CYP2D6: venlafaxine 1538/1539/1540

AUC = area under the concentration-time curve, CGI-I = Clinical Global Impressions-Improvement scale, GCI-S = Clinical Global Impressions-Severity of Illness scale, CI = confidence interval, C_{ss} = steady state plasma concentration, CTCAE = Common Terminology Criteria for Adverse Events, DV = *O*-desmethylvenlafaxine, $HDRS_6$ = 6-item Hamilton Rating Scale for Depression, $HDRS_{17}$ = 17-item Hamilton Rating Scale for Depression, $HDRS_{21}$ = 21-item Hamilton Rating Scale for Depression, IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), MADRS = Montgomery-Asberg Depression Rating Scale, NM = normal metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), QIDS-C_{16} = 16-item Quick Inventory of Depressive Symptomatology Clinician-rated scale, S = significant, SD = standard deviation, SmPC = Summary of Product Characteristics, UM = ultra-rapid metaboliser (gene dose $\geq$ 2.75) (elevated CYP2D6 enzyme activity), V = venlafaxine

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:
Venlafaxine is mainly converted by CYP2D6 to the active metabolite O-desmethylvenlafaxine. Venlafaxine and O-desmethylvenlafaxine are primarily converted by CYP3A4 and CYP2C19 to inactive metabolites (N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine respectively).
The therapeutic range is reported to be 100-400 ng/ml for the sum of venlafaxine and O-desmethylvenlafaxine and values higher than 1000 ng/ml are considered to be toxic. However, Jiang 2015 indicates that it is difficult to establish venlafaxine therapy that is both effective and well tolerated in patients with low O-desmethylvenlafaxine/venlafaxine ratios (PM and IM). Accordingly, Ahmed 2019 (study with 10 PM or gene dose 0.25-0.5 and 7 UM) found an decreased depression remission rate in PM+gene dose 0.25-0.5 and an increased rate in UM, Lobello 2010 found a reduced effectiveness in depression patients with a low O-desmethylvenlafaxine/venlafaxine ratio, as occurs in PM, and Veefkind 2000 found that all 3 PMs in the study were non-responders. In addition, Shams 2006 found an increase in the number of side effects for PM, McAlpine 2007 reported 5 IM cases in which the treatment had to be stopped because of side effects, Lessard 1999 reported 4 PM with cardiac side effects, and Austin-Zimmerman 2021 showed venlafaxine to elevate HbA_{1c} level in diabetes patients more in PM (study with 15 diabetic PM). Although Brandl 2014 found a reduction in marked or severe side effects for PM+IM+UM, the study did not find an effect for PM versus IM versus (NM+gene dose 1/0) versus UM. Based on these data and despite a small meta-analysis and other studies not confirming an effect of CYP2D6 phenotype on response (Lin 2019, Scherf-Clavel 2022, Taranu 2017, Brandl 2014, Ng 2013, Van Nieuwerburgh 2009 and Shams 2006) or side effects (Lin 2019 and Ng 2013), the KNMP Pharmacogenetics Working Group decided that a gene-drug interaction is present and that therapy adjustments are required for PM and IM (yes/yes-interactions).
Clinical effects in UMs (total of 27 UMs) have only been examined in five studies (Ahmed 2019, Taranu 2017, Brandl 2014, Shams 2006 and Veefkind 2000). Of these five studies, only one found a significant effect on therapeutic effectiveness: Ahmed 2019, including 7 UM, found a higher depression remission rate in UM. Shams 2006 and Veefkind 2000 did not find an effect on adverse events. Brandl 2014 found a reduction in marked or severe side effects for PM+IM+UM, but did not find an effect for PM versus IM versus (NM+gene dose 1/0) versus UM. In addition, the weighted mean of the calculated decrease in venlafaxine + O-desmethylvenlafaxine exposure of 24% (range 23-41%) (based on the 31 UM from Kringen 2020, Shams 2006, and Veefkind 2000 for whom mean values were compared to NM) or 22% (range -48-41%) (after inclusion of the 2 UM from Ganesh 2021 for whom median values were compared to NM) is relatively low compared to the width of the therapeutic range. For these reasons, the KNMP Pharmacogenetics Working Group decided that a gene-drug interaction is present, but that therapy adjustment is not required for UM (yes/no-interaction).
Justification of recommended therapy adjustments
In general, the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine is used to determine whether the plasma concentration lies within the therapeutic range, but the side effects do not appear to be related to this sum. As it is not clear what the side effects are related to, it is not possible to calculate a dose reduction or dose increase in such a way that the risk of side effects for PM, IM and UM would be equal to that of the risk for NM.
In addition, results for PM appear to indicate that the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine is not a good measure of the effectiveness for depression. Indeed, Jiang 2015 indicates that it is diffi-

cult to establish venlafaxine therapy that is both effective and well tolerated in patients with low O-desmethylvenlafaxine/venlafaxine ratios.

PM: The study by Shams 2006 found an increase in the number of side effects without a difference in the sum concentration of venlafaxine and O-desmethylvenlafaxine. In other words, the side effects do not appear to be dependent on this sum concentration. In addition, Jiang 2015 found that O-desmethylvenlafaxine/venlafaxine > 4 showed high precision in predicting venlafaxine responders/partial-responders (92%) and patients without venlafaxine-related adverse events (88%), whereas PMs are characterised by much smaller ratios. Finally, Ahmed 2019 found a diminished depression remission rate in PM+gene dose 0.25-0.5 and Austin-Zimmerman 2021 showed venlafaxine to elevate HbA_{1c} level in diabetes patients more in PM.
It is therefore preferable to select an alternative that is not metabolised by CYP2D6, or to a lesser extent. If this really is impossible, the dose must be reduced if side effects occur and the effectiveness must be monitored. As side effects and effectiveness are both not related to the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine, it is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while effectiveness is maintained. Furthermore, there are indications that the effectiveness for depression is reduced in PM (Ahmed 2019, Veefkind 2000, and Lobello 2010).
Based on 132 PM from 5 studies for whom mean values were compared to NM, the weighted mean of the calculated dose adjustment for achieving the same AUC or Css of venlafaxine + O-desmethylvenlafaxine as for NM is a dose reduction to 77% of the normal dose (median 67%, range 58%-100%) (Kringen 2020, Waade 2014, Hermann 2008, Shams 2006, and Veefkind 2000). If also the 15 PM from Ghanesh 2021 for whom only median values were compared to NM are added to this calculation, the values are comparable: a weighted mean of 77% (median 73%, range 58%-100%). A dose reduction to less than 77% of the normal dose therefore increases the risk of ineffectiveness.

IM: Although venlafaxine is potentially cardiotoxic (see PM), no cardiotoxicity has been reported to date in IMs. For IM, the sum concentration of venlafaxine and O-desmethylvenlafaxine does not change at all, or only slightly. In contrast to the effectiveness, the side effects do not appear to be dependent on this sum concentration. In addition, Jiang 2015 found that O-desmethylvenlafaxine/venlafaxine > 4 showed high precision in predicting venlafaxine responders/partial-responders (92%) and patients without venlafaxine-related adverse events (88%), whereas IMs are characterised by smaller ratios.
It is therefore preferable to select an alternative that is not metabolised by CYP2D6, or to a lesser extent. If this really is impossible, the dose must be reduced if side effects occur and the effectiveness must be monitored. As side effects and effectiveness are both not related to the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine, it is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while effectiveness is maintained. Furthermore, there are indications that the effectiveness for depression is reduced in PM (Ahmed 2019, Veefkind 2000, and Lobello 2010).
Based on 475 IM from 8 studies for whom mean values were compared to NM, the weighted mean of the calculated dose adjustment for achieving the same AUC or C_{ss} of venlafaxine + O-desmethylvenlafaxine as for NM is a dose reduction to 93% of the normal dose (median 88%, range 67%-99%) (Kringen 2020, Waade 2014, Jiang 2015, Hermann 2008, Shams 2006, Fukuda 2000, Veefkind 2000, and Fukuda 1999). If also the 100 IM from Ghanesh 2021 for whom only median values were compared to NM are added to this calculation, the values are comparable: a weighted mean of 94% (median 88%, range 67%-99%). A dose reduction to less than 93% of the normal dose therefore increases the risk of ineffectiveness.

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

The clinical implication of the gene-drug interaction scores 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):

No severe clinical effects were observed in users of venlafaxine with a variant phenotype. The maximum severity code was C corresponding to CTCAE grade 2. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).

The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).

The Summary of Product Characteristics (SmPC) of venlafaxine mentions the CYP2D6 PM phenotype to influence the pharmacokinetics of venlafaxine. 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/phe-

notype mentioned in the SmPC, but not mentioned as a contra-indication in the corresponding section and no recommendation to genotype).

