CYP2D6: olanzapine 1560/1561/1562

AUC = area under the concentration-time curve, BMI = body-mass index, Cl_{or} = oral clearance, CSF = cerebrospinal fluid, C_{ss} = plasma concentration in steady state, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP-2D6 enzyme activity), MR = metabolic ratio, NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 enzyme activity)

Brief summary and justification of choices:
Olanzapine is primarily metabolised by UGT and CYP1A2 and to a far lesser extent by CYP2D6 and CYP3A4.
The therapeutic range of olanzapine serum concentrations is 20-80 µg/L. Toxicity occurs at olanzapine serum concentrations > 100 µg/L, and lethality has been reported at olanzapine serum concentrations ≥ 160 µg/L.
Of the 11 studies, only 4 showed a significant effect of genetically decreased CYP2D6 enzyme activity (poor or intermediate metabolisers (PM or IM)) on olanzapine pharmacokinetics or clinical effects (Miroshnichenko 2020, Djordjevic 2020, Skogh 2011, Ellingrod 2002). However, in all four cases the evidence was limited.
Miroshnichenko 2020 showed a 2.7 fold higher median dose-corrected olanzapine trough concentration in 10 IM patients. However, the association between olanzapine dose and olanzapine trough concentration did not reach significance in the patient group in this study. This questions the adequacy of using the dose-corrected olanzapine trough concentration as an outcome measure in this study. Four other studies in patients and three studies in healthy volunteers did not find a significant effect of CYP2D6 phenotype on olanzapine pharmacokinetics (Okubo 2016 (5 IM), Skogh 2011 (7 PM, 2 UM), Nozawa 2008 (10 IM), Carillo 2003 (4 PM), Zubiaur 2021 (18 IM, 4 PM, 5 (UM or gene dose 2.25-2.5)), Cabaleiro 2013 (22x (IM + gene dose 1.25-1.5), 2x (PM + gene dose 0.25-0.75 + gene dose 0.5/0.5), 4 UM), Hägg 2001 (5 PM)).
Djordjevic 2020 showed a better treatment response in 3 PM based on the Clinical Global Impressions Improvement scale. However, based on two other scales (the Positive and Negative Syndrome Scale and Global Assessment of Functioning scale), the PM phenotype had no effect on treatment response in this study. Two other studies in patients did not find an effect of CYP2D6 phenotype on treatment response (Thomas 2008 (12 IM, 1 PM), Carillo 2003 (4 PM)).
Skogh 2011 showed a 30% lower olanzapine daily dose in 7 PM patients, which was significant after adjustment for smoking. However, no effect of the PM phenotype was found on the dose-corrected olanzapine serum concentration in this study. So, the effect on olanzapine dose in this study was not due to a difference in olanzapine pharmacokinetics.
Ellingrod 2002 found an increase in the percent change in BMI, but no increase in the endpoint BMI, for 5 IM patients. However, none of the other three studies in patients and two studies in healthy volunteers found an effect of CYP2D6 phenotype on adverse events (Djordjevic 2020 (43 IM, 3 PM), Thomas 2008 (12 IM, 1 PM), Carillo 2003 (4 PM)), Zubiaur 2021 (18 IM, 4 PM, 5 (UM or gene dose 2.25-2.5)), Cabaleiro 2013 (22x (IM + gene dose 1.25-1.5), 2x (PM + gene dose 0.25-0.75 + gene dose 0.5/0.5), 4 UM)), with Djordevic 2020 finding no effect on BMI change for 43 IM + 4 PM.
Based on this, the KNMP Pharmacogenetics Working Group decided that there is not enough evidence for a CYP-2D6-olanzapine interaction, and thus no reason to recommend a dose adjustment or an alternative (no/no-interactions).
You can find an overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

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

Source	Code	Effect	Comments
ref. 1 Zubiaur P et al. Impact of polymorphisms in transporter and metabolizing enzyme genes on olanzapine	3	43 healthy volunteers received a single dose of olanzapine 2.5 or 5 mg twice. Administrations were separated by a 14 day wash-out period. 24 healthy volunteers (16 NM, 6 IM, 2 UM or gene dose 2.25-2.5) received olanzapine 5 mg/day for 5 days. For olanzapine, a period of 5 days is too short to reach steady state. The AUC_{72h} determined in the single dose study and the AUC_{24h} determined in the multiple dose study were merged into a generic AUC variable for analysis of pharmacokinetics. As expected, the dose- and	Author's conclusion: 'Our interest was to explore the impact of CYP-2D6 phenotypes on the pharmacokinetics and

