



Canadian Society of Addiction Medicine
La Société Médicale Canadienne sur l'Addiction

ECG / Qtc & Methadone – Should we be worried?

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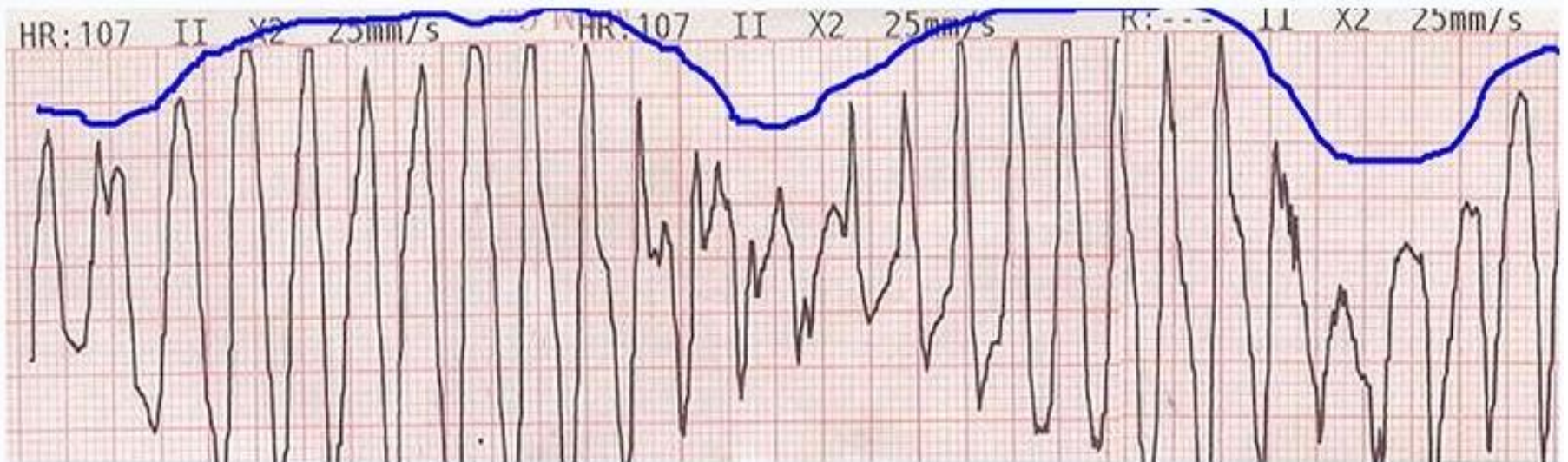
Intrinsic Variability in Electrocardiograph QT/QTc Interval Length
in Opioid-Dependent Patients Receiving Methadone
Maintenance Treatment

