Check for updates

Received: 5 July 2023 | Revised: 27 November 2023 | Accepted: 15 December 2023

DOI: 10.1111/bcpt.13975

FOCUSED REVIEW

BCPT Basic & Clinical Pharmacology & Toxicology

Methadone pharmacokinetics in opioid agonist treatment: Influencing factors and clinical implications

Fatemeh Chalabianloo[1,2] | **Lars Thore Fadnes**[1,2] | **Kjell Arne Johansson**[1,2] | **Gudrun Høiseth**[3,4,5] | **Jørn Henrik Vold**[1,2,6] | **Marianne K. Kringen**[4] | **Olav Spigset**[7,8] | **Jørgen G. Bramness**[9,10,11]

[1]Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway

[2]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[3]Department of Forensic Medicine, Oslo University Hospital, Oslo, Norway

[4]Center for psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway

[5]Norwegian Center for Addiction Research, University of Oslo, Oslo, Norway

[6]Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

[7]Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway

[8]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[9]Institute of Clinical Medicine, UiT – Norway's Arctic University, Tromsø, Norway

[10]Department of Alcohol, Tobacco and Drugs, Norwegian Institute of Public Health, Oslo, Norway

[11]Norwegian National Competency Centre for Dual Disorder, Innland Hospital Trust, Hamar, Norway

Correspondence
Fatemeh Chalabianloo, Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway.
Email: fatemeh.chalabianloo@helse-bergen.no

Funding information
Western Health Region, Norway, Grant/Award Numbers: F-11328-912126, «Åpen prosjektstøtte»; Norwegian Research Council, Grant/Award Number: 269855

Abstract

Background: A considerable inter-individual variability has been reported in the relationship between methadone doses applied and serum concentrations achieved in methadone maintenance treatment. However, the underlying causes for this variability are not fully understood.

Objectives: We investigated the influence of genetic, pathophysiological and pharmacological factors on serum methadone concentration-to-dose ratio (CDR) and discussed the clinical implications of the findings.

Methods: We used data from two retrospective laboratory databases and a prospective cohort study to investigate the impact on methadone CDR of hepatic cytochrome P450 enzyme system (CYP) genetic polymorphisms, age, sex, concomitant medication, liver fibrosis and body mass index through linear mixed model analyses.

Findings: A positive association was found between CDR and the homozygous *CYP2B6*6* genotype, concurrent treatment with CYP3A4 inhibitors and

This focused review is based on the corresponding author's PhD thesis. Reference: Bergen Open Research Archive: Steady state methadone pharmacokinetics in opioid agonist treatment: Influencing factors and clinical outcomes (uib.no) 14.12.2022.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2023 The Authors. *Basic & Clinical Pharmacology & Toxicology* published by John Wiley & Sons Ltd on behalf of Nordic Association for the Publication of BCPT (former Nordic Pharmacological Society).

body mass index. CDR was lower among women and during concomitant use of CYP inducers. CDR was not associated with age or the degree of liver fibrosis in our investigations.

Conclusions: This research work supports the need for individually tailored dosage considering the various factors that influence methadone CDR. The gained knowledge can contribute to reducing the risks associated with the treatment and optimizing the desired outcomes.

KEYWORDS
dose adjustment, methadone, opioid agonist treatment, pharmacokinetic, serum concentration

1 | INTRODUCTION

Methadone maintenance treatment (MMT) is an evidence-based pharmacological intervention that reduces overdose risk and mortality among people with opioid dependence.[1,2] However, a significant inter-individual variability in methadone pharmacokinetics poses challenges in establishing a clear relationship between dose and serum concentration.[3] The effectiveness of MMT is primarily determined by outcomes such as a reduction in illicit opioid use and improved treatment retention.[4] Dose-related effects are observed, with most patients achieving stabilization and alleviating withdrawal symptoms and craving at daily methadone dosages of 60–120 mg.[5] Higher doses have been associated with increased risk of adverse effects.[6,7] There is limited data regarding the relationship between serum concentrations and treatment outcomes,[8] although some researchers have suggested a range of 150–600 ng/mL through methadone concentrations to suppress opioid craving.[3,9] Currently, clinical signs, patient-reported withdrawal symptoms and illicit opioid use remain the primary indicators of dose adequacy.

Methadone is a synthetic opioid receptor agonist, usually administered orally as a racemic mixture of R- and S-methadone enantiomers, although predominantly the R-enantiomer is seen to account for the opioid effect. The peak plasma concentration is achieved after 2–4 h, and the elimination half-life at steady state is 24–28 h.[3,10] Oral methadone has a high bioavailability (70%–80%) and is also largely (60%–90%) bound to plasma proteins.[11,12] The drug is extensively metabolized, mainly by the cytochrome P450 enzyme system (CYP) in the liver, resulting in at least 10 inactive metabolites excreted in faeces.[3,13] In vitro and in vivo investigations have suggested the involvement of several CYP enzymes in the metabolism of methadone.[14–19] Some population pharmacokinetic studies have demonstrated the importance of CYP3A4 and CYP2B6 among other factors to describe pharmacokinetics and toxicity for each methadone enantiomer.[20,21] There is, however, no consensus on the relative contributions of each enzyme to the overall disposition of methadone, although some research has supported the impact of CYP3A4.[22,23] Some new in vivo studies on the other side have suggested that CYP2B6 accounts for a major role in its metabolism,[14,24] at least of the S-enantiomer.[25]

Although the efficacy of MMT is well established, the impact of methadone pharmacokinetics on dose requirements and clinical outcomes remains controversial.[14] This may be due to a lack of knowledge concerning factors that influence methadone disposition and consequently the serum concentration-to-dose ratio (CDR). Generally, in addition to genetic variations in metabolizing enzymes, other characteristics such as age, sex, body mass index, hepatic and renal function, as well as extrinsic factors such as concomitant medication are presumed to influence a drug's pharmacokinetics. However, the supporting evidence regarding MMT is still limited.[22,23,26] More knowledge in this field is needed to improve the therapeutic outcomes and minimize the adverse effects, including fatal overdoses.

This research, based on three studies as part of a PhD thesis,[27–29] aimed to investigate the influence of genetic, pathophysiological and pharmacological factors on methadone CDR in MMT. The results suggest that CDR is associated with various factors including CYP genetic polymorphisms, sex, body mass index and concurrent medication which should be considered when adjusting methadone dosage.

2 | METHODS

Table 1 provides an overview of the methods and materials applied for this research.

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13973 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 An overview on the applied methods and materials for this research.

