CYP1A2: olanzapine 4646 to 4651

AUC = area under the concentration-time curve, IM = intermediate metaboliser (a fully functional or *1F allele in combination with an allele resulting in an enzyme with reduced or absent activity other than *1C) (reduced CYP1A2 enzyme activity), NM = normal metaboliser (two fully functional alleles) (normal CYP1A2 enzyme activity), NS = non-significant, OR = odds ratio, OR_{adj} = adjusted odds ratio, PM = poor metaboliser (two alleles resulting in an enzyme with reduced or absent activity that are not both *1C) (strongly reduced or absent CYP1A2 enzyme activity), S = significant, SNP = single nucleotide polymorphism, $t_{1/2}$ = half-life, *1A = a fully functional allele, *1C = the most common allele in the Netherlands reported to result in an enzyme with decreased activity, *1C-heterozygote = a genotype with one *1C and one other allele or genotype group *1C-heterozygote (defined as all combinations of *1C and a fully active or *1F allele, for example *1A/*1C, *1C/*1D and *1C/*1F) (reported to have reduced CYP1A2 enzyme activity), *1F = an allele reported to result in increased inducibility of CYP1A2 expression, '*1F' = an allele that contains other gene variants alongside the gene variant in *1F (-163C>A), e.g. the alleles *1K and *1W (the presence of other gene variants alongside the one in *1F has been reported to abolish the increased inducibility of CYP1A2 expression, with *1K even being reported to result in an enzyme with reduced activity), *1A/*1F = genotype *1A/*1F or genotype group *1A/*1F (defined as all combinations of an *1F allele and a fully functional allele, for example *1A/*1F, *1B/*1F and *1D/*1F), *1F/*1F = the most common genotype in the Netherlands (reported to result in increased inducibility of CYP1A2 expression).

Brief summary and justification of choices:

Olanzapine is mainly converted by CYP1A2 to the metabolite 4'-N-desmethyl-olanzapine. Olanzapine is also converted by direct glucuronidation. 4'-N-desmethyl-olanzapine also appears to be metabolised by CYP1A2: plasma concentrations do not increase with induction of CYP1A2.

*1F is the most common gene variant in the Netherlands. Pharmacogenetic guidelines for *1F/*1F are therefore not useful.

No abnormal activity has been demonstrated for rs2470893 and rs2472304. Czerwensky 2015 found reduced metabolism by *1D in a study including 98 patients. However, Yan 2020 (241 patients), Ghotbi 2010 (112 patients), and the meta-analysis of Na Takuathung 2019 pooling the data of Czerwensky 2015 and Ghotbi 2010, did not find an effect of *1D. The CYP allele nomenclature website (http://www.cypalleles.ki.se/cyp1a2.htm) also does not state that *1D has reduced activity and the effect of the *1D allele in Czerwensky 2015 did not lead to clinical consequences. Söderberg, 2013 found non-standard activity for rs2472297. However, the effect was small (2% of the variation in the olanzapine concentrations) and there is no second article to confirm the abnormal activity of this polymorphism. Djordjevic 2020 showed no effect of rs2472297 on olanzapine effectiveness and adverse events. These polymorphisms therefore fall under NM for the time being, as does *1A/*1A.

1A/*1F Yan 2020 (241 patients) found a higher odds for a good response in *1A/*1F than in *1F/*1F. This was accompanied by a significant increase in the dose-corrected olanzapine plasma concentration, but this increase was only 7%. Because it concerns a positive effect, therapy adjustment is not necessary. In addition, despite the kinetic effect being statistically significant for NM versus *1A/*1F versus *1F/*1F, the small size of the effect for *1A/*1F (only 1.7% of the width of the therapeutic range and only 27% of the normal biological variation of 25%) does not suggest this effect to be clinically relevant. So, despite the statistically significant results, the kinetic results actually do not support the clinical results. Despite the effect of smoking on olanzapine plasma concentration being well established, Yan 2020 did not find a significant effect of smoking on olanzapine response. Two other studies did not find a difference in response for *1A/*1F (Czerwensky 2015 (98 patients using olanzapine, and 209 patients of whom 192 used olanzapine or both olanzapine and clozapine) and Thomas 2008 (130 patients)).

No significant differences in adverse events were found for *1A/*1F in patients and healthy volunteers (Yan 2020 (241 patients), Hattori 2020 (91 patients), Czerwensky 2015 (98 patients), Looman 2013 (92 patients), and Cabaleiro 2013 (61 healthy volunteers receiving a single olanzapine dose)).

Two studies found a significantly higher dose-corrected olanzapine plasma concentration compared to *1F/*1F (Yan 2020 (241 patients; increase with 7%) and Czerwensky 2015 (98 patients; increase with 40% for *1A/*1F, but decrease with 7% for *1A/*1A)). However, 4 studies including 37-342 patients, a meta-analysis of 3 patient studies including Czerwensky 2015, and a study including 61 volunteers found no significant kinetic effects of *1A (Söderberg 2013 (342 patients), Skogh 2011 (37 patients), Ghotbi 2010 (112 patients), Nozawa 2008 (47 patients), Na Takuathung 2019 (meta-analysis of 3 studies), and Cabaleiro 2013 (61 healthy volunteers receiving a single olanzapine dose)). The largest patient study did not find an effect in smokers either (Söderberg 2013 (342 patients)).

Based on this, the KNMP Pharmacogenetics Working Group decided that there is not enough evidence for

a gene-drug interaction (no/no-interaction).