<table>
<tr>
<td>pharmacokinetics and safety in healthy volunteers.
Biomed Pharmacother 2021;133:111087.
PMID: 33378980.

ref. 1, continuation</td>
<td>PM: AA
IM: AA
UM: AA</td>
<td>weight-corrected AUC and half-life of olanzapine were lower and the oral clearance was higher in the multiple dose trial than in the single dose trials.
Causality assessment of adverse events was performed following the algorithm of the Spanish pharmacovigilance system. Only those adverse events with a definite, probable or possible relationship with olanzapine intake were considered adverse drug reactions.
Co-medication, alcohol, grapefruit, caffeine, and smoking were excluded (CYP1A2 inhibitors and inducers from 2-4 weeks before olanzapine start).
Bonferroni correction was used to correct for multiple comparisons (i.e. between the four phenotypes).

Genotyping:
- 40x NM (16 from the multiple dose trial)
- 18x IM (6 from the multiple dose trial)
- 4x PM (none from the multiple dose trial)
- 5x UM or gene dose 2.25-2.5 (2 from the multiple dose trial)

Results:
<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM+gene dose 2.25-2.5</td><td>value for NM</td></tr>
<tr><td>adverse drug reactions</td><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.25-2.5</td><td></td></tr>
<tr><td rowspan="2">AUC olanzapine</td><td>x 1.38</td><td>x 0.95</td><td>x 0.92</td><td rowspan="2">2536 ng/ml per mg/kg</td></tr>
<tr><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.25-2.5</td></tr>
<tr><td rowspan="2">Cl_{or} olanzapine</td><td>x 0.79</td><td>x 1.02</td><td>x 1.09</td><td rowspan="2">292.5 ml/h per kg</td></tr>
<tr><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.25-2.5</td></tr>
<tr><td rowspan="2">$t_{1/2}$ olanzapine</td><td>x 1.01</td><td>x 0.94</td><td>x 0.93</td><td rowspan="2">31.6 h</td></tr>
<tr><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.25-2.5</td></tr>
</table>
Note: Genotyping was for *3-*10, *14, *17, *41, and gene multiplication. These are the most important gene variants in this Spanish population.</td>
<td>safety of olanzapine, especially the impact of UM. Neither of which had an effect in this work.‘</td>
</tr>
<tr>
<td>ref. 2
Miroshnichenko II et al.
Therapeutic drug monitoring of olanzapine and cytochrome P450 genotyping in nonsmoking subjects.
Ther Drug Monit 2020;42:325-9.
PMID: 31425442.</td>
<td>3

IM: A</td>
<td>48 non-smoking patients were treated with olanzapine 5-25 mg/day. Patients attained steady-state olanzapine concentrations for at least 8 days.
53% of patients had olanzapine trough concentrations within the therapeutic range (20-80 ng/ml), 27% below the therapeutic range and 20% above the therapeutic range. In one of the patients, a potentially toxic level (184 ng/ml) was observed. In another, olanzapine was not detectable in the serum.
Co-medication with CYP1A2 inhibitors was excluded, but co-medication with CYP2D6 inhibitors was not.
One of the originally 49 patients is not analysed, but the authors do not indicate which patient is excluded and why.

Genotyping:
- 38x NM
- 10x IM

Results:
<table>
<tr><td colspan="3">Results for IM compared to NM:</td></tr>
<tr><td></td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="2">median dose-corrected olanzapine trough concentration</td><td>x 2.72 (S)</td><td rowspan="2">2.02 ng/ml.mg</td></tr>
<tr><td>Results were also S for the difference between the mean</td></tr>
</table></td>
<td>Author’s conclusion:
‘Evidence indicating that CYP2D6 polymorphism has a significant effect on the pharmacokinetics of olanzapine was obtained, confirming the beneficial effects of therapeutic drug monitoring (TDM) for olanzapine.‘

Median dose-corrected olanzapine trough concentration compared to NM:
IM: 272%</td>
</tr>
</table>

<table>
<tr><td>ref. 2, continuation</td><td></td><td>
<table>
<tr><td></td><td>dose-corrected olanzapine trough concentrations.</td><td></td></tr>
<tr><td colspan="3">Note: The association between olanzapine dose and olanzapine trough concentration did not reach significance in this patient group.</td></tr>
</table>