	Study I[27]	Study II[28]	Study III[29]
Design	Retrospective observational cohort study	Retrospective observational cohort study	Prospective observational cohort study
Sources	Laboratory TDM database, Diakonhjemmet Hospital, Oslo, Norway	Laboratory TDM database, St. Olav University Hospital, Trondheim, Norway	Clinical and laboratory data, Haukeland University Hospital, Bergen, Norway
Patients included	62	1691	155
Serum samples included	155	4425	155
Main laboratory analyses	Serum methadone concentration and CYP genotypes	Serum methadone concentration	Serum methadone concentration and CYP genotypes
Measures included	Serum methadone concentration, dose, age, sex, time between last dose and sampling, concomitant medications, *CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5* genotypes	Serum methadone concentration and dose, age, sex, time between last dose and sampling, concomitant medications	Serum methadone concentration and dose, age, sex, time between last dose and sampling, concomitant medications, BMI, eGFR, fibrosis stage, *CYP2B6, CYP3A5* genotypes
Independent variables	*CYP2B6* genotypes	Interacting medications	Liver fibrosis degree
Dependent variable	Serum methadone concentration-to-dose ratio (CDR)	Serum methadone concentration-to-dose ratio (CDR)	Serum methadone concentration-to-dose ratio (CDR)
Other co-variables	Age, sex, time between last dose and sampling, *CYP2C9, CYP2C19, CYP2D6, CYP3A5* genotypes	Age, sex, time between last dose and sampling	Age, sex, time between last dose and sampling, BMI, *CYP2B6, CYP3A5* genotypes

Abbreviations: BMI, body mass index; CYP, cytochrome P450 liver enzymes; eGFR, estimated glomerular filtration rate; OAT, opioid agonist treatment; TDM, therapeutic drug monitoring.

2.1 | Data sources

Observational data from three different sources was used; retrospective therapeutic drug monitoring (TDM) laboratory databases at the Center for Psychopharmacology, Diakonhjemmet Hospital (Oslo, Norway) and the Department of Clinical Pharmacology, St. Olav University Hospital (Trondheim, Norway), and prospective cohort data from the INTRO-HCV study[30] conducted at the Department of Addiction Medicine, Haukeland University Hospital (Bergen, Norway).

2.2 | Research data

All databases contained information about methadone daily doses and steady state serum concentrations, age, sex and concurrent medications. In addition, genetic polymorphisms of *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6* and *CYP3A5* were retrospectively collected from 62 patients (155 serum samples) during the period 2006–2015 using the laboratory databases at the Center for Psychopharmacology, Diakonhjemmet Hospital (Oslo, Norway). The laboratory database at the Department of Clinical Pharmacology, St. Olav University Hospital (Trondheim, Norway) also contained the time of last dose intake and blood sampling obtained from 1691 patients (4425 serum samples) in the period 1999–2017. The prospective cohort database at the Department of Addiction Medicine, Haukeland University Hospital (Bergen, Norway) was additionally included information on body mass index, genotypes of *CYP2B6* and *CYP3A5*, degree of liver stiffness, estimated glomerular filtration rate, status of hepatitis C-virus infection (presence of antibody and RNA) and human immunodeficiency virus (HIV) infection obtained from 155 patients (155 serum samples).

2.3 | Serum concentration analysis of methadone

The analysis of racemic methadone in serum was performed by comparable validated and certified ultra-performance liquid chromatography with tandem mass

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

spectrometry (HPLC-MS/MS) methods developed at the abovementioned centres. During the development phase of the method as well as in routine use, methadone concentrations were measured in nmol/L (the conversion factor from nmol/L to ng/mL for methadone is 0.310). The analytical methods are described in detail in other publications.[27–29]

2.4 | Concentration-to-dose ratio

Dose-adjusted serum concentration of methadone was expressed as CDR to consider the large variations in methadone daily doses used when the samples were obtained. CDR was calculated by dividing the measured serum concentration (ng/mL or nmol/L) by the daily dose (mg) used by the patient at the time of sampling, that is, (ng/mL or nmol/L)/(mg/day). By using this measure, the estimated values could be compared within as well as between subjects without taking variations in the dosage into consideration. The choice of the unit for each study was based on the publishing journal's guidelines.

2.5 | Genotyping

Genotyping of the blood samples was performed using TaqMan-based real-time polymerase chain reaction assays at the Center for Psychopharmacology, Diakonhjemmet Hospital (Oslo, Norway). The determination of the *CYP2B6*6* haplotype was based on genotyping of 516G > T (rs3745274) and 785A > G (rs2279343) variants. The presence of both variants 516TT and 785GG was interpreted as *CYP2B6*6/*6*, whereas the presence of 516GT and 785AG or 785GG was interpreted as *CYP2B6*1/*6*.

2.6 | Assessment of liver stiffness

Liver stiffness measurements (LSMs) were assessed by vibration-controlled transient elastography (VCTE) using FibroScan (Model 430 Mini). The LSM was calculated using the median value of 10 repeated measurements on an empty stomach. LSM is correlated to the liver fibrosis stage.[31] Exclusion criteria were pregnancy, presence of an implantable medical device and obesity (body mass index $\geq$30 kg/m^2 to avoid erroneous measurements using standard probes that were not adapted to obese individuals). The cutoff values for fibrosis measures were: LSM $\leq$ 7 kPa for no/limited fibrosis, LSM 7 < kPa < 12 for fibrosis, LSM $\geq$ 12 kPa for cirrhosis and LSM $\geq$ 20 kPa for cirrhosis with probable significant portal hypertension.[31,32]

2.7 | Concomitant medication

A total of 46 drugs were most recorded in at least 20 samples in the laboratory database at the Department of Clinical Pharmacology, St. Olav University Hospital (Trondheim, Norway) to be used in combination with methadone. These drugs as well as some inhibitors and inducers of the CYP isoenzymes having possible pharmacokinetic drug interactions with methadone,[33] were defined as the relevant co-medications. The CYP3A4 inhibitors were atazanavir ($n = 6$), diltiazem ($n = 1$), erythromycin ($n = 2$), fluconazole ($n = 3$), indinavir ($n = 1$), nelfinavir ($n = 1$) and saquinavir ($n = 1$). The inducers included were carbamazepine ($n = 30$), nevirapine ($n = 1$), phenobarbital ($n = 4$) and efavirenz ($n = 2$).