NM Yan 2020 (241 patients) found a higher odds for a good response in *1A/*1A than in *1F/*1F. This was accompanied by a significant increase in the dose-corrected olanzapine plasma concentration, but this increase was only 16%. Because it concerns a positive effect, therapy adjustment is not necessary. In addition, despite the kinetic effect being statistically significant for NM versus *1A/*1F versus *1F/*1F, the small size of the effect for NM (only 4.1% of the width of the therapeutic range and only 66% of the normal biological variation of 25%) does not suggest this effect to be clinically relevant. So, despite the statistically significant results, the kinetic results actually do not support the clinical results. Despite the effect of smoking on olanzapine plasma concentration being well established, Yan 2020 did not find a significant effect of smoking on olanzapine response. Three other studies did not find a difference in response for NM (Djordjevic 2020 (120 patients), Czerwensky 2015 (98 patients using olanzapine, and 209 patients of whom 192 used olanzapine or both olanzapine and clozapine), and Thomas 2008 (130 patients)).
Looman 2013 (92 patients) is the only patient study that found a difference in adverse events for NM. However, this was a favourable effect. The degree of uncontrolled glucose was less for NM than for *1F/*1F. The clinical effect was not confirmed in other studies. Djordjevic 2020 (120 patients) did not find a difference in the change in fasting serum glucose for NM. It is also very likely that metabolic side effects are not dose related. The affinity for metabolic receptors seems to be high to the extent that side effects also occur at low doses and plasma concentrations. An association with kinetic genes therefore does not seem likely. A study with 24 healthy volunteers receiving olanzapine during 5 days showed a lower incidence of palpitations for (NM+ *1A/*1F+*1C-heterozygote) (Koller 2021), but this was not confirmed by a significant kinetic effect for this group (Koller 2020). In addition, only female volunteers developed palpitations on olanzapine and/or aripiprazole and the percentage of women in this group was lower than in the reference group of (*1F/*1F+*1B/*1F) (41% versus 71%). Furthermore, this was not confirmed in patient studies. Other adverse events did not differ for (NM+*1A/*1F+*1C-heterozygote) in this study. No significant differences in adverse events were found for NM in other studies in patients and healthy volunteers (Yan 2020 (241 patients), Hattori 2020 (91 patients), Djordjevic 2020 (120 patients), Czerwensky 2015 (98 patients), and Cabaleiro 2013 (61 healthy volunteers receiving a single olanzapine dose)).
Two studies found a significant difference in dose-corrected olanzapine plasma concentration compared to *1F/*1F, but the change was in opposite direction (Yan 2020 (241 patients; increase with 16%) and Czerwensky 2015 (98 patients; decrease with 7%)). In addition, 4 studies including 37-342 patients, a meta-analysis of 3 patient studies including Czerwensky 2015, and a study including 61 volunteers found no significant kinetic effects of *1A (Söderberg 2013 (342 patients), Skogh 2011 (37 patients), Ghotbi 2010 (112 patients), Nozawa 2008 (47 patients), Na Takuathung 2019 (meta-analysis of 3 studies), and Cabaleiro 2013 (61 healthy volunteers receiving a single olanzapine dose)). The largest patient study did not find an effect in smokers either (Söderberg 2013 (342 patients)).
Based on this, the KNMP Pharmacogenetics Working Group decided that there is insufficient evidence for a gene-drug interaction (no/no-interaction).

*1C A study with healthy volunteers receiving olanzapine during 5 days showed a lower incidence of palpitations for 17 (NM or *1A/*1F or *1C-heterozygote) (Koller 2021), but this was not confirmed by a significant kinetic effect for this group (Koller 2020). In addition, only female volunteers developed palpitations on olanzapine and/or aripiprazole and the percentage of women in this group was lower than in the reference group of (*1F/*1F+*1B/*1F) (41% versus 71%). Furthermore, this was not confirmed in patient studies. Other adverse events did not differ for (NM or *1A/*1F or *1C-heterozygote) in this study.
No significant effects on adverse events (Yan 2020 (98x *1C-heterozygote, 18x *1C/*1C), Hattori 2020 (35x (*1C-heterozygote or *1C/*1C)), Looman 2013 (6x *1C-heterozygote), Cabaleiro (4x *1C-heterozygote; healthy volunteers, single dose)), response (Thomas 2008 (11x (*1C-heterozygote or *1C/*1C))), and olanzapine kinetics (Yan 2020 (98x *1C-heterozygote, 18x *1C/*1C), Nozawa 2008 (14x *1C-heterozygote, 4x *1C/*1C), Cabaleiro (4x *1C-heterozygote; healthy volunteers, single dose)) were found for *1C.
Based on this, the KNMP Pharmacogenetics Working Group decided that there is insufficient evidence to support a gene-drug interaction for *1C-heterozygote and *1C/*1C (no/no-interactions).

IM and PM Literature for IM and PM was lacking. There is therefore no evidence to support a gene-drug interaction for IM and PM (no/no-interactions).

You can find an overview of the observed clinical and kinetic effects per genotype group in the background information text of the gene-drug interactions in the KNMP Kennis Bank. You may also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below uses the KNMP nomenclature for CYP1A2 polymorphisms. As a result, the nomenclature in the table below can differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Koller D et al. Safety and	3	24 healthy volunteers received olanzapine 5 mg/day during five days. For olanzapine, a period of 5 days is too short to reach steady state.	Authors' conclusions: 'We propose

<table>
<tr>
<td>cardiovascular effects of multiple-dose administration of aripiprazole and olanzapine in a randomised clinical trial. Hum Psychopharmacol 2021;36:1-12. PMID: 32991788.

ref. 1, continuation</td>
<td>(*1F/*1F + *1A/*1F): B

(NM+ *1A/*1F+ *1C-heterozygote): AA#</td>
<td>There were no serious or life-threatening adverse events. All volunteers experienced at least one adverse drug reaction. All volunteers experienced somnolescence.
Genotypes were grouped based on the total activity score (1-1.5, 1.75-2.5, and 2.75-3), with an activity score of 1 assigned to *1A, 0.5 assigned to *1C, 1.5 assigned to *1F, and 1.25 assigned to *1B.
Co-medication was excluded, but smoking was not.
Bonferroni correction was used to correct for multiple comparisons.

Genotyping:
- 17x (*1A/*1A or *1A/*1B or *1A/*1F or *1B/*1B or *1B/*1C or *1C/*1F)
- 7x (*1B/*1F or *1F/*1F)

Results:
<table>
<tr><td colspan="3">Results for (*1B/*1F or *1F/*1F) compared (*1A/*1A or *1A/*1B or *1A/*1F or *1B/*1B or *1B/*1C or *1C/*1F):</td></tr>
<tr><td></td><td></td><td>value for all volunteers</td></tr>
<tr><td>decrease in systolic blood pressure on day 1</td><td>NS</td><td>-14.7 mmHg</td></tr>
<tr><td>decrease in diastolic blood pressure on day 1</td><td>NS</td><td>-10.2 mmHg</td></tr>
<tr><td>decrease in heart rate on day 1</td><td>NS</td><td>-13.4 bpm</td></tr>
<tr><td>% with dizziness</td><td>NS</td><td>29%</td></tr>
<tr><td>% with asthenia</td><td>NS</td><td>13%</td></tr>
<tr><td>% with constipation</td><td>NS</td><td>13%</td></tr>
<tr><td>% with dry mouth</td><td>NS</td><td>13%</td></tr>
<tr><td>% with headache</td><td>NS</td><td>13%</td></tr>
<tr><td>% with nausea</td><td>NS</td><td>13%</td></tr>
<tr><td rowspan="2">% with palpitations</td><td>28.6% vs. 0% (S)</td><td rowspan="2">8%</td></tr>
<tr><td>Note: When aripiprazole was administered to the same volunteers, palpitations only developed in women (n = 5). Also the 2 volunteers developing palpitations on olanzapine were women. 71% of (*1B/*1F or *1F/*1F) was woman versus 41% of (*1A/*1A or *1A/*1B or *1A/*1F or *1B/*1B or *1B/*1C or *1C/*1F).</td></tr>
</table>
Note: genotyping was for *1B, *1C, and *1F. These are the most important gene variants in this Spanish population. Gene variant *1B is not known to affect enzyme activity.</td>
<td>that HTR2A, HTR2C, DRD2, DRD3, OPRM1, UGT1A1 and CYP1A2 polymorphisms have a role in the development of adverse drug reactions to aripiprazole and olanzapine. Consequently, some polymorphisms may explain the difference in the incidence of adverse drug reactions among subjects.’</td>
</tr>
<tr>
<td>ref. 2
Yan P et al. Association of the genetic polymorphisms of metabolizing enzymes, transporters, target receptors and their interactions with treatment</td>
<td>4</td>
<td>241 patients were treated with olanzapine monotherapy for a period of 4 weeks. Olanzapine was started at a dose of 5 mg/day, which was gradually increased to a therapeutic dose of 10-20 mg/day within the first week. After that, the dose was adjusted based on individual tolerance to the treatment. Only patients completing the whole study period were included. Of the 26 patients not completing the study, 9 failed to do so because of severe adverse events. The included patients had mild to moderate adverse events.
Good response was defined as a reduction in the Positive and Negative Syndrome Scale (PANSS) score ≥50%, and poor response as a reduction in the PANSS score <50%.
Steady-state serum concentrations were determined.</td>
<td>Authors’ conclusions:
‘Multivariate logistic regression analysis suggested that the genetic polymorphisms of CYP-1A2 rs762551, UGT1A4 rs2011425, ABCB1</td>
</tr>
</table>

