Received: 10 October 2023 | Revised: 11 January 2024 | Accepted: 11 January 2024

DOI: 10.1111/bcpt.13982

ORIGINAL ARTICLE

BCPT Basic & Clinical Pharmacology & Toxicology

Effect on QTc interval by switching from methadone to equipotent R-methadone dose in methadone maintenance treatment patients

Stine Marie Havig[1] | **Riikka Mari Berg-Pedersen**[2] | **Hege-Merete Krabseth**[1] | **Lill Dannevig Müller**[1] | **Kristina Haugaa**[3,4] | **Hasse Khiabani Zare**[1] | **Knut Gjesdal**[4] | **Peter Krajci**[2] | **Mimi Stokke Opdal**[1,4]

[1]Department of Pharmacology, Oslo University Hospital, Oslo, Norway

[2]Department of Substance Use Disorder Treatment, Oslo University Hospital, Oslo, Norway

[3]Department of Cardiology, Oslo University Hospital, Oslo, Norway

[4]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Correspondence
Stine Marie Havig, Department of Forensic Sciences, Oslo University Hospital, Oslo, Norway.
Email: stinh@ous-hf.no

Present addresses
Stine Marie Havig, Department of Forensic Sciences, Oslo University Hospital, Oslo, Norway; Riikka Mari Berg-Pedersen, Askerlegene, Asker, Norway; and Hege-Merete Krabseth, Department of Clinical Pharmacology, St. Olav's Hospital, Trondheim, Norway.

Funding information
Department of Pharmacology and the Department of Substance Use Disorder Treatment at Oslo University Hospital; University of Oslo

Abstract

Methadone (R,S-methadone) can prolong the QT interval. R-methadone inhibits cardiac potassium channel function less than S-methadone. We tested if switching from methadone to R-methadone would reduce corrected QT (QTc) intervals in methadone maintenance treatment (MMT) patients. Nine patients, with automatically read QTc intervals ≥450 ms, were required to detect a 20 ms (clinically relevant) reduction in QTc intervals with 15 ms standard deviation (SD) and 90% power. Nine stabilized MMT patients, using median (range) 70 (40–120) mg methadone, were included. Data (ECG recordings, serum samples, and withdrawal symptoms) were collected both before drug intake (C_{min}) and at 3 h after drug intake (C_{max}), and were collected on the day before the switch from methadone to equipotent R-methadone dose and at 14 and 28 days after the switch. A cardiologist calculated QTc intervals retrospectively. Serum electrolytes and methadone concentrations were measured. Mean QTc intervals at C_{min} were 472 ms and 422 ms on methadone (automatically and manually read) and 414 ms on R-methadone (manually read). Mean (SD) change in QTc intervals was −8 (10) ms ($p = 0.047$) at C_{min} but non-significant at C_{max}. R-methadone showed a concentration-dependent relationship with QTc intervals. Switching to R-methadone reduced QTc intervals, but far less than the 20 ms considered clinically relevant.

KEYWORDS
arrhythmia, levomethadone, methadone, QT interval, R-methadone

Peter Krajci and Mimi Stokke Opdal should be considered joint senior authors.

1 | INTRODUCTION AND BACKGROUND

Methadone is a synthetic opioid, used for managing pain and maintenance treatment in opioid dependence. The drug is a racemic mixture of R-(laevorotatory) and S-(dextrorotatory) stereoisomers. R-methadone has approximately a 10-fold higher binding affinity to opioid receptors than S-methadone and accounts for most of the drug's analgesic and abstinence-relieving properties.[1,2]

A possible side effect of methadone is prolongation of the QT interval, which reflects the de- and repolarization phases of the ventricular myocytes. Methadone inhibits a channel encoded by the human *ether-à-go-go*-related gene (hERG), responsible for the rapid component of the delayed rectifier potassium current in the cardiomyocyte, which causes a delay in cardiac repolarization.[3] This inhibition of the hERG channel by methadone appears to be concentration-dependent.[4,5] QT interval prolongation puts the heart at risk of developing a sudden polymorphic ventricular tachyarrhythmia called Torsades des Pointes (TdP),[6] which in turn can lead to cardiac arrest and sudden death. In vitro, R-methadone has less inhibitory effect on the hERG channel compared with S-methadone.[7,8]

The risk of life-threatening arrhythmias among hospitalized patients with acquired long corrected QT (QTc) intervals >500 ms appears around 4%,[9] regardless of cause. A nearly three-fold increased risk of sudden cardiac death has been reported among those using non-cardiac QTc prolonging drugs.[10] Roughly 30% of methadone maintenance treatment (MMT) patients may present with prolonged QTc intervals >450 ms,[11] and severe QTc interval prolongation (>500 ms) appears to be more common in MMT patients than in other hospitalized patients,[12–14] making the MMT-patient population particularly at risk. Thus, some guidelines for drug-assisted rehabilitation of opioid addiction recommend recording an electrocardiogram (ECG) when commencing treatment and after dose stabilization, while others only recommend recording ECGs in patients with cardiac risk factors or concomitant use of other QT prolonging drugs.[15,16]

Among the options for reversing methadone-related prolonged QT intervals is dose reduction, as there is some evidence that drug effects on QT intervals are dose-dependent,[11,17,18] or switching to buprenorphine or morphine, which both have little documented effect on the hERG channel and the QT interval.[5,11,13] A third option is switching to R-methadone,[19] thereby avoiding the S-enantiomer mostly linked to the prolongation.[7,8] A small reduction in the QTc interval has been observed in a group of MMT patients after switching from methadone to R-methadone,[20] but little is known about the possible effects of switching among those experiencing prolonged QTc intervals.

The aims of our study were to investigate if switching to R-methadone would lead to clinically relevant reductions in QTc intervals of at least 20 ms[21] in MMT patients with intervals ≥450 ms (automatically read) and to elucidate possible relationships between serum methadone concentrations and QTc intervals. The presence of opioid withdrawal symptoms[22,23] and serum electrolytes levels, known to affect the QTc interval, were also studied.