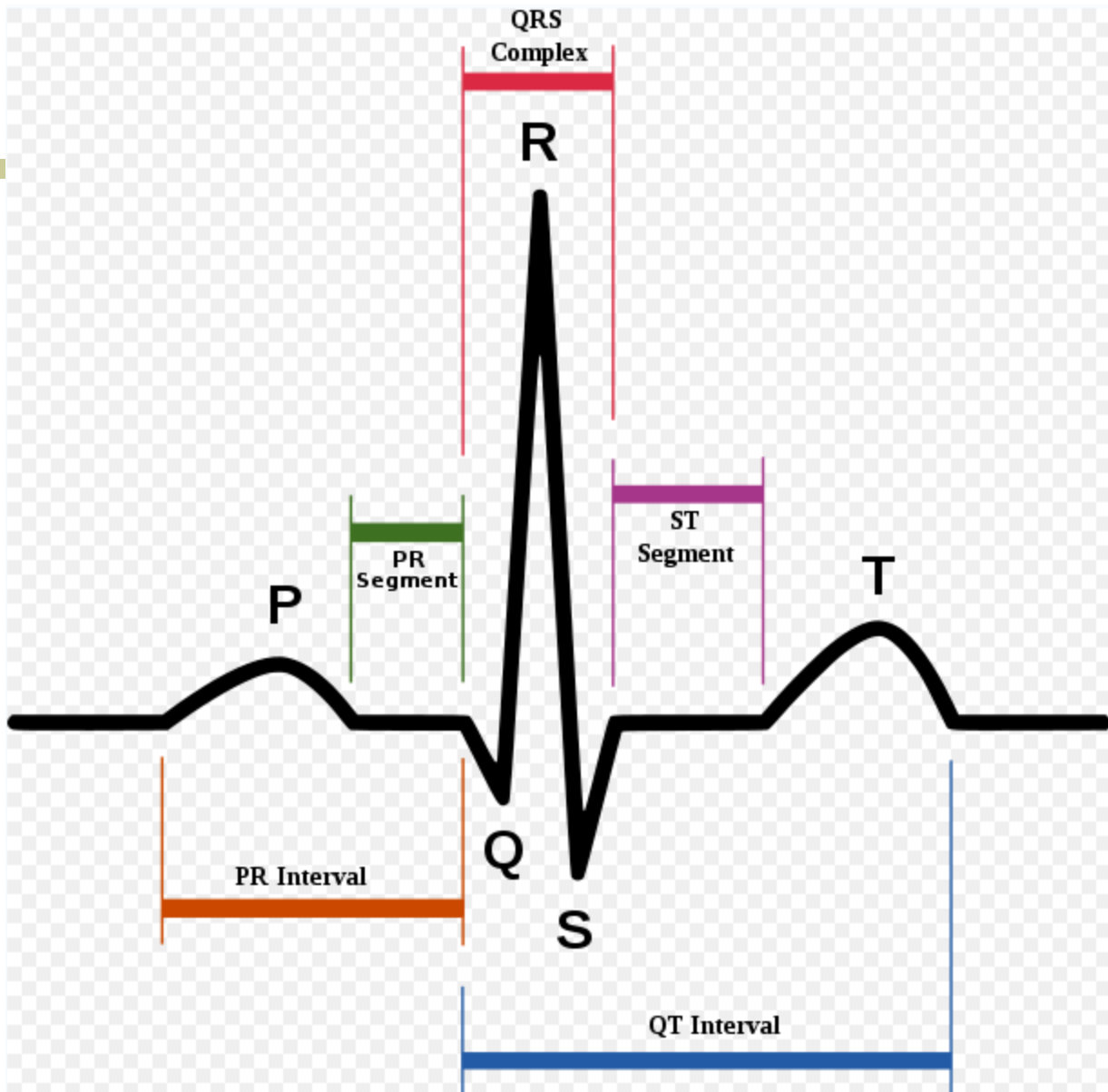
Andrew Worster, MD, Michael Varenbut MD, Jeff Daiter MD, Girish M. Nair, MD, Carolyn Plater-Zyberk, MSW, Lauren Griffith, PhD, Jihui Ma, MSc, Gus Zachos, MD, Marco Sivilotti, MD

[Overview]

- What is TdP and Qtc?
- Presentation & Clinical factors
- Medications & Drugs to watch
- Current recommendations
- Proposed guidelines
- Future plans

