

Appendix A

Table S1: List of intermediate and strong inducers and inhibitors of CYP3A4 and CYP2D6. Compounds in bold are strong inhibitors/inducers. Based on the KNMP kennisbank from the Royal Dutch Pharmacists Associations and the FDA Drug Development and Drug Interaction: Table of Substrates, Inhibitors and Inducers.

CYP3A4		CYP2D6	
<i>Inhibitors</i>	<i>Inducers</i>	<i>Inhibitors</i>	<i>Inducers</i>
Clarithromycin	Carbamazepine	Bupropion	None
Cobicistat	Efavirenz	Cinacalcet	
Erythromycin	Enzalutamide	Fluoxetine	
Itraconazole	Hypericum	Quinidine	
Ketoconazole	Mitotane	Paroxetine	
Posaconazole	Nevirapine	Terbinafine	
Ritonavir	Phenobarbital	Abiraterone	
Voriconazole	Phenytoin	Duloxetine	
Aprepitant	Primidone	Mirabegron	
Crizotinib	Rifabutin		
Diltiazem	Rifampicin		
Fluconazole	Apalutamide		
Fluvoxamine	Bosentan		
Imatinib			
Verapamil			

Oxycodone Goodness-of-fit plots

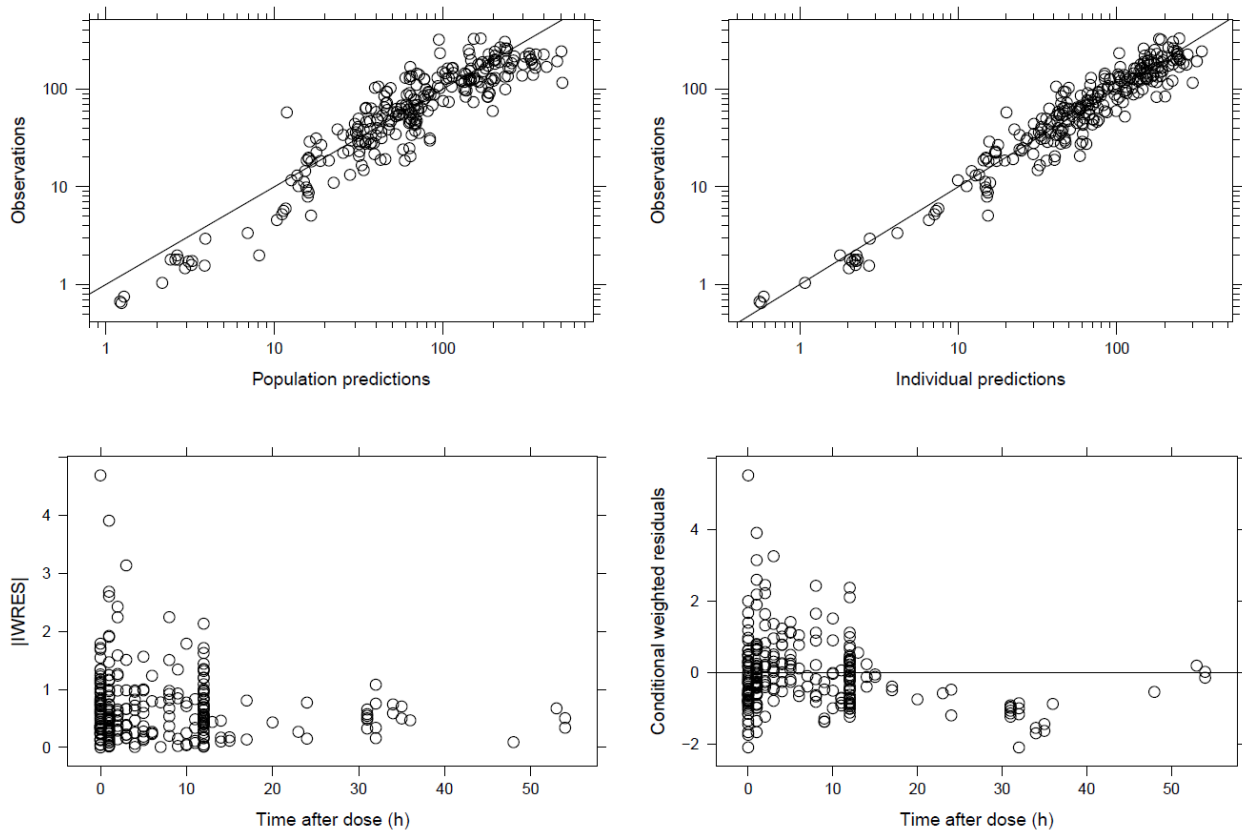


Figure S1: Goodness of fit plots (GOF) of oxycodone. Top left: log-transformed population predictions vs. observations with a unity line. Top right: Log transformed individual predictions versus observations with a unity line. Bottom left: Individual weighed residual errors (IWRES) vs. Time after dose. Bottom right: Conditional weighted residual errors vs. Time after dose.