The table below follows the KNMP definition for NM, PM, IM and UM. 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
Scherf-Clavel M et al.
Effects of pharmacokinetic gene variation on therapeutic drug levels and antidepressant treatment response.
Pharmacopsychiatry
2022 Jul 15. Online ahead of print.
PMID: 35839823.</td>
<td>3</td>
<td>258 patients from two cohorts (130 and 128 patients from each of the cohorts) were treated with venlafaxine (final dose 25-525 mg/day (mean 280 mg/day)).
The cohort from which 130 patients were derived, included patients with at least a moderate depressive period (Hamilton Depression Rating Scale-21 ($HDRS_{21}$) > 14). Therapeutic drug monitoring was performed in week 3, 5, and 7 of treatment and used to adjust the dose. Patients were analysed after 7 weeks of treatment.
The other cohort included patients with unipolar depression. Therapeutic drug monitoring was performed according to the doctor’s choice and not per protocol and used to adjust the dose. Patients were analysed after 6 weeks of treatment.
49% of patients were responders (69% in the cohort from which the 130 patients were derived and 28% in the other cohort). Treatment response was defined as ≥ 50% reduction in $HDRS_{21}$-score. 30% of patients showed remission (43% in the cohort from which the 130 patients were derived and 16% in the other cohort).
Adverse drug reactions were assessed in the cohort from which 130 patients were derived (6 mild and 6 medium adverse drug reactions were observed), change of antidepressant due to adverse drug reactions was assessed in the other cohort (observed in 1 patient).
Clinical improvement was measured as the percentual reduction in the $HDRS_{21}$-score. Remission was defined as a $HDRS_{21}$-score ≤ 7.
Trough serum concentrations in steady state were determined. Dimensional outliers (≥ 4 SD from the mean) from (dose-corrected) serum concentrations and metabolic ratio O-desmethylvenlafaxine/venlafaxine were set as missing data.
Relevant comedication was not excluded, but dose-corrected concentrations, metabolic ratio, and clinical improvement were also determined in a post-hoc, explorative analysis excluding patients using CYP2D6 inhibitors. The authors do not indicate whether the difference in response and remission between the two cohorts is significant and do not correct for the cohort from which the patient was derived.
P-values were Bonferroni-corrected for the total number of genes (7) and the total number of drugs (4 for concentrations and 2 for metabolic ratios) investigated. As a result p ≤ 0.001 or p ≤ 0.002 was considered significant.

Genotyping:
The number of NM, IM, PM and UM+gene dose 2.5 is not mentioned.

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 2.5</td><td>value for NM</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘Serum concentration of amitriptyline was associated with CYP2D6 (higher concentrations in poor metabolizers compared to normal metabolizers), of venlafaxine with CYP2C19 (higher concentrations in intermediate metabolizers compared to rapid/ultrarapid metabolizers) and CYP2D6 (lower metabolite-to-parent ratio in poor compared to intermediate and normal metabolizers, and intermediate compared to normal and ultrarapid metabolizers). Pk gene variation did not affect treatment response.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td>PM: A
IM: A

UM: A</td>
<td>
<table>
<tr><td>clinical improvement (percentual reduction in $HDRS_{21}$ score)</td><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.5
Similar results were obtained after exclusion of patients using CYP2D6 inhibitors.</td><td></td></tr>
<tr><td>% of patients with remission</td><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.5</td><td></td></tr>
<tr><td>dose-corrected concentration of venlafaxine + O-desmethyl-venlafaxine</td><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.5

(The association was S before Bonferroni-correction.)
Similar results were obtained after exclusion of patients using CYP2D6 inhibitors.</td><td></td></tr>
<tr><td>metabolic ratio O-desmethyl-venlafaxine/ venlafaxine</td><td>x 0.08 (S)</td><td>x 0.39 (S)</td><td>x 1.73 (NS)</td><td>5.32</td></tr>
<tr><td></td><td colspan="3">S for PM versus IM versus NM versus UM+gene dose 2.5
Similar results were obtained after exclusion of patients using CYP2D6 inhibitors.</td><td></td></tr>
</table>
Note: Genotyping was for *2 through *6, *9, *10, *41, and gene multiplication. These are the most important gene variants in this German population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Austin-Zimmerman I et al.
The influence of CYP2D6 and CYP-2C19 genetic variation on diabetes mellitus risk in people taking antidepressants and antipsychotics.
Genes (Basel) 2021;12:1758.
PMID: 34828364.</td>
<td>3

PM: B</td>
<td>
Data from a biobank on 1885 unrelated patients treated with venlafaxine, among whom 182 with diabetes, were analysed.
Diabetes was defined as a self-reported diagnosis of diabetes or self-reported use of antidiabetic medication.
Comedication with CYP2D6 inhibitors was not excluded, but adjusted for in the linear regression analyses. However, the outcome of the study (HbA_{1c} level) is suboptimal. Although antidepressants, like venlafaxine, have been associated with increase in body weight, they have not been associated with increase in HbA_{1c} level. Besides, HbA_{1c} levels in patients with diabetes are highly dependent on the antidiabetic drug treatment.
P-values were Bonferroni-corrected for the total number of drugs investigated separately (6). As a result $p \leq 0.0083$ was considered significant.
The linear regression analyses adjusted for antidiabetic medication use, CYP2D6 inhibitor use, BMI, sex, age, genetically determined ancestry group, and unless stratified based on diabetes status, for diabetes status.

Genotyping:
all patients:
- 1352x NM + gene dose 0.75-1
- 430x IM
- 103x PM
diabetic patients:
- 135x NM + gene dose 0.75-1
- 32x IM
- 15x PM

Results:
<table>
<tr><td colspan="4">Difference in HbA_{1c} level (in mmol/mol) compared to NM:</td></tr>
<tr><td>patients</td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>all</td><td>NS</td><td>NS</td><td>38</td></tr>
<tr><td>diabetic</td><td>+10.15 (95% CI:</td><td>NS</td><td>43</td></tr>
</table>
</td>
<td>Author’s conclusion:
‘Among participants with diabetes who were taking venlafaxine, CYP2D6 poor metabolizers had higher HbA1c levels compared to normal metabolizers (mean differences: 10.15 mmol/mol; $p < 0.001$).’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>IM: AA</td>
<td>
<table>
<tr><td></td><td>2.63-17.67 (S)</td><td></td><td></td></tr>
<tr><td>non-diabetic</td><td>NS</td><td>NS</td><td>36</td></tr>
<tr><td colspan="4">The analysis was stratified by whether participants had diabetes or not, because the interaction of diabetes status and CYP2D6 phenotype was consistently found to be statistically significant (diabetes: IM: difference 3.62 (95% CI: 1.27-5.98) (S) and diabetes: PM: difference 11.44 (95% CI: 8.05-14.84) (S)).</td></tr>
<tr><td colspan="4">Diabetes and CYP2D6 phenotype explained 52% of the variation in HbA_{1c} level. CYP2D6 phenotype explained 23% of the variation in HbA_{1c} level in diabetic patients.</td></tr>
</table>

Note: Genotyping was by Affymetrix arrays, investigating a large range of gene variants. Apart from *5 and gene duplication, these arrays determine the most important gene variants in this population from the UK. Gene variants *3, *4, *9, *10, *29, and *41 were found in this population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Ganesh SV et al. Therapeutic drug monitoring of psychotropics as a diagnostic tool for CYP2D6 poor metabolizer phenotype. Ther Drug Monit 2021;43:672-80. PMID: 33560096.</td>
<td>3

PM: A
IM: A
UM: AA</td>
<td>Data of 189 patients treated with venlafaxine extended-release (median venlafaxine daily dose 131 mg) were analysed. The patient group was enriched for patients with the CYP2D6 PM phenotype. Routine therapeutic drug monitoring of trough serum concentrations was performed. The mean number of concentration measurements per patient was 2.4. Means were calculated when multiple values were known for one patient. Serum concentrations below the detection level of the analytical test were converted to the lower limit of detection of the test.
Comedication that strongly interfered with CYP2D6 or CYP-3A4 during or less than 7 days before blood sampling was excluded, but comedication with weak inhibitors and inducers was not. PM did not differ in age, creatinine concentration (kidney function), sex and daily dose from non-PM.
P-values were adjusted for multiple testing using the Benjamini and Hochberg (FDR) method.

Genotyping:
- 72x NM
- 100x IM
- 15x PM
- 2x 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>median dose-corrected serum concentration of venlafaxine + O-desmethylvenlafaxine</td><td>x 1.26 (NS)</td><td>x 1.06 (NS)</td><td>x 1.48 (NS)</td><td>2.08 µg/L per mg/day</td></tr>
<tr><td>median dose-corrected serum concentration of venlafaxine</td><td>x 4.53 (S)</td><td>x 1.79 (S)</td><td>x 0.54 (NS)</td><td>0.44 µg/L per mg/day</td></tr>
<tr><td>ratio O-desmethylvenlafaxine/venlafaxine</td><td>x 0.07 (S)</td><td>x 0.48 (S)</td><td>x 2.86 (NS)</td><td>4.1</td></tr>
</table>

Note: Genotyping was for *3 through *6, *9, *10, *41, and</td>
<td>Authors' conclusion: 'Although the metabolic ratio (MR), dose-corrected serum concentration of substrate (CDR), and dose-corrected sum concentration of substrate and metabolite (Sum CDR) all predicted the CYP2D6 PM phenotype, the predictive value of the MR was most robust for venlafaxine and aripiprazole, and the Sum CDR was inferior for all 3 psychotropics.'

median dose-corrected serum concentration of venlafaxine + O-desmethylvenlafaxine versus NM:
PM: 126%
IM: 106%
UM: 148%</td>
</tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td></td><td>gene duplication. These are the most important gene variants in this Dutch population.</td><td></td></tr>
<tr><td>ref. 4
Kringen MK et al.
The influence of combined CYP2D6 and CYP2C19 genotypes on venlafaxine and O-desmethylvenlafaxine concentrations in a large patient cohort.
J Clin Psychopharmacol
2020;40:137-44.
PMID: 32134850.</td><td>3

PM: A
IM: A
UM: A</td><td>Data of 1000 patients treated with venlafaxine were analysed. The median venlafaxine dose was 150 mg/day (range: 75-225 mg/day). Therapeutic drug monitoring of trough serum concentrations was performed in steady state. For patients with more than one serum concentration measurement, the last measurement was included.
Comedication with potent CYP2D6 and CYP2C19 enzyme inhibitors (bupropion, fluoxetine, levomepromazine, or paroxetine) or CYP3A4 inducers (carbamazepine, phenobarbital, or phenytoin) was excluded, but comedication with weak CYP2D6 inhibitors was not. Serum concentrations of venlafaxine or O-desmethylvenlafaxine below lower limit of quantification were excluded, as were measurements with information on the requisition forms indicating suspected noncompliance.
Multivariate regression models adjusted for age (> 65 years), sex, and time between last dose intake and blood sampling.