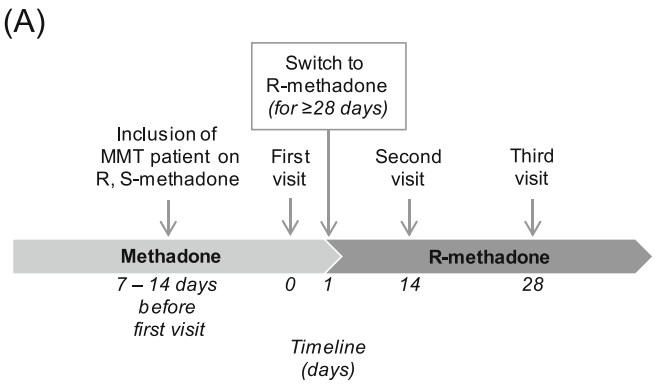
2 | MATERIALS AND METHODS

2.1 | Study design

In this clinical study, MMT patients presenting with QTc intervals ≥450 ms from automatically read ECGs were switched from methadone to R-methadone, between May 2015 and July 2018. QTc intervals were calculated from manually read ECGs[24] in retrospect, recorded on the day before and at 14 and 28 days after the switch (Figure 1A). Nine patients had to be included to detect a clinically relevant reduction in the QTc interval of at least 20 ms[21] with a standard deviation (SD) of 15 ms (estimated from previous studies[25,26]) and 90% power,[27] using a one sample Student's *t* test (mean paired comparison, two sided).

MMT patients were included from the Department of Substance Use Disorder Treatment at Oslo University Hospital (OUH). At inclusion, patients had already been stabilized on the same methadone dose for at least 4 weeks. Additional inclusion criteria were as follows: 18 years or older, not pregnant, no ongoing serious untreated psychiatric or somatic illnesses, willing to participate at three separate visits to the research unit, and complying with daily observed methadone intakes, both before and during the study period, either at a pharmacy, in the outpatient clinic, or by a home nurse. Oral liquid solutions of methadone and R-methadone were supplied by Dne Pharma (Oslo, Norway). At initiation of the study, R-methadone was not a registered drug with marketing approval in Norway. Levopidon (levomethadone), produced by Dne Pharma, received marketing approval on 12 June 2018.

Between 7 to 14 days after inclusion, the methadone-stabilized patients presented at the research unit for their first visit. The following day, patients received their first dose of R-methadone, which was half of their original methadone dose. Patients met again at the research unit at 14 and 28 days following the switch for their second and third visits, respectively. The 14-day interval between the switch and the second visit was set to ensure complete elimination of S-methadone (>10 × methadone's half-life of approximately 33 h) from the body. The



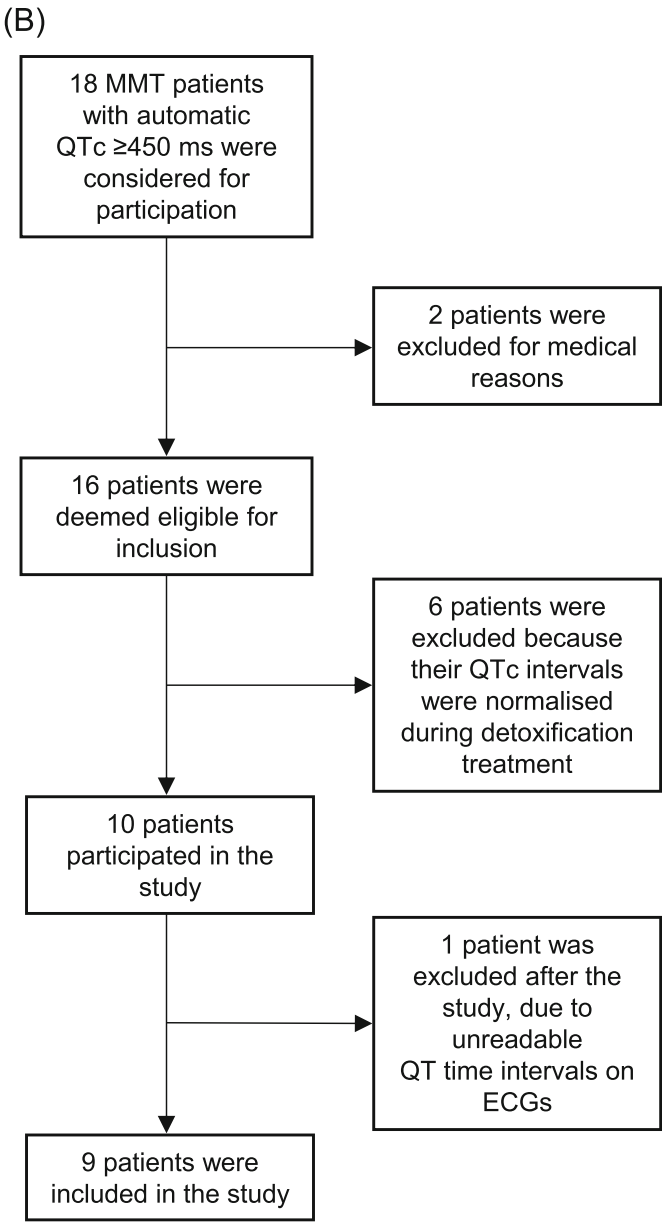


FIGURE 1 (A) Interventional study: nine methadone maintenance treatment patients, presenting with QTc intervals ≥450 ms, were switched to an equipotent R-methadone dose. (B) Patient inclusion flow chart [Correction added on 8 February 2024, after first online publication: Figure 1B has been corrected in this version.].

purpose of the third visit was to ensure persisting effects of the drug change. ECG recordings, heart rate and blood pressure measurements, Clinical Opioid Withdrawal Scale (COWS) assessment,[28] and blood sampling for biochemical and serum methadone concentration analyses were performed at each visit before the patient received their daily methadone dose (at C_{min}). These same tests, except for the biochemical assessments, were repeated approximately 3 h after drug intake (at C_{max}). A urine sample for drug testing and the current list of drugs (prescribed and non-prescribed) were collected during each visit. On the first visit, blood was sampled for cytochrome P450-analyses of relevance to methadone metabolism. At inclusion, patients' clinical and family history were assessed for syncopal/presyncopal tendencies and heart disease to reveal a possible long QT syndrome (LQTS),[29] using a questionnaire developed by the participating cardiologist.