Noroxycodone Goodness-of-fit plots

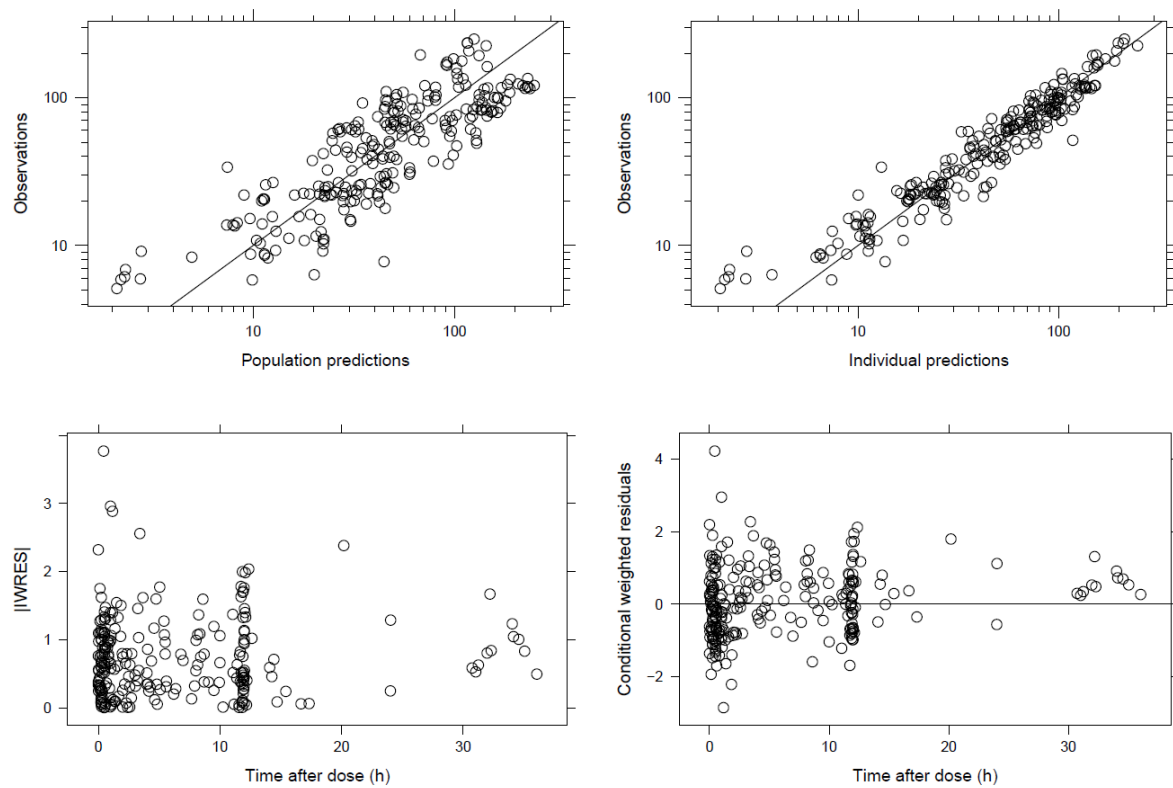


Figure S2: Goodness of fit plots (GOF) of nor-oxycodone. Top left: log-transformed population predictions vs. observations with a unity line. Top right: Log transformed individual predictions versus observations with a unity line. Bottom left: Individual weighed residual errors (IWRES) vs. Time after dose. Bottom right: Conditional weighted residual errors vs. Time after dose.

