QTc Prolongation of Slow-release Oral Morphine vs Methadone for Opioid Use Disorder: A Population-based Study

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BACKGROUND

- Buprenorphine and methadone, first-line medications for opioid use disorder (MOUD), reduce morbidity and mortality with opioid use disorder (OUD) [1-4]
- However, further medication options for OUD are needed to optimize side effect profiles, provide additional options for patient preferences, and improve retention in treatment. [5]
- Slow-release oral morphine (SROM) has emerged as an alternative MOUD with some evidence suggesting comparable efficacy to methadone in reducing illicit opioid use and improving retention in treatment [6-7]
- Small studies suggest that SROM may result in less QT prolongation on the electrocardiogram (ECG) compared to methadone [8]
- Torsades de pointes is a polymorphic ventricular arrythmia occurring in patients with a prolonged QT interval that can lead to cardiac arrest and death [9]
- Methadone is known to cause QT prolongation through its effects on the cardiac hERG (human ether-a-go-go-related gene) channel, which results in delayed cardiac repolarization and risk of torsades de pointes [10]
- SROM is not known to cause QT prolongation however studies are limited
- One small crossover RCT (n=198) demonstrated that the QTc interval (corrected QT interval) with SROM treatment was lower compared methadone (418.33±22.17 ms vs 431.08±26.37 ms; p<0.0001) [8]
- However, larger population studies examining the real-world differences in QT prolongation as well as impacts on cardiac events between methadone and SROM are lacking.

STUDY OBJECTIVES

- To compare the QTc prolongation of methadone vs SROM using population-level data.
- We evaluated the change in QTc interval with treatment well as assess whether this translates into a clinically increased risk of cardiac arrest or arrythmia events.

METHODS

- Pre-specified secondary analysis of QTc outcomes in the pRESTO target emulated trial
- Retrospective cohort study using de-identified administrative health data from the Vancouver Coastal Health Authority region from July 2017 and June 2024

Inclusion:
- Adults aged 19 to 65 years with OUD
- Both a pre-treatment ECG and on-treatment ECG with methadone or SROM*

Exclusion:
- Long QT syndrome (acquired and congenital)
- Baseline malignancy diagnosis

Definitions: *Pre-treatment ECG – greater than 5 half-lives without a dose. 6 consecutive days without a methadone dose ($T_{1/2}$=24h) or 3 consecutive days without SROM ($T_{1/2}$=12h). On-treatment ECG – during a 7-day period with at least 3 consecutive daily doses, or 5 daily doses of methadone or SROM. One dose in the last 3 days before the ECG

- Outcomes:
  - Primary: Change in QTc length (ms) with treatment
  - Secondary: QTc > 500 ms, proportion of patients with QTc prolongation based on sex-specific cut-offs (females > 460 ms, males > 450 ms), cardiac arrythmia/arrest events
- We assessed QTc outcomes during the pre-treatment and on-treatment ECGs using a difference-in-differences analysis to assess for causal inference
- Inverse probability weight was used to adjust for baseline differences in common confounders including age, sex, modified Elixhauser comorbidity index,[11] and QTc prolonging medications

