CYP2D6: aripiprazole 1541/1542/1543

AP = aripiprazole, AUC = area under the concentration-time curve, BMI = body-mass index, Cl_{or} = oral clearance, C_{ss} = plasma concentration in steady state, DAP = dehydroaripiprazole, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose $\geq$ 2.75) (increased CYP2D6 enzyme activity)

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

Brief summary and justification of choices:
Aripiprazole is primarily metabolised by CYP3A4 and CYP2D6, resulting in formation of the metabolite dehydro-aripiprazole, which has an activity similar to that of aripiprazole. Dehydroaripiprazole is further metabolised by CYP3A4 and CYP2D6 to inactive metabolites. The therapeutic range of aripiprazole is 100-300 ng/ml and values higher than 500 ng/ml are considered to be toxic. In literature, a therapeutic range of aripiprazole + dehydroaripi-prazole of 150-500 ng/ml is mentioned.
The presence of genetic variants of CYP2D6 can result in either an absent or reduced CYP2D6 enzyme activity (poor or intermediate metabolisers (PM or IM)) or an increased CYP2D6 enzyme activity (ultra-rapid metaboliser (UM)).
6 out of 11 studies showed a statistically significant effect of the CYP2D6 genotype on exposure to the active moiety (aripiprazole + dehydroaripiprazole) (significant effect: Tveito 2020, Jukic 2019, Belmonte 2018, Suzuki 2014, Suzuki 2011 and Hendset 2007; no significant effect: Koller 2020, Patteet 2016, Van der Weide 2015, Kubo 2007 and Kubo 2005).

PM: For 87 PM, a study found no difference in the percentage of patients switched to another antipsychotic (Jukic 2019). In a subgroup of patients without relevant comedication, this study found a decrease in dose with 17% for 62 PM. This dose decrease might have contributed to the absence of a clinical effect, although the dose should have been decreased with 35% to compensate for the increase in exposure to aripiprazole + dehydroaripiprazole observed in the 62 PM. A study with 14 (genotype predicted) PM and with 134 PM based on either genotype or the presence of a strong CYP2D6 inhibitor, showed an 18% increase in side effects being the reason for discontinuation for the genotype and/or inhibitor based PM, but no effect for the genotype predicted PM (Jallaq 2021). The study showed conflicting results on the change in BMI percentile, i.e. an increase in genotype predicted PM and an increase with the number of CYP2D6 substrates/inhibitors used, but no increase in the genotype and/or inhibitor based PM. For neither kind of PM, the study showed a difference in the maximum aripiprazole dose compared to NM. A study with 148 healthy volunteers receiving a single dose of 10 mg aripriprazole, showed an effect of the CYP2D6 genotype on the frequency of nausea and vomiting, but not on the frequency of any adverse event (Belmonte 2018; 3 PM). Adverse events were reported in a PM patient, who was receiving twice the standard maximum dose of aripiprazole (Oosterhuis 2007). The authors emphasise the possible risk of long-term toxicity in PMs, where the increased plasma concentration is not evidenced by the occur-rence of adverse drug reactions. However, the increase in the plasma concentration of aripiprazole was much greater in this case (by approx. 700%) than has been found for PM in other studies (73-80%). Based on these clinical data and on the calculated dose adjustment being higher than the normal biolo-gic variability of approximately 25%, the KNMP Pharmacogenetics Working Group decided that action is required for PMs receiving aripiprazole (yes/yes-interaction). Because the PM in the case report only developed adverse events after doubling the dose to 300 mg/day, the recommendation is limited to the warning not to prescribe a dose for PM any higher than the PM-corrected standard maximum dose of aripiprazole. Dose adjustments were calculated on the basis of the C_{ss} and AUC of aripiprazole+dehydro-aripiprazole. Based on 5 studies with a total of 89 PM, the weighted mean of the resulting calculated reduced dose reduction is 68% of the standard dose (median 76%; range 65-83%). For direct release

aripiprazole, 68% of the standard maximum dose of 15 mg/day amounts to 10 mg/day. Although the calculated reduced dose is mainly based on direct release aripiprazole, Tveito 2020 shows the effect of the CYP2D6 phenotype on aripiprazole exposure to be similar for oral (direct release) aripiprazole and the extended-release injectable suspension. So, the calculated reduced dose also applies to the extended-release injectable suspension. Dose reduction to 68% of the standard dose corresponds to 272 mg of the extended-release injectable suspension once monthly (normal dose 400 mg once monthly). To be more feasible in clinical practice and taken into the account the median value of the calculated reduced dose of 76%, this is rounded off to 300 mg once a month.

IM, UM: For 102 IM and 33 UM, a study found no difference in the percentage of patients switched to another antipsychotic (Jukic 2019). In a subgroup of patients without relevant comedication, this study found no effect on aripiprazole dose for 73 IM and 16 UM. So, the lack of a clinical effect cannot be explained by dose adjustment. A study with 101 (genotype predicted) IM and with 67 IM based on genotype and comedication (genotype predicted IM without CYP2D6 inhibitor or genotype predicted NM with a moderate CYP2D6 inhibitor), did not show an increase in side effects being the reason for discontinuation or in the change in BMI percentile for either definition of IM (Jallaq 2021). The study showed no difference in the maximum aripiprazole dose compared to NM for both definitions of IM and UM (4 genotype predicted UM, 1 genotype and comedication predicted UM (i.e. the only UM without a strong CYP2D6 inhibitor)), A study with 148 healthy volunteers receiving a single dose of 10 mg aripriprazole, showed an effect of the CYP2D6 genotype on the frequency of nausea and vomiting, but not on the frequency of any adverse event (Belmonte 2018; 55 IM and 7 UM). There were no case reports of adverse events in IM patients. Neither were there any case reports of a lack of effectiveness in UM patients. In addition, especially for IM, the size of the change in AUC or C_{ss} is smaller than the normal biologic variability of 25% (a weighted mean and median increase of 1% and 8% for IM and a weighted mean and median decrease of 22% and 20% for UM). Based on the limited data on clinical significance and the relatively small kinetic effect, the KNMP Pharmacogenetics Working Group does not consider dose adjustment or the selection of an alternative to be useful. For this reason, no action is recommended for IM and UM receiving aripiprazole (yes/no-interactions).

You can find a detailed overview of the observed kinetic and clinical effects 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 aripiprazole to be potentially beneficial for 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 aripiprazole 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 Summaries of Product Characteristics (SmPCs) of aripiprazole mention the CYP2D6 PM phenotype, but don't mention this phenotype as a contra-indication and don't recommend pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

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

Source	Code	Effect	Comments
ref. 1 Jallaq SA et al. CYP2D6 phenotype influences aripipra-	3	277 paediatric patients with mood disorders and known CYP2D6 genotype were treated with aripiprazole. 36.8% of patients discontinued treatment due to side effects, 24.5% due to inefficacy. 77 patients (27.8%) discontinued	Authors' conclusion: 'Phenoconverted CYP2D6 metaboli-zer status is asso-

<table>
<tr>
<td>zole tolerability in pediatric patients with mood disorders. J Child Adolesc Psychopharmacol 2021;31:56-62. PMID: 32845723.

ref. 1, continuation</td>
<td>UM: AA

PM: C
IM: AA</td>
<td>due to unknown reasons or did not discontinue and were excluded from the discontinuation analyses.
Change in BMI percentile was calculated from the BMI percentile nearest to the start and end of aripiprazole treatment. Patients with eating disorders in the problem list were excluded from the change in BMI percentile analysis.
Due to the small sample size, UMs were only included in the analysis of the maximum aripiprazole dose.
72% of patients used a CYP2D6 inhibitor. Some patients used more than one CYP2D6 inhibitor. Patients using strong CYP2D6 inhibitors (fluoxetine or bupropion) were assigned the phenotype PM. Patients using moderate CYP2D6 inhibitors (duloxetine, fluvoxamine or sertraline) were assigned to a phenotype based on half of their gene dose.
Linear regression was used for the analyses.