2.2 | Ethics

This study, registered at ClinicalTrials.gov (NCT04254731), was approved by the Norwegian Regional Committee for Medical and Health Research Ethics South-East (2012/793) and by the Data Protection Officer at OUH, according to the World Medical Association Declaration of Helsinki. The study was conducted in accordance with the *Basic & Clinical Pharmacology & Toxicology* policy for experimental and clinical studies.[30] All included patients read and signed a written consent form before participating in the study. Included patients were offered to continue their treatment with R-methadone following their participation.

2.3 | ECG, heart rate, and blood pressure recordings

At the research unit, a standard 12-lead ECG was recorded by a MAC 5500 (GE Medical Systems, USA), at a speed of 50 mm/s and gain of 10 mm/mV. At inclusion, different ECG machines were used (results not included). A participating cardiologist measured the QT interval and the RR interval in lead V2 on each ECG recording, blinded and retrospectively, and calculated the QTc interval using Fridericia's formula[17,21,31,32]: $QTc = \frac{QT}{\sqrt[3]{RR}}$, with QT and RR in seconds. The end of the QT interval was the intersection between the tangent to the steepest downward slope of the T wave and the isoelectric baseline. As a control, a second set of QTc interval readings was performed by another cardiologist. Original

readings by the primary cardiologist were used in the study. Heart rate and blood pressure were recorded using the Philips IntelliVue MX450 (Royal Philips, Amsterdam, The Netherlands). For comparison, QTc intervals calculated using Bazett's formula are included in the Supporting Information.

2.4 | Quantification of methadone

Analyses of methadone in serum were performed by a previously published UHPLC–MS/MS method.[25] The standard range was 100–3000 nmol/L with a linear curve, $r^2 = 0.98$. Lower limit of quantification in serum was validated at 20 nmol/L. Variation coefficient of imprecision was less than 12.9% at serum control levels of 20, 150, 700, and 1500 nmol/L. Accuracy at all serum control levels compared to spiked levels was less than 103%. Expanded uncertainty with a 95% confidence interval $= 2 * \sqrt{bias^2 + CV^2}$ was calculated to 26%.

2.5 | Urine drug testing

Urine was sampled from all patients except Patient 4, who had no urine production, and tested for pH, creatinine, and the presence of amphetamines, benzodiazepines, cannabinoids, cocaine, ecstasy, ethanol, and opioids (opiates, buprenorphine, and methadone), using the routine drug of abuse screening programme on Beckman Coulter AU680 (Thermo Fischer, Oslo, Norway) at the Department of Pharmacology, OUH.

2.6 | Biochemistry and cytochrome P450 testing

Serum was analysed for creatinine (to calculate eGFR), CRP, troponin T, potassium, magnesium, and total calcium, using Cobas 8000 modular analyser series (Roche, Oslo, Norway) at the Department of Medical Biochemistry, OUH.

DNA was isolated from blood by Magna Pure 96 (Roche, Oslo, Norway) and screened for common polymorphisms in CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 by a routine PCR technique, using Light Cycle 480 (Roche, Oslo, Norway) at the Department of Medical Biochemistry and Pharmacology, OUH.

2.7 | Statistics

Microsoft Excel 2016 and IBM SPSS statistics version 29 were used to analyse the data. All values from after the switch are averages of the second and third visits. Most data are presented as median and range (minimum to maximum values) and were tested using related samples Wilcoxon signed rank test. Individual patient data from all three visits are also presented (biochemistry and blood pressure values are in the Supporting Information). QTc intervals are presented as means with 95% confidence intervals (95% CI) and were tested using mean paired comparison of a one sample Student's t test (two sided). The significance level was $p < 0.05$. Relationships between serum drug concentrations and QTc intervals were assessed by simple linear regression, and squared correlation coefficients (from Pearson's correlation coefficient, r) are reported.

3 | RESULTS

3.1 | Demographic characteristics

In total, 18 MMT patients were considered for the study (Figure 1B). Nine patients (50% of considered patients) aged median (range) 49 (38–63) years, counting four females, and treated with 70 (40–120) mg of methadone, were included (Tables 1–3). Reasons for the drop-out of patients are explained in the flowchart. All but one had CYP polymorphisms, but only Patient 9 had a polymorphism considered important for serum methadone concentrations (homozygous for CYP2B6*6).[33] None reported previous heart-related syncope/presyncope tendencies, but several had experienced syncope related to illegal drug use. Prescribed drugs remained constant throughout the study. Illegal drug use varied between patients but less over time (Table 3). Patient 8 did not show up for the second visit.

3.2 | Methadone pharmacology, biochemistry, and cardiovascular variables

Serum methadone concentrations, at C_{min} and C_{max}, were significantly reduced after the switch to an equipotent dose of R-methadone (Table 2). On average, the reduction at C_{min} was 42%. Three patients (2, 6, and 8) presented with concentrations above the upper reference values at C_{min},[34–36] both before and after the switch (Tables 2 and 3). No patient reported more than mild opioid withdrawal symptoms immediately before their next dose, neither with methadone nor with R-methadone (Tables 2 and 3). Patients 3 and 4 had kidney failure. Electrolytes, other biochemical values, heart rates, and blood pressures at C_{min} were within reference ranges on group levels before and after the switch (Table 2). Individual values (Table 3) also

TABLE 1 Baseline demographics and clinical characteristics.