2.8 | Statistical analyses

The quantitative analyses for this study were performed using IBM SPSS version 21.0 (International Business Machines, Chicago, USA), STATA/SE 15.1 (StataCorp, TX, USA) and STATA/SE 16.0 (StataCorp, TX, USA). Statistical significance was set at the $p < 0.05$ level. Mean and standard deviation (SD) or median and interquartile range were calculated for continuous descriptive variables, and 1-way analysis of variance was used to test the differences between groups. For categorical descriptive variables contingency table and Pearson χ^2 or Fisher exact tests were used. The impact of CYP genetic polymorphisms, age, sex, co-medication, liver fibrosis and body mass index on methadone CDR were investigated by linear mixed model analyses with a 95% confidence interval (CI). As we have benefited from longitudinal data with repeated measurements for all the papers included in this thesis, the linear mixed model was considered the most appropriate method to adjust for possible confounders and accordingly to reduce the risk of systematic biases. Yet, the cohort studies in this thesis are at risk for confounding as the effect of other unknown confounders only can be handled by true randomization. Each of the independent variables, that is, CYP2B6 genotypes, interacting comedications and the degree of liver fibrosis were separately inserted in the analysis together with the other covariates shown in Table 1. CDR was the dependent variable. The linear mixed model analysis allows for adjustment between repeated measurements of methadone serum concentrations within each subject. We dealt with any missing information by including only the samples with complete

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

data sets. More detailed descriptions of the statistical analyses are provided in the related publications.[27–29]

3 | RESULTS

3.1 | CYP genetic polymorphisms

Homozygous carriers of *CYP2B6*6* had higher CDR compared with non-carriers ($p < 0.001$), whereas heterozygous carriers of *CYP2B6*6* were not significantly different from non-carriers ($p = 0.925$). The respective estimated mean CDRs were 17.8 (95% CI: 12.1, 26.1) and 9.1 (6.1, 13.4) (nmol/L)(mg/day) for homozygous and heterozygous carriers of *CYP2B6*6*, and 9.2 (6.6, 12.9) for non-carriers. The distribution of individual CDRs according to the *CYP2B6* genotype is presented in Figure 1. No other CYP enzyme polymorphisms were notably associated with methadone CDR.

3.2 | Age, sex and body mass index

CDR was not influenced by age (mean age: 38.4; range: 21–78). Women used on average 8 (95% CI: 5, 10) mg higher daily methadone doses compared to men but had about 26 (14, 37) ng/mL lower serum concentrations, resulting in 9% (1, 10) (nmol/L)(mg/day) lower CDR. Participants with overweight (a body mass index of 25–30 kg/m^2) had about 15% higher CDR (coefficient: 2.34; 95% CI: 0.22, 4.45; *p*: 0.031) compared with normal-weight individuals (body mass index <25 kg/m^2).

3.3 | Liver fibrosis

There was no significant relationship between liver fibrosis and CDR (0.70; CI: −2.16, 3.57; $p = 0.631$) or cirrhosis (−0.50; CI −4.59, 3.59; $p = 0.810$) compared to no/limited fibrosis according to the adjusted linear mixed model analysis (Figure 2).

3.4 | Concomitant medication

Concurrent treatment with CYP inducers reduced methadone CDR by 36% (95% CI: 28, 44), whereas CYP3A4 inhibitors as a group increased CDR by 36% (10, 68). The combined effects of age, sex, and CYP inducers and inhibitors on CDR in the adjusted regression analysis are shown in Table 2.

4 | DISCUSSION

The present study demonstrates that *CYP2B6* genetic polymorphisms, sex, body mass index and concomitant medication with CYP enzyme inducers and CYP3A4 inhibitors may explain some of the variations in dose-adjusted serum methadone concentration. We also observed that age, degree of liver fibrosis and the other CYP polymorphisms investigated were not associated with methadone CDR. Nevertheless, all included factors only explained a fraction of the variation in CDR.

Our findings support previous reports demonstrating a considerable variation in the relationship between

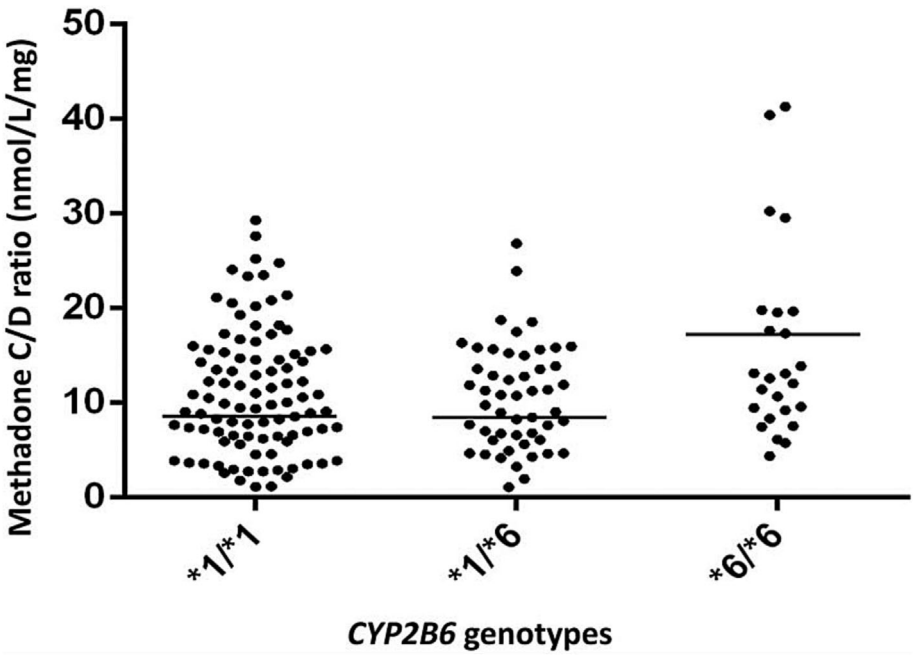

FIGURE 1 Individual serum concentration-to-dose ratios (CDR) (nmol/L)(mg/day) in different *CYP2B6* genotype groups. Lines represent estimated mean values for CDR calculated in the mixed model analyses. The respective mean CDRs were: 9.2 for non-carriers (**1/*1*), 9.1 for heterozygous carriers (**1/*6*) and 17.8 for homozygous carriers of *CYP2B6*6* (**6/*6*); *homozygotes compared to non-carriers: ($p < 0.001$)*; *heterozygotes compared to non-carriers* ($p = 0.925$). Adapted from Kringen et al.[27]

