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Electronic Supplementary Material

to

Physiologically-based pharmacokinetic modeling predicted altered maternal pharmacokinetics of amitriptyline during pregnancy

Short running title: Amitriptyline PBPK model during pregnancy

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1 Clinical Studies

The clinical studies for amitriptyline and nortriptyline model building and evaluation are summarized in table S1.

Table S1 All clinical studies used for amitriptyline model building and evaluation.

Study	PMID	Treatment	Dose	n	n(men/women)	Age (mean±SD) (range)	Dataset	Reference
Amitriptyline iv								
Fridrich et al, 2007	17512256	iv, SD, 1h	25				training	[1]
Fridrich et al, 2007	17512256	iv, SD, 1h	50				training	[1]
Fridrich et al, 2007	17512256	iv, SD, 1h	100				training	[1]
Fridrich et al, 2007	17512256	iv, SD, 2h	25				training	[1]
Schulz et al., 1983	6825390	iv, SD, 2h	43	1	1/0	21	test	[2]
Nortriptyline								
Alvan et al., 1977	852498	im, SD	42	6			training	[3]
Hotha et al., 2010	20853465	po, SD	25	3			test	[4]
Jensen et al., 2012	21999196	po, SD	25	67			test	[5]
Dalen et al., 1998	9585799	po, SD	25	26			test	[6]
Alvan et al., 1977	852498	po, SD	40	6			test	[3]
Amitriptyline po								
Liedholm et al., 1998	9818297	po, SD	25	9	0/9	(25-54)	training	[7]
Mellström et al., 1983	6617075	po, SD	50	9	5/4	(25-49)	training	[8]
Gupta et al., 1998	9597561	po, MD	75	29	19/10	30.2 (19-49)	training	[9]
Venkatakrishnan et al., 2001	11583471	po, SD	50	8	7/1	(24-45)	test	[10]
Gupta et al., 1999	10383563	po, SD	75	15	15/0	29 (21-37)	test	[11]
Nam et al., 2015	25308868	po, SD	10				test	[12]
Nam et al., 2015	25308868	po, SD	25				test	[12]
Balant-Gorgia et al., 1982	7159207	po, SD	75	7	6/1	(22-29)	test	[13]
Baumann et al., 1986	3571944	po, MD	150	30	9/21	45.9	test	[14]
Miljkovic et al., 1996	8980924	po, MD	150	6	3/3	49.8 (31-59)	test	[15]
Miljkovic et al., 1996	8980924	po, MD	75	9	3/6	46.1 (39-56)	test	[15]
Vandel et al., 1993	8436164	po, MD	125	17	7/10	(24-69)	test	[16]
Own_data_50mg (2023-2024)		po, MD	50	269	105/164	55.1±20.0 (18-86)	test	
Own_data_75mg (2023-2024)		po, MD	75	231	89/143	54.6±15.2 (19-81)	test	
Own_data_100mg (2023-2024)		po, MD	100	423	187/236	50.7±17.8 (19-87)	test	
Own_data_125mg (2023-2024)		po, MD	125	86	44/42	48.9±17.0 (18-80)	test	
Own_data_150mg (2023-2024)		po, MD	150	198	113/85	47.0±16.4 (19-79)	test	
Own_data_200mg (2023-2024)		po, MD	200	41	23/18	44.8±12.6 (27-78)	test	

PMID, PubMed-ID; iv, intravenous; SD, single dose; im, intramuscular; po, peroral; MD, multiple dose; n, number; mean±SD, mean±standard deviation

When data on study populations were not available, pharmacokinetics were predicted in a virtual population of 100 individuals. As the study populations were not limited to women of child-bearing age, and pregnant women were not included in the studies, population was build based on a European reference human according to [17]. Mean weight was 68 kg, mean age 53 (predefined age range: 18-100 years) and mean height was 173.10 cm[17]. Mean weight was 68 kg, mean age 53 (predefined age range: 18-100 years) and mean height was 173.10 cm [18].

2 Pregnancy-related enzyme activity changes

Enzyme activity changes due to pregnancy are summarized in table S2.

Table S2 Pregnancy-related enzyme activity changes.

