QTc…… as easy as 123

Managing Drug-Induced QTc prolongation

PRESENTER

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CPED

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Managing Drug-Induced QTc prolongation

Learning Objectives

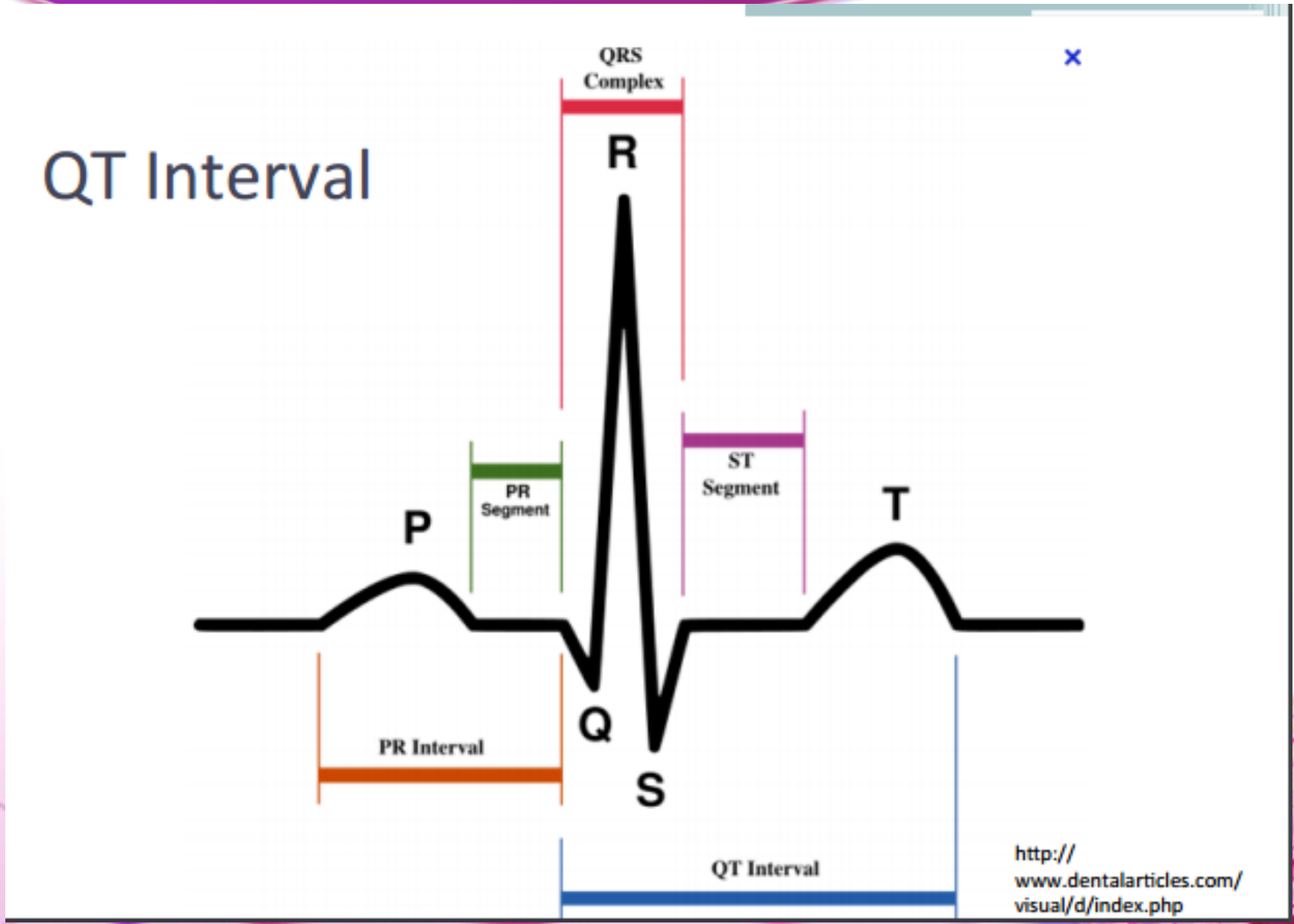
By the end of this session, participants will be able to:

- Recognize QTc prolongation and association with morbidity and mortality
- Apply a risk stratification scheme to individual patients to determine risk of QTc prolongation
- Recommend management and monitoring strategies for patients at risk of QTc prolongation

QTc Prolongation Outline

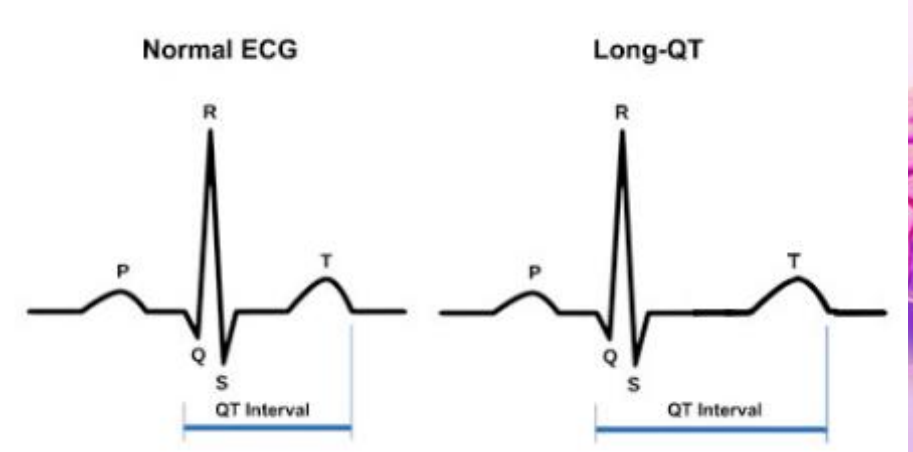
- What is the QT interval and QTc Prolongation
- How Common is QTc prolongation
- QTc Effect Literature Review
- Assessing Multiple Risk Factors
- Managing Common QTc Drug Therapy Problems
- Monitoring Plan for High Risk Patients
- Case
- Summary

What is the QTc Interval?



What is the QTc Interval?