response to olanzapine in chinese han schizophrenia patients. Psychiatry Res 2020;293:113470. PMID: 32992097.

ref. 2, continuation

Comedication other than lorazepam and trihexyphenidyl was excluded. 15% of patients was smoker.
Multivariate logistic regression adjusting for age, gender, BMI, age of onset, duration of illness and smoking status, was used to determine the effect of gene variants on dose-corrected steady-state serum concentration.
To adjust for the comparisons for 14 different gene variants in this study (11 for other genes than CYP1A2), Bonferroni correction was applied to the comparisons of genotype frequencies between good and bad responders, i.e. $p < 0.0036$ (0.05/14) was considered significant. Then stepwise logistic regression including the parameters with $p < 0.05$ was carried out to analyse the associations between genotypes and the efficacy of olanzapine. Stepwise logistic regression adjusted for confounding factors including age, gender, BMI, age of onset, duration of illness, smoking status, and variants in other genes.
Gene-gene interactions were investigated by using multifactor dimensionality reduction (MDR) software.

Genotyping:

*1F:	*1C:
- 52x no *1F	- 125x no *1C
- 105x *1F-heterozygous	- 98x *1C-heterozygous
- 84x *1F/*1F	- 18x *1C/*1C

Results:

Results compared to no gene variant:				
		homozygous variant	heterozygous	value for no variant (or for all patients for the adverse events)
good response	*1F	x 0.56, OR_{adj} = 0.12 (95% CI: 0.04-0.38) (S)	x 0.77, OR_{adj} = 0.23 (95% CI: 0.08-0.70) (S)	81% of patients
		S for the trend *1F/*1F versus *1F-heterozygous versus no *1F in univariate analysis.		
		There were interactions between *1F and variants in 3 other genes (DRD2 rs1799978, 5-HTR2A rs6311, ABCB1 rs1045642) (S).		
	*1C	NS	NS	66% of patients
weight gain	*1F	NS	NS	2.57 kg
	*1C	NS	NS	
somnolescence	*1F	NS	NS	17% of patients
	*1C	NS	NS	
extrapyramidal symptoms	*1F	NS	NS	8% of patients
	*1C	NS	NS	
dose-corrected clozapine concentration	*1F	x 0.86 (S)	x 0.92 (NS)	3.26 ng/ml per mg
		S for the trend *1F/*1F versus *1F-heterozygous versus no *1F.		
	*1C	x 0.93 (NS)	x 0.97 (NS)	3.04 ng/ml per mg

*1F/*1F: C

*1A/*1F: AA[#]
NM: AA[#]

*1C/*1C: AA
*1C-heterozygote: AA

rs1045642, DRD2 rs1799732 and rs1799978, 5-HTR2A rs6311 were significantly associated with olanzapine response. Multifactor dimensionality reduction (MDR) analysis showed that there was a negative interaction between CYP1A2 rs762551, ABCB1 rs1045642, DRD2 rs1799978, 5-HTR2A rs6311 and the interaction model was the optimal model.'

<table>
<tr><td>ref. 2, continuation</td><td>*1D: AA</td><td>Note: Smoking did not affect response rate in this study, but there was a trend for a higher response rate in smokers (p = 0.109) (NS).

Note: genotyping was for *1C, *1D, and *1F. These are the most important gene variants in this Chinese population.
Data for gene variant *1D are not included in the summary, because this gene variant is not known to affect enzyme activity. Correspondingly, the study did not find an effect on dose-corrected olanzapine concentration. The study found a difference in genotype distribution between good and bad responders, but no significant result in multivariate analysis.</td><td></td></tr>
<tr><td>ref. 3
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.

and personal communication (supplementary files)</td><td>(*1F/*1F + *1A/*1F): AA

(NM+ *1A/*1F+ *1C-heterozygote): AA</td><td>Plasma concentrations were analysed for the 24 healthy volunteers receiving olanzapine 5 mg/day during five days in the study of Koller 2021. For olanzapine, a period of 5 days is too short to reach steady state.
Co-medication was excluded, but smoking was not.
Bonferroni correction was used to correct for multiple comparisons.
Multiple linear regression models were used to study factors related to all pharmacokinetic dependent variables.

Genotyping:
- 17x (*1A/*1A or *1A/*1B or *1A/*1F or *1B/*1B or *1B/*1C or *1C/*1F)
- 7x (*1B/*1F or *1F/*1F)

Results:
<table>
<tr><td colspan="3">Results for (*1B/*1F or *1F/*1F) compared (*1A/*1A or *1A/*1B or *1A/*1F or *1B/*1B or *1B/*1C or *1C/*1F):</td></tr>
<tr><td></td><td></td><td>value for (*1A/*1A or *1A/*1B or *1A/*1F or *1B/*1B or *1B/*1C or *1C/*1F)</td></tr>
<tr><td>AUC clozapine</td><td>x 1.79 (S, but NS in multiple linear regression analysis)</td><td>63090 ng.h/ml</td></tr>
<tr><td>oral clearance clozapine</td><td>x 0.73 (S, but NS in multiple linear regression analysis)</td><td>74.0 L/h.kg</td></tr>
<tr><td>clozapine half-life</td><td>NS</td><td>60.5 h</td></tr>
</table>
Note: genotyping was for *1B, *1C, and *1F. These are the most important gene variants in this Spanish population. Gene variant *1B is not known to affect enzyme activity.</td><td>Authors' conclusions:
'Olanzapine did not cause any changes in any of the pupillometric parameters.
…
Aripiprazole, dehydro-aripiprazole and olanzapine pharmacokinetics were significantly affected by polymorphisms in CYP-2D6, CYP3A, CYP1A2, ABCB1 and UGT1A1 genes.'</td></tr>
<tr><td>ref. 4
Hattori S et al. The association of genetic polymorphisms in CYP1A2, UGT1A4, and ABCB1 with autonomic nervous system dysfunction in schizophrenia patients treated with olanzapine.
BMC Psychiatry 2020;20:72.
PMID:</td><td>3</td><td>91 patients were treated with olanzapine monotherapy for at least 3 months.
Olanzapine is associated with autonomous nervous system disfunction. A 5-min measurement of resting heart rate variability was conducted to evaluate autonomic nervous system activity. A greater low frequency (0.03–0.15 Hz) heart rate variability score indicates higher sympathetic activity. A greater high frequency heart rate variability score (0.15–0.40 Hz) indicates higher parasympathetic activity, and a greater total power (0.03–0.40 Hz) heart rate variability score indicates higher autonomic nervous system activity. It is presumed that higher heart rate variability is generally indicative of better health because previous studies have reported that lower heart rate variability is associated with increased risk of death and cardiovascular disease.
Comedication with an effect on CYP1A2 was excluded (only anticholinergic antiparkinsonian drugs and benzodiazepines were used as comedication). 6.6% of patients was smoker.
Bonferroni correction for multiple comparisons (7 gene variants of which 5 in other genes than CYP1A2) was applied: the Bonferroni-</td><td>Authors' conclusions:
'The findings of this study suggest that while UGT1A4 genetic polymorphisms do affect olanzapine-related sympathetic nervous system activity, polymorphisms in CYP1A2 and ABCB1 do not.'</td></tr>
</table>