Noroxymorphone Goodness-of-fit plots

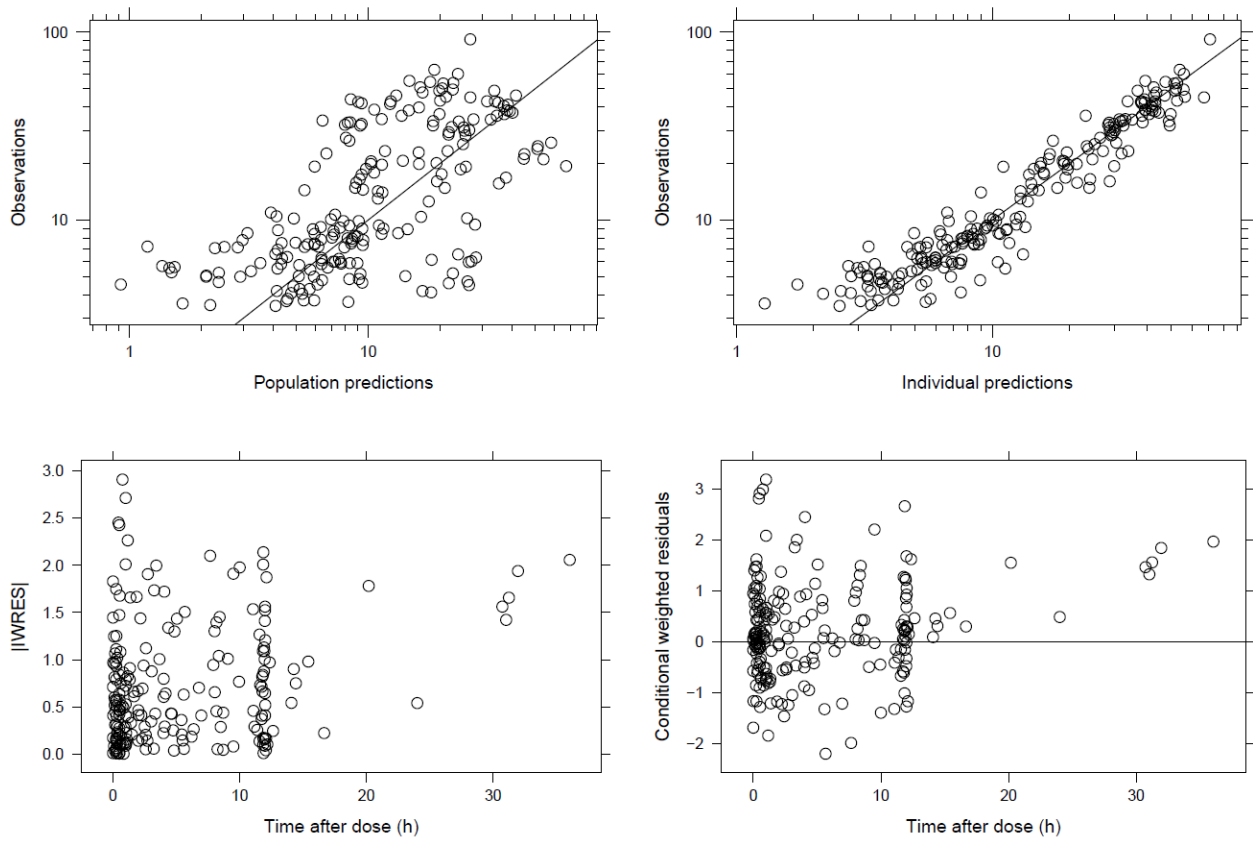


Figure S3: Goodness of fit plots (GOF) of nor-oxymorphone. Top left: log-transformed population predictions vs. observations with a unity line. Top right: Log transformed individual predictions versus observations with a unity line. Bottom left: Individual weighed residual errors (IWRES) vs. Time after dose. Bottom right: Conditional weighted residual errors vs. Time after dose.