Predicted CYP2D6 phenotypes:
based on genotype:
- 158x NM
- 101x IM
- 14x PM
- 4x UM+gene dose 2.5

based on genotype and CYP2D6 inhibitor use
- 75x NM (all genetically NM)
- 67x IM (genetically IM or genetically NM with a moderate CYP-2D6 inhibitor)
- 134x PM (14x genetically PM, 117x genetically IM or NM with a strong CYP2D6 inhibitor, and 3x genetically UM+gene dose 2.5 with a strong CYP2D6 inhibitor)
- 1x UM or gene dose 2.5

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>
<tr><td colspan="5">Genotype predicted phenotypes</td></tr>
<tr><td>side effects being the reason for discontinuation</td><td colspan="2">NS for PM versus IM versus NM</td><td></td><td></td></tr>
<tr><td>inefficacy being the reason for discontinuation</td><td colspan="2">NS for PM versus IM versus NM</td><td></td><td></td></tr>
<tr><td>BMI percentile change</td><td colspan="2">S for PM versus IM versus NM (with uncorrected mean values being slightly higher for PM and lower for IM compared to NM)</td><td></td><td></td></tr>
<tr><td>maximum aripiprazole dose (mg/day)</td><td colspan="3">NS for PM versus IM versus NM versus UM+gene dose 2.5</td><td></td></tr>
<tr><td colspan="5">Genotype and CYP2D6 inhibitor predicted phenotypes</td></tr>
<tr><td>side effects being the reason for discontinuation</td><td>x 1.18</td><td>x 0.89</td><td></td><td>57%</td></tr>
<tr><td></td><td colspan="2">S for PM versus IM versus NM</td><td></td><td></td></tr>
<tr><td>inefficacy</td><td colspan="2">NS for PM versus IM</td><td></td><td></td></tr>
</table>
</td>
<td>ciated with aripiprazole discontinuation. In addition, dose adjustments based on CYP2D6 metabolizer status and concomitant medications could improve aripiprazole treatment outcomes.’</td>
</tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td></td><td>
<table>
<tr><td>being the reason for discontinuation</td><td>versus NM</td><td></td><td></td></tr>
<tr><td>BMI percentile change</td><td>NS for PM versus IM versus NM
However, BMI percentile change increased with the number of CYP2D6 inhibitors/substrates (S), suggesting that this increase was not due to the effect of these comedications on CYP2D6 activity, but on other effects of the CYP2D6 substrates.</td><td></td><td></td></tr>
<tr><td>maximum aripiprazole dose (mg/day)</td><td colspan="2">NS for PM versus IM versus NM versus UM+gene dose 2.5</td><td></td></tr>
</table>

NOTE: Genotyping was performed for *2A, *3-*11, *14, *15, *17-*20, *40-*42, *44 and duplication. These are the most important gene variants in this population from the USA.
</td><td></td></tr>
<tr><td>ref. 2
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>3

IM: A
UM: A</td><td>24 healthy volunteers received aripiprazole 10 mg/day for 5 days. For aripiprazole, a period of 5 days is too short to reach steady state.
Co-medication was excluded.
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:
- 16x NM
- 6x IM
- 2x UM or gene dose 2.5

Results:
<table>
<tr><td colspan="4">AUC (in ng.h/mL) compared to NM:</td></tr>
<tr><td></td><td>IM</td><td>UM</td><td>value for NM</td></tr>
<tr><td>aripiprazole + dehydroaripiprazole</td><td>x 1.02 (NS)</td><td>x 0.43 (NS)</td><td>119309</td></tr>
<tr><td>aripiprazole</td><td>x 1.12 (NS)
S in multivariate analysis for IM versus NM versus UM</td><td>x 0.30 (NS)</td><td>79899</td></tr>
<tr><td>dehydroaripiprazole</td><td>x 0.82 (NS)
NS in multivariate analysis for IM versus NM versus UM</td><td>x 0.68 (NS)</td><td>39410</td></tr>
</table>

Note: Genotyping was for *3-*10, *14, *17, *29, *41, and gene multiplication. These are the most important gene variants in this Spanish population.
*3, *6-*8, *14 and *17 were not in Hardy-Weinberg equilibrium, which was due to the low frequencies of these variant alleles and the small sample size.</td><td>Author’s conclusion:
‘Aripiprazole, dehydro-aripiprazole and olanzapine pharmacokinetics were significantly affected by polymorphisms in CYP2D6, CYP3A, CYP1A2, ABCB1 and UGT1A1 genes.‘

AUC aripiprazole + dehydroaripiprazole versus NM:
IM: 102%
UM: 43%</td></tr>
<tr><td>ref. 3
Tveito M et al.
Impact of age and</td><td>4</td><td>635 patients were treated with aripiprazole, 469 with oral aripiprazole and 166 with long-acting injectable aripiprazole. Routine therapeutic drug monitoring was performed. A mean</td><td>Authors’ conclusion:
‘In conclusion, doses should be</td></tr>
</table>

CYP2D6 genetics on exposure of aripiprazole and dehydroaripiprazole in patients using long-acting injectable versus oral formulation: relevance of poor and intermediate metabolizer status.
Eur J Clin Pharmacol 2020;76:41-9.
PMID: 31637453.

ref. 3, continuation

PM: A
IM: A

UM: A

of 2.2 measurements per patient was included. 74% of measurements was after genotyping (70% for oral aripiprazole and 83% for long-acting injectable aripiprazole). A serum therapeutic window of aripiprazole+dehydroaripiprazole 200-1300 nmol/L (90-583 ng/ml) was used. 9.1% of concentrations measured was subtherapeutic (11.2% for oral aripiprazole and 4.0% for long-acting injectable aripiprazole) and 4.4% was supratherapeutic (5.3% for oral aripiprazole and 2.0% for long-acting injectable aripiprazole).
The data in this study were from the same database as the patients in Jukic 2019, so the patient groups are very likely to be subsets of or at least overlapping with the patients in Jukic 2019.
Patients with aripiprazole measurement below the limit of quantification were excluded. None of them were UM.
Co-medication interacting with aripiprazole metabolism was excluded.
Multivariate model analysis, adjusting for sex, age, and blood sampling time, was used. Bonferroni correction was used to correct for multiple comparisons.