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

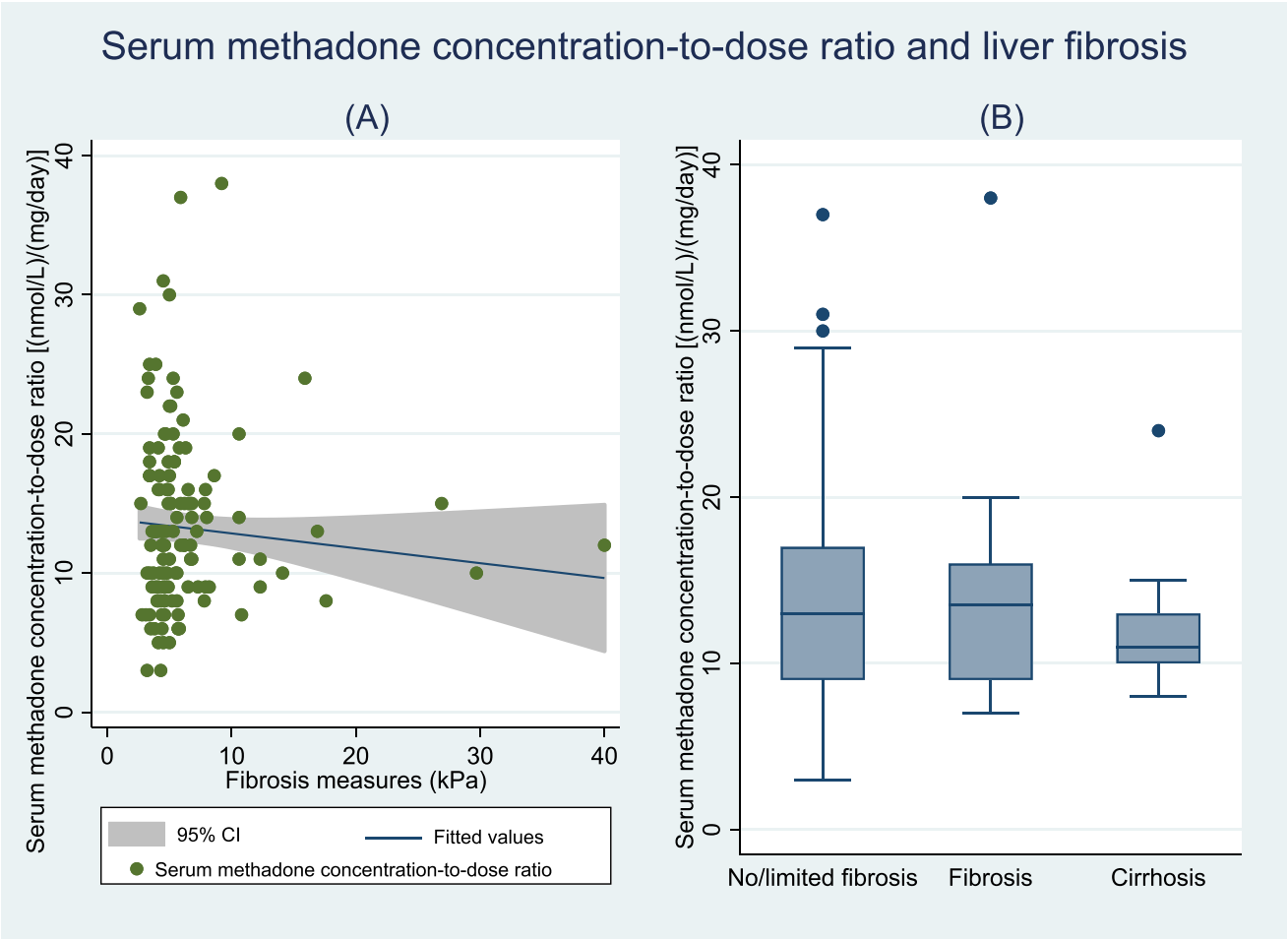

FIGURE 2 Serum methadone concentration-to-dose ratio (CDR), and liver fibrosis measures and stages in study participants on methadone maintenance treatment. Respective liver stiffness measures and mean CDRs (with standard deviations): no/limited fibrosis: ≤7 kPa, 14 (6); fibrosis: 7 < kPa < 12, 14 (8); cirrhosis: ≥12 kPa, 12 (5); no significant relationships between liver fibrosis and CDR (coefficient: 0.70; CI: −2.16, 3.57; $p = 0.631$) or cirrhosis (coefficient: −0.50; CI −4.59, 3.59; $p = 0.810$) compared to no/limited fibrosis were found. Adapted from Chalabianloo et al.[29]

TABLE 2 The effects of age, gender, sampling time and CYP inducers and inhibitors on the $\log_e$-transformed and expected methadone serum concentration-to-dose ratio (CDR) in linear mixed model.

	Log_e (methadone CDR)			Expected methadone CDR (ng/mL)/(100 mg/day)	
Variable	**Estimate**	**95% CI**	***p*-value**	**Mean (95% CI)**	**Change (%) (95% CI)**
Intercept[a]	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)
Woman	−0.092	−0.144, −0.040	**0.001**	282 (239, 332)	**−9 (−13, −4)**
Sampling time[b]	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)

Note: The variables showed in bold font had a significant effect on CDR. Adapted from Chalabianloo et al.,[28]

Abbreviations: CI, confidence interval; CYP, cytochrome P450 enzyme system.

[a]The intercept represents a 40-year-old man not using any of the interacting drugs, having a blood sample obtained 24 h after the last methadone intake.

[b]Hour (the difference between recorded time and 24 h from the last dose intake).

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

methadone dose and serum concentration.[3,26] Although some limited studies with small sample sizes were able to show significant correlations between methadone dose and serum concentration,[34,35] dosage does not entirely explain the variability of methadone concentrations, even in patients without concomitant medications.[36] For a given dose, a broad range of 6–41-fold inter-individual variability in the steady state serum concentrations of both racemic methadone and its active R-enantiomer alone is reported in patients without and with concomitant use of other medications, respectively.[34,36] Regarding serum concentration–effect relationships, a mean daily dose of 100 mg methadone in MMT has been associated with therapeutic response, that is, the absence of illicit opioid in urinary tests, at steady state concentrations of at least 400 ng/mL for racemic methadone and at least 250 ng/mL for R-methadone, whereas no such limit was fond for S-methadone.[36] However, there is limited knowledge in this area.[8] Understanding possible factors that may influence methadone disposition and CDR is important in clinical decision-making on dose requirements to optimize treatment outcomes. Some important factors may include:

4.1 | Genetic factors

Although the impact of *CYP2B6* genotype on inter-individual variability of methadone pharmacokinetics (particularly S-methadone) has been investigated in several previous studies,[14–16,18,19] the findings are still not conclusive. We showed that the homozygous carriers of *CYP2B6*6* had the largest increase in CDR (>90%) compared with non-carriers, which is in line with the predicted slow metabolizer phenotype and agrees with the results of Crettol et al.[16] They showed through an observational study on 245 MMT patients that *CYP2B6*6/*6* carriers had significantly higher steady state through S-methadone serum concentrations and a trend toward higher R-methadone serum levels, presenting a higher total racemic methadone serum concentration. Other previous studies failed to find a significant effect of the *CYP2B6* genotype on methadone serum concentration,[14,37] although a trend supporting the findings was observed. The most expected clinical consequence of increased serum concentration is a higher risk of undesirable effects. For instance, prolongation of the QT interval in an electrocardiogram (the interval between the heart contracting and relaxing) is presumably related to a higher S-methadone serum concentration.[38] A report examining methadone-related deaths concluded that the risk of methadone fatality may be partly related to the *CYP2B6*6* polymorphism.[39] However, there is limited knowledge regarding the influence of the *CYP2B6*6* polymorphism on the total methadone serum concentration and possible clinical outcomes. The overall conclusion would be that the clinical impact of *CYP2B6* genetic polymorphism in methadone disposition and dose adjustments is still unclear.

The present study showed no notable impact on methadone CDR by genetic polymorphisms of other CYP enzymes. Not surprisingly, there is limited clinical research on the role of *CYP3A5* polymorphisms on methadone metabolism, as the expression of the active allele among whites is rare.[40] A possible in vivo impact of CYP3A5 on methadone disposition is anticipated in a few clinical studies, nevertheless, the results are conflicting.[16,17] CYP2C9, CYP2C19 and CYP2D6 have also, to some extent, been related to methadone metabolism,[14,15] however, the limited and conflicting results are unlikely to support a clinical relevance, which is in line with our findings.

4.2 | Physiological factors

Currently, there are limited clinical studies on the influence of age and sex on methadone metabolism, and the findings are not conclusive.[7,41] We showed that women had 9% lower CDR compared to men, whereas the ratio was not influenced by age. Others have stated that methadone metabolism is significantly accelerated in the third trimester of pregnancy.[7] At that time, the daily dose often needs to be increased to prevent withdrawal symptoms and drug-seeking behaviour in the mother. This knowledge and some other studies indicate an inducing effect of estradiol on methadone metabolism related to CYP2B6[42] and CYP3A4[43] as an explanation for the sex difference, which should be taken into consideration in clinical practice. The lack of an age effect on methadone metabolism in our study may be due to the inclusion of only a few patients over 60 years of age. Others have suggested that age may at least explain some of the inter-individual variations in steady state methadone levels,[44] however, studies supporting this statement are lacking. Thus, to date, there is no evidence to recommend methadone dose reduction with increasing age.

We found a direct association between being overweight (body mass index 25–30 kg/m^2) and having a higher CDR. The impact of body weight on methadone metabolism has not been sufficiently investigated in previous studies. Nevertheless, a recent study demonstrated that overweight subjects had higher dose-adjusted serum methadone concentrations,[45] which is in line with our finding. Possible explanations for this observation could

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

be liver steatosis[46] or chronic inflammation with increased levels of cytokines leading to CYP inhibition.[47] The clinical implication of the current knowledge may be that being overweight does not necessitate higher methadone dosages; in fact, some patients may need dose reduction.

4.3 | Pathological factors

Although the present study did not find an association between liver fibrosis and methadone dose-adjusted serum concentrations, it does not appear that available research can definitively conclude on this topic.[45,48–50] Reduced metabolism of methadone among patients with opioid use disorder infected by hepatitis C-virus was demonstrated in one study,[48] but no association between methadone serum levels and liver fibrosis was found. Another study[49] reported a higher concentration of total methadone and the active R-enantiomer in hepatitis C-virus seropositive patients compared to seronegative patients. Both studies suggest consideration of dose adjustments in MMT patients with a history of hepatitis C-virus infection. However, the clearance of drugs, in general, is not considerably altered in patients with chronic active viral hepatitis without cirrhosis.[51] In a study on patients undergoing MMT, the researchers could not demonstrate notable changes in methadone concentrations in individuals with mild to moderate chronic liver disease.[50] In line with our results, a recent study[45] did not show a significant effect of liver stiffness on methadone metabolic rate in patients with ongoing hepatitis C-virus infection. Our findings may thus indicate that increased liver fibrosis probably caused by ongoing hepatitis C-virus infection does not immediately warrant methadone dose adjustment without further clinical assessments.

In very severe liver disease, the oral bioavailability of methadone may increase due to portal hypertension and the development of cirrhotic portosystemic shunts, leading to a reduced first-pass metabolism.[52] Increased bioavailability and decreased hepatic clearance can cause a possible drug accumulation.[53] Further, a strong inverse relationship between the activity of hepatic CYP enzymes and the severity of cirrhosis has been demonstrated, in which the content and activity of some CYP enzymes, such as CYP3A, appear to be particularly vulnerable to impaired liver function.[54] Although we did not find any interacting factor between liver stiffness and the CYP genotypes regarding methadone CDR, the pattern of CYP enzyme alterations may differ based on the aetiology of liver disease.[54] Due to the large bioavailability and protein binding capacity, and a long half-life, as well as the considerable inter- and intra-individual variability in methadone pharmacokinetics, a close clinical monitoring has been recommended in patients with severe hepatic impairment, nevertheless, no dose adjustment is suggested in mild and moderate liver diseases.[11]

4.4 | Pharmacological factors

Based on our data, almost one-quarter of the patients used other medications in addition to methadone, some of which were potential inducers or inhibitors of hepatic CYP enzymes. CYP inducers were found to reduce methadone CDR by approximately a third. A previous study[41] showed that plasma levels of methadone were significantly reduced days after co-administration of carbamazepine with subsequent clinical opioid withdrawal symptoms. The authors proposed methadone dose reduction after discontinuation of carbamazepine to avoid methadone-induced respiratory depression. Also, withdrawal symptoms have been reported days after starting nevirapine among patients on MMT.[55] This may indicate an inducing effect of the drug on methadone metabolism; however, predicting a net effect is more complicated and depends on the possible influences of other antivirals in the recommended combination regimes.

