Methadone Destabilizes Cardiac Repolarization During Sleep

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Methadone, a widely prescribed medication for chronic pain and opioid addiction, is associated with respiratory depression and increased predisposition for torsades de pointes, a potentially fatal arrhythmia. Most methadone-related deaths occur during sleep. The objective of this study was to determine whether methadone’s arrhythmogenic effects increase during sleep, with a focus on cardiac repolarization instability using QT variability index (QTVI), a measure shown to predict arrhythmias and mortality. Sleep study data of 24 patients on chronic methadone therapy referred to a tertiary clinic for overnight polysomnography were compared with two matched groups not on methadone: 24 patients referred for overnight polysomnography to the same clinic (clinic group), and 24 volunteers who had overnight polysomnography at home (community group). Despite similar values for heart rate, heart rate variability, corrected QT interval, QTVI, and oxygen saturation (SpO2) when awake, patients on methadone had larger QTVI (P = 0.015 vs. clinic, P < 0.001 vs. community) and lower SpO2 (P = 0.008 vs. clinic, P = 0.013 vs. community) during sleep, and the increase in their QTVI during sleep vs. wakefulness correlated with the decrease in SpO2 (r = −0.54, P = 0.013). QTVI positively correlated with methadone dose during sleep (r = 0.51, P = 0.012) and wakefulness (r = 0.73, P < 0.001). High-density ectopy (> 1,000 premature beats per median sleep period), a precursor for torsades de pointes, was uncommon but more frequent in patients on methadone and those with high QT variability. This study demonstrates that chronic methadone use is associated with increased cardiac repolarization instability. Methadone’s pro-arrhythmic impact may be mediated by sleep-related hypoxemia, which could explain the increased nocturnal mortality associated with this opioid.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✓ Methadone is associated with increased risk for respiratory depression, cardiac arrhythmias, and nocturnal death.

WHAT QUESTION DID THIS STUDY ADDRESS?
✓ Whether methadone is associated with increased ventricular repolarization lability during sleep.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
✓ Beat-to-beat QT interval variability, a measure of ventricular repolarization lability, was higher in patients on chronic methadone therapy than matched comparators, in a dose-dependent manner, during sleep but not while awake. As expected, oxygen saturation levels during sleep were lower in methadone users potentially due to its agonism for the µ-opioid receptor. High-density premature ventricular beats, a potential precursor of torsades de pointes, although uncommon, were more frequent in patients on methadone and those with high QT variability.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
✓ This study suggests that sleep increases the repolarization instability associated with methadone use, in part through decreased oxygen saturation. This study indicates the possibility that the combination of hERG-blocking agents with other opioids may lead to increased proarrrhythmia due to a reduction in ventilatory drive.

Methadone is a synthetic long-acting opioid mainly used to treat chronic pain, restless-leg syndrome, and opioid use disorder. It is among the top four prescription opioids involved in overdose-related deaths. Whereas accounting for only about 1% of all opioid prescriptions, 20% of opioid-related deaths in 2014 were attributed to methadone. In a 2009 report from the Centers for Disease Control and Prevention, methadone was 8 times more likely to be involved in a single-drug-associated death compared with oxycodone, 9 times more likely than hydrocodone, and 100 times more likely than buprenorphine when compared on a morphine

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milligram equivalent basis. Although methadone has been associated with QT interval prolongation and decreased respiratory drive, the pathophysiology of its mortality risk remains unclear.

Several case series have suggested that methadone at high doses is associated with QT prolongation and the life-threatening polymorphic ventricular tachycardia referred to as “torsades de pointes.” Methadone inhibits cardiac human ether-à-go-go-related gene (hERG)-associated K+ current, the rapid component of the delayed rectifier current (I_Kr), which determines the duration of the resting QT interval. Reducing this current prolongs the repolarization phase of the cardiac action potentials, lengthens the QT interval, and increases vulnerability to arrhythmias. There is, however, a paucity of ambulatory electrocardiography (ECG)-based data in methadone users. Furthermore, there is no pathologic “signature” of arrhythmic death, hence inferences regarding the precise mechanism of demise in unwatched methadone-related deaths are often inconclusive. It therefore remains to be determined whether arrhythmia accounts for a significant percentage of deaths associated with methadone or other opioids.