- The time from the electrical stimulation (depolarization) of the heart's pumping chambers (ventricles), to their recharging (repolarization).
- The QT interval varies with heart rate. It shortens as the rate increases and lengthens as the rate decreases.
- Therefore, there is no single QT interval that is normal or abnormal.



Range of QTc Intervals

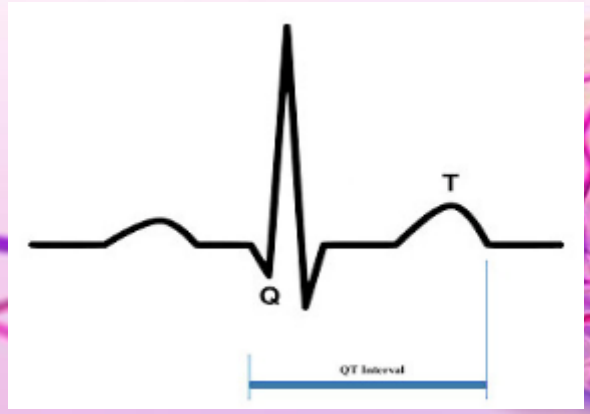
In order to determine if a given QT is appropriate for a given heart rate, the QT is corrected for the heart rate using a mathematical formula, and this quantity is called the QTc.

	Males	Females
Normal	Less than 430 msec	Less than 450 msec
Borderline	430-450 msec	450-470 msec
Prolonged	Greater than 450 msec	Greater than 470 msec

What is QTc Prolongation?

- An inherited or acquired disturbance of the heart's electrical system caused by abnormalities of ion channels found in heart cells.

- Ions (K^+, Na^+, Ca^{2+} and Cl^-) pass across the cell membrane through channels and generate the electrical activity (depolarization and repolarization) that initiates the heart's mechanical function.



What is QTc Prolongation?

These electrical signals are recorded as the electrocardiogram (EKG or ECG).

The abnormal function of one or more ion channels prolongs the repolarization process and the QT interval. This predisposes patients to cardiac arrhythmias.

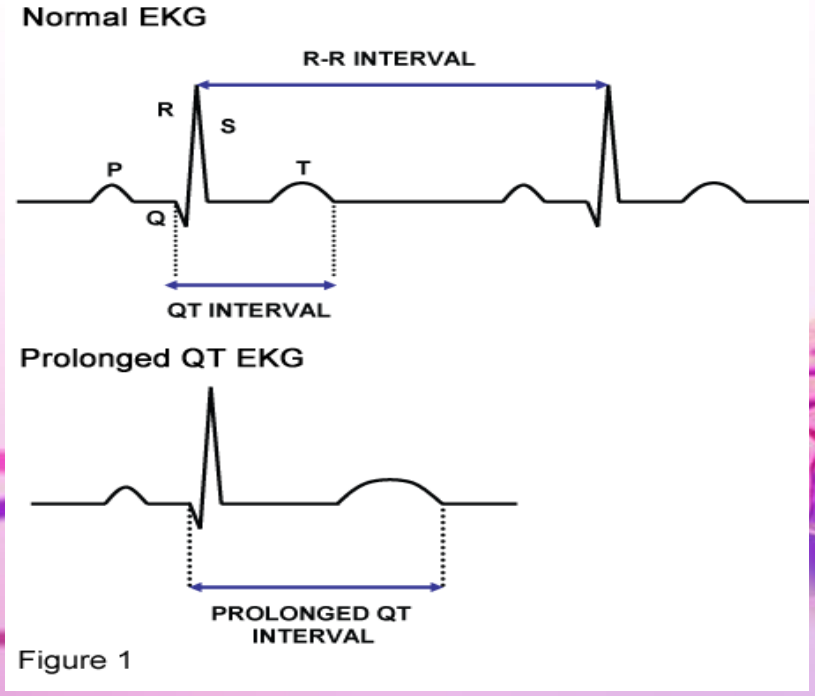


Figure 1

What is QTc Prolongation?

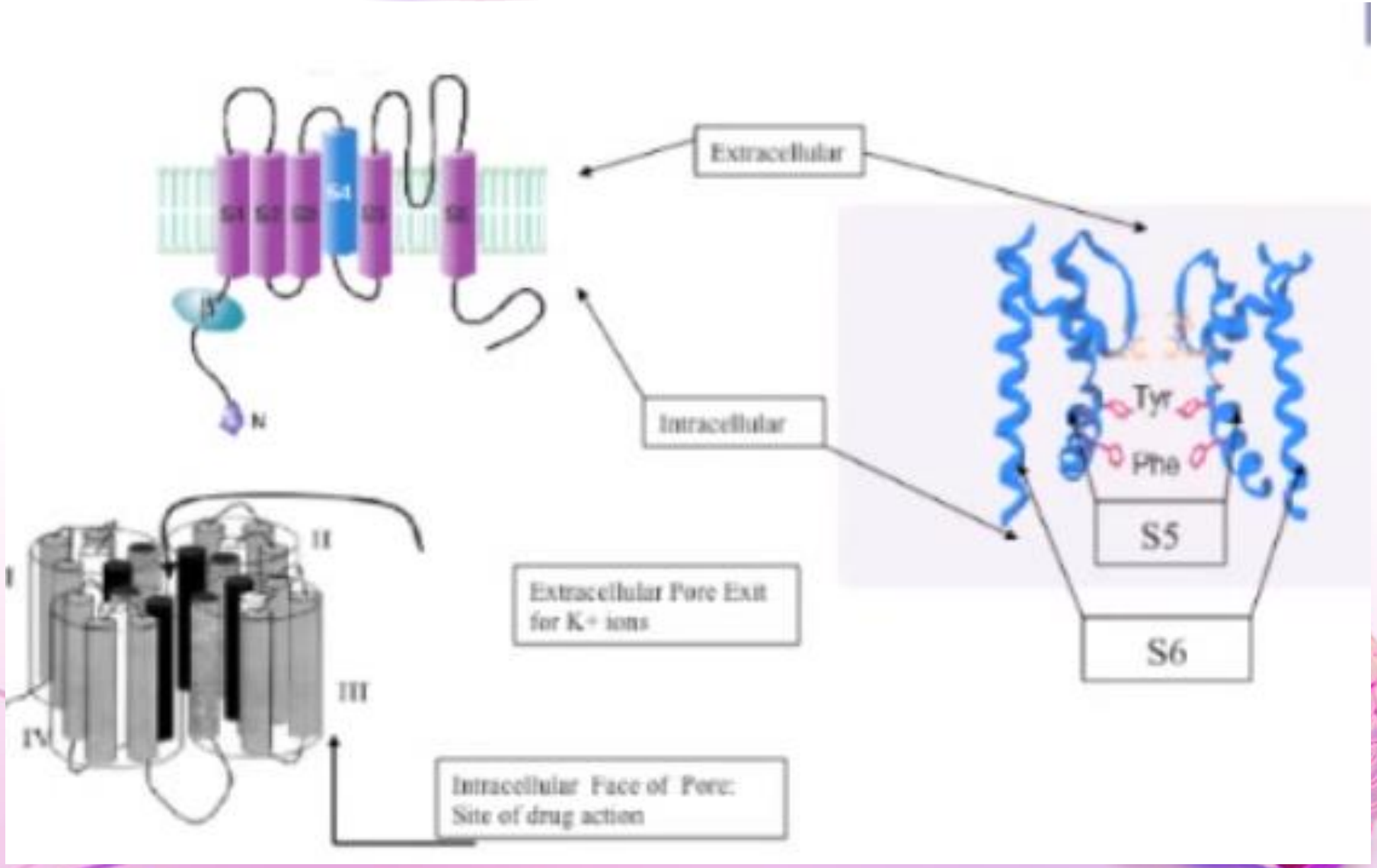
- Health Canada:

  "increases in QT/QTc to >500ms or of >60ms over baseline are commonly used for thresholds for potential discontinuation"

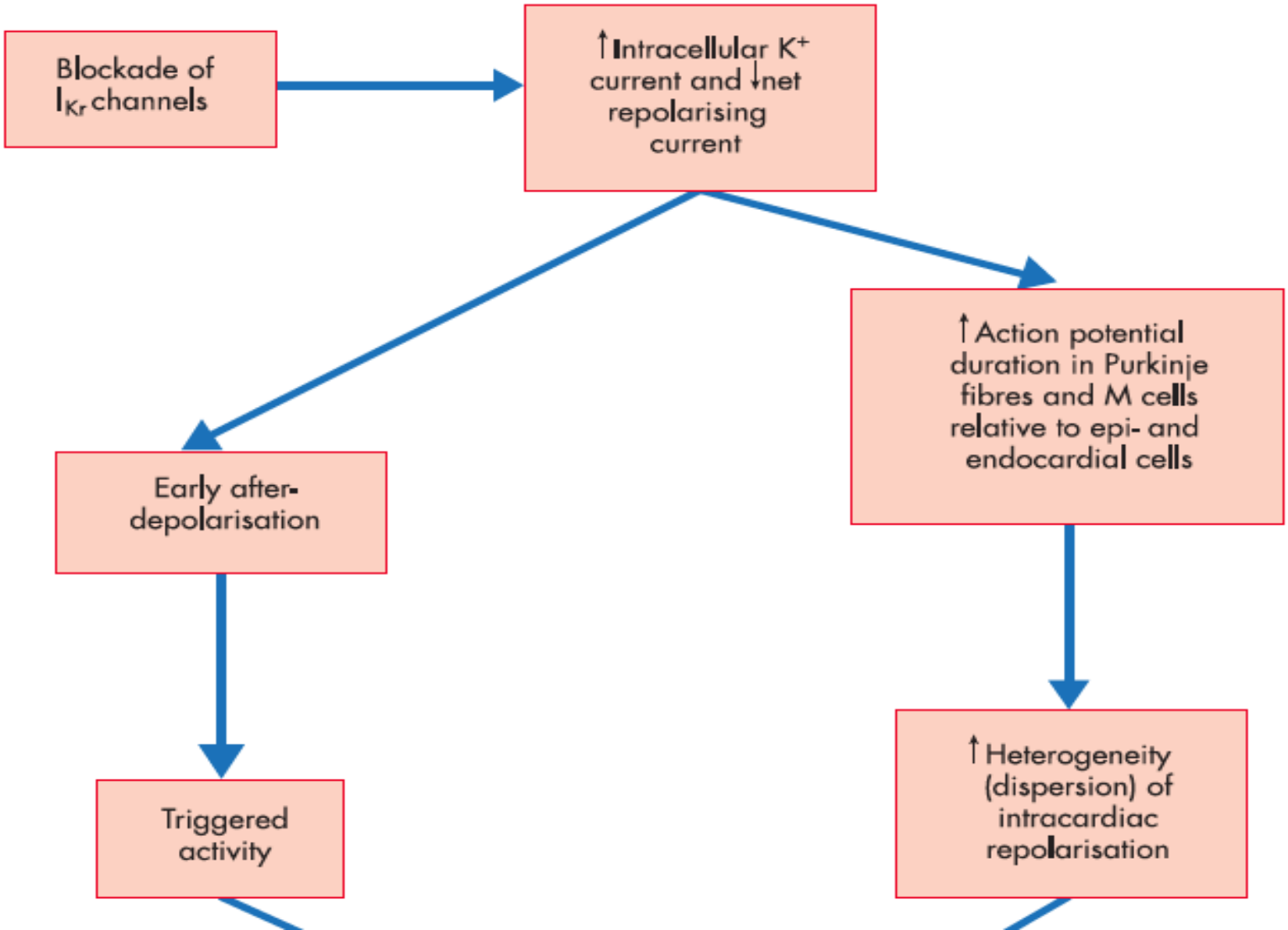
- US Food and Drug Administration

  "Marked prolongation of the QT/QTc interval during treatment…….>500ms or >60ms over baseline are commonly used…."