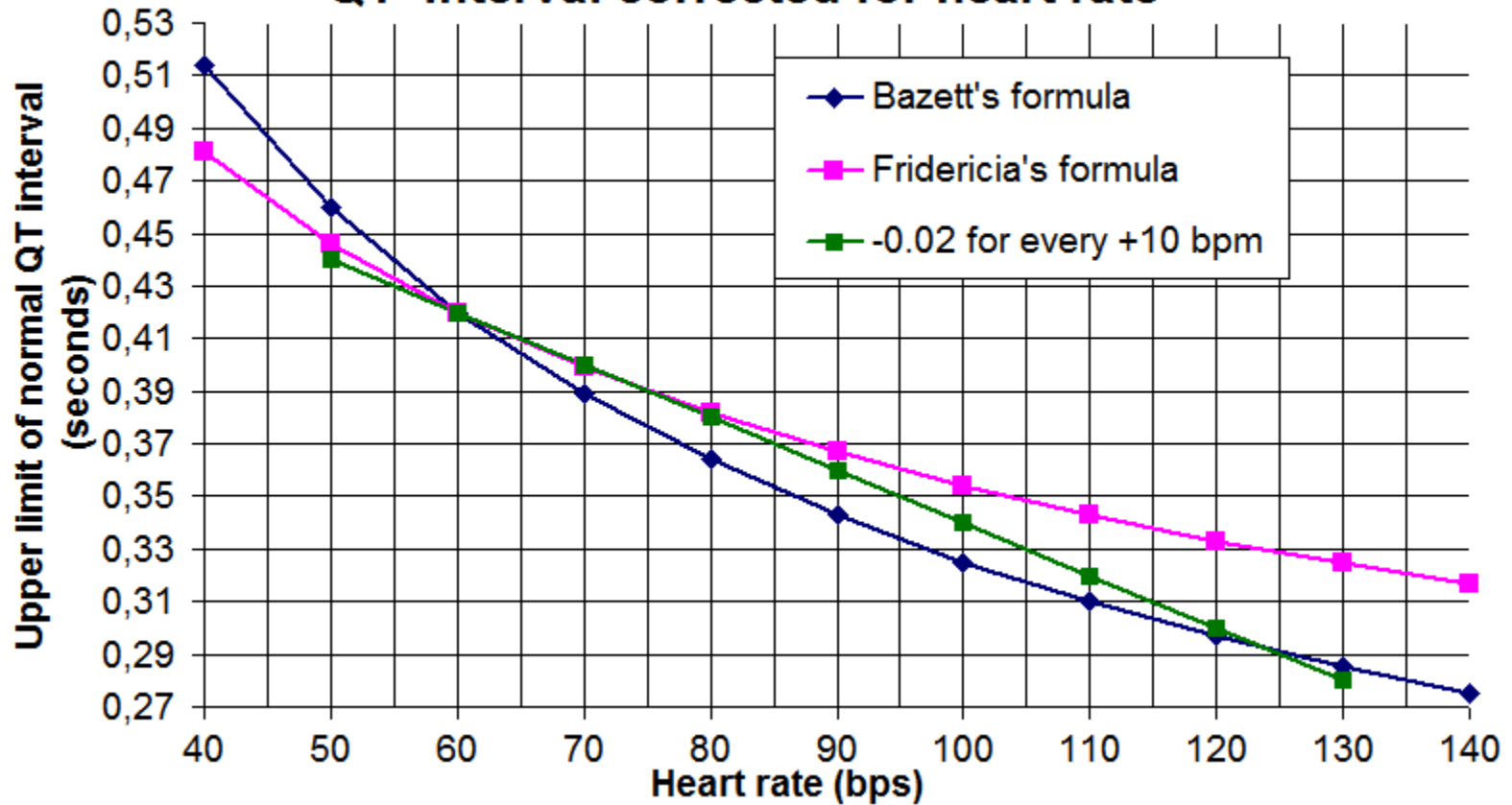
Torsade de pointes (Tdp) – “Twisting of the points”







QT interval corrected for heart rate



Presentation

- ECG – rapid, polymorphic V-tach, or V-fib
- Fall in Blood pressure, fainting
- Sudden death

QTc

- Upper limits of Normal:
- 440 ms – men (450 ms)
- 460 ms – women (470 ms)
- Increased risk if:
 - Over 500 ms
 - Increase over 60 ms from baseline

Table 2: Clinical Factors for Assessing Cardiac Arrhythmia Risk*

Family History (blood relatives)

Sudden or unexplained death at a young age (< age 50)

Patient History

Drug use (cocaine, amphetamines, alcohol, diuretics, etc., and OTC products [particularly ephedra])

Prescribed QT-prolonging or P450-inhibiting drugs

Congenital long QT syndrome (LQTS)

Known heart disease (particularly CAD or CHF)

Eating disorders (including bulimia and anorexia)

Laboratory Tests

Urine toxicology (showing proarrhythmic drugs, such as amphetamines or cocaine)

Depleted electrolytes (potassium, magnesium)

Recent Symptoms

Unexplained seizures

Exertional chest pain/discomfort

Exertional dyspnea (breathlessness)

Orthopnea (breathlessness on lying down)

Unexplained syncope (fainting) or unexplained near-syncope (dizzy, faint feeling)