CYP2D6 genotyping:

oral aripiprazole:	long-acting injectable aripiprazole:
- 384x NM+gene dose 1/0	- 137x NM+gene dose 1/0
- 39x IM (only gene dose 0.25, 0.5 and 0.5/0.5)	- 14x IM (only gene dose 0.25, 0.5 and 0.5/0.5)
- 39x PM	- 7x PM
- 7x UM	- 8x UM

Results:

Results compared to NM+gene dose 1/0:

	PM	IM	UM	value for NM+ gene dose 1/0
Oral aripiprazole				
daily dose	NS	NS	NS	13 mg
dose-adjusted concentration aripiprazole+ dehydroaripiprazole	x 1.45 (S)	x 1.45 (S)	x 0.88 (NS)	40 nmol/L per mg
	The CYP2D6 genotype explained 6.3% of the variation in the dose-adjusted concentration.			
dose-adjusted concentration aripiprazole	x 1.66 (S)	x 1.59 (S)	x 0.86 (NS)	29 nmol/L per mg
	The CYP2D6 genotype explained 14% of the variation in the dose-adjusted concentration.			
dose-adjusted concentration dehydroaripiprazole	x 0.91 (NS)	x 1.09 (NS)	x 0.90 (NS)	11 nmol/L per mg
Long-acting injectable aripiprazole				
daily dose	NS	NS	x 1.31 (S)	13 mg
dose-adjusted concentration aripiprazole+ dehydroaripiprazole	x 1.55 (S)	x 1.40 (S)	x 0.88 (NS)	40 nmol/L per mg
	The CYP2D6 genotype explained 6.7% of the variation in the dose-adjusted concentration.			

adjusted according to CYP2D6 genotype when initiating treatment with aripiprazole long-acting Injectable or tablets, while advanced age do not affect the exposure of the active moiety of aripiprazole treatment regardless of formulation.'

Not used for dose calculation, because data were only known compared to NM+gene dose 1/0, which, based on the frequencies of 24.2% for alleles with gene dose 0 and 12.0% for alleles with gene dose 0.25-0,5, should consist for 35.5% of gene dose 1/0 (IM). In addition, the patient groups are very likely to overlap with those in Jukic 2019.

<table>
<tr>
<td>ref. 3, continuation</td>
<td></td>
<td>
<table>
<tr><td rowspan="2">dose-adjusted concentration aripiprazole</td><td>x 1.70 (S)</td><td>x 1.50 (S)</td><td>x 0.90 (NS)</td><td rowspan="2">30 nmol/ L per mg</td></tr>
<tr><td colspan="3">The CYP2D6 genotype explained 8.5% of the variation in the dose-adjusted concentration.</td></tr>
<tr><td>dose-adjusted concentration dehydroaripiprazole</td><td>x 1.10 (NS)</td><td>x 1.20 (NS)</td><td>x 0.86 (NS)</td><td>10 nmol/ L per mg</td></tr>
</table>

NOTE: Genotyping was performed for *3-*6, *9, *10, *41 and gene duplication. These are the most important gene variants in this Norwegian population.
Patients were excluded if they were heterozygous for alleles with different gene doses and had more than 2 gene copies, because the assay provided no information on which allele was duplicated.
</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Jukic MM et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry 2019;6(5):418-26. PMID: 31000417.

and personal communication (correct number of patients per phenotype and per genotype group in the kinetics subgroup)</td>
<td>4</td>
<td>
1334 CYP2D6-genotyped patients were treated with aripiprazole. For 2 patients, CYP2D6 was genotyped after discontinuation of aripiprazole. Kinetic analysis was based on the last routine therapeutic drug monitoring measurement of a subgroup of 890 adult patients using oral aripiprazole. Measurements were excluded in case of recent aripiprazole start, a dose change less than 15 days before sampling, sampling > 10 hr after the last dose intake, or a note of suspected non-compliance or measured serum concentrations below the quantification limits. A serum therapeutic window of aripiprazole+dehydroaripiprazole 150-500 ng/ml was used.
Treatment failure was measured as the number of patients switched from aripiprazole to another antipsychotic drug within 1 year after the last therapeutic drug monitoring analysis.
For the analysis of pharmacokinetic parameters, CYP2D6 inhibitors and CYP3A4 inhibitors and inducers were excluded. Logistic regression, adjusting for sex, age, and the presence of a CYP2D6 inhibitor, CYP3A4 inducer, or CYP3A4 inhibitor, was used to analyse therapeutic failure.

CYP2D6 genotyping:
<table>
<tr><td>all patients:</td><td>kinetics subgroup:</td></tr>
<tr><td>- 1112x NM+gene dose 1/0</td><td>- 739x NM+gene dose 1/0 (500x NM, 239x gene dose 1/0)</td></tr>
<tr><td>- 102x IM (only gene dose 0.25, 0.5 and 0.5/0.5)</td><td>- 73x IM (only gene dose 0.25, 0.5 and 0.5/0.5)</td></tr>
<tr><td>- 87x PM</td><td>- 62x PM</td></tr>
<tr><td>- 33x UM</td><td>- 16x UM</td></tr>
</table>

Results:
<table>
<tr><td colspan="2">% of patients switched to another antipsychotic drug compared to NM+gene dose 1/0 (19% of patients switched):</td></tr>
<tr><td>PM</td><td>NS</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td>UM</td><td>NS</td></tr>
</table>

<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM (including gene dose</td><td>UM</td><td>value for NM</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘CYP2D6 genotype had a substantial clinical effect on risperidone and aripiprazole exposure and on the therapeutic failure of risperidone. Pre-emptive CYP2D6 genotyping would be valuable for individualising risperidone and aripiprazole dosing and treatment optimisation.’

Dose-corrected serum concentration aripiprazole + dehydroaripiprazole</td>
</tr>
</table>

<table>
<tr>
<td>ref. 4, continuation</td>
<td>PM: A
IM: A
UM: AA</td>
<td>
<table>
<tr><td></td><td></td><td>1/0)</td><td></td><td></td></tr>
<tr><td>dose-adjusted serum concentration aripiprazole+dehydro-aripiprazole</td><td>x 1.55 (S)</td><td>x 1.23 (S)</td><td>x 0.80 (NS)</td><td>36.60 nmol/ L per mg</td></tr>
<tr><td>aripiprazole daily dose</td><td>x 0.83 (S)</td><td>x 0.91 (NS)</td><td>x 1.05 (NS)</td><td>15.11 mg</td></tr>
<tr><td colspan="5">The doses administered to PM metabolisers were lower, but not low enough to compensate for the increased aripiprazole+dehydroaripiprazole exposure. As a result, supratherapeutic concentrations (aripiprazole+dehydroaripiprazole > 500 ng/ml) were numerically more frequent in IM+PM than in NM+gene dose 1/0+UM (18% and 7%, respectively), and subtherapeutic concentrations (aripiprazole+dehydroaripiprazole < 150 ng/ml) were numerically less frequent in IM+PM than in NM+gene dose 1/0+UM (23% and 33%, respectively).</td></tr>
<tr><td colspan="5">It was possible to explain only around half the variability in aripiprazole metabolism by CYP2D6 genotype.</td></tr>
</table>

