CYP2D6: haloperidol 1551/1552/1553

AUC = area under the concentration-time curve, BMI = body-mass index, Cl_{or} = oral clearance C_{ss} = steady state concentration, EPS = extrapyramidal symptoms, HAL = haloperidol, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), MR = metabolic ratio, NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), R-HAL = reduced haloperidol, S = significant, SmPC = Summary of Product Characteristics, UM = ultra-rapid metaboliser (gene dose ≥ 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:
Haloperidol is primarily metabolised via glucuronidation and to a lesser extent by CYP3A4, CYP2D6 and carbonyl reduction. The metabolite reduced haloperidol, can be oxidised back to haloperidol by CYP2D6 and CYP3A4. Haloperidol is a CYP2D6 inhibitor.
The therapeutic range is a haloperidol serum trough concentration of 5-15 µg/L. Haloperidol serum through concentrations > 20 µg/L are considered to be toxic. There is no clear relationship between the serum concentration of haloperidol and the (severity of the) toxic effects.
Genetic variants in CYP2D6 can result in a decreased CYP2D6 enzyme activity (intermediate metabolisers (IM)), an absent CYP2D6 enzyme activity (poor metabolisers (PM)) or an increased CYP2D6 enzyme activity (ultra-rapid metabolisers (UM)).
Of the 21 studies investigating the influence of CYP2D6 phenotypes on pharmacokinetics (serum concentration, AUC, clearance or dose), 12 studies found a significant influence on pharmacokinetics of haloperidol (Waade 2021 (137 patients, 47 IM, 6 PM), Van der Weide 2015 (308 patients, 134 IM, 30 PM, 6 UM), Gassó 2013 (25 volunteers, 8 PM, 7 UM), Panagiotidis 2007 (26 patients, 8 IM, 1 PM, 1 UM), Llerena 2004 (33 patients, 13 IM, 7 PM), Ohara 2003 (110 patients, 34 IM; only significant effect in 51 smokers, not in the 59 non-smokers), Inada 2003 (320 patients, approximately 45 IM), Desai 2003 (16 volunteers, 3 PM), Brockmoller 2002 (175 patients, 56 IM, 5 PM, 5 UM), Yasui-Furukori 2001 (76 patients (45 IM+PM), Roh 2001 (51 patients on a haloperidol dose < 20 mg/day, 16 IM), Llerena 1992 (12 volunteers, 6 PM)), 4 studies found a significant influence on pharmacokinetics of reduced haloperidol, but not of haloperidol (Patteet 2016 (11 patients, 5 IM + gene dose 1.25-1.5, 2 PM, 1 UM), Pan 1999 (63 patients, 5 PM), Mihara 1999 (67 patients, 7 IM), Suzuki 1997 (50 patients, 6 IM)), and the remaining 5 studies found no significant influence (Trogrlić 2020 (22 delirium patients, 7 IM, 3 PM), Park 2006 (19 volunteers, 10 IM), Ohnuma 2003 (111 patients, 26 IM), Someya 2003 (88 patients, 20 IM), Shimoda 2000 (66 patients, 13 IM)). Based on this, the KNMP Pharmacogenetics Working Group concluded the presence of a CYP2D6-haloperidol interaction.
For PM, Brockmoller 2002 reported a higher extrapyramidal symptom score, but no effect on tardive dyskinesia and akathisia (study with 175 patients, including 5 PM). Panagiotidis 2007 did not find an effect of CYP2D6 phenotype on scores on the positive and negative syndrome and extrapyramidal symptom rating scales in 26 patients treated with haloperidol (16 NM, 1 PM, 8 IM and 1 UM). Šimić 2016 reported a PM with extrapyramidal symptoms (acute dystonia) and extreme sedation after a single dose of haloperidol concomitant with the CYP3A4 inhibitor ciprofloxacine. Butwicka 2014 reported a PM with neuroleptic malignant syndrome after addition of a single dose of haloperidol to treatment with olanzapine 10 mg/day and levomepromazine 37.5 mg/day. However, because the patient already developed neuroleptic malignant syndrome symptoms before haloperidol addition, it is not clear if and to what extent haloperidol contributed to the development of the syndrome. Gassó 2013 found an effect of CYP2D6 phenotype on actigraphy of the non-dominant arm, but no effect on extrapyramidal symptom scales, negative symptoms, sedation, dopamine D2 receptor occupancy and prolactin levels after a single haloperidol dose in healthy volunteers (10 NM, 8 PM, 7 UM). Desai 2003 found no effect of the PM phenotype on QT_c interval elongation in a study with healthy volunteers (3 PM). Because there are some indications for an increased risk of adverse events and because of the rather narrow therapeutic window and despite the lack of a clear relationship between the serum concentration of haloperidol and the (severity of the) toxic effects, the KNMP Pharmacogenetics Working Group decided to recommend therapy adjustment for PM (yes/yes-interaction).
For IM, Inada 2003 found a trend, but no significant effect on occurrence of acute extrapyramidal symptoms and no effect on tardive dyskinesia in a study with 320 patients (approximately 45 IM). Brockmoller 2002 found no effect of the IM phenotype on extrapyramidal symptom score, tardive dyskinesia, akathisia, improvement of symptoms and treatment modification due to adverse events (stopping haloperidol, addition of other medicines or haloperidol dose

reduction) (study with 175 patients, including 56 IM). Sychev 2016 found a stronger decrease in symptom scores and a stronger increase in adverse event scores in 17 IM with an exacerbation of alcohol addiction treated with haloperidol for 5 days. However, the difference between NM and IM was only 4-15% of the symptom score before treatment and only 13-24% of the adverse event score before treatment. Therefore, these differences are unlikely to be clinically significant. Panagiotidis 2007 did not find an effect of CYP2D6 phenotype on scores on the positive and negative syndrome and extrapyramidal symptom rating scales in 26 patients treated with haloperidol (16 NM, 8 IM, 1 PM and 1 UM). Park 2006 did not find a significant effect of the IM phenotype on the proportion of volunteers stopping study participation, side effects and the QT_c interval (study with 10 IM). Because none of the studies found a clinically significant increase in adverse events (with none of the studies in schizophrenic patients showing a statistically significant effect either) and because of the small effect on haloperidol kinetics (with a weighted mean of the observed increase in exposure of 13% (see 'Calculated dose adjustments' below)), the KNMP Pharmacogenetics Working Group decided that there is not enough evidence for the need to adjust therapy in IM (yes/no-interaction).
For UM, Brockmoller 2002 reported a smaller improvement of symptoms and a higher frequency of treatment modification due to adverse events (stopping haloperidol, addition of other medicines or haloperidol dose reduction), but no effect on tardive dyskinesia and akathisia (study with 175 patients, including 5 UM). Panagiotidis 2007 did not find an effect of CYP2D6 phenotype on scores on the positive and negative syndrome and extrapyramidal symptom rating scales in 26 patients treated with haloperidol (16 NM, 1 UM, 8 IM and 1 PM). Gassó 2013 found an effect of CYP2D6 phenotype on actigraphy of the non-dominant arm, but no effect on extrapyramidal symptom scales, negative symptoms, sedation, dopamine D2 receptor occupancy and prolactin levels after a single haloperidol dose in healthy volunteers (10 NM, 8 PM, 7 UM). Because there are some indications for an increased risk of a smaller therapeutic effect and because of the rather narrow therapeutic range, the KNMP Pharmacogenetics Working Group decided to recommend therapy adjustment for UM (yes/yes-interaction).
Calculated dose adjustments
Dose adjustments were calculated on the basis of the AUC, C_{ss} or Cl_{or} for haloperidol. The reduced haloperidol was not included in calculations of the dose adjustment, because it is not known to what extent this metabolite is active. If the effect is only known versus NM + IM (as was the case, for example, in Desai 2003), then it was assumed that NM + IM is approximately equal to NM, considering the much lower prevalence of IM.
There is insufficient data to be able to make a substantiated recommendation on dose adjustments for administration of haloperidol as an intramuscular depot (only two studies: Panagiotidis 2007 and Patteet 2016). As the results of the first study do not differ very much from the results of studies involving oral haloperidol and the second study only reported data for oral and intramuscular administration together, they were included in the dose calculations.