Genotyping:
- 547x NM
- 336x IM
- 94x PM
- 23x UM

Results:
Dose-corrected serum concentrations, adjusted for age (> 65 years), sex, and time between last dose intake and blood sampling, compared to NM (significance not determined):
<table>
<tr><td></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM (in µg/L per mg/day)</td></tr>
<tr><td>venlafaxine + O-desmethylvenlafaxine</td><td>x 1.25 (NS)</td><td>x 1.03 (NS)</td><td>x 0.77 (NS)</td><td>2.22</td></tr>
<tr><td>venlafaxine</td><td>x 3.24 (NS)</td><td>x 1.49 (NS)</td><td>x 0.68 (NS)</td><td>0.67</td></tr>
<tr><td>O-desmethyl-venlafaxine</td><td>x 0.42 (NS)</td><td>x 0.84 (NS)</td><td>x 0.81 (NS)</td><td>1.51</td></tr>
</table>
Multivariate regression models showed that CYP2D6 phenotype explained 24% of the variation in dose-adjusted venlafaxine serum concentration, 13% of the variation in dose-adjusted O-desmethylvenlafaxine serum concentration, and 2% of the variation in dose-adjusted venlafaxine + O-desmethylvenlafaxine serum concentration (S).

Note: Genotyping was for *3 through *6, *9, *10, *41, and gene multiplication. These are the most important gene variants in this Norwegian population.
All the variant alleles were in Hardy-Weinberg equilibrium, except *4 and *10. This and the overrepresentation of PM in the patient group is probably caused by the selection toward cases with therapeutic problems and a PM phenotype.</td><td>Authors' conclusion: 'CYP2D6 and CYP-2C19 phenotypes explained 24% and 11% of the interindividual variability in dose-adjusted venlafaxine serum concentrations, respectively, and 2% and 8% of dose-adjusted sum concentrations of venlafaxine + DV.'

Dose-corrected serum concentration of venlafaxine + O-desmethylvenlafaxine, adjusted for age (> 65 years), sex, and time between last dose intake and blood sampling, versus NM:
PM: 125%
IM: 103%
UM: 77%</td></tr>
<tr><td>ref. 5
Lin XQ et al.
The associations between CYP2D6 metabolizer status</td><td>3</td><td>Meta-analyses of the effect of CYP2D6 phenotype on effectiveness and adverse events. One of the included studies (Lobello 2010) used phenotyping of PM instead of genotyping (by determining the O-desmethylvenlafaxine/venlafaxine concentration ratio). This study had detailed descrip-</td><td>Authors' conclusion: 'CYP2D6 metabolizer status had significant influence on venlafaxine pharma-</td></tr>
</table>

<table>
<tr>
<td>and pharmacokinetics and clinical outcomes of venlafaxine: a systematic review and meta-analysis. Pharmacopsychiatry 2019;52:222-31. PMID: 30485867.

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

IM: AA</td>
<td>tions for 5 of the 10 items in the checklist for quality assessment derived from the Strengthening the Reporting of Genetic Association recommendations for reports on genetic association studies. For the other 8 included studies, this varied from 7 to 9 of the 10 items.
4 studies with a total of 81 PM and 634 non-PM investigated response (measured as ≥ 50% decrease in the Hamilton Depression Rating Scale-17 ($HDRS_{17}$) score in 3 studies and as ≥ 35% decrease in the Yale-Brown Obsessive Compulsive Scale (YBOCS) score in 1 study). 2 studies with a total of 30 IM+PM and 59 NM+UM investigated the decrease in the Hamilton Depression Rating Scale-17 ($HDRS_{17}$) score.
4 studies with a total of 69 PM and 443 non-PM investigated adverse events. 1 of these was a patient study and 3 were studies in healthy volunteers.
All 4 studies investigating response (Taranu 2017, Lobello 2010, Van Nieuwerburgh 2009, and Veefkind 2000) and both studies investigating decrease in $HDRS_{17}$ score (Ng 2013 and Whyte 2006) were also included in this risk analysis separately. Of the 4 studies investigating adverse events, 2 were also included in this risk analysis separately (Lobello 2010 and Preskorn 2009).
Meta-analyses were performed with a fixed-effects model in case of low heterogeneity between the studies and with a random-effects model in case of high heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised. Publication bias analysis was not performed.

Results:
<table>
<tr><td colspan="3">Results for PM compared to non-PM:</td></tr>
<tr><td></td><td></td><td>value for NM</td></tr>
<tr><td rowspan="2">% of patients with response</td><td>NS</td><td rowspan="2">54%</td></tr>
<tr><td>There was also no difference in the absolute reduction in the $HDRS_{17}$ score for IM+PM compared to NM+UM (NS) (value for NM+UM 10.9).</td></tr>
<tr><td>% of patients or volunteers with adverse events</td><td>NS</td><td>92%</td></tr>
<tr><td colspan="3">Heterogeneity between the studies was low and not-significant for response (high and not-significant if only the 3 studies defining response based on $HDRS_{17}$ were compared).
Heterogeneity between the studies was absent and not-significant for:
- absolute reduction in the $HDRS_{17}$ score
- adverse events</td></tr>
</table>
</td>
<td>cokinetics, but insufficient evidence demonstrated that CYP2D6 metabolizer status was associated with its therapeutic effects and overall rate of adverse events, which provided further evidence regarding the relationship between CYP2D6 metabolizer status and venlafaxine.’</td>
</tr>
<tr>
<td>ref. 6
Ahmed AT et al. Pharmacokinetic-pharmacodynamic interaction associated with venlafaxine-XR remission in patients with major depressive disorder</td>
<td>3</td>
<td>80 patients, in whom citalopram previously failed, were treated with venlafaxine extended-release for a period of 8 weeks. Venlafaxine dose was titrated and maximum dose was reached at week 8. 4 additional patients discontinued venlafaxine prematurely because of ineffectiveness or adverse events.
Remission was defined as a 16-item Quick Inventory of Depressive Symptomatology Clinician-rated (QIDS-C_{16}) score ≤ 5. The maximum score on the QIDS-C_{16} is 27.</td>
<td>Authors’ conclusion: ‘Our results suggest that CYP2D6 ultra-rapid metabolizer status contributes to venlafaxine-XR treatment remission in major depressive disorder patients.’</td>
</tr>
</table>

<table>
<tr>
<td>with history of citalopram / escitalopram treatment failure.
J Affect Disord 2019;246:62-8.
PMID: 30578947.

ref. 6, continuation</td>
<td>PM+IM: C
UM: AA#</td>
<td>Significance was determined with a linear regression model and OR was calculated assuming a linear effect for PM versus NM+IM versus UM.
It is not mentioned whether relevant comedication is excluded.

Genotyping:
- 63x NM+gene dose 1
- 10x PM+gene dose 0.25-0.5
- 7x UM

Results:
<table>
<tr><td colspan="4">Results compared to NM+gene dose 1:</td></tr>
<tr><td></td><td>PM+gene dose 0.25-0.5</td><td>UM</td><td>value for NM+ gene dose 1</td></tr>
<tr><td rowspan="3">% of patients with remission</td><td>x 0.29</td><td>x 2.0</td><td rowspan="3">35%</td></tr>
<tr><td colspan="2">S for PM+gene dose 0.25-0.5 versus NM+gene dose 1 versus UM</td></tr>
<tr><td colspan="2">OR = 4.7 (S) for PM+gene dose 0.25-0.5 versus NM+gene dose 1 versus UM</td></tr>
<tr><td colspan="4">Including the 4 additional patients, who discontinued venlafaxine prematurely because of ineffectiveness or adverse events, did not change the significance.</td></tr>
</table>
Note: Genotyping was for *2A, *3 through *6, *9, *10, *17, *41, and gene duplication, These are the most important gene variants in this White population.</td>
<td></td>
</tr>
<tr>
<td>ref. 7
Watanabe Y et al. Factors impacting the efficacy of venlafaxine extended release 75-225 mg/day in patients with major depressive disorder: exploratory post hoc subgroup analyses of a randomized, double-blind, placebo-controlled study in Japan. Neuropsychiatr Dis Treat 2018;14:1261-72. PubMed PMID: 29844674.</td>
<td>3</td>
<td>300 patients with major depressive disorder treated with venlafaxine for 8 weeks were compared with 159 patients treated with placebo. 152 patients were treated with a maximum venlafaxine dose of 75 mg/day, 148 with a maximum dose of 225 mg/day. Initial venlafaxine dose was 37.5 mg/day. In week 1, the dose could be increased to 75 mg/day, and in week 2, based on tolerability, it could be increased to 150 mg/day in the high dose group. If a dose of 150 mg/day was tolerated, the dose was titrated to 225 mg/day in the high dose group in week 3, in spite of an acceptable response at a lower dose. Dose reduction was allowed in case of intolerance at higher doses.
Response was determined as the change in the scores on the 17 items Hamilton Depression Rating Scale ($HDRS_{17}$), the $HDRS_6$ (consisting of $HDRS_{17}$ items 1, 2, 7, 8, 10 and 13) and the Montgomery Åsberg Depression Rating Scale (MADRS). Differences from placebo were calculated.
Patients receiving at least one dose of the study drug and having $HDRS_{17}$ determined at baseline and at least once after baseline were included in the analyses.
Relevant co-medication was not excluded.