NOTE: Genotyping was performed for *3-*6, *9, *10, *41 and gene duplication. These are the most important gene variants in this Norwegian population.
Patients were excluded if they were heterozygous for alleles with different gene doses and had more than 2 gene copies, because the assay provided no information on which allele was duplicated.
</td>
<td>versus NM:
PM: 155%
IM: 123%
UM: 80%</td>
</tr>
<tr>
<td>ref. 5
Belmonte C et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers.
Basic Clin Pharmacol Toxicol 2018;122:596-605.
PubMed PMID: 29325225.</td>
<td>3</td>
<td>148 healthy volunteers received a single dose of aripiprazole 10 mg on two separate occasions with an interval of 28 days.
Dehydroaripiprazole was determined in 103 volunteers.
Adverse drug reactions were defined as adverse events with definite, probably or possible causality of aripiprazole. 73% of the volunteers had at least one adverse drug reaction. The most frequent adverse drug reactions were dizziness (38.5%), nausea/vomiting (30.4%), prolonged QTc interval (21.6%), and headache (19.6%). Most adverse drug reactions (52.0%) were neurological and 31.8% was gastrointestinal. Factors relating to the following adverse drug reactions were identified: any adverse drug reaction, dizziness, headache and nausea/vomiting.
Plasma sampling time was 72 hours, which was not long enough for an adequate evaluation of dehydroaripiprazole and of aripiprazole in volunteers with a long elimination half-life like PM.
Co-medication was excluded.

Genotyping:
- 77x NM
- 61x (IM + gene dose 1.5) (55x IM, 6x gene dose 1.5)
- 3x PM
- 7x UM (6x gene dose 3, 1x gene dose 4)

Results:
<table>
<tr><td colspan="5">Results versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM + gene dose 1.5</td><td>UM</td><td>value for NM</td></tr>
<tr><td>any adverse drug reaction</td><td colspan="3">No association with CYP2D6 phenotype (NS).</td><td></td></tr>
<tr><td>nausea and</td><td>x 1.60</td><td>x 2.13</td><td>x 0.69</td><td>20.8%</td></tr>
</table>
</td>
<td>Authors' conclusion: 'Pharmacokinetics of aripiprazole is affected by CYP2D6 phenotype but also by sex and C1236T (ABCB1 gene), while dehydro-aripiprazole pharmacokinetics is affected by CYP2D6 and C1236T. Concentrations of aripiprazole, sex, CYP3A5*3 and CYP2D6 were involved in the development of adverse drug reactions.'</td>
</tr>
</table>

ref. 5, continuation	PM: B IM: B UM: AA[#]	vomiting	S for the trend PM versus (IM + gene dose 1.5) versus NM versus UM				AUC_{0-72h} AP+DAP versus NM: PM: 131% IM+gendose 1.5: 110% UM: 97%
			In multiple regression analysis, nausea and vomiting was only influenced by the AUC_{0-72h} of aripiprazole, not by the CYP-2D6 phenotype. This suggests that the CYP2D6 phenotype exerts its effect via its influence on the AUC_{0-72h} of aripiprazole (and the AUC_{0-72h} of aripiprazole + dehydroaripiprazole),				
		dizziness	No association with CYP2D6 phenotype (NS).				
		headache	No association with CYP2D6 phenotype (NS).				
		AUC_{0-72h} aripiprazole + dehydroaripiprazole	x 1.31 (NS), S in multiple regression analysis (adjusted for dose/ weigth)	x 1.10 (NS)	x 0.97 (NS)	1932.9 ng.h/ml	
			As the number of active alleles increased, the AUC_{0-72h} of aripiprazole + dehydroaripiprazole decreased (S, NS after correcting for dose/weight, but S in multiple regression analysis).				
		AUC_{0-72h} aripiprazole	x 1.50 (S), also S in multiple regression analysis (adjusted for dose/ weigth)	x 1.20 (S), also S in multiple regression analysis (adjusted for dose/ weigth)	x 0.89 (NS)	1497.9 ng.h/ml	
			As the number of active alleles increased, the AUC_{0-72h} of aripiprazole decreased (S, also S in multiple regression analysis).				
		AUC_{0-72h} dehydroaripiprazole	x 0.68 (NS)	x 0.79 (S), also S in multiple regression analysis (adjusted for dose/ weigth)	x 1.23 (NS)	431.9 ng.h/ml	
			As the number of active alleles increased, the AUC_{0-72h} of dehydro-aripiprazole increased (S, also S in multiple regression analysis).				

<table>
<tr><td>ref. 5, continuation</td><td></td><td>The authors indicate that aripiprazole concentrations are more important than dehydroaripiprazole concentrations in inducing side effects due to a blockage of dopamine receptors, like nausea/vomiting.

NOTE: Genotyping was performed for *3-*7, *9 and multiplication of *1 and *4. These are the most important gene variants in this Spanish population.</td><td></td></tr>
<tr><td>ref. 6
Patteet L et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. Eur J Clin Pharmacol 2016;72:175-84. PubMed PMID: 26514968.</td><td>3

PM: A
IM: A
UM: A</td><td>18 patients were treated with aripiprazole. Patients were on the same oral dose for at least 7 days (n = 17; 5-30 mg/day, median 15 mg/day) or received at least twice the same dose of long-acting subcutaneous therapy (n = 1; 14.3 mg/day (calculated as the dose of the depot formulation divided by the number of days between two injections)). 67% of patients received more than one antipsychotic.
Relevant co-medication was not excluded. Of the total group of 82 patients treated with paliperidone, risperidone, aripiprazole, haloperidol and/or zuclopenthixol, 6.1 % used a strong CYP2D6 inhibitor. None of the patients treated with aripiprazole used a moderate CYP2D6 inhibitor. Patients using strong CYP2D6 inhibitors were assigned a phenotype PM. Patients using moderate CYP2D6 inhibitors were assigned to the phenotype based on half of their gene dose.

Phenotype based on genotype and CYP2D6 inhibitor use:
- 5x NM (gene dose 2), of which 1 patient was a outlier and not included in the concentration calculations
- 9x (IM + gene dose 1.25-1.5) (approximately 67% IM)
- 3x PM (genetically PM or gene dose 0.25-2 with a strong CYP2D6 inhibitor)
- 1x UM