Additionally, we showed that CYP3A4 inhibitors increased CDR by approximately one-third. This finding confirms some of the previous research data using in vitro, in vivo, and clinical studies on the impact of CYP3A4 in methadone metabolism.[16,22,23,56] However, a possible influence of some of the drugs in this group on CYP2B6-related methadone metabolism cannot be ruled out, as the effect of many drugs on CYP2B6 enzyme activity is unknown. Having only three patients with concurrent use of clopidogrel, which is a selective CYP2B6 inhibitor,[57] our work cannot predict the role of CYP2B6 inhibitors on methadone CDR. In addition, CYP2B6 involves stereo-selective methadone metabolism, preferentially metabolizing the inactive S-methadone, which was not measured separately in our research, whereas CYP3A4 exhibits no clear-cut enantiomer preference.[13,18] This suggests that stereo-selective inhibition might play a role in the varied total methadone serum concentration.[58] Several studies have suggested the primary roles of CYP3A4 and CYP2B6 in methadone's metabolism with minimal roles of CYP2C9, CYP2C19, CYP2D6, CYP3A5 and other enzymes,[14–25] which are in line with our results. A systematic drug–drug interaction analysis from 2019[59] downgrades the role of CYP3A and concludes that CYP2B6 plays a prominent role in methadone metabolism.

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methadone is also more likely to be co-administered with antiviral drugs used to treat infections like HIV and chronic hepatitis C-virus infection.[60] For certain agents, which are dual inhibitors and inducers of CYP enzymes, the effect on methadone pharmacokinetics can change with time since induction is delayed compared to inhibition.[56] Close clinical monitoring is thus required with respect to efficacy and toxicity, particularly shortly after the start of treatment. Clinical and laboratory-based assessments, including measurements of serum methadone concentration, could be crucial in decision-making regarding the need for dose adjustments, especially among patients with multiple comorbid conditions.

5 | STRENGTHS AND LIMITATIONS

The major strength of this research work is the use of several laboratory and clinical databases obtained from Norwegian patients undergoing MMT enabling us to access a large pool of information to conduct the research. The naturalistic observation setting of the study that reflects real life and actual clinical challenges in the daily practice of MMT may constitute both a strength and limitation of this work. In addition to some possible classic biases related to selection, information and confounding, the use of retrospective TDM data for research purposes also implies some methodological limitations such as compliance, uncertainties about the exact dose, the time interval between dose ingestion and sampling, and whether the sample had been collected at steady state. We therefore only included the samples where the most crucial information was available and correctly obtained. Administration of daily methadone doses under supervision may also have reduced the risk of non-compliance and diversion. We used the regression model of analysis to adjust for possible confounders and accordingly to reduce the risk of systematic biases. Yet, the cohort studies in this research are at risk for confounding as the effect of other unknown factors only can be fully adjusted by true randomization.

Additionally, the low number of observations may have resulted in type I and type II errors. A small sample size does not allow for drawing certain conclusions about the possible influences of the important clinical and genetic confounders. The naturalistic nature of the prospective study could also have contributed to some limitations by allowing the clinicians to adjust the methadone dose based on their clinical judgement. Finally, other factors that are beyond the scope of this research, such as the individual's psychosocial condition, may have influenced the results.

6 | CONCLUSIONS

The present study highlights the substantial inter-individual variability in methadone pharmacokinetics, reinforcing the existing clinical and research challenges in MMT. Consistent with previous research, our findings emphasize the impact of various factors including CYP genetic polymorphisms, sex, body mass index and concurrent medication, which should be considered during treatment. These factors contribute to the need for tailored dosing strategies to achieve adequate serum concentrations and alleviate distressing symptoms. However, the variability in the relationship between methadone dose and serum concentration, along with the influence of diverse factors, presents a major challenge. Consequently, the use of therapeutic drug monitoring in MMT should be limited to specific clinical scenarios such as abnormal metabolism, concurrent use of possible interacting medications or severe organ impairment. Understanding the complex dynamics between methadone dosage, serum concentration and treatment response is crucial for improving treatment outcomes and optimizing patient care based on clinical-oriented decision making in daily practice.

ACKNOWLEDGEMENTS

We would especially like to thank all the researchers, clinicians, institutions and funders involved in this research project. Thanks to the research nurses in Intro-HCV, Bergen Addiction Research group and all the clinical staff at the Department of Addiction Medicine, Section for Opioid Agonist Treatment, Haukeland University Hospital for their incredible efforts on data collection including all clinical interviews and surveys, blood samplings and close follow-up of the participants. We would also like to thank the laboratory staff at the Department of Medical Biochemistry and Clinical Pharmacology, Haukeland University Hospital in Bergen; the Center for Psychopharmacology, Diakonhjemmet Hospital in Oslo; and the Department of Clinical Pharmacology, St. Olav University Hospital in Trondheim for the analyses of methadone samples and for a close cooperation during the project period. This work was supported by the research funding of Western Health Region, Norway [project number F-11328-912126]. The INTRO-HCV study was funded by the Norwegian Research Council (BEHANDLING, funding no. 269855, grant received by LTF et al.) and the Western Health Region, Norway (Helse Vest «Åpen prosjektstøtte», grant received by LTF et al.) with the Department of Addiction Medicine, Haukeland University Hospital as the responsible institution. The funder had no role in the study design, data collection and analysis, decision to publish

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

or preparation of the manuscript. The authors are funded by their respective affiliations.

CONFLICT OF INTEREST STATEMENT

No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Fatemeh Chalabianloo https://orcid.org/0000-0003-1242-1972
Lars Thore Fadnes https://orcid.org/0000-0001-8757-2092
Kjell Arne Johansson https://orcid.org/0000-0001-8912-8710
Gudrun Høiseth https://orcid.org/0000-0003-0872-9536