PM: Decrease the dose to 60% of the normal dose. This dose adjustment was calculated for the change in kinetic parameters of haloperidol from 8 studies with a total of 61 PM. The reference Pan 1999 was not included due to the strongly deviating value, which could be the result of the co-medication used. The weighted mean of the calculated dose adjustments was a reduction to 60% (median 65%, range 25%-106%).

IM: A dose adjustment does not appear to be necessary based on the strongly varying results for IMs. Dose adjustments calculated based on haloperidol kinetic parameters from 12 studies with a total of 386 IM call for a dose varying from 58% to 100% of the normal dose (median 83% of the normal dose). If the weighted mean is calculated for the dose adjustments, only a small reduction of the dose appears to be necessary: reduction to 88% of the normal dose. This corresponds to a weighted mean increase in haloperidol exposure in IM of 13%. Considering the normal biological variation being approximately 25%, exposure increases and dose reductions of less than 15% are unlikely to be clinically significant. Indeed, no clinically significant effects have been observed for IM.

UM: Increase the dose to 1.5 fold the normal dose. This dose adjustment was calculated for the change in kinetic parameters of haloperidol from 5 studies with a total of 20 UM. The weighted mean of the calculated dose adjustments was an increase to 1.64 fold the normal dose (median 1.55 fold, range 1.04-2.09 fold).
Instead of increasing the dose, physicians may choose an alternative. From the group of classic antipsychotics, flupentixol and penfluridol are not metabolised by CYP2D6. From the group of atypical antipsychotics, clozapine, olanzapine and quetiapine are not metabolised by CYP2D6. As is the case with haloperidol, flupentixol is also available as a depot injection. Penfluridol is slowly released from adipose tissue after weekly oral dosing.

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

Recommendation concerning pre-emptive genotyping, including justification of choices:
The Dutch Pharmacogenetics Working Group considers genotyping before starting haloperidol to be potentially beneficial for the prevention of side effects and for drug efficacy. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the Dutch Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 1 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):

Severe clinical effects were only observed in one case report. Butwicka 2014 reported a PM with neuroleptic malignant syndrome after addition of a single dose of haloperidol to treatment with olanzapine 10 mg/day and levomepromazine 37.5 mg/day (severity code E corresponding to CTCAE grade 4). However, because the patient already developed neuroleptic malignant syndrome symptoms before haloperidol addition, it is not clear if and to what extent haloperidol contributed to the development of the syndrome. Therefore, this maximum severity score was not used for determining the clinical implication score. In the other publications, the maximum severity code was C corresponding to CTCAE grade 2. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).
The lack of a severe clinical effect in a study 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 (only points for at least one study (level of evidence score ≥ 3) supporting the 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) (only points for NNG ≤ 1000).
The Summaries of Product Characteristics (SmPCs) of haloperidol mention the CYP2D6 PM phenotype, but do not mention this phenotype as a contra-indication and do not recommend pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contraindication and no recommendation to genotype).

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.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1, oral
Waade RB et al.
Impact of CYP2D6 on serum concentrations of flupentixol, haloperidol, perphenazine and zuclopenthixol.
Br J Clin Pharmacol 2021;87:2228-35.
PMID: 33118660.</td><td>4

PM: AA
IM: A</td><td>137 patients were treated with haloperidol. Therapeutic drug monitoring was routinely done. The mean number of measurements per patient was 1.8 for NM, 3.3 for IM and 2.0 for PM. Genotyping was performed either before or after treatment start. Due to the small number, UMs were not included. Trough serum concentrations were determined (10 to 26 hours after dosing). Only measured serum concentrations within the lower and upper limits of quantification were included.
Measurements were also excluded if the requisition forms (lacking for approximately 11% of measurements) provided information on possible noncompliance, or on use of co-medication inhibiting or inducing the CYP enzymes involved in haloperidol metabolism.

Genotyping:
- 84x NM
- 47x IM
- 6x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>dose-corrected trough concentration of haloperidol</td><td>x 1.36 (NS)</td><td>x 1.20 (S)</td><td>1.35 nmol/L. mg</td></tr>
<tr><td>trough concentration of haloperidol</td><td>NS</td><td>NS</td><td>5.37 nmol/L</td></tr>
<tr><td>haloperidol dose</td><td>trend for a decrease (p = 0.062 (NS)</td><td>NS</td><td>4.32 mg/day</td></tr>
</table>
NOTE: Genotyping was performed for *3-*6, *9, *10, *41, and gene multiplication. These are the most important gene variants in this Norwegian population.
Patients with multiplied, functional alleles were excluded from the study due to few samples.</td><td>Authors' conclusion: 'This study shows that CYP2D6 is important for the metabolism of perphenazine and zuclopenthixol, but not for haloperidol and flupentixol.'

Dose-corrected trough concentration of haloperidol versus NM:
PM: 136%
IM: 120%</td></tr>
</table>

<table>
<tr>
<td>ref. 2, i.v.
Trogrlić Z et al. Pharmacogenomic response of low dose haloperidol in critically ill adults with delirium. J Crit Care 2020;57:203-7. PubMed PMID: 32208328.

and

personal communication (CYP2D6*4 was genotyped in this study, but incorrectly not mentioned in the article as one of the genotyped alleles)</td>
<td>3

IM: AA
PM: AA</td>
<td>22 ICU patients with delirium were treated with a median intravenous haloperidol dose of 3.0 mg/day. The ICU delirium treatment protocol advocated intravenous haloperidol for all patients who developed delirium (Intensive Care Delirium Screening Checklist score (ICDSC) ≥4) at a starting dose of 1 mg every 8 hours (0.5 mg every 8 hours if age ≥ 80 years old; 2 mg every 8 hours if agitation present) within 8 hours of delirium detection. If delirium was still present 24 hours later intravenous haloperidol was increased by 0.5 mg to a maximum of 2 mg every 8 hours. The haloperidol dose was decreased when the ICDSC was ≤3 for more than 24 hours, and was stopped when the ICDSC was ≤3 for more than 48 hours. No patient experienced QTc interval prolongation (≥500 ms).
Serum concentrations were corrected for the most recent haloperidol dose administered.
CYP2A6 and CYP3A4 inducers were excluded, but other relevant comedication was not. 82% of patients received one or more CYP2D6 inhibitors and 59% one or more CYP3A4 inhibitors.
Outliers were excluded from analysis. Results were adjusted for age, admission SOFA (Sequential Organ Failure Assessment) score, and ICU day,

Genotyping:
- 12x NM
- 7x IM
- 3x PM

Results:
<table>
<tr><td colspan="2">Median dose-corrected trough serum concentration of haloperidol compared to NM:</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td>PM</td><td>NS</td></tr>
</table>