Genotyping:
maximum of 75 mg/day - 102x NM+UM - 50x ‘PM+IM’
maximum of 225 mg/day - 108x NM+UM - 40x ‘PM+IM’
placebo - 107x NM+UM - 52x ‘PM+IM’

Results:
<table>
<tr><td>Response compared to placebo:</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘There were no consistent trends in the subgroup of patients with the two CYP2D6 phenotypes.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 7, continuation</td>
<td>NM+IM: AA</td>
<td>
<table>
<tr><td>rating scale</td><td>maximum dose</td><td>‘PM+IM’</td><td>NM+UM</td></tr>
<tr><td>HDRS$_{17}$</td><td>75 mg/day</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td>225 mg/day</td><td>NS</td><td>NS</td></tr>
<tr><td>HDRS$_{6}$</td><td>75 mg/day</td><td>trend for a higher response (NS)</td><td>trend for a higher response (NS)</td></tr>
<tr><td></td><td>225 mg/day</td><td>trend for a higher response (NS)</td><td>higher response (S)</td></tr>
<tr><td></td><td colspan="3">The significance of the difference between ‘PM+IM’ and NM+UM was not investigated, but the large overlap of the 95% confidence intervals indicate these differences to be unlikely to be significant (NS).</td></tr>
<tr><td>MADRS</td><td>75 mg/day</td><td>NS</td><td>higher response (S)</td></tr>
<tr><td></td><td>225 mg/day</td><td>NS</td><td>higher response (S)</td></tr>
<tr><td></td><td colspan="3">The significance of the difference between ‘PM+IM’ and NM+UM was not investigated, but the large overlap of the 95% confidence intervals indicate these differences to be unlikely to be significant (NS). In addition, for the maximum dose of 225 mg/day, the calculated response was the same for ‘PM+IM’ as for NM+UM. Only the 95% confidence interval was wider for ‘PM+IM’ than for NM+UM.</td></tr>
</table>

Note: Neither the gene variants determined nor the phenotype definition is indicated in the publication. Because *10 is the most prevalent allele in this Japanese population, ‘IM+PM’ is most probably *1/*10+*10/*10, and thus NM+IM instead of IM+PM.
</td>
<td></td>
</tr>
<tr>
<td>ref. 8
Taranu A et al. Should a routine genotyping of CYP-2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? Pharmacogenomics 2017;18:639-50. PubMed PMID: 28480819.</td>
<td>3</td>
<td>184 patients with a unipolar major depressive episode in the context of major depressive disorder were treated with venlafaxine for 6 months. The mean starting dose was 111.5 mg/day. Dosing was adapted by the psychiatrists, who were not aware of the CYP2D6 genotypes of the patients. The drop-out rate was high with 148 patients completing 1 month, 107 patients 3 months and 83 patients 6 months. Efficacy was determined as the change in the scores on the 17 items Hamilton Depression Rating Scale (HDRS$_{17}$) and as response and remission rates. Response was defined as a decrease in the HDRS$_{17}$ score of at least 50%. Remission was defined as a HDRS$_{17}$ score of 7 or less. The HDRS$_{17}$ score was ≥ 18 before treatment with a mean of 25.23. Co-medication with other antidepressants and with antipsychotics or mood stabilizers was excluded, but co-medication with effect on CYP2D6 was not.
The percentage of female patients differed significantly between the different phenotypes (50% for PM, 68.6% for IM, 64% for NM and 100% for UM).

Genotyping:
<table>
<tr><td>1 month:</td><td>3 months:</td><td>6 months:</td></tr>
<tr><td>- 90x NM+IM (gene dose 0.25/0.25 or 1-2.5)</td><td>- 69x NM+IM (gene dose 0.25/0.25 or 1-2.5)</td><td>- 52x NM+IM (gene dose 0.25/0.25 or 1-2.5)</td></tr>
<tr><td>- 43x IM (gene dose 0.5/0 or</td><td>- 29x IM (gene dose 0.5/0 or</td><td>- 24x IM (gene dose 0.5/0 or</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘CYP2D6 and CYP-2C19 phenotypes were associated neither with the Hamilton depression rating scale score improvement, nor with response and remission.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td>PM: AA
IM: AA
UM: AA</td>
<td>
0.25)
- 7x PM
- 8x UM

0.25)
- 4x PM
- 5x UM

0.25)
- 4x PM
- 3x UM

Results:
<table>
<tr><td colspan="6">Efficacy for the different phenotypes:</td></tr>
<tr><td colspan="2"></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM+ IM</td></tr>
<tr><td rowspan="6">% improvement in $HDRS_{17}$ score</td><td rowspan="3">1 month</td><td colspan="3">trend for an increase for PM versus IM versus NM+IM versus UM (p = 0.07) (NS)</td><td rowspan="3">46%</td></tr>
<tr><td colspan="3">There was a trend for a decrease for UM versus NM+IM (p = 0.07) (NS).</td></tr>
<tr><td rowspan="4">3 months</td><td colspan="3">increase for PM versus IM versus NM+IM versus UM (S)</td><td rowspan="4">51%</td></tr>
<tr><td colspan="3">There was a decrease for UM versus NM+ IM+PM (S).</td></tr>
<tr><td colspan="3">Significance was lost after controlling for sex in multivariate analysis (NS).</td></tr>
<tr><td>6 months</td><td colspan="3">NS for PM versus IM versus NM+IM versus UM</td><td>59%</td></tr>
<tr><td rowspan="3">% responders</td><td>1 month</td><td colspan="3">NS</td><td>40%</td></tr>
<tr><td rowspan="2">3 months</td><td colspan="3">trend for an increase for PM versus IM versus NM+IM versus UM (p = 0.05) (NS)</td><td rowspan="2">51%</td></tr>
<tr><td colspan="3">There was a trend for a decrease for UM versus NM+IM, IM and PM (p = 0.05) (NS).</td></tr>
<tr><td>6 months</td><td colspan="3">NS</td><td>73%</td></tr>
<tr><td rowspan="3">% remitters</td><td>1 month</td><td colspan="3">NS</td><td>19%</td></tr>
<tr><td>3 months</td><td colspan="3">NS</td><td>25%</td></tr>
<tr><td>6 months</td><td colspan="3">S for PM versus IM versus NM+IM versus UM, with PM and UM having high values and IM and NM+IM having low values

Repeated measures multivariate analysis of variance failed to show an association between the CYP2D6 phenotype and the $HDRS_{17}$ score improvement for these patients (NS).</td><td>44%</td></tr>
<tr><td rowspan="3">venlafaxine dose (in mg/day)</td><td>1 month</td><td colspan="3">NS</td><td>163.2</td></tr>
<tr><td>3 months</td><td colspan="3">NS</td><td>187.8</td></tr>
<tr><td>6 months</td><td colspan="3">NS</td><td>183.9</td></tr>
<tr><td>% of</td><td>0-1 month</td><td colspan="3">NS</td><td>21%</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td></td>
<td>
<table>
<tr><td rowspan="2">patients that dropped out</td><td>1-3 months</td><td>NS</td><td>23%</td></tr>
<tr><td>3-6 months</td><td>NS</td><td>25%</td></tr>
</table>

Note: Genotyping was for *3 through *6, *10, *41 and gene duplication. These are the most important gene variants in this French population.

Note: The authors report a very high frequency of gene dose 0.5/0 or 0.25. In addition, they report the frequency of *10 to be higher than the frequency of *4 in this population. This might indicate that they classified patients heterozygous for both the *4- and *10-defining polymorphisms to be *4/*10 (gene dose 0.25) instead of *1/*4 (gene dose 1). The latter would be the right classification, because the *4-allele always contains both polymorphisms. Thus, the IM group in this study might contain both gene dose 1 and gene dose 0.25. Both are IM according to the KNMP definition.
</td>
<td></td>
</tr>
<tr>
<td>ref. 9
Berm E et al.
Relation between CYP2D6 genotype, phenotype and therapeutic drug concentrations among nortriptyline and venlafaxine users in old age psychiatry.
Pharmacopsychiatry 2016;49:186-190.
PubMed PMID: 27101231

and personal communication (correction: total number of patients with sub- and supra-therapeutic plasma-concentrations after 3 weeks were switched in table 3, and total number of patients with TDM after 3 weeks was 37)</td>
<td>3

PM: AA
IM: AA</td>
<td>37 patients with major depressive disorder, aged 60 years or older with a mean age of 72 years, were treated with venlafaxine. Dosing was adapted based on clinical efficacy. Therapeutic drug monitoring was performed 3, 5 and 12 weeks after start of venlafaxine (in respectively 37, 35 and 27 patients). The reason for patients not completing therapeutic drug monitoring was loss to follow-up.
Co-medication with psychotropic drugs was restricted to oxazepam, temazepam, haloperidol or risperidone, but somatic medication with effect on CYP2D6 was not excluded.