Note: Genotyping was for *3 and *4. *3 was not found. *4 is the most important gene variant in this Russian population.</td><td></td></tr>
<tr><td>ref. 3
Djordjevic N et al.
Cigarette smoking and heavy coffee consumption affecting response to olanzapine: The role of genetic polymorphism.
World J Biol Psychiatry 2020;21:29-52.
PMID: 30513034.</td><td>4

IM: AA
PM: AA#</td><td>116 patients with an acute exacerbation of schizophrenia symptoms were treated with olanzapine for a period of 30 days. The olanzapine dose in the first two weeks was 10 mg/day and was adjusted at day 15 to a maximum of 20 mg/day based on the treatment response. The median dose at the end of the treatment period was 15 mg/day (range 10-20 mg/day).
Treatment response was assessed as the change in the ratings on the Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning (GAF) scale and as the score on the Clinical Global Impressions Improvement (CGI-I) scale. Scores on the CGI-I range from 0 (marked improvement with no adverse drug reactions) to 4 (unchanged or worse, with adverse drug reactions outweighing the therapeutic effects).
Olanzapine adherence, cigarette use and coffee intake were closely monitored.
Alcohol use and co-medication interacting with olanzapine, including other antipsychotics, anticonvulsants, narcotic pain relievers and many more, were excluded. Benzodiazepines were excluded with the exception of lorazepam as a rescue therapy, but not more than 4 mg per week, not more than three consecutive days, and not ≤24 h before treatment response scales rating.
Bonferroni correction was used to correct for multiple comparisons. Results for all gene variants together were adjusted for other covariates.

Genotyping:
*4:
- 76x *1/*1 (NM)
- 37x *1/*4 (IM)
- 3x *4/*4 (PM)
*3:
- 114x *1/*1 (NM)
- 2x *1/*3 (IM)
*6:
- 112x *1/*1 (NM)
- 4x *1/*6 (IM)

Results:
<table>
<tr><td colspan="3">Results for IM+PM (*4 and all variants) or IM (*3 and *6) compared to NM:</td></tr>
<tr><td colspan="3">treatment response</td></tr>
<tr><td rowspan="4">Positive and Negative Syndrome Scale score change</td><td>*4</td><td>NS</td></tr>
<tr><td>*3</td><td>NS</td></tr>
<tr><td>*6</td><td>NS</td></tr>
<tr><td>*3, *4 and *6</td><td>NS</td></tr>
<tr><td rowspan="4">Clinical Global Impressions Improvement score</td><td>*4</td><td>NS</td></tr>
<tr><td>*3</td><td>NS</td></tr>
<tr><td>*6</td><td>NS</td></tr>
<tr><td>*3, *4 and *6</td><td>NS, S for PM compared to NM+IM.
The median score on this 4 point scale was 1.00 for PM and 2.00 for NM+IM after adjustment for other covariates, indicating a better treatment response in PM.</td></tr>
<tr><td rowspan="4">Global Assessment of Functioning score change</td><td>*4</td><td>NS</td></tr>
<tr><td>*3</td><td>NS</td></tr>
<tr><td>*6</td><td>NS</td></tr>
<tr><td>*3, *4 and *6</td><td>NS</td></tr>
<tr><td colspan="3">adverse events</td></tr>
</table>
</td><td>Author’s conclusion:
‘Olanzapine treatment outcome is also affected by dose, sex, age and CYP2D6 metabolizer status.‘</td></tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td></td>
<td>
<table>
<tr><td>BMI change</td><td>*4</td><td>NS</td></tr>
<tr><td></td><td>*3</td><td>NS</td></tr>
<tr><td></td><td>*6</td><td>NS</td></tr>
<tr><td></td><td>*3, *4 and *6</td><td>NS</td></tr>
<tr><td>fasting serum glucose change</td><td>*4</td><td>NS</td></tr>
<tr><td></td><td>*3</td><td>NS</td></tr>
<tr><td></td><td>*6</td><td>S, increase with 0.90 mmol/L for IM and decrease with 0.10 mmol/L for NM</td></tr>
<tr><td></td><td></td><td>Because a significant effect was not found for *4, involving 10 times the number of variant allele carriers, including 3 PM, the significant result for *6 is likely to be a chance finding.</td></tr>
<tr><td></td><td>*3, *4 and *6</td><td>NS</td></tr>
<tr><td>total cholesterol change</td><td>*4</td><td>NS</td></tr>
<tr><td></td><td>*3</td><td>NS</td></tr>
<tr><td></td><td>*6</td><td>NS</td></tr>
<tr><td></td><td>*3, *4 and *6</td><td>NS</td></tr>
<tr><td>low density lipoprotein change</td><td>*4</td><td>NS</td></tr>
<tr><td></td><td>*3</td><td>NS</td></tr>
<tr><td></td><td>*6</td><td>NS</td></tr>
<tr><td></td><td>*3, *4 and *6</td><td>NS</td></tr>
<tr><td>triglyceride change</td><td>*4</td><td>NS</td></tr>
<tr><td></td><td>*3</td><td>NS</td></tr>
<tr><td></td><td>*6</td><td>NS</td></tr>
<tr><td></td><td>*3, *4 and *6</td><td>NS</td></tr>
<tr><td>extrapyramidal symptoms</td><td>*4</td><td>NS</td></tr>
<tr><td></td><td>*3</td><td>NS</td></tr>
<tr><td></td><td>*6</td><td>NS</td></tr>
<tr><td></td><td>*3, *4 and *6</td><td>NS</td></tr>
</table>