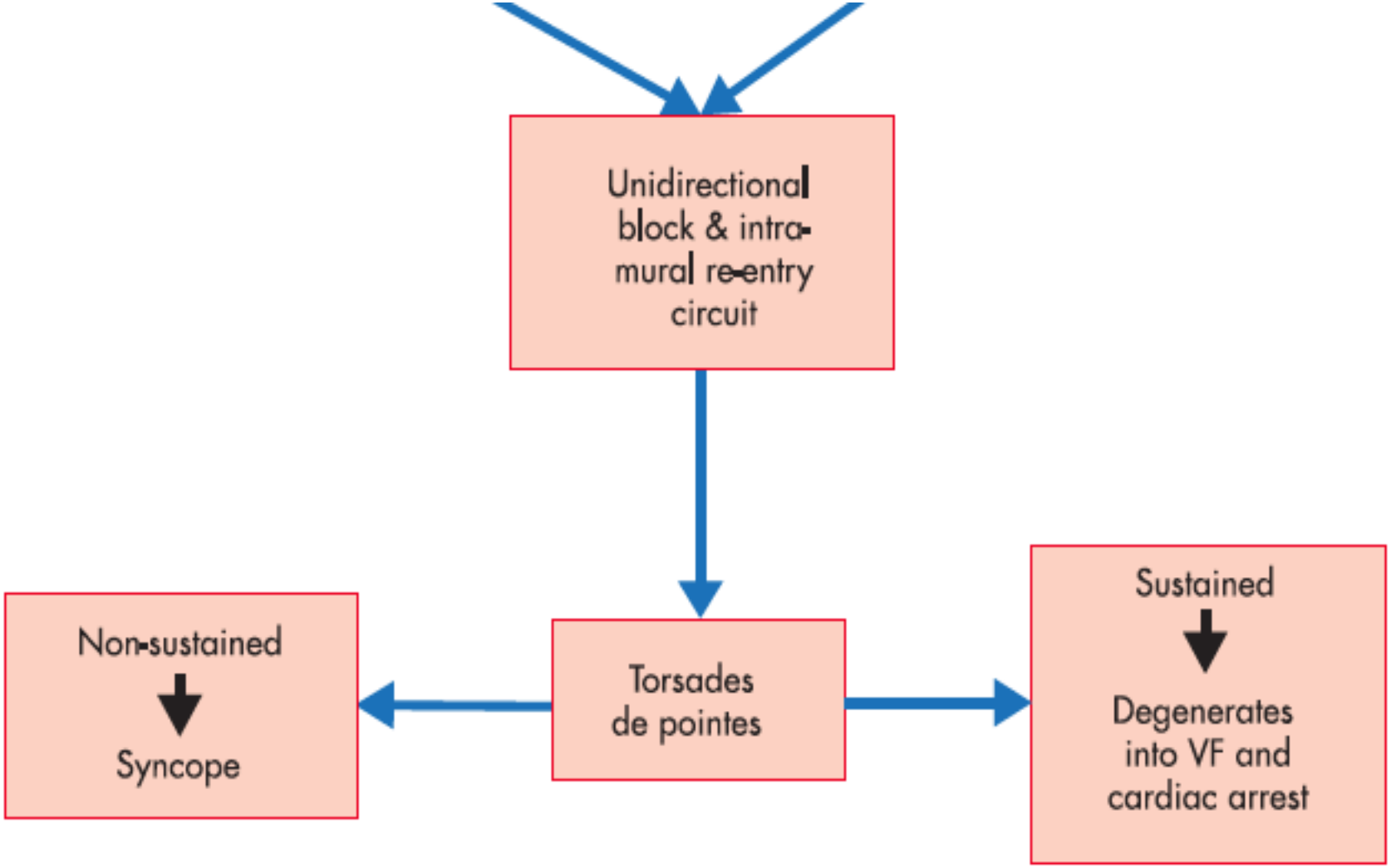
Mechanism of Drug Induced QTc Prolongation



Mechanism of Drug Induced QTc Prolongation



Mechanism of Drug Induced QTc Prolongation



Mechanism of Drug Induced QTc Prolongation

Reduced Repolarization Reserve (Roden 2003) is the reduction in the amount of K-mediated repolarizing channels (Ik_r)

- Decrease number of available Ik_r channels
  - Drug Concentrations
  - Heart Failure/ACS
  - Genetic Variants in drug transport proteins
  - Genetic Variants in channels themselves
  - Potassium level
  - Magnesium level
  - Bradycardia

How Common is QTc Prolongation ?

Most studies indicate 18-35% of hospital inpatients on medical and cardiac care units have QTc prolongation.

How Common is QTc Prolongation ?

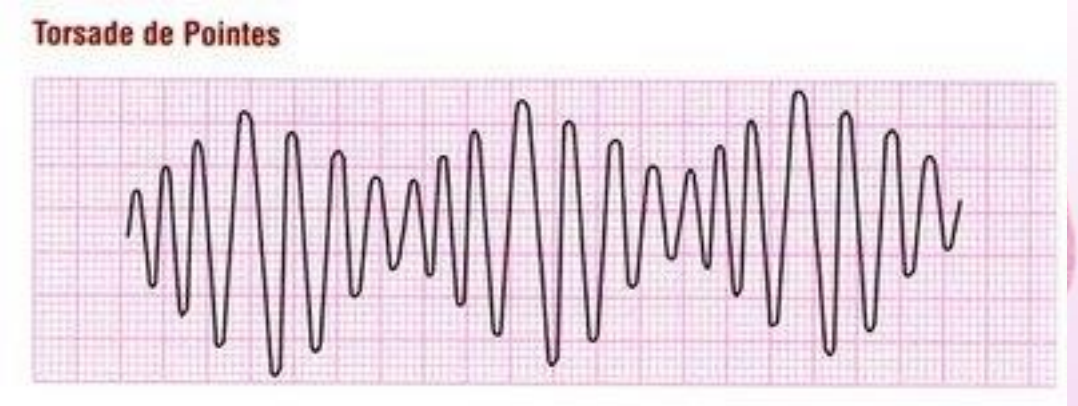
Mambasa (2011) *Canadian Journal of Hospital Pharmacy*

- Patients admitted to hospital already on a drug known to cause QTc prolongation
  - 26% of these patients had a prolonged QTc interval on the 12-lead ECG on admission
    - Patients in this group were prescribed on average 1.5 medications known to prolong QTc interval while admitted
    - 18% had an arrhythmia that resolved
    - 4% died, 2 patients (Torsades and V fib)

Why are we concerned..?