The QT variability index (QTVI), a manifestation of cardiac repolarization instability, has been found to be a reliable predictor of cardiac arrhythmias, cardiac arrest, or cardiac death in several cohorts of patients. In the current study, QTVI was examined in a group of patients on chronic methadone therapy along with two matched groups undergoing continuous ECG and respiratory monitoring during sleep as part of multichannel polysomnography. It was hypothesized that the use of methadone would be associated with an increase in QTVI, which may be most notable during sleep.

**METHODS**

**Study sample**

Twenty-four patients on chronic methadone therapy were identified from a series of patients referred for overnight polysomnography to a tertiary care center (methadone group; Figure 1). None had a history of congestive heart failure or myocardial infarction or were on any medication known to cause QT interval prolongation. The physician-documented prescribed dosages of methadone at the time of the overnight sleep study were used for the analysis of dose-related effects.

Two comparator groups were also selected who matched (1:1) with the methadone group on age, sex, and body-mass index. The first group was selected from patients who were referred for diagnostic polysomnography to the same tertiary care center but were not on methadone (clinic group). Patients in the clinic group were matched to the methadone group also on the Apnea-Hypopnea Index (AHI) as well. To overcome any bias inherent to clinical samples, a second comparator group was also included, which consisted of a matched (1:1) group of subjects selected from a cohort of community-based volunteers undergoing home full-montage polysomnography as part of an ongoing multicenter epidemiologic study (community group; from the Sleep Heart Health Study NCT00005275). Approval to use the de-identified data used in the current retrospective study was acquired from the Johns Hopkins University Institutional Review Board (NA_00010790).

**Polysomnography**

The in-laboratory polysomnogram for the patients recruited from the sleep center included recordings of C3 and C4 electroencephalograms, right and left electrooculograms, and submental and bilateral anterior tibialis electromyograms. Sleep-stage scoring was performed in 30-second epochs. Respiration was monitored with a nasal pressure transducer, nose and mouth thermocouples, and thoracic and abdominal strain gauges. Recording of the oxyhemoglobin saturation (SpO2) was obtained with Biox 3700 pulse oximeter (Ohmeda, Englewood, CO) at 10 Hz and averaged over each 30-second epoch. Apneas were identified if airflow was absent in thermocouples and nasal cannula channels for at least 10 seconds. Hypopneas were identified if there was at least 30% reduction in airflow for at least 10 seconds accompanied with at least 4% oxyhemoglobin desaturation. AHI was determined as the frequency of apneas and hypopneas per hour of total sleep time. The in-laboratory polysomnography was conducted using the Embla N-7000 system (Natus Medical, Pleasanton, CA). Polysomnography for the community participants was performed at home, using the Compumedics P-series recording system (Compumedics, Abbotsford, Victoria, Australia).

**ECG analysis**

Continuous single-lead ECG was acquired during all sleep studies at 256 Hz for the methadone and clinic groups and at 128 Hz for the community group. Sleep ECG data for all 72 subjects were available and included in the analysis. Analyzable ECG data recorded during the wake period prior to sleep onset were only available for 67 subjects due to excess artifact in the rest of the recordings (Figure 1).

ECG signals from the study cohort were analyzed using a semi-automated software developed in MATLAB (Mathworks, Natick, MA), which calculated mean heart rate (HR) and heart rate variability...
(SDNN: SD of normal-to-normal intervals), and applied a template-matching algorithm\(^1\) for QT interval analysis, including the assessment of mean QT corrected for HR using the Bazett formula (QTc = QT/√RR) as well as QT variability measures.\(^18\) QTVI represents the ratio between the normalized variance of the QT interval and the normalized variance of the HR, and is calculated as QTVI = log[(QTc/QTv)/(HRv/HR)] or equally as QTVI = log(QTv/QTc) – log(HRv/HR), where HRv is the heart rate variance, and QTv is the QT interval variance. Therefore, an increase in QTVI may reflect an increase in QT variability, a decrease in HR variability, or both. Premature ventricular contractions (PVCs) were also identified and used as a measure for the burden of ventricular arrhythmias during sleep. All parameters were computed over consecutive 30-second intervals to align with the standard for sleep stage scoring.