Patient	Sex[a]	Age (years)	Body mass index[b] (kg/m^2)	CYP polymorphisms[c]	Suspected heart-related syncope tendencies	Number (and names) of other prescribed drugs
1	F	63	24.5	CYP2C19*2/*17 CYP2D6*1/*3	No	1 (furosemide)
2	F	48	35.1	CYP2B6*1/*6 CYP2C9*1/*2 CYP2C19*1/*17	No	3 (esomeprazole, metoprolol, rivaroxaban)
3	F	59	18.2	CYP2C19*17/*17 CYP2D6*1/*3	No	7 (calcium, calcitriol, ferroglycine sulfate complex, pantoprazole, sevelamer, sodium bicarbonate, vitamin D3)
4	M	49	20.7	CYP2B6*1/*5 CYP2C9*2/*2	No	11 (calcium, calcium carbonate, calcium polystyrene sulfonate, calcitriol, darbepoetin alfa, furosemide, nifedipine, oxazepam, sodium bicarbonate, simvastatin, vitamin D3)
5	M	44	24.9		No	1 (acetylsalicylic acid)
6	M	38	25.4	CYP2B6*5/*6 CYP2C19*2/*17	No	3 (nitrazepam, oxazepam, diazepam)
7	M	45	24.7	CYP2C19*1/*17	No	2 (oxazepam, salbutamol)
8	M	63	24.6	CYP2B6*1/*6 CYP2D6*1/*4	No	5 (emtricitabine, low molecular weight heparin, nitrazepam, oxazepam, tenofovir disoproxil)
9	F	58	27.4	CYP2B6*6/*6 CYP2C19*1/*2	No	5 (aripiprazole, esomeprazole, naproxen, oxazepam, quetiapine)
Median (range)		49 (38–63)	24.7 (18.2–35.1)			3 (1–11)

[a]F = female; M = male.
[b]Reference values: 18.5–25 kg/m^2.
[c]Wild type (normal gene): CYP2C9*1/*1; CYP2C19*1/*1; CYP2D6*1/*1; CYP3A5*3/*3 in Nordic population; CYP2B6*1/*1.

TABLE 2 Methadone pharmacology, biochemistry, and cardiovascular variables summarized from before and after the switch.

	Reference values	On methadone ($n = 9$)	On R-methadone[a] ($n = 9$)	P[b]
Methadone pharmacology				
Methadone dose/day (mg)	*60–120 mg for methadone* *30–60 mg for R-methadone*	70 (40–120)	35 (20–60)	-
Serum methadone concentration at C_{min}[c] (nmol/L)	*600–1200 for methadone*[34,35] *300–600 for R-methadone*[d36]	1076 (459–1501)	535 (262–839)	0.008
Serum methadone concentration at C_{max}[e] (nmol/L)	*400–4056 for methadone*[37] *200–2028 for R-methadone*[d]	1478 (782–2266)	840 (396–1228)	0.008
COWS[f] at C_{min}[c]	*Mild: 5–12* *Moderate: 13–24* *Moderately severe: 25–36* *Severe: >36*	4 (0–8)	3 (0–7)	0.52
Biochemistry				
eGFR[g] (ml/min/1.73 m^2)	*>60*	101 (5–115)	100 (5–117)	0.30
Potassium (mmol/L)	*3.6–4.6*	4.3 (3.6–5.6)	4.2 (3.7–4.6)	0.59
Calcium (mmol/L)	*2.15–2.51*	2.34 (2.04–2.65)	2.21 (2.11–2.46)	0.093
Magnesium (mmol/L)	*0.71–0.94*	0.82 (0.73–1.50)	0.86 (0.64–1.29)	0.44
Troponin T (ng/L)	*<14*	7 (<5–92)	7 (<5–84)	0.93
CRP[h] (mg/L)	*<4*	2.6 (<0.6–40.0)	4.6 (<0.6–70.0)	0.33
Cardiovascular variables at C_{min}[c]				
Heart rate (beats per minute)	*60–100*	70 (54–92)	72 (65–92)	0.12
Systolic blood pressure (mmHg)	*<140*	132 (110–166)	122 (106–182)	0.21
Diastolic blood pressure (mmHg)	*<90*	73 (58–90)	75 (63–112)	0.64

[a]Average of second and third visits (day 14 and 28).
[b]Data presented are median (range); compared using related samples Wilcoxon signed rank test, $p < 0.05$ significance level.
[c]Concentration measured approximately 24 h after last drug intake (C_{min}). In the study by Chalabianloo,[35] 68% of patients had concentrations between 600 and 1800 nmol/L.
[d]Reference values for R-methadone at C_{min} and C_{max} are half of those reported for methadone, since the racemic mixture of methadone consisted of 50% of each enantiomer.
[e]Concentration measured approximately 3 h after drug intake (C_{max}).
[f]Clinical Opioid Withdrawal Scale (COWS).
[g]Estimated glomerular filtration rate (eGFR) using CKD-EPI formula.
[h]C-reactive protein (CRP).

revealed that most patients' heart rates were within the reference range, except for in Patient 2 who had low rates before the switch.

3.3 | QTc intervals

On methadone (before the switch), mean (95% CI) QTc intervals at C_{min} were 472 (452–492) ms and 422 (408–436) ms when ECGs were automatically and manually read, respectively. On average, the automatic QTc interval values were around 10% longer than the manual readings. On R-methadone (after the switch), the mean (95% CI) QTc interval at C_{min} was 414 (398–431) ms (when manually read). The mean (SD) change in the QTc interval at C_{min} after the switch was −8 (10) ms ($p = 0.047$; $p = 0.038$ with Wilcoxon signed rank test) (Figure 2). QTc intervals at C_{min} were reduced in seven patients after the switch, with 25 ms in Patient 3 being the largest individual decrease (Figure 2). The reduction of 9 (19) ms at C_{max} was not significant ($p = 0.21$).

We found a positive correlation between serum R-methadone concentrations and QTc intervals at C_{min} ($r = 0.796$, $n = 8$, $p = 0.018$) that was non-significant for methadone ($r = 0.543$, $n = 8$, $p = 0.164$), when removing Patient 4 from the group (Figure 3). Using 30 mg of R-methadone after the switch, Patient 4 presented with a slightly prolonged QTc interval at C_{min} of 458 ms along with a serum methadone concentration of 262 nmol/L. This patient had kidney failure and a value outside the

TABLE 3 Individual drug doses, drug use, withdrawal symptoms, serum drug concentrations, heart rate, and QTc intervals from before and after the switch.

