CYP2D6: oxycodone 1586/1587/1588

C_{ss} = steady-state plasma concentration, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metaboliser (gene dose 0,5-1) (decreased CYP2D6 enzyme activity), MR = metabolic ratio, NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, UM = ultrarapid metaboliser (gene dose ≥ 3) (enhanced 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:
Oxycodone is predominantly metabolised by CYP3A4 to noroxycodone and to a lesser extent by CYP2D6 to oxymorphone. Oxymorphone has approximately 14x the analgesic activity of oxycodone, for noroxycodone this is approximately 0.01x. Noroxymorphone is a strong μ-opioid receptor agonist, but does not penetrate the blood-brain barrier and therefore lacks a central effect.
Pharmacokinetic studies show a decreased plasma concentration of oxymorphone in patients with gene variants leading to absent or diminished CYP2D6 activity (poor metabolisers (PM) and intermediate metabolisers (IM), indicating a gene-drug interaction.
In cases and in studies involving administration of a single dose, an increased incidence of side effects has been observed in patients with gene variants leading to an enhanced CYP2D6 activity (ultrarapid metabolisers (UMs); 1 case) and inadequate pain relief in poor metabolisers (PM; 3 cases). However, none of the 9 studies in patients (with the number of patients varying from 20 to 918 and including 4 studies with more than 100 patients) showed a significant clinical effect of a variant CYP2D6 phenotype. Reasons for this might be that oxycodone is always titrated guided by pain, that patients often use additional analgesics and that the effect of differences in pain intensity between patients is much stronger than the effect of CYP2D6 phenotype. The Pharmacogenetics Working Group considers the evidence for an effect of CYP2D6 phenotype on oxycodone treatment in patients insufficient. For this reason, no action is advised for these gene-drug interactions (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 on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below follows the KNMP definitions for EM, PM, IM and UM. The definitions of EM, 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 Cajanus K et al. Analgesic plasma concentrations of oxycodone after surgery for breast cancer-which factors matter? Clin Pharmacol Ther 2017 Jun 23 [Epub ahead of print]. PubMed PMID: 28643329.	3	918 women were treated with intravenous oxycodone for approximately 2.5 hours after surgery for breast cancer. The women received oxycodone 1-3 mg every 5 minutes until the pain intensity they reported on a 10-point scale was less than 3. After this, pain scores were recorded every 15 minutes until the women needed a new dose. Preoperatively, the women received 1 g of paracetamol and directly after the operation 1 μg/kg of intravenous fentanyl. Because 397 patients did not need a new dose after the first state of satisfactory analgesia, data on the concentrations when patients needed a new dose were only available for 521 patients. 75% of patients had a moderate motion pain intensity (score 4-6 on a 10-point scale), 18% had a high motion pain intensity (score ≥ 7). The CYP2D6 phenotype distribution of 47 women, who did not need oxycodone after surgery, did not differ from that of	Authors' conclusion: 'CYP2D6 and CYP-3A genotypes did not affect analgesic concentration or duration of analgesia.'

<table>
<tr>
<td>ref. 1, continuation</td>
<td>PM: A
IM: A
UM: A</td>
<td>
the 918 women who needed oxycodone.
Relevant co-medication was not excluded.
The measured mean oxymorphone concentrations were around the lower limit of quantification (0.1 ng/ml). Oxymorphone concentrations below the limit of quantification were replaced with half of the quantification limit.

Genotyping:
- 799x ‘EM’
- 16x ‘IM’
- 23x ‘PM’
- 80x ‘UM’