**Statistical analysis**

Average measures for parameters, such as QTVI, were calculated for each participant as the within-person averages of repeated values measured during the wake period prior to sleep onset and during the sleep period (excluding the periods of wake after the sleep onset). All measures are reported as mean ± SD unless otherwise stated. To assess statistical associations, Student’s t-test, Pearson’s correlation coefficient, and Fisher’s exact test were used. Statistical significance was set at \(P < 0.05\). The reported \(P\) values were rounded to three decimal points. Normality was tested using the Lilliefors test. Multivariable linear regression based on least-squares estimation was used to investigate the association between QTVI and methadone dose, using the data for all the subjects in the three groups. The R statistical package (The R Foundation for Statistical Computing, Vienna, Austria), MATLAB (Mathworks), and Origin (OriginLab, Northampton, MA) were used for data analysis.

**RESULTS**

**Study population**

Each of the three groups consisted of 12 men and 12 women between the ages of 31 and 92 (55.9 ± 13.5) years. Demographic data for the three groups are presented in Table 1. Patients on methadone used 5–140 mg/day of methadone (31.7 ± 39.8 mg/day; median: 15 mg/day) for the management of chronic pain or restless leg syndrome, and the AHI in this group ranged from 0 to 33.3 (median: 7.7). Patients in the methadone and clinic groups were matched on AHI, and 7 of the 24 patients in each of these groups had no evidence of sleep-disordered breathing (AHI < 5). Patients in the methadone and clinic groups had a similar arousal index (5.9/hour on average for both groups, \(P = 0.992\)).

**Methadone and QT variability**

During the wake period prior to sleep onset, no significant differences were noted in HR, SDNN, QTc, or QTVI measures between the methadone group and any of the comparator groups (Table 2).

During sleep, HR, SDNN and QTc measures were similar between the methadone group and the comparator groups; however, patients on chronic methadone had a significantly higher mean QTVI than either comparator group (\(P = 0.015\) vs. clinic, and \(P < 0.001\) vs. community groups; Figure 2; Table 2). In addition, the methadone group had a significantly larger log-transformed normalized QTc (log(QTc/QTc\(^2\))) than both comparator groups (\(P = 0.037\) vs. clinic, and \(P < 0.001\) vs. community groups). There were no statistically significant differences in the log-transformed normalized HRv (log(HRv/HRv\(^2\))) between the methadone and the two comparator groups. Thus, the greater mean QTVI of the methadone group during sleep reflects increased repolarization instability and not reduced HR variance.

Mean QTVI values calculated during rapid eye movement (REM) and non-REM stages of sleep were also both significantly larger in patients on methadone than in the comparator groups during the respective sleep stages (Table 2). Within subjects in any of the three groups, there were no statistically significant differences in mean QTVI between REM and non-REM periods.

There was a positive association between age and QTVI during wake in the clinic (\(r = 0.50, P = 0.013\)) and community (\(r = 0.61, P = 0.002\)) groups, but not in the methadone group (Figure 3). In the methadone group, mean QTVI was positively associated with methadone dose, both during sleep (\(r = 0.51, P = 0.012\)) and awake (\(r = 0.73, P < 0.001\)). Based on multivariable linear regression

| Variable                  | Methadone  | Clinic     | Community  |
|---------------------------|------------|------------|------------|
| Age (years)               | 55.7 (14.6)| 55.5 (13.4)| 56.4 (12.3)|
| BMI (kg/m\(^2\))          | 31.1 (5.5) | 30.8 (5.0) | 30.2 (4.7) |
| AHI (events/hour)         | 9.2 (7.2)  | 8.7 (5.9)  | 4.8 (4.1)  |
| Sleep duration (REM + non-REM, minutes) | 341.9 (109.3) | 397.4 (111.4) | 413.6 (123.5) |
| Coronary artery disease   | 2          | 2          | 2          |
| Hypertension              | 10         | 7          | 10         |
| Diabetes                  | 3          | 2          | 1          |
| Stroke                    | 1          | 1          | 1          |
| Atrial fibrillation       | 0          | 0          | 0          |
| Congestive heart failure  | 0          | 0          | 0          |
| High cholesterol          | 9          | 8          | 15         |

Entries are mean (SD) or count, depending on the type of variable. AHI, Apnea-Hypopnea Index; BMI, body mass index; REM, rapid eye movement.
During the wake period prior to sleep onset, there were no statistically significant differences in SpO\textsubscript{2} levels between the methadone and any of the comparator groups (Table 2).