NOTE: Genotyping was performed for *2, *2A, *3-*10, *12, *14/*114, *17, *29 and gene multiplication. These are the most important gene variants in this Dutch population.</td>
<td>Authors' conclusion: 'This pilot study, the first to evaluate the pharmacogenomic response of low-dose haloperidol when used to treat delirium in the ICU, suggests CYP2D6/ CYP3A4 metabolizer status does not affect the serum haloperidol concentrations.'</td>
</tr>
<tr>
<td>ref. 3, oral, i.v.
Sychev DA et al. The correlation between CYP2D6 isoenzyme activity and haloperidol efficacy and safety profile in patients with alcohol addiction during the exacerbation of the addiction. Pharmgenomics Pers Med 2016;9:89-95. PubMed PMID: 27695358.</td>
<td>3</td>
<td>70 patients with exacerbation of alcohol addiction were treated with haloperidol for 5 days. 38 patients received oral haloperidol at a mean dose of 4.3 mg once daily. 32 patients received intravenous haloperidol at a mean dose of 6.1 mg once daily.
Addiction, anxiety and depression symptoms were rated with the following scales: Scale of Pathological Addiction, Hamilton Anxiety Rating Scale, Beck Anxiety Inventory, Covi Anxiety Rating Scale, Zung Self-Rating Anxiety Scale, Sheehan Clinical Anxiety Rating Scale, and Hamilton Rating Scale for Depression. Adverse events were rated with The UKU Side Effects Rating Scale and Simpson-Angus Scale for Extrapyramidal Symptoms. Higher scores on these scales indicate more addiction, depression or adverse events.
Other antipsychotics were excluded, but comedication affecting CYP2D6 and CYP3A4 was not.

Genotyping:
oral haloperidol:
- 30x NM
- 8x IM

intravenous haloperidol:
- 23x NM
- 9x IM

Results:
<table>
<tr><td>Decrease in symptom scores and increase in adverse</td></tr>
</table>
</td>
<td>Authors' conclusion: 'This study demonstrated the correlations between the activity of CYP2D6 isozyme and the efficacy and safety of haloperidol in patients with alcohol addiction.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>IM: A</td>
<td>
event scores during treatment for IM compared to NM:
<table>
<tr><th></th><th>route of administration</th><th></th><th>value for NM</th></tr>
<tr><td rowspan="2">Scale of Pathological Addiction</td><td>oral</td><td>x 1.11 (S)</td><td>10.6</td></tr>
<tr><td>intravenous</td><td>x 1.18 (S)</td><td>10.3</td></tr>
<tr><td rowspan="2">Hamilton Anxiety Rating Scale</td><td>oral</td><td>x 1.15 (S)</td><td>13.4</td></tr>
<tr><td>intravenous</td><td>x 1.17 (S)</td><td>13.3</td></tr>
<tr><td rowspan="2">Beck Anxiety Inventory</td><td>oral</td><td>x 1.16 (S)</td><td>20.1</td></tr>
<tr><td>intravenous</td><td>x 1.22 (S)</td><td>19.5</td></tr>
<tr><td rowspan="2">Covi Anxiety Rating Scale</td><td>oral</td><td>x 1.08 (S)</td><td>4.16</td></tr>
<tr><td>intravenous</td><td>x 1.14 (S)</td><td>4.05</td></tr>
<tr><td rowspan="2">Zung Self-Rating Anxiety Scale</td><td>oral</td><td>x 1.13 (S)</td><td>16.5</td></tr>
<tr><td>intravenous</td><td>x 1.17 (S)</td><td>16.0</td></tr>
<tr><td rowspan="2">Sheehan Clinical Anxiety Rating Scale</td><td>oral</td><td>x 1.22 (S)</td><td>33.0</td></tr>
<tr><td>intravenous</td><td>x 1.17 (S)</td><td>33.5</td></tr>
<tr><td rowspan="2">Hamilton Rating Scale for Depression</td><td>oral</td><td>x 1.08 (S)</td><td>11.5</td></tr>
<tr><td>intravenous</td><td>x 1.29 (S)</td><td>11.5</td></tr>
<tr><td rowspan="2">UKU Side Effects Rating Scale</td><td>oral</td><td>x 1.27 (S)</td><td>7.79</td></tr>
<tr><td>intravenous</td><td>x 1.38 (S)</td><td>7.44</td></tr>
<tr><td rowspan="2">Simpson-Angus Scale for Extrapyramidal Symptoms</td><td>oral</td><td>x 1.13 (S)</td><td>4.08</td></tr>
<tr><td>intravenous</td><td>x 1.20 (S)</td><td>3.94</td></tr>
</table>
NOTE: For the symptom scales, the absolute difference in decrease in score between IM and NM varied from 4% to 15% of the mean score before start of treatment. Although statistically significant, this is unlikely to be clinically significant.
For the adverse event scales, the absolute difference in increase in score between IM and NM varied from 13% to 24% of the mean score before start of treatment. Although statistically significant, this is unlikely to be clinically significant.

NOTE: Genotyping was performed for *4. This is the most important gene variant in this Russian population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 4, oral
Šimić I et al.
CYP2D6 *6/*6 genotype and drug interactions as cause of haloperidol-induced extrapyramidal symptoms.
Pharmacogenomics 2016;17:1385-9.
PubMed PMID: 27469576.</td>
<td>1

PM: C</td>
<td>A 66 year old male patient developed extrapyramidal syndrome (acute dystonia) and extreme sedation after a 1 mg dose of oral haloperidol concomitant with the CYP3A4 inhibitor ciprofloxacin. Extrapyramidal syndrome gradually resolved after discontinuation of both haloperidol and ciprofloxacin. Patient was discharged after 10 days without extrapyramidal symptoms, but was readmitted 5 days later with coma (Glasgow Coma Scale 3), dyspnoea, hypotension and tachycardia and died from cardiac arrest the next day.
The patient had previously been treated with haloperidol 1 mg twice daily, but was noncompliant. He had liver cirrhosis. The patient was CYP2D6 PM (*6/*6), CYP3A4 NM, and UGT2B7 IM (-161 CT).</td>
<td>Authors’ conclusion: ‘It was the introduction of ciprofloxacin which was a trigger for the development of adverse drug reaction due to inhibition of CYP3A4, which was in presented patient main metabolic pathway for haloperidol since he was CYP2D6 poor metabolizer.’</td>
</tr>
<tr>
<td>ref. 5, oral, i.m. depot
Patteet L et al.
Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone</td>
<td>3</td>
<td>11 patients were treated with haloperidol. Patients received at least twice the same dose of long-acting intramuscular therapy (n = 7; 2.7-4.8 mg/day, median 3.6 mg/day (calculated as the dose of the depot formulation divided by the number of days between two injections)) or were on the same oral dose for at least 7 days (n = 4; 2.5-15 mg/day, median 6.3 mg/day). 67% of patients received more than one antipsychotic.
Relevant co-medication was not excluded. Of the total group of 82 patients treated with paliperidone, risperidone, aripiprazole, haloperidol and/or zuclopenthixol, 6.1 % used</td>
<td>Authors’ conclusion: ‘It was demonstrated that CYP2D6 polymorphisms affect the serum concentrations of haloperidol.’</td>
</tr>
</table>

<table>
<tr>
<td>and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84. PubMed PMID: 26514968.

ref. 5, continuation</td>
<td>PM: A

IM: A
UM: A</td>
<td>a strong CYP2D6 inhibitor. None of the patients treated with haloperidol used a moderate CYP2D6 inhibitor. Patients using strong CYP2D6 inhibitors were assigned a phenotype PM.