Patient	Dose[a]/day (mg)	Drug use[b] (urine)	Withdrawal symptoms (COWS[c])		Drug concentration (nmol/L)		Heart rate (bpm[f])		QTc interval[g] (ms)	
			C_{min}[d]	C_{max}[e]	C_{min}[d]	C_{max}[e]	C_{min}[d]	C_{max}[e]	C_{min}[d]	C_{max}[e]
On methadone (day 0)										
1	50	Negative	8	1	582	867	71	68	411	404
2	80	BZD, CNB	7	0	1290	1670	54	45	442	454
3	40	AMP, OPI	1	1	910	1230	69	74	405	413
4	60	Missing	0	0	459	782	64	59	459	489
5	120	CNB, OPI	4	2	697	1336	70	72	414	433
6	70	AMP, BZD, CNB, OPI	4	2	1451	1828	92	84	431	415
7	80	CNB, OPI	0	0	1076	1478	77	77	404	424
8	100	BZD, CNB	4	2	1501	2266	86	73	418	436
9	60	BZD	0	0	1199	1651	68	67	414	409
On R-methadone (day 14)										
1	25	Negative	6	3	383	488	69	73	396	427
2	40	BZD, CNB, OPI	3	1	715	967	65	59	427	430
3	20	BZD, OPI	1	1	495	500	92	83	363	363
4	30	Missing	0	0	312	469	73	62	447	521
5	60	BZD, CNB, OPI	7	3	440	736	71	63	408	409
6	35	BZD, CNB, OPI	6	1	761	1091	89	84	437	425
7	40	BZD, CNB	1	0	897	1117	87	78	405	403
8	50	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing
9	30	BZD	3	0	520	881	71	65	399	399
On R-methadone (day 28)										
1	25	Negative	4	2	386	518	71	73	404	425
2	40	BZD, CNB, OPI	2	0	693	878	64	60	423	408
3	20	AMP, BZD, OPI	3	Missing	458	532	86	85	397	422
4	30	Missing	0	0	212	322	59	65	468	476
5	60	BZD, CNB, OPI	5	2	629	Missing	73	58	405	421
6	35	AMP, BZD, CNB, OPI	7	1	914	1339	95	89	409	432
7	40	CNB	4	0	540	712	79	78	414	394
8	50	BZD, CNB	7	5	839	1228	76	79	422	423
9	30	BZD, CNB	0	0	522	798	72	65	408	389

[a]Racemic methadone was given before the switch and R-methadone was given after the switch.
[b]Amphetamines (AMP), benzodiazepines (BZD), cannabinoids (CNB), cocaine, ecstasy, ethanol, and opioids (OPI).
[c]Clinical Opioid Withdrawal Scale (COWS): mild: 5–12; moderate: 13–24; moderately severe: 25–36; severe: >36.
[d]Concentrations measured at 24 h after last drug intake (C_{min}).
[e]Concentrations measured at 3 h after drug intake (C_{max}).
[f]Beats per minute.
[g]Measured QT interval adjusted for heart rate (Fridericia's formula).

95% CI on the scatterplot and was considered an outlier. When including Patient 4, no such linear relationship was found for R-methadone nor methadone at C_{min} (data not presented). There were no positive correlations between serum drug concentrations and QTc intervals at C_{max} (data not presented).

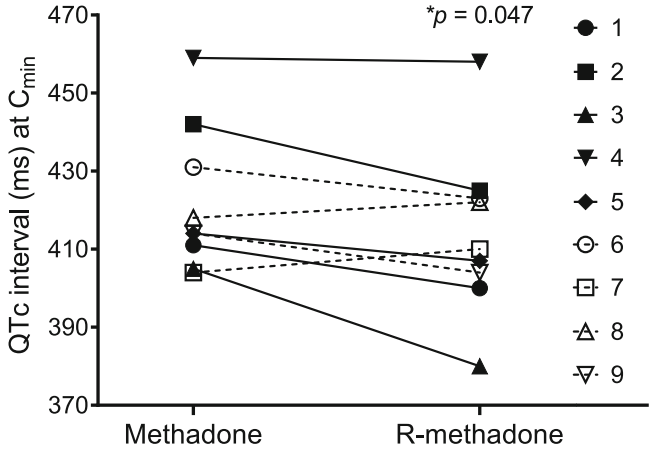


FIGURE 2 Individual QTc intervals before and after the switch ($n = 9$). Patient numbers are provided next to symbols representing the individual QTc intervals. Intervals were recorded at C_{min} and manually read. Values from after the switch are means of the second and third visits. *A mean reduction was observed after the switch.

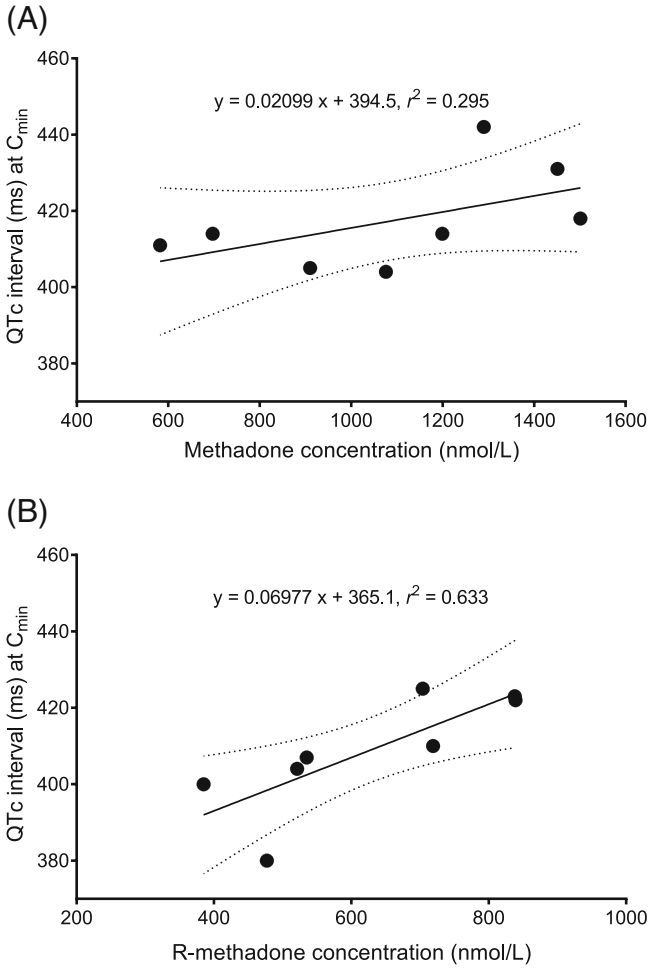


FIGURE 3 Relationships between QTc intervals and serum methadone concentrations before and after the switch ($n = 8$). (A) Methadone, measured before the switch. (B) R-methadone, measured after the switch. Intervals and concentrations are measured at C_{min}. Values from after the switch are means of the second and third visits.

