Jukic 2019. Based on the majority of kinetic studies showing an effect of CYP2D6 phenotype group on (the ratio of) risperidone exposure and 9-hydroxyrisperidone exposure, the KNMP Pharmacogenetics Working Group decided that there is a gene-drug interaction. For PM and UM, the KNMP Pharmacogenetics Working Group decided, that therapy adjustment is required (yes/yes-interactions). For IM, the KNMP Pharmacogenetics Working Group decided that no therapy adjustment is required (yes/no-interaction).
The therapeutic recommendations for PM and UM and their justification are indicated below:

PM: For a total of 139 PM, the weighted mean of the dose adaptation based on the exposure to the active moiety (risperidone+9-hydroxyrisperidone) is a decrease to 67% of the normal dose (median 69%; range 47-91%). The dose adjustment calculated above would result in the plasma concentration of the active moiety to be similar in PM and NM. However, Jukic 2019 indicated that brain-to-blood distribution ratio of risperidone is twice that of 9-hydroxyrisperidone. For PM, risperidone contributes much more to the active moiety than 9-hydroxyrisperidone. This indicates that the same plasma concentration of the active moiety for PM and NM would correspond to a higher brain concentration of the active moiety for PM than for NM. Jukic 2019 reports the active moiety to consist of 11% risperidone and 89% 9-hydroxyrisperidone for (NM + gene dose 1/0) and 75% risperidone and 25% 9-hydroxyrisperidone for PM. Van der Weide 2015 reports the active moiety to consist of 39% risperidone and 61% 9-hydroxyrisperidone for NM and 80% risperidone and 20% 9-hydroxyrisperidone for PM. Based on the Jukic data, the brain concentration of the active moiety in PM would be 158% of that in (NM + gene dose 1/0) when the plasma concentration would be the same. Based on the Van der Weide data, this would be 129%. Thus an additional dose reduction with 37% (Jukic) or 23% (Van der Weide) would be required to obtain a similar brain concentration of the active moiety in PM. This would amount to a total reduction to 42% (Jukic) or 52% (Van der Weide) of the normal dose. This was rounded up to 50% to be more achievable in clinical practice.
The therapeutic recommendation is to adjust the dose to 67% of the normal dose. In case central nervous system side effects are still a problem at this reduced dose, the recommendation is to reduce the dose further to 50% of the normal dose.

UM: Jukic 2019 did not find a significant difference in the exposure of the active moiety (risperidone+9-hydroxyrisperidone) for 19 UM compared to NM + gene dose 1/0. Accordingly, for a total of 52 UM, the weighted mean of the dose adaptation based on the exposure to the active moiety is an increase to only 113% of the normal dose (median 111%; range 98-153%). A dose increase that small is unlikely to be clinically significant. Apparently, it is not the reduction in the active moiety that is the problem. The different ratio of risperidone versus

9-hydroxyrisperidone seems more likely to be the problem. For this reason, an alternative antipsychotic is recommended.

The active metabolite 9-hydroxyrisperidone (paliperidone) is an antipsychotic itself. So, a high percentage of 9-hydroxyrisperidone should not mean, that it is not possible to find a working dose. Jukic 2019 indicated that brain-to-blood distribution ratio of risperidone is twice that of 9-hydroxyrisperidone. Correspondingly is the maximum dose for paliperidone higher than for risperidone (for adults 120% of the oral risperidone dose and 150% of the intramuscular risperidone dose). For UM, Jukic 2019 reports the active moiety of risperidone to consist for 97% of 9-hydroxyrisperidone, and Van der Weide 2015 reports a percentage of 61%. For this reason, titrating the risperidone dose based on the maximum dose for paliperidone (orally 12 mg/day for adults and children from 15 years weighing 51 kg or more, and 6 mg/day for children from 15 years weighing less than 51 kg; intramuscularly 75 mg per 2 weeks) should be optimal.

The therapeutic recommendation is to choose an alternative antipsychotic or titrate the risperidone dose based on the maximum dose for paliperidone.

Results from the pharmacodynamics studies smaller than Jukic 2019 are provided below per phenotype group:

PM: The studies Bork 1999 (2 PM), De Leon J Clin Psychopharmacol 2005 (38 PM), De Leon J Clin Psychiatry 2005 (27 PM) and Oshikova 2019 (15 PM) found an increase in side effects. However, the first article by De Leon found no significant increase in tardive dyskinesia, only in tardive dyskinesia of the mouth in males. Furthermore, the doses were higher for PM with tardive dyskinesia, which suggests a dosing problem. In addition, Oshikova 2019 only obtained a significant result for PM+IM compared to NM+UM. The percentage of patients with adverse events increased in this study in the order NM, PM, UM and IM, suggesting a trend based on CYP2D6 activity to be unlikely. Jovanović 2010 (8 PM), Almoguera Pharmacogenomics J 2013 (3 PM) and Vandenberghe 2015 (10 PM) found no increase in side effects. Dos Santos Júnior 2016 (7 PM+IM) found an increase in obesity or overweight patients and in hypertension for PM+IM, but a decrease in serum alanine transaminase levels. However, none of the p-values in this study were high enough to remain significant if correction for multiple comparisons would have been applied.

Mixed results were found regarding prolactin levels and hyperprolactinemia (Vandenberghe 2015 (10 PM) and Schoretsanitis 2018 (3 PM)). The fact that none of the studies found increased prolactin levels or hyperprolactinemia to be symptomatic, makes these outcomes less interesting.

Almoguera Pharmacogenet Genomics 2013 (3 PM) found a stronger improvement in the schizophrenia symptoms, but Jovanović 2010 (8 PM), Xu 2016 (1 PM), and Kaur 2017 (14 PM) found no effect on response. Ivaturi 2017 (4 PM) also did not find an effect on response, but they accounted for the active moiety in investigating this.

With inpatient initiation of risperidone, Mas 2012 (15 PM) found a dose that was 20% lower for PM than for NM.

Almoguera Pharmacogenet Genomics 2013 found a stronger decrease in schizophrenia symptoms for PM.

IM: Lane 2006 (50 IM) found a stronger increase in body weight, but Almoguera Pharmacogenomics J 2013 (32 IM) did not. Almoguera Pharmacogenomics J 2013 (32 IM) neither found an increase in other side effects. Dos Santos Júnior 2016 (7 PM+IM (two CYP2D6 gene variants) and 36 NM+IM (one CYP2D6 gene variant)) found an increase in obesity or overweight patients and in hypertension for PM+IM, a decrease in serum alanine transaminase levels for PM+IM, and a decrease in the average rank of insulin resistance for NM+IM. However, none of the p-values in this study were high enough to remain significant if correction for multiple comparisons would have been applied. Oshikova 2019 (18 IM) found an increase in side effects, but only for PM+IM. The percentage of patients with adverse events increased in this study in the order NM, PM, UM and IM, suggesting a trend based on CYP2D6 activity to be unlikely. None of the 4 studies investigating extrapyramidal symptoms found an increase for IM patients (Ganoci 2021 (35 IM), Almoguera Pharmacogenomics J 2013 (32 IM), Jovanović 2010 (32 IM), Kakihara 2005 (9 IM)).

Mixed results were found regarding prolactin levels and hyperprolactinemia (Wang 2007 (39 IM), Vandenberghe 2015 (41 IM), Dos Santos Júnior 2015 (7 PM+IM (two CYP2D6 gene variants) and 36 NM+IM (one CYP2D6 gene variant)), Sukasem 2016 (74 IM) and Schoretsanitis 2018 (9 IM)). The fact that none of the studies found increased prolactin levels or hyperprolactinemia to be symptomatic, makes these outcomes less interesting. Llerena 2004 (10 IM) found an effect on QT_c elongation, but the elongation was not clinically relevant.

Studies also did not find any decreased effectiveness (Riedel 2005 (8 IM), Wang 2007 (39 IM), Almoguera Pharmacogenet Genomics 2013 (28 IM), Xu 2016 (91 IM), Kaur 2017 (97 IM), Cui 2020 (59 IM), Ganoci 2021 (35 IM)). Ivaturi 2017 (11 IM) also did not find an effect on response, but they accounted for the active moiety in investigating this.

With inpatient initiation of risperidone, Mas 2012 (37 IM) found a dose that was 13% lower for IM than for NM. The yes/no-interaction for IM is strengthened by the small increase in the active moiety (risperidone+9-hydoxyrisperidone) observed for IM. For a total of 644 IM, the weighted mean of the dose adaptation based on the exposure to the active moiety is a decrease to 87% of the normal dose (median 86%; range 64-117%). A dose increase that small is unlikely to be clinically significant

UM: Studies found no decreased effectiveness (Almoguera Pharmacogenet Genomics 2013 (1 UM)) and no increase in side effects (Almoguera Pharmacogenomics J 2013 (3 UM), Schoretsanitis 2018 (3 UM), and Oshikova 2019 (6 UM)).

With inpatient initiation of risperidone, Mas 2012 (8 UM) found a dose that was 19% higher for UM than for NM.

You can find an overview of the observed clinical and kinetic consequences per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The KNMP Pharmacogenetics Working Group considers genotyping before starting risperidone to be potentially beneficial for the prevention of side effects and for drug effectiveness. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.

The clinical implication of the gene-drug interaction scores 0 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):

An increase in the percentage of males with tardive dyskinesia of the mouth was observed for PM compared to NM (De Leon J Clin Psychopharmacol 2005). This adverse event has a severity code D corresponding to CTCAE grade 3. However, the KNMP Pharmacogenetics Working Group decided to exclude this article from the clinical implication score, because it does not provide enough evidence that this increased risk was due to the PM phenotype and not to the risperidone dose level and due to risperidone and not to typical antipsychotics. In this study, PM with tardive dyskinesia both had a significantly higher maximum risperidone dose and a significantly longer duration of typical antipsychotic treatment. Logistic regression analysis in this study did not adjust for risperidone dose and only adjusted for duration of typical antipsychotic treatment ≥ 5 years, whereas this duration was > 10 years for both groups of PM. Duration of risperidone treatment was short compared to duration of typical antipsychotic treatment. In the study, only 26% of patients (had) used risperidone for more than 1 year. Apart from the De Leon J Clin Psychopharmacol 2005, which was excluded from the clinical implication score, no articles showed severe clinical effects in users of risperidone 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 study with sufficient evidence for 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 risperidone mentions the CYP2D6 PM phenotype, but suggests it has no clinical implication (“The pharmacokinetics of risperidone and 9-hydroxyrisperidone combined (i.e. the active antipsychotic fraction), after single and multiple doses, are similar in normal and poor metabolisers”). This therefore does not qualify for the 1 point for at least one genotype/phenotype mentioned in the SmPC. 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.