Phenotype based on genotype and CYP2D6 inhibitor use:
- 3x NM (gene dose 2)
- 5x (IM + gene dose 1.25-1.5) (approximately 67% IM)
- 2x PM (genetically PM or gene dose 0.25-2 with a strong CYP2D6 inhibitor)
- 1x UM

Results:
<table>
<tr><td colspan="5">Results compared to gene dose 2:</td></tr>
<tr><td></td><td>PM</td><td>IM + gene dose 1.5</td><td>UM</td><td>value for gene dose 2</td></tr>
<tr><td rowspan="2">median dose-corrected serum concentration of haloperidol</td><td>x 1.0</td><td>x 0.8</td><td>x 0.8</td><td rowspan="2">0.5 ng/ml. mg</td></tr>
<tr><td colspan="3">NS for PM versus (IM + gene dose 1.25-1.5) versus gene dose 2 versus UM</td></tr>
<tr><td rowspan="2">mean dose-corrected serum concentration of haloperidol</td><td>x 1.07</td><td></td><td>x 0.86</td><td rowspan="2">0.47 ng/ml. mg</td></tr>
<tr><td colspan="3">NS for PM versus gene dose 2 versus UM (significance not determined)</td></tr>
<tr><td rowspan="2">median dose-corrected serum concentration of reduced haloperidol</td><td>x 9.9 (S compared to NM+IM)</td><td>x 1.1 (NS)</td><td>x 0.79 (NS)</td><td rowspan="2">0.14 ng/ml. mg</td></tr>
<tr><td colspan="3">S for PM versus (IM + gene dose 1.25-1.5) versus gene dose 2 versus UM</td></tr>
<tr><td rowspan="2">median dose-corrected serum concentration of haloperidol + reduced haloperidol</td><td>x 3.0 (S compared to NM+IM)</td><td>x 0.92 (NS)</td><td>x 0.78 (NS)</td><td rowspan="2">0.63 ng/ml. mg</td></tr>
<tr><td colspan="3">Trend for PM versus (IM + gene dose 1.25-1.5) versus gene dose 2 versus UM (p = approximately 0.05) (NS).
S for PM versus NM+IM versus UM.</td></tr>
<tr><td rowspan="2">median dose</td><td>x 2.8</td><td>x 1.0</td><td>x 1.3</td><td rowspan="2">3.6 mg/day</td></tr>
<tr><td colspan="3">NS for the differences between subgroups (significance not determined).</td></tr>
</table>
NOTE: Genotyping was performed for *2-*11, *15, *17, *29, *35, *41 and gene duplication. These are the most important gene variants in this Belgium population.</td>
<td>Dose-corrected serum concentration of haloperidol versus gene dose 2:
PM: 107%
UM: 86%</td>
</tr>
<tr>
<td>ref. 6, oral
van der Weide K et al.
The influence of the CYP3A4*22 polymorphism and CYP-2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozi-</td>
<td>3</td>
<td>308 patients were treated with haloperidol. Therapeutic drug monitoring was routinely done. Trough serum 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 serum concentrations.
Relevant co-medication was not excluded. 6 patients used CYP3A4 inhibitors and 35 patients CYP3A4 inducers. Multiple regression analysis showed a significant effect of CYP-3A4 inhibitors on dose-corrected trough concentrations, but</td>
<td>Authors' conclusion: 'Heterozygous presence of CYP3A4 *22 does not increase serum levels of antipsychotics metabolized by both CYP3A4 and CYP-2D6, whereas CYP-2D6 polymorphisms</td>
</tr>
</table>

<table>
<tr>
<td>de, and risperidone in psychiatric patients.
J Clin Psychopharmacol 2015;35:228-36.
PubMed PMID: 25868121.

and personal communication (mean dose-corrected trough concentrations)

ref. 6, continuation</td>
<td>PM: A
IM: A

UM: A</td>
<td>no significant effect of CYP3A4 inducers.
Parameters included in multiple regression analysis were sex, age, dose, CYP2D6 phenotype, CYP3A4*22 genotype and use of CYP3A4 inhibitors and inducers.

Genotyping:
- 138x NM
- 134x IM
- 30x PM
- 6x UM

Results:
<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM</td></tr>
<tr><td rowspan="3">median dose-corrected trough concentration of haloperidol</td><td>x 1.86 (S)</td><td>x 1.43 (S)</td><td>x 1.14 (NS)</td><td rowspan="3">0.7 ng/ml. mg</td></tr>
<tr><td colspan="3">Multiple regression analysis showed that CYP2D6 phenotype explained 4% of the variation (S).</td></tr>
<tr><td colspan="3">Multiple regression analysis showed that haloperidol dose explained 11% of the variation (S), pointing to non-linear kinetics which is to be expected if haloperidol is a CYP2D6 inhibitor and thus inhibits its own metabolism.</td></tr>
<tr><td>mean dose-corrected trough concentration of haloperidol</td><td>x 1.75 (S)</td><td>x 1.00 (NS)</td><td>x 0.58 (NS)</td><td>1.2 ng/ml. mg</td></tr>
<tr><td rowspan="2">median trough concentration of haloperidol</td><td>x 2.0 (NS)</td><td>x 1.0 (NS)</td><td>x 1.1 (NS)</td><td rowspan="2">2.0 ng/ml</td></tr>
<tr><td colspan="3">Multiple regression analysis showed that CYP2D6 phenotype explained 2% of the variation (S).</td></tr>
<tr><td>median dose</td><td>x 1.0 (NS)</td><td>x 1.0 (NS)</td><td>x 2.3 (NS)</td><td>2.0 mg/day</td></tr>
</table>
NOTE: Genotyping was performed for *3-*6, *9, *10, *41 and gene multiplication. These are the most important gene variants in this Dutch population.</td>
<td>Dose-corrected trough concentration of haloperidol versus NM:
PM: 175%
IM: 100%
UM: 58%</td>
</tr>
<tr>
<td>ref. 7, i.v.
Butwicka A et al. Neuroleptic malignant syndrome in an adolescent with CYP2D6 deficiency. Eur J Pediatr 2014;173:1639-42.
PubMed PMID: 24253372.</td>
<td>1</td>
<td>A 16 year old male patient developed neuroleptic malignant syndrome (unconsciousness, muscular rigidity, extrapyramidal symptoms, fever, hypotension, tachycardia, tachypnoea, elevated leukocyte count, and elevated serum creatinine phosphokinase) after addition of a single intravenous dose of haloperidol 2.5 mg to treatment with olanzapine 10 mg/day, levomepromazine 37.5 mg/day and lorazepam 1-3 mg/day. The following day, the patient had a Glasgow Coma Scale of 7 points (range 3-15 points), indicating a state of coma, and required mechanical ventilation because of respiratory insufficiency. Generalized tonic-clonic seizures were observed. Elevated troponin levels and myoglobin detected in urine suggested myocardial injury and an echocardiogram showed left ventricular hypokinesis. The condition of the patient gradually improved in 6 months. The adverse events of muscular rigidity, extrapyramidal symptoms, fever, and tachycardia already developed before</td>
<td>Authors' conclusion: 'Genotyping of CYP-2D6 might be considered in patients with symptoms suggestive of drug toxicity who are treated with neuroleptics metabolized via the CYP2D6 pathway, as carriage of one or more non-functional alleles may increase the risk for adverse reactions, such as neuroleptic malignant syndrome.'</td>
</tr>
</table>