4 | DISCUSSION

The QTc interval was reduced by 8 ms at C_{min} after switching to R-methadone in the nine included MMT patients. All patients tolerated the switch to R-methadone well during the 4 weeks of treatment and chose to continue with R-methadone after the end of the study. The lack of change in opioid withdrawal symptoms after the switch was as expected, based on a larger study reporting that the drugs can safely be exchanged using a dose ratio of 2:1.[38] Although some of the other prescribed drugs may have reduced opioid withdrawal symptoms,[23] their consistent use throughout the study support that there were no increase in symptoms.

The reduction observed in the QTc interval is comparable to the finding in a similar study by Ansermot et al.,[20] reporting a mean reduction of 7.8 ms at C_{min} in 39 MMT patients. Neither of these studies, however, demonstrates a clinically relevant reduction in the QTc interval of 20 ms.[21] This clinical criterion is based on a 5%–7% increase in the risk of developing TdP for every 10 ms increase in the QTc interval,[39] with a substantial increase in the risk for every 20 ms increase.[21] We can speculate if switching from higher methadone doses than 70 (40–120) mg used in our study could lead to larger reductions in the QTc interval.[5,17,18]

The relationship for R-methadone with QTc intervals at C_{min} was concentration-dependent but not for methadone in our study. Several studies have observed that methadone can increase the QTc interval in both a dose- and concentration-dependent way, while others have reported prolongations and TdP across a wide range of doses.[11,18,40] Previous studies have also suggested concentration-dependent relationships for R-methadone with QTc intervals.[7,41,42] The regression equation from Figure 3B suggests that increasing R-methadone concentrations to twice the upper reference value will prolong the QTc interval; however, patients should not be treated with dosages causing such high concentrations.

It is well known that QT intervals can be affected by several other factors,[14,43] such as electrolyte imbalances, other QT prolonging drugs, female sex, bradycardia, cardiovascular disease,[44,45] and genetic polymorphisms of ion channels.[46] Because MMT patients are a heterogeneous population, we controlled for other factors affecting the QT interval. Serum electrolyte values and heart rates were within their reference ranges and, together with prescribed drug use, did not differ on group levels before and

after the switch, ruling out these factors as possible causes of the small reduction observed in the QTc interval. In two patients (7 and 8), the QTc interval did not decrease after the switch for which we found no explanation.

Despite the close follow-up of the patients in this study, patients misused amphetamines, cannabinoids, and opiates. Five patients (2, 3, 5, 6, and 7) misused other opiates at some point during the study period. Opiates such as morphine, however, are not reported to affect hERG or the QT interval.[5,18] Patients 3 and 6 misused amphetamines before but not after the switch. There is some evidence that amphetamines can prolong the QTc interval.[47]

Three patients (2, 6, and 8) had slightly elevated serum methadone concentrations at C_{min}, both before and after the switch, which could not be explained by pharmacokinetic drug interactions.[34,48] Patient 9 was the only patient homozygous for CYP2B6*6, which can increase methadone concentrations.[7,33] Using 60 mg of methadone, this patient had a serum concentration of 1199 nmol/L at C_{min}. Despite also being treated with the antipsychotic drug quetiapine, considered a conditional risk factor for TdP,[49] this patient's QTc intervals at C_{min} were only 414 ms before and 404 ms after the switch.

Seven of the nine patients (2, 3, 4, 5, 6, 8, and 9) had additional risk factors for QT interval prolongation that for the most part remained stable throughout the study, a share that is similar to what has been reported by a large study from the FDA spontaneous reporting system.[50] Patients 3 and 4 had increased troponin T values, which could indicate cardiac ischemia, but were more likely caused by severe kidney failure.[51] Five patients (2, 3, 5, 6, and 8) had slight to moderately elevated CRP levels at some point during the study, indicating inflammation, which is common in this group of patients.

5 | LIMITATIONS

Only 10 of 18 patients participated in the study, even though the inclusion period lasted more than 3 years. The low number of eligible patients was unexpected, as a previous study showed a much higher prevalence of prolonged QTc intervals among MMT patients included from the same geographic area.[13] An explanation for this discrepancy could be that QTc interval prolongation in MMT patients is actually not as common as previously reported. In addition to the patients whose prolonged QTc intervals were normalized during detoxification treatments, two patients were excluded for medical reasons (Figure 1B). Because of the low number of patients included in this study, our results must be interpreted with caution.

Patients were included based on automatically read QTc intervals from ECGs performed outside the research unit. Our manually measured QT intervals by the tangent method resulted in QTc intervals that were approximately 10% shorter than those measured by the machine, which uses the threshold method (the intersection of the end of the T wave with the baseline).[14,52] When the QTc intervals were manually read in retrospect, they were not necessarily above 450 ms, showing that QTc intervals should be based on manual QT interval and RR readings. QT intervals are usually measured in leads II or V5, but among the included patients, the T waves were often flat and hard to read in these leads. Lead V2 had the most distinct T waves and was considered acceptable for use.[53] One patient was excluded from the study due to difficulty with manual reading of the ECGs because of flat T waves.

We did not consider it necessary to separate the enantiomers when analysing the serum methadone concentrations. Knowing methadone's half-life, which is between 24 and 33 h in the opioid-tolerant patient,[54] only very small amounts of S-methadone (<1%) were expected to be present in plasma 14 days after the last methadone intake.[20]

The urine drug screening programme used in this study does not include tramadol. Tramadol is another opioid that can prolong the QT interval[49] and may be used illegally.[55]

Finally, we cannot exclude that the patients' participation in the study inherently might also have contributed to a reduction of the QT interval. The close follow-up of the patients for several weeks may, for example, have reduced their use of non-prescribed drugs or altered other factors that can contribute to prolonged QT intervals.

6 | CONCLUSIONS

In this interventional study with nine MMT patients, removal of S-methadone resulted in a small and not clinically relevant reduction in QTc interval. Consistent with previous reports, this study suggests a risk that supratherapeutic R-methadone concentrations can cause prolonged QTc intervals.