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 Ganoci L et al. ABCB1, ABCG2 and CYP2D6 polymorphism effects on disposition and response to long-acting risperidone. Prog Neuropsychopharmacol Biol Psychiatry 2021;104:110042. PMID: 32682874**.**	3	101 patients were treated with long-acting injectable risperidone for 24 weeks. Because patients started on risperidone, they also received oral risperidone during the first 3 weeks. Starting doses were determined with respect to disease severity and remained fixed. Doses of long-acting injectable risperidone were 50 mg (n = 50), 37.5 mg (n = 48) or 25 mg (n = 3) every two weeks. Steady state plasma concentrations were determined at the expected peak (4 days after dosing) and trough after the 4th injection. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). Relevant PANSS response was defined as ≥30% PANSS reduction at 12 weeks and ≥ 45% at 24 weeks. Extrapyramidal syndrome was evaluated using the Simpson-Angus scale (SAS). The outcome of interest was the proportion of patients with raw SAS score ≥ 3 points at week 12. Multivariate analyses adjusted for sample time, age and CYP inhibitor use in case of plasma concentrations, and for dose (50 mg or lower), age, sex, and time of measurement (12 or 24 weeks) for the probability of a relevant reduction in schizophrenia symptom score (PANSS). All analyses adjusted for ABCG2 and ABCB1 genotypes. In addition, also analyses adjusting for multiplicity were performed for all outco-	Author’s conclusion: ”CYP2D6 normal/ultrarapid metabolizers (NM/UM) (vs. other) had lower risperidone (29%) and active moiety levels (24%) (9-OH-risperidone not affected). …. CYP2D6 NM/UM phenotype tended to lower odds of PANSS response. …. CYP2D6 phenotype effect on

<table>
<tr>
<td>ref. 1, continuation</td>
<td>IM+PM+phenotype unknown: A</td>
<td>mes.
Other psychiatric treatments and comedication with influence on risperidone were not excluded. Plasma concentrations were adjusted for CYP inhibitors, but clinical results were not. In addition, CYP2D6 inhibitors were only a small subset of the CYP inhibitors (mainly CYP3A4 inhibitors).
Significance was not determined for the univariate analyses (indicated as NS in the table below).

Genotyping:
- 4x UM
- 54x NM
- 5x phenotype unknown (4x (*1/*4)xN (either gene dose 2 or gene dose 1 for N = 2), 1x (*1/*41)xN (either gene dose 2.5 or gene dose 2 for N = 2))
- 35x IM
- 3x PM

Results:
<table>
<tr><td colspan="3">Results for (IM+PM+phenotype unknown) compared to (NM+UM)):</td></tr>
<tr><td></td><td></td><td>value for (NM+UM)</td></tr>
<tr><td>% of patients with symptom score (PANSS) reduction ≥ 30% after 12 weeks</td><td>NS</td><td>17.2%</td></tr>
<tr><td>% of patients with symptom score (PANSS) reduction ≥ 45% after 24 weeks</td><td>NS</td><td>27.6%</td></tr>
<tr><td>probability of relevant PANSS reduction (≥ 30% after 12 weeks, ≥ 45% after 24 weeks)</td><td>NS (also after adjustment for multiplicity)</td><td></td></tr>
<tr><td>% of patients with extrapyramidal syndrome score (SAS) ≥ 3 after 3 months</td><td>NS</td><td>29.3%</td></tr>
<tr><td>probability of SAS score ≥ 3</td><td>NS</td><td></td></tr>
<tr><td>median trough dose-corrected plasma concentration of risperidone+9-hydroxyrisperidone</td><td>x 0.99 (NS)</td><td>1.07 nmol/L per mg</td></tr>
<tr><td>median peak dose-corrected plasma concentration of risperidone+9-hydroxyrisperidone</td><td>x 1.51 (NS)</td><td>1.56 nmol/L per mg</td></tr>
<tr><td>dose-corrected plasma concentration of risperidone+9-hydroxyrisperidone</td><td>geometric mean ratio = 1.32 (95% CI: 1.08-1.61) (S, also after adjustment for multiplicity)</td><td></td></tr>
<tr><td colspan="3">For the dose-corrected plasma concentration of risperidone+9-hydroxyrisperidone, there was an interaction between CYP2D6 and ABCG2 gene variants. The ABCG2 variant decreased the dose-corrected plasma concentration of risperidone+9-hydroxyrisperidone in CYP2D6 NM+UM, but not in (IM+PM+phenotype unknown). As a result, the increase in the dose-corrected plasma concentration of risperidone+9-hydroxyrisperidone in (IM+PM+phenotype unknown) compared to NM+UM was more pronounced in ABCG2 variant carriers than in non-carriers.
However, there was no CYP2D6-ABCG2 interaction for probability of relevant PANSS reduction.</td></tr>
</table>

Note: Genotyping was for *3-*6, *41, and gene duplication.
These are the most important gene variants in this Croatian population.</td>
<td>systemic exposure is conditional on the ABCG2 421C > A polymorphism.”</td>
</tr>
<tr>
<td>ref. 2
Cui Y et al.
CYP2D6 geno-</td>
<td>3</td>
<td>130 patients were treated with risperidone 2-7 mg/day for more than 4 weeks.
Clinical response was measured with the Positive and Negative</td>
<td>Author’s conclusion:
”Significant diffe-</td>
</tr>
</table>

type-based dose recommendations for risperidone in Asian people. Front Pharmacol 2020;11:936. PMID: 32848719. **ref. 2, continuation**	IM: A	Syndrome Scale (PANSS). Dose-corrected steady state trough plasma concentrations were determined for 13 patients with genotype *1/*1 and 49 IM patients. Other antipsychotics, antidepressants, antianxiety medications and mood stabilisers were excluded, but CYP2D6 inhibitors and CYP3A4 inhibitors not belonging to these drug classes were not. Patients were advised not to take drugs known to induce liver enzymes from two weeks prior to enrolment. Participants had to minimize usage of acetylsalicylic acid and other non-steroidal anti-inflammatory drugs. Genotyping: clinical study: - 71x NM; - 59x IM pharmacokinetic study: - 13x *1/*1; - 49x IM Results: Change in schizophrenic symptom score (PANSS) after 2, 4 and 6 weeks of treatment for IM compared to NM: NS Median dose-corrected plasma concentration of risperidone+9-hydroxyrisperidone for IM compared to *1/*1 (value 10.5 ng/ml per mg): x 0.86 (NS) Genotype *1/*1 was used as a reference group instead of NM, because the European NM group (consisting mainly of gene dose 2) is more similar to *1/*1 than to the Asian NM group (consisting mainly of gene dose 1.25). Note: The median metabolic ratio 9-hydroxyrisperidone/risperidone was 45% lower for IM than for *1/*1 (S). Note: The meta-analyses and dose calculations are not included in this summary, because the method differs too much from the method of the KNMP Pharmacogenetics Working Group to provide useful data for this risk analysis. In addition, Asian NM as reference and the Asian frequencies of the phenotype groups are used for Asian patients. As a result, the calculated dose adjustments for Asian patients only apply to Asians in Asian countries, not to Asians in European countries, where the reference group and phenotype group frequencies are different. Differences in methodology include: the data are weighed based on the width of the confidence interval (inverse variance method), whereas the KNMP Pharmacogenetics Working Group weighs pharmacokinetic data based on the number of patients with the variant phenotype; it is assumed that the doses are also suboptimal for NM, requiring the need of generalized ethnicity specific phenotype frequencies for dose calculations, whereas the KNMP Pharmacogenetics Working Group assumes the normal dose being mainly based on and so optimal for NM (i.e. largest patient group); for all Asian studies dose calculations are extrapolated for missing phenotypes, whereas the KNMP Pharmacogenetics Working Group never extrapolates; for Whites 7 out of 11 studies were excluded from the dose calculations because of lack of a significant difference between the phenotypes, whereas the KNMP Pharmacogenetics Working Group doesn't exclude studies not showing significant differences because this has the risk of selecting for the studies showing the largest effect (smallest number of patient needed to show a significant effect) and thus overestimating the required dose adjustment. Note: Genotyping was for *2-*4, *6, *7, *9-*11, *14, *17, *19, *20, *41, *43, *44, *49, *56, and gene duplication. These are the most important gene variants in this Chinese population. Gene duplication, *3, *7, *9, *11, *14, *20, *44, and *56 were not observed in this patient group.	rences between the normal metabolizer and intermediate metabolizer groups were observed for dose-adjusted risperidone level, 9-hydroxyrisperidone level, and risperidone/9-hydroxyrisperidone ratio, but not for the total active moiety." Median dose-corrected plasma concentration risperidone + 9-hydroxyrisperidone versus *1/*1: IM: 86%
ref. 3	4	1288 patients were treated with risperidone. Routine therapeutic drug	Author's conclu-

Jukic MM et al. Effect of CYP-2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry 2019;6:418-26. PubMed PMID: 31000417.

ref. 3, continuation

PM: C
UM: C

monitoring was performed during treatment. The authors indicate that CYP2D6 genotype was known during risperidone treatment, except for 12 patients for whom CYP2D6 genotyping was done in between risperidone discontinuation and first therapeutic drug monitoring of the replacement drug. However, the authors suggest that dose adjustments and switching to another antipsychotic were driven by adverse events and effectiveness (and possibly therapeutic drug monitoring), not by CYP2D6 genotype. Pharmacokinetic and dose analysis was performed for 725 of these patients, all using oral risperidone. Risperidone treatment failure, was estimated by the percentage of patients who were switched from risperidone to another antipsychotic within the 1-year follow-up after the last therapeutic drug monitoring analysis of risperidone.
CYP2D6 inhibitors (bupropion, citalopram, escitalopram, fluoxetine, levomepromazine, and paroxetine), CYP3A4 inducers (carbamazepine, phenobarbital, phenytoin and rifampicin), and CYP3A4 inhibitors (clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, nelfinavir, ritonavir, and verapamil) were excluded in the patients selected for pharmacokinetic analysis, but not in the other patients. However, the therapeutic failure analysis adjusted for the presence of a CYP2D6 inhibitor, CYP3A4 inducer, or CYP3A4 inhibitor.

Genotyping:

All patients	Pharmacokinetic subgroup
- 35x UM	- 19x UM
- 1072x NM + gene dose 1/0 (694x NM (532x *1/*1, 162x gene dose 1.25-1.5), 378x gene dose 1/0)	- 577x NM + gene dose 1/0 (365x NM (270x *1/*1, 95x gene dose 1.25-1.5), 212x gene dose 1/0)
- 91x IM (22x gene dose 0.5/0.5, gene dose 0.75 or gene dose 0.5, 69x gene dose 0.5 or gene dose 0.25)	- 71x IM (19x gene dose 0.5/0.5, gene dose 0.75 or gene dose 0.5, 52x gene dose 0.5 or gene dose 0.25)
- 90x PM	- 58x PM

Results:

Results compared to (NM + gene dose 1/0) (% of patients switched to another antipsychotic, metabolic ratio), to (NM + gene dose 1/0 + UM) (% of patients with active moiety plasma concentration above or below the therapeutic range), or to NM (other outcomes):

	PM	IM[@]	UM	value for reference group
risk of switch to another antipsychotic	OR = 1.87 (95% CI: 1.13-3.11) (S)	NS	OR = 2.93 (95% CI: 1.44-5.99) (S)	16%
risperidone dose	x 0.79 (S)	x 0.94 (NS)	x 1.22 (NS)	2.98 mg/day
% of patients with suprathera-peutic plasma concentration (active moiety > 110 nM)	x 1.75 (NS (significance not determined))			8%
% of patients with subthera-peutic plasma concentration (active moiety < 47 nM)	x 0.80 (NS (significance not determined))			55%

sion:
"CYP2D6 genotype had a substantial clinical effect on risperidone and aripiprazole exposure and on the therapeutic failure of risperidone. Pre-emptive CYP2D6 genotyping would be valuable for individualising risperidone and aripiprazole dosing and treatment optimisation."