During sleep, the average duration of each disordered breathing episode was not significantly different across the three groups (14.42 ± 2.08 seconds in the methadone, 15.88 ± 2.77 seconds in the clinic, and 14.84 ± 1.53 seconds in the community groups). In the methadone and the clinic groups, SpO\textsubscript{2} levels during sleep were significantly lower than their values during wake (\(P < 0.001\) for the methadone and \(P = 0.006\) for the clinic group; Figure 5). Whereas the methadone and the clinic groups were matched on AHI, SpO\textsubscript{2} levels in the methadone group were significantly lower than those of both comparator groups (\(P = 0.008\) vs. clinic and \(P = 0.013\) vs. community).

In the clinic group, QTVI was negatively correlated with SpO\textsubscript{2} levels (\(r = -0.50\) and \(P = 0.014\) during wake and \(r = -0.49\) and \(P = 0.014\) during sleep). In the methadone group, the difference in mean QTVI between wake and sleep periods was moderately correlated with the difference in SpO\textsubscript{2} levels between wake and sleep (\(r = -0.54\), \(P = 0.013\)). Neither the absolute mean SpO\textsubscript{2} levels—as opposed to the change in SpO\textsubscript{2}—nor the frequency of hypopnea/apnea episodes were significantly correlated with methadone dose. Based on the multivariable linear regression analysis that included adjustments for age and SpO\textsubscript{2}, the QTVISleep increased 0.26 (95% confidence interval: 0.16–0.35, \(P < 0.001\)) for every 20 mg increment in methadone dose (Table 4; Figure 4b).

In the methadone and community groups, during epochs with disordered breathing events (e.g., apnea or hypopnea), QTVI was significantly lower while log(QTv)/log(QT\textsuperscript{2}) were significantly larger (Table 5). The same trend existed for the clinic group but it was not statistically significant. In all three groups, SDNN and log(HR\textsubscript{v}/HR\textsuperscript{2}) were significantly larger during epochs with disordered breathing episodes (Table 5). These findings suggest that the lower QTVI measures during apnea or hypopnea

### Table 2 Heart rate and QT variability measures and SpO\textsubscript{2} during wakefulness and sleep

| State    | Variable     | Methadone | Clinic | Community |
|----------|--------------|-----------|--------|-----------|
| Wake     | HR, beats/minute | 67.05 (11.49) | 70.72 (10.94) [0.284] | 69.47 (8.77) [0.438] |
|          | SDNN, milliseconds | 46.82 (29.13) | 38.92 (17.61) [0.273] | 34.75 (15.45) [0.091] |
|          | QTc, milliseconds | 449.78 (42.10) | 437.94 (37.10) [0.351] | 451.17 (46.12) [0.878] |
|          | QTVI         | -1.13 (0.85) | -1.02 (0.68) [0.647] | -1.45 (0.45) [0.121] |
|          | SpO\textsubscript{2}, % | 94.47 (2.20) | 95.53 (1.94) [0.090] | 95.26 (2.45) [0.263] |
| Sleep    | HR           | 63.17 (9.70) | 65.09 (9.95) [0.504] | 65.22 (8.93) [0.450] |
|          | SDNN         | 45.34 (30.60) | 48.71 (28.82) [0.697] | 39.45 (17.54) [0.418] |
|          | QTc          | 436.27 (35.11) | 443.23 (36.09) [0.502] | 441.25 (32.12) [0.611] |
|          | QTVI         | -0.85 (0.76) | -1.34 (0.56) [0.015] | -1.55 (0.37) [0.000] |
|          | SpO\textsubscript{2}   | 92.92 (2.87) | 94.80 (1.70) [0.008] | 94.89 (2.42) [0.013] |
| REM      | QTVI         | -0.80 (0.86) | -1.31 (0.63) [0.028] | -1.51 (0.39) [0.000] |
|          | SDNN         | 46.02 (35.67) | 52.24 (24.68) [0.498] | 41.40 (20.08) [0.587] |
| Non-REM  | QTVI         | -0.86 (0.76) | -1.34 (0.55) [0.017] | -1.55 (0.38) [0.000] |
|          | SDNN         | 45.36 (30.12) | 47.687 (29.67) [0.789] | 38.75 (17.50) [0.357] |