Genotyping:
- 17x NM
- 17x IM
- 3x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td colspan="2"></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="3">% of patients with a suprathe-rapeutic plasma concentration (venlafaxine + O-desmethylvenla-faxine > 400 ng/ml)</td><td>3 weeks</td><td colspan="2">NS for PM versus IM versus NM</td><td>0%</td></tr>
<tr><td>5 weeks</td><td colspan="2">NS for PM versus IM versus NM</td><td>35%</td></tr>
<tr><td>12 weeks</td><td colspan="2">NS for PM versus IM versus NM</td><td>55%</td></tr>
</table>

Note: Genotyping was for *3 and *4. Next to *5 and gene multiplication, these are the most important gene variants in this Dutch population.
</td>
<td>Authors' conclusion: 'Genotype information could be used as a valuable tool, in addition to therapeutic drug monitoring, to prevent suprathe-rapeutic drug levels of nortriptyline or venlafaxine in elderly patients with a PM genotype.'</td>
</tr>
<tr>
<td>ref. 10
Jiang F et al.
The influences of CYP2D6 genotypes and drug interactions on the pharmacokinetics of venlafaxine: exploring predictive biomarkers for treatment</td>
<td>3</td>
<td>24 healthy volunteers selected for their CYP2D6 genotype received a single dose of venlafaxine extended release 75 mg, either with or without a CYP3A4 inhibitor (clarithromycin 250 mg twice per day) or a CYP3A4 and CYP2D6 inhibitor (clarithromycin 250 mg twice per day + paroxetine 10 mg once per day) starting 6 days before venlafaxine dosing. Use of co-medication, nutritional supplements, tobacco, alcohol, caffeine and grapefruit juice was excluded.
It was calculated that a minimum of ten individuals would be required to demonstrate a 30% difference in venlafaxine</td>
<td>Authors' conclusion: 'Significant venlafaxine pharmacokinetic variations were observed between the NM and IM groups (geometric mean ratio of area under the curve, 3.0).'</td>
</tr>
</table>

<table>
<tr>
<td>outcomes.
Psychopharmacology (Berl) 2015;232:1899-909.
PubMed PMID: 25510856.

ref. 10, continuation</td>
<td>IM: A</td>
<td>area under the curve (AUC) at a level of significance of p = 0.05 and power of 80%.

Genotyping:
- 12x NM (*1/*1 or *1/*2)
- 12x IM (*10/*10)

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>pre-treatment</td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="3">AUC of venlafaxine + O-desmethylvenlafaxine</td><td>-</td><td>x 1.50 (S)</td><td>2184.9 ng.h/ml</td></tr>
<tr><td>CYP3A4 inhibitor</td><td>x 1.81 (S)</td><td>2129.6 ng.h/ml</td></tr>
<tr><td>CYP3A4 + 2D6 inhib.</td><td>X 1.63 (NS)</td><td>3248.3 ng.h/ml</td></tr>
<tr><td rowspan="3">AUC ratio O-desmethylvenlafaxine/venlafaxine</td><td>-</td><td>x 0.20 (S)</td><td>4.5</td></tr>
<tr><td>CYP3A4 inhibitor</td><td>x 0.18 (S)</td><td>3.9</td></tr>
<tr><td>CYP3A4 + 2D6 inhib.</td><td>X 0.44 (S)</td><td>0.9</td></tr>
</table>

Note: The authors analysed the relationship between venlafaxine+O-desmethylvenlafaxine and O-desmethylvenlafaxine/venlafaxine with treatment outcomes in two previous patient studies (29 patients from Veefkind 2000 and a study with 83 adolescents treated with venlafaxine monotherapy for at least 12 weeks). Because plasma sampling times were at different time points after dosing in the latter study, venlafaxine+O-desmethylvenlafaxine could not be determined in this study. In the patient studies, O-desmethylvenlafaxine/ venlafaxine > 4 showed high precision in predicting venlafaxine responders/partial-responders (92%) and patients without venlafaxine-related adverse events (88%). The O-desmethylvenlafaxine/venlafaxine < 4 and venlafaxine+O-desmethylvenlafaxine > 400 ng/ml combination showed higher precision (100%) than O-desmethylvenlafaxine/venlafaxine < 4 alone (65%) in predicting venlafaxine non-responders.

Note: Genotyping was for *1, *2, *5, *10 and gene duplication. These are the most important gene variants in this Korean population. Only patients with two fully functional alleles or two *10 alleles were selected.</td>
<td>AUC venlafaxine+O-desmethylvenlafaxine versus NM:
IM: 150%</td>
</tr>
<tr>
<td>ref. 11
Waade RB et al. Impact of age on serum concentrations of venlafaxine and escitalopram in different CYP2D6 and CYP2C19 genotype subgroups.
Eur J Clin Pharmacol 2014;70:933-40.
PubMed PMID: 24858822.</td>
<td>4</td>
<td>255 patients were treated with venlafaxine 18.75-900 mg per day. 462 routine therapeutic drug monitoring samples obtained 10-26 hours after dosing from patients using the same venlafaxine dose for at least 3 days were available. Samples with drug concentrations below the lower limit of quantification were excluded, as were patients carrying multiplications of functional CYP2D6 alleles.
Co-medication with CYP2D6 and CYP3A4 inhibitors and inducers was excluded.
Median sampling time was significantly shorter after dosing in the PM aged > 65 years than in the other subgroups (12 hours (range 12-15 hours) versus 21-24 hours (range 10-26 hours)), but statistically significant covariates were included in the multivariate mixed model analyses.

Genotyping:
- 142x NM (68x < 40 years, 55x 40-65 years, 19x > 65 years of age)</td>
<td>Authors’ conclusion: ‘This study suggests that the effect of age on serum concentration of venlafaxine is dependent on CYP genotype. Thus, to prevent potential side effects, it might be particularly relevant to consider CYP2D6 genotyping prior to initiation of venlafaxine treatment in older patients.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 11, continuation</td>
<td>PM: AA
IM: AA</td>
<td>
- 87x IM (28x < 40 years, 39x 40-65 years, 20x > 65 years of age)
- 26x PM (8x < 40 years, 15x 40-65 years, 3x > 65 years of age)

Results:
<table>
<tr><td colspan="5">Results compared to NM (NS: significance not determined):</td></tr>
<tr><td colspan="2"></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="4">dose-corrected plasma concentration of venlafaxine + O-desmethylvenlafaxine (in nmol/L per mg/day)</td><td>all ages</td><td>x 1.49</td><td>x 1.13</td><td>5.4</td></tr>
<tr><td>< 40 years</td><td>x 0.76</td><td>x 1.04</td><td>5.1</td></tr>
<tr><td>40-65 years</td><td>x 1.60</td><td>x 1.14</td><td>5.0</td></tr>
<tr><td>> 65 years</td><td>x 2.49</td><td>x 1.04</td><td>7.9</td></tr>
<tr><td rowspan="4">ratio venlafaxine/O-desmethylvenlafaxine</td><td>all ages</td><td>x 23</td><td>x 1.7</td><td>0.3</td></tr>
<tr><td>< 40 years</td><td>x 4.8</td><td>x 1.3</td><td>0.4</td></tr>
<tr><td>40-65 years</td><td>x 19</td><td>x 2.0</td><td>0.3</td></tr>
<tr><td>> 65 years</td><td>x 163</td><td>x 3.0</td><td>0.2</td></tr>
<tr><td colspan="5">The percentage of PM patients with a supratherapeutic plasma concentration of venlafaxine + O-desmethylvenlafaxine (> 1500 nmol/L) was numerically but not statistically higher for > 65 year (100%) than for < 40 years (25%) (NS) and for 40-65 years (40%) (NS).</td></tr>
<tr><td colspan="5">There were no significant differences in venlafaxine dose between the different groups (NS).</td></tr>
</table>
Note: Genotyping was for *3 through *6. These are the most important gene variants in this Norwegian population. Patients with multiplication of functional alleles were excluded from the study.
</td>
<td>Dose-corrected plasma concentration venlafaxine+O-desmethylvenlafaxine versus NM:
PM: 149%
IM: 113%</td>
</tr>
<tr>
<td>ref. 12
Brandl EJ et al. Influence of CYP-2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. Pharmacogenomics J 2014;14:176-81. PubMed PMID: 23545896.</td>
<td>3</td>
<td>
53 patients with obsessive-compulsive disorder were treated with venlafaxine at a dose of 225 mg/day or higher for more than 10 weeks. Response and side effects were assessed by patient interviews some time after treatment discontinuation. Response was measured using an OCD-adjusted CGI Improvement scale. Patients who showed a minimal improvement on this scale were included in the group of the non-responders. Patients with mild side effects were included in the group without significant side effects. Co-medication was not excluded.