Dose-corrected plasma concentration risperidone + 9-hydroxyrisperidone versus NM:

<table>
<tr>
<td>ref. 3, continuation</td>
<td>IM: A</td>
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<table>
<tr><td rowspan="2">dose-corrected plasma concentration of the active moiety (risperidone plus 9-hydroxyrisperidone)</td><td>x 1.52 (S)</td><td>x 1.22 (S)</td><td>x 1.02 (NS)</td><td rowspan="2">19.6 nM per mg/ day</td></tr>
<tr><td colspan="3">Except for UM and gene dose 1.25-1.5, the difference was S for all separate genotype groups compared to *1/*1, so also for gene dose 1/0 (S).</td></tr>
<tr><td rowspan="2">median metabolic ratio 9-hydroxyrisperidone/ risperidone</td><td>x 0.04 (S)</td><td>x 0.12 (S)</td><td>x 3.69 (S)</td><td rowspan="2">8.4</td></tr>
<tr><td colspan="3">The difference was also S for all separate genotype groups compared to *1/*1, so also for gene dose 1/0 and for UM (S).</td></tr>
<tr><td colspan="5">@ IM includes only gene dose 0.5/0.5 and gene dose 0.25-0.75 for comparisons with (NM + gene dose 1/0). IM includes all IM-genotypes (i.e. also gene dose 1/0) for comparisons with NM.</td></tr>
</table>

Note: The authors indicated that CYP2D6 genotype explained only around half of the variability in the risperidone metabolism.

Note: The authors indicated the therapeutic range to be 47-110 nM (20-45 ng/ml) for the sum of risperidone and 9-hydroxyrisperidone. In addition, the authors indicated that brain-to-blood distribution ratio of risperidone is twice that of 9-hydroxyrisperidone.

Note: Genotyping was for *3-*6, *9, *10, *41, and gene duplication. Patients with alleles differing in functionality and gene duplication were excluded from the study, because it was impossible to determine which allele was duplicated.
</td>
<td>PM: 152%
IM: 122%
UM: 102%</td>
</tr>
<tr>
<td>ref. 4
Oshikoya KA et al.
CYP2D6 genotype and adverse events to risperidone in children and adolescents.
Pediatr Res 2019;85:602-6.
PubMed PMID: 30661084.</td>
<td>3

IM+PM: C
UM: AA</td>
<td>
Electronic health records of 257 children, treated with risperidone for at least 4 weeks, were analysed.
76 children (30%) experienced 20 different types of adverse events and a total of 104 adverse events. The most common adverse events were weight change (9%), sedation (6%), and extrapyramidal symptoms (6%).
There was no causality assessment of adverse events.
CYP2D6 inhibitors were not excluded. An association of use of strong CYP2D6 inhibitors with adverse events was only tested in the control group (NM + gene dose 1 + UM), but not in the IM group. No association was found.
Multivariate analysis adjusted for age, sex, race, and initial risperidone dose, but not for the indication for risperidone. The indications self-injurious behaviours and aggression were associated with more adverse events, while there was a trend for the indication irritability (p = 0.06). However, the percentage of patients with these indications did not differ significantly between the investigated group (IM + PM) and the control group (NM + gene dose 1 + UM).

Genotyping:
- 6x UM
- 218x NM + gene dose 1 (146x NM (96x gene dose 2, 50x gene dose 1.25-1.5), 72x gene dose 1)
- 18x IM (all gene dose 0.25-0.5)
- 15x PM

Results:
<table>
<tr><td colspan="3">Percentage of patients with adverse events compared to (NM + gene dose 1) (27%):</td></tr>
<tr><td>PM</td><td>x 1.25</td><td rowspan="3">S for (PM + IM) versus (NM + gene dose 1 + UM): OR = 2.38 (95% CI: 1.12-5.09)</td></tr>
<tr><td>IM</td><td>x 2.09</td></tr>
<tr><td>UM</td><td>x 1.88</td></tr>
<tr><td colspan="3">The authors indicate that due to inadequate power in the small phenotype groups (UM, IM and PM), they were unable to assess all phenotypes individually or identify a trend across all phenotypes (NS). However, the percentages of patients with adverse events increasing in the order (NM + gene dose 1), PM, UM, and IM argues against such a trend being present.</td></tr>
</table>
</td>
<td>Author’s conclusion:
”Children with CYP2D6 poor or intermediate metabolizer phenotypes are at greater risk for risperidone adverse events.”</td>
</tr>
</table>

<table>
<tr><td>ref. 4, continuation</td><td></td><td>Note: Genotyping was by next generation sequencing. In addition, gene duplication and deletion were analysed.
Genotyping identified the following alleles in this USA population: *1-*6, *9, *10, *17, *29, *33, *35, *41, and *46.</td><td></td></tr>
<tr><td>ref. 5
Schoretsanitis G et al.
Prolactin levels: sex differences in the effects of risperidone, 9-hydroxyrisperidone levels, CYP2D6 and ABCB1 variants.
Pharmacogenomics 2018;19:815-823.
PubMed PMID: 29914302.</td><td>3

UM: AA#
IM: A
PM: A</td><td>Data of 110 patients from the study of De Leon 2005, J Clin Psychiatry were analysed. 49 patients were female, 61 were male. Of the originally 111 patients, one female with an atypically low plasma prolactin concentration that caused lack of fit in regression models, was excluded from the analysis.
A CYP2D6 activity level of 0 was assigned to *3-*8, *11, *15, *19, *20, *40 and *4xn; of 0.2 to *10 and *36; of 0.4 to *9, *29, *41 and *10xn; of 0.8 to *41xn; of 1 to *1, *2, *35 and *17; and of 2 to *1xn, *2xn, *35xn and *17xn alleles. Thus, *17 was considered a fully active allele instead of an allele with decreased activity. In addition, *36 was considered a partially active allele instead of a non-functional allele, and duplication of *10 and *41 was considered not to lead to full functionality.
None of the patients used also other antipsychotics. Co-medication with CYP2D6 and CYP3A4 inhibitors and CYP3A4 inducers was not excluded, nor was it adjusted for in linear regression.
Linear regression models included trough plasma concentrations of risperidone and 9-hydroxyrisperidone next to the number of CYP2D6 active alleles.

Genotyping:
females: - 3x UM; - 39x NM + gene dose 1/0; - 5x IM; - 2x PM
males: - 0x UM; - 56x NM + gene dose 1/0; - 4x IM; - 1x PM

Results:
Percentage change in the median plasma prolactin level associated with 1 additional active CYP2D6 gene, after adjusting for the other variables including trough plasma risperidone and 9-hydroxyrisperidone levels:
all: -19% (95% CI: -30% - -6%) (S)
females: NS
males: -30% (95% CI: -42% - -16%) (S)
The effect in females was also not significant if only Caucasian females were included in the analysis.
The authors indicate that they have no definitive explanation of the precise nature of this additional CYP2D6 role beyond risperidone metabolism, but that some authors have suggested that the brain's CYP2D6 may influence dopamine and serotonin activity.

Note: In males, an increase in 9-hydroxyrisperidone levels correlated with an increase in plasma prolactin concentrations (S). In females, an increase in risperidone levels correlated with an increase in plasma prolactin concentrations (S). This suggests that, when not adjusting for risperidone and 9-hydroxyrisperidone concentrations, an increase in the number of CYP2D6 active alleles would have an opposite effect on plasma prolactin concentrations in males and females.

Note: In the total group, the size of the effect of female sex was 4.5 times higher than the size of the effect of 1 additional active CYP2D6 gene.</td><td>Author's conclusion:
"After correcting for confounders including R and 9-OH-R concentration, the CYP-2D6 activity was important only in men, with each CYP2D6 active allele being associated with a significant 30% decrease in plasma prolactin concentrations. A backward selection procedure in the combined sample suggested that sex, plasma 9-OH-R concentrations and CYP2D6 activity had significant effects on plasma prolactin concentrations."</td></tr>
<tr><td>ref. 6
Kaur G et al.
Identification of genetic correlates of response to risperidone:</td><td>3</td><td>419 patients were treated with risperidone for 12 weeks. Risperidone was started at 1 mg/week and the dose was increased each week by 1 mg/week. 88 patients did not complete the 12 week treatment period (drop outs).
Non response was defined as a reduction of less than 25% on the Positive and Negative Syndrome Scale (PANSS). Partial response</td><td>Author's conclusion:
"The CYP2D6*4 polymorphism differed significantly when drop</td></tr>
</table>

<table>
<tr>
<td>findings of a multicentric schizophrenia study from India.
Asian J Psychiatr 2017;29:174-82.
PubMed PMID: 28692863.

ref. 6, continuation</td>
<td>IM: AA
PM: AA</td>
<td>was defined as a reduction of 25-50% on the PANSS. Response was defined as a reduction of more than 50% on the PANSS. When comparing only responders and non-responders, the partial responders were considered to be non-responders. No systematic recording of the reasons for drop out was done. None of the patients developed intolerable adverse effects.
Long acting antipsychotic agents were excluded, as was co-medication other than trihexyphenidyl and lorazepam or diazepam.
No correction was performed for the PANSS scores at baseline and for the duration of illness, despite the study showing both to be associated with response. In addition, drop outs were not included in the outcome response.

Genotyping:
*4 *10
- 310x *1/*1 - 352x *1/*1
- 95x *1/*4 - 65x *1/*10
- 14x *4/*4 - 2x *10/*10

Results:
<table>
<tr><td colspan="3">Effect of gene variants on clinical outcome:</td></tr>
<tr><td></td><td>*4</td><td>*10</td></tr>
<tr><td>non-responders versus partial responders versus responders versus drop outs</td><td>NS</td><td>NS</td></tr>
<tr><td>non-responders versus responders</td><td>S, but NS after logistic regression analysis</td><td>NS</td></tr>
</table>
Note: This study did not find a relationship between plasma risperidone and plasma 9-hydroxyrisperidone concentrations and clinical outcome.