<table>
<tr><td>ref. 7, continuation</td><td>PM: E</td><td>administration of haloperidol, as well as catatonic symptoms (mutism, refusal of food and fluid intake, and decreased and excessive motor activity).
The patient was CYP2D6 PM (*4/*4). Six weeks after the last administration of neuroleptics, haloperidol was detected in his urine, but olanzapine was not.</td><td></td></tr>
<tr><td>ref. 8, oral
Gassó P et al. Relationship between CYP2D6 genotype and haloperidol pharmacokinetics and extrapyramidal symptoms in healthy volunteers. Pharmacogenomics 2013;14:1551-63. PubMed PMID: 24088126.</td><td>3

UM: AA#</td><td>25 healthy volunteers, selected for their CYP2D6 genotype, received a single dose of haloperidol 5 mg. Of the original group of 26 volunteers, one volunteer dropped out of the study due to the appearance of akathisia. The authors do not mention the CYP2D6 genotype of this volunteer, nor whether akathisia developed after haloperidol intake or not.
Rating scales for motor signs and negative symptoms were assessed at baseline and 3 hours after haloperidol intake, except for the Subjective Deficit Syndrome Scale, which was applied at baseline and 24 hours after haloperidol intake.
Actigraphy of the nondominant arm was used to estimate the accumulated activity counts while awake. This reflects total motor activity without interference with manual work. Low-actigraphy records would be considered akinesia, therefore demonstrating the presence of extrapyramidal symptoms.
Visual analog scales for the assessment of sedative effects were assessed 4 hours after haloperidol intake, which was the time at which the maximum effect was observed.
Brain dopamine 2 receptor occupancy was determined in 1 NM, 1 PM and 2 UM by measuring striatum/occipital cortex uptake of the tracer iodine-123-iodobenzamine 3 hours after haloperidol or placebo intake.
Approximately 50% of the volunteers presented values of reduced haloperidol below the limit of quantification.
Co-medication other than medication required to treat adverse events, alcohol, caffeine-containing beverages, grapefruit juice and smoking were excluded.
Parameters included in multiple linear regression analysis were variables related to negative symptoms, sedative effects, hepatic and renal functions, sex, age and BMI.

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

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 colspan="4">Extrapyramidal symptoms</td></tr>
<tr><td>Simpson-Angus Rating Scale</td><td colspan="2">NS for PM versus NM versus UM</td><td>0.40</td></tr>
<tr><td>Barnes Rating Scale for Drug-Induced Akathisia</td><td colspan="2">NS for PM versus NM versus UM</td><td>0.20</td></tr>
<tr><td rowspan="3">actigraphy of the non-dominant arm</td><td>x 0.99 (NS)</td><td>x 1.46 (S)</td><td rowspan="3">712.16</td></tr>
<tr><td colspan="2">S for PM versus NM versus UM</td></tr>
<tr><td colspan="2">Multiple linear regression analysis showed CYP2D6 phenotype to be an independent predictor, that explained 20% of the variation (S).</td></tr>
</table></td><td>Authors' conclusion: 'The best predictor of extrapyramidal symptoms measured as wakefulness activity was the model including haloperidol area under the plasma concentration-time curve, sex and tranquilization, which explained 48.3% of the total variance. However, other markers need to be identified in order to explain the observed variability of haloperidol response and to develop pharmacogenetic predictors of haloperidol-induced extrapyramidal symptoms.'</td></tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td>PM: A</td>
<td>
<table>
<tr><td colspan="4">Negative symptoms</td></tr>
<tr><td>Brief Psychiatric Rating Scale</td><td colspan="2">NS for PM versus NM versus UM</td><td>1.90</td></tr>
<tr><td>Scale for the Assessment of Negative Symptoms</td><td colspan="2">NS for PM versus NM versus UM</td><td>7.10</td></tr>
<tr><td>Subjective Deficit Syndrome Scale</td><td colspan="2">NS for PM versus NM versus UM</td><td>0.20</td></tr>
<tr><td colspan="4">Sedation</td></tr>
<tr><td>mental sedation</td><td colspan="2">NS for PM versus NM versus UM</td><td>37.40</td></tr>
<tr><td>physical sedation</td><td colspan="2">NS for PM versus NM versus UM</td><td>54.60</td></tr>
<tr><td>tranquilisation</td><td colspan="2">NS for PM versus NM versus UM</td><td>48.50</td></tr>
<tr><td colspan="4">Pharmacodynamic parameters</td></tr>
<tr><td>dopamine 2 receptor occupancy</td><td colspan="2">NS for PM versus NM versus UM</td><td>35.9</td></tr>
<tr><td>prolactin</td><td colspan="2">NS for PM versus NM versus UM</td><td>56.3 ng/ml</td></tr>
<tr><td colspan="4">Pharmacokinetic parameters</td></tr>
<tr><td rowspan="3">AUC of haloperidol</td><td>x 1.24 (NS)</td><td>x 0.48 (S)</td><td rowspan="3">19.76 ng.h/ml</td></tr>
<tr><td colspan="2">S for PM versus NM versus UM</td></tr>
<tr><td colspan="2">Multiple linear regression analysis showed CYP2D6 phenotype to be an independent predictor and that CYP2D6 phenotype and sex explained 47% of the variation (S).</td></tr>
<tr><td rowspan="3">AUC of reduced haloperidol</td><td>x 3.68 (NS)</td><td>x 0.14 (NS)</td><td rowspan="3">1.84 ng.h/ml</td></tr>
<tr><td colspan="2">trend for PM versus NM versus UM (p = 0.067) (NS)</td></tr>
<tr><td colspan="2">Multiple linear regression analysis showed CYP2D6 phenotype to be an independent predictor, that explained 35% of the variation (S).</td></tr>
<tr><td rowspan="4">AUC of (haloperidol + reduced haloperidol)</td><td>x 2.10 (NS)</td><td>x 0.38 (NS)</td><td rowspan="4">30.03 ng.h/ml</td></tr>
<tr><td colspan="2">S for PM versus NM versus UM</td></tr>
<tr><td colspan="2">According to these results the AUC of (haloperidol + reduced haloperidol) was considerably larger than the AUC of haloperidol + the AUC of reduced haloperidol.</td></tr>
<tr><td colspan="2">Multiple linear regression analysis showed CYP2D6 phenotype to be an independent predictor and that CYP2D6 phenotype and sex explained 50% of the variation (S).</td></tr>
</table>
NOTE: Genotyping was performed for *3-*6 and gene multiplication. These are the most important gene variants in this Spanish population.
</td>
<td>AUC of haloperidol versus NM:
PM: 124%
UM: 48%</td>
</tr>
</table>