RESULTS

Figure 1. Flow Diagram of Participant Inclusion into the Study

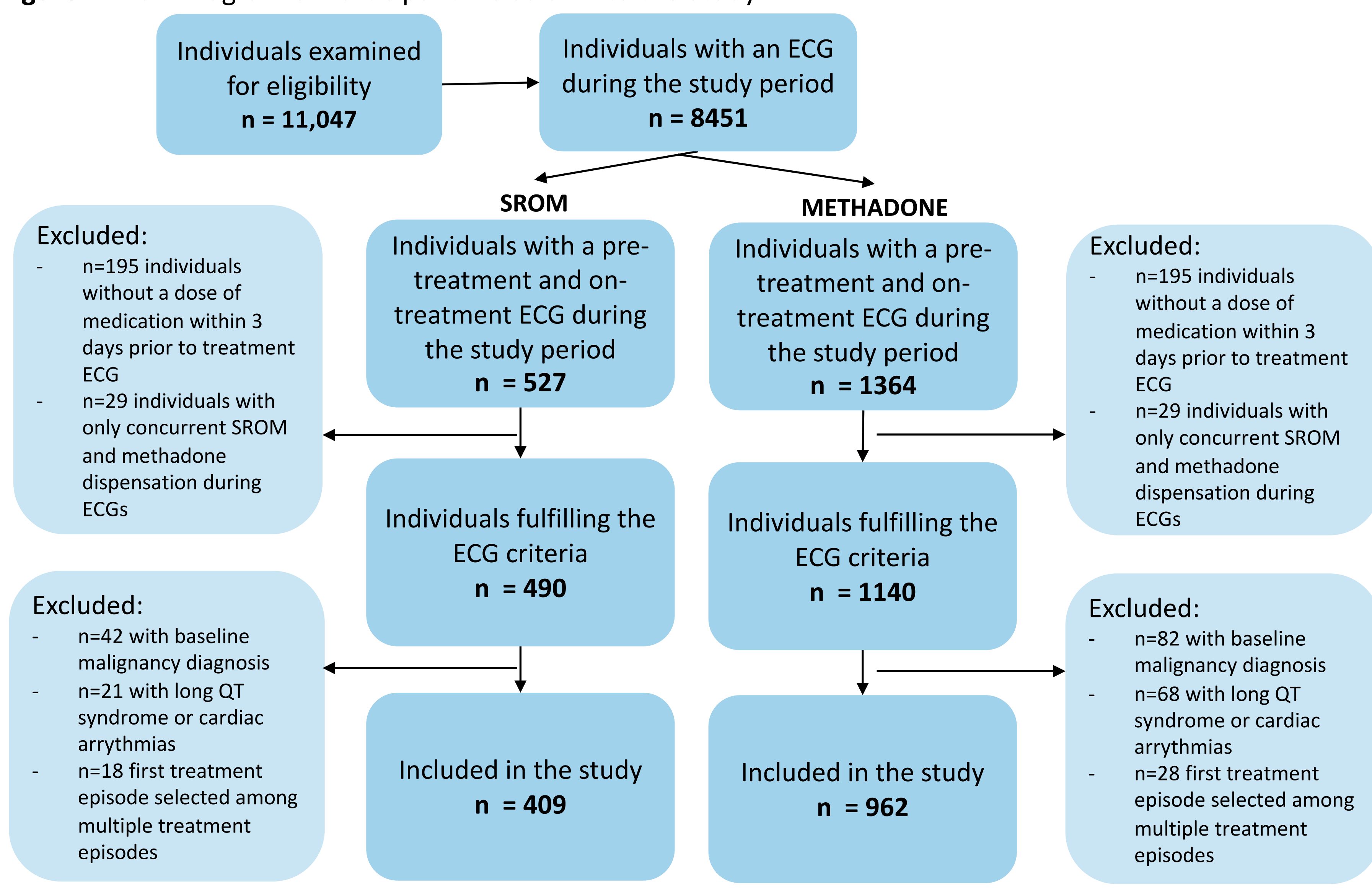

Table 1. Baseline and on-treatment characteristics of patients initiating methadone or SROM (n=1371)

Variables	Overall (n=1371)	Treatment Arm: Methadone (n=962)	Treatment Arm: SROM (n=409)	SMD: Before IPW	SMD: After IPW
Baseline Demographics					
Age	45 (36-54)	45 (36-54)	45 (35-55)	0.013	-0.002
Age group					
19-64	1301 (94.9)	916 (95.2)	385 (94.1)		
≥65	70 (5.1)	46 (4.8)	24 (5.9)	0.046	0.051
Sex					
Female	389 (28.4)	257 (26.7)	132 (32.3)		
Male	982 (71.6)	705 (73.3)	277 (67.7)	-0.119	0.003
Elixhauser Comorbidity Index in the last 5 years					
none	797 (58.1)	580 (60.3)	217 (53.1)		
1 or more	574 (41.9)	382 (39.7)	192 (46.9)	0.145	-0.030
Calendar year of pre-treatment ECG				-0.129	-0.050
2017	74 (5.4)	44 (4.6)	30 (7.3)		
2018	156 (11.4)	103 (10.7)	53 (13.0)		
2019	182 (13.3)	124 (12.9)	58 (14.2)		
2020	197 (14.4)	131 (13.6)	66 (16.1)		
2021	234 (17.1)	178 (18.5)	56 (13.7)		
2022	246 (17.9)	187 (19.4)	59 (14.4)		
2023	249 (18.2)	173 (18.0)	76 (18.6)		
2024	33 (2.4)	22 (2.3)	11 (2.7)		
Number of QTc prolonging medications at pre-treatment ECG				0.070	0.018
0	1189 (86.7)	840 (87.3)	349 (85.3)		
1	167 (12.2)	114 (11.9)	53 (13.0)		
>=2	15 (1.1)	8 (0.8)	7 (1.7)		