Parameter	Unit	Value used in PBPK model	trimester	Value used in pregnancy model	CYP-activity in pregnancy	Reference
AMITRIPTYLINE						
CYP2C19 Demethylation						
kcat	1/min	17.37				
			1. trimester		ND	[19]
			2. trimester	8.685	50% decrease	[19]
			3. trimester	8.685	50% decrease	[19]
CYP2D6 Hydroxylation						
kcat	1/min	2.71				[20]
			1. trimester	3.415	ND; 26% increase	[19,21]
			2. trimester	3.66	ND; 35% increase	[19,21]
			3. trimester	4.065	50% increase; 48% increase	[19,21]
NORTRIPTYLINE						
CYP1A2 Demethylation						
kcat	1/min	0.11				
			1. trimester	0.0726	33% decrease	[19]
			2. trimester	0.055	50% decrease	[19]
			3. trimester	0.0385	65% decrease	[19]
CYP2C19 Demethylation						
kcat	1/min	1.55				
			1. trimester		ND	[19]
			2. trimester	0.775	50% decrease	[19]
			3. trimester	0.775	50% decrease	[19]
CYP2D6 Demethylation						
kcat	1/min	0.32				
			1. trimester	0.4032	ND; 26% increase	[19,21]
			2. trimester	0.432	ND; 35% increase	[19,21]
			3. trimester	0.48	50% increase; 48% increase	[19,21]
CYP2D6 Hydroxylation						
kcat	1/min	4.7				
			1. trimester	5.922	ND; 26% increase	[19,21]
			2. trimester	6.345	ND; 35% increase	[19,21]
			3. trimester	7.05	50% increase; 48% increase	[19,21]

kcat, katalytic rate constant; ND, No data

3 Model evaluation

3.1 Non-pregnant patients

3.1.1 Goodness-of-fit plots of predicted vs observed serum concentrations

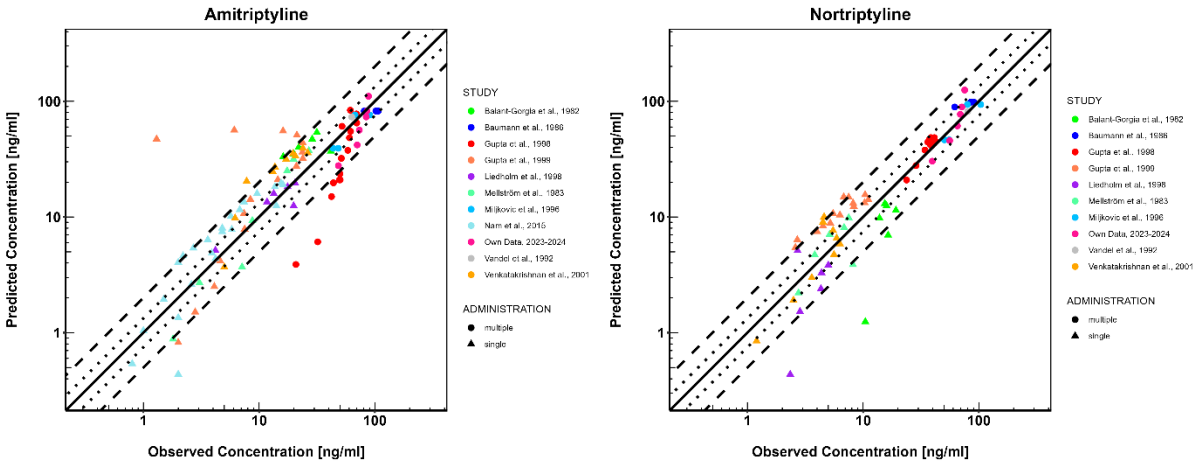


Figure S1 Goodness-of-fit plots for AMI (left) and NOR (right) comparing the predicted serum concentrations with the observed serum concentrations. Line of identity (black solid line), 1.25-fold deviation (black dotted lines), and 2-fold deviation (black dashed lines) are shown.

3.1.2 Bias, precision and mean relative of serum concentrations

Table S3 Bias (mean prediction error), precision (mean absolute precision error) and mean relative deviation (MRD) of the AMI PBPK model

Dose, Administration	MPE	MAPE	MRD
AMITRIPTYLINE			
10mg, SD	41.14%	56.03%	1.13
25mg, SD	9.82%	36.97%	1.11
50mg, SD	36.94%	60.99%	1.19
75mg, SD	86.07%	101.72%	1.27
75mg, MD	-33.55%	41.65%	1.32
75mg(3x25), MD	-14.30%	14.30%	1.01
125mg, MD	1.40%	14.43%	1.01
150mg, MD	-11.10%	11.90%	1.01
150mg (3x50mg), MD	-1.41%	14.26%	1.01
Mean	12.78%	39.14%	1.12
Min	-33.55%	11.90%	1.01
Max	86.07%	101.72%	1.32
NORTRIPYLINE			
25mg, SD	-21.97%	51.51%	1.35
50mg, SD	-1.70%	42.75%	1.39
75mg, SD	41.42%	66.67%	1.26
75mg, MD	10.23%	14.40%	1.01
75mg(3x25), MD	-12.23%	12.23%	1.01
125mg, MD	6.61%	6.61%	1.00
150mg, MD	22.98%	22.98%	1.02
150mg (3x50mg), MD	4.07%	13.64%	1.01
Mean	6.18%	28.85%	1.13
Min	-21.97%	6.61%	1.00
Max	41.42%	66.67%	1.39