Results:
<table>
<tr><td colspan="6">Results compared to ‘EM’:</td></tr>
<tr><td></td><td colspan="3">‘PM’ ‘IM’ ‘UM’</td><td>value for ‘EM’</td></tr>
<tr><td colspan="5">First state of satisfactory analgesia:</td></tr>
<tr><td>total amount of oxycodone needed</td><td colspan="3">NS for PM versus IM versus EM versus UM</td><td>0.11 mg/kg</td></tr>
<tr><td>duration of the analgesic effect</td><td colspan="3">NS for PM versus IM versus EM versus UM</td><td>67.3 min</td></tr>
<tr><td>oxycodone concentration</td><td colspan="3">NS for PM versus IM versus EM versus UM, both in univariate and in multivariate logistic regression analysis.</td><td>33.0 ng/ml</td></tr>
<tr><td rowspan="2">oxymorphone concentration</td><td>x 0.45</td><td>x 0.55</td><td>x 1.5</td><td rowspan="2">0.11 ng/ml</td></tr>
<tr><td colspan="3">S for PM versus IM versus EM versus UM</td></tr>
<tr><td rowspan="2">noroxymorphone concentration</td><td>x 0.29</td><td>x 0.41</td><td>x 1.5</td><td rowspan="2">0.17 ng/ml</td></tr>
<tr><td colspan="3">S for PM versus IM versus EM versus UM</td></tr>
<tr><td colspan="5">When the patient needed a new dose:</td></tr>
<tr><td>oxycodone concentration</td><td colspan="3">NS for PM versus IM versus EM versus UM</td><td>21.6 ng/ml</td></tr>
<tr><td rowspan="2">oxymorphone concentration</td><td>x 0.43</td><td>x 0.64</td><td>x 1.6</td><td rowspan="2">0.14 ng/ml</td></tr>
<tr><td colspan="3">S for PM versus IM versus EM versus UM</td></tr>
<tr><td rowspan="2">noroxymorphone concentration</td><td>x 0.10</td><td>x 0.27</td><td>x 1.6</td><td rowspan="2">0.62 ng/ml</td></tr>
<tr><td colspan="3">S for PM versus IM versus EM versus UM</td></tr>
<tr><td colspan="5">The oxycodone concentrations, and thus the total amount of oxycodone needed, varied strongly within each of the phenotypes (by a factor of 12-23 for PM, 3-6 for IM, 248-3110 for EM and 9-12 for UM).</td></tr>
<tr><td colspan="5">There was no correlation between the need of a new dose of oxycodone after initial satisfactory analgesia and the CYP2D6 genotype (NS).</td></tr>
</table>

NOTE: genotyping was performed for 10 gene variants using Taqman genotyping assays and for gene duplication (with determination of the number of copies). It was not stated which gene variants were determined and how the phenotypes were defined. The higher number of PM versus IM suggests that the phenotype definition differs from our definition.
</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Lam J et al.
Putative association of ABCB1 2677G>T/A with oxycodone-indu-</td>
<td>3</td>
<td>A nested case-control study compared 16 breastfeeding, oxycodone using mothers with symptoms of sleepiness and lethargy in the infant with 50 breastfeeding oxycodone using mothers with asymptomatic infants. The study also compared the 40 mothers with symptoms of sleepiness and</td>
<td>Authors’ conclusion: ‘Genetic variants in the maternal CYP-2D6, ABCB1, CYP-3A5, and OPRM1</td>
</tr>
</table>

<table>
<tr>
<td>ced central nervous system depression in breastfeeding mothers.
Ther Drug Monit 2013;35:466-72.
PubMed PMID: 23783165.

ref. 2, continuation</td>
<td>PM: AA
UM: AA</td>
<td>lethargy during oxycodone use with the 26 asymptomatic mothers. Oxycodon dose and treatment duration varied between patients.
Co-medication with other sedative medications and with inhibitors of CYP2D6, CYP3A4 and P-glycoprotein was excluded.
The authors indicate that the study had only a power of 9.21% to detect the effect of CYP2D6 genotype on neonatal central nervous system depression.

Genotyping:
- 57x (EM+IM)
- 6x PM
- 3x UM

Results:
<table>
<tr><td colspan="4">Percentage of patients with oxycodone-induced symptoms of sleepiness and lethargy versus (EM+IM):</td></tr>
<tr><td></td><td>UM</td><td>PM</td><td>value for EM+IM</td></tr>
<tr><td>infants</td><td>NS</td><td>NS</td><td>25%</td></tr>
<tr><td>mothers</td><td>NS</td><td>NS</td><td>61%</td></tr>
<tr><td colspan="4">1 of the 3 UMs had a symptomatic infant and one of the 3 UMs was symptomatic herself. The UM with the symptomatic infant used a higher oxycodone dose (0.455 versus 0.043 mg/kg per day), used oxycodone for a longer period of time during breastfeeding (7 versus 3 days) and did not supplement breastfeeding with formula since birth.</td></tr>
<tr><td colspan="4">The number of days breastfeeding during oxycodone use, was associated most strongly with neonatal central nervous symptom depression. Durations longer than 4 days increased the risk.</td></tr>
</table>
NOTE: The authors indicate that maternal oxycodone use was associated with a similar incidence of neonatal central nervous system depression in breastfed infants compared with codeine, while the incidence of central nervous system depression in mothers was 17x higher with oxycodone compared with codeine.