Entries are mean (SD) [\(P\) vs. methadone group]; \(P\) values of 0.000 represent \(P < 0.001\).

HR, heart rate; QTVI, QT variability index; REM, rapid eye movement; SDNN, SD of normal-to-normal intervals; SpO\textsubscript{2}, oxygen saturation.

**Oxygen saturation levels during sleep and QTVI**

During the wake period prior to sleep onset, there were no statistically significant differences in SpO\textsubscript{2} levels between the methadone and any of the comparator groups (Table 2).

During sleep, the average duration of each disordered breathing episode was not significantly different across the three groups (14.42 ± 2.08 seconds in the methadone, 15.88 ± 2.77 seconds in the clinic, and 14.84 ± 1.53 seconds in the community groups). In the methadone and the clinic groups, SpO\textsubscript{2} levels during sleep were significantly lower than their values during wake (\(P < 0.001\) for the methadone and \(P = 0.006\) for the clinic group; Figure 5). Whereas the methadone and the clinic groups were matched on AHI, SpO\textsubscript{2} levels in the methadone group were significantly lower than those of both comparator groups (\(P = 0.008\) vs. clinic and \(P = 0.013\) vs. community).

In the clinic group, QTVI was negatively correlated with SpO\textsubscript{2} levels (\(r = -0.50\) and \(P = 0.014\) during wake and \(r = -0.49\) and \(P = 0.014\) during sleep). In the methadone group, the difference in mean QTVI between wake and sleep periods was moderately correlated with the difference in SpO\textsubscript{2} levels between wake and sleep (\(r = -0.54\), \(P = 0.013\)). Neither the absolute mean SpO\textsubscript{2} levels—as opposed to the change in SpO\textsubscript{2}—nor the frequency of hypopnea/apnea episodes were significantly correlated with methadone dose. Based on the multivariable linear regression analysis that included adjustments for age and SpO\textsubscript{2}, the QTVISleep increased 0.26 (95% confidence interval: 0.16–0.35, \(P < 0.001\)) for every 20 mg increment in methadone dose (Table 4; Figure 4b).

In the methadone and community groups, during epochs with disordered breathing events (e.g., apnea or hypopnea), QTVI was significantly lower while log(QTv)/log(QT\textsuperscript{2}) were significantly larger (Table 5). The same trend existed for the clinic group but it was not statistically significant. In all three groups, SDNN and log(HR\textsubscript{v}/HR\textsuperscript{2}) were significantly larger during epochs with disordered breathing episodes (Table 5). These findings suggest that the lower QTVI measures during apnea or hypopnea...
were mainly due to an increase in HR variability imposed by sleep-disordered breathing.

**Methadone and ventricular arrhythmias**

High frequency premature ventricular beats are a recognized risk factor for sustained ventricular arrhythmias and sudden death. Four of the patients on methadone had more than 1,000 PVCs per median sleep period (382 minutes), compared to only 1 of 48 subjects in the comparator groups (Fisher’s exact test, \( P = 0.039 \)).

Among the 18 subjects in the top quartile of QTVI sleep, 5 (4 of which were from the methadone group) had more than 1 PVC per 30-second epoch of sleep period, compared with only 4 (1 of which was from the methadone group) of the 54 subjects in the lower QTVI sleep quartiles (Fisher’s exact test, \( P = 0.038 \)).

**DISCUSSION**

The results of this study show that chronic methadone use is significantly associated with increased variability of QT interval during sleep in a dose-dependent manner. Moreover, patients on chronic methadone therapy had significantly lower mean oxygen saturation levels during sleep than those in either comparator group. Collectively, these findings suggest that methadone destabilizes cardiac repolarization, and that sleep-related hypoxemia may potentially mediate this effect.