QTc is a Surrogate for Torsades de Pointes(TdP)

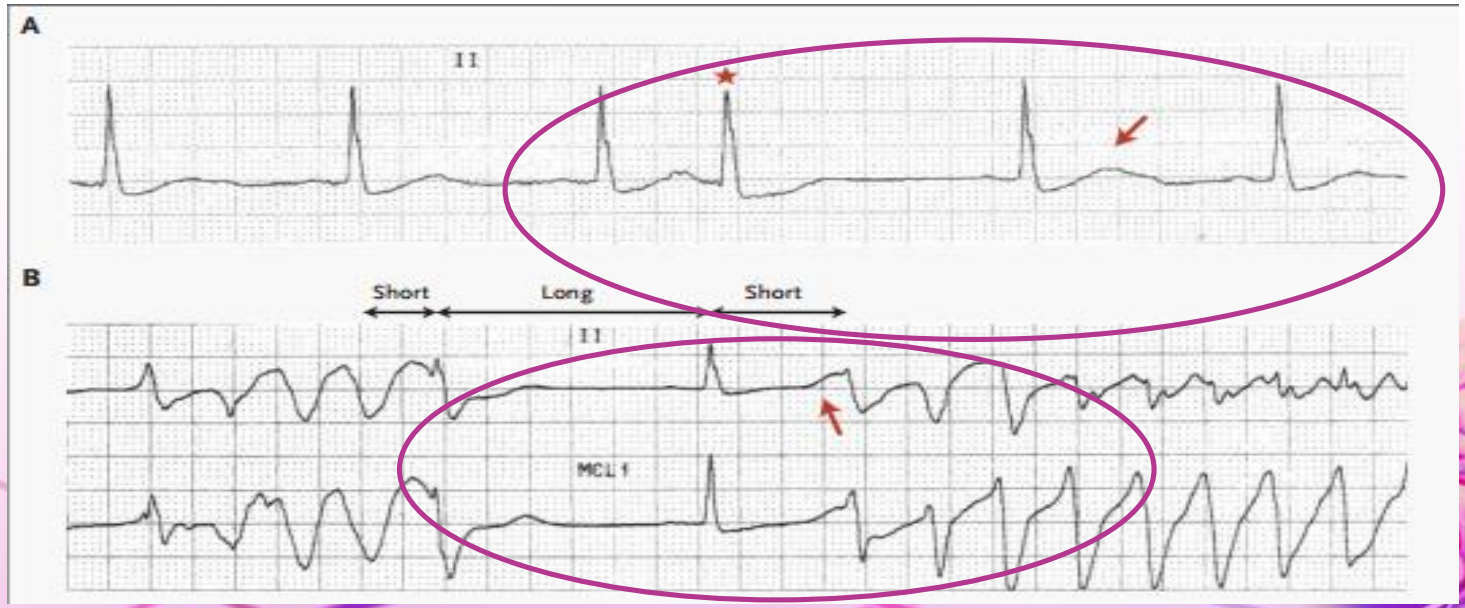
- TdP (twisting of the points) refers to a polymorphic ventricular tachycardia, associated with prolonged QTc interval and bradycardia.
- TdP is thought to be caused by early after-depolarizations during prolonged repolarization. It is often self-limiting but may be **potentially fatal**, sometimes leading to syncope and/or sudden death.
- TdP can be either congenital (1 in 2500) or acquired due to **most commonly drugs (1 in 10-100,000)**
- The actual incidence of TdP is unknown.
- Numerous drugs have the potential to cause TdP and have been taken off the market for that reason!



Why are we concerned..?

QTc is a Surrogate for Torsades de Pointes(TdP)

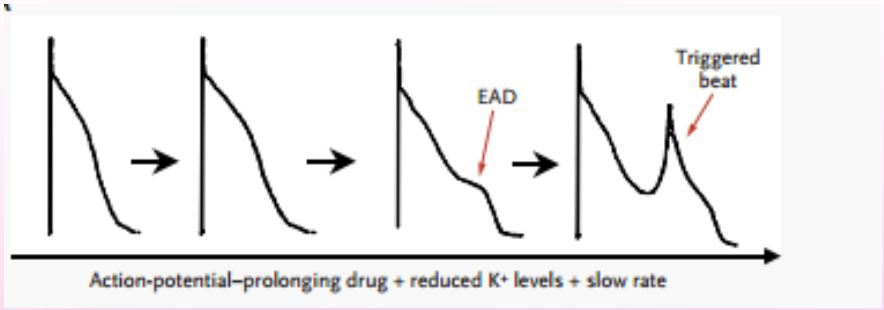
- QTc prolongation = Wide and Flat T wave
- TdP = Polymorphic (beat-to-beat) changes in QRS
  - Short- Long- Short R-R interval presentation
  - R on T phenomenom

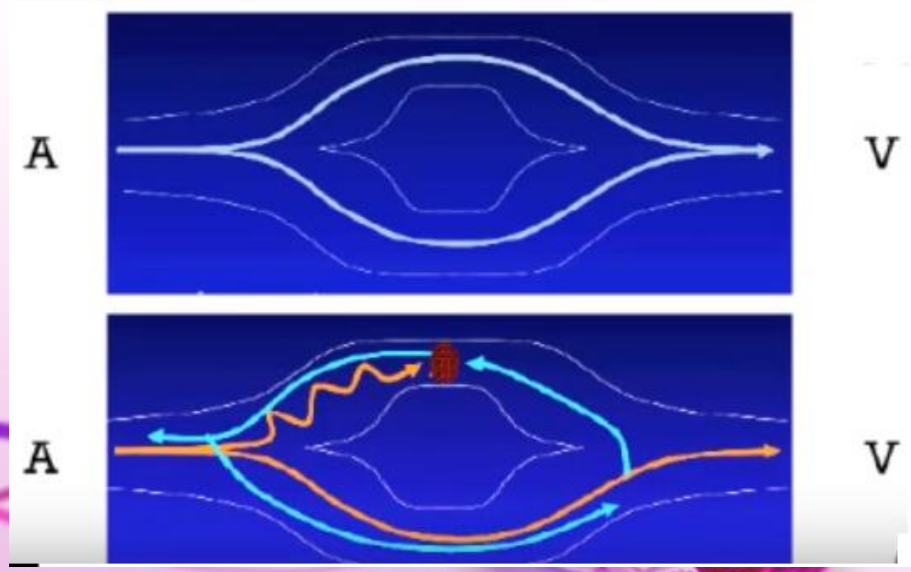


Why are we concerned..?