<table>
<tr>
<td>32070304.

ref. 4, continuation</td>
<td>*1F/*1F: AA
*1A/*1F: AA
NM: AA

*1C/*1C: AA
*1C-heterozygote: AA</td>
<td>corrected critical p-value was 0.05/7 (i.e., p < 0.007).
Multiple regression analysis adjusted for age, body mass index, Positive and Negative Syndrome Scale (PANSS) score, dosages of antipsychotic, antiparkinsonian, and benzodiazepine agents, and genetic polymorphisms identified as potentially affecting autonomic nervous system activity.

Genotyping:
*1F:
- 21x no *1F
- 70x (*1F-heterozygous or *1F/*1F)

*1C:
- 56x no *1C
- 35x (*1C-heterozygous or *1C/*1C)

Results:
<table>
<tr><td colspan="3">Heart rate variability for (heterozygous or homozygous variant) compared to no gene variant:</td></tr>
<tr><td rowspan="2">low frequency (sympathetic activity)</td><td>*1F</td><td>trend for a decrease (p is 1.9 times the significance limit) (NS) in univariate analysis, also NS in multiple regression analysis</td></tr>
<tr><td>*1C</td><td>NS</td></tr>
<tr><td rowspan="2">high frequency (parasympathetic activity)</td><td>*1F</td><td>NS in univariate and multiple regression analysis</td></tr>
<tr><td>*1C</td><td>NS</td></tr>
<tr><td rowspan="2">total power (autonomic nervous system activity)</td><td>*1F</td><td>NS in univariate and multiple regression analysis</td></tr>
<tr><td>*1C</td><td>NS</td></tr>
</table>
Note: genotyping was for *1C and *1F. These are the most important gene variants in this Japanese population.</td>
<td></td>
</tr>
<tr>
<td>ref. 5
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</td>
<td>120 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. 29% of patients were both cigarette smokers (smoking at least five cigarettes per day) and heavy coffee consumers (drinking at least three cups of coffee per day). 20% were cigarette smokers (smoking at least five cigarettes per day)/coffee non-consumers and 21% were heavy coffee consumers/non-smokers. The other patients did not smoke at all and did not drink coffee at all.
Bonferroni correction was used to correct for multiple comparisons. The estimated number needed per group to detect the effect of a CYP1A2 inducer on olanzapine efficacy (with 95% power) has been estimated to be 14, based on the report of Carrillo 2003 that cigarette smoking affects the total Brief Psychiatric Rating Scale score in patients on olanzapine therapy (12.5 ± 14% vs 30.4 ± 10% in smo-</td>
<td>Author’s conclusion:
‘We confirm the effect of cigarette smoking and heavy coffee consumption on olanzapine efficacy and safety. The relevance of CYP1A2 genotype for the described effect needs further investigation.‘</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>(*1A/*1F + *1F/*1F): AA
NM: AA

rs2472297: AA</td>
<td>
kers vs non-smokers, respectively, P<0.01). Assuming a comparison between *1F/*1F and no *1F/*1F to be relevant and the 45% expected frequency of the *1F/*1F, to detect the effect of a CYP1A2 inducer in relation to CYP1A2 genotype the number of subjects per group was increased to 30, i.e., the total sample size was calculated to be 120.

Genotyping:
*1F:
- 13x no *1F
- 56x *1F-heterozygous
- 51x *1F/*1F

rs2472297C>T:
- 86x rs2472297CC
- 31x rs2472297CT
- 3x rs2472297TT

Results:
<table>
<tr><td colspan="3">Results for (heterozygous + homozygous variant) compared to no gene variant:</td></tr>
<tr><td colspan="3">treatment response</td></tr>
<tr><td rowspan="2">Positive and Negative Syndrome Scale score change</td><td>*1F</td><td>NS
Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers.</td></tr>
<tr><td>rs2472297C>T</td><td>NS</td></tr>
<tr><td rowspan="2">Clinical Global Impressions Improvement score</td><td>*1F</td><td>NS
Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers.</td></tr>
<tr><td>rs2472297C>T</td><td>NS</td></tr>
<tr><td rowspan="2">Global Assessment of Functioning score change</td><td>*1F</td><td>NS
Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers.</td></tr>
<tr><td>rs2472297C>T</td><td>NS</td></tr>
<tr><td colspan="3">adverse events</td></tr>
<tr><td rowspan="2">BMI change</td><td>*1F</td><td>NS
Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers.</td></tr>
<tr><td>rs2472297C>T</td><td>NS</td></tr>
<tr><td rowspan="2">fasting serum glucose change</td><td>*1F</td><td>NS
Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers.</td></tr>
<tr><td>rs2472297C>T</td><td>NS</td></tr>
<tr><td rowspan="2">total cholesterol change</td><td>*1F</td><td>NS
Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers.</td></tr>
<tr><td>rs2472297C>T</td><td>trend for an effect (p = 0.08) (NS), increase with 0.10 mmol/L for rs2472297CT and decrease with 0.47 mmol/L for rs2472297TT</td></tr>
<tr><td rowspan="2">low density lipoprotein change</td><td>*1F</td><td>NS
Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