Results:
<table>
<tr><td colspan="6">Results versus NM (gene dose 2):</td></tr>
<tr><td></td><td>PM</td><td>IM + gene dose 1.25-1.5</td><td>UM</td><td>value for NM</td><td></td></tr>
<tr><td rowspan="2">median dose-corrected C_{ss} aripiprazole + dehydroaripiprazole</td><td>x 1.20</td><td>x 1.28</td><td>x 0.58</td><td>16.0 ng/ml. mg</td><td rowspan="2">Median dose-corrected C_{ss} AP+DAP versus *1/*1:
PM: 120%
IM+gendose 1.5: 128%
UM: 58%</td></tr>
<tr><td colspan="3">NS for the trend PM versus (IM + gene dose 1.25-1.5) versus NM versus UM</td></tr>
<tr><td></td><td colspan="4">For NM (gene dose 2), the ratio between the highest and lowest dose-corrected C_{ss} was 1.4, indicating a high variability also within one phenotype.</td></tr>
<tr><td rowspan="2">median dose-corrected C_{ss} aripiprazole</td><td>x 1.54</td><td>x 1.22</td><td>x 0.60</td><td>10.1 ng/ml. mg</td><td></td></tr>
<tr><td colspan="3">NS for the differences between subgroups, but S for the trend PM versus (IM + 1.25- 1.5) versus NM versus UM</td></tr>
<tr><td></td><td colspan="4">For NM (gene dose 2), the ratio between the highest and lowest dose-corrected C_{ss} was 1.6, indicating a high variability also within one phenotype.</td></tr>
<tr><td rowspan="2">median dose-corrected C_{ss} dehydroaripiprazole</td><td>x 0.74</td><td>x 1.26</td><td>x 0.64</td><td>5.0 ng/ml. mg</td><td></td></tr>
<tr><td colspan="3">NS for the trend PM versus (IM + gene dose 1.25-1.5) versus NM versus UM</td></tr>
<tr><td></td><td colspan="4">For NM (gene dose 2), the ratio between the highest and lowest dose-corrected C_{ss} was 1.4, indicating a high variability also</td></tr>
</table>
</td><td>Authors' conclusion: 'It was demonstrated that CYP2D6 polymorphisms affect the serum concentrations of aripiprazole.'</td></tr>
</table>

<table>
<tr><td>ref. 6, continuation</td><td></td><td>
<table>
<tr><td></td><td colspan="4">within one phenotype.</td></tr>
<tr><td>median dose</td><td>x 1.0 (NS)</td><td>x 1.0 (NS)</td><td>x 1.7</td><td>15.0 mg/day</td></tr>
</table>

NOTE: Genotyping was performed for *2-*11, *15, *17, *29, *35, *41 and duplication. These are the most important gene variants in this Belgium population.
</td><td></td></tr>
<tr><td>ref. 7
van der Weide K et al.
The influence of the CYP3A4*22 polymorphism and CYP-2D6 polymorphisms on serum concentrations of aripiprazole, haloperidol, pimozide, and risperidone in psychiatric patients.
J Clin Psychopharmacol 2015;35:228-36.
PubMed PMID: 25868121.</td><td>3

PM: A
IM: A
UM: A</td><td>128 patients were treated with aripiprazole. Therapeutic drug monitoring was routinely done. Trough plasma concentrations were determined in steady state (12 to 16 hours after dosing). For each patient, the first measured serum level and the immediate preceding daily dose were used for calculating dose-corrected plasma concentrations.
Relevant co-medication was not excluded. None of the patients used CYP3A4 inhibitors. The effect of CYP3A4 inducers on dose-corrected concentrations was not significant in multiple regression analysis.
Parameters included in multiple regression analysis were sex, age, dose, CYP2D6 phenotype, CYP3A4*22 genotype and use of CYP3A4 inducers.

Genotyping:
- 69x NM
- 44x IM
- 13x PM
- 2x UM

Results:
<table>
<tr><td colspan="5">Results versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM</td><td>value for NM</td></tr>
<tr><td rowspan="2">median dose-corrected C_{ss} aripiprazole + dehydroaripiprazole</td><td>x 1.30 (S)</td><td>x 0.89 (NS)</td><td>x 0.87 (NS)</td><td rowspan="2">14.7 ng/ml. mg</td></tr>
<tr><td colspan="3">Multiple regression analysis showed that CYP2D6 did not explain part of the variation (NS).</td></tr>
<tr><td></td><td colspan="4">The ratio between the highest and lowest dose-corrected C_{ss} was 16.8 for NM and 3.18 for PM, indicating a higher variability within one phenotype than between phenotypes.
The multiple regression analysis did not identify any parameters contributing to this high variability.</td></tr>
<tr><td rowspan="2">median dose-corrected C_{ss} aripiprazole</td><td>x 1.56 (S)</td><td>x 1.04 (NS)</td><td>x 0.89 (NS)</td><td rowspan="2">10.3 ng/ml. mg</td></tr>
<tr><td colspan="3">Multiple regression analysis showed that CYP2D6 explained 4% of the variation (S).</td></tr>
<tr><td></td><td colspan="4">The ratio between the highest and lowest dose-corrected C_{ss} was 19.2 for NM and 3.16 for PM, indicating a higher variability within one phenotype than between phenotypes.
The multiple regression analysis did not identify any other parameters contributing to this high variability.</td></tr>
<tr><td rowspan="2">median dose-corrected C_{ss} dehydroaripiprazole</td><td>x 0.58 (S)</td><td>x 0.80 (S)</td><td>x 0.93 (NS)</td><td rowspan="2">4.0 ng/ml. mg</td></tr>
<tr><td colspan="3">Multiple regression analysis showed that CYP2D6 explained</td></tr>
</table>
</td><td>Authors' conclusion: 'Heterozygous presence of CYP3A4 *22 does not increase serum levels of antipsychotics metabolized by both CYP3A4 and CYP-2D6, whereas CYP-2D6 polymorphisms do affect serum levels to a limited extent.'

Median dose-corrected C_{ss} AP+DAP versus NM:
PM: 130%
IM: 89%
UM: 87%</td></tr>
</table>

<table>
<tr><td>ref. 7, continuation</td><td></td><td>
<table>
<tr><td></td><td colspan="3">7% of the variation (S).</td><td></td></tr>
<tr><td></td><td colspan="4">The ratio between the highest and lowest dose-corrected C_{ss} was 14.7 for NM and 11.4 for PM, indicating a higher variability within one phenotype than between phenotypes.
Apart from the dose explaining 2.4%, the multiple regression analysis did not identify any other parameters contributing to this high variability.</td></tr>
<tr><td>median dose</td><td>x 1.0 (NS)</td><td>x 1.0 (NS)</td><td>x 1.0 (NS)</td><td>15 mg/day</td></tr>
</table>
NOTE: Genotyping was performed for *3-*6, *9, *10, *41 and multiplication. These are the most important gene variants in this Dutch population.
</td><td></td></tr>
<tr><td>ref. 8
Suzuki T et al. Effects of genetic polymorphisms of CYP2D6, CYP3A5, and ABCB1 on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. Ther Drug Monit 2014;36:651-5. PubMed PMID: 24682161.</td><td>4

IM: A</td><td>89 patients were treated with fixed doses aripiprazole for at least 2 weeks. The dose was 24 mg (n = 56) or 12 mg (n = 33) once daily. Blood samples were taken 19.5 hours after dosing.
Co-medication other than biperiden and flunitrazepam was excluded.
Parameters included in multiple regression analysis were sex, age, smoking, absence of CYP2D6 *1, presence of CYP3A5 *3, absence of ABCB1 3435 wild type allele, and absence of ABCB1 2677 wild type allele.