NOTE: genotyping was performed for *3 to *10, *12, *14, **17, *29, *41 and gene duplication of *1, *2, *4 and *41 (with determination of the number of copies).

NOTE: it was not explicitly specified how the phenotype groups were defined. The reporting of 0 IMs, points to IM being defined as a genotype without a fully functional allele and with one or two partially functional alleles. This in turn points to inclusion of patients with one fully functional and one inactive allele in the EM phenotype. The genotyping results are interpreted accordingly.</td>
<td>genes alone did not correlate with oxycodone-induced CNS depression in infants. Genetic variants in CYP2D6, CYP3A5, and OPRM1 were not significantly associated with oxycodone-induced maternal CNS depression.’</td>
</tr>
<tr>
<td>ref. 3
Stamer UM et al.
CYP2D6 genotype dependent oxycodone metabolism in postoperative patients.
PloS One 2013;8:e60239.
PMID: 23555934.</td>
<td>3</td>
<td>121 patients were treated postoperatively with 0.05 mg/kg intravenous oxycodone and metamizole or paracetamol 1 g. In the event of severe pain after waking from anaesthesia, doses of 1-2 mg oxycodone were administered. Patients could subsequently self-administer doses of 1 mg oxycodone (up to once/8 minutes). All patients were also given intravenous metamizole 5 g/day or paracetamol 4 g/day. Relevant co-medication was not excluded.

Genotyping:
- 70x EM</td>
<td>Authors’ conclusion: ‘In this postoperative setting, the number of functionally active CYP2D6 alleles had an impact on oxycodone metabolism. The genotype also impacted analgesic consumption, thereby causing variation</td>
</tr>
</table>

ref. 3, continuation	 PM: A IM: A UM: A	- 38x IM - 8x PM - 5x UM PM versus IM versus EM versus UM: - no differences in the percentage of patients needing additional doses of oxycodone after waking from anaesthesia (NS) - no differences in pain scores at rest or on mobilisation (NS) - decrease in cumulative oxycodone consumption until 12 hours after surgery (S). The difference between PM and EM was significant. The difference was not significant in the 12-24 hour post-operative period. - decrease in the equi-analgesic dose versus piritramide (S) - increase in the plasma concentration of oxymorphone (S) - none of the patients required a switch to piritramide due to lack of efficacy or side effects - only 2 of the patients were dissatisfied with the level of pain relief (1 PM and 1 EM) - 25% of the PM, 11% of the IM, 9% of the EM and 0% of the UM reported that the opioid doses were too low (NS) NOTE: genotyping was performed for *3 to *8, *10, *41 and gene duplication.	of equianalgesic doses piritramide: oxycodone. Different analgesic needs by genotypes were met by PCA technology in this postoperative cohort.'
ref. 4 Andreassen TN et al. Do CYP2D6 genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study. Eur J Clin Pharmacol 2012;68:55-64. PubMed PMID: 21735164.	3 PM: A UM: AA	450 cancer patients were treated for at least 3 days with oral, intravenous or subcutaneous oxycodone. Relevant co-medication was not excluded. Similar results were found after correction of plasma concentrations for factors including CYP3A4 inhibitors or inducers, total daily dose and time since previous dose. The same was true after correction of pain intensity for paracetamol usage and oxymorphone concentrations and after correction of cognitive function for CYP2D6 inhibitors. There was a significant difference in CYP3A4 inducer usage between the genotype groups. Genotyping: - 413 EM+IM (243x *1/*1, 23x *1/*5, 12x*1/*3, 124x *1/*4, 11x *1/*6) - 27 PM (2x *3/*4, 22x *4/*4 and 3x *4/*6) - 10 UM (*2/*2xN) PM versus EM+IM versus UM: - no difference in pain intensity, fatigue, nausea, cognitive function and depression (NS). This did not change after exclusion of 7 EM and 2 UM patients who also used another opioid. - decrease in the median total daily dose of oxycodone (80, 75 and 70 mg/day respectively) (NS) - increase in the median serum concentration of oxymorphone (0.2, 1.6 and 2.3 nM respectively) (S). The difference between PM and EM was significant, but the difference between EM and UM was not. - decrease in median oxycodone serum concentration (110, 107 and 74 nM respectively) (NS) NOTE: genotyping was performed for *3 to *8 and gene duplication.	Authors' conclusion: 'CYP2D6 genotypes caused expected differrences in pharmacokinetics, but they had no pharmacodynamic consequence. CYP2D6 genotypes did not influence pain control, the adverse symptoms nausea and sedation or the risk for cognitive failure in this study of patients treated with oxycodone for cancer pain.'
ref. 5 Naito T et al. CYP3A5*3 affects plasma disposition of	3	62 patients were treated with sustained-release oxycodone twice daily. Plasma concentrations were determined 4 days after reaching the first stable dose. In the subsequent 4 weeks, doses were increased if 3 additional doses of 1/6th	Authors' conclusion: 'Oxymorphone predose plasmaconcentrations and its