Note: Genotyping was for *4 and *10. These are the most important gene variants in this Indian population.</td>
<td>outs were excluded from analysis.”</td>
</tr>
<tr>
<td>ref. 7
Ivaturi V et al. Exposure-response analysis after subcutaneous administration of RBP-7000, a once-a-month long-acting Atrigel formulation of risperidone.
Br J Clin Pharmacol 2017;83:1476-98.
PubMed PMID: 28133766.</td>
<td>3</td>
<td>After randomisation, 111 patients were treated with long-acting subcutaneous risperidone 90 mg every 4 weeks, 114 patients were treated with long-acting subcutaneous risperidone 120 mg every 4 weeks, and 112 patients received placebo. Study duration was 8 weeks. Long-acting subcutaneous risperidone 90 mg every 4 weeks is intended for substitution of oral risperidone 3 mg/day, long-acting subcutaneous risperidone 120 mg every 4 weeks for substitution of oral risperidone 4 mg/day.
Both risperidone doses were generally well tolerated.
Response was measured every two weeks with both the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression severity scale (CGI-S).
Total active moiety plasma concentrations were calculated as the sum of risperidone and 9-hydroxyrisperidone plasma concentrations, corrected by molecular weight of risperidone and 9-hydroxyrisperidone to obtain risperidone-equivalent concentrations.
Relevant co-medication was not excluded, nor was co-medication included as a covariate in modelling.
A population pharmacokinetic model and pharmacokinetic/ pharmacodynamic models correlating PANSS and CGI-S scores with the sum of the plasma concentration of the active moiety were developed. The article does not report raw data.

Genotyping:
90 mg 120 mg
- 98x NM + gene dose 1/0 - 97x NM + gene dose 1/0
- 7x inconclusive phenotype - 6x inconclusive phenotype
- 4x IM - 7x IM</td>
<td>Author’s conclusion:
”CYP2D6 phenotype on risperidone metabolism was the only identified covariate.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 7, continuation</td>
<td>PM: A
IM: A</td>
<td>
- 1x PM - 3x PM
- 1x missing genotype - 1x missing genotype

Results:
<table>
<tr><td colspan="3">Results compared to (NM + gene dose 1/0 + inconclusive phenotype):</td></tr>
<tr><td></td><td>PM</td><td>IM</td></tr>
<tr><td>overall disease progression and placebo effect</td><td colspan="2">NS (no significant effect of CYP2D6 phenotype)</td></tr>
<tr><td>response (PANSS)</td><td colspan="2">NS (no significant effect of CYP2D6 phenotype after accounting for the active moiety)</td></tr>
<tr><td>response (CGI-S)</td><td colspan="2">NS (no significant effect of CYP2D6 phenotype after accounting for the active moiety)</td></tr>
<tr><td>formation rate of 9-hydroxy-risperidone</td><td>x 0.06 (S)</td><td>x 0.24 (S)</td></tr>
<tr><td>plasma concentration of the active moiety (risperidone plus 9-hydroxyrisperidone)</td><td colspan="2">NS (similar between phenotypes)</td></tr>
</table>

Note: The study found a correlation between the plasma concentration of the active moiety (risperidone plus 9-hydroxy-risperidone) and clinical outcome (both on the PNASS and CGI-S).

Note: The authors do not state which CYP2D6 alleles were determined nor how the CYP2D6 phenotypes were defined. However, the small number of IMs compared to PMs is only possible if patients with one fully active and one inactive allele (gene dose 1/0) are included in the NM-group.
</td>
<td></td>
</tr>
<tr>
<td>ref. 8
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.</td>
<td>4

PM: AA
IM: AA</td>
<td>
283 patients were treated with risperidone for 2 months. Risperidone was started at 1 mg/day and gradually increased to 4-6 mg/day within the first week. After week 2, the dose was adjusted according to individual tolerance.
Response was defined as a ≥ 50% decrease of the score on the Positive and Negative Syndrome Scale (PANSS).
Co-medication other than trihexylphenidyl, clonazepam, lorazepam or sennoside, was excluded.
Bonferroni correction for multiple testing was applied.
A power calculation indicated that the study was sufficiently powered (at least 82.86% power) to detect a genotypic relative risk of 1.5 at a significance level of 0.05 for polymorphisms with a risk allele frequency > 0.2.

Genotyping:
<table>
<tr><td>*4</td><td>*10</td><td>*2 (886C>T)</td><td>*2 (1457G>C)</td></tr>
<tr><td>- 278x *1/*1</td><td>- 52x *1/*1</td><td>- 126x *1/*1</td><td>- 136x *1/*1</td></tr>
<tr><td>- 3x *1/*4</td><td>- 129x *1/*10</td><td>- 75x *1/*2</td><td>- 119x *1/*2</td></tr>
<tr><td>- 1x *4/*4</td><td>- 91x *10/*10</td><td>- 21x *2/*2</td><td>- 28x *2/*2</td></tr>
</table>

Results:
<table>
<tr><td colspan="3">Effect of gene variants on the percentage of patients with a response:</td></tr>
<tr><td>gene variant</td><td></td><td>value for *1/*1</td></tr>
<tr><td>*4</td><td>NS</td><td>63%</td></tr>
<tr><td>*10</td><td>NS</td><td>77%</td></tr>
<tr><td>*2 (886C>T)</td><td>NS</td><td>73%</td></tr>
<tr><td>*2 (1457G>C)</td><td>NS</td><td>62%</td></tr>
</table>

Note: Genotyping was for *4, *10, and two polymorphisms in *2 (886C>T and 1457G>C). These are the most important gene variants in this Chinese population, but the *2 polymorphisms do not change the activity of the CYP2D6 enzyme.
</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>ref. 9
Sukasem C et al.
Impact of pharmacogenetic markers of CYP2D6 and DRD2 on prolactin response in risperidone-treated Thai children and adolescents with autism spectrum disorders.
J Clin Psychopharmacol 2016;36:141-6.
PubMed PMID: 26872113.</td>
<td>4

IM: AA</td>
<td>147 children and adolescents with autism spectrum disorder were treated with risperidone for at least 4 weeks (mean 46 months). The mean risperidone dose was 1 mg/day (0.03 mg/kg per day).
Hyperprolactinemia was defined as a prolactin level greater than the 97.5th percentile on the basis of normative data for age and sex.
Relevant co-medication was excluded.

Genotyping:
- 73x NM (11x gene dose 2, 4x gene dose 1.5, 58x gene dose 1.25)
- 74x IM (13x gene dose 1, 6x gene dose 0.75, 45x gene dose 0.5, 10x gene dose 0.25)

Results:
<table>
<tr><td colspan="3">Effect of gene variants:</td></tr>
<tr><td></td><td></td><td>value for *1/*1 or NM</td></tr>
<tr><td>% of patients with hyperprolactinemia</td><td>NS for gene variants *4, *5, *10, and *41, for each of the genotypes, and for IM versus NM</td><td>42-46%</td></tr>
<tr><td>median prolactin level</td><td>NS for gene variants *4, *5, *10, and *41, for each of the genotypes, and for IM versus NM</td><td>14.8-17.1 ng/ml</td></tr>
</table>
Note: Genotyping was for *4, *5, *10, *41, and gene multiplication. These are the most important gene variants in this Thai population.</td>
<td>Author’s conclusion:
”There was no significant correlation between the concentrations of prolactin among the CYP-2D6 genotypes. In addition, there were no statistical differences in the prolactin response among the CYP2D6-predicted phenotypes of normal metabolizer and intermediate metabolizer.”</td>
</tr>
<tr>
<td>ref. 10
Dos Santos-Júnior A et al.
Pharmacogenetics of risperidone and cardiovascular risk in children and adolescents.
Int J Endocrinol 2016;2016: 5872423.
PubMed PMID: 26880915.</td>
<td>3

PM+IM: C</td>
<td>120 children and adolescents with mental and behavioural disorders were treated with risperidone for at least 24 months (on average more than 1.5 years). The mean risperidone dose was 0.04 mg/kg per day.
73.3% of patients also used one or more other psychotropic drugs.
The BMI (kg/m^2) was calculated and transformed into a z-score. BMI z-scores, also called BMI standard deviation scores, are clinical measures of relative weight adjusted for a child or an adolescent age and sex. Obese patients were defined as having z-scores of at least +2 SD and overweight patients as having a z-score of at least +1 SD but less than +2 SD.
Hypertension was defined following the National Heart, Lung and Blood Institute criteria, correlated with percentiles specific to sex, height, and age.
The relationship between insulin and fasting glucose levels was used to calculate the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), which is considered normal when ≤ 2.89.
Relevant co-medication was not excluded. There was no difference in the prevalence of obesity, altered waist circumference, hypertension, and metabolic syndrome between patients on risperidone monotherapy and patients using also other psychotropic drugs.

Genotyping:
- 77x NM (*1/*1)
- 36x NM+IM (*1/*4 or *1/*10)
- 7x PM+IM (*4/*4, *4/*10 or *10/*10)

Results:
<table>
<tr><td colspan="4">Effect of the gene variant:</td></tr>
<tr><td></td><td>PM+IM</td><td>NM+IM</td><td>value for *1/*1 (unless indicated otherwise)</td></tr>
<tr><td>% of obese of overweight patients</td><td>x 2.20</td><td>x 0.60</td><td>32.5%</td></tr>
<tr><td></td><td colspan="2">S for PM+IM versus NM+IM versus NM, and S for PM+IM versus at least one *1 allele</td><td></td></tr>
</table></td>
<td>Author’s conclusion:
”Single nucleotide polymorphism associations were found for CYP2D6 with BMI, blood pressure, alanine transaminase (ALT), and Homeostatic Model Assessment of Insulin Resistance.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 10, continuation</td>
<td>PM+IM: AA#

NM+IM: AA#</td>
<td>
<table>
<tr><td>% of patients with hypertension</td><td>x 7.33
S for PM+IM versus NM+IM versus NM</td><td>x 2.13</td><td>3.9%</td></tr>
<tr><td>average rank of serum alanine transaminase (ALT) level</td><td>x 0.64 (S versus at least one *1 allele)</td><td></td><td>at least one *1 allele: 91.14</td></tr>
<tr><td>average rank of insulin resistance (HOMA-IR)</td><td></td><td>x 0.91 (S versus *1/*1 + *4/*4 + *4/*10 + *10/*10)</td><td>*1/*1 + *4/*4 + *4/*10 + *10/*10: 62.27</td></tr>
</table>

Note: None of the p values was small enough to remain significant after correction for 4 comparisons. The authors tested the influence of 8 polymorphisms in 6 genes on 7 parameters and compared different genotype combinations in doing this.

Note: Genotyping was for a polymorphism present in both *4 and *10. This is the most important gene variant in this Brazilian population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 11
dos Santos Júnior A et al. Hyperprolactinemia in children and adolescents with use of risperidone: clinical and molecular genetics aspects.
J Child Adolesc Psychopharmacol 2015;25:738-48.
PubMed PMID: 26682995.</td>
<td>3

PM+IM: AA

NM+IM: AA</td>
<td>Prolactin concentrations of the patients in dos Santos Júnior 2016 were analysed. Hyperprolactinemia was defined as values >20 mg/dl in males and 25 mg/dl in females, in the absence of hypothyroidism. None of the patients had hypo- or hyperthyroidism.
65.8% of patients had hyperprolactinemia, which was asymptomatic. Hyperprolactinemia occurred more often in patients who were on risperidone therapy for less than 12 months than in patients on risperidone therapy for more than 12 months.
Relevant co-medication was not excluded. There was no difference in the prevalence of hyperprolactinemia between patients on risperidone monotherapy and patients using also other psychotropic drugs.