ref. 5, continuation				heavy coffee consumers.	
			rs2472297C>T	NS	
		triglyceride change	*1F	NS	
				Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers.	
			rs2472297C>T	NS	
		extrapyramidal symptoms	*1F	NS	
				Also NS in cigarette smokers, in heavy coffee consumers and in smokers who are also heavy coffee consumers. There was a trend for an effect in the heavy coffee consumers (p= 0.09) (NS).	
			rs2472297C>T	NS	
		There were also no significant effects for the CYP1A2 haplotypes (alleles) (NS), and for *1F/*1F compared to (*1F-heterozygous and no *1F).			
		Results for cigarette smoking compared to no cigarette smoking:			
		treatment response			
		Positive and Negative Syndrome Scale score change	all	decrease (S)	
			no *1F	NS	
			*1F carrier	decrease (S)	
			no rs2472297T	decrease (S)	
			rs2472297T carrier	decrease (S)	
		Clinical Global Impressions Improvement score	all	increase (S)	
			no *1F	NS	
			*1F carrier	increase (S)	
			no rs2472297T	increase (S)	
			rs2472297T carrier	increase (S)	
		Global Assessment of Functioning score change	all	decrease (S)	
			no *1F	NS	
			*1F carrier	decrease (S)	
			no rs2472297T	decrease (S)	
			rs2472297T carrier	decrease (S)	
		adverse events			
		BMI change	all	decrease (S)	
			no *1F	trend for a decrease (p = 0.09) (NS)	
			*1F carrier	decrease (S)	
			no rs2472297T	decrease (S)	
			rs2472297T carrier	decrease (S)	
		fasting serum glucose change	all	NS	
			no *1F	NS	
			*1F carrier	NS	
			no rs2472297T	NS	
			rs2472297T carrier	NS	
		total cholesterol change	all	decrease (S)	
			no *1F	NS	
			*1F carrier	decrease (S)	
			no rs2472297T	decrease (S)	
			rs2472297T carrier	NS	
		low density lipoprotein change	all	decrease (S)	
			no *1F	NS	
			*1F carrier	decrease (S)	
			no rs2472297T	decrease (S)	
			rs2472297T carrier	decrease (S)	
		triglyceride	all	decrease (S)	

<table>
<tr>
<td>ref. 5, continuation</td>
<td></td>
<td>
<table>
<tr><td>change</td><td>no *1F</td><td>trend for a decrease (p = 0.07) (NS)</td></tr>
<tr><td></td><td>*1F carrier</td><td>decrease (S)</td></tr>
<tr><td></td><td>no rs2472297T</td><td>decrease (S)</td></tr>
<tr><td></td><td>rs2472297T carrier</td><td>NS</td></tr>
<tr><td>extrapyramidal symptoms</td><td>all</td><td>decrease (S)</td></tr>
<tr><td></td><td>no *1F</td><td>NS</td></tr>
<tr><td></td><td>*1F carrier</td><td>decrease (S)</td></tr>
<tr><td></td><td>no rs2472297T</td><td>NS</td></tr>
<tr><td></td><td>rs2472297T carrier</td><td>decrease (S)</td></tr>
<tr><td colspan="3">Similar results were obtained for heavy coffee consumption compared to no coffee consumption and for simultaneous cigarette smoking and heavy coffee consumption compared to neither smoking nor coffee consumption.</td></tr>
<tr><td colspan="3">Note: The no *1F group consist of only 13 patients. This is lower than the estimated number needed per group of 14 to detect the effect of a CYP1A2 inducer on olanzapine efficacy (with 95% power). Stratification of this group into smokers and non-smokers or into heavy coffee consumers and coffee non-consumers reduces the group size even more to 5-8 patients per group. This might be a trivial explanation of the lack of a significant effect in this group in the table above, and so explain the apparent discrepancy between the effect of the *1F variant in this and the former table.</td></tr>
</table>

Note: Genotyping was for *1C, *1F, and rs2472297 (located between the CYP1A1 and CYP1A2 genes). These are the most important gene variants in this Serbian population. *1C was not found in this patient group.
Haplotype analysis revealed complete linkage disequilibrium between *1F and rs2472297C>T, with (no *1F) only present in combination with rs2472297C.
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Na Takuathung M et al.
Impact of CYP-1A2 genetic polymorphisms on pharmacokinetics of antipsychotic drugs: a systematic review and meta-analysis.
Acta Psychiatr Scand 2019;139:15-25.
PMID: 30112761.</td>
<td>4

*1F/*1F: AA
*1A/*1F: AA
NM: AA</td>
<td>Meta-analyses of 3 pharmacokinetic studies, including a total of 257 patients (24x no *1F, 100x *1F-heterozygous, 133x *1F/*1F). All included studies were of good quality, scoring 68-71 points of the maximum of 77 points on the 11-item quality scale for genetic studies Q-Genie.
All 3 studies in the meta-analysis are also included in our risk analysis separately (Czerwensky 2015, Ghotbi 2010, Nozawa 2008).
The review protocol was registered at the PROSPERO international prospective register of systematic reviews (CRD42017079514).
Meta-analyses were performed with a random-effects model in case of significant heterogeneity between the studies and with a fixed-effect model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data exaction was standardised.
Publication bias analysis was performed for all comparisons.

Results:
<table>
<tr><td colspan="2">Standard mean difference of the dose-corrected clozapine plasma concentration compared to no *1F:</td></tr>
<tr><td>*1F-heterozygous</td><td>NS</td></tr>
<tr><td>*1F/*1F</td><td>NS</td></tr>
<tr><td colspan="2">Heterogeneity between the studies was lacking for *1F/*1F compared to no *1F.
Heterogeneity between the studies was mild for *1F-heterozygous compared to no *1F.</td></tr>
<tr><td colspan="2">There were no indications for publication bias for *1F/*1F compared to no *1F.
There were indications for publication bias (funnel plot asymmetry indicative of the evidence of small study effects) for *1F-heterozygous compared to no *1F.</td></tr>
</table>
</td>
<td>Authors' conclusions:
'The pooled-effect estimates through meta-analyses of seven studies demonstrated no significant associations between the -163C>A or -2467delT polymorphism and clozapine or olanzapine concentrations in the blood.'</td>
</tr>
</table>

<table>
<tr><td>ref. 6, continuation</td><td>*1D: AA</td><td>Note: The results of the meta-analysis investigating the pharmacokinetic effect of *1D were not included in this abstract, because *1D is a fully functional allele. As expected, no impact of *1D on olanzapine plasma concentration was found (NS).</td><td></td></tr>
<tr><td>ref. 7
Czerwensky F et al.
CYP1A2*1D and *1F polymorphisms have a significant impact on olanzapine serum concentrations.
Ther Drug Monit 2015;37:152-60.
PubMed PMID: 25090458.</td><td>3

(*1A/*1F +*1A/*1A): A

*1F/*1F: A</td><td>Olanzapine plasma concentrations were determined in 98 patients, who used olanzapine for at least 4 weeks (2.5-30 mg/day; mean 14.7 mg/day). 28% of the patients also used other antipsychotics. Relevant co-medication was not excluded. 41% of the patients were smokers. Co-medication with carbamazepine (n = 7) led to subtherapeutic plasma concentrations. Dose adjustment was adequate for smokers. There were no significant differences in distribution of carbamazepine, CYP1A2 substrates and CYP1A2 inducers (smoking, carbamazepine and valproic acid) over the CYP1A2 genotypes.
Response was also determined in 209 patients using either olanzapine or clozapine. Olanzapine was the only antipsychotic in 118 patients, clozapine the only antipsychotic in 18 patients and 132 patients were on combination therapy. De mean olanzapine dose was 14.2 mg/day. 39% of the patients were smokers. Relevant co-medication was not excluded. Clinical outcomes were determined at 4 weeks using the Paranoid Depressive Scale - Paranoid (PDS-P) (psychotic disorders only) and the Clinical Global Impression Scale (CGI).
Both patients with psychotic disorders as those with other indications for olanzapine were included.
Corrections were made for age, gender, weight, the other CYP1A2 genotype and CYP1A2 inducers (smoking, carbamazepine, valproic acid).