Genotyping:
- 33x *1/*1
- 49x NM+IM (43x *1/*10, 6x *1/*5)
- 7x IM (6x *10/*10, 1x *5/*10)

Results:
<table>
<tr><td colspan="4">Results versus *1/*1:</td></tr>
<tr><td></td><td>IM</td><td>NM+IM</td><td>value for *1/*1</td></tr>
<tr><td>dose-corrected C_{ss} aripiprazole + dehydroaripiprazole</td><td>x 1.66 (S)
Multiple regression analysis showed an effect of the *1-allele (S).</td><td>x 1.42 (S)</td><td>15.9 ng/ml. mg</td></tr>
<tr><td>dose-corrected C_{ss} aripiprazole</td><td>x 1.95 (S)
Multiple regression analysis showed an effect of the *1-allele (S).</td><td>x 1.45 (S)</td><td>10.4 ng/ml. mg</td></tr>
<tr><td>dose-corrected C_{ss} dehydroaripiprazole</td><td>x 1.1 (NS)
Multiple regression analysis did not show an effect of the *1-allele (NS).</td><td>x 1.3 (NS)</td><td>5.6 ng/ml. mg</td></tr>
<tr><td colspan="4">The authors indicate that the large overlaps among the different CYP2D6 genotype groups and the large inter-individual variation in each genotype group suggest that the genotyping for CYP2D6 before starting aripiprazole is of limited value for the prediction of the C_{ss} of aripiprazole and the sum of aripiprazole and dehydroaripiprazole.</td></tr>
</table>
NOTE: Genotyping was performed for *5, *10 and *14. These are the most important gene variants in this Japanese population.</td><td>Authors' conclusion: 'The findings of this study suggest that CYP2D6 genotypes play an important role in controlling steady-state plasma concentrations of aripiprazole and the sum of aripiprazole and dehydroaripiprazole in Asian subjects, whereas CYP3A5 and ABCB1 genotypes seemed unlikely to have an impact.'

Dose-corrected C_{ss} AP+DAP versus *1/*1:
IM: 166%</td></tr>
<tr><td>ref. 9
Suzuki T et al. Effects of the CYP-</td><td>4</td><td>63 patients with only the *1- and/or *10-allele were treated with fixed doses aripiprazole for at least 2 weeks. The dose was 24 mg (n = 40) or 12 mg (n = 23) once daily. Blood</td><td>Authors' conclusion: 'This study suggests that the *10 allele</td></tr>
</table>

<table>
<tr><td>2D6*10 allele on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. Ther Drug Monit 2011;33:21-4. PubMed PMID: 21157400.

ref. 9, continuation</td><td>

IM: A</td><td>samples were taken 19.5 hours after dosing.
Co-medication other than biperiden and flunitrazepam was excluded.

Genotyping:
- 27x *1/*1
- 31x *1/*10
- 5x IM (*10/*10)

Results:
<table>
<tr><td colspan="4">Results versus *1/*1:</td></tr>
<tr><td></td><td>*10/*10</td><td>*1/*10</td><td>value for *1/*1</td></tr>
<tr><td>dose-corrected C_{ss} aripiprazole + dehy-droaripiprazole</td><td>x 1.77 (S)</td><td>x 1.34 (S)</td><td>13.9 ng/ml.mg</td></tr>
<tr><td>dose-corrected C_{ss} aripiprazole</td><td>x 2.11 (S)</td><td>x 1.41 (S)</td><td>9.0 ng/ml.mg</td></tr>
<tr><td>dose-corrected C_{ss} dehydroaripiprazole</td><td>x 1.20 (NS)</td><td>x 1.20 (NS)</td><td>4.9 ng/ml.mg</td></tr>
<tr><td>dose</td><td colspan="2">no difference between the genotypes (NS)</td><td></td></tr>
<tr><td colspan="4">The authors indicate that there were large overlaps in the dose-corrected C_{ss} of aripiprazole, dehydroaripiprazole, and the sum of aripiprazole and dehydroaripiprazole among the three genotype groups and large interindividual variations in each patient group.</td></tr>
</table>
NOTE: Genotyping was performed for *5, *10 and *14. These are the most important gene variants in this Japanese population. Patients with *5 and/or *14 were excluded.</td><td>plays an important role in controlling the steady-state plasma concentra-tions of aripiprazole and the sum of aripiprazole and dehydroaripiprazole in Asian subjects.’

Dose-corrected C_{ss} AP+DAP versus *1/*1:
IM: 177%</td></tr>
<tr><td>**ref.** 10
Hendset M et al. Impact of the CYP-2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. Eur J Clin Pharmacol 2007;63:1147-51.</td><td>4

PM: A

IM: A</td><td>The plasma concentrations were determined during routine therapeutic drug monitoring in 62 patients (37x NM (*1/*1), 17x IM (16x *1/*4, 1x *1/*5), 8x PM (4x *4/*4, 3x *4/*5, 1x *5/*6)) receiving aripiprazole 5-40 mg/day. Co-medication with strong CYP2D6 inhibitors, CYP3A4 inhibitors and CYP3A4 inducers was excluded.

PM versus NM:
- increase in median Css[a] AP+DAP from 37.0 to 53.9 nM/mg (S by 46%)
- increase in median Css[a] AP from 26.3 to 45.5 nM/mg (S by 73%)
- increase in median Css[a] DAP from 7.9 to 8.4 nM/mg (NS by 6%)

IM versus NM:
- increase in median Css[a] AP+DAP from 37.0 to 42.6 nM/mg (S by 15%)
- increase in median Css[a] AP from 26.3 to 33.5 nM/mg (S by 27%)
- increase in median Css[a] DAP from 7.9 to 8.2 nM/mg (NS by 4%)

NOTE: Genotyping was performed for *3-*8 and gene dupli-cation.</td><td>Authors’ conclusion: “The present study demonstrates that serum concentra-tions of both ARI and the active sum of ARI + DARI in psychiatric patients were significantly affected by CYP2D6 genotype. The ob-served differences in median C/D ratios indicate that PMs typically need 30–40% lower doses to achieve a similar steady-state serum concentration as NMs.”

Median Css[a] AP+ DAP versus NM:
PM: 146%
IM: 115%</td></tr>
<tr><td>**ref. 11**
Kubo M et al. Pharmacokinetics of aripiprazole, a new antipsychotic, follo-wing oral dosing in</td><td>4</td><td>A total of 20 healthy Japanese volunteers (9x NM (1x *1/*1, 2x *1/*2, 5x *1/*10, 1x *2/*41), 11x IM (5x *10/*10, 4x *5/*10, 1x *1/*5, 1x *41/*41)) received a single dose of aripiprazole 6 mg.