Results:
<table>
<tr><td colspan="3">Results for PM+IM versus NM+IM versus *1/*1:</td></tr>
<tr><td></td><td></td><td>value for *1/*1</td></tr>
<tr><td>% of patients with hyperprolactinemia</td><td>NS</td><td>66%</td></tr>
</table>
</td>
<td>Author’s conclusion:
”Regarding the SNP of the DRD2 and CYP2D6 genes, unlike in reports in the literature, in the present study, they were not associated with hyperprolactinemia.”</td>
</tr>
<tr>
<td>ref. 12
Vandenberghe F et al. Genetics-based population pharmacokinetics and pharmacodynamics of risperidone in a psychiatric cohort.
Clin Pharmacokinet 2015;54:1259-72.
PubMed PMID: 26129906.</td>
<td>3</td>
<td>A population pharmacokinetic model was generated based on data of 150 patients treated with risperidone for a median of 7.3 months. The risperidone dose was 0.5-8 mg/day. Only 11% of patients received a dose higher than 4 mg/day. Risperidone was either dosed once daily (in the majority of patients) or twice daily. 55% of patients was male.
Simulations of 1000 individuals for each CYP2D6 phenotype based on the final model with variability were conducted to derive the average AUC from time zero to 24 h with 95% prediction intervals for risperidone, 9-hydroxyrisperidone and the active moiety.
The median prolactin concentration was 31 and 85 µg/L in male and females, respectively. Three patients treated with haloperidol, levomepromazine and pipamperone, as well as two patients with a prolactin level of 345 µg/L (previous co-administration of pipamperone) and 238 µg/L (breast cancer) were withdrawn from the prolactin analysis.
Side effects were measured with the Udvalg for Kliniske Undersøgelser (UKU) rating scale. 43%, 40%, 7%, 45% and 30% of patients reported neurologic, autonomic, cardiovascular, psychic and sexual dysfunction side effects, respectively. Nine patients were withdrawn from the side effect analysis, because of using one or more of the following drugs concomitantly: biperiden, haloperidol, levomepromazine and pipamperone.
Relevant co-medication was not excluded, but was introduced as a covariate in the population pharmacokinetic model. 48 patients used weak CYP2D6 inhibitors concomitantly and 7 patients strong CYP2D6 inhibitors.</td>
<td>Author’s conclusion:
”Genetic polymorphisms of CYP2D6 play an important role in risperidone, 9-hydroxyrisperidone and active moiety plasma concentration variability, which were associated with common side effects.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 12, continuation</td>
<td>PM+IM +CYP-2D6 inhibitors: A

PM: A

IM: A</td>
<td>Genotyping:
- 6x UM
- 93x NM
- 41x IM
- 10x PM

Results:
<table>
<tr><td colspan="4">Results for PM versus IM versus EM+UM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for EM+UM</td></tr>
<tr><td>% of patients with side effects</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td></td><td colspan="2">Results were also NS if both CYP2D6 phenotype and CYP-2D6 inhibitors were taken into account.</td><td></td></tr>
<tr><td>prolactin concentration, all patients</td><td colspan="2">NS for PM+IM with CYP2D6 inhibitors compared to EM+UM</td><td></td></tr>
<tr><td>prolactin concentration, males</td><td colspan="2">NS for PM+IM with CYP2D6 inhibitors compared to EM+UM</td><td></td></tr>
<tr><td>prolactin concentration, females</td><td colspan="2">higher concentrations for PM+IM with CYP2D6 inhibitors compared to EM+UM (S)</td><td></td></tr>
<tr><td></td><td colspan="2">Note: the p value was too high to remain significant after correction for 2 comparisons.</td><td></td></tr>
<tr><td>predicted AUC of the active moiety</td><td>x 1.37 (S)</td><td>x 1.01 (NS)</td><td>737 ng.h/ml</td></tr>
<tr><td>predicted AUC of risperidone</td><td>x 8.02 (S)</td><td>x 1.79 (S)</td><td>94 ng.h/ml</td></tr>
<tr><td>predicted AUC of 9-hydroxyrisperidone</td><td>x 0.40 (S)</td><td>x 0.90 (S)</td><td>643 ng.h/ml</td></tr>
<tr><td>predicted fraction of the dose converted to 9-hydroxyrisperidone</td><td>x 0.09 (S)</td><td>x 0.91 (S)</td><td>93%</td></tr>
<tr><td></td><td colspan="2">There was a 2-fold difference between the population mean and the final prediction for PM (21% and 9% of the value for EM+UM respectively).
The values for EM and UM did not differ significantly.</td><td></td></tr>
</table>
Note: The study did not find an association between prolactin concentration and sexual dysfunction side effects. In addition, the study only found an effect of the plasma concentration of the active moiety on tremor, not on other side effects.

Note: Genotyping was for *3-*6, and gene multiplication. These are the most important gene variants in this Swiss population.</td>
<td>predicted AUC risperidone + 9-hydroxyrisperidone versus NM:
IM: 101%
PM: 137%</td>
</tr>
<tr>
<td>ref. 13
van der Weide K et al.
The influence of the CYP3A4 *22 polymorphism and CYP2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients.</td>
<td>3</td>
<td>389 patients were treated with risperidone. Therapeutic drug monitoring and CYP2D6 genotyping were routinely done. Trough plasma concentrations were determined in steady state (12 to 16 hours after dosing). For each patient, the first measured serum level and the immediate preceding daily dose were used for calculating dose-corrected plasma concentrations.
Relevant co-medication was not excluded. The effect of CYP3A4 inhibitors and CYP3A4 inducers on dose-corrected concentration of the active moiety (risperidone plus 9-hydroxyrisperidone) and on metabolic ratio was not significant in multiple regression analysis.
Parameters included in multiple regression analysis were sex, age, dose, CYP2D6 phenotype, CYP3A4*22 genotype, use of CYP3A4 inducers, and use of CYP3A4 inhibitors.

Genotyping:
- 8x UM</td>
<td>Authors' conclusion:
"Heterozygous presence of CYP3A4*22 does not increase serum levels of antipsychotics metabolized by both CYP3A4 and CYP2D6, whereas CYP-2D6 polymorphisms do affect serum levels to a limited extent."</td>
</tr>
</table>

<table>
<tr>
<td>J Clin Psychopharmacol 2015;35:228-36.
PubMed PMID: 25868121.

and personal communication (mean values)

ref. 13, continuation</td>
<td>UM: A

PM: A

IM: A</td>
<td>- 197x NM
- 151x IM
- 33x PM

Results:
<table>
<tr><td colspan="5">Results versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM</td></tr>
<tr><td>median risperidone dose</td><td>x 0.74 (NS)</td><td>x 0.74 (NS)</td><td>x 0.74 (NS)</td><td>2.7 mg/day</td></tr>
<tr><td>median plasma concentration of the active moiety (risperidone plus 9-hydroxyrisperidone)</td><td>x 2.0 (S)
Multiple regression analysis showed that CYP2D6 explained 4% of the variation (S).</td><td>x 1.3 (NS)</td><td>x 0.78 (S)</td><td>20 ng/ml</td></tr>
<tr><td>median dose-corrected plasma concentration of the active moiety (risperidone plus 9-hydroxyrisperidone)</td><td>x 1.73 (S)
Multiple regression analysis showed that CYP2D6 explained 5% of the variation (S).</td><td>x 1.08 (NS)</td><td>x 0.55 (NS)</td><td>10.0 ng/ml per mg/day</td></tr>
<tr><td>median metabolic ratio 9-hydroxyrisperidone/ risperidone</td><td>x 0.10 (S)
Multiple regression analysis showed that CYP2D6 explained 17% of the variation (S).</td><td>x 0.55 (S)</td><td>x 0.41 (NS)</td><td>3.0</td></tr>
<tr><td>dose-corrected plasma concentration of the active moiety (risperidone plus 9-hydroxyrisperidone)</td><td>x 1.71 (NS)
Significance not determined.</td><td>x 1.17 (NS)</td><td>x 0.66 (NS)</td><td>11.9 ng/ml per mg/day</td></tr>
<tr><td>metabolic ratio 9-hydroxyrisperidone/risperidone</td><td>x 0.16 (S)</td><td>x 0.68 (NS)</td><td>x 0.98 (NS)</td><td>1.6</td></tr>
</table>
NOTE: Genotyping was performed for *3-*6, *9, *10, *41, and multiplication. These are the most important gene variants in this Dutch population. Patients with alleles differing in functionality and gene multiplication were excluded from the study, because it was impossible to determine which allele was multiplicated.</td>
<td>Dose-corrected trough plasma concentration risperidone + 9-hydroxyrisperidone versus NM:
PM: 171%
IM: 117%
UM: 66%</td>
</tr>
<tr>
<td>ref. 14
Suzuki Y et al. Effect of risperidone metabolism and P-glycoprotein gene polymorphism on QT interval in patients with schizophrenia. Pharmacogenomics J 2014;14:452-6.
PubMed PMID: 24589909.</td>
<td>4

IM+PM: A</td>
<td>A total of 66 schizophrenia patients were treated with risperidone (mean 4.8 mg/day). The dose was adjusted according to the clinical situation. Relevant co-medication was excluded.

Genotyping:
- 29x gene dose 2 (*1/*1)
- 24x gene dose 1.25 (*1/*10) or 1 (*1/*5)
- 13x gene dose 0.5 (*10/*10) or 0.25 (*5/*10) or 0 (*5/*5)
The allele frequency of *10 was 11.6x higher than that of *5. Gene dose 1.25 or 1 is therefore primarily gene dose 1.25. Gene dose 0.5 or 0.25 or 0 is therefore primarily gene dose 0.5.

(Gene dose 0.5 or 0.25 or 0) versus (gene dose 1.25 or 1) versus gene dose 2:
- no difference in QT_c interval (NS)
- increase in the median C_{ss} risperidone (12.5 versus 8.0 versus 4.2 ng/mL) (S for the trend and for (gene dose 0.5 or 0.25 or 0) versus gene dose 2)
- no difference in the median C_{ss} 9-hydroxy-risperidone (NS)
- no difference in the median dose of risperidone (NS)
- decrease in C_{ss} magnesium (2.2 versus 2.3 versus 2.4 mEq/L) (S for</td>
<td>Authors' conclusion:
"In this study, the number of variant alleles of the CYP2D6 gene did not affect the QTc interval."</td>
</tr>
</table>

<table>
<tr><td>ref. 14, continuation</td><td></td><td>the trend)

NOTE: Genotyping was performed for *5 and *10. These are the most important alleles in this Asian patient group.</td><td></td></tr>
<tr><td>ref. 15
Gassó P et al.
Effect of CYP2D6 on risperidone pharmacokinetics and extrapyramidal symptoms in healthy volunteers: results from a pharmacogenetic clinical trial.
Pharmacogenomics 2014;15:17-28.
PubMed PMID: 24329187.</td><td>3

PM: A
UM: AA</td><td>25 healthy volunteers, selected for their CYP2D6 genotypes, received a single 2.5 mg dose of risperidone.
Relevant co-medication was excluded.