Heart palpitations

Physical Examination

Abnormal pulse rate/rhythm

Jugular venous distension

Pulmonary rales (crackles)

Abnormal heart gallop

Causes

- Long QT syndrome:
 - inherited as congenital mutations of ion channels carrying the cardiac impulse/action potential or
 - acquired as a result of drugs or toxins that block these cardiac ion currents

Causes – Long QT

- **Familial Long QT syndrome (genetic)**
- **Antiarrhythmic drugs (Class IA & III)**
- **Hypomagnesemia (e.g diarrhea, anorexia)**
- **Hypokalemia**
- **Hypocalcemia**
- **Hypoxia**
- **Acidosis**
- **Heart failure**
- **LVH**
- **Bradycardia**
- **Female gender**
- **Hypothermia**
- **Subarachnoid Hemorrhage**

Table 1: Drugs That May Predispose to Prolonged QTc or TdP (alphabetical order)

adenosine (Adenocard) ^C	maprotiline (Ludiomil) ^C
amantadine (Symmetrel) ^B	mesoridazine (Serentil) ^A
amiodarone (Cordarone) ^{A#}	methadone (Disket, Dolophine, Methadose) ^A
amitriptyline (Elavil) ^{C#}	moexipril/HCTZ (Uniretic) ^B
arsenic trioxide (Trisenox) ^A	moxifloxacin (Avelox) ^B
astemizole (Hismanal) ^{C#}	naratriptan (Amerge) ^C
bepidil (Vascor) ^A	nicardipine (Cardene) ^B
chlorpromazine (Thorazine) ^{A#}	nortriptyline (Aventyl, Pamelor) ^{C#}
cisapride (Propulsid) ^{A#}	octreotide (Sandostatin) ^B
citalopram (Celexa) ^C	ondansetron (Zofran) ^{B#}
clarithromycin (Biaxin) ^{A#}	paroxetine (Paxil) ^{C#}
desipramine (Norpramin) ^C	pentamidine (Pentam, NebuPent) ^A
disopyramide (Norpace) ^{A#}	pimozide (Orap) ^A
dofetilide (Tikosyn) ^A	procainamide (Procan, Pronestyl) ^A
dolasetron (Anzemet) ^B	propafenone (Rythmol) ^C
domperidone (Motilium) ^A	quetiapine (Seroquel) ^B
doxepin (Sinequan) ^C	quinidine (Cardioquin, Quinaglute) ^{A#}
droperidol (Inapsine) ^A	risperidone (Risperdal) ^B
erythromycin (EES, Erythrocin) ^{A#}	rizatriptan (Maxalt) ^C
felbamate (Felbatol) ^B	salmeterol (Serevent) ^{B#}
flecainide (Tambocor) ^{B#}	sertraline (Zoloft) ^{C#}
fluoxetine (Prozac) ^{C#}	sotalol (Betapace) ^A
foscarnet (Foscavir) ^B	sparfloxacin (Zagam) ^A
fosphenytoin (Cerebyx) ^B	sumatriptan (Imitrex) ^C
gatifloxacin (Tequin) ^B	tacrolimus (Prograf) ^B
granisetron (Kytril) ^B	tamoxifen (Nolvadex) ^{B#}
halofantrine (Halfan) ^A	telithromycin (Ketek) ^B
haloperidol (Haldol) ^{A#}	thioridazine (Mellaril) ^{A#}
ibutilide (Corvert) ^A	tizanidine (Zanaflex) ^B
imipramine (Tofranil) ^{C#}	venlafaxine (Effexor) ^{B#}
indapamide (Lozol) ^B	voriconazole (Vfend) ^B
isradipine (DynaCirc) ^B	ziprasidone (Geodon) ^B
ketoconazole (Nizoral) ^{C#}	zolmitriptan (Zomig) ^C
levomethadyl (Orlaam) ^{A#}	
levofloxacin (Levaquin) ^B	
lithium (Eskalith, Lithobid) ^B	

Medications to watch...