ref. 9, i.m. depot Panagiotidis G et al. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. Ther Drug Monit 2007;29:417-22.	4 PM: A IM: A UM: A	A total of 26 patients, 16x NM, 8x IM (one functional allele), 1x PM, 1x UM (3 functional alleles), haloperidol 0.45-14.3 mg/day as a long-acting intramuscular depot, no relevant co-medication. PM versus IM versus NM versus UM: - decrease in the dose-corrected trough concentration with the number of active alleles (6.7 versus 2.3 versus 1.7 versus 1.1 nmol.week/L.mg) (S). - no correlation with scores on the Positive and Negative Syndrome Scale for Schizophrenia and the Extrapyramidal Symptom Rating Scale (NS). The absence of a clinical effect can be explained by the fact that the dose was determined according to symptoms and side effects, resulting in a relatively small variation in trough concentrations (1-20 nmol/L with an outlier of 49 nmol/L). NOTE: Genotyping was performed for *3, *4, *5 and gene duplication.	Authors' conclusion: 'With good prediction models, it should be possible to further optimize treatment and reach target steady state concentrations of haloperidol more quickly. Yet, the cost effectiveness of pretreatment genotyping remains to be proven.' Css[a] haloperidol following i.m. injection versus NM: PM: 394% IM: 135% UM: 65%
ref. 10, oral Park JY et al. Combined effects of itraconazole and CYP2D6*10 genetic polymorphism on the pharmacokinetics and pharmacodynamics of haloperidol in healthy subjects. J Clin Psychopharmacol 2006;26:135-42.	3 IM: AA	A total of 19 healthy volunteers, 9x *1/*1, 10x *10/*10, a single dose of 5 mg haloperidol, no co-medication, non-smokers; *kinetic endpoint,*10/*10 versus *1/*1:* - increased AUC HAL from 21.7 to 33.5 ng.h/mL (NS by 55%). - decreased oral clearance from 4.7 to 3.6 L/hr/kg (NS by 24%). *clinical endpoint* - more *10/*10 (n=3) than *1/*1 (n=1) stopped taking part in the study prematurely due to side effects (acute dystonia or akathisia) (NS). - Those with *10/*10 had higher scores for side effects, measured using two different scales, than those with *1/*1 (NS). - There was no difference in QTc interval elongation between the various genotypes. There was no correlation between the HAL plasma concentration and the QTc interval elongation. NOTE: The presence of other alleles common in Asians (*2, *2xN, *3, *4, *5, *14, *18, *21 and *41) in the study subjects was ruled out by genotyping.	Authors' conclusion: 'The moderate effects of the CYP-2D6*10 genotype on the pharmacokinetics and pharmacodynamics of haloperidol seem to be augmented by the presence of CYP-3A4 inhibitor(s) including itraconazole.' AUC haloperidol versus NM: IM: 155%
ref. 11, oral LLerena A et al. Relationship between haloperidol plasma concentration, debrisoquine metabolic ratio, CYP2D6 and CYP-2C9 genotypes in psychiatric patients. Pharmacopsychiatry 2004;37:69-73.	4 PM: A IM: AA	A total of 33 patients, 30 without co-medication (4x PM phenotyped with debrisoquine, genotyped 1x PM (*4/*4), 13x IM (*1/*4) and 16x NM), 3 patients with CYP2D6 inhibitor as co-medication (all phenotyped PM, genotyped *1/*1, *1/*4 and *4/*4), haloperidol 1.5-30 mg/day, 73% were smokers; - There is a correlation between phenotype (log MR-debrisoquine) and dose of HAL, as well as C_{ss} HAL (S). There is no correlation between genotype (number of active alleles) and dose or C_{ss}[a] HAL.	
ref. 12, oral Ohara K et al. Effects of smoking and cytochrome P450 2D6*10 allele on the plasma halo-	4 IM: AA	A total of 110 patients, 46x *1/*1, 30x *1/*10, 34x *10/*10, haloperidol 0.75-80 mg/day, no CYP2D6 inhibitors as co-medication, 51 smokers and 59 non-smokers; - *10/*10: increase in C_{ss}[b] HAL versus NM (*1/*10+*1/*1) from 57.1 to 65.4 ng/mL/mg/kg (NS by 15%). Subgroup	Css[b] haloperidol versus NM: IM: 115%

peridol concentration/dose ratio. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:945-9.		smokers: increase in C_{ss}[b] HAL from 49.1 to 66.9 ng/mL/mg/kg (S by 54%). Subgroup non-smokers: increase in C_{ss}[b] HAL from 59.8 to 75.6 ng/mL/mg/kg (NS by 9.7%). No difference in C_{ss}[b] HAL between smokers and non-smokers for this genotype. - *1/*10 and *1/*1: C_{ss}[b] HAL in smokers is significantly lower than in non-smokers.	
ref. 13, oral Inada T et al. Cytochrome P450 IID6 gene polymorphisms and the neuroleptic-induced extrapyramidal symptoms in Japanese schizophrenic patients. Psychiatric Genetics 2003;13:163-8.	3 IM: A	A total of 320 patients who received haloperidol, 196 controls without haloperidol, 154x *1/*1, 91x *1/*2, 8x *2/*2, 190x *1/*10, 73x *10/*10, mean dose of haloperidol 9-16 mg/day, co-medication unknown; *kinetic endpoints* - *10/*10: increase in C_{ss}[a] HAL versus *1/*1 from 1.2 to 1.4 ng/mL/mg (S by 17%). *clinical endpoints* There is a positive association between the presence of *2 (S) or *10 (NS) and the occurrence of acute EPS within 3 months of starting HAL. There is no association for tardive dyskinesia. NOTE: no distinction between smokers/non-smokers	Css[a] haloperidol versus NM: IM: 117%
ref. 14, oral Ohnuma T et al. Haloperidol plasma concentration in Japanese psychiatric subjects with gene duplication of CYP2D6. Br J Clin Pharmacol 2003;56:315-20.	4 IM: AA	A total of 111 patients, 29x *1/*1, 10x *1/*2, 39x *1/*10, 7x *2/*10, 26x *10/*10, haloperidol 1-45 mg/day, no CYP2D6 inhibitors as co-medication; No significant difference was found for C_{ss}[a] HAL between any of the genotype groups, even when the groups were split into dose < 20 mg/day and dose ≥ 20 mg/day. NOTE: no distinction between smokers/non-smokers	Authors' conclusion: 'These alleles [= *10, red.] did not show any influence on the plasma concentration of HAL and could not explain the large interindividual differences revealed in these subjects.'
ref. 15, oral Someya T et al. Effect of CYP2D6 genotypes on the metabolism of haloperidol in a Japanese psychiatric population. Neuropsychopharmacology 2003;28:1501-5	4 IM: AA	A total of 88 patients, 17x *1/*1, 12x *1/ *2, 2x *2/*2, 4x *1/*5, 23x *1/*10, 14x *2/*10, 3x *5/*10, 13x *10/*10, dose of haloperidol 2-42 mg, no CYP2D6 inhibitors as co-medication; - *10/*10: increase in C_{ss}[a] HAL versus no *10 from 0.68 to 0.69 ng/mL/mg (NS by 1%), decrease versus 1x*10 from 0.70 to 0.69 (NS by 1%). For R-HAL, there was an increase in C_{ss}[a] HAL versus no *10 from 0.28 to 0.40 ng/mL/mg (NS by 43%), versus 1x*10 from 0.31 to 0.40 ng/mL/mg (NS by 29%). When the dose was split to < or ≥ 10 mg/day, there was only a significant difference for R-HAL versus no *10, increase from 0.18 to 0.43 ng/mL/mg (S by 139%). - IM (*10/*10 + *1/*5 + *5/*10) versus NM (*1/*1 + *1/*2 + *2/*2 + *1/*10 + *2/*10): increase in C_{ss}[a] HAL from 0.69 to 0.85 ng/mL/mg (NS by 23%). - 1x *5: at dose < 10 mg/day, C_{ss}[a] HAL is 1.16 ng/mL/mg and C_{ss}[a] R-HAL is 1.10 ng/mL/mg. NOTE: no distinction between smokers/non-smokers	C_{ss} haloperidol versus NM: IM: 123%
ref. 16, oral Desai M et al. Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of	3 PM: A	A total of 16 healthy volunteers, 8x *1/*1, 2x *1/*4, 2x *1/*10, 1x *17/*17, 3x *4/*4, a single dose of 10 mg haloperidol, no co-medication; *Kinetic endpoint* - *4/*4: decrease in Cl_{or} HAL versus all other genotypes from 27.0 to 12.8 mL/min/kg (S by 53%), t½ is 19.1 hours.	Authors' conclusion: 'Although the participation of CYP2D6 genotype in haloperidol disposition was confirmed, the pharmacokinetic changes observed were