REFERENCES

1. Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat*. 2005;28(4):321-329. Review. doi:10.1016/j.jsat.2005.02.007
2. Ma J, Bao YP, Wang RJ, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review. *Mol Psychiatry*. 2019;24(12):1868-1883. doi:10.1038/s41380-018-0094-5
3. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet*. 2002;41(14):1153-1193. doi:10.2165/00003088-200241140-00003
4. National Institutes of Health. Effective medical treatment of opiate addiction. National Consensus Development Panel on effective medical treatment of opiate addiction. *Jama*. 1998;280:1936-1943.
5. Donny EC, Brasser SM, Bigelow GE, Stitzer ML, Walsh SL. Methadone doses of 100 mg or greater are more effective than lower doses at suppressing heroin self-administration in opioid-dependent volunteers. *Addiction*. 2005;100(10):1496-1509. doi:10.1111/j.1360-0443.2005.01232.x
6. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2017;10:Cd012509. doi:10.1002/14651858.CD012509
7. Kreek MJ, Borg L, Ducat E, Ray B. Pharmacotherapy in the treatment of addiction: methadone. *J Addict Dis*. 2010;29(2):200-216. doi:10.1080/10550881003684798
8. Chalabianloo F, Fadnes LT, Høiseth G, et al. Subjective symptoms and serum methadone concentrations: what should guide dose adjustments in methadone maintenance treatment? A naturalistic cohort study from Norway. *Subst Abuse Treat Prev Policy*. 2021;16(1):39. doi:10.1186/s13011-021-00367-w
9. Dole VP. Implications of methadone maintenance for theories of narcotic addiction. *Jama*. 1988;260(20):3025-3029. doi:10.1001/jama.1988.03410200081030
10. Wolff K, Rostami-Hodjegan A, Shires S, et al. The pharmacokinetics of methadone in healthy subjects and opiate users. *Br J Clin Pharmacol*. 1997;44(4):325-334. doi:10.1046/j.1365-2125.1997.t01-1-00591.x
11. Bosilkovska M, Walder B, Besson M, Daali Y, Desmeules J. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. *Drugs*. 2012;72(12):1645-1669. doi:10.2165/11635500-000000000-00000
12. Olsen GD. Methadone binding to human plasma proteins. *Clin Pharmacol Ther*. 1973;14(3):338-343. doi:10.1002/cpt1973143338
13. Gerber JG, Rhodes RJ, Gal J. Stereoselective metabolism of methadone N-demethylation by cytochrome P4502B6 and 2C19. *Chirality*. 2004;16(1):36-44. doi:10.1002/chir.10303
14. Fonseca F, De la Torre R, Diaz L, et al. Contribution of cytochrome P450 and ABCB1 genetic variability on methadone pharmacokinetics, dose requirements, and response. *PLoS ONE*. 2011;6(5):e19527. doi:10.1371/journal.pone.0019527
15. Crettol S, Déglon JJ, Besson J, et al. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther*. 2005;78(6):593-604. doi:10.1016/j.clpt.2005.08.011
16. Crettol S, Deglon JJ, Besson J, et al. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. *Clin Pharmacol Ther*. 2006;80(6):668-681. doi:10.1016/j.clpt.2006.09.012
17. De FS, Gallelli L, De SA, et al. Role of CYP3A5 in abnormal clearance of methadone. *Ann Pharmacother*. 2008;42(6):893-897. doi:10.1345/aph.1K539
18. Totah RA, Sheffels P, Roberts T, Whittington D, Thummel K, Kharasch ED. Role of CYP2B6 in stereoselective human methadone metabolism. *Anesthesiology*. 2008;363–374(3):363-374. doi:10.1097/ALN.0b013e3181642938
19. Wang SC, Ho IK, Tsou HH, et al. Functional genetic polymorphisms in CYP2C19 gene in relation to cardiac side effects and treatment dose in a methadone maintenance cohort. *Omics*. 2013;17(10):519-526. doi:10.1089/omi.2012.0068
20. Bart G, Lenz S, Straka RJ, Brundage RC. Ethnic and genetic factors in methadone pharmacokinetics: a population pharmacokinetic study. *Drug Alcohol Depend*. 2014;145:185-193. doi:10.1016/j.drugalcdep.2014.10.014
21. Csajka C, Crettol S, Guidi M, Eap CB. Population genetic-based pharmacokinetic modeling of methadone and its relationship with the QTc interval in opioid-dependent patients. *Clin Pharmacokinet*. 2016;55(12):1521-1533. doi:10.1007/s40262-016-0415-2
22. Shiran MR, Lennard MS, Iqbal MZ, et al. Contribution of the activities of CYP3A, CYP2D6, CYP1A2 and other potential covariates to the disposition of methadone in patients undergoing MMT. *Br J Clin Pharmacol*. 2009;67(1):29-37. doi:10.1111/j.1365-2125.2008.03312.x
23. Kharasch ED, Hoffer C, Whittington D, Sheffels P. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin*