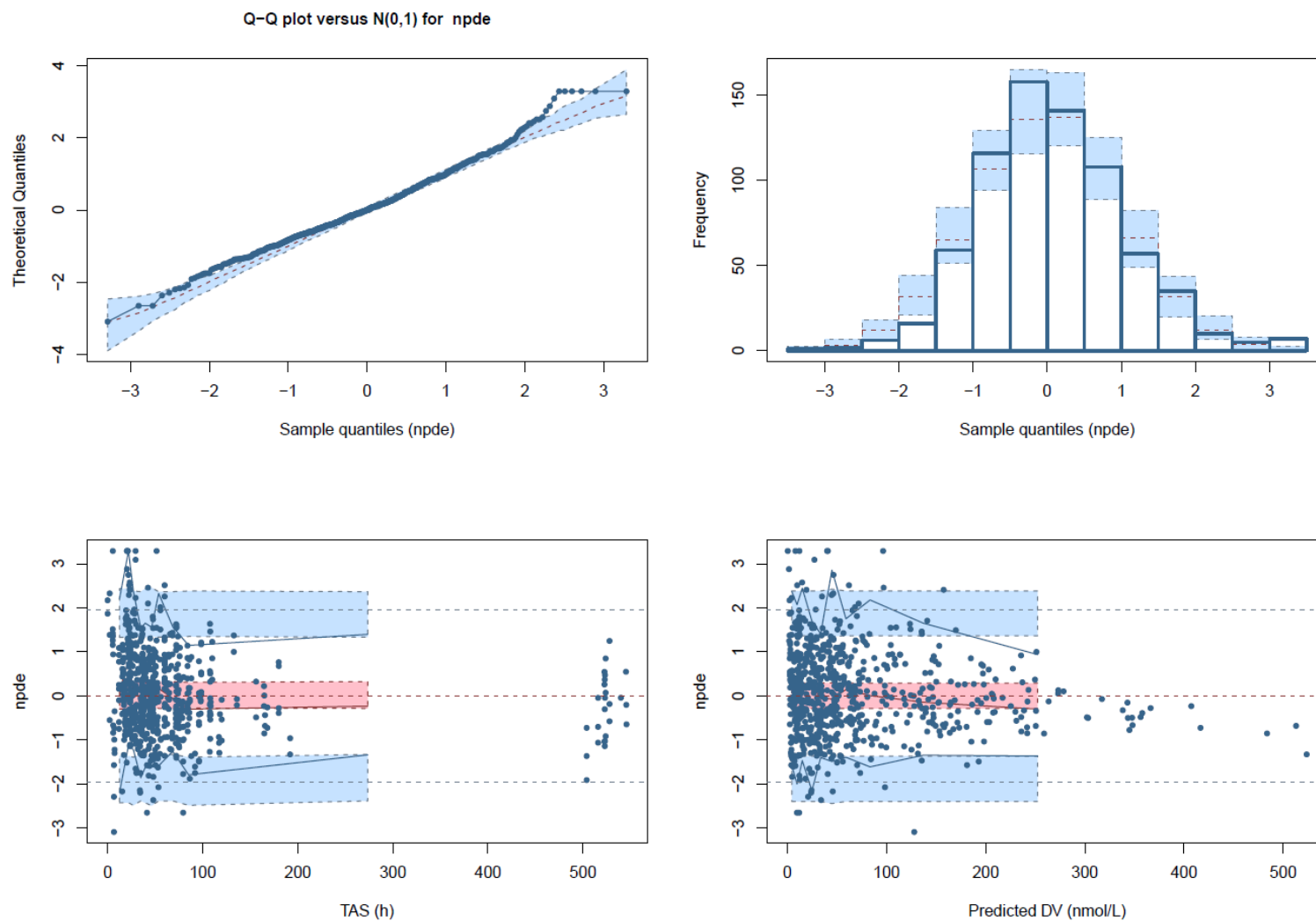


Figure S4: Normalized Prediction Distribution Error (NDPE) plots. Top left QQ plot between observed and simulated data. Top right: Histogram of NPDE. Light blue areas: theoretical normal distribution. Bottom left: Scatterplot of NPDE versus time after start (TAS). Bottom right: Scatterplot of NPDE versus predicted plasma concentrations (DV).

Document S1: Covariate equations

Covariate equations:

Power model:

$$P_i = CL_{pop} * \left(\frac{COV}{median\ COV} \right)^{\theta_{COV}} * exp^{(\eta_i)}$$

Exponential model:

$$P_i = CL_{pop} * \left(\frac{COV}{median\ COV} \right) * \theta_{COV} * exp^{(\eta_i)}$$

Proportional model

$$P_i = CL_{pop} * \theta_{cat}^{FLAG} * exp^{(\eta_i)}$$

Genotype models

Dominant model

$$P_i = CL_{pop} * \theta_{GEN}^{FLAG(VAR+HZ)} * exp^{(\eta_i)}$$

Recessive model

$$P_i = CL_{pop} * \theta_{GEN}^{FLAG(VAR)} * exp^{(\eta_i)}$$

Exponential model

$$P_i = CL_{pop} * ((\theta_{GEN} * HZ) + (2 * \theta_{GEN} * VAR)) * exp^{(\eta_i)}$$

Document S2: Control stream of the final model:

FINAL MODEL CONTROL STREAM

```
$PROBLEM PK
$INPUT CENSOR ID TIME AMT DV EVID MDV TAD CMT HT WT AGE IR GNDR TYPE BMI ALBU
CREAT CYP2D6 CYP3A4 UGT2B7
$DATA PKPD_Oxy_181220COV.csv IGNORE=C

$SUBROUTINES ADVAN6 TOL=3

$MODEL
      NCOMPS=5
      COMP (ABSIR, DEFDOSE)          ;DOSE COMPARTMENT IR
      COMP (ABSER)                   ;DOSE COMPARTMENT ER
      COMP (CENTRAL)                 ;CENTRAL COMPARTMENT
      COMP (METAB1)                  ;NOROXYCODONE
      COMP (METAB3)                  ;NOROXYMORPHONE

$PK
TVV3 = THETA(4)
V3 = TVV3

TVV4 = THETA(7)
V4 = TVV4

TVV5 = THETA(12)
V5 = TVV5

;scaling from nmol/L (observations) to mmol (dosages)
S3 = V3/1000000
S4 = V4/1000000
S5 = V5/1000000

;when a patient was sampled prior to the first dosage in the study
IF (A_0FLG.EQ.1) THEN
      IF (MDV.EQ.0) THEN
            A_0(3) = DV*S3
            A_0(4) = NOROXY*S4
            A_0(5) = NORMOR*S5
      ENDIF
ENDIF

K13 = THETA(5)
K23 = THETA(6)
K30 = THETA(3)
K34 = THETA(9) * EXP(ETA(1))
K40 = THETA(8) * EXP(ETA(2))
```

K45 = THETA(14)
K50 = THETA(13) * EXP(ETA(3))