ACKNOWLEDGEMENTS

We thank the bioengineers at the Section of Clinical Pharmacology in the Department of Pharmacology, Oslo University Hospital, for measuring methadone in the serum samples. We also thank Leiv Sandvik, Cathrine Brunborg, and Chi Zhang at Oslo Centre for Biostatistics & Epidemiology (OCBE), Oslo University Hospital and the University of Oslo, for their statistical advice. Finally, we want to acknowledge the highly skilled nurses at the Research

Unit in the Department of Pharmacology, Oslo University Hospital, who carried out the blood sampling and took excellent care of the patients during each visit.

The Department of Pharmacology and the Department of Substance Use Disorder Treatment at Oslo University Hospital and the University of Oslo paid all the costs of this study. This project did not receive any other specific funding from neither commercial nor not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interests to declare.

DATA AVAILABILITY STATEMENT

The data generated in this project are available from the corresponding author on reasonable request. Most of the data (individual patient data) are already presented in the manuscript (in tables and figures) and in the Supporting Information.

ORCID

Stine Marie Havig https://orcid.org/0000-0001-6229-2246

REFERENCES

1. Kreutzwiser D, Tawfic QA. Methadone for pain management: a pharmacotherapeutic review. *CNS Drugs*. 2020;34(8):827-839. doi:10.1007/s40263-020-00743-3
2. Seewald RM. Chapter 2: use of methadone in opioid maintenance treatment. In: Cruciani RA, Knotkova H, eds. *Handbook of Methadone Prescribing and Buprenorphine Therapy*. 1st ed. Springer; 2013:15-30. doi:10.1007/978-1-4614-6974-2_2
3. Katchman AN, McGroary KA, Kilborn MJ, et al. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. *J Pharmacol Exp Ther*. 2002;303(2):688-694. doi:10.1124/jpet.102.038240
4. Zunkler BJ, Wos-Maganga M. Comparison of the effects of methadone and heroin on human ether-a-go-go-related gene channels. *Cardiovasc Toxicol*. 2010;10(3):161-165. doi:10.1007/s12012-010-9074-y
5. El Sherbini A, Liblik K, Lee J, Baranchuk A, Zhang S, El-Diasty M. Opioids-induced inhibition of HERG ion channels and sudden cardiac death, a systematic review of current literature. *Trends Cardiovasc Med*. 2023. doi:10.1016/j.tcm.2023.03.006
6. Keating MT, Sanguinetti MC. Molecular genetic insights into cardiovascular disease. *Science*. 1996;272(5262):681-685. doi:10.1126/science.272.5262.681
7. 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
8. Lin C, Somberg T, Molnar J, Somberg J. The effects of chiral isolates of methadone on the cardiac potassium channel IKr. *Cardiology*. 2009;113(1):59-65. doi:10.1159/000167043
9. Yu H, Zhang L, Liu J, et al. Acquired long QT syndrome in hospitalized patients. *Heart Rhythm*. 2017;14(7):974-978. doi:10.1016/j.hrthm.2017.03.014
10. Straus SM, Sturkenboom MC, Bleumink GS, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J*. 2005;26(19):2007-2012. doi:10.1093/eurheartj/ehi312
11. Behzadi M, Joukar S, Beik A. Opioids and cardiac arrhythmia: a literature review. *Med Princ Pract*. 2018;27(5):401-414. doi:10.1159/000492616
12. Ehret GB, Voide C, Gex-Fabry M, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Arch Intern Med*. 2006;166(12):1280-1287. doi:10.1001/archinte.166.12.1280
13. Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction*. 2009;104(6):993-999. doi:10.1111/j.1360-0443.2009.02549.x
14. Haugaa KH, Bos JM, Tarrell RF, Morlan BW, Caraballo PJ, Ackerman MJ. Institution-wide QT alert system identifies patients with a high risk of mortality. *Mayo Clin Proc*. 2013;88(4):315-325. doi:10.1016/j.mayocp.2013.01.013
15. Legemiddelassistert rehabilitering (LAR) ved opioidavhengighet. Helsedirektoratet; May 23, 2022. Updated November 30, 2022. Accessed August 15, 2023. https://www.helsedirektoratet.no/retningslinjer/behandling-ved-opioidavhengighet
16. Strain E. Opioid use disorder: pharmacologic management. UpToDate Updated November 14, 2023. Accessed December 10, 2023. https://www.uptodate.com/contents/opioid-use-disorder-pharmacologic-management
17. Florian J, Garnett CE, Nallani SC, Rappaport BA, Throckmorton DC. A modeling and simulation approach to characterize methadone QT prolongation using pooled data from five clinical trials in MMT patients. *Clin Pharmacol Ther*. 2012;91(4):666-672. doi:10.1038/clpt.2011.273
18. Mujtaba S, Romero J, Taub CC. Methadone, QTc prolongation and torsades de pointes: current concepts, management and a hidden twist in the tale? *J Cardiovasc Dis Res*. 2013;4(4):229-235. doi:10.1016/j.jcdr.2013.10.001
19. Levometadon - fare for overdosering. Statens Legemiddelverk; December 6, 2018. Updated December 7, 2018. Accessed August 15, 2023. https://legemiddelverket.no/nyheter/levometadon-fare-for-overdosering
20. Ansermot N, Albayrak O, Schlapfer J, et al. Substitution of (R,S)-methadone by (R)-methadone: impact on QTc interval. *Arch Intern Med*. 2010;170(6):529-536. doi:10.1001/archinternmed.2010.26
21. ICH Topic E 14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04). European Medicine Agency; November 2005. Accessed August 15, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-14-clinical-evaluation-qt/qts-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic-drugs-step-5_en.pdf
22. Pergolizzi JV Jr, Raffa RB, Rosenblatt MH. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: current understanding and approaches to management. *J Clin Pharm Ther*. 2020;45(5):892-903. doi:10.1111/jcpt.13114