Note: Genotyping was for *3, *4 and *6. Except for *5, these are the most important gene variants in this Serbian population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Okubo M et al. Individual differences in in vitro and in vivo metabolic clearances of the antipsychotic drug olanzapine from non-smoking and smoking Japanese subjects genotyped for cytochrome P4502D6 and flavincontaining monooxygenase 3. Hum Psychopharmacol 2016;31:83-92. PMID: 26856397.</td>
<td>3

IM: AA</td>
<td>21 patients were treated with a mean olanzapine dose of 15.6 mg/day (range 2.5-20 mg/day).
Relevant co-medication was not excluded. 62% of patients used a CYP2D6 inhibitor concomitantly, 24% a CYP inducer. Of the IM patients, 20% used a CYP2D6 inhibitor concomitantly. 29% of the patients was smoker (40% of the IM patients).

Genotyping:
- 16x NM
- 5x IM

Results:
<table>
<tr><td colspan="3">Dose-corrected olanzapine trough concentration for IM compared to NM or gene dose 2:</td></tr>
<tr><td></td><td>IM</td><td>value for NM or gene dose 2</td></tr>
<tr><td>compared to NM</td><td>x 0.63 (NS)</td><td>2.5 ng/ml.mg</td></tr>
<tr><td>compared to gene dose 2</td><td>x 0.84 (NS)</td><td>1.9 ng/ml.mg</td></tr>
</table>

Note: There was no significant of smoking on the dose-corrected olanzapine trough concentration in this patient group.

Note: Genotyping was for *2, *5 and *10. These are the most important gene variants in this Japanese population.</td>
<td>Author’s conclusion:
‘Olanzapine clearance was not affected by CYP-2D6 or FMO3 genotypes or smoking behavior as a single factor under the present conditions because olanzapine clearance is mediated by multiple enzymes involved in two major and one minor pathways.‘

Dose-corrected olanzapine trough concentration compared to gene dose 2:
IM: 84%</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5
Cabaleiro T et al. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum Psychopharmacol 2013;28:205-14. PMID: 23559402.</td>
<td>3

PM: AA
IM: AA
UM: AA</td>
<td>61 healthy volunteers received a single 5-mg dose of olanzapine on two or four timepoints separated by 14-day wash-out periods.
The most frequent adverse events in this study were somnolence (100%), fatigue (30%), hypotension (29%), and dizziness (25%). Both QT interval prolongation and vomiting were only observed in one volunteer.
Relevant co-medication and smoking were excluded.