- Cisapride (Propulsid)
- Clarithromycin (Biaxin)
- Domperidone (Motilium)
- Erythromycin
- Lithium
- Levofloxacin (Levaquin)
- Quetiapine (Seroquel)
- Venlafaxine (Effexor)

QTc Interval Screening in Methadone Treatment

Mori J. Krantz, MD; Judith Martin, MD; Barry Stimmel, MD; Davendra Mehta, MD; and Mark C.P. Haigney, MD

Description: An independent panel developed cardiac safety recommendations for physicians prescribing methadone.

Methods: Expert panel members reviewed and discussed the following sources regarding methadone: pertinent English-language literature identified from MEDLINE and EMBASE searches (1966 to June 2008), national substance abuse guidelines from the United States and other countries, information from regulatory authorities, and physician awareness of adverse cardiac effects.

Recommendation 1 (Disclosure): Clinicians should inform patients of arrhythmia risk when they prescribe methadone.

Recommendation 2 (Clinical History): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.

Recommendation 3 (Screening): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and a

follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.

Recommendation 4 (Risk Stratification): If the QTc interval is greater than 450 ms but less than 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.

Recommendation 5 (Drug Interactions): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone.

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For author affiliations, see end of text.

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Research Recommendations

- “QTc prolongation during opioid maintenance treatment: congenital long Qt syndrome and cardiac management”, Anchersen, katinka (Norway, 2009)
- QTc > 500 ms – Repeat ECG, Consider Stress test, 24 hr holter, electrolytes, cardiac consultation, consider dose reduction, consider Buprenorphine (Krantz et al, 2009)

“Proposed ECG Guidelines”

- All patients pre MMTP start (baseline)
- Follow-up ECG in 30 days
- Repeat with doses over 100 mg
- Repeat annually
- Repeat at anytime if clinically indicated

Proposed ECG Guidelines- cont'd

- QTc over 450 ms:
 - Discuss with patient
 - Monitor more closely
 - Consider reversible causes
 - Consider dose reduction
 - Consider Suboxone
 - Consider 24 hr Holter, stress test, cardiac consultation

Research study

- The Research Ethics Board of Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada approved this study.
- Collaborative effort of researchers from U. of T., McMaster, Queens, OATC.

Research study - Aim

- To discern the differences between QT measurements using different ECG leads, different correction formulae, and both automated and manual measurement in order to determine the degree of intrinsic variability in QT/QTc interval within patients on methadone maintenance treatment (MMT).

Research study

- **Design:** All participants submitted to a standard electrocardiograph (ECG) for five consecutive days.
- **Setting:** A Canadian based community MMT clinic.

Research study - Participants

- 26 MMT participants, 18 years or older, and all met the DSM IV criteria for opioid dependence.
- All participants were stable in their recovery and received a consistent daily dose of methadone for a minimum of three days prior to and during the data collection period.

Research study - Measurements

- QT intervals manually measured by two investigators as well as ECG software.
- QTc intervals were calculated using both Bazett's and Framingham formulae.

Research study

- **Bazett's formula:**

$$QTc = QT/\sqrt{RR} \text{ (in seconds)}$$

- **Framingham (Sagie et al) formula:**

$$QTc = QT+0.154 (1000-RR) \text{ in ms}$$

Research study - Findings

- QT consistent and stable in the same patient from day to day over 5 days studied, thus -
- Can use a single ECG to assess risk
- The QTc intervals calculated by the machine and Bazett's formula were the longest, but not significant clinically. Thus machine measurements are reliable for assessing QTc.

Research study - Findings

- The results confirm that the relative length of the QT and calculated QTc intervals are dependent upon the methods used to measure and calculate them respectively.
- The intra-class correlation coefficient (ICC) from different ECG measurements at the same dose for the same patient are all similar.

[Research study - Conclusions]

- Under standardized ECG recording methods, the differences between the various methods of measuring the QT interval, calculating the QTc, and the intrinsic variability are relatively low.
- Further studies should confirm whether these differences are low enough to assess the impact of methadone on QT/QTc using only the machine-calculated QTc from just one ECG/patient at a given dose.

Future plans

- Gather data on all OATC patients for the next 12-18 months
- To date 4000 ECG's collected
- Largest patient cohort in the world...
- Publish findings, and new recommendations...next year

Questions / comments

