Understanding How HIV and Hepatitis C Virus (HCV) Infection Affects *CYP2B6* Enzymatic Activity and Methadone Pharmacokinetics

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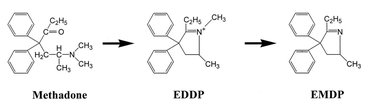
Background

- Methadone is one of three medications approved for the treatment of opioid use disorder (OUD).
- Its narrow therapeutic index and inter-individual variability in disposition create dosing challenges.
- While overdose can lead to toxicity and death, sub-therapeutic doses can potentiate withdrawal.
- We seek to develop safe, effective methadone dosing strategies by elucidating the associations between *CYP2B6* genetic polymorphisms and methadone disposition in HIV and HCV patients.

Rationale

- *CYP2B6* is a polymorphic, methadone metabolic enzyme with 38 variant alleles identified through single-nucleotide polymorphisms (SNP)
- Several loss-of-function alleles (*CYP2B6*5*, *CYP2B6*6*, *CYP2B6*7*, *CYP2B6*16*, *CYP2B6*18*) express low enzymatic activity and catalyze less methadone N-demethylation to metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) compared to wild-type (*CYP2B6*1*)



Hypothesis

- We hypothesize that HIV and HCV infection affects *CYP2B6* enzymatic activity

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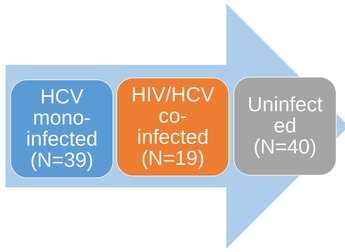
Study Design and Entry Criteria

- We enrolled adult patients receiving once-daily methadone for opioid replacement therapy (ORT) cross-sectionally.
- HIV and HCV infection status assessed within one year.
- Patients required stable methadone dose for at least 14 days with ≥80% adherence and at least 90 days on ORT.
- Body mass index <40 kg/m² and no active HCV treatment.



Study Activities

- FibroScan® assessments
  - Liver stiffness
  - Steatosis
- Demographic and medical history data
- Methadone pre-dose trough concentration
- *CYP2B6* genetic testing

Study Assessments

- Ultrasound-based vibration controlled transient elastography (FibroScan®) assessed hepatic stiffness (elasticity) (i.e. fibrosis) and controlled attenuation parameter (CAP) (i.e. steatosis).
- Demographic data included height, weight, age, gender, race, ethnicity, methadone dose, nicotine and alcohol consumption, substance use, and concomitant medications.
- Laboratory data included liver function, hematology, virologic status, and blood chemistry obtained from medical records.
- (R)- and (S)-methadone and (R)- and (S)-EDDP concentrations were assessed on plasma trough samples (~24 hours post-dose).
- Genomic DNA was extracted from whole blood and genotyped for the *CYP2B6* 516G>T (rs3745274), 785A>G (rs2279343), 983T>C (rs28399499) and 1459C>T (rs3211371) SNP.

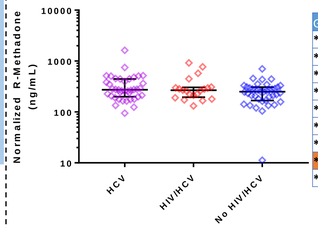
Baseline Characteristics

Characteristic	HCV	HIV/HCV	Uninfected	Total
Gender				
Male	28 *(72%)*	11 *(58%)*	18 *(45%)*	57 *(58%)*
Female	11 *(28%)*	8 *(42%)*	22 *(55%)*	41 *(42%)*
Race				
Black or African American	22 *(56%)*	9 *(47%)*	28 *(69%)*	59 *(60%)*
Caucasian	13 *(33%)*	9 *(47%)*	6 *(15%)*	28 *(29%)*
Others	4 *(11%)*	1 *(6%)*	6 *(16%)*	11 *(11%)*
Ethnicity				
Non-Hispanic or Latino	24 *(62%)*	11 *(58%)*	31 *(77.5%)*	66 *(67%)*
Hispanic or Latino	15 *(38%)*	8 *(42%)*	9 *(22.5%)*	32 *(33%)*

Baseline Characteristics (cont.)