23. Kosten TR, Baxter LE. Review article: effective management of opioid withdrawal symptoms: a gateway to opioid dependence treatment. *Am J Addict*. 2019;28(2):55-62. doi:10.1111/ajad.12862
24. ICH guideline E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs (R3)—questions and answers Step 5. European Medicine Agency; January 25, 2016. Accessed August 15, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e14-clinical-evaluation-qt/qtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic-drugs-r3-questions-answers-step_en.pdf
25. Opdal MS, Arnesen M, Muller LD, et al. Effects of hemodialysis on methadone pharmacokinetics and QTc. *Clin Ther*. 2015;37(7):1594-1599. doi:10.1016/j.clinthera.2015.04.009
26. Malik M, Hnatkova K, Batchvarov V, Gang Y, Smetana P, Camm AJ. Sample size, power calculations, and their implications for the cost of thorough studies of drug induced QT interval prolongation. *Pacing Clin Electrophysiol*. 2004;27(12):1659-1669. doi:10.1111/j.1540-8159.2004.00701.x
27. Sample size calculation results. Statulator. Accessed January 3, 2019. http://statulator.com/SampleSize/ss1P.html
28. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253-259. doi:10.1080/02791072.2003.10400007
29. Khan IA. Long QT syndrome: diagnosis and management. *Am Heart J*. 2002;143(1):7-14. doi:10.1067/mhj.2002.120295
30. Tveden-Nyborg P, Bergmann TK, Jessen N, Simonsen U, Lykkesfeldt J. BCPT 2023 policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2023;133(4):391-396. doi:10.1111/bcpt.13944
31. Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. 1920. *Ann Noninvasive Electrocardiol*. 2003;8(4):343-351. doi:10.1046/j.1542-474x.2003.08413.x
32. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc*. 2016;5(6):e003264. doi:10.1161/JAHA.116.003264
33. Kringen MK, Chalabianloo F, Bernard JP, Bramness JG, Molden E, Hoiseth 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
34. Metadon dne (summary of product characteristcs). Den norske Eterfabrikk; April 5, 2005. Updated May 11, 2023. Accessed August 15, 2023. https://www.legemiddelsok.no/_layouts/15/Preparatomtaler/Spc/04-2423.pdf
35. 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
36. Meini M, Moncini M, Daini L, et al. Relationship between plasma concentrations of the l-enantiomer of methadone and response to methadone maintenance treatment. *Eur J Clin Pharmacol*. 2015;760:1-6. doi:10.1016/j.ejphar.2015.03.081
37. Methadone: pharmacokinetics (in-depth answers). Merative Micromedex. Updated December 5, 2023. Accessed December 10, 2023. https://www.micromedexsolutions.com/
38. Verthein U, Ullmann R, Lachmann A, et al. The effects of racemic D,L-methadone and L-methadone in substituted patients—a randomized controlled study. *Drug Alcohol Depend*. 2005;80(2):267-271. doi:10.1016/j.drugalcdep.2005.04.007
39. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121(8):1047-1060. doi:10.1161/circulationaha.109.192704
40. Isbister GK, Brown AL, Gill A, Scott AJ, Calver L, Dunlop AJ. QT interval prolongation in opioid agonist treatment: analysis of continuous 12-lead electrocardiogram recordings. *Br J Clin Pharmacol*. 2017;83(10):2274-2282. doi:10.1111/bcp.13326
41. 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
42. Bogen DL, Hanusa BH, Perel JM, Sherman F, Mendelson MA, Wisner KL. Corrected QT interval and methadone dose and concentrations in pregnant and postpartum women. *J Clin Psychiatry*. 2017;78(8):e1013-e1019. doi:10.4088/JCP.16m11318
43. Heemskerk CPM, Pereboom M, van Stralen K, et al. Risk factors for QTc interval prolongation. *Eur J Clin Pharmacol*. 2018;74(2):183-191. doi:10.1007/s00228-017-2381-5
44. Weissler-Snir A, Gollob MH, Chauhan V, Care M, Spears DA. Evaluation of prolonged QT interval: structural heart disease mimicking long QT syndrome. *Pacing Clin Electrophysiol*. 2017;40(4):417-424. doi:10.1111/pace.13040
45. Kenigsberg DN, Khanal S, Kowalski M, Krishnan SC. Prolongation of the QTc interval is seen uniformly during early transmural ischaemia. *J Am Coll Cardiol*. 2007;49(12):1299-1305. doi:10.1016/j.jacc.2006.11.035
46. Lieve KV, Wilde AA. Inherited ion channel diseases: a brief review. *Europace*. 2015;17(suppl 2):ii1-ii6. doi:10.1093/europace/euv105
47. Schrantee A, Václavů L, Reneman L, Verberne HJ, Booij J, Tan HL. QT prolongation by dexamphetamine: does experience matter? *J Cardiovasc Electrophysiol*. 2017;28(8):912-916. doi:10.1111/jce.13235
48. 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
49. Woosley RL, Heise CW, Gallo T, Woosley D, Lambson J, Romero KA. QTdrugs List. AZCERT Accessed August 15, 2023. https://www.crediblemeds.org
50. Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf*. 2005;14(11):747-753. doi:10.1002/pds.1112
51. Banerjee D, Perrett C, Banerjee A. Troponins, acute coronary syndrome and renal disease: from acute kidney injury through end-stage kidney disease. *Eur Cardiol*. 2019;14(3):187-190. doi:10.15420/ecr.2019.28.2

52. Vink AS, Neumann B, Lieve KVV, et al. Determination and interpretation of the QT interval. *Circulation*. 2018;138(21):2345-2358. doi:10.1161/circulationaha.118.033943
53. Wagner GS, Macfarlane P, Wellens H, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation*. 2009;119(10):e262-e270. doi:10.1161/CIRCULATIONAHA.108.191098
54. Grissinger M. Keeping patients safe from methadone overdoses. *P t*. 2011;36(8):462-466.
55. Narkotika- og dopingstatistikk 2022. Kripos; January 24, 2023. Accessed December 10, 2023. https://www.politiet.no/globalassets/tall-og-fakta/narkotika/narkotikastatistikk-2022.pdf

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Havig SM, Berg-Pedersen RM, Krabseth H-M, et al. Effect on QTc interval by switching from methadone to equipotent R-methadone dose in methadone maintenance treatment patients. *Basic Clin Pharmacol Toxicol*. 2024;134(4):519-530. doi:10.1111/bcpt.13982.