Genotyping:
- 40x NM+gene dose 1/0
- 8x IM (gene dose 0.25-0.75 and gene dose 0.5/0.5)
- 1x PM
- 4x UM

Results:
<table>
<tr><td colspan="2">PM versus IM versus (NM+gene dose 1/0) versus UM:</td></tr>
<tr><td rowspan="3">treatment response</td><td>NS</td></tr>
<tr><td>There was also no difference for IM+PM+UM compared to NM+gene dose 1/0 (NS).</td></tr>
<tr><td>There was also no difference for (gene dose 0) versus (gene dose 0.5/0 or 0.25) versus (gene dose 0.25/0.25 or 0.75-1)</td></tr>
</table>
</td>
<td>Authors' conclusion: "CYP2D6 metabolizer status was associated with side effects to venlafaxine."</td>
</tr>
</table>

<table>
<tr><td>ref. 12, continuation</td><td>PM+IM+UM: AA#</td><td>
<table>
<tr><td></td><td>versus (gene dose 1.25-1.5) versus (gene dose 2) versus (gene dose 2.25-2.5) versus (gene dose ≥ 3) (NS).</td></tr>
<tr><td></td><td>There was also no difference between the gene doses after taken into account that venlafaxine is a weak CYP2D6 inhibitor by correcting the gene doses with the following inhibitor factors: 0.5 for gene dose > 1.75, 0.75 for gene dose 0.5-1.5 and 1 for gene dose 0 (NS).
Note: In calculating the gene dose to be corrected, *10 was considered to have gene dose 0.5 instead of 0.25.</td></tr>
<tr><td>marked or severe side effects</td><td>NS</td></tr>
<tr><td></td><td>The percentage of IM+PM+UM with marked or severe side effects was 0.38x the percentage of (NM+gene dose 1/0) with marked or severe side effects (S).
The percentages of patients with marked or severe side effects were 0%, 25%, 60% and 25% for PM, IM, NM+gene dose 1/0, and UM, respectively.
The authors indicate, that due to the relatively small sample size of 53 venlafaxine treated patients and small group sizes in the PM, IM and UM groups, no final conclusions can be drawn from this observation.</td></tr>
</table>
NOTE: Genotyping was for *3, *4, *5, *10, *17, *41 and gene multiplication. These are the most important gene variants in this Canadian population.
</td><td></td></tr>
<tr><td>Ref. 13
Ng C et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Hum Psychopharmacol 2013;28:516-22. PubMed PMID: 24014145.</td><td>3

PM+IM: AA</td><td>44 patients with major depressive disorder were treated with venlafaxine 37.5-375 mg/day for 8 weeks. Venlafaxine dose was 75 mg/day during the first week and adjusted on the basis of treatment response and side effects thereafter. The mean dose at endpoint was 155.9 mg/day. Response was measured using the Hamilton Rating Scale for Depression (HDRS) and the Clinical Global Impressions (CGI)-Severity and Improvement scales. The latter two scales were only used in dose titration. Adverse events were measured with the UKU scale.
Other psychotropic medication was excluded, but non-psychotropic medication with influence on CYP2D6 was not.

Genotyping:
- 14x ‘NM+UM’
- 30x ‘PM+IM’

Results:
<table>
<tr><td colspan="3">‘PM+IM’ compared to ‘NM+UM’:</td></tr>
<tr><td></td><td>‘PM+IM’</td><td>value for ‘NM+UM’</td></tr>
<tr><td>reduction in HDRS score after 8 weeks</td><td>NS</td><td>14.4</td></tr>
<tr><td>% increase in UKU subscale during the first week:</td><td></td><td></td></tr>
<tr><td>psychic subscale</td><td>NS</td><td>-2,3%</td></tr>
<tr><td>neurologic subscale</td><td>NS</td><td>52%</td></tr>
<tr><td>autonomic subscale</td><td>NS</td><td>25%</td></tr>
<tr><td>“other” subscale</td><td>NS</td><td>3,2%</td></tr>
<tr><td>% of patients with one or</td><td></td><td></td></tr>
</table>
</td><td>Authors’ conclusion: “No significant associations between any of the genotypes and adverse effects were found. ….. No difference in the reduction of HDRS was found between CYP2D6 PM/IM polymorphisms and CYP-2D6 EM/UM polymorphisms.”</td></tr>
</table>

<table>
<tr><td>ref. 13, continuation</td><td></td><td>
<table>
<tr><td>more reported adverse events belonging to the UKU subscale during the first week:</td><td></td><td></td></tr>
<tr><td>psychic subscale</td><td>NS</td><td>100%</td></tr>
<tr><td>neurologic subscale</td><td>NS</td><td>16%</td></tr>
<tr><td>autonomic subscale</td><td>NS</td><td>37%</td></tr>
<tr><td>“other” subscale</td><td>NS</td><td>100%</td></tr>
</table>

NOTE: The authors refer for the genotype-phenotype translation to an article lacking a definition for IM. For this reason, it is not known whether their genotype-phenotype translation is the same as ours.

NOTE: Genotyping was for *5, gene multiplication, and alleles not specified by the authors. It seems probable that the most important gene variants in these Australian Caucasian and Singaporean Han Chinese populations have been determined.</td><td></td></tr>
<tr><td>ref. 14
Lobello KW et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. J Clin Psychiatry 2010;71:1482-7. PubMed PMID: 20441720.</td><td>3

PM: C</td><td>A total of 464 patients with severe depression in 4 trials (phenotyping: 415x NM+IM+UM, 49xPM), venlafaxine in fixed dose (75-375 mg/day) or in variable dose (75-150 mg/day or ER 25-225 mg/day). There was no difference in use of relevant co-medication (CYP2D6 inhibitors) between NM and PM (7% and 8% of the patients respectively). The most commonly used CYP2D6 inhibitors (5% of the patients) were weak inhibitors. There was no interaction between the venlafaxine formulation and the phenotype with regard to the effectiveness and no significant effect of the formulation on the effectiveness.

PM versus NM+IM+UM:
- no difference in the mean dose (128.6 versus 129.1 mg/day) or the variation in dose (23.0-316.4 versus 19.7-339.6 mg/day)
- increase in C_{ss} V by 259% (from 77.08 to 276.76 ng/mL) (S)
- decrease in C_{ss} DV by 50% (from 221.37 to 109.97 ng/mL) (S)
- non-significant increase in C_{ss} V+DV by 30% (from 298.44 to 386.73 ng/mL) (NS)
- decrease in the improvement of depression, as measured using the 17-item and 6-item Hamilton Rating Scale for Depression (decrease in the score by 9.55 versus 12.22 and 5.76 versus 7.43 respectively), the Montgomery-Asberg Depression Rating Scale (decrease by 11.45 versus 15.43) and the Clinical Global Impressions-Improvement scale (score 2.39 versus 1.91) (S)
- non-significant decrease in the improvement of depression, as measured using the Clinical Global Impressions-Severity of Illness scale (decrease by 1.49 versus 1.80) (NS)
- decrease in the percentage of patients with a response (decrease in the score on the $HDRS_{17}$ or MADRS by ≥ 50% or based on the GCI-I) by a factor of 1.3-1.6 (S) (from 65% to 45%, from 61% to 39% and from 76% to 57% respectively)
- decrease in the percentage of patients with remission on the MADRS (score ≤ 12) by a factor of 1.5 (from 56% to 37%) (S)
- non-significant decrease in the percentage of patients with remission on the $HDRS_{17}$ (score ≤ 7) by a factor of 1.4 (from 41% to 29%) (NS)
- there was no difference in the percentage of patients that</td><td>Authors’ conclusion:
‘Venlafaxine treatment in NMs was associated with greater efficacy in major depressive disorder on virtually all measures compared with PMs, with no important tolerability differences.’
‘After subtracting the placebo response and remission rates, venlafaxine-treated NM patients achieved 2- to 3-fold higher rates of response and remission compared with venlafaxine-treated PM patients at comparable doses.’