Genotyping (for *1D not in Hardy-Weinberg equilibrium):
Small group
*1F:
- 8x *1A/*1A
- 36x *1A/*1F
- 54x *1F/*1F
*1D:
- 89x *1A/*1A
- 6x *1A/*1D
- 3x *1D/*1D
Large group
- Results not reported

Results in small group:
<table>
<tr><td colspan="4">Results versus *1F/*1F:</td></tr>
<tr><td></td><td>*1A/*1A</td><td>*1A/*1F</td><td>Value for *1F/*1F</td></tr>
<tr><td rowspan="4">Dose-corrected trough concentration of olanzapine</td><td>x 0.93</td><td>x 1.40</td><td rowspan="4">1.5 ng/mL.mg</td></tr>
<tr><td colspan="2">S for *1A/*1A versus *1A/*1F versus *1F/*1F</td></tr>
<tr><td colspan="2">S for (*1A/*1A + *1A/*1F) versus *1F/*1F, both with and without correction.
A trend was found for the subgroup with CYP1A2 inducers (mainly smoking) (p = 0.084), while the effect was NS in the subgroup without inducers.</td></tr>
<tr><td colspan="2">24% of the variation was explained by *1D, *1F and CYP1A2 induction</td></tr>
<tr><td rowspan="2">Dose- and weight-corrected trough concentration of olanzapine</td><td>x 0.90</td><td>x 1.37</td><td rowspan="2">109.9 ng.kg/mL.mg</td></tr>
<tr><td colspan="2">Trend for *1A/*1A versus *1A/*1F versus *1F/*1F (p = 0.068) (NS)</td></tr>
<tr><td rowspan="2">Side effects</td><td>NS</td><td>NS</td><td rowspan="2"></td></tr>
<tr><td colspan="2">The effect was also NS in the subgroup with ≥ 2 risk factors for</td></tr>
</table></td><td>Authors' conclusions:
'We, for the first time, identified a significant influence of polymorphisms in CYP1A2 in combination with CYP1A2 inducer status on the clinical outcome. Therefore, genotyping for CYP1A2*1D and *1F may be a useful tool for dose optimization and identification of high-risk patients. Further and larger studies are needed before genotype-based dosage recommendations can help patients treated with CYP1A2 metabolized drugs.'</td></tr>
</table>

<table>
<tr>
<td>ref. 7, continuation</td>
<td>*1D: A</td>
<td>
<table>
<tr><td></td><td colspan="2">high plasma concentrations (no CYP1A2 induction, *1A/*1A or *1A/*1F genotype, *1D allele)</td><td></td></tr>
<tr><td>Response</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td></td><td colspan="2">The effect was also NS in the subgroup with ≥ 2 risk factors for high plasma concentrations (no CYP1A2 induction, *1A/*1A or *1A/*1F genotype, *1D allele)</td><td></td></tr>
</table>

<table>
<tr><td colspan="4">Results versus *1A/*1A:</td></tr>
<tr><td></td><td>*1D/*1D</td><td>*1A/*1D</td><td>Value for *1A/*1A</td></tr>
<tr><td>Dose-corrected trough concentration of olanzapine</td><td>x 2.31</td><td>x 1.51</td><td>1.6 ng/ mL.mg</td></tr>
<tr><td></td><td colspan="2">S for *1D/*1D versus *1A/*1D versus *1A/*1A</td><td></td></tr>
<tr><td></td><td colspan="2">S for (*1A/*1D + *1D/*1D) versus *1A/*1A, both with and without correction.</td><td></td></tr>
<tr><td></td><td colspan="2">24% of the variation was explained by *1D, *1F and CYP1A2 induction</td><td></td></tr>
<tr><td>Dose- and weight-corrected trough concentration of olanzapine</td><td>x 1.93</td><td>x 1.75</td><td>116.2 ng.kg/ mL.mg</td></tr>
<tr><td></td><td colspan="2">S for *1D/*1D versus *1A/*1D versus *1A/*1A</td><td></td></tr>
<tr><td>Side effects</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td></td><td colspan="2">The effect was also NS in the subgroup with ≥ 2 risk factors for high plasma concentrations (no CYP1A2 induction, *1A/*1A or *1A/*1F genotype, *1D allele)</td><td></td></tr>
<tr><td>Response</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td></td><td colspan="2">The effect was also NS in the subgroup with ≥ 2 risk factors for high plasma concentrations (no CYP1A2 induction, *1A/*1A or *1A/*1F genotype, *1D allele)</td><td></td></tr>
</table>

Results in large group:
<table>
<tr><td></td><td>*1F allele</td><td>*1D allele</td></tr>
<tr><td>Response</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td colspan="2">Response was significantly increased in the subgroup with ≥ 2 risk factors for high plasma concentrations (no CYP1A2 induction, *1A/*1A or *1A/*1F genotype, *1D allele) (S).</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 8
Looman NMG et al.
Associatie van genetische variatie in CYP1A2 en UGT1A4 met metabole stoornissen bij gebruikers van clozapine en olanzapine [Association of genetic variation in CYP1A2</td>
<td>3</td>
<td>92 patients used olanzapine (2.5-40 mg/day; mean 13.9 mg/day). Relevant co-medication was not excluded. 65% of the patients were smokers.
ORs were corrected for age, gender, diagnosis, duration of disease, dose and smoking.
The use of CYP1A2 inducers and inhibitors in the patient group was too low to be able to correct for these. The number of patients was too low to consider smokers and non-smokers separately. Correction for the duration of olanzapine usage was not possible as these data were missing for a large proportion of the patients.

Genotyping:
- 10x *1A/*1A
- 50x *1A/*1F
- 26x *1F/*1F
- 6x *1F/*1L (*1L = *1C+*1F)</td>
<td>Authors' conclusions:
'This study showed that there is no relationship between genetic variation in CYP1A2 and UGT1A4 and the occurrence of metabolic syndrome in users of clozapine and olanzapine.'</td>
</tr>
</table>

<table>
<tr>
<td>and UGT1A4 with metabolic disorders in users of clozapine and olanzapine].
PW Wetenschappelijk Platform 2013;7:a1310.

ref. 8, continuation</td>
<td>*1A/*1F: AA

*1F/*1F: A
*1A/*1A: AA#

*1F/*1L = *1F/(*1C +*1F): AA</td>
<td>Results:
<table>
<tr><td colspan="5">Metabolic side effects versus *1A/*1A:</td></tr>
<tr><td></td><td>*1A/*1F</td><td>(*1F/*1F + *1F/*1L)</td><td>(*1A/*1F + *1F/*1F + *1F/*1L)</td><td>Value for *1A/*1A</td></tr>
<tr><td>Metabolic syndrome (OR_{corr})</td><td>NS</td><td>NS</td><td>NS</td><td>30%</td></tr>
<tr><td>Uncontrolled glucose</td><td></td><td>Increase (S)</td><td></td><td></td></tr>
</table>

<table>
<tr><td>*1F/*1L versus *1F/*1F:</td></tr>
<tr><td>- No difference in results (NS)</td></tr>
</table>

NOTE 1: The power calculation performed retrospectively showed that a significant difference would require a much larger number of patients (appr. 1,800).