Genotyping:
- 33x NM
- 22x (IM + gene dose 1.25-1.5)
- 2x (PM + gene dose 0.25-0.75 + gene dose 0.5/0.5)
- 4x UM

Results:
<table>
<tr><td colspan="2">Results for (PM + gene dose 0.25-0.75 + gene dose 0.5/0.5) versus (IM + gene dose 1.25-1.5) versus NM versus UM:</td></tr>
<tr><td colspan="2">adverse events and plasma prolactin increase</td></tr>
<tr><td>fatigue</td><td>NS</td></tr>
<tr><td>hypotension</td><td>NS</td></tr>
<tr><td>dizziness</td><td>NS</td></tr>
<tr><td>dry mouth</td><td>NS</td></tr>
<tr><td>syncope</td><td>NS</td></tr>
<tr><td>irritability</td><td>NS</td></tr>
<tr><td>headache</td><td>NS</td></tr>
<tr><td>QT interval prolongation</td><td>NS</td></tr>
<tr><td>vomiting</td><td>NS</td></tr>
<tr><td>plasma prolactin increase</td><td>NS</td></tr>
<tr><td colspan="2">pharmacokinetics</td></tr>
<tr><td>AUC olanzapine</td><td>NS</td></tr>
<tr><td>Cl_{or} olanzapine</td><td>NS</td></tr>
<tr><td>$t_{1/2}$ olanzapine</td><td>NS</td></tr>
</table>
Note: Genotyping was for *2-*11, *14, *15, *17-*20, *25, *29, *31, *35, *41, *114, and duplications of *1, *2, *4, *10, *17, *35, and *41. These are the most important gene variants in this Spanish population.</td>
<td>Author’s conclusion:
‘We found no association between polymorphisms in UGT1A1, CYP-1A2, CYP2D6, and CYP3A4 and the pharmacokinetics of olanzapine, although UGT1A1 and CYP3A4 were associated with side effects.‘</td>
</tr>
<tr>
<td>ref. 6
Skogh E et al. High correlation between serum and cerebrospinal fluid olanzapine concentrations in patients with schizophrenia or schizoaffective disorder medicating with oral olanzapine as the only antipsychotic drug. J Clin Psychopharmacol 2011;31:4-9. PMID: 21192135.</td>
<td>3

UM: AA</td>
<td>37 patients were treated with olanzapine (mean dose 11.6 mg/day) for at least 4 weeks. Cerebrospinal fluid (CSF) was available for 29 patients.
Serum and cerebrospinal fluid were obtained median 12 hours (range 9-14.5 hours) after the last dose.
Relevant co-medication was excluded (the only concomitant drugs used were benzodiazepines and/or zopiclone and lithium). 27% of the patients was smoker (43% or 57% of the PM patients).

Genotyping:
- 28x NM+IM
- 7x PM
- 2x UM

Results:
<table>
<tr><td colspan="4">Results compared to NM+IM:</td></tr>
<tr><td></td><td>PM</td><td>UM</td><td>value for NM+IM</td></tr>
<tr><td rowspan="2">dose-corrected olanzapine serum concentration</td><td colspan="2">NS for PM versus NM+IM versus UM</td><td rowspan="2"></td></tr>
<tr><td colspan="2">NS for PM compared to NM+IM after adjustment for smoking</td></tr>
<tr><td rowspan="2">dose-corrected olanzapine CSF concentration</td><td colspan="2">NS for PM versus NM+IM versus UM</td><td rowspan="2"></td></tr>
<tr><td colspan="2">NS for PM compared to NM+IM after adjustment for</td></tr>
</table></td>
<td>Author’s conclusion:
‘Normal metabolizers of CYP2D6 had higher daily doses than poor metabolizers when the influence of smoking was taken into account.‘</td>
</tr>
</table>

<table>
<tr><td>ref. 6, continuation</td><td>PM: A</td><td>
<table>
<tr><td></td><td colspan="2">smoking</td><td></td></tr>
<tr><td>olanzapine serum concentration</td><td colspan="2">NS for PM versus NM+IM versus UM</td><td></td></tr>
<tr><td>olanzapine CSF concentration</td><td colspan="2">NS for PM versus NM+IM versus UM</td><td></td></tr>
<tr><td>ratio CSF/serum olanzapine concentration</td><td colspan="2">NS for PM versus NM+IM versus UM</td><td></td></tr>
<tr><td rowspan="3">olanzapine daily dose</td><td>x 0.70</td><td></td><td>12.3 mg</td></tr>
<tr><td colspan="2">NS for PM versus NM+IM versus UM</td><td></td></tr>
<tr><td colspan="2">S for PM compared to NM+IM after adjustment for smoking</td><td></td></tr>
</table>
Note: Genotyping was for *3-*6, *41, and gene duplication. These are the most important gene variants in this Swedish population.
</td><td></td></tr>
<tr><td>ref. 7
Thomas P et al. Correlates of response to olanzapine in a North Indian schizophrenia sample. Psychiatry Res 2008;161:275-83.</td><td>3

IM: AA
PM: AA</td><td>A total of 117 patients, 104x *1/*1, 12x *1/*4, 1x *4/*4, olanzapine for 6 weeks (start 5-10 mg with weekly increases by 5 mg/day, based on effectiveness and side effects, to a maximum of 20 mg/day; in approximately 10% of the patients an increase to 25 or 30 mg/day; average 16.5 mg/day), no relevant co-medication.