Variables	Overall (n=1371)	Treatment Arm: Methadone (n=962)	Treatment Arm: SROM (n=409)
On-Treatment Characteristics			
Average medication dose in 3 days prior to ECG (mg)	120 (65-250)	90 (55-140)	550 (300-900)
Average medication dose in 3 days prior to ECG (number of patients)			
Low	425 (31.0)	250 (26.0)	175 (42.8)
Moderate	254 (18.5)	195 (20.3)	59 (14.4)
High	692 (50.5)	517 (53.7)	175 (42.8)
Days on medication treatment before on treatment ECG	57 (15-182)	68 (16-222)	41 (12-119)
Number of QTc prolonging medications during on treatment ECG			
0	1170 (85.3)	829 (86.2)	341 (83.4)
1	185 (13.5)	125 (13.0)	60 (14.7)
>=2	16 (1.2)	8 (0.8)	8 (2.0)
ECG Characteristics			
Average QTc of pre-treatment ECG, ms	429.5±30.2	431.2±30.5	425.6±29.1
Average QTc of on treatment ECG, ms	433.9±34.9	437.6±35.7	425.1±31.2
Number of patients with pre-treatment ECGs with:			
QTc > 500 ms	25 (1.8)	20 (1.8)	5 (1.2)
QTc > 460 ms for females or QTc > 450 ms for males	257 (18.8)	193 (20.1)	64 (15.7)
Number of on-treatment ECGs with:			
QTc > 500 ms	54 (3.9)	43 (4.2)	11 (2.7)
QTc > 460 ms for females or QTc > 450 ms for males	329 (24.0)	274 (28.5)	55 (13.5)

Figure 2. QTc length pre-treatment and on treatment with methadone and SROM, with 95% CIs

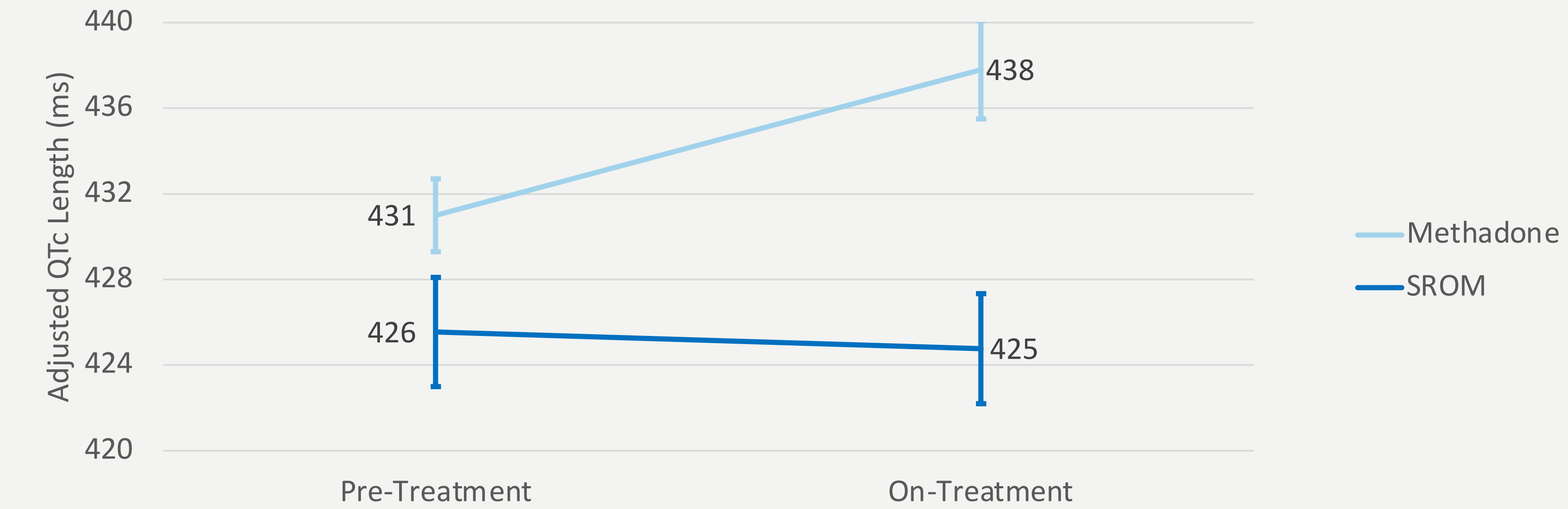

Figure 3. Number of patients with prolonged QTc (QTc > 460 for females and QTc > 450 ms for males)