NOTE 2: Genotyping was for *1F and *1C were genotyped. *1C was only found in combination with *1F. As *1L is the only allele known to have both polymorphisms, this allele was called *1L.</td>
<td></td>
</tr>
<tr>
<td>ref. 9
Söderberg MM et al.
Influence of CYP1A1/CYP1A2 and AHR polymorphisms on systemic olanzapine exposure.
Pharmacogenet Genomics 2013;23:279-85.
PubMed PMID: 23492908.</td>
<td>4

*1F: AA
*1A: AA

rs2472304: AA</td>
<td>Routine determination of plasma concentrations was performed in 342 patients on long-term olanzapine therapy (2.5-60 mg/day; median 15 mg/day for all patients, 10 mg/day for non-smokers and 20 mg/day for smokers). Use of CYP1A2 or UGT1A4 inhibitors or inducers was excluded, with the exception of smoking (n=195) and co-medication with valproic acid (n=26, of which 14 smokers) or lamotrigine. Logarithms of plasma concentrations and ratios were compared.

Genotyping: Five haplotypes with a frequency higher than 1% were identified using 4 SNPs (1 upstream of CYP1A1 (rs2470893), 1 between CYP1A1 and CYP1A2 (rs2472297), the SNP for *1F and 1 in intron 4 of CYP1A2 (rs2472304)):
- 92x haplotype 1 (the only one without *1F, also has variant rs2472304)
- 77x haplotype 2 (reference haplotype: the most common allele for all SNPs)
- 68x haplotype 3 (the only one with variant rs2472297, also variant rs2470893)
- 40x haplotype 4 (variant rs2472304)
- 16x haplotype 5 (variant rs2470893)
- 1x rare haplotype

Haplotype 1 (*1F and variant rs2472304) versus haplotype 2:
- No differences in dose-corrected plasma concentrations of olanzapine and the ratio of N-desmethyl-olanzapine/olanzapine in smokers and non-smokers (NS)

Haplotype 4 (variant rs2472304) versus haplotype 2:
- No differences in dose-corrected plasma concentrations of olanzapine in non-smokers and smokers (NS)
- Decrease in the ratio of N-desmethyl-olanzapine/olanzapine in non-smokers (S), but not in smokers (NS). The decrease in non-smokers was no longer significant after correction for a polymorphism in the gene for the aryl hydrocarbon receptor, the starting point for the induction of CYP1A2 by cigarette smoke.

Variant rs2472297:
- Haplotype 3 (variant rs2472297 and variant rs2470893) versus haplotype 2:
  - Decrease in dose-corrected plasma concentrations of olanzapine</td>
<td>Authors' conclusion:
"The reported influence of CYP1A2 *1F (also known as CYP1A2-163A, rs762551C> A) on systemic olanzapine exposure could not be verified. CYP1A1/CYP1A2 rs2472297C > T and AHR rs4410790C > T are potentially useful genetic markers associated with variability in CYP1A2-mediated metabolism, but are of minor quantitative importance for systemic olanzapine exposure."</td>
</tr>
</table>

ref. 9, continuation	rs2470893: AA rs2472297: A	in non-smokers (S), but no difference in smokers (NS) - Increase in the ratio of N-desmethyl-olanzapine/olanzapine in non-smokers and smokers (NS) - Haplotype 5 (variant rs2470893) versus haplotype 2: - No difference in dose-corrected plasma concentrations of olanzapine and the ratio of N-desmethyl-olanzapine/olanzapine in smokers and non-smokers (NS) - Multivariable linear regression analysis: - rs2472297C>T is a new, independent predictor of dose-corrected olanzapine concentrations and explains 2% of the variation in this concentration (S). However, dose-corrected olanzapine plasma concentrations in carriers of rs2472297T were not significantly lower than in homozygotes for rs2472297C (7.3 versus 8.0 nmol/L per mg) (NS). - rs2472297C>T is an independent predictor for the logarithm of the N-desmethyl-olanzapine/olanzapine ratio (S). The ratio in carriers of rs2472297T was 25% higher than in homozygotes for rs2472297C (S).	
ref. 10 Cabaleiro T et al. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum Psychopharmacol 2013;28:205-14. PubMed PMID: 23559402.	3 *1F: AA *1A: AA *1C: AA	61 healthy volunteers received a single dose of olanzapine 5 mg. Co-medication and smoking were excluded. Genotyping: - 5x *1A/*1A - 52x (*1F/*1F of *1A/*1F) - 4x *1C/*1F Results: - No association between CYP1A2 and AUC, $t_{1/2}$ and clearance of olanzapine (NS) - No association between CYP1A2 and induction of prolactin by olanzapine (NS) - No association between CYP1A2 and side effects (NS). One patient with the *1A/*1A genotype developed QT prolongation. Logistic regression analysis did not reveal any association (NS).	Authors' conclusion: "The main genes involved in the metabolism of olanzapine are UGT-1A1, CYP1A2, CYP2D6, and CYP3A4. However, we found no association between polymorphisms in these genes and the pharmacokinetics of olanzapine. Administration of a single dose of olanzapine may not be sufficient to observe the effect of UGT-1A1, CYP1A2, and CYP2D6 genotypes on pharmacokinetic parameters."
ref. 11 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 Psycho-	4 *1F/*1F: AA *1A/*1F+	37 patients, including 10 smokers, were treated with a stable dose of olanzapine (2.5-25 mg/day). Co-medication affecting CYP1A2 was excluded. The only co-medication consisted of benzodiazepines and/or zopiclone (n=10) and lithium (n=3). Corrections were made for smoking, ABCB1 polymorphisms, CYP2D6 polymorphisms and age. Genotyping: - 5x *1A/*1A - 13x *1A/*1F - 19x *1F/*1F *1F/*1F versus (*1A/*1F + *1A/*1A): - No differences in dose-corrected concentrations of olanzapine and N-desmethyl-olanzapine in plasma and cerebrospinal fluid (NS) - Increase in the N-desmethyl-olanzapine/olanzapine ratio in cerebrospinal fluid of smokers with the *1F/*1F genotype versus the	Authors' conclusion: "We analyzed the potential influence of the -163C>A polymorphism in the CYP1A2 gene on olanzapine disposition. No statistically significant association was found in serum. The CSF data are in line with an increased induc-