IM versus NM:</td><td></td></tr>
</table>

healthy adult Japanese volunteers: influence of CYP2D6 polymorphism. Drug Metab Pharmacokinet 2007;22:358-66. **ref. 11, continuation**	IM: A	- increase in AUC for AP from 1459 ng.h/mL to 2487 ng.h/mL (S by 70%) - decrease in Cl_{or} for AP from 4186 mL/hour to 2569 mL/hour (S by 38%) A total of 15 healthy Japanese volunteers (11x NM# (2x *1/*1, 2x *1/*2, 6x *1/*10, 1x *1/*5), 1x IM (*10/*10), 3x Type *2 (1x *2/*2, 1x *2/*5, 1x *2/*10)) received aripiprazole 3 mg/day for a period of 2 weeks. IM versus NM#: - increase in AUC_{24hr} AP+DAP from 731.5 to 1977.7 ng.hour/mL (NS by 170%) - increase in AUC_{24hr} AP from 556.13 to 1683.2 ng.hour/mL (NS by 203%) - increase in AUC_{24hr} DAP from 175.33 to 294.5 ng.hour/mL (NS by 68%) Type *2 (IM+NM) versus NM#: - increase in AUC_{24hr} AP+DAP from 731.5 to 977.2 ng.hour/mL (NS by 34%) - increase in AUC_{24hr} AP from 556.13 to 789.6 ng.hour/mL (NS by 42%) - increase in AUC_{24hr} DAP from 175.33 to 187.53 ng.hour/mL (NS by 7%) NOTE: Genotyping was performed for (*2 or *41), *4, *5, *10, *14, *18 and *36. NOTE: NM# consists of 91% NM and 9% IM (*1/*5).	AUC of AP+DAP versus NM#: IM: 270%
ref. 12 Oosterhuis M et al. Safety of aripiprazole: high serum levels in a CYP2D6 mutated patient. Am J Psychiatry 2007;164:175.	2 PM: C	A 51-year-old female patient experienced progressive symptoms of lethargy and memory loss following an increase in the aripiprazole dose from 15 to 30 mg/day due to insufficient clinical effectiveness. C_{ss} AP was found to be 2990 ng/mL, approximately 7 times the expected plasma concentration at a dose of 30 mg/day (320-584 ng/mL). The patient was found to be *4/*4. Pharmacokinetic interactions with CYP3A4 were excluded, since the patient did not use concomitant medication, herbals or grapefruit juice. The side effects improved once aripiprazole was replaced by quetiapine 400 mg/day. As the plasma concentration in this patient was in the same order of magnitude as toxic concentrations in animal studies, the authors indicated that - due to the good tolerability of aripiprazole - poor metabolisers are at risk of long-term toxicity due to high plasma concentrations of AP that go undetected. NOTE: Normally, the maximum dose of aripiprazole is 15 mg/day. Problems only occurred after exceeding this maximum dose.	Authors' conclusion: "The high serum levels of aripiprazole, not the adverse events, are disconcerting. Assuming our patient to represent all poor metabolizers, many patients would potentially be at risk of long-term toxicity because of the good tolerability of aripiprazole."
ref. 13 Kim E et al. Effects of DRD2 and CYP2D6 genotypes on delta EEG power response to aripiprazole in healthy male volunteers: a preliminary study. Hum Psychopharmacol 2006;21:519-28.	3 IM: AA	A total of 17 healthy volunteers (5x NM (3x *1/*1, 1x *2/*2, 1x *2/*41), 2x IM (2x *1/*5), 9x IM+NM (4x *10/*10, 5x *1/*10), (1x UM (*2N/*10)) received a single dose of aripiprazole 10 mg. Absolute delta power derived from a quantitative EEG was used as a pharmacodynamic parameter, because this exhibits a significant change in schizophrenic patients on aripiprazole. *1/*5 versus NM+UM (gene dose ≥ 2): - increase in AUC_{72hr} AP from 1557.2 to 1957.1 ng.hour/mL (NS by 26%) - decrease in Cl_{or} AP from 4.7 to 3.5 L/hour (NS by 26%) - increase in $t_{1/2}$ AP from 46.0 to 54.7 hours (NS by 19%)	Authors' conclusion: "The linear relationship between AUC and AUEC and the trend of different AUC according to CYP2D6 genotypes suggest that the clinical effects of aripiprazole could be influenced by CYP2D6 genotypes and that dose ad-

ref. 13, continuation		- trend towards higher area under the EEG response-time curve ($AUEC_{6hr}$) IM+NM (*10/*10 + *1/*10) versus NM+UM (gene dose ≥ 2): - increase in AUC_{72hr} AP from 1557.2 to 1749 ng.hour/mL (NS by 12%) - decrease in Cl_{or} AP from 4.7 to 3.6 L/hour (NS by 23%) - increase in $t_{1/2}$ AP from 46.0 to 64.0 hours (NS by 39%) Plasma concentrations of DAP were much lower than those of AP and were not included in the analysis. After exclusion of two outliers, a significant linear relationship was found between AUC AP and AUEC for the periods from 0-2 hours and 0-6 hours after ingestion. In addition to *1/*5, a trend towards higher $AUEC_{6hr}$ was also observed in *1/*10. NOTE: Genotyping was performed for *2, *5, *10, *17, *41 and gene duplication.	justment of aripiprazole could be needed according to CYP2D6 genotypes."
ref. 14 Kubo M et al. Influence of itraconazole co-administration and CYP2D6 genotype on the pharmacokinetics of the new antipsychotic aripiprazole. Drug Metab Pharmacokinet 2005;20:55-64.	3 IM: A	A total of 24 healthy study subjects, 18x NM (4x *1/*1, 10x *1/*10, 4x *2/*10), 6x IM (3x*10/*10, 3x *1/*5), single dose of 3 mg aripiprazole, no relevant co-medication; IM versus NM: - increase in AUC AP+DAP from 990 to 1011 ng.hour/mL (significance unknown, by 2%) - increase in AUC AP from 702 to 800 ng.hour/mL (significance unknown, by 14%) - decrease in AUC DAP from 288 to 211 ng.hour/mL (significance unknown, by 27%) *10/*10 versus *1/*1: - increase in AUC AP+DAP from 931 to 1176 ng.hour/mL (significance unknown, by 26%) - increase in AUC AP from 612 to 960 ng·hour/mL (S by 87%) - decrease in AUC DAP from 319 to 216 ng·hour/mL (NS by 32%), NOTE: Genotyping was performed for *2, *4, *5, *10, *14, *18 and *36. NOTE: in this case, *2 is either *2 or *41 (see Kubo, 2007).	AUC AP+DAP versus NM: IM: 102%
ref. 15 SmPC Abilify (aripiprazole) 20-10-20.	0 PM: AA	<u>Pharmacokinetics</u>: The mean elimination half-lives for aripiprazole are approximately 75 hours in normal metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6. <u>Interactions</u>: In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 normal metabolisers.	
ref. 16 SmPC Abilify Maintena (aripiprazole for prolonged-release suspension) 02-12-20.	0 PM: A	<u>Dose</u>: In patients who are known to be CYP2D6 poor metabolisers: • One injection start: The starting dose should be 300 mg Abilify Maintena and continue treatment with prescribed dose of oral aripiprazole per day for 14 consecutive days. • Two injection start: The starting dose should be 2 separate injections of 300 mg Abilify Maintena along with one single dose of the previous prescribed dose of oral aripiprazole. For known CYP2D6 poor metabolisers administer in either two separate deltoid muscles or one deltoid and one gluteal muscle. DO NOT inject into two gluteal muscles.	Dose versus NM: PM: 75%