C_{ss} V+DV versus NM+IM+UM:
PM: 130%</td></tr>
</table>

ref. 14, continuation		stopped the study due to insufficient response/lack of effectiveness (NS) - there was no difference in the percentage of patients that stopped the study due to side effects (NS). However, there was also no difference between users of placebo and venlafaxine. - there was no difference in percentage of patients with side effects (98.0% versus 93.5%) - however, differences were found for three specific side effects: - increase in the number of patients with elevated alkaline phosphatase by a factor of 20.5 (from 0.2% to 4.1%) (S) - increase in the number of patients with sweating as side effect by a factor of 1.9 (from 13.3% to 24.5%) (S) - increase in the number of patients with insomnia by a factor of 1.7 (from 22.4% to 38.8%) (S) PM versus patients on placebo: - increase in the improvement of depression, measured using all five of the abovementioned depression scales (S) - increase in the response measured by the GCI-I (S, OR = 2.06) - no difference in the percentage of patients with a response, measured using the $HDRS_{17}$ and MADRS (NS) - no difference in the percentage of patients with remission, measured using the $HDRS_{17}$ and MADRS (NS) There was no association between plasma concentrations of V, DV or V+DV and either improvement on one of the scales or response. NOTE: Phenotyping was performed based on the ratio of DV/V (< 1: PM, ≥ 1: NM, IM or UM)	
ref. 15 Van Nieuwerburgh FC et al. Response to serotonin reuptake inhibitors in OCD is not influenced by common CYP2D6 polymorphisms. Int J Psychiatry Clin Pract 2009;13:345-8. PubMed PMID: 20174590.	4 IM+PM: A	A total of 39 patients with obsessive compulsive disorder and without severe depression (17x NM, 17x 1 variant allele (NM+IM: *1/*10, *1/*4, *1/*41 or *1/*6), 5x 2 variant alleles (IM+PM: *10/*10, *4/*4 or *4/*10)) were treated with venlafaxine for 12 weeks (dose was increased slowly to 300 mg/day according to a set schedule). Relevant co-medication was excluded. 1 or 2 variant alleles versus NM: - increase in C_{ss} V by 158% (from 151 to 390 ng/mL) (S) - non-significant decrease in C_{ss} DV (NS) - non-significant increase in C_{ss} V+DV (NS) - no significant difference in response (decrease in the score on the Yale Brown Obsessive Compulsive Scale by > 25% or > 35%) (NS) 2 variant alleles versus NM: - increase in C_{ss} V (S) - decrease in C_{ss} DV (S) - increase in C_{ss} V+DV (S) - no significant difference in response (decrease in the score on the Yale Brown Obsessive Compulsive Scale by > 25% or > 35%) (NS) NOTE: Genotyping was performed for the four most common gene polymorphisms: *10, *4, *41 and *6 (allele frequencies 0.26; 0.24; 0.08 and 0.02 respectively), which together account for 80-90% of the alleles with reduced activity in a Caucasian population.	Authors' conclusion: 'Our results show that the investigated CYP2D6 polymorphisms are not a decisive factor in the response to paroxetine and venlafaxine treatment in OCD in spite of their highly significant effect on the blood levels of these medicines.'
ref. 16 Preskorn S et al.	3	13 healthy study subjects (7x NM+IM (3x gene dose 2, 4x gene dose 1-1.5), 6x PM) received a single dose of venla-	Authors' conclusion: 'Compared with an

Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. J Clin Psychopharmacol 2009;29:39-43. PubMed PMID: 19142106. **ref. 16, continuation**	PM: A	faxine 75 mg. No co-medication. PM versus NM+IM: - increase in AUC V by 331% from 591 to 2548 ng·hour/mL (S) - decrease in AUC DV by 73% from 3078 to 844 ng·hour/ mL (S) - decrease in AUC V+DV by 8% from 3669 to 3392 ng·hour/mL (NS) - 33% of the PM and 29% of the NM experienced nausea as a side effect (NS) - 17% of the PM and 0% of the NM experienced headache as a side effect (NS) - there were no serious side effects and no one stopped taking part in the study due to side effects NOTE: Genotyping was performed for *2 through *10, *17, *29, *41 and duplication.	NM phenotype, a PM phenotype had a significant effect on venlafaxine and desvenlafaxine plasma concentrations after venlafaxine ER administration.' C_{ss} V+DV versus NM+IM: PM: 108%
ref. 17 Hermann M et al. Serum concentrations of venlafaxine and its metabolites O-desmethylvenlafaxine and N-desmethylvenlafaxine in heterozygous carriers of the CYP-2D6*3, *4 or *5 allele. Eur J Clin Pharmacol 2008;64:483-7. PubMed PMID: 18214456.	4 IM: A PM: A	In 43 patients (20x NM, 18x IM (2x *1/*3, 13x *1/*4, 3x *1/*5), 5x PM (all *4/*4)), the dose of venlafaxine XR tablets was based on therapeutic drug monitoring. No relevant co-medication. Included some smokers. IM versus NM: - increase in C_{ss}[a] V+DV from 5.0 to 6.1 nM/mg (NS by 22%) - decrease in the DV/V ratio from 3.1 to 1.5 (S by 52%) PM versus NM: - increase in C_{ss}[a] V+DV from 5.0 to 8.5 nM/mg (NS by 70%) - decrease in the DV/V ratio from 3.1 to 0.2 (S by 94%) The decrease in the DV/V ratio is primarily caused by an increase in the C_{ss}[a] of venlafaxine. NOTE: Genotyping was performed for *3 through *8 and duplication.	Authors' conclusion: 'The study showed a shift in the metabolic pathway resulting in substantially higher levels of N-desmethylvenlafaxine in IMs than in NMs. The metabolic pattern of venlafaxine in IMs was similar to previous observations in PMs and possibly represents an increased risk of venlafaxine-related side effects in IM patients.' C_{ss}[a] V+DV versus NM: IM: 122% PM: 170%
ref. 18 McAlpine DE et al. Cytochrome P450 2D6 genotype variation and venlafaxine dosage. Mayo Clin Proc 2007;82:1065-8.	3 IM: C	A total of 38 patients (5x IM (gene dose 0.25-0.5), 33x IM+NM+ UM (gene dose ≥ 1)), who either experienced side effects or no clinical response to venlafaxine, were genotyped after this occurred. Gene dose 0.25-0.5 compared to gene dose: ≥ 1: - decrease in the percentage of patients with maintenance dose venlafaxine > 75 mg/day from ≥ 79% to 0% (S by 100%) Cases of the 5 IM with gene dose 0.5 or 0.25: - A 44-year-old female (*3/*9) with dysthymic disorder reported a dry mouth, increased appetite and a decrease in depressive symptoms on venlafaxine 75 mg/day. Following an increase in the dose to 112.5 mg/day, the depression increased and she was fatigued. She then functioned well for 4 months on 75 mg/day. - A 16-year-old girl (*3/*9) with ADHD, depression, psychotic symptoms and bipolar disorder had to stop taking venlafaxine 75 mg/day due to excessive drowsiness and lack of improvement in her mood. - A 54-year-old female (*4/*17) with clinical depression had	Authors' conclusion: 'In an outpatient psychiatric practice, patients who did not have at least 1 fully active allele of the 2D6 gene were not successfully treated with dosages of venlafaxine greater than 75 mg/d. Physicians should be alert to the possibility that an adverse reaction may indicate a slow metabolizer and consider genotyping such patients.'

ref. 18, continuation		to stop treatment with 37.5 mg/day due to unacceptable nausea, drowsiness and decreased appetite. - A 46-year-old male (*4/*41) with generalised anxiety disorder became more anxious and developed palpitations on venlafaxine 37.5 mg/day. Anxiety symptoms improved after stopping venlafaxine. - A 15-year-old girl (*4/*10) with clinical depression had to stop treatment with 75 mg/day due to unacceptable side effects. NOTE: Genotyping was performed for *1 through *12, *17, *41 and gene duplication.	
ref. 19 Shams ME et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. J Clin Pharm Ther 2006;31:493-502.	4 PM: C IM: A UM: A	A total of 25 depression patients (10x NM (9x *1/*1, 1x *1x2/*4), 5x IM (*1/*4), 4x PM (2x *4/*5, 1x *4/*6, 1x *6/*6), 6x UM (all *1x2/*1)) on venlafaxine with abnormal ratios of DV/V were genotyped. No co-medication with CYP2D6 inhibitors. PM versus NM: - no difference in C_{ss}[a] V+DV (both 1.29 ng/mL per mg) (NS by 0%) - decrease in the DV/V ratio from 3.45 to 0.25 (S by 93%) - increase in C_{ss}[a] of the inactive metabolite N-desmethylvenlafaxine from 0.23 to 0.75 nM/mg (S by 232%) PM versus NM+IM: - increase in the number of side effects per patient from 0.49 to 2.3 (S by 369%) - decrease in the plasma concentration of sodium from 142 to 138 nmol/L (S by 3%) - increase on the scale of therapeutic effectiveness from 1.7 to 2.0 points (NS by 18%) IM versus NM: - increase in C_{ss}[a] V+DV from 1.29 to 1.30 (NS by 1%) - decrease in the DV/V ratio from 3.45 to 1.16 (S by 66%) - increase in C_{ss}[a] of the inactive metabolite N-desmethylvenlafaxine from 0.23 to 0.43 nM/mg (NS by 90%) UM versus NM: - decrease in C_{ss}[a] V+DV from 1.29 to 0.98 (NS by 24%) - increase in DV/V ratio from 3.45 to 10.3 (S by 199%) - decrease in C_{ss}[a] of the inactive metabolite N-desmethylvenlafaxine from 0.23 to 0.09 nM/mg (NS by 60%) UM versus NM+IM: - decrease in the number of side effects per patient from 0.49 to 0.3 (NS by 39%) - increase in the plasma concentration of sodium from 142 to 144 nmol/L (NS by 1%) - no difference on the scale of therapeutic effectiveness (both 1.7 points) (NS by 0%) The increase in the DV/V ratio with increasing gene dose is primarily caused by an decrease in the C_{ss}[a] of venlafaxine. The increase in the plasma concentration of sodium was inversely proportional to the C_{ss}[a] of venlafaxine. Venlafaxine possibly has a greater effect on the side effects than O-desmethylvenlafaxine. NOTE: Genotyping was performed for *3 through *6, *9 and duplication.	Authors' conclusion: 'A PM phenotype of CYP2D6 increases the risk of side effects.' C_{ss}[a] V+DV versus NM: PM: 100% IM: 101% UM: 76%
ref. 20 Whyte EM et al.	3	A total of 46 elder patients (30x NM, 13x IM (*1/*4), 3x PM (*4/*4)) received venlafaxine for 4 weeks (start 37.5 mg/day,	Authors' conclusion: 'Future clinical appli-