QTc is a Surrogate for Torsades de Pointes (TdP)

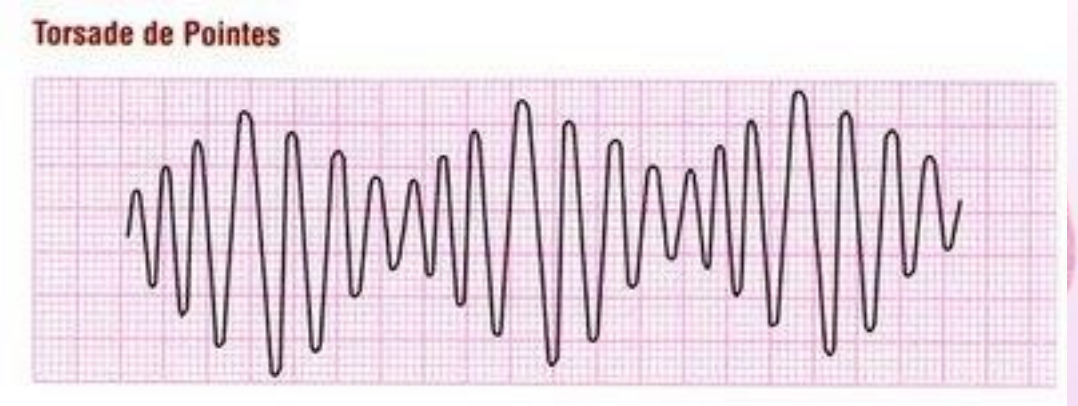
- QTc prolongation = Wide and Flat T wave
  - Heterogeneity in the development of prolongation of the action potential and early **afterdepolarizations** results in a myocardium that is vulnerable to **reentrant excitation**, the probable proximate cause of TdP





QTc as a Surrogate for TdP

- Each 10-ms increase in QT_c contributes approximately a 5% to 7% exponential increase in risk for TdP in these patients.
  - Therefore, a patient with a QT_c of 540 ms has a 60%- 95% higher risk of developing TdP than a patient with a QT_c of 440 ms.
- 97% of cases of torsades are in cases of QT_c>500 ms
- Data from congenital LQTS studies indicate that a QT_c>500 ms is associated with a 2- to 3-fold higher risk for TdP.
- Case reports and small series of patients with drug-induced TdP show similar increased risk when the threshold of QT_c >500 ms is exceeded.



QTc as a Surrogate for TdP

- Drugs that prolong the QT interval appear to have a TdP incidence of 1% to 10%. (ex: quinidine, disopyramide, procainamide sotalol, dofetilide, ibutilide).
- Many non-antiarrhythmic drugs have also been associated with TdP through multiple case reports and small case series (ex: haloperidol, seroquel, domperidone)
  - Less than 1%
  - You may not always find this information in the product monograph

QTc as a Surrogate for TdP

QTc as an Independent Risk Factor for Sudden Cardiac Death (SCD)

- Over an average of 6.7 years, the prevalence of cardiovascular comorbidity increased with an increasing QTc interval.
- Abnormal QTc prolongation was associated with 2x increase in sudden cardiac death
  - An abnormally prolonged QTc interval (>450 ms in men, >470 ms in women) was associated with a three-fold increased risk of sudden cardiac death.
- Inconsistently elevated vs consistently vs normal QTc
  - Only Consistently QTc prolonged > normal QTc

QTc as a Surrogate for TdP

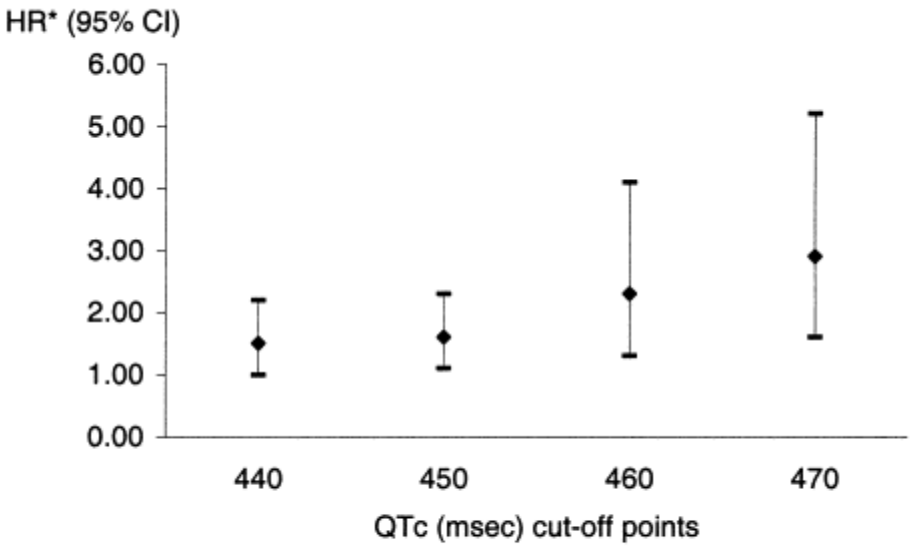


Figure 2.
Risk of sudden cardiac death (SCD) at different heart rate corrected QT (QTc) interval cutoff points. *Adjusted for age, gender, body mass index, cholesterol/high-density lipoprotein ratio, smoking, hypertension, diabetes, myocardial infarction, and heart rate. CI = confidence interval; HR = hazard ratio.

Remember this?

Health Canada | Santé Canada

Domperidone Maleate - Association with Serious Abnormal Heart Rhythms and Sudden Death (Cardiac Arrest) - For Health Professionals

Starting date:	January 20, 2015
Posting date:	January 20, 2015
Type of communication:	Dear Healthcare Professional Letter
Subcategory:	Drugs
Source of recall:	Health Canada
Issue:	Important Safety Information
Audience:	Healthcare Professionals
Identification number:	RA-43423

Report a Concern

This is duplicated text of a letter from **Apotex Incorporated, Dominion Pharmacal, Jamp Pharma Corporation, Marcan Pharmaceuticals Inc., Mylan Pharmaceuticals ULC, Pharmascience Inc., Pro Doc Limitée, Ranbaxy Pharmaceuticals Inc., Sanis Health Inc., Sivem Pharmaceuticals ULC** and **Teva Canada Limited and ratiopharm Inc.** Contact the companies for a copy of any references, attachments or enclosures.