Despite its adverse side-effect profile, methadone has a prominent role in the treatment of opioid use disorder and chronic pain. Combining methadone with other sedatives, such as alcohol, benzodiazepines, or other opioids, is suspected to increase the risk of overdose, respiratory depression, and cardiovascular death. Nonetheless, in the treatment of opioid use disorder, methadone is highly effective at reducing the risk of death from all causes. Methadone prescribed for chronic pain seems to be the main driver of methadone-related mortality rates.

In a prospective study evaluating sudden cardiac deaths occurring during a 4-year period in Portland, OR, 128 deaths without evidence of recreational drug use or drug overdose underwent a detailed autopsy. Of these cases, 22 had evidence of therapeutic serum methadone levels, whereas only 11 of the remaining 106 cases had an opioid analgesic other than methadone identified on a toxicologic screen. Cardiac abnormalities associated with sudden cardiac death were noted in 60%
of the 106 subjects with no evidence of methadone in their blood. However, among the subjects on methadone, only 23% had significant cardiac abnormalities that could have predisposed them to sudden cardiac death. Given the low prevalence of identifiable cardiac disease in the subjects on methadone, this drug was likely a contributor to the pathogenesis of sudden cardiac death in that subgroup.

Other than antiarrhythmic medications, methadone is the most frequently reported drug associated with QTc prolongation and torsades de pointes ventricular tachycardia. The mechanism by which methadone causes torsades is not entirely clear. In vitro, methadone inhibits the rapid component of the delayed rectifier channel in the low micromolar range, but the free concentrations in vivo are likely to be an order of magnitude lower than the half maximal inhibitory concentration due to strong protein binding. Methadone has also been associated with an increase in U-wave integral and appears to inhibit the inward rectifier channel. It is unclear whether and to what extent the interaction between these effects may be synergistic. Consistent with a significant effect on cardiac repolarization, Wedam and colleagues found that methadone was associated with a significant 34-msec increase in QTc over 16 weeks. The doses of methadone in that randomized controlled trial were between 60 and 100 mg/day, more than 4 times the median dose (15 mg/day) in the present study. In our study, patients on methadone doses ≥ 60 mg/day had longer wake-time QTc than the rest of the group (P = 0.032). The data presented herein indicate that methadone can increase beat-to-beat variability in the QT interval even in the absence of statistically significant QT prolongation.

The impact of the increased QT variability observed in the methadone group can be estimated by comparison to other published studies that used a similar methodology. The mean QTVI
levels observed during sleep in methadone patients are comparable to those observed in the top quartile (mean QT VI over 24 hours ≥ −0.84) of 268 patients with heart failure in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca (GISSI-HF) trial. The methadone group had, on average, higher values of QT VI than the mean of this heart failure cohort (−1.01 ± 0.34). Heart failure is associated with a significant risk for sudden death, and in GISSI-HF a QT VI of ≥ −0.84 was associated with a twofold risk for total and cardiovascular mortality compared to the rest of the heart failure cohort who experienced a mortality rate of 20% over 47 months.16

In GISSI-HF, QT VI was lower during the hours of sleep (QT VI = −1.18) and higher during the hours of waking (P < 0.0001).28 Viigimae et al. studied QT VI in subjects with and without obstructive sleep apnea and found that in men with sleep-disordered breathing, QT VI values were lower during sleep than during wake.29 In study samples with varying degrees of obstructive sleep apnea, Schmidt et al. found that QT VI was lower during all stages of sleep except stage 3, slow-wave sleep.30 Similarly, in our study, the patients in the clinic group had lower QT VI during sleep than during wake (P < 0.001). It is therefore concerning that methadone use would be associated with an increase in QT VI during sleep. The mechanism for this destabilizing effect appears to be, in part, attributable to a decrease in oxygen saturation levels during sleep.