MPE; mean prediction error; MAPE, mean absolute prediction error; MRD, mean relative deviation; SD, single dose; MD, multiple dose; Min, minimum; Max, maximum

3.1.3 Sensitivity analysis

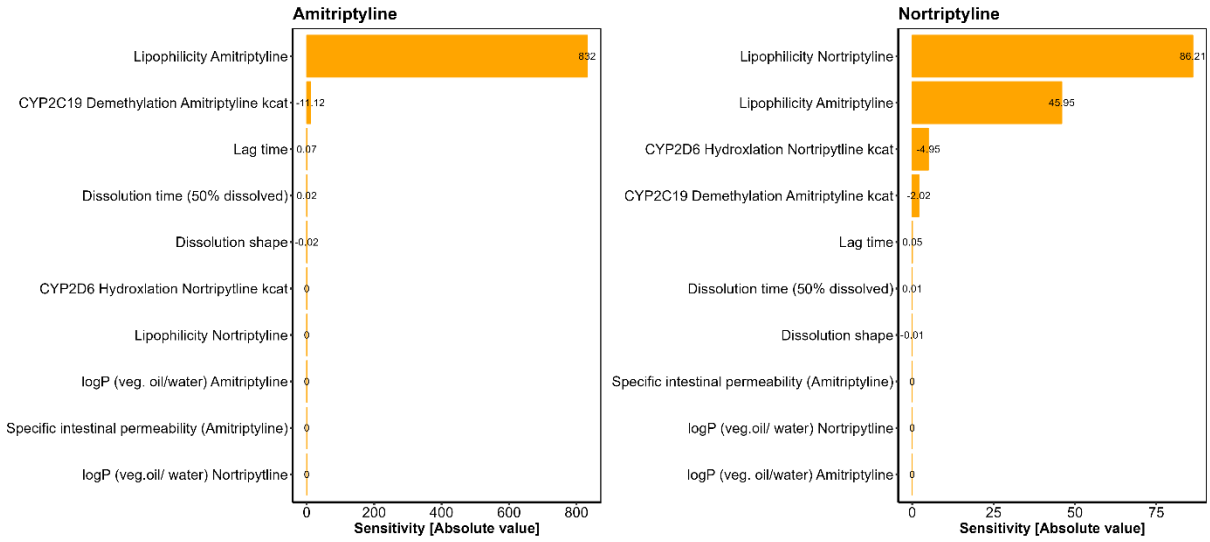


Figure S2 Sensitivity for parameters that were estimated during model building was measured as relative changes in c_{trough} of multiple dose administration (75mg) of AMI. Variation range was range was 10.0 with maximum number of steps = 9.

3.2 Pregnant patients

3.2.1 Goodness-of-fit plots of predicted vs observed serum concentrations

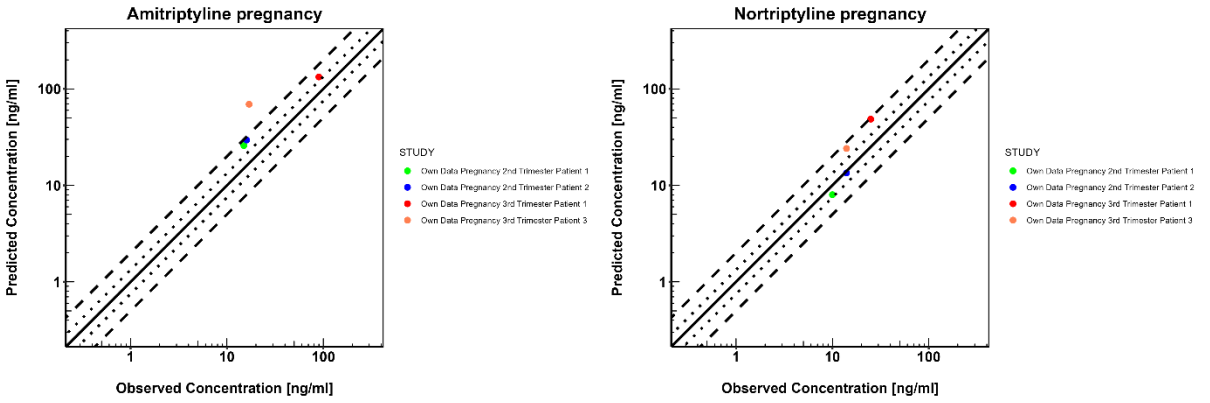


Figure S3 Goodness-of-fit plots for AMI (left) and NOR (right) comparing the predicted serum concentrations with the observed serum concentrations in pregnancy. Line of identity (black solid line), 1.25-fold deviation (black dotted lines), and 2-fold deviation (black dashed lines) are shown.