Genotyping:
- 7x UM
- 10x NM
- 8x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>UM</td><td>value for NM</td></tr>
<tr><td rowspan="3">AUC of the active moiety (risperidone plus 9-hydroxy-risperidone)</td><td>x 1.10</td><td>x 0.95</td><td rowspan="2">291 ng.h/ml</td></tr>
<tr><td colspan="2">NS for PM versus NM versus UM</td></tr>
<tr><td colspan="3">Linear regression analysis showed that sex and CYP2D6 together explained 69.1% of the total variance in the active moiety AUC, with sex having the largest effect and lowest p-value (S).</td></tr>
<tr><td rowspan="2">metabolic ratio 9-hydroxy-risperidone/risperidone</td><td>x 0.18 (S)</td><td>x 2.85 (NS)</td><td>2.7</td></tr>
<tr><td colspan="2">S for PM versus NM versus UM</td><td></td></tr>
</table>
NOTE: Genotyping was performed for *3-*6 and gene duplication. These are the most important gene variants in this Spanish population. Patients with alleles differing in functionality and gene duplication were excluded from the study.</td><td>Authors' conclusion:
"Our study demonstrates that CYP2D6 predicted 65% of the risperidone metabolism variability."

AUC risperidone + 9-hydroxyrisperidone versus NM:
PM: 110%
UM: 95%</td></tr>
<tr><td>ref. 16
Almoguera B et al.
CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment.
Pharmacogenet Genomics 2013;23:627-30.
PubMed PMID: 24026091.</td><td>4

IM: AA
UM: AA

PM: AA[#]</td><td>A total of 69 schizophrenia patients without any other conditions were treated in the hospital for a median 13.9 days with oral and/or intramuscular risperidone. The dose was adjusted according to the clinical situation. Relevant co-medication was not excluded, but correction was performed for co-medication with a significant effect on the outcome measures. Symptoms were measured using the Positive and Negative Syndrome Scale (PANSS) (total score (PANSS-T) and subscales for positive symptoms (PANSS-P) and negative symptoms (PANSS-N)). Response was defined as a decrease in the score on one of the scales by ≥ 50%. Anticholinergic medicines had a significant effect on the PANSS-N score and mood stabilisers had a significant effect on the PANSS-T score.

Genotyping:
- 37x NM (29x gene dose 2 (14x *1/*1, 10x *1/*2, 2x *1/*35, 2x *2/*2, 1x *2/*35), 7x gene dose 1.5 (*1/*41) and 1x gene dose 1.25 (*2/*10))
- 28x IM (23x gene dose 1 (9x *1/*4, 7x *2/*4, 3x *4/*35, 3x *41/*41, 1x *2/*6), 4x gene dose 0.5 (2x *4/*9, 2x *4/*41) and 1x gene dose 0.25 (*4/*10))
- 3x PM (*4/*4)
- 1x UM (*1xN/*1)

PM versus IM versus NM versus UM:
- no difference in the percentage of responders on the PANSS-T, PANSS-P or PANSS-N (NS: significance determined with Bonferroni correction ($p < 0.002$)).
There was a trend towards an improved response for PM on the PANSS-T after correction for mood stabilisers ($p = 0.029$) and on the PANSS-N after correction for anticholinergic medicines ($p = 0.049$).</td><td>Authors' conclusion:
"CYP2D6 poor metabolism was significantly associated with greater clinical improvement in total PANSS."</td></tr>
</table>

ref. 16, continuation		- PM exhibited a stronger improvement in the PANSS-T score than NM after correction for atypical antipsychotics and MDR1 genotype (S) NOTE: Genotyping was performed for 30 alleles and gene duplication.	
ref. 17 Almoguera B et al. Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. Pharmacogenomics J 2013;13:197-204. PubMed PMID: 22212732.	3 PM: AA IM: AA UM: AA	A total of 102 patients with acute schizophrenia were treated in the hospital with oral and/or intramuscular risperidone. The dose was adjusted according to the clinical situation. Relevant co-medication was not excluded. Genotyping: 64x NM 32x IM 3x PM 3x UM PM versus IM versus NM versus UM: - no difference in the percentage of patients with drowsiness, weight gain, extrapyramidal disorder or sexual side effects upon discharge from the hospital (NS: significance determined by logistic regression analysis with Bonferroni correction for 19 tested hypotheses ($p < 0.003$)) The study had a low evidential value (power of 80% to detect ORs > 4 or < 0.25). However, there were also no trends for CYP2D6. NOTE: Genotyping was performed for *3 through *11, *14, *15, *17, *19, *20, *25, *26, *29 through *31, *35, *40, *41 and gene duplication of *1, *2, *4, *10, *17, *35 and *41.	Authors' conclusion: "Strikingly, variants in CYP2D6 and MDR1, which have been reported to influence risperidone plasma concentrations did not yield significant results. According to their role in risperidone pharmacokinetics, it was expected for CYP-2D6 and MDR1 to impact significantly the development of adverse events. However, once again, the small sample size studied could have been responsible for the negative findings."
ref. 18 Mas S et al. Intuitive pharmacogenetics: spontaneous risperidone dosage is related to CYP2D6, CYP3A5 and ABCB1 genotypes. Pharmacogenomics J 2012;12:255-9. PubMed PMID: 21173786.	3 PM: A IM: A UM: A	The genotype was determined for 151 patients after initiation of risperidone. Relevant co-medication was not excluded. Genotyping: 91x NM 37x IM 15x PM 8x UM PM versus IM versus NM versus UM: - decrease in the set daily dose (5.9 versus 6.5 versus 7.4 versus 8.8 mg/day) (S for the trend, but not for the comparison between two groups) NOTE: Genotyping was performed for *3 through *6 and gene duplication.	Authors' conclusion: "Despite not knowing patients' metabolic status, clinicians modify risperidone dosage in order to obtain the best therapeutic option."
ref. 19 Jovanović N et al. The role of CYP2D6 and ABCB1 pharmacogenetics in drug-naïve patients with first-episode schizophrenia treated with risperidone. Eur J Clin Phar-	3	A total of 83 patients with a first episode of schizophrenia were treated with risperidone (1-8 mg/day, mean 3.96 mg/day) for 8 weeks. Co-medication with psychotropic medication other than anticholinergics (biperidene) and benzodiazepines (diazepam) was ruled out. 7 patients whose condition deteriorated to such an extent several days before the endpoint of the study that a dose increase (n=4) or another antipsychotic was required were excluded, as was one UM. The Positive and Negative Syndrome Scale (PANSS) was used to determine both the total score and the scores on the subscales for positive symptoms, negative symptoms and general psychopathology. Genotyping: 43x NM 32x IM	Authors' conclusion: "Our findings suggest that CYP2D6 and ABCB1 G2677T and C3435T may be useful determinants of risperidone plasma concentrations, but the clinical implications of these associa-

<table>
<tr>
<td>macol 2010;66:1109-17.
PubMed PMID: 20563569.

ref. 19, continuation</td>
<td>PM: A
IM: A</td>
<td>8x PM

PM versus IM versus NM:
- no difference in severity of the symptoms before and after treatment (NS)
- no difference in clinical response (decrease in the PANSS score by 50%) (NS)
- no difference in the incidence of extrapyramidal symptoms with severity > 3 on the Simpson-Angus scale (NS)
- increase in the dose-corrected C_{ss} of risperidone + 9-hydroxyrisperidone (13.4 versus 7.2 versus 5.7 nmol/L per mg) (S for the trend and for PM versus NM)
- increase in the dose-corrected C_{ss} of risperidone (35.1 versus 7.6 versus 4.4 nmol/L per mg) (S for the trend and for PM versus NM)
- decrease in the dose-corrected C_{ss} of 9-hydroxyrisperidone (7.9 versus 18.6 versus 14.4 nmol/L per mg) (S for the trend and for PM versus NM)
No correlation was found between PANSS scores and Simpson-Angus scale scores and the plasma concentrations.
The frequency of PM in the patient group was 3x higher than in the general population in Croatia. The reason for this is not known.

NOTE: Genotyping was performed for *3 through *6 and gene duplication.</td>
<td>tions in relation to treatment response and side-effects remain unclear.”</td>
</tr>
<tr>
<td>ref. 20
Novalbos J et al.
Effects of CYP-2D6 genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers.
J Clin Psychopharmacol 2010;30:504-11.
PubMed PMID: 20814331.</td>
<td>3

PM: A
IM: A
UM: AA</td>
<td>71 healthy volunteers received a single 1 mg dose of risperidone. The single dose was repeated after 14 days.
Relevant co-medication was excluded.

Genotyping:
- 6x UM
- 34x NM + (*1/*4)xN (32x NM, 2x (*1/*4)xN (either NM or IM depending on the allele duplicated))
- 25x IM
- 6x PM

Results:
Results versus NM:
<table>
<tr><th></th><th>PM</th><th>IM</th><th>UM</th><th>value for NM + (*1/*4)x N</th></tr>
<tr><td>AUC of the active moiety (risperidone plus 9-hydroxyrisperidone)</td><td>x 1.24 (NS)</td><td>x 1.12 (NS)</td><td>x 0.92 (NS)</td><td>163 ng.h/ml</td></tr>
<tr><td>metabolic ratio 9-hydroxyrisperidone/risperidone</td><td>x 0.05 (S)</td><td>x 0.44 (S)</td><td>x 2.25 (NS)</td><td>5.6</td></tr>
</table>
NOTE: Women showed higher values of AUC of the active moiety. These sex differences did not alter the differences between CYP2D6 polymorphisms and can be explained by the lower body weight of women because statistical significance disappeared if the authors added weight of the subject as covariate in the general linear model. The women/men ratios in the study were 0.5 for PM, 1.1 for IM, 1.3 for NM+(*1/*4)xN, and 0.2 for UM

NOTE: Genotyping was performed for *3-*7, *9, and gene duplication. These are the most important gene variants in this Spanish population.</td>
<td>Authors’ conclusion:
“There was a clear relationship between the number of active alleles and the pharmacokinetic parameters for risperidone and 9-hydroxyrisperidone, but there were no differences for total active moiety.”