In the current study, there were no differences in the duration and frequency of disordered breathing events between the methadone and clinic groups. However, the mean oxygen saturation levels during sleep were significantly lower in the methadone group, and the decrease in oxygen saturation levels was statistically associated with the level of increase in QT VI. Interestingly, in the methadone group, during epochs with disordered breathing episodes, QT VI was significantly lower despite the significantly larger

| Variable          | Coefficient estimate (95% CI) | t-Statistic | P value |
|-------------------|------------------------------|------------|---------|
| (Intercept)       | 2.527 (−2.618 to 7.672)      | 0.963      | 0.339   |
| Methadone dose    | 0.013 (0.009 to 0.017)        | 5.369      | < 0.001 |
| Age               | 0.013 (0.003 to 0.023)        | 2.552      | 0.013   |
| SpO2              | −0.049 (−0.102 to −0.004)    | −1.847     | 0.069   |

Number of observations: 72, error degrees of freedom: 68, root mean squared error: 0.509, R-squared: 0.407, adjusted R-squared: 0.381, F-statistic vs. constant model: 15.6, P value < 0.001. CI, confidence interval; SpO2, oxygen saturation; QT VI, QT variability index.

Table 4 Multivariable linear regression model of mean QT VI during sleep as QT VI sleep = 1 + methadone dose + SpO2 + age

| State            | Variable | Epochs without apnea/hypopnea | Epochs with apnea/hypopnea | P value |
|------------------|----------|-------------------------------|----------------------------|---------|
| Methadone        | QT VI    | −0.84 (0.76)                  | −0.93 (0.74)*              | 0.032   |
|                  | log(QTVI)| 1.27 (0.60)                   | 1.33 (0.60)*               | 0.035   |
|                  | log(QTVI/QT2) | −0.99 (0.59)          | −0.92 (0.60)*              | 0.030   |
|                  | log(HRV/HR2)  | −0.15 (0.54)               | 0.01 (0.53)*               | < 0.001 |
|                  | SDNN      | 43.91 (29.53)                | 53.55 (36.89)*             | < 0.001 |
|                  | SpO2 %    | 92.90 (2.84)                 | 92.97 (3.12)               | 0.636   |
|                  | min SpO2 %| 92.01 (3.08)                 | 91.29 (3.41)*              | < 0.001 |
| Clinic           | QT VI    | −1.33 (0.56)                  | −1.37 (0.59)               | 0.277   |
|                  | log(QTVI)| 0.95 (0.46)                   | 1.04 (0.45)                | 0.073   |
|                  | log(QTVI/QT2) | −1.31 (0.46)          | −1.22 (0.45)               | 0.070   |
|                  | log(HRV/HR2)  | 0.02 (0.43)               | 0.15 (0.42)*               | 0.006   |
|                  | SDNN      | 47.77 (28.91)                | 56.61 (28.42)*             | < 0.001 |
|                  | SpO2 %    | 94.82 (1.70)                 | 94.58 (1.76)               | 0.113   |
|                  | min SpO2 %| 93.89 (1.99)                 | 92.92 (2.15)*              | < 0.001 |
| Community        | QT VI    | −1.53 (0.39)                  | −1.59 (0.36)*              | 0.042   |
|                  | log(QTVI)| 0.60 (0.31)                   | 0.77 (0.30)*               | 0.003   |
|                  | log(QTVI/QT2) | −1.66 (0.31)          | −1.48 (0.29)*              | 0.002   |
|                  | log(HRV/HR2)  | −0.13 (0.34)               | 0.11 (0.33)*               | < 0.001 |
|                  | SDNN      | 37.12 (18.08)                | 49.40 (19.42)*             | < 0.001 |
|                  | SpO2 %    | 94.90 (2.41)                 | 94.33 (2.59)               | 0.273   |
|                  | min SpO2 %| 94.38 (2.44)                 | 93.01 (2.79)*              | < 0.001 |