CYP2D6. Pharmacogenomics 2003;3:105-13. **ref. 16, continuation**		*clinical endpoint* There was no difference in QTc interval elongation between *4/*4 and all other genotypes. There was no correlation between the HAL plasma concentration and the QTc interval elongation. 3 individuals developed dystonia, their genotypes were: *1/*4, *1/*10 and *4/*4. NOTE: no distinction between smokers/non-smokers.	not sufficient to bring about clinically important pharmacodynamic consequences.' Cl_{or} haloperidol versus NM+IM: PM: 47%
ref. 17, oral Brockmoller J et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002;72:438-52.	4 IM: A PM: C UM: C	A total of 175 patients, 106x NM+IM (= at least 1 functional allele or 2 partially functional alleles), 56x IM (1 fully dysfunctional allele), 5x PM (= 2 fully dysfunctional alleles), 5x UM (duplication of functional allele + functional allele), screened for *1 through *17 alleles and *1xn and *2xn, mean dose of haloperidol 12-14 mg/day, CYP2D6 inhibitors as co-medication in 3x UM, 63% smokers and 37% non-smokers; *kinetic endpoints* - PM versus NM+IM: **decrease** in C_{ss} HAL from 7.3 to 6.9 µg/L (NS by 6%), decrease in Cl_{or} HAL from 48.7 to 34.7 L/h (S by 29%). For R-HAL there was an increase in C_{ss} R-HAL from 2.0 to 9.5 µg/L (S by 375%), ratio R-HAL/HAL was elevated by 433%. - IM versus NM+IM: increase in C_{ss} HAL from 7.3 to 8.6 µg/L (NS by 18%), decrease in Cl_{or} HAL from 48.7 to 44.1 L/h (S by 9%). For R-HAL there was an increase in C_{ss} R-HAL from 2.0 to 4.2 µg/L (S by 110%), ratio R-HAL/HAL was elevated by 33%. - UM versus NM+IM: decrease in C_{ss} HAL from 7.3 to 7.0 µg/L (NS by 4%), increase in Cl_{or} HAL from 48.7 to 57.3 L/h (S by 18%). For R-HAL there was an increase in C_{ss} R-HAL from 2.0 to 7.2 µg/L (S by 260%), ratio R-HAL/HAL was elevated by 367%. *clinical endpoints* The EPS score is significantly higher for PM than for other phenotypes. Tardive dyskinesia and akathisia differed non-significantly for the various phenotypes. They were not correlated to the C_{ss} HAL. Side effects that resulted in changes to medication (= stopping/addition/dose reduction) were the most common in UM (100%), followed by IM (73%) and then NM (66%). Improvement of the symptoms was smallest for UM, no correlation between improvement in symptoms and C_{ss} HAL.	Authors' conclusion: 'We conclude that the CYP2D6 genotype is an important determinant of haloperidol and reduced haloperidol disposition and for the risk of serious adverse events. CYP2D6 genotype-based dose adjustments would provide poor metabolizers with only 60% of the standard average dose, whereas normal metabolizers are probably better treated with doses above the average. Ultrafast metabolizers should receive drugs whose biotransformation is not affected by the CYP2D6 polymorphisms.' C_{ss} haloperidol versus NM+IM: PM: 95% IM: 118% UM: 96%
ref. 18, oral Yasui-Furukori N et al. Effect of the CYP-2D6 genotype on prolactin concentration in schizophrenic patients treated with haloperidol. Schizophr Res 2001;52:139-42.	3 IM + PM: A	A total of 76 patients, 31x *1/*1, 45x *1/mt or mt/mt (mt = *3, *4, *5, *10), haloperidol 12 mg/day, no CYP2D6 inhibitors as co-medication; - *1/mt + mt/mt: for men there was an increased C_{ss} HAL versus *1/*1, from 7.4 to 10.6 ng/mL (S by 43%), increase in C_{ss} R-HAL from 2.0 to 3.7 ng/mL (S by 85%). For women there was an increased C_{ss} HAL versus *1/*1, from 8.5 to 10.9 ng/mL (S by 28%), increase in C_{ss} R-HAL from 2.4 to 3.6 ng/mL (S by 50%). NOTE: no distinction between smokers/non-smokers.	
ref. 19, oral Roh HK et al. Plasma concentra-	4	A total of 120 patients, 3x *10/*5, 33x *10/*10 (of whom 21 on a haloperidol dose ≥ 20 mg/day), 1x *1/*5, 60x *1/*10 (of whom 30 on a haloperidol dose ≥ 20 mg/day) and 23x *1/*1	

tions of haloperidol are related to CYP-2D6 genotype at low, but not high doses of haloperidol in Korean schizophrenic patients. Br J Clin Pharmacol 2001;52:265-71. **ref. 19, continuation**	IM: A	(of whom 18 on a haloperidol dose ≥ 20 mg/day), haloperidol 3-60 mg/day, no CYP2D6 inhibitors as co-medication; - *10/*10 and HAL < 20 mg/day: increase in C_{ss}[a] HAL versus *1/*1 from 2.0 to 3.9 (S by 95%), increase in C_{ss}[a] R-HAL from 0.6 to 1.5 (S by 150%). - IM (*10/*10 + *10/*5 + *1/*5) versus EM (*1/*1 + *1/*10), HAL <20 mg/day: increase in C_{ss}[a] HAL from 2.2 to 3.8 (S met 71%) At doses < 20 mg/day, there is a significant difference for HAL and not for R-HAL between the three genotypes *1/*1, *1/*10 and *10/*10, at doses ≥20 mg/day there is no significant difference for HAL and R-HAL. NOTE: no distinction between smokers/non-smokers.	Css[a] haloperidol versus NM: IM: 171%
ref. 20, oral Shimoda K et al. CYP2D6*10 alleles are not the determinant of the plasma haloperidol concentrations in Asian patients. Ther Drug Monit 2000;22:392-6.	4 IM: AA	A total of 66 patients, 13x *10/*10, 20x *1/*10, 8x *2/*10, 16x *1/*1, 6x *1/*2 and 3x *2/*2, haloperidol 1.5-36 mg/day, no CYP2D6 inhibitors as co-medication, fewer smokers in *10/*10 group than in groups with 0-1x *10; - *10/*10: increase in C_{ss}[c] HAL versus no *10 from 56.1 to 63.2 ng/mL·mg/kg (NS 13%). At dose < 0.3 mg/kg there was an increase from 52.7 to 65.2 ng/mL·mg/kg (NS by 24%). increase in C_{ss}[c] HAL versus NM (0-1x*10) from 58.7 to 63.2 ng/mL·mg/kg (NS 8%). - 1x*10: increase in C_{ss}[c] HAL versus no *10 from 56.1 to 61.0 ng/mL·mg/kg (NS by 9%). At dose < 0.3 mg/kg there was an increase from 52.7 to 61.3 ng/mL·mg/kg (NS by 16%).	Authors' conclusion: 'We found no clear relationship between the steady-state concentrations of HAL and the number of *10 alleles.' C_{ss}[c] haloperidol versus NM: IM: elevated by 108%
ref. 21, oral Pan L et al. Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. Ther Drug Monit 1999;21:489-97.	3 PM: A	A total of 92 patients, with 63 patients on haloperidol oral, 5x PM, 58x NM, haloperidol mean 7 mg/day, CYP2D6 and CYP3A4 inhibitors and CYP3A4 inducers as co-medication; - PM: **decrease** in C_{ss}[a] HAL versus NM from 0.50 to 0.33 ng/mL/mg (NS by 34%), increase in C_{ss}[a] R-HAL from 0.25 to 1.08 ng/mL/mg (S by 332%). Increase in ratio R-HAL/HAL from 0.69 to 2.05 (S by 197%). NOTE: genotyping was performed, but results were not presented in the article. Only distinction between NM and PM, no IM, so NM is probably NM+IM.	Authors' conclusion: 'All this suggests that CYP2D6 plays an important role in R-HAL metabolism, but less in HAL metabolism.' (C_{ss}[a] haloperidol versus NM+IM: PM: 66% reduction of the C_{ss} is probably a result of the co-medication used.)
ref. 22, oral Mihara K et al. Effects of the CYP-2D6*10 allele on the steady-state plasma concentrations of haloperidol and reduced haloperidol in Japanese patients with schizophrenia. Clin Pharmacol Ther 1999;65:291-4.	3 IM: A	A total of 67 patients, 7x *10/*10, 26x *1/*10, 34x *1/1, haloperidol 12 mg/day, no relevant co-medication, 36 smokers: - *10/*10: increase in C_{ss}[b] HAL versus *1/*1, from 22.8 to 31.2 nM (NS by 37%), increase in C_{ss}[b] R-HAL from 6.1 to 9.9 nM (S by 62%). increase in C_{ss}[b] HAL versus NM (*1/*1 + *1/*10) from 26.0 to 31.2 nM (NS by 20%), - *1/*10 increase in C_{ss}[b] HAL versus *1/*1, from 22.8 to 30.1 nM (S by 32%), increase in C_{ss}[b] R-HAL from 6.1 to 9.5 nM (S by 56%).	Css[b] haloperidol versus NM: IM: 120%
ref. 23, oral Suzuki A et al. Effects of the CYP-2D6 genotype on the steady-state	4	A total of 50 patients, 6x mt/mt (4x *10/*10, and 2x *10/*5), 22x *1/mt (15x *1/*10 and 7x *1/*5) and 22x *1/*1, haloperidol 12 mg/day, no relevant co-medication, 30 smokers; - mt/mt: increase in C_{ss}[b] HAL versus *1/*1, from 18.4 to	Css[b] haloperidol versus NM:

plasma concentrations of haloperidol and reduced haloperidol in Japanese schizophrenic patients. Pharmacogenetics 1997;7:415-8.	IM: A	29.4 nM (NS by 60%), increase in C_{ss}[b] R-HAL from 5.2 to 9.0 nM (S by 73%). - *1/mt: increase in C_{ss}[b] HAL versus *1/*1, from 18.4 to 27.3 nM (S by 48%), increase in C_{ss}[b] R-HAL from 5.2 to 9.5 nM (S by 83%).	IM: 160%
ref. 24, oral Lane HY et al. Dextromethorphan phenotyping and haloperidol disposition in schizophrenic patients. Psychiatry Res 1997;69:105-11.	4	A total of 18 patients, 18x NM (phenotyped using dextromethorphan), haloperidol 10 mg/day, no relevant co-medication; There was a significant correlation between MR-dextromethorphan and C_{ss} HAL, C_{ss} R-HAL and ratio R-HAL/HAL. 10 patients with extrapyramidal symptoms had a significantly higher C_{ss} R-HAL and ratio R-HAL/HAL than the other 8 patients. There were no significant differences in C_{ss} HAL, C_{ss} R-HAL, ratio R-HAL/HAL and MR-dextromethorphan between therapy responders and non-responders NOTE: genotype unknown NOTE: no distinction between smokers/non-smokers.	
ref. 25, oral Llerena A et al. Haloperidol disposition is dependent on the debrisoquine hydroxylation phenotype: increased plasma levels of the reduced metabolite in poor metabolizers. Ther Drug Monit 1992;14:261-4.	3 PM: A	A total of 12 healthy volunteers, 6x PM and 6x NM (phenotyped with debrisoquine) of which 1 was not included in the analysis, a single dose of haloperidol 2 or 4 mg, no co-medication, 1 smoker; - PM: increase in C[a] R-HAL versus NM 10 hours after ingestion, from 0.4 to 1.7 nM (S by 325%), after 32 hours there was an increase from 0.3 to 0.7 nM (NS by 133%). NOTE: genotype unknown	
ref. 26, oral Llerena A et al. Haloperidol disposition is dependent on debrisoquine hydroxylation phenotype. Ther Drug Monit 1992;14:92-7.	3 PM: A	A total of 12 healthy volunteers, 6x PM and 6x NM (phenotyped with debrisoquine) of which 1 was not included in the analysis, a single dose of haloperidol 2 or 4 mg, no co-medication, 1 smoker: - PM: decrease in Cl_{or} HAL versus NM from 2.49 to 1.16 L/h/kg (S by 53%), increase in t½ from 16.3 to 29.4 hours. Significant increase in C[a] HAL at 10, 24 and 32 hours after ingestion. NOTE: genotype unknown. Phenotyping was not able to distinguish between NM and IM, meaning that NM is equal to NM + IM.	Cl_{or} haloperidol versus NM+IM: PM: 47%
ref. 27, oral SmPC Haldol (haloperidol) 23-05-19 a.o.[1]	0 PM: A	<u>Warning</u>: Next to sudden death, QTc-elongation and/or ventricular arrythmias have been reported with haloperidol. Caution is also required in patients in whom high plasma concentrations can occur (poor CYP2D6 metabolisers). Poor CYP2D6 metabolisers: Haldol should be used with caution in patients know to be poor metabolisers for cytochrome P450 (CYP) 2D6 who are being administered a CYP3A4 inhibitor concomitantly. <u>Pharmacokinetics</u>: The apparent clearance of haloperidol after extravascular administration varies from 0.9 up to 1.5 L/hour/kg and is decreased in poor metabolisers for CYP2D6.	

[a] corrected for the dose

[b] corrected for the body weight
[c] corrected for the dose and body weight
[1] Haldol Decanoas (haloperidol decanoate) 13-07-20.

Risk group	IMs with CYP2D6 inhibitor

Comments:
- From 2020 onwards, studies with kinetic endpoints were only included if exposure of the sum of haloperidol for at least one of the phenotypes PM, IM or UM was compared with exposure for NM or *1/*1. 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 our definition. 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.

Date of literature search: 14 July 2021.

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

Mechanism:
Haloperidol is primarily metabolised via glucuronidation and to a lesser extent by CYP3A4, CYP2D6 and carbonyl reduction. The metabolite reduced haloperidol, can be oxidised back to haloperidol by CYP2D6 and CYP3A4. Haloperidol is a CYP2D6 inhibitor.
The therapeutic range is a haloperidol serum trough concentration of 5-15 µg/L. Haloperidol serum through concentrations > 20 µg/L are considered to be toxic. There is no clear relationship between the serum concentration of haloperidol and the (severity of the) toxic effects.
A CYP2D6 genetic polymorphism may cause a change in the plasma concentrations of haloperidol and reduced haloperidol. There are some reports that an elevated ratio of reduced haloperidol/haloperidol is associated with the occurrence of side effects. However, the NVZA therapeutic drug monitoring monography of haloperidol does not mention reduced haloperidol.

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+	1+
Corresponding Clinical Implication Score:		Potentially beneficial