noroxycodone and dose escalation in cancer patients receiving oxycodone. J Clin Pharmacol 2011;51:1529-38. PubMed PMID: 21209234. **ref. 5, continuation**	IM: A	to 1/4th of the daily dose were needed the day before (dose escalation). Relevant co-medication was not excluded, apart from triazole derivatives. Genotyping: - 46x EM + gene dose 1-0 (*1/*1, *1/*2, *2/*2, *1/*10, *2/*10, *1/*5, *2/*5) - 16x gene dose 0.5-0.5 + gene dose 0.5 (*10/*10, *5/*10) (Gene dose 0.5-0.5 + gene dose 0.5) versus (EM + gene dose 1-0): - no difference in dose escalation, not in the percentage of patients requiring dose increases or in the actual percentage dose increase (NS) - whether the first stable dose and C_{ss} of oxycodone and oxymorphone at this dose were different is not known: the dose is not given and the C_{ss} is only given after correction for dose and body weight - no effect on the incidence of the side effect drowsiness (NS) - 18% decrease in oxycodone dose- and weight-corrected C_{ss} (from 126 to 103 ng/mL per mg/kg) (NS) - 53% decrease in the oxymorphone dose- and weight-corrected C_{ss} (from 1.69 to 0.79 ng/mL per mg/kg) (S) NOTE: Genotyping was performed for *2, *5 and *10. These are the most common alleles in this Japanese patient population.	ratio to oxycodone predose plasma concentrations were significantly higher in CYP2D6 extensive metabolizers than in intermediate metabolizers but did not affect dose escalation.'
ref. 6 Zwisler ST et al. Impact of CYP2D6 genotype on post-operative intravenous oxycodone analgesia. Acta Anaesthesiol Scan 2010;54:232-40. PubMed PMID: 19719813.	3 PM: A	270 patients were treated postoperatively with intravenous oxycodone for 24 hours. The dose was 5 mg after the operation. In the event of high pain score (n=96), this was repeated once or twice on waking from anaesthesia. Patients could subsequently self-administer doses of 2 mg oxycodone (up to once/15 minutes). Approximately 60% self-administered. Analgesic co-medication was paracetamol 1 g 4x daily and diclofenac 50 mg 3x daily. Intravenous morphine (5 mg) was given in the event that oxycodone delivered inadequate pain relief. Strong CYP2D6 inhibitors (fluoxetine, paroxetine or terbinafine) were excluded. Genotyping: - 246x EM+IM (125x *1/*1, 18x *1/*9, 10x *1/*3, 86x *1/*4, 5x *1/*6, 2x *4/*9) - 24x PM (3x *3/*4, 19x *4/*4, 1x *4/*6 and 1x *6/*6) PM versus EM+IM: - 4-fold decrease in the percentage of patients needing morphine or who were dissatisfied with the level of pain relief (from 17.0% to 4.2% (NS) - no difference in the area under the pain score curve (NS) - no difference in sedation, nausea/vomiting, fatigue/drowsiness and itching (NS) - 18% decrease in cumulative self-administered oxycodone dose (from 6.89 to 5.67 mg) (NS) - 12% decrease in total cumulative oxycodone dose (from 14.7 to 12.96 mg) (NS) - 67% decrease in the oxymorphone plasma concentration (from 0.12 to 0.04 ng/mL) (S) - no difference in the oxycodone plasma concentration (41.9 versus 40.9 ng/mL) (NS) NOTE: genotyping was performed for *3, *4, *6 and *9.	Authors' conclusion: 'This study showed for the first time in patients that the oxymorphone formation depends on CYP2D6, but we found no difference in the post-operative analgesic effect of intravenous oxycodone between the two CYP2D6 genotypes.'