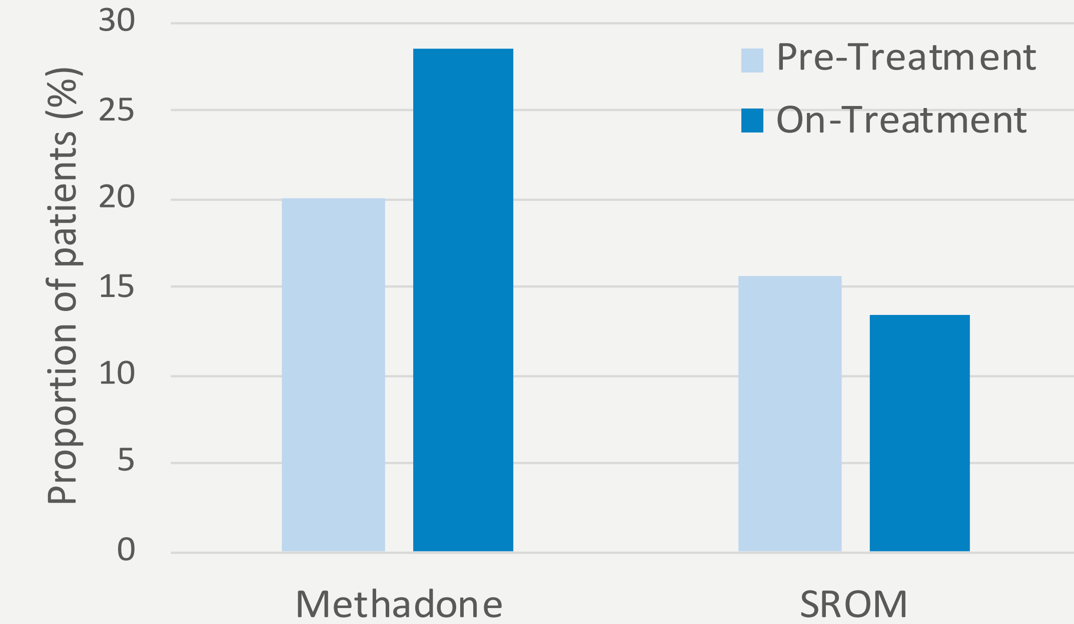

Figure 4. Number of new cardiac arrythmia events during the study period

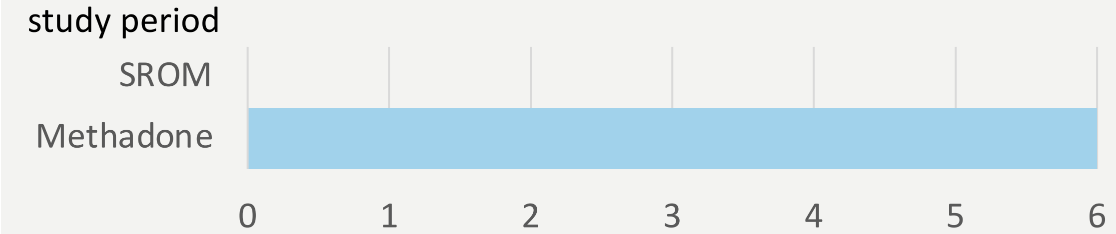

Table 2. Difference-in-differences analysis with multivariable linear or logistic regression of primary QTc outcomes on electrocardiogram (ECG)

Outcome	Difference-in-Differences Estimate (95% CI)*: Estimate	p-value
Change in QTc length (ms)	Adjusted difference	
Treatment (SROM vs methadone)	-4.76 (-8.33, -1.19)	0.009
Time (post vs pre)	6.56 (4.09, 9.02)	**<0.001**
Treatment x pre-post	-7.46 (-11.81, -3.10)	**<0.001**
Number of ECGs with QTc > 500 ms	Adjusted odds ratio	
Treatment (SROM vs Methadone)	0.67 (0.24, 1.87)	0.449
Time (post vs pre)	2.33 (1.38, 3.93)	**0.002**
Treatment x pre-post	0.78 (0.23, 2.67)	0.693
Number of ECGs with QTc > 460 ms for females or QTc > 450 ms for males	Adjusted odds ratio	
Treatment (SROM vs Methadone)	0.82 (0.59, 1.13)	0.225
Time (post vs pre)	1.62 (1.34, 1.95)	**<.001**
Treatment x pre-post	0.48 (0.31, 0.73)	**<.001**

DISCUSSION

- This study is consistent with the current literature that methadone is associated with increased QTc prolongation compared to SROM, with one RCT (n=198) reporting a difference in 12 ms [8]
- A recent systematic review of observational studies found that methadone had an incidence of QTc prolongation of 34% and torsades de pointes occurring in 2%,[12] comparable to 28% and 0.6% in our study, respectively
- Multivariable analysis could not be performed on the cardiac arrest/arrythmias outcome due to zero events in one group

CONCLUSIONS

- This study is the first to compare QTc prolongation between methadone vs SROM using population-level data.
- There was a statistically significant increase in QTc interval with methadone treatment compared to SROM, as well as increased odds of developing QTc prolongation during methadone treatment.
- Future research is needed to evaluate whether the QTc prolongation with methadone compared to SROM translates into a clinically meaningful increased risk of cardiac arrhythmia/arrest.

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