pharmacol 2011;31:4-9. PubMed PMID: 21192135. **ref. 11, continuation**	*1A/*1A: AA	other groups (smokers with *1A/*1F + *1A/*1A, non-smokers with both genotype groups) (0.58 versus 0.25; 0.28 and 0.33 respectively) (S) NOTE: Alleles *1C, *1D, *1E, *1F and *1K were genotyped. As *1C and *1K did not occur, *1E occurred only once and *1D only twice, only *1F was studied.	tion of olanzapine demethylation in smokers homozygous for the CYP1A2*1F allele."
ref. 12 McClay JL et al. Genomewide pharmacogenomic analysis of response to treatment with antipsychotics. Mol Psychiatry 2011;16:76-85. PubMed PMID: 19721433.	3 CYP1A2: AA	245 patients were treated with olanzapine (7.5-30 mg/day) for 6-18 months. Relevant co-medication was not excluded. There were no data available about smoking. The effect of the treatment was measured using the Positive and Negative Syndromes Scale (PANSS) and its 5 subscales (Positive, Negative, Disorganisation, Excitement and Emotional Stress). The study was a genome-wide association study. In addition, candidate genes were also tested, including CYP1A2 (2 polymorphisms in this genome area). Results: - CYP1A2 was not associated with the effectiveness of olanzapine therapy (NS)	
ref. 13 Ghotbi R et al. Carriers of the UGT1A4 142 T>G gene variant are predisposed to reduced olanzapine exposure--an impact similar to male gender or smoking in schizophrenic patients. Eur J Clin Pharmacol 2010;66:465-74. PubMed PMID: 20143052.	3 *1F: AA *1A: AA *1D: AA	112 patients, of which 41% were smokers, were treated with olanzapine (2.5-40 mg/day; mean 12.2 mg/day). According to the authors, there was no co-medication with CYP1A2 inhibitors, but co-medication with fluoxetine and paroxetine was reported. Multiple regression analysis found no effect of co-medication with fluoxetine, paroxetine, perphenazine or levomepromazine. Olanzapine plasma concentrations were not determined at a fixed time after the last dose. Multivariate regression analysis corrected for this using the mean $t_{1/2}$ for olanzapine. Plasma concentrations lower than the detection limit of 6.2 ng/mL (n=8) were set to 3.1 ng/mL. Genotyping: *1F: - 7x *1A/*1A - 38x *1A/*1F - 67x *1F/*1F *1D: - 92x *1A/*1A - 18x *1A/*1D - 2x *1D/*1D Results: - No association between dose-corrected plasma concentrations of olanzapine and *1F and *1D (NS for univariate and multiple regression analysis) - In smokers, no differences were found in dose-corrected plasma concentrations of olanzapine between *1F/*1F, *1F heterozygote and (no *1F) (NS in univariate analysis) Note: Alleles *1D, *1F and *1K were genotyped. *1K was not present.	Authors' conclusion: "Age, body weight, and MDR1 or CYP-1A2 haplotype did not have a significant impact on olanzapine plasma levels."
ref. 14 Nozawa M et al. The relationship between the response of clinical symptoms and plasma olanzapine concentration, based on pharmacogenetics:	3	47 patients, of which approx. 31% were smokers, were switched from classic antipsychotics to olanzapine (5-20 mg/day; mean 15.7 mg/day). Co-medication was unknown. Correction for smoking was not performed. Genotyping: '*1F': - 9x *1A/*1A - 26x *1A/'*1F' - 12x '*1F'/'*1F' *1C: - 29x *1A/*1A	Authors' conclusion: "The functional gene polymorphisms of UGT-1A4, CYP1A2, and CYP2D6 had no effect on the plasma olanzapine and metabolite concentrations."

Juntendo University Schizophrenia Projects (JUSP). Ther Drug Monit 2008;30:35-40. PubMed PMID: 18223460.	'*1F': AA *1A: AA *1C: AA	- 14x *1A/*1C - 4x *1C/*1C Results: - No effect of '*1F' and *1C on dose-corrected plasma concentrations of olanzapine and N-desmethyl-olanzapine and the olanzapine/N-desmethyl-olanzapine ratio (NS) Note: Genotyping of *1F was performed only on the basis of the -163 C>A polymorphism. This polymorphism also occurs in *1J, *1K, *1L, *1V and *1W. In this Japanese population group, it is not known to what extent this polymorphism represents *1F or the other alleles.	
ref. 15 Thomas P et al. Correlates of response to olanzapine in a North Indian schizophrenia sample. Psychiatry Res 2008;161:275-83. PubMed PMID: 19000940.	3 '*1F': AA *1A: AA *1C: AA	130 patients were treated with olanzapine for 6 weeks (mean 16.5 mg/day; initial dose 5-10 mg/day, weekly increase by 5 mg/day guided by effect and side effects, to a maximum of 30 mg/day in week 6). Response was defined as a ≥ 30% decrease in the PANSS score (Positive and Negative Syndromes Scale). There was no relevant co-medication: only lorazepam, diazepam and medications for Parkinson's disease were permitted as co-medication. There were no data available about smoking. '*1F': - No differences in the frequency of '*1F'/'*1F', '*1F' heterozygote and (no '*1F') between responders and non-responders (NS) - Linear regression analysis: no association with the decrease in PANSS score (NS) *1C: - No difference in the frequency of (homozygote + heterozygote *1C) and (no *1C) between responders and non-responders (NS) (12% (homozygote + heterozygote *1C) in 47 non-responders and 7% (homozygote + heterozygote *1C) in 70 responders) - Linear regression analysis: no association with the decrease in PANSS score (NS) Note: Genotyping of *1F was performed only on the basis of the -163 C>A polymorphism. This polymorphism also occurs in *1J, *1K, *1L, *1V and *1W. In this North Indian population group, it is not known to which extent this polymorphism represents *1F or the other alleles.	Authors' conclusion: "10 polymorphic markers from seven genes (among which CYP1A2), together with demographic and clinical variables, were analyzed as potential predictors of response. No significant allelic or genotypic associations were observed with poor/no response."

Risk group	-

Comments:

- The following article was not included because this is a previous, preliminary publication of part of the results on *1F, which have been described in Czerwensky 2015:
  Laika B et al. Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome. Pharmacogenomics J 2010;10:20-9. PubMed PMID: 19636338.

Date of literature search: 11 August 2021.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	*1A/*1F	4 A	no	no	13 September 2021
	NM	4 AA	no	no	
	*1C-heterozygote	4 AA	no	no	
	*1C/*1C	4 AA	no	no	
	IM	-	no	no	
	PM	-	no	no	

Mechanism:
Olanzapine is mainly converted by CYP1A2 to the metabolite 4'-N-desmethyl-olanzapine. Olanzapine is also converted by direct glucuronidation. 4'-N-desmethyl-olanzapine also appears to be metabolised by CYP1A2: plasma concentrations do not increase with induction of CYP1A2.
The NVZA (Dutch association of hospital pharmacists) mentions a therapeutic range of olanzapine of 20-80 ng/mL with concentrations > 100 ng/mL being toxic and concentrations from 160 ng/mL being lethal. In literature, the same therapeutic range is mentioned (Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62).