Notice about Health Canada advisories

Health Canada Endorsed Important Safety Information on domperidone maleate

January 20, 2015

Dear Healthcare Professional:

Subject: Domperidone maleate associated with serious ventricular arrhythmias and sudden cardiac death

The manufacturers of domperidone in collaboration with Health Canada would like to inform you of important additional safety information regarding a small increased risk of serious ventricular arrhythmias or sudden cardiac death in association with domperidone.

Domperidone is indicated in adults for the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis. Domperidone is also indicated to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents.

A review of epidemiological studies and recent post-market safety data has demonstrated that domperidone exposure was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. Based on this new evidence, the labelling of domperidone is being further strengthened to better reflect and address these cardiac risks.

- **Domperidone may be associated with a small increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients:**
  - **older than 60 years of age;**
  - **using daily doses greater than 30 mg;**
  - **having predisposing factors for QT prolongation including concomitant use of QT-prolonging drugs or CYP 3A4 inhibitors.**
- **Domperidone is now contraindicated in patients:**
  - **with prolongation of cardiac conduction intervals, particularly QT;**
  - **with significant electrolyte disturbances;**
  - **with cardiac disease (such as congestive heart failure);**
  - **with moderate or severe liver impairment;**
  - **receiving QT-prolonging drugs and potent CYP3A4 inhibitors.**
- **Domperidone should be used at the lowest effective dose to a maximum recommended daily dose of 30 mg and for the shortest possible duration.**

Bozzo P, Koren G, Ito S. Health Canada advisory on domperidone should I avoid prescribing domperidone to women to increase milk production [corrected]?. Can Fam Physician. 2012;58(9):952-3.

Remember this?

Health Canada Santé Canada

Health Canada Endorsed Important Safety Information on Celexa (citalopram)

January 25, 2012

Dear Health Care Professional,

Subject: Association of CELEXA® (citalopram hydrobromide) with Dose - Dependent QT Prolongation

Lundbeck Canada, in collaboration with Health Canada, would like to inform you that the antidepressant Celexa® (citalopram hydrobromide; also marketed as generics), should no longer be used at doses greater than 40 mg per day due to study results indicating a dose-dependent potential for QT prolongation. Previously, the Celexa® (citalopram hydrobromide) Canadian Product Monograph stated that certain patients may require 60 mg per day.

Celexa® (citalopram hydrobromide) is a selective serotonin reuptake inhibitor (SSRI) indicated for the symptomatic relief of depressive illness. It is available as 20 mg and 40 mg tablets.

- **A thorough QT study, conducted according to international standards, assessing the effects of citalopram 20 mg per day and 60 mg per day on the QT interval has shown that citalopram causes dose-dependent QT prolongation.**
- **Celexa® (citalopram hydrobromide) should no longer be prescribed at doses greater than 40 mg per day.**
- **20 mg per day is the maximum recommended dose for patients with hepatic impairment, patients who are 65 years of age or older, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine or another CYP2C19 inhibitor.**
- **Celexa® (citalopram hydrobromide) is contraindicated in patients with congenital long QT syndrome or known QT interval prolongation.**

Bozzo P, Koren G, Ito S. Health Canada advisory on domperidone should I avoid prescribing domperidone to women to increase milk production [corrected]?. Can Fam Physician. 2012;58(9):952-3.

Remember This?

Health Canada | Santé Canada

Antidepressant Cipralex (escitalopram): Updated information regarding dose-related heart risk

Starting date: May 7, 2012
Posting date: May 7, 2012
Type of communication: Advisory
Subcategory: Drugs
Source of recall: Health Canada
Issue: Product Safety, Labelling and Packaging
Audience: General Public
Identification number: RA-110005613

Report a Concern

- Issue
- What you should do
- Report health or safety concerns
- Media enquiries
- Public enquiries

Issue

Health Canada is informing Canadians of a labelling update for the prescription drug Cipralex (the brand name of the drug escitalopram) regarding a dose-related risk of abnormal heart rhythms. Cipralex is used to treat depression and belongs to a family of drugs known as Selective Serotonin Reuptake Inhibitors (SSRIs).

Clinical trial data has shown that Cipralex can cause electrical changes in the heart known as QT interval prolongation. These electrical changes can lead to abnormal heart rhythms, which can be life threatening. The risk is dose-related, meaning that the risk increases as dosage increases.

A warning on the dose-related risk of QT interval prolongation has been added to the drug label for Cipralex, as well as revised prescribing and dosing recommendations:

- Cipralex **should not** be used in patients with a heart condition known as congenital long QT syndrome, or in patients with QT interval prolongation.
- Use of Cipralex is **discouraged** in patients who are also taking drugs that prolong QT interval or that decrease electrolyte levels in the body. Examples of drugs that affect QT interval include: drugs used to treat heart rhythm problems, certain antipsychotics, certain antidepressants, opioid painkillers and certain drugs used to treat infections. Examples of drugs that may affect electrolyte levels include: diuretics (water pills) and laxatives (including enemas).
- 10 mg per day is the maximum recommended dose for patients who:
  - are 65 years of age or older, or
  - have liver problems, or
  - are taking the heartburn drugs omeprazole or cimetidine which can increase the blood level of Cipralex.

20 mg per day is still the **maximum** recommended dose for most other patients.

http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43423a-eng.php

Remember This?