AUC risperidone + 9-hydroxyrisperidone versus (NM + (*1/*4)xN):
PM: 124%
IM: 112%
UM: 92%</td>
</tr>
<tr>
<td>ref. 21
Wang L et al.
Serum prolactin levels, plasma risperidone</td>
<td>4</td>
<td>A total of 102 Chinese patients (65x NM (22x *1/*1, 41x *1/*10), 39x IM (*10/*10)) received risperidone 2-8 mg/day for 8 weeks (start: 2 mg/day, increased gradually to 6 mg/day, with dose adjustment from week 3 onwards based on clinical response). No relevant co-medication.</td>
<td>Authors’ conclusion:
“There was no difference in the active moiety</td>
</tr>
</table>

levels, polymorphism of cytochrome P450 2D6 and clinical response in patients with schizophrenia. J Psychopharmacol 2007;21:837-42. **ref. 21, continuation**	IM: A	IM versus *1/*1 (NM): - increase in the R/HR ratio from 0.25 to 0.42 (S by 68%) - increase in the percentage improvement in the score on the Brief Psychiatric Rating Scale from 37.49% to 41.31% (NS by 10%) - no significant increase in C_{ss}[a] R+HR (data not shown) *1/*10 versus *1/*1 (both NM): - increase in the R/HR ratio from 0.25 to 0.28 (S by 12%) - increase in the percentage improvement in the score on the Brief Psychiatric Rating Scale from 37.49% to 45.32% (NS by 21%) - no significant increase in C_{ss}[a] R+HR (data not shown) There was no significant correlation between C_{ss}[a] R+HR and clinical effect. There was no difference in prolactin levels between the groups. NOTE: Genotyping was performed for *3, *4, *5 and *10.	among the genotypes of CYP2D6 and no correlation within the genotypes of CYP2D6 with respect to clinical response. This suggests that the clinical importance of the polymorphism is limited."
ref. 22 de Leon J et al. A study of genetic (CYP-2D6 and ABCB1) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. Pharmacopsychiatry 2007;40:93-102.	3 PM: A IM: A UM: A	Regression analysis was performed on the 277 risperidone users in the study by De Leon, J Clin Psychiatry, 2005 (20x PM, 30x IM[#] (= reduced functionality of allele + dysfunctional allele or 2x reduced functionality of allele), 8x UM, 219x NM[#] (= 1-2 functional alleles)) to determine which factors correlate with the R/HR ratio and with C_{ss}[a] R+HR. PM versus NM+IM+UM: - significant association with increase in the R/HR ratio - significant association with increase in C_{ss}[a] R+HR - strong association with R/HR ratio > 14 (OR=8.2) Gene dose: - significant negative association with the R/HR ratio - following correction, there was a weak negative association with C_{ss}[a] R+HR Median C_{ss}[a] R+HR: - UM: 6.0 - NM[#]: 7.0 - IM[#]: 7.8 - PM: 11.0 NOTE: A gene dose of 0.2 was used for *10 and *36 as gene dose of the alleles with decreased functionality, a gene dose of 0.4 for *9, *29, *41 and *10xn, and a gene dose of 0.8 for *41xn.	Authors' conclusion: "Our study indicated that the CYP2D6 PM phenotype may have a major role in personalizing R doses, whereas the CYP3A5 PM phenotype probably has no role. CYP inducers and inhibitors appear to be relevant to R dosing." Median C_{ss}[a] R+HR versus NM[#]: PM: 157% IM[#]: 111% UM: 86%
ref. 23 Cho HY et al. Pharmacokinetics and bioequivalence evaluation of risperidone in healthy male subjects with different CYP2D6 genotypes. Arch Pharm Res 2006;29:525-33.	3 IM: A	A total of 24 healthy Korean volunteers (14x NM (7x *1/*1, 7x *1/*10), 10x IM (*10/*10)) received a single dose of risperidone 2mg. IM versus *1/*1 (NM): - increase in AUC R+HR from 182.6 to 207.0 ng.hour/mL (NS by 13%) - decrease in $t_{1/2}$ R+HR from 15.1 to 11.5 hours (S by 24%) *1/*10 versus *1/*1 (both NM): - decrease in AUC R+HR from 182.6 to 172.9 ng.hour/mL (NS by 5%) - decrease in $t_{1/2}$ R+HR from 15.1 to 11.9 hours (S by 21%) All side effects were mild and disappeared without treatment. NOTE: genotyping was only performed for *10.	Authors' conclusion: "The lack of relationship between the genotype and the active moiety indicates that the CYP2D6 polymorphism may be of limited importance for the clinical outcome during risperidone treatment." AUC R+HR versus NM: IM: 116%
ref. 24 Lane HY et al. Risperidone-related weight	4	A total of 123 Han Chinese patients (66x NM (29x *1/*1, 37x *1/*10), 50x IM (*10/*10)) received risperidone mean 4.0 mg/ day for 14-42 days (dose adjusted according to effect and side effects (except weight gain)). Co-medication with lorazepam and benzatropine was	

gain: genetic and nongenetic predictors. J Clin Psychopharmacol 2006;26:128-34. **ref. 24, continuation**	IM: B	permitted. Linear regression analysis was used to identify factors that could influence weight gain by risperidone. Weight compared to *1/*1 (NM): - increase by 1.14 kg for *1/*10 (also NM) (S) - increase by 0.799 kg for (IM) (S) - increase by 0.638 kg for NM (*1/*1 + *1/*10) The weight gain for risperidone decreases with age of the patients. NOTE: genotyping was performed for *10.	
ref. 25 de Leon J et al. Polymorphic variations in GSTM1, GSTT1, PgP, CYP2D6, CYP-3A5, and dopamine D2 and D3 receptors and their association with tardive dyskinesia in severe mental illness. J Clin Psychopharmacol 2005;25:448-56.	3 PM: D	Linear regression models were used to identify factors that could affect tardive dyskinesia in 516 patients, including 38 PM, who were using or had used risperidone (see the study by De Leon, J Clin Psychiatry, 2005). 27 of the PM were white males. Of the total of 516 patients, 162 had tardive dyskinesia, with 49 experiencing severe tardive dyskinesia. Linear regression did not adjust for dose and duration of treatment with risperidone. It only adjusted for duration of treatment with typical antipsychotics ≥ 5 years, Mean duration of typical antipsychotic treatment was 11.3 years, whereas only 26% of CYP2D6 PM used risperidone for more than 1 year. Because the study was cross-sectional, not longitudinal, patients were not followed up 3 months later to verify whether dyskinetic movements were still present. PM versus NM+IM+UM: - increase in percentage of patients with tardive dyskinesia from 31% to 42% (OR = 1.7) (NS by 35%) - OR = 2.6 within the sub-group of white males (NS, n = 225) - increase in percentage of white males with tardive dyskinesia of the mouth from 15% to 39% (OR = 4.8) (S by 160%) NOTE: The maximum risperidone dose during the study was higher in the 16 PMs with tardive dyskinesia than in the 22 PMs without tardive dyskinesia (6.0 versus 3.7 mg/day; S). The CYP2D6 PMs with tardive dyskinesia also had a significantly longer duration of typical antipsychotic treatment (19.6 versus 12.2 years; S). NOTE: The dose in patients with tardive dyskinesia was higher and the duration of treatment was longer (NS). Tardive dyskinesia disappears following dose increase and recurs with dose reduction. No conclusions can be drawn for this based on this study.	Authors' conclusion: "The CYP2D6 and CYP3A5 absence showed potential for significant associations in larger samples, particularly in white men."
ref. 26 Riedel M et al. Risperidone plasma levels, clinical response and side-effects. Eur Arch Psychiatry Clin Neurosci 2005;255:261-8.	4 IM: AA	A total of 59 patients (51x *1/*1; 8x *1/*4) received risperidone mean 4.3 mg/day for 6 weeks. Co-medication with lorazepam, zolpidem and biperidene was permitted. IM versus NM: - decrease in C_{ss} R+HR from 42.1 to 41.4 ng/mL (NS by 2%) - increase in the R/HR ratio from 0.5 to 1.9 (NS by 280%) - decrease in percentage of responders from 42% to 33% (NS) - no significant difference in clinical response (improvement in the total score on the Positive and Negative Syndrome Scale over 6 weeks) Non-responders had a significantly higher C_{ss} R+HR than responders, without the doses being significantly higher. NOTE: genotyping was performed for *4, *6 and *16.	C_{ss} R+HR versus NM: IM: 98%
ref. 27 Kato D et al. Delirium resolving upon switching from risperidone to	1 IM: C	Patient received risperidone 1 mg/day; Extrapyramidal side effects developed two days after start. Side effects disappeared within one week after stopping treatment. Patient was found to be IM (*5/*10). Quetiapine did not cause side effects.	

quetiapine: implication of CYP2D6 genotype. Psychosomatics 2005;46:374-5.			
ref. 28 Kakihara S et al. Prediction of response to risperidone treatment with respect to plasma concentrations of risperidone, catecholamine metabolites, and polymorphism of cytochrome P450 2D6. Int Clin Psychopharmacol 2005;20:71-8.	4 IM: AA	A total of 136 patients, with 39 genotyped, 16x *1/*1, 14x *1/*10, 9x *10/*10, dose 1-8 mg/day, smokers + non-smokers, no co-medication that affects risperidone; No difference found in kinetic parameters (Css R+HR, R/HR ratio), clinical effect or extrapyramidal symptoms between the different genotypes.	
ref. 29 de Leon J et al. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. J Clin Psychiatry 2005;66:15-27.	4 PM: C	A total of 537 patients, of which 325 using risperidone and 212 stopped using risperidone. 325 risperidone users: 27x PM, 30x IM (= reduced functional allele + non-functional allele or 2x reduced functional allele), 12x UM, 256x NM (= 1-2 fully functional alleles). 212 stopped: 11x PM, 32x IM, 5x UM and 164x NM, (genotyping with AmpliChip), dose of risperidone varied from less than 0.75 mg/day to more than 6 mg/day, co-medication included CYP2D6 and CYP3A4 inhibitors and CYP3A4 inducers; Risk (odds ratio) of stopping risperidone as a result of side effects is 6.0 for PM (S). Side effects: primarily extrapyramidal. Note: Genotyping was for *1-*11, *15, *17, *19, *20, *29, *35, *36, *40, *41, and gene duplication. These are the most important gene variants in this population from the USA. *17 was considered a fully active allele instead of an allele with decreased activity. In addition, *36 was considered a partially active allele instead of a non-functional allele, and duplication of *10 and *41 was considered not to lead to full functionality.	Authors' conclusion: "The results of this study suggest the CYP2D6 poor metabolizer phenotype is associated with an increase in moderate-to-marked adverse drug reactions (ADR) and increased risperidone discontinuation due to ADRs. Suggestions that the CYP2D6 poor metabolizer status is unimportant with regard to risperidone therapy appear unfounded in light of these consistent results."
ref. 30 Llerena A et al. QTc interval, CYP2D6 and CYP2C9 genotypes and risperidone plasma concentrations. J Psychopharmacol	4 PM: AA UM: AA	A total of 35 patients, 1x *4/*4, 10x *1/*4, 23x *1/*1, 1x *1xn/*1, risperidone 2-14 mg/day, no co-medication; *kinetic endpoints* - *4/*4: increase in C_{ss}[a] R+HR versus NM from 22.5 to 48.2 nM/mg (NS by 114%), increase in R/HR ratio from 0.15 to 7.1 (NS by 4633%). - *1/*4: increase in C_{ss}[a] R+HR versus NM from 22.5 to 35.3 nM/mg (S by 57%), increase in R/HR ratio from 0.15 to 0.43 (S by 187%). - *1xn/*1: decrease in C_{ss}[a] R+HR versus NM from 22.5 to 20.3 nM/mg (NS by 10%), decrease in R/HR ratio from 0.15 to 0.04 (NS by 73%).	C_{ss} R+HR versus NM: PM: 214% IM: 157% UM: 90%