Entries are mean (SD).
HR, heart rate; HRV, variance of the heart rate; SpO2, oxygen saturation; QT VI, variance of the QT interval; SDNN, SD of normal-to-normal intervals.
*P < 0.05 vs. epochs without apnea/hypopnea.
Obstructive sleep apnea is associated with large swings in HR due to the mechanical clearance of obstruction, and this increases HR variability and lowers QTVI in a manner that can be challenging to interpret. Even though participants in the current study had only mild sleep apnea, there was greater HR variability (SDNN) during epochs with apnea/hypopnea \((P < 0.001\) for all three groups; Table 5). Because of the confounding effect of severe sleep-disordered breathing on QTVI, evaluation of the log-transformed variance in QT may be more appropriate during episodes of apnea. Baumert et al.\(^1\) found that in subjects with severe sleep apnea (mean RDI: 49 events/hour), log(QTv) was larger during 5-minute epochs with at least one hypopnea/apnea episode and negatively correlated with the minimum oxygen saturation levels \((r = -0.55, P = 0.01)\). Although all three groups reported in the current study had evidence of mild sleep apnea (mean AHI: 7.5 events/hour), the results from the methadone group conform with the published findings for those with severe sleep apnea.

Consistent with previous research, subjects with higher QTVI in the current study had a higher burden of ventricular arrhythmias. Specifically, high-density premature ventricular beats, a potential precursor of torsades de pointes arrhythmias,\(^2\) although only present in five subjects in our study, were significantly more frequent in patients on chronic methadone therapy than comparators collectively.

There are several limitations that need consideration. The sample of patients on methadone therapy was small, the methadone doses were moderate, and the therapeutic indications were for either pain or restless leg syndrome. Thus, the results may not be generalizable to other patient samples where methadone is used for other indications, such as opioid use disorder or opioid withdrawal. Moreover, the study design was retrospective and thus may have the potential for residual confounding. \(\text{SpO}2\) measures and ECG data, including QTVI and the frequency of premature beats, prior to the initiation of methadone therapy were not available for comparison. It should be noted that a “thorough QT study,” in which pre-drug and on-drug data were measured, has never been performed for methadone.

Indeed, conducting a prospective, randomized trial of methadone on cardiac repolarization cannot be ethically justified due to the very long half-life and the addictive effects of this opioid. Future prospective polysomnography studies comparing patients on methadone and other opioids for other indications and those without sleep-related disorders could extend the results of the current study.

**CONCLUSION**

Methadone use is associated with a dose-dependent increase in instability of cardiac repolarization during sleep to a degree that is similar to that seen in heart failure populations with a high risk of sudden death. The effect appears to be partly associated with a decrease in blood oxygen saturation levels, although higher doses were associated with higher QTVI values even when awake with normal oxygen saturation. It is plausible that the inhibition of cardiac repolarizing currents accounts for this latter effect, and that mild hypoxemia during sleep increased the impact of methadone on repolarization. This may account for some of the nocturnal sudden deaths associated with this opioid. However, these findings might not be exclusive to methadone. Further research is needed to understand whether the depression of respiratory drive seen with all opioids contributes to increased repolarization instability, particularly in patients on concomitant therapy that prolongs the QT interval or alters the opioid metabolism. Sleep is a time of increased incidence of arrhythmias in patients with long QT2, a congenital condition associated with a reduction in hERG-encoded current that is similar to the effect of drugs such as methadone.\(^3,4\)

Hypoxemia due to the use of other drugs or in patients with sleep-disordered breathing might similarly increase repolarization instability and arrhythmogenicity. Additional research is needed to evaluate the impact of sleep, respiratory depression, and drug-induced hERG blockade on nocturnal sudden death. The findings of the current study also suggest that patients on methadone should be assessed for nocturnal hypoxemia associated with sleep-disordered breathing.

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**CONFLICT OF INTEREST**

Dr. Crainiceanu is a consultant with Bayer and Johnson and Johnson on methods development for wearable devices in clinical trials. The details of the contracts are disclosed through the Johns Hopkins University eDisclose system and have no direct or apparent relationship with this manuscript. All other authors declared no competing interests for this work.

**AUTHOR CONTRIBUTIONS**

All authors wrote the manuscript. S.S., N.P., and M.H. designed the research. S.S., N.P., A.I., and C.C. performed the research and analyzed the data.

**DISCLAIMERS**

The opinions and assertions expressed herein are those of the authors and are not to be construed as reflecting the views of Uniformed Services University of the Health Sciences, the National Institutes of Health, or the United States Department of Defense.

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