<table>
<tr>
<td>ref. 16, continuation</td>
<td></td>
<td>In patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP3A4 inhibitor:
• The one injection start: The starting dose should be reduced to 200 mg and continue treatment with the prescribed dose of oral aripiprazole per day for 14 consecutive days.
• Two injection start is not to be used in patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP3A4 inhibitor.
After the injection start, see table below for the recommended maintenance dose of Abilify Maintena. Abilify Maintena should be administered once monthly as a single injection (no sooner than 26 days after the previous injection).
Maintenance dose adjustments of Abilify Maintena in patients who are taking concomitant strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, and/or CYP3A4 inducers for more than 14 days
<table>
<tr><th></th><th>Adjusted dose</th></tr>
<tr><td>Patients taking 300 mg of Abilify Maintena</td><td></td></tr>
<tr><td>Strong CYP2D6 or strong CYP3A4 inhibitors</td><td>200 mg*</td></tr>
<tr><td>Strong CYP2D6 and strong CYP3A4 inhibitors</td><td>160 mg*</td></tr>
<tr><td>CYP3A4 inducers</td><td>Avoid use</td></tr>
</table>
* 200 mg and 160 mg can be achieved via adjustment of the injection volume only by using Abilify Maintena powder and solvent for prolonged-release suspension for injection.
Pharmacokinetics:
Based on population pharmacokinetic evaluation of Abilify Maintena, the total body clearance of aripiprazole was 3.71 L/h in normal metabolisers of CYP2D6 and approximately 1.88 L/h (approximately 50% lower) in poor metabolisers of CYP2D6.
Interactions:
In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 normal metabolisers.</td>
<td>Dose versus NM:
PM: 67-80%</td>
</tr>
<tr>
<td>ref. 17
SmPC Abilify (aripiprazole) 02-05-20, USA.</td>
<td>0
PM: A</td>
<td>Dose:
Known CYP2D6 poor metabolizers: Half of the usual dose.
Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers (see Table).
Dosage adjustments for Abilify in patients who are known CYP2D6 poor metabolizers
<table>
<tr><th>Factors</th><th>Dosage adjustments for Abilify</th></tr>
<tr><td>Known CYP2D6 poor metabolizers</td><td>Administer half of usual dose</td></tr>
<tr><td>Known CYP2D6 poor metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)</td><td>Administer a quarter of usual dose</td></tr>
</table>
When adjunctive Abilify is administered to patients with major depressive disorder, Abilify should be administered without dosage adjustment.
Pharmacokinetics:
The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydroaripiprazole, respectively. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.
Use in specific populations:
Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM).</td>
<td>Dose versus NM:
PM: 50%</td>
</tr>
</table>

<table>
<tr><td>ref. 17, continuation</td><td></td><td>Interactions:
Based on simulation, a 4.5-fold increase in mean C_{max} and AUC values at steady-state is expected when normal metabolizers of CYP2D6 are administered with both strong CYP-2D6 and CYP3A4 inhibitors. A 3-fold increase in mean C_{max} and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.</td><td></td></tr>
<tr><td>ref. 18
SmPC Aristad (aripiprazole lauroxil, extended-release injectable suspension) 27-08-20, USA.</td><td>0
PM: A</td><td>Dose:
Dose adjustments are required for known CYP2D6 poor metabolizers.
Aristada dose adjustments with concomitant CYP450 modulators added for more than 2 weeks
<table>
<tr><th>Concomitant medicine</th><th>Dose change for Aristada[a]</th></tr>
<tr><td>Strong CYP3A4 inhibitor</td><td>Reduce the dose of Aristada to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg Aristada, if tolerated.
For patients known to be poor metabolizers of CYP2D6: Reduce dose to 441 mg from 662 mg, 882 mg, or 1064 mg. No dosage adjustment is necessary in patients taking 441 mg Aristada, if tolerated.</td></tr>
<tr><td>Strong CYP2D6 inhibitor</td><td>Reduce the dose of Aristada to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg Aristada, if tolerated.
For patients known to be poor metabolizers of CYP2D6: No dose adjustment required.</td></tr>
</table>
[a] For the 882 mg dose administered every 6 weeks and the 1064 mg administered every 2 months, the next lower strength should be 441 mg administered monthly.
Administer one 675 mg injection of Aristada Initio and one 30 mg dose of oral aripiprazole in conjunction with the first Aristada injection. Avoid use of Aristada Initio in known CYP2D6 poor metabolizers.
Use in specific populations:
Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM).
Interactions:
Based on simulation, a 4.5-fold increase in mean C_{max} and AUC values at steady-state is expected when normal metabolizers of CYP2D6 are administered with both strong CYP-2D6 and CYP3A4 inhibitors. After oral administration, a 3-fold increase in mean C_{max} and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.</td><td>Dose versus NM:
PM: 41-67%</td></tr>
</table>

[a] Corrected for dose.

Risk group	PM and IM and use of CYP3A4 inhibitors, UM and use of CYP3A4 inducers

Comments:

- From 2008 onwards, studies with kinetic endpoints were only included if exposure of the sum of aripiprazole and dehydroaripiprazol for at least one of the phenotypes PM, IM or UM was compared with exposure for NM or *1/*1. The meta-analysis of Milosavljevic 2021 (Milosavljevic F et al. Association of CYP2C19 and CYP2D6 poor and intermediate metabolizer status with antidepressant and antipsychotic exposure: a systematic review and meta-analysis. JAMA Psychiatry 2021;78:270-80) was not included, because there seems to be some irregularities and the IM definition used seems to differ from our definition. For Van der Weide 2015, the included data were based on aripiprazole instead of aripiprazole + dehydroaripiprazole. In addition, IM data from Van

der Weide 2015 and Belmonte 2018 were ignored, whereas IM data from studies defining gene dose 1/0 (which is the major IM group in the Netherlands) as NM were included in the meta-analysis.
Studies investigating the effect of CYP2D6 phenotype on adverse events were only included if they involved at least 1 PM or at least 10 IM. Studies investigating the effect of CYP2D6 phenotype on surrogate parameters like prolactin concentration were only included if an effect of (dehydro)aripiprazole concentration on this parameter had been shown, and from 2018 only if it were multiple dose studies. Reports on results of genotype-guided dosing were only included if they involved more dan 1 patient.
Other studies did not contribute sufficiently to the burden of proof.

Date of literature search: 30 June 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetic Working Group decision	PM	4 C	yes	yes	13 September 2021
	IM	4 B	yes	no	
	UM	4 A	yes	no	

Mechanism:
Aripiprazole is primarily metabolised by CYP3A4 and CYP2D6, resulting in formation of the metabolite dehydro-aripiprazole, which has an activity similar to that of aripiprazole. Dehydroaripiprazole is further metabolised by CYP3A4 and CYP2D6 to inactive metabolites. A CYP2D6 genetic polymorphism may cause a change in the plasma concentration of aripiprazole and the active metabolite.
According to the NVZA, the therapeutic range of aripiprazole is 100-300 ng/ml and values higher than 500 ng/ml are considered to be toxic.
The NVZA states that the therapeutic range of aripiprazole + dehydroaripiprazole is unknown, but in literature, a therapeutic range of aripiprazole + dehydroaripiprazole of 150-500 ng/ml is mentioned (Hiemke C et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 2018; 51:9-62).

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