\$THETA
(0, 0.343) ;1 PROP ERR OXYCODONE
(0) FIX ;2 ADD ERR OXYCODONE
(0, 0.01224) FIX ;3 K30
(0, 566) ;4 V3
(0, 3.52) ;5 K13
(0, 0.385) ;6 K23
(0, 16.3) FIX ;7 V4
(0, 3.256) ;8 K40
(0, 0.0888) ;9 K34
(0, 0.177) ;10 PROP ERR NOROXYCODONE
(0, 3.29) ;11 ADD ERR NOROXYCODONE
(0, 64.1) FIX ;12 V5
(0, 1.975) ;13 K50
(0, 1.51) ;14 K45
(0, 0.177) ;15 PROP ERR NOROXYMORPHONE
(0, 1.29) ;16 ADD ERR NOROXYMORPHONE

\$DES
DADT(1)= -K13*A(1)
DADT(2)= -K23*A(2)
DADT(3)= K13*A(1) + K23*A(2) - K30*A(3) - K34*A(3)
DADT(4)= K34*A(3) - K40*A(4) - K45*A(4)
DADT(5) = K45*A(4) -K50*A(5)

\$ERROR ;; M3 method CMT specific
IPRED = F
IRES = DV-IPRED

IF(CMT.EQ.3) W1 = IPRED*THETA(1)+THETA(2)
IF(W1.EQ.0) W1 = 1
IF(CMT.EQ.3.AND.TYPE.EQ.1) THEN
 IWRES = IRES/W1
 Y = IPRED+W1*ERR(1)
 F_FLAG = 0
ENDIF

IF(CMT.EQ.4) W2 = IPRED*THETA(10)+THETA(11)
IF (W2.EQ.0) W2 = 1
IF(CMT.EQ.4.AND.TYPE.EQ.1) THEN
 IWRES = IRES/W2
 Y = IPRED+W2*ERR(2)
 F_FLAG = 0
ENDIF


```

IF(CMT.EQ.5) W3 = IPRED*THETA(15)+THETA(16)
IF (W3.EQ.0) W3 = 1
IF(CMT.EQ.5.AND.TYPE.EQ.1) THEN
    IWRES = IRES/W3
    Y = IPRED+W3*ERR(3)
    F_FLAG = 0
ENDIF

```

```

IF(CMT.EQ.3)LLOQ = 0.6342
IF(CMT.EQ.4)LLOQ = 3.318511
IF(CMT.EQ.5)LLOQ = 3.480561

```

```

IF(CMT.EQ.3.AND.TYPE.EQ.2) THEN
    F_FLAG = 1
    DEL=0.000001
    DUM = (LLOQ - IPRED)/(W1+DEL)
    CUMD = PHI(DUM)
    Y = CUMD
    MDVRES = 1
ENDIF

```

```

IF(CMT.EQ.4.AND.TYPE.EQ.2) THEN
    F_FLAG = 1
    DEL=0.000001
    DUM = (LLOQ - IPRED)/(W2+DEL)
    CUMD = PHI(DUM)
    Y = CUMD
    MDVRES = 1
ENDIF

```

```

IF(CMT.EQ.5.AND.TYPE.EQ.2) THEN
    F_FLAG = 1
    DEL=0.000001
    DUM = (LLOQ - IPRED)/(W3+DEL)
    CUMD = PHI(DUM)
    Y = CUMD
    MDVRES = 1
ENDIF

```

```

$OMEGA BLOCK(3)
0.134 ; K34
0.107 0.277 ;K40
0.01 0.01 0.03 ;K50

```

```

$SIGMA
1 FIX ;OXYCODON
1 FIX ;NOROXYCODON

```

1 FIX ;NOROXYMORFON

\$EST METHOD=COND INTER NOABORT MAXEVAL=9000 NOABORT LAPLACIAN SIG=2 PRINT=1
POSTHOC
\$COV PRINT=E