- no significant association between genotype and the improvement on the scale for clinical effectiveness.
- no significant association between genotype and non-response.
- no significant association between genotype and extrapyramidal side effects and changes in insulin levels.

NOTE: Screening only for *4.</td><td></td></tr>
<tr><td>ref. 8
Nozawa M et al. The relationship between the response of clinical symptoms and plasma olanzapine concentration, based on pharmacogenetics: Juntendo University Schizophrenia Projects (JUSP). Ther Drug Monit 2008;30:35-40.</td><td>3

IM: AA</td><td>A total of 47 patients, 21x *1/*1, 16x *1/*10, 10x *10/*10 (screening for *5 and *10), olanzapine 5-20 mg/day (average 15.7 mg/day), co-medication not excluded, 26% smokers.

*10/*10 versus *1/*10 versus *1/*1:
- no significant difference in C_{ss}[a] (NS). The same applies to the subgroup of non-smokers (n=35). Values were 3.2 ng/mL.mg for *10/*10, 3.1 ng/mL.mg for *1/*10 and 3.7 ng/mL.mg for *1/*1.

IM (*10/*10) versus NM (*1/*1 + *1/*10):
- decrease in C_{ss}[a] from 3.4 to 3.2 ng/mL per mg/day (NS by 7%).</td><td>Css[a] versus *1/*1:
IM: 86%</td></tr>
<tr><td>ref. 9
Iwahashi K. Olanzapine metabolism by CYP1A2/CYP2D6 and hyperglycaemia. Acta Neuropsychiatrica 2004;16:229-230.</td><td>1

IM: AA</td><td>- patient 1: *1/*1 for CYP2D6 and *1/*1c and *1F/*1F for CYP1A2, no CYP2D6 inhibitors as co-medication, smoking unknown; with olanzapine 5 mg/day, the fasting blood glucose concentration was 103 mg/dL, with 10 mg/day it was 182 mg/dL, weight gain 3 kg. NOTE: olanzapine concentrations unknown
- patient 2: *10/*10 for CYP2D6 and *1F/*1F for CYP1A2, olanzapine 10 mg/day, no CYP2D6 inhibitors as co-medication, smoking unknown; fasting blood glucose concentration was 95 mg/dL, weight loss 0.5 kg. C_{ss} is 49.9 ng/mL.
- patient 3: *1/*1 for CYP2D6 and CYP1A2, olanzapine 10 mg/day, co-medication unknown, non-smoker; fasting blood glucose concentration was 150 mg/dL, weight gain 5 kg. C_{ss} is 23.4 ng/mL.</td><td></td></tr>
<tr><td>ref. 10
Carillo JA et al.</td><td>3</td><td>17 patients, 4x PM and 13x NM[#] (phenotyped with debrisoquine), olanzapine 10 mg/day for smokers and 5-10 mg/day for non-smokers,</td><td>Authors' conclusion:</td></tr>
</table>

<table>
<tr>
<td>Role of the smoking-induced cytochrome P450 (CYP) 1A2 and polymorphic CYP-2D6 in steady-state concentration of olanzapine.
J Clin Psychopharmacol 2003;23:119-27.</td>
<td>PM: AA</td>
<td>no co-medication, smoking status was known, but correction was not performed for this;

- PM: increase in C_{ss}[a] versus NM from 4.0 to 7.7 ng·mg·mL (NS by 93%). Effectiveness of the therapy and the occurrence of side effects were elevated, but differences compared to NM were non-significant.

NOTE: genotype unknown. Phenotyping can only distinguish between PM and the other phenotypes, so NM[#] is actually equal to IM, NM and UM.</td>
<td>‘In contrast, the contribution of the polymorphic CYP2D6-dependent metabolism is likely to be minor.’