ref. 7 Lemberg KK et al. Does co-administration of paroxetine change oxycodone analgesia: an interaction study in chronic pain patients. Scan Jour Pain 2010:1;24-33. No Pubmed ID.	3 UM: AA IM: AA	20 patients were initiated on a stable twice daily sustained-release oxycodone dose, on 3 days of which they were allowed to use morphine no more than twice daily for breakthrough pain. This dose was continued for 1 week. Outcome parameters were measured on the 7th day. Most patients also used non-opioid analgesics. Strong CYP2D6 inhibitors were excluded. Genotyping: - 14x EM - 4x IM - 2x UM UM versus EM versus IM: - no difference in pain scores (NS) - no difference in pharmacokinetics (NS) The authors stated that the lack of results may have been caused by the small sample size. NOTE: genotyping was performed for *3 to *8, *41 and gene duplication.	Authors' conclusion: 'No statistically significant associations of the CYP2D6 or CYP3A4/5 genotype of the patients and the pharmacokinetics of oxycodone or its metabolites or analgesic effects were observed probably due to the limited number of patients studied.'
ref. 8 Samer CF et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. Br J Pharmacol 2010;16:919-30. PubMed PMID: 20590588.	3 PM: B UM: B	9 volunteers received a single dose of 0.2 mg/kg oxycodone. Various tests were performed 0.5, 1, 1.5, 2, 3 and 6 hours after administration. Naloxone was administered 1.5 hours after administration. Co-medication was excluded. Genotyping: - 6x EM + gene dose 1 (1x *1/*41, 1x *2/*41, 1x *5/*35, 1x *4/*35, 1x *1/*4 and 1x *1/*6) - 2x PM + gene dose 0.5 (*4/*4, *5/*41) - 2x gene duplications (*41/*41xN, *1/*2xN) (PM + gene dose 0.5) versus (EM + gene dose 1) versus gene duplication: - decreased pain threshold on exposure to ice water and on electrical nerve stimulation (S) - decreased pupillary constriction (opioids decrease pupil size) (S) - decreased sedation (S) - increased oxygen saturation (NS, but a trend) - increased functioning in psychomotor test (replacing a numerical digit) (S for UM versus EM, not determined for PM versus EM) - decreased percentage of patients with spontaneously reported side effects (0% versus 17% versus 100%) (NS). Side effects were mild for EM and mild to severe for UM. In a parallel experiment, ketoconazole-driven CYP3A4 inhibition doubled the number of side effects reported. NOTE: genotyping was performed for all 32 alleles and gene duplication (AmpliChip).	Authors' conclusion: 'CYP2D6 activity was correlated with oxycodone experimental pain assessment. CYP2D6 ultra-rapid metabolizers experienced increased pharmacodynamic effects, whereas cold pressor test and pupil size were unchanged in CYP2D6 poor metabolizers, relative to extensive metabolizers.'
ref. 9 Comer SD et al. Abuse liability of oxycodone as a function of pain and drug use history. Drug Alcohol Depend 2010;109:130-8. PubMed PMID: 20079977	3 IM+PM: AA	9 volunteers addicted to prescription opioids and 8 volunteers who had used prescription opioids but who were not addicted were genotyped. Results: - higher percentage of IM+PM in the addicted group versus the non-addicted group (89% versus 38%) (NS) The authors stated that the results are to be interpreted with caution due to the small sample size.	Authors' conclusion: 'In the present study 89% of the prescription opioid abusers had a genotype consistent with either a poor or intermediate metabolizer phenotype, compared to 38% of the non-drug abusers.'