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13973 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Pharmacol Ther. 2004;76(3):250-269. doi:10.1016/j.clpt.2004.05.003
24. Kharasch ED. Current concepts in methadone metabolism and transport. *Clin Pharmacol Drug Dev*. 2017;6(2):125-134. doi:10.1002/cpdd.326
25. Wang H, Tompkins LM. CYP2B6: new insights into a historically overlooked cytochrome P450 isozyme. *Curr Drug Metab*. 2008;9(7):598-610. doi:10.2174/138920008785821710
26. Mouly S, Bloch V, Peoc'h K, et al. Methadone dose in heroin-dependent patients: role of clinical factors, comedications, genetic polymorphisms and enzyme activity. *Br J Clin Pharmacol*. 2015;79(6):967-977. doi:10.1111/bcp.12576
27. Kringen MK, Chalabianloo F, Bernard JP, Bramness JG, Molden E, Høiseth G. Combined Effect of CYP2B6 Genotype and Other Candidate Genes on a Steady State Serum Concentration of Methadone in Opioid Maintenance Treatment. *Ther Drug Monit*. 2017;39(5):550-555. doi:10.1097/FTD.0000000000000437
28. Chalabianloo F, Westin AA, Skogvoll E, Bramness JG, Spigset O. Methadone serum concentrations and influencing factors: a naturalistic observational study. *Psychopharmacology (Berl)*. 2019;236(11):3159-3167. doi:10.1007/s00213-019-05277-1
29. Chalabianloo F, Høiseth G, Vold JH, et al. Impact of liver fibrosis and clinical characteristics on dose-adjusted serum methadone concentrations. *J Addict Dis*. 2022;31(1):1-11. doi:10.1080/10550887.2022.2057140
30. Fadnes LT, Aas CF, Vold JH, et al. Integrated treatment of hepatitis C virus infection among people who inject drugs: a multicenter randomized controlled trial (INTRO-HCV). *PLoS Med*. 2021;18(6):e1003653. doi:10.1371/journal.pmed.1003653
31. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med*. 2013;158(11):807-820. doi:10.7326/0003-4819-158-11-201306040-00005
32. Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology*. 2011;53(3):726-736. doi:10.1002/hep.24105
33. Preston CL. *Stockley's drug interactions*. Pharmaceutical Press; 2016.
34. Foster DJR, Somogyi AA, Dyer KR, White JM, Bochner F. Steady state pharmacokinetics of (R)- and (S)-methadone in methadone maintenance patients. *Br J Clin Pharmacol*. 2000;50(5):427-440. doi:10.1046/j.1365-2125.2000.00272.x
35. Wolff K, Hay A. Methadone concentrations in plasma and their relationship to drug dosage. *Clin Chem*. 1992;38(3):438-439. doi:10.1093/clinchem/38.3.438
36. Eap CB, Bourquin M, Martin J, et al. Plasma concentrations of the enantiomers of methadone and therapeutic response in MMT. *Drug Alcohol Depend*. 2000;61(1):47-54. doi:10.1016/S0376-8716(00)00121-6
37. Zanger UM, Klein K. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. *Front Genet*. 2013;4:24.
38. Eap CB, Crettol S, Rougier JS, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther*. 2007;81(5):719-728. doi:10.1038/sj.clpt.6100120
39. Bunten H, Liang WJ, Pounder D, Seneviratne C, Osselton MD. CYP2B6 and OPRM1 gene variations predict methadone-related deaths. *Addict Biol*. 2011;16(1):142-144. doi:10.1111/j.1369-1600.2010.00274.x
40. Hustert E, Haberl M, Burk O, et al. The genetic determinants of the CYP3A5 polymorphism. *Pharmacogenetics*. 2001;11(9):773-779. doi:10.1097/00008571-200112000-00005
41. Kapur BM, Hutson JR, Chibber T, Luk A, Selby P. Methadone: a review of drug-drug and pathophysiological interactions. *Crit Rev Clin Lab Sci*. 2011;48(4):171-195. doi:10.3109/10408363.2011.620601
42. Dickmann LJ, Isoherranen N. Quantitative prediction of CYP2B6 induction by estradiol during pregnancy: potential explanation for increased methadone clearance during pregnancy. *Drug Metab Dispos*. 2013;41(2):270-274. doi:10.1124/dmd.112.047118
43. Westin AA, Brekke M, Molden E, Skogvoll E, Castberg I, Spigset O. Treatment with antipsychotics in pregnancy: changes in drug disposition. *Clin Pharmacol Ther*. 2018;103(3):477-484. doi:10.1002/cpt.770
44. Wolff K, Rostami-Hodjegan A, Hay AW, Raistrick D, Tucker G. Population-based pharmacokinetic approach for methadone monitoring of opiate addicts: potential clinical utility. *Addiction*. 2000;95(12):1771-1783. doi:10.1046/j.1360-0443.2000.951217717.x
45. Talal AH, Ding Y, Venuto CS, et al. Toward precision prescribing for methadone: determinants of methadone deposition. *PLoS ONE*. 2020;15(4):e0231467. doi:10.1371/journal.pone.0231467
46. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol*. 2008;64(12):1147-1161. doi:10.1007/s00228-008-0553-z
47. Zarezadeh M, Saedisomeolia A, Shekarabi M, Khorshidi M, Emami MR, Müller DJ. The effect of obesity, macronutrients, fasting and nutritional status on drug-metabolizing cytochrome P450s: a systematic review of current evidence on human studies. *Eur J Nutr*. 2021;60(6):2905-2921. doi:10.1007/s00394-020-02421-y
48. Kljucevic Z, Benzon B, Kljucevic N, Versic Bratincevic M, Sutlovic D. Liver damage indices as a tool for modifying MMT: a cross-sectional study. *Croat Med J*. 2018;59(6):298-306. doi:10.3325/cmj.2018.59.298
49. Wu SL, Wang SC, Tsou HH, et al. Hepatitis C virus infection influences the S-methadone metabolite plasma concentration. *PLoS ONE*. 2013;8(7):e69310. doi:10.1371/journal.pone.0069310
50. Novick DM, Kreek MJ, Fanizza AM, Yancovitz SR, Gelb AM, Stenger RJ. Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther*. 1981;30(3):353-362. doi:10.1038/clpt.1981.172
51. Larrey D, Pageaux G. Prescribing drugs in liver disease. In: Rodes J, Benhamou J, Blei A, eds. *Textbook of hepatology: from basic science to clinical practice*. Blackwell; 2007:1912-1922. doi:10.1002/9780470691861.ch23c
52. Blaschke TF, Rubin PC. Hepatic first-pass metabolism in liver disease. *Clin Pharmacokinet*. 1979;4(6):423-432. doi:10.2165/00003088-197904060-00002
53. McLean AJ, Morgan DJ. Clinical pharmacokinetics in patients with liver disease. *Clin Pharmacokinet*. 1991;21(1):42-69. doi:10.2165/00003088-199121010-00004

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

54. Villeneuve J-P, Pichette V. Cytochrome P450 and liver diseases. *Curr Drug Metab*. 2004;5(3):273-282. doi:10.2174/1389200043335531
55. Stocker H, Kruse G, Kreckel P, et al. Nevirapine significantly reduces the levels of racemic methadone and (R)-methadone in human immunodeficiency virusinfected patients. *Antimicrob Agents Chemother*. 2004;48(11):4148-4153. doi:10.1128/AAC.48.11.4148-4153.2004
56. Volpe DA, Xu Y, Sahajwalla CG, Younis IR, Patel V. Methadone metabolism and drug-drug interactions: in vitro and in vivo literature review. *J Pharm Sci*. 2018;107(12):2983-2991. doi:10.1016/j.xphs.2018.08.025
57. Totah RA, Allen KE, Sheffels P, Whittington D, Kharasch ED. Enantiomeric metabolic interactions and Stereoselective human methadone metabolism. *J Pharmacol Exp Ther*. 2007;321(1):389-399. doi:10.1124/jpet.106.117580
58. Chang Y, Fang WB, Lin S-N, Moody DE. Stereo-selective metabolism of methadone by human liver microsomes and cDNA-expressed cytochrome P450s: a reconciliation. *Basic Clin Pharmacol Toxicol*. 2011;108(1):55-62. doi:10.1111/j.1742-7843.2010.00628.x
59. Younis IR, Lakota EA, Volpe DA, Patel V, Xu Y, Sahajwalla CG. Drug-drug interaction studies of methadone and antiviral drugs: lessons learned. *J Clin Pharmacol*. 2019;59(8):1035-1043. doi:10.1002/jcph.1405
60. Ogbuagu O, Friedland G, Bruce RD. Drug interactions between buprenorphine, methadone and hepatitis C therapeutics. *Expert Opin Drug Metab Toxicol*. 2016;12(7):721-731. doi:10.1080/17425255.2016.1183644

How to cite this article: Chalabianloo F, Fadnes LT, Johansson KA, et al. Methadone pharmacokinetics in opioid agonist treatment: Influencing factors and clinical implications. *Basic Clin Pharmacol Toxicol*. 2024;134(3):333-344. doi:10.1111/bcpt.13975

17427843, 2024, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13975 by Norwegian Institute Of Public Healt Invoice Receipt DFO, Wiley Online Library on [14/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License