C_{ss}[a] versus NM+IM+UM:
PM: 193%</td>
</tr>
<tr>
<td>ref. 11
Ellingrod VL et al.
CYP2D6 polymorphisms and atypical antipsychotic weight gain.
Psychiatr Genet 2002;12:55-8.
PMID: 11901361.</td>
<td>4

IM: B</td>
<td>11 patients were titrated to a fixed dose of olanzapine (ranging from 7.5 to 20 mg/day) for up to 47 weeks (10.8 months). The mean duration of treatment was 13.8 months.
There was a trend for a higher age in the IM group (p = 0.06).
Co-medication other than lorazepam was excluded.
Linear regression analysis, adjusting for olanzapine dose, duration of treatment, age, smoking status, baseline weight/BMI, and interactions, was performed. 82% of the patients smoked at least one-half a pack of cigarettes per day, but there was no relationship between cigarette smoking and percent change in BMI.
The power to detect differences between the phenotypes was >0.8.

Genotyping:
- 6x NM
- 5x IM

Results:
<table>
<tr><td colspan="3">Results for IM compared to NM:</td></tr>
<tr><td></td><td></td><td>value for NM</td></tr>
<tr><td>percent change in BMI</td><td>approximately x 2 (S)</td><td>appr. 13%</td></tr>
<tr><td>baseline BMI</td><td>NS</td><td>28.0 kg/m^2</td></tr>
<tr><td>endpoint BMI</td><td>NS</td><td rowspan="2">31.8 kg/m^2</td></tr>
<tr><td></td><td>Endpoint BMI was numerically slightly lower in IM (31.4 kg/m^2).</td></tr>
<tr><td>mean olanzapine dose</td><td>NS</td><td>13.6 mg/day</td></tr>
</table>
Note: The authors indicate that the relationship between atypical antipsychotic serum concentration and weight gain is unknown.

Note: Genotyping was for *3 and *4. Presence of *5 was excluded. These are the most important gene variants in this population from the USA.</td>
<td>Author’s conclusion:
‘Genotype was significant for those with a *1/*3 or *4 genotype experiencing a larger percent BMI change than those with a *1/*1 genotype. This may be due to increased olanzapine concentrations leading to increased exposure, which may trigger atypical antipsychotic weight gain.‘</td>
</tr>
<tr>
<td>ref. 12
Hägg S et al.
Olanzapine disposition in humans is unrelated to CYP1A2 and CYP2D6 phenotypes.
Eur J Clin Pharmacol 2001;57:493-7.</td>
<td>3

PM: AA</td>
<td>17 healthy study subjects, 5x PM and 12x NM[#] (phenotyped with debrisoquine), a single dose of 7.5 mg olanzapine, non-smokers, no relevant co-medication;

- PM: decrease in the AUC versus NM from 1,772 to 1,336 nM·hr (NS by 25%), increase in Cl_{or} from 0.203 to 0.246 L/hr/kg (NS by 21%), t½ is 27.4 hours.

NOTE: genotype unknown. Phenotyping can only distinguish between PM and the other phenotypes, so NM[#] is actually equal to IM, NM and UM.</td>
<td>AUC versus NM+IM+UM:
PM: 75%</td>
</tr>
</table>

[a] corrected for the dose

Risk group	--

Comments:

- A case report of a PM patient showing olanzapine-associated rhabdomyolysis (Skryabin VY et al. Olanzapine-associated rhabdomyolysis: a case report. 2021;13:e12568. PMID: 33564555) was not included in the risk analysis. Because no plasma concentration was determined, it is not known whether a high clozapine plasma concentration and thus a reduced clozapine metabolism was involved.
  A study in healthy volunteers (Koller D et al. The effects of aripiprazole and olanzapine on pupillary light reflex and its relationship with pharmacogenetics in a randomized multiple-dose trial. Br J Clin Pharmacol 2020;86: 2051-62. PMID: 32250470) was not included, because the kinetic data concern a subset of the patients in Zubiaur 2021 (the 24 patients receiving olanzapine daily for 5 days) and olanzapine had no effect on pupillary light reflex.

Date of literature search: 29 July 2021.

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

Mechanism:

Olanzapine is primarily metabolised by UGT and CYP1A2 and to a far lesser extent by CYP2D6 and CYP3A4. The therapeutic range of olanzapine serum concentrations is 20-80 µg/L. Toxicity occurs at olanzapine serum concentrations > 100 µg/L, and lethality has been reported at olanzapine serum concentrations ≥ 160 µg/L.