ref. 10 Jannetto PJ et al. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. Pharmacogenomics 2009;10:1157-67.	3 PM: AA IM: AA	29 chronic pain patients (2x PM, 14x IM, 13x EM; genotyping for *3 to *8 and gene duplication), who used oxycodone monotherapy or combination therapy with methadone, tramadol or hydrocodone; 32 additional patients on tramadol, methadone or hydrocodone therapy; co-medication not excluded. PM versus IM versus EM; all patients: - therapy delivers complete pain relief in 0% versus 20% versus 21%. - therapy delivers no pain relief in 0% versus 12% versus 21%. - trend towards a decrease in C_{ss} with an increase in the number of functional genes. - higher percentage of patients with side effects for PM + IM (4%) than for EM (2%). The only EM with side effects also used multiple CYP2D6 substrates. PM versus EM; oxycodone: - decrease in C_{ss}[a] by 74% (from 39 to 20 ng/mL per mg/kg). However, this was caused by non-compliance of both PMs. IM versus EM; oxycodone: - increase in C_{ss}[a] by 54% (NS, from 39 to 60 ng/mL per mg/kg). Oxycodone, all genotypes: - therapeutic response only if C_{ss} > 15 ng/mL. This is consistent with the previously reported therapeutic range of 20-50 ng/mL. - on average, patients with complete response had lower C_{ss} than patients with partial response (approximately 19 ng/mL versus approximately 27 ng/mL) (NS).	Authors' conclusion: 'These results suggest that patient care may be improved by genotyping and following therapeutic drug concentrations. In addition, this study clearly demonstrated a relationship between oxycodone steady-state drug concentrations and pain relief.' C_{ss} oxycodone versus EM: IM: 154%
ref. 11 Zwisler ST et al. The hypoalgesic effect of oxycodone in human experimental pain models in relation to the CYP2D6 oxidation polymorphism. Basic Clin Pharmacol Toxicol 2009;104:335-44.	3 PM: B	33 volunteers, 17x PM and 16x EM[#] (phenotyped using tramadol), a single dose of 20 mg oxycodone or placebo at a 1 week interval, no relevant co-medication and alcohol. Plasma concentrations were determined approximately 1 hour after administration of the medication. PM versus EM[#]: - decrease in pain threshold and pain tolerance on electrical stimulation of the calf nerve by 55% and 42% respectively (S, from 20% to 9% and from 26% to 15% respectively). - decrease in the area under the pain-time curve in a cold pressor test by 46% (S, from 26% to 14%). - decrease in the total score for the severity of side effects by 28% (NS, from 9.5 to 6.8). - increase in the lengthening of response time in the total choice reaction test by 81% (S, mean from 6% to 11%). - decrease in the oxymorphone/oxycodone plasma concentration ratio by 58% (S, from 0.010 to 0.0042). NOTE: genotype unknown. It is not possible to distinguish between EM, IM and UM based on phenotyping. EM[#] is therefore equal to EM + IM + UM.	Authors' conclusion: 'The results indicate that oxycodone metabolism to oxymorphone via CYP2D6 is contributing to the analgesic effect of oxycodone, but it is not responsible for all of its effect.'
ref. 12 Foster A et al. Complicated pain management in a CYP450 2D6 poor metabolizer. Pain Pract	1 PM: B	- female patient, *4/*4, history of inadequate response to codeine and nausea/vomiting on morphine, oxycodone 20 mg plus paracetamol 650 mg every 4 hours for post-traumatic pain relief; No or inadequate pain relief achieved. The patient was switched to hydrocodone, which delivered some pain relief and seems to be tolerated better than	

2007;7:352-6.		other opioids.	
ref. 13 Susce MT et al. Response to hydrocodone, codeine and oxycodone in a CYP-2D6 poor metabolizer. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1356-8.	2 PM: B	- female patient, *4/*6, with codeine intolerance, received oxycodone 10-30 mg/day after hip surgery, no CYP2D6 inhibitors as co-medication; Nausea and vomiting, no analgesic effect, tramadol requirement. Hydrocodone 20-25 mg/day results in better pain relief and fewer side effects.	Authors' conclusion: 'This case report appears to suggest that, like codeine, oxycodone may need CYP2D6 to provide analgesic effects.'
ref. 14 de Leon J et al. Adverse drug reactions to oxycodone and hydrocodone in CYP2D6 ultrarapid metabolizers. J Clin Psychopharmacol 2003;23:420-1.	1 UM: B	- male patient, *2xn/*1, used 10 mg oxycodone twice and developed insomnia, anxiety and extra alertness.	
ref. 15 Maddocks I et al. Attenuation of morphine-induced delirium in palliative care by substitution with infusion of oxycodone. J Pain Symptom Manage 1996;12:182-9.	2 PM: B	13 cancer patients with delirium on morphine, 1x PM, 11x EM# and 1x phenotype not known (phenotyped using dextromethorphan), continuous oxycodone SC for 6 days 15-250 mg/24h, including the CYP2D6 inhibitor haloperidol as co-medication; - PM: initial dose (200 mg/24h) and final dose (250 mg/24h) of oxycodone were higher than in EM# patients. Delirium resolved but pain scores (visual analogue scale) worsened, from 1.0 to 3.46 while EM# patients showed a non-significant decrease from 3.0 to 1.62. The patient needed 13 times fentanyl for breakthrough pain. NOTE: genotype unknown. It is not possible to distinguish between EM, IM and UM based on phenotyping. EM# is therefore equal to EM + IM + UM.	