3.2.2 Sensitivity analysis

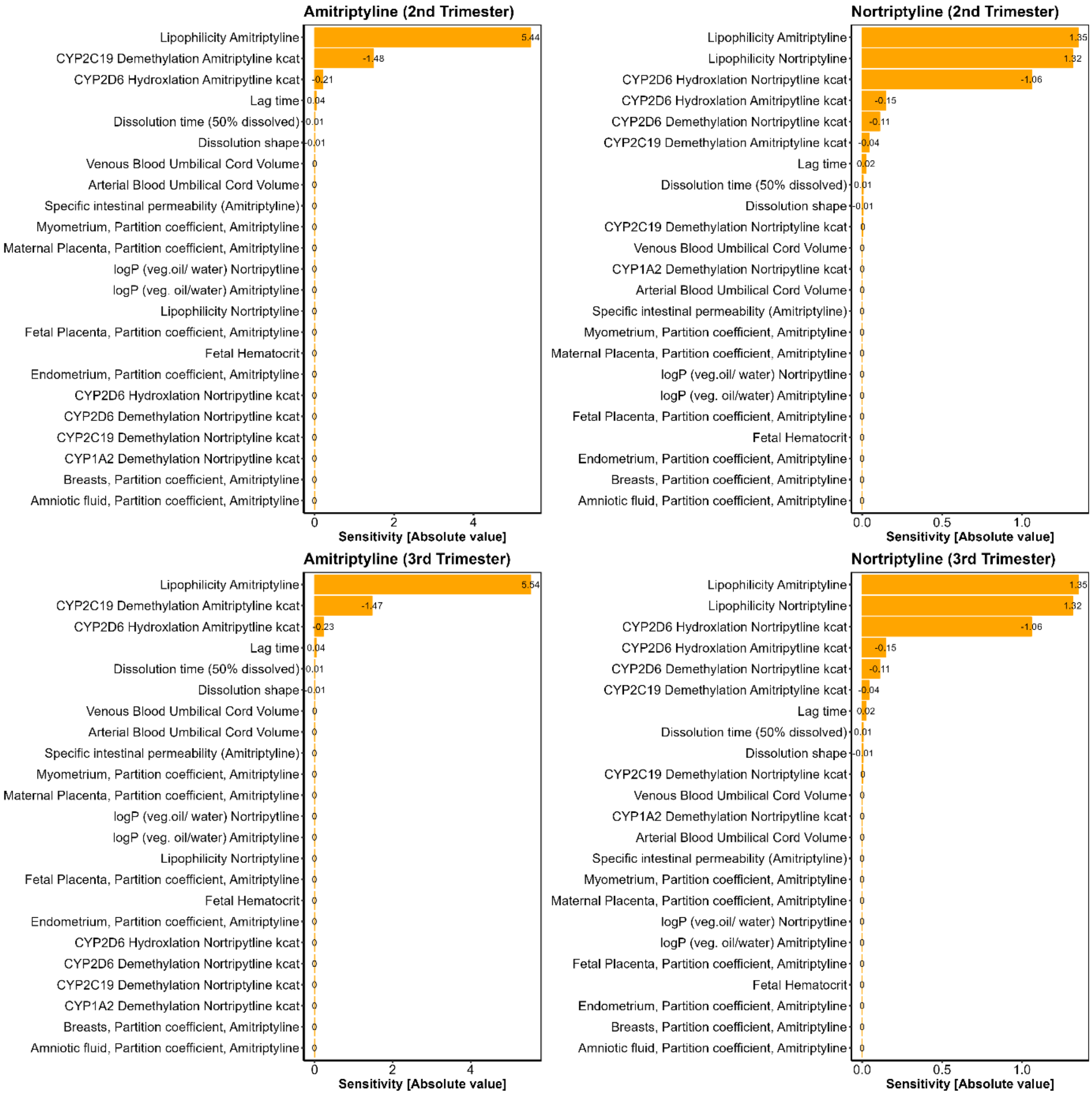


Figure S4 Sensitivity for parameters that were estimated during model building, as well as the 9 pregnant specific compartments and the new included CYP2D6 hydroxylation of amitriptyline was measured as relative changes in c_{trough} of multiple dose administration (75mg) of AMI during pregnancy. Variation range was range was 10.0 with maximum number of steps = 9.