CYP2D6 genotype and venlafaxine-XR concentrations in depressed elderly. Int J Geriatr Psychiatry 2006;21:542-9. **ref. 20, continuation**	IM+PM: A IM: A PM: A	if possible increase to 150 mg/day during the next 2 weeks). Relevant co-medication was not excluded. IM+PM versus NM: - increase in C_{ss}[a] V+DV from 3.21 to 4.00 ng/mL per mg (significance unknown, by 25%) - increase in C_{ss}[a] V from 0.69 to 2.26 ng/mL per mg (S, by 228%) - decrease in C_{ss}[a] DV from 2.52 to 1.74 ng/mL per mg (S, by 31%) - greater decrease in the number of points on the depression scale: from -7.3 to -7.9 (NS by 8%) - increase in the number of points on the side effects scale: from 9.8 to 10.7 (NS by 9%) - increase in the prevalence of QT interval ≥ 440 msec (12 weeks after start of the study): from 6.7% to 9.1% (NS by 36%) - no significant difference in the percentage of patients that stopped the study There was a significant positive and negative correlation respectively with the number of mutant alleles of Css[a] V and C_{ss}[a] DV. NOTE: Genotyping was performed for *3, *4 and *6 through *8.	cation of pharmacogenetics to examine 2D6-dependent medications may help reduce the incidence of medication adverse events particularly in those elders at higher risk for medication adverse events due to impaired renal or cardiac function.'
ref. 21 Eap CB et al. Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. Pharmacogenetics 2003;13:39-47.	4 PM: A	12 healthy study subjects, 7x NM (4x *1/*1, 3x *1/*4), 5x PM (1x *3/*4, 4x *4/*4), venlafaxine 18.75 mg twice daily, co-medication unknown: - PM: increase in AUC S-venlafaxine+ R-venlafaxine from 0.58 to 2.27 μmol·hour/L (S by 291%).	
ref. 22 Fukuda T et al. The impact of the CYP2D6 and CYP-2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. Eur J Clin Pharmacol 2000;56:175-80.	3 IM: A	A total of 28 healthy study subjects, 5x *10/*10, 11x *10 (2x *1/*10, 9x *2/*10), 11x no *10 (2x *1/*1, 4x *1/*2, 5x *2/*2) and 1x residual (*1/*5), venlafaxine 37.5-150 mg/day, no co-medication; *10/*10 versus no *10: - increase in AUC[a] venlafaxine from 185.0 to 1024.5 ng·hour/mL (S by 454%) - increase in AUC[a] V+DV from 1636.9 to 1974.0 ng·hour/ mL (S by 21%) 1x *10 versus no *10: - increase in AUC[a] venlafaxine from 185.0 to 407.3 ng·hour/mL (S by 120%) - increase in AUC[a] V+DV from 1636.9 to 1742.4 ng·hour/ mL (NS by 6%) *1/*5 versus no *10: - increase in AUC[a] venlafaxine from 185.0 to 826.4 ng·hour/mL (NS by 347%) - increase in AUC[a] V+DV from 1636.9 to 1957.0 ng·hour/ mL (NS by 20%)	AUC V+DV versus NM: IM: 117%
ref. 23 Lessard E et al. Influence of CYP-2D6 activity on the disposition and cardiovascular toxicity of the antide-	4 PM: A	14 healthy study subjects, 8x NM, 6x PM, venlafaxine 18.75 mg twice daily, no co-medication: - PM: for venlafaxine, increase in AUC from 0.9 to 3.1 μmol·hour/L (S by 244%), decrease in Cl_{or} from 100 to 23 L/h (S by 77%).	The authors noted that they saw 4 other PMs with cardiac side effects (syncope, palpitations, severe dizziness).

pressant agent venlafaxine in humans. Pharmacogenetics 1999;9:435-43.		NOTE: phenotyping and genotyping was performed, but the results were not reported.	
ref. 24 Veefkind AH et al. Venlafaxine serum levels and CYP2D6 genotype. Ther Drug Monit 2000;22:202-8.	4 PM: A IM: AA UM: AA PM: C	A total of 33 depression patients, 3x *4/*4, 4x *1/*4, 3x *2/*4, 1x *1xn, 1x *2xn, 15x *1/*2, 6x *1/*1, venlafaxine 225 mg/day, no relevant co-medication; *kinetic endpoints* - *4/*4: increase in C_{ss} V+DV versus "no *4" from 311 to 539 μg/L (NS by 73%). Increase in C_{ss} V from 64 to 476 μg/L (S by 644%). C_{ss} DV was reduced by 74% (S). The C_{ss} DV/V ratio was reduced by 97% (S) - *1/*4 and *2/*4: increase in C_{ss} V+DV versus "no *4" from 311 to 344 μg/L (NS by 11%), increase in C_{ss} V from 64 to 113 μg/L (NS by 77%). C_{ss} DV was reduced by 6% (NS), the C_{ss} DV/V ratio was reduced by 56%. - *1xn and *2xn: decrease in C_{ss} V+DV versus "no *4" from 311 to 182 μg/L (NS by 41%), decrease in C_{ss} V from 64 to 12 μg/L (NS by 81%), the C_{ss} DV was reduced by 1% and the C_{ss} DV/V was elevated by 139% (from 6.1 to 14.6). *clinical endpoints* - *4/*4: all three non-responders - *1xn and *2xn: 1 responder and 1 non-responder	C_{ss}[a] V+DV versus NM: PM: 173% IM: 111% UM: 59%
ref. 25 Fukuda T et al. Effect of the CYP-2D6*10 genotype on venlafaxine pharmacokinetics in healthy adult volunteers. Br J Clin Pharmacol 1999;47:450-3.	3 IM: A	A total of 12 healthy study subjects, 1x *5/*10, 3x *10/*10, 2x *1/*10, 2x *2/*10, 2x *1/*1, 2x *2/*2, co-medication unknown, venlafaxine 25-37.5 mg/day; - *10/*10 and *5/*10: for venlafaxine, increase in the AUC[b] versus *1/*1+*2/*2 from 219.2 to 1280.0 ng·hour/ mL (S by 484%), increase in t½ from 3.44 to 6.32 hours (NS by 84%). Increase in AUC[b] V+DV from 2864.7 to 3379.2 ng·hour/mL (NS by 18%). - *1/*10 and *2/*10: for venlafaxine, increase in the AUC[b] versus *1/*1+*2/*2 from 219.2 to 421.9 ng·hour/ mL (NS by 92%), increase in t½ from 3.44 to 4.05 hours (NS by 18%). Increase in AUC[b] V+DV from 2864.7 to 3080.1 ng·hour/mL (NS by 8%).	Authors' conclusion: 'However, concentrations of venlafaxine + O-desmethylvenlafaxine were not different between groups and since O-desmethylvenlafaxine is equally effective, the effect of genotype on pharmacokinetics is not expected to be translated into differences in response.' AUC V+DV versus NM: IM: 114%
ref. 26 SmPC Efexor XR (venlafaxine) 19-04-22.	0 PM: A	<u>Pharmacokinetics</u>: Venlafaxine plasma concentrations were higher for poor CYP2D6 metabolisers than for extensive metabolisers. As the total exposure (AUC) of venlafaxine and ODV is comparable in both the poor and the extensive metabolisers, there is no reason for different venlafaxine dosing schedules for these two groups. <u>Drug-drug Interactions</u>: Ketoconazole (CYP3A4 inhibitor) A pharmacokinetic study with ketoconazole in rapid (NM) and poor (PM) CYP2D6 metabolisers resulted in a higher AUC of venlafaxine (70% and 21% in CYP2D6 PM and NM individuals respectively) and O-desmethylvenlafaxine (33% and 23% in CYP2D6 PM and NM individuals respectively) following administration of ketoconazole.	
ref. 27 SmPC Effexor XR	0	<u>Pharmacokinetics</u>: In vitro studies indicate that the formation of ODV is cataly-	

(venlafaxine), USA, 15-08-22. **ref. 27, continuation**	PM: A	zed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels (poor metabolizers) had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 levels (normal metabolizers).	

[a] corrected for dose
[b] corrected for dose and body weight

Risk group	IM with CYP2D6 inhibitor, IM and PM with strong CYP3A4 inhibitor

Comments:
- For the period after 2007, articles that only reported a kinetic effect but not the percentual extent of the effect on the (dose-corrected) V + DV plasma concentration and cases were not included in the risk analysis. The same applies to kinetic studies, in which the categorisation into phenotypes was based solely on the venlafaxine kinetics (V/DV ratio).
  So, the pharmacokinetic meta-analyses in Lin 2019 describing only mean differences instead of percentual differences were not included in the risk analysis.

Date of literature search: 19 July 2022.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	PM	4 C	yes	yes	14 November 2022
	IM	4 C	yes	yes	
	UM	4 A	yes	no	

Mechanism:
Venlafaxine is mainly converted by CYP2D6 to the active metabolite O-desmethylvenlafaxine. Venlafaxine and O-desmethylvenlafaxine are primarily converted by CYP3A4 and CYP2C19 to inactive metabolites (N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine respectively). The therapeutic range is 100-400 ng/ml for the sum of venlafaxine and O-desmethylvenlafaxine and values higher than 1000 ng/ml are considered to be toxic. However, Jiang 2015 indicates that it is difficult to establish venlafaxine therapy that is both effective and well tolerated in patients with low O-desmethylvenlafaxine/venlafaxine ratios (PM and IM).
Venlafaxine is a weak CYP2D6 inhibitor, thereby inhibiting its own metabolism.

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