[a] Corrected for dose and body weight.

Risk group	-

Comments:

- Articles published after 2009 including kinetic data alone were not included, because they do not contribute sufficiently to the burden of proof**.** Enzyme activity is the limiting factor for PM and IM patients and dose increase will therefore have no or little effect. Adequate pain relief can be achieved in UM patients without the occurrence of side effects.
  Studies in which clinical effects were modelled instead of measured were not included in the risk analysis.
- Existing guidelines:
  - Crews KR et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. Clin Pharmacol Ther 2012;91:321-6. PubMed PMID: 22205192
    and
    Crews KR et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014;95:376-82. PubMed PMID: 24458010.
    CPIC does not have a guideline for oxycodone, but the guideline for codeine contains also information on oxycodone.
    CPIC uses the same definition for PM as we do. However, CPIC uses other definitions for EM (gene dose 1-2), IM (gene dose 0.5) and UM (gene dose ≥ 2.5). In the recommendations below, the KNMP definitions for EM, PM, IM and UM are used. CPIC indicates that classifying patients with an activity score of 1.0 as EMs in this guideline is based on data specific for formation of morphine from codeine in these patients (Lötsch J et al. Can

extremely low or high morphine formation from codeine be predicted prior to therapy initiation? Pain 2009;144:119-24).
CPIC indicates that CYP2D6 poor metabolizers have been shown to have lower peak concentrations of oxymorphone after a dose of oxycodone as compared with extensive metabolizers (Zwisler 2010 and Andreassen 2012). However, conflicting data exist on the association of CYP2D6 metaboliser phenotype with the analgesic effect and toxicity of oxycodone in prospective clinical studies. Differential analgesic response to experimental pain was observed between extensive metabolisers and poor metabolisers, as well as between ultrarapid metabolisers and extensive and poor metabolisers in two studies in healthy volunteers (Zwisler 2009 and Samer 2010). However, clinical studies in postoperative patients and in cancer patients failed to demonstrate a significant difference in analgesia or side effects of oxycodone across CYP2D6 phenotypes (Zwisler 2010 and Andreassen 2012). Due to these conflicting data, it is difficult to conclude whether CYP2D6 metaboliser phenotype affects oxycodone analgesia or risk of toxicity. The differences in reported associations of CYP2D6 phenotype with hydrocodone and oxycodone analgesia as compared with that of codeine may be due to differing relative roles of the parent drug and the circulating metabolites in analgesia among these CYP2D6 substrates (Lalovic B et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther 2006;79:461-79.).
Based on the data above, CPIC concludes that it is premature to recommend routine therapy adjustment for oxycodone on the basis of CYP2D6 genotype, but that use of an analgesic other than the CYP2D6 substrates tramadol, hydrocodone, or oxycodone in poor metabolizers may be preferable.

Phenotype/ genotype group	**Considerations for alternative opioids (i.e. alternatives for codeine)**
UM + gene dose 2.5	Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[a]
PM	Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[a]

[a] Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with non-opioid analgesics, may be considered as alternatives for use in CYP2D6 PMs and UMs.

The recommendations above are still the same after the last update on 20-4-2017 on the PharmGKB-site.

Date of literature search: 18 October 2017.

	Phenotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
Decision of the Dutch Pharmacogenetics Working Group	PM	3 B	yes	no	20 November 2017
	IM	3 A	yes	no	
	UM	3 B	yes	no	

Mechanism:
Oxycodone is predominantly metabolised by CYP3A4 to noroxycodone and to a lesser extent by CYP2D6 to oxymorphone. Oxymorphone has approximately 14x the analgesic activity of oxycodone, for noroxycodone this is approximately 0.01x. Noroxymorphone is a strong μ-opioid receptor agonist, but does not penetrate the blood-brain barrier and therefore lacks a central effect.
A CYP2D6 genetic polymorphism may change the plasma concentrations of oxycodone and oxymorphone.