

# Methadone serum concentrations and influencing factors: A naturalistic observational study

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**Lisbon Addictions**

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# Disclosure

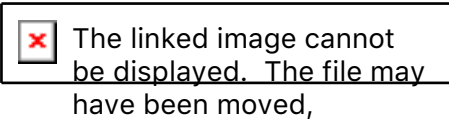
- No conflicts of interest

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# Research topic

- Methadone maintenance treatment (MMT)
- Challenges and clinical outcomes (variations in dose and serum con.)
- The role of therapeutic drug monitoring (cor. dose and serum con.)
- Current knowledge on methadone pharmacokinetics (CYP-450)

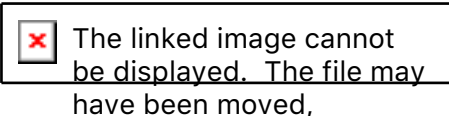


# Aims

- Effects of comedication on methadone serum concentration-to-dose ratio (CDR)
- Effects of age and gender on CDR

# Methods

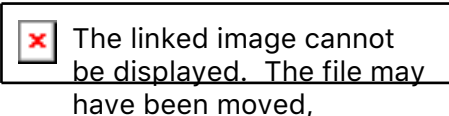
- Retrospective cohort study
- 4425 routine serum methadone concentrations from 1691 MMT patients in the period October 1999 to July 2017
- Available data in the laboratory database: doses, age, gender, time since last dose and concurrent medications
- Concomitant medication with at least one out of totally 170 drugs was recorded in one quarter of the samples
- Eighteen CYP inhibitors and four CYP inducers were recorded in 79 and 37 samples, respectively.



Drug (number of samples)	Enzyme inhibited					
	CYP3A4	CYP2D6	CYP2C19	CYP2B6	CYP2C9	CYP1A2
<b>Inhibitors of specific CYPs (N)</b>						
Atazanavir <sup>a</sup> (6)	+					
Bupropion (2)		+				
Ciprofloxacin (4)						+
Clopidogrel (3)				+		
Diltiazem (1)	+					
Duloxetine (4)		+				
Erythromycin (2)	+					
Esomeprazol (21)			+			
Fluconazole (3)	+		+		+	
Fluoxetine (7)		+				
Fluvoxamine (1)			+			+
Indinavir (1)	+					
Moclobemide (1)			+			
Nelfinavir (1)	+					
Omeprazole (4)			+			
Paroxetine (14)		+				
Saquinavir (1)	+					
Terbinafine (3)		+				
<b>General CYP inducers (N)</b>						
Carbamazepine (30)						
Efavirenz (2)						
Nevirapine (1)						
Phenobarbital (4)						

# Methods

- 26 other most frequently used drugs were recorded in 20 samples or more (most freq: valproate, oxazepam, mirtazapine, alimemazine, chlorprothixene, olanzapin)
- Vi included: comedication with inhibitors of CYP3A4, CYP2D6, CYP2C19, CYP inducers, and 26 other most frequently used drugs, as well as age, gender and time since last dose as covariates
- A log-linear mixed model was used when analyzing the data



# Results

- Mean age was 38.4 (range, 21–78) years, 70% were men
- Mean dose was 111 (range, 40–500) mg/d
- Mean serum concentration was 344 (8–1898) ng/mL
- Mean CDR was 332 (range, 7–1776) (ng/mL)/(100 mg/d)



# Gender differences

**Table 1** Total and gender-specific measures of age, methadone dose, serum concentration, concentration-to-dose ratio (CDR) and sampling time

Variable		Total <i>N</i> = 4425	Men <i>N</i> = 3013	Women <i>N</i> = 1412	<i>p</i> value <sup>a</sup>	Mean difference <sup>b</sup> (95% CI)
Age (year)	Mean (min, max)	38.4 (21, 78)	38.9 (22, 66)	37.5 (21, 78)	<0.001	+ 1.4 (+ 1.0, + 1.9) ←
Dose (mg/day)	Mean (min, max)	111 (40, 500)	108 (40, 360)	116 (40, 500)	<0.001	- 8 (- 10, - 5) ←
Concentration (ng/mL)	Mean (min, max)	344 (8, 1898)	353 (8, 1898)	327 (13, 1552)	<0.001	+ 26 (+ 14, + 37) ←
CDR (ng/mL)/(100 mg/d)	Mean (min, max)	332 (7, 1776)	345 (12, 1776)	305 (7, 1572)	<0.001	+ 40 (+ 28, + 51) ←
Sampling time <sup>c</sup> (hours)	Mean (min, max)	- 0.5 (- 14, 2)	- 0.4 (- 14, 2)	- 0.7 (- 14, 2)	0.008	+ 0.2 (+ 0.1, + 0.4)




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**Table 4** The effects of study variables in adjusted linear mixed model on the  $\log_e$ -transformed and expected methadone serum concentration-to-dose ratio (CDR)

Variable	Log <sub>e</sub> (methadone CDR)			Expected methadone CDR (ng/mL) / (100 mg/d)	
	Estimate	95% CI	<i>p</i> value	Mean (95% CI)	Change (%) (95% CI)
Intercept <sup>a</sup>	1.128	1.017, 1.239	<0.001	309 (276, 345)	
Age (per year)	0.002	-0.001, 0.005	0.176	310 (276, 343)	+0 (-0, +1)
Gender (women)	-0.092	-0.144, -0.040	→ 0.001	282 (239, 332)	-9 -13, -4)
Sampling time <sup>b</sup>	0.007	-0.017, 0.030	0.560	311 (272, 335)	+1 (-2, +3)
CYP inducer	-0.452	-0.588, -0.324	→ <0.001	197 (154, 250)	-36 (-44, -28)
CYP3A4 inhibitor	0.304	0.094, 0.515	→ 0.005	419 (304, 578)	+36 (+10, +68)
CYP2D6 inhibitor	-0.071	-0.222, 0.080	0.360	288 (221, 374)	-7 (-20, +8)
CYP2C19 inhibitor	0.003	-0.153, 0.146	0.965	310 (237, 399)	+0 (-14, +16)

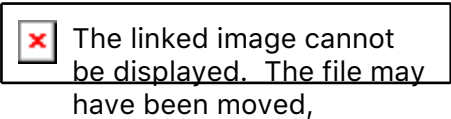
- CDRs were significantly lower in:  
 women (-9%; confidence interval (CI), -13%, -4%; *p* = 0.001) and  
 with concurrent CYP inducers (-36%; CI, -44%, -28%; *p* <0.001)
- CDRs were significantly higher using:  
 CYP3A4 inhibitors concurrently (+36%; CI, +10%, +68%; *p* = 0.005)

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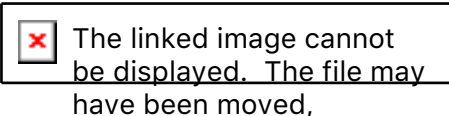
# Conclusion

- Concomitant use of CYP inducers reduced methadone serum concentrations
- Concomitant use of CYP3A4 inhibitors increased its concentrations
- Females had lower dose adjusted methadone serum concentrations compared to men



# Implications

- Clinicians should be aware of potential drug interactions with methadone
- Avoid underdosing of women
- Close clinical assessment is still the most important approach
- Measurements of methadone serum concentrations as a supplementary tool



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