Characteristic	HCV		HIV/HCV		Non-Infected		Total	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age, years	58	13	60	13	53	10.75	56	13.75
BMI, kg/m²	25.63	7.30	22.86	2.99	28.55	9.15	25.22	8
Methadone dose, mg	80	72.5	80	50	90	72.5	82.5	63.75
Elasticity, kPa	7.9 (F2)	8.75	8.7 (F2)	7.6	5.7 (F0)	3.8	6.8	6.4
CAP, dB/m	235 (S0)	80.5	226 (S0)	47	249 (S1)	87	235	75

BMI, body mass index; CAP, Continuous attenuation parameter; IQR: Interquartile Range

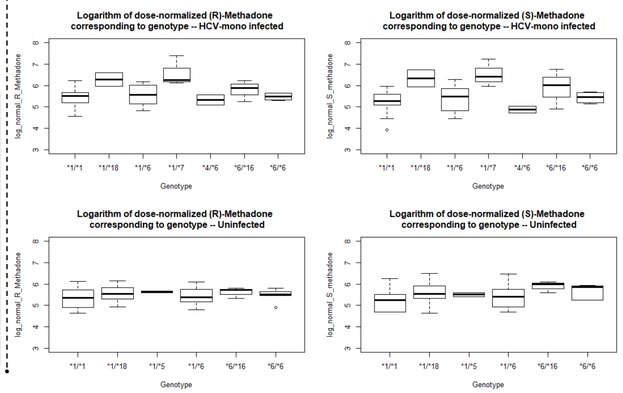


Genotype	516G>T	785A>G	983T>C	1459C>T	Frequency
*1/*1	GG	AA	TT	CC	24(25%)
*1/*4	GG	GA	TT	CC	1(1%)
*1/*5	GG	AA	TT	TC	3(3%)
*1/*6	GT	GA	TT	CC	34(35%)
*1/*7	GT	GA	TT	TC	7(7%)
*1/*18	GG	AA	CT	CC	9(9%)
*4/*6	GT	GG	TT	CC	2(2%)
*6/*16	GT	GA	CT	CC	6(6%)
*6/*6	TT	GG	TT	CC	12(12%)

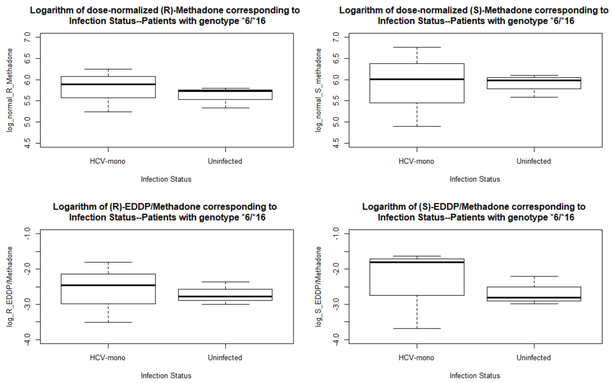
Baseline Characteristics Summary

- Most participants are male, African American, non-Hispanic.
- BMI was highest in uninfected and lowest in HIV/HCV co-infected.
- Liver stiffness was highest in HIV/HCV co-infected, and lowest in uninfected.
- Steatosis was highest in uninfected and lowest in HIV/HCV co-infected.
- Dose-normalized (R)-methadone did not differ significantly by infection status.
- *1/*1 and *1/*6 were the two most frequent CYP2B6 alleles.

CYP Allele Affect on Methadone PK



Allele *6/*16 Affect on Methadone PK



PID	Disease Status	Race	Ethnicity	Gender	Age	BMI	Elasticity	CAP
2	HCV-mono	Black	Non-Hispanic	Male	63	25.72	6.2	260
10	Uninfected	Black	Non-Hispanic	Female	66	20.37	4	255
16	Uninfected	Black	Non-Hispanic	Female	57	29.37	12.1	252
20	HCV-mono	Black	Non-Hispanic	Female	44	37.93	4.9	232
50	Uninfected	Black	Non-Hispanic	Female	63	30.99	*	*
51	HCV-mono	Black	Non-Hispanic	Male	63	21.14	6.8	200

Results

- Dose-normalized (R)- and (S)-methadone concentrations appear to be affected by HCV infection.
- CYP2B6 *6/*16 appears to be a novel SNP responsible for methadone metabolism.
- HCV infection also appears to affect CYP2B6 *6/*16 methadone metabolism.
- HIV/HCV co-infection also appears to affect CYP2B6 *1/*6 and *6/*6 methadone metabolism (data not shown).

Conclusions

- We noted an inverse relationship between liver stiffness and steatosis based upon infection status.
- HCV and HIV infection status appear to influence methadone metabolism by different alleles.
- CYP2B*6/*16 may be a novel SNP.
- Further investigation is needed to discern if these findings persist in larger populations and to elucidate potential mechanisms.

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