2004;18:189-93. **ref. 30, continuation**	IM: A	*clinical endpoint* QT_c interval was greater for *1/*4 than for *1/*1 (S), but did not exceed 450 ms for women or 470 ms for men. No correlation between QT_c interval and dose or C_{ss} R+HR, C_{ss} risperidone or C_{ss} HR.	
ref. 31 Yasui-Furukori N et al. Effects of various factors on steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone: lack of impact of MDR-1 genotypes. Br J Clin Pharmacol 2004;57:569-75.	4 IM: A	A total of 85 patients, 37x wt/wt (wt = *1 or *2), 30x wt/*10, 9x wt/*5, 5x *10/*10, 3x *5/*10, 1x *4/*14, risperidone 3 mg twice daily, no co-medication that affects CYP2D6; There is a correlation between C_{ss} risperidone and the number of mutated alleles. No correlation was found between C_{ss} HR or C_{ss} R+HR and the number of mutated alleles.	
ref. 32 Kohnke MD et al. Cytochrome P450 2D6 deficiency and its clinical relevance in a patient treated with risperidone. Pharmacopsychiatry 2002;35:116-8.	2 PM: C	Patient (*4/*4) receiving risperidone 6 mg/day experienced extrapyramidal symptoms, which persisted after reduction of the dose to 4 mg/day; C_{ss} R+HR was then 63 μg/L, R/HR ratio was 2.9. The symptoms disappeared after stopping risperidone.	
ref. 33 Roh HK et al. Risperidone metabolism in relation to CYP-2D6*10 allele in Korean schizophrenic patients. Eur J Clin Pharmacol 2001;57:671-5.	4 IM: AA	A total of 82 patients, 22x *10/*10, 43x *1/*10, 17x *1/*1, risperidone 1-8 mg/day, no co-medication: - *10/*10: increase in C_{ss}[b] R+HR versus *1/*1 from 15.5 to 23.2 nM/mg (NS by 50%), increase in C_{ss}[b] R/HR ratio from 0.25 to 0.52 (NS by 108%). - *1/*10: increase in C_{ss}[b] R+HR versus *1/*1 from 15.5 to 18.3 nM/mg (NS by 18%), increase in R/HR ratio from 0.25 to 0.47 (NS by 88%).	C_{ss} R+HR versus NM: IM: 133%
ref. 34 Guzey C et al. Risperidone metabolism and the impact of being a cytochrome P450 2D6 ultrarapid metabolizer. J Clin Psychiatry 2000;61:600-1.	2 UM: C	2 patients (both UM: *1/*2xn), both with risperidone dose 4 mg/day, no co-medication; - patient 1: no therapeutic effect, C_{ss} risperidone and HR < 2 ng/mL and 22 ng/mL respectively. - patient 2: ditto, concentrations < 0.4 ng/mL and 9.6 ng/mL respectively.	
ref. 35 Scordo MG et al. Cytochrome P450 2D6	4	A total of 37 patients, 4x PM (*4/*5), 15x IM (*1/*4, *1/*5), 16x NM (*1/*1), 3x UM (*1xn/*1), risperidone 4-8 mg/day, no co-medication that affects CYP2D6: - PM: increase in C_{ss}[a] R+HR versus NM from 35.5 to 40.4 nM/mg (NS	C_{ss} R+HR versus

genotype and steady state plasma levels of risperidone and 9-hydroxy-risperidone. Psychopharma-cology 1999;147:300-5.	PM: A IM: A UM: AA	by 14%), increase in C_{ss}[a] R/HR ratio from 0.04 to 0.79 (S by 1875%). - IM: increase in C_{ss}[a] R+HR versus NM from 35.5 to 42.7 nM/mg (NS by 20%), increase in C_{ss}[a] R/HR ratio from 0.04 to 0.23 (S by 475%). - UM: decrease in C_{ss}[a] R+HR versus NM from 35.5 to 28.5 nM/mg (NS by 20%), decrease in C_{ss}[a] R/HR ratio from 0.04 to 0.03 (NS by 25%).	NM: PM: 114% IM: 120% UM: 80%
ref. 36 Bork JA et al. A pilot study on risperidone metabolism: the role of cyto-chromes P450 2D6 and 3A. J Clin Psychia-try 1999;60:469-76.	2 PM: C	13 patients, 7x wt/wt, 1x wt/?, 3x wt/*4, 2x PM (*4/*4 and *5/*5), dose 4-12 mg/day, with co-medication that affects CYP2D6 and/or CYP-3A4: Prevalence of moderate or severe side effects (extrapyramidal side effects, parkinsonism, sedation) was 100% for PMs and 35% for the other genotypes.	
ref. 37 SmPC Risper-dal (risperi-done) 28-02-21. ao.	0 PM: AA	<u>Pharmacokinetics</u>: Normal CYP2D6 metabolisers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolisers convert it much more slowly. Although normal metabolisers have lower risperi-done and higher 9-hydroxyrisperidone concentrations than poor meta-bolisers, the pharmacokinetics of risperidone and 9-hydroxyrisperi-done combined (i.e. the active antipsychotic fraction). after single and multiple doses, are similar in normal and poor metabolisers of CYP-2D6.	
ref. 38 SmPC Risper-dal (risperi-done), USA, 12-02-21.	0 PM: AA	<u>Pharmacokinetics</u>: CYP2D6 is subject to genetic polymorphism (about 6%-8% of Cauca-sians, and a very low percentage of Asians, have little or no activity and are “poor metabolizers”) and to inhibition by a variety of substra-tes and some non-substrates, notably quinidine. Normal CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. Although normal metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the phar-macokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in normal and poor metaboli-zers. The therapeutic benefits and adverse effects of Risperdal in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of poor metabolizers given oral Risperdal do not suggest important differences between poor and normal metabo-lizers.	

ao.: SmPC Risperdal Consta (risperidone for prolonged-release suspension) 14-09-18.
[a] concentration corrected for dose
[b] concentration corrected for dose and mean body weight
NM [#] and IM [#]: NM and IM are defined differently from the CYP2D6 translation table used by KNMP.

Risk group	IM and PM with CYP3A inhibitor, UM with CYP3A inducer, IM with CYP2D6 inhibitor

Comments:

- For the period after 2014, clinical studies were only included if they examined long-term treatment of more than 100 patients. For the period from 2008-2014, clinical studies were only included if they examined long-term treatment of more than 50 patients. Short-term treatment of healthy volunteers does not provide enough information about long-term side effects. Smaller studies do not contribute sufficiently to the evidence. For the period after 2007, studies providing only kinetic data were only included if they contained information on the (dose-corrected) exposure of the sum of risperidone and 9-hydroxyrisperidone for at least 9 PM, at least 38 IM, or at least 3 UM compared to NM. Smaller kinetic studies did not contribute sufficiently to the burden of

proof.
The study of Rossow 2021 (Rossow KM et al. Evidence for pharmacogenomic effects on risperidone outcomes in pediatrics. J Dev Behav Pediatr 2021;42:205-12. PMID: 33759847) was not included, because it concerns a re-analysis of the data in Oshikoya 2019. The meta-analysis 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 the IM definition (and correspondingly the NM definition) used by the authors seems to differ from the definition of the KNMP Pharmacogenetics Working Group. IM data from Van der Weide 2015 were ignored, whereas IM data from studies defining gene dose 1/0 (which is the major IM group in the Netherlands) as NM were included in the meta-analysis. The meta-analysis of Zhang 2020 (Zhang L et al. CYP2D6 genetic polymorphisms and risperidone pharmacokinetics: a systematic review and meta-analysis. Pharmacotherapy 2020;40:632-47. PMID: 32519344) was not included, because the data are weighed based on the width of the confidence interval (inverse variance method), whereas the KNMP Pharmacogenetics Working Group weighs pharmacokinetic data based on the number with patients with the variant phenotype. In addition, for the second largest study in the meta-analysis of the plasma concentration of the active moiety (van der Weide 2015) the ratio of the median is used by Zhang 2020 instead of the ratio of the mean, and the value for UM does not correspond with the value in van der Weide 2015. For Van der Weide 2015, the KNMP Pharmacogenetics Working Group has and uses the mean values. For these reasons, the meta-analysis of Zhang 2020 does not provide useful data for this risk analysis. The study Zeng L et al. CYP2D6 polymorphisms are associated with effects of risperidone on neurocognitive performance in schizophrenia. Schizophr Res 2017;188: 50-1. PubMed PMID: 28131599 was not included in the risk analysis, because the authors only report (significant) results for two single nucleotide polymorphisms in CYP2D6 *2, which has normal activity. Molden E et al. Impact of ageing on serum concentrations of risperidone and its active metabolite in patients with known CYP2D6 genotype. Basic Clin Pharmacol Toxicol 2016;119:470-475. PubMed PMID: 27145399 was not included in the risk analysis, because the patients in this study are a subgroup of the patients in Jukic 2019. Hendset M et al. Impact of CYP2D6 genotype on steady-state serum concentrations of risperidone and 9-hydroxyrisperidone in patients using long-acting injectable risperidone. J Clin Psychopharmacol 2009;29:537-41. PubMed PMID: 19910717 was not included in the risk analysis, because the patient group in this study overlaps with that in Jukic 2019. Cabaleiro T et al. Effect of polymorphisms on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. Hum Psychopharmacol 2014; 29:459-69. PubMed PMID: 25042870 was not included, because the patients in this study are a subgroup of the patients in Novalbos 2010.

Date of literature search: 19 July 2021.

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

Mechanism:
Risperidone is primarily metabolised by CYP2D6 and to a lesser extent by CYP3A4. This results in - among others - the active metabolite 9-hydroxyrisperidone (paliperidone). A CYP2D6 genetic polymorphism may cause a change in the plasma concentration of risperidone and 9-hydroxyrisperidone.
For risperidone, no relationship has been determined between the plasma concentration of risperidone + 9-hydroxyrisperidone (the active substances) and the clinical effectiveness. Similarly, no relationship has been determined between the plasma concentration of the active substances and the occurrence of side effects. However, the Dutch Association of Hospital Pharmacists (NVZA) indicates that several studies show it to be likely that an optimal effect and the fewest adverse events are reached within a range of 20-60 ng/ml (approximately 47-146 nM) for the sum of risperidone and 9-hydroxyrisperidone, with concentrations > 120 ng/ml to be considered toxic. This is confirmed by Hiemke 2018 (Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62). However, Jukic 2019 reports the therapeutic range to be estimated as 20-45 ng/ml (approximately 47-110 nM), with 45 ng/ml (110 nM) chosen as upper limit because higher exposure leads to a D2 receptor occupancy of more than 80%, which is associated with the occurrence of extrapyramidal side effects. In addition, the NVZA indicates that there are indications that the therapeutic range is lower in children than in adults. Based on Klampfl 2010, a therapeutic range of 8-26 mg/ml (approximately 19-63 nM) for the sum of risperidone and 9-hydroxyrisperidone is assumed for the treatment of children and adolescents with impulsive-aggressive symptoms (Klampfl K et al. Serum concentrations, therapeutic response and side effects in children and adolescents with impulsive-aggressive symptoms during risperidone therapy. Pharmacopsychiatry 2010;43:58-65).

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	0+
Corresponding Clinical Implication Score:		Potentially beneficial