4 Comparison of PK in non-pregnant and pregnant individuals

Comparison of median and IQR of trough serum concentrations for amitriptyline, nortriptyline and the active moiety in non-pregnant, as well as pregnant women are shown in figure S5.

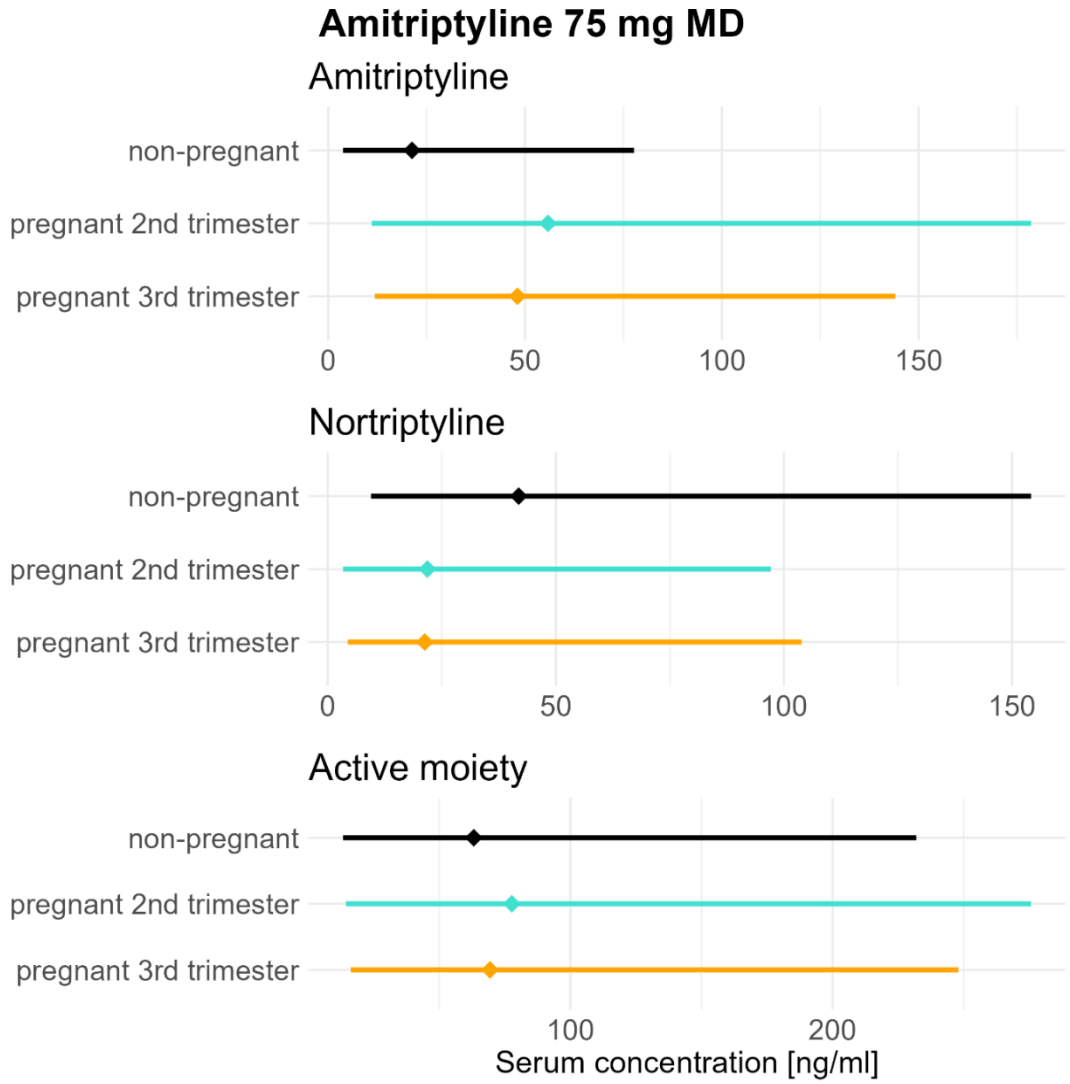


Figure S5 Comparison of median and IQR of trough serum concentrations for amitriptyline, nortriptyline and the active moiety in non-pregnant, as well as pregnant women.

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