Health Canada Santé Canada

The concomitant use of <brand name> with another QT/QTc-prolonging drug is <contraindicated/discouraged>. Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- *Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide);*
- *Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide);*
- *Class 1C antiarrhythmics (e.g., flecainide, propafenone);*
- *antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone);*
- *antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline);*
- *opioids (e.g., methadone);*
- *macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus);*
- *quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin);*
- *pentamidine;*
- *antimalarials (e.g., quinine, chloroquine);*
- *azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);*
- *domperidone*
- *5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., dolasetron, ondansetron);*
- *tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib);*

http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43423a-eng.php

Challenges for Clinicians

- Poor quality evidence is difficult to apply to our patients
- Prevalence is low enough that studies need to be longer and bigger
  - Hence we need to rely on post-marketing analysis years after approval
- Study population lack multiple risk factors like we see today
  - Post marketing and RCT before approval didn't include multiple QTc prolonging drugs like we see today or other risk factors
- Very difficult to capture QTc prolongation on ECG before they present in torsades, V tach, V fib or arrest
  - Variability throughout the day

Challenges for Clinicians

- "QTc risk" is the most common flag in Computerized Physician Order Entry (CPOE) EMR programs for hospitalized patients
- It's the number 2 reason for drug relabeling next to LFT elevation in the last 5 years
- There's currently no risk stratification approach built into these programs that can give us summation of the risk
- Ethically
- Treating a value in an otherwise asymptomatic patient (unless SOB) is also difficult for balancing risk and benefits

Why do we care about risk factors?

- It is important to keep in mind that the QT interval is simply a surrogate marker for the risk of TdP.

- The risk of TdP does not correlate linearly with the QT interval or the extent of QT-interval prolongation.

Why do we care about risk factors?

"Torsades de pointes is an adverse drug reaction that is highly dependent on the presence of risk factors, and drug-induced TdP is an extremely rare event in patients without any risk factors. Over 90% of patients who develop TdP have ≥1 risk factors, and 71% have ≥2 risk factors."

AHA 2010 Statement on QTc Prolongation

Modifiable Risk Factors for TdP For Hospitalized Patients

- Use of QT-prolonging drugs
- Concurrent use of more than 1 QT-prolonging drug
- Rapid infusion by intravenous route
- Drug-Drug Interactions (including hepatic metabolic inhibition)
- Hypokalemia, Hypomagnesemia, and Hypocalcemia
- Treatment with diuretics
- Impaired hepatic or renal drug metabolism (due to drugs)
- Sepsis

AHA 2010 Statement on QTc Prolongation

Non-Modifiable Risk Factors For Hospitalized Patients

- Congestive heart failure and LVH
- Myocardial infarction
- Sinus bradycardia, heart block, incomplete heart block with pauses, recent conversion from afib
- Advanced age (68 years)
- Female sex
- Impaired hepatic or renal drug metabolism (due to disease)
- Premature complexes leading to short-long-short cycles
- Congenital LQTS
- QTc > 500 ms

How do we put it all together?

How do we put it all together?

Risk Stratification and Managing Multiple Risks

Original Article

Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients

James E. Tisdale, PharmD; Heather A. Jaynes, MSN; Joanna R. Kingery, PharmD; Noha A. Mourad, MS; Tate N. Trujillo, PharmD; Brian R. Overholser, PharmD; Richard J. Kovacs, MD

Circ Cardiovasc Qual Outcomes 2013;6:479-87

Risk Stratification and Managing Multiple Risks

Risk Factors	Points
Age ≥68 y	1
Female sex	1
Loop diuretic	1
Serum K^+ ≤3.5 mEq/L	2
Admission QT_c ≥450 ms	2
Acute MI	2
≥2 QT_c-prolonging drugs	3
sepsis	3
Heart failure	3
One QT_c-prolonging drug	3
Maximum Risk Score	21

Risk Score Category	Risk Score
Low	<7
Moderate	7–10
High	≥11

Circ Cardiovasc Qual Outcomes 2013;6:479-87

Risk Stratification and Managing Multiple Risks

MAYO CLINIC

ORIGINAL ARTICLE

Institution-Wide QT Alert System Identifies Patients With a High Risk of Mortality

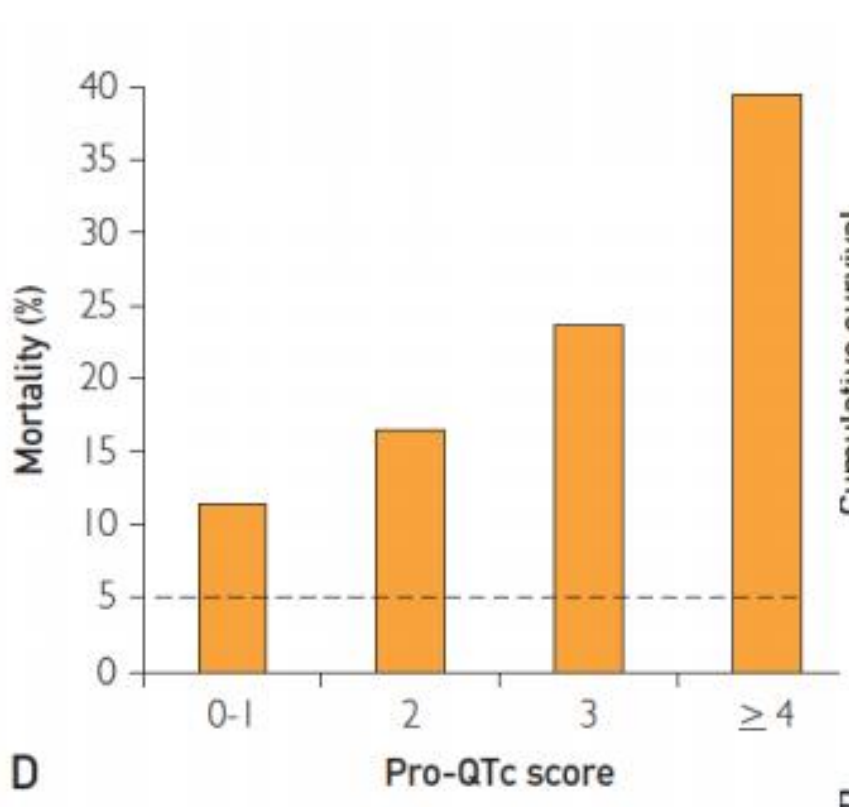
Kristina H. Haugaa, MD, PhD; J. Martijn Bos, MD, PhD; Robert F. Tarrell, MS; Bruce W. Morlan, MS; Pedro J. Caraballo, MD; and Michael J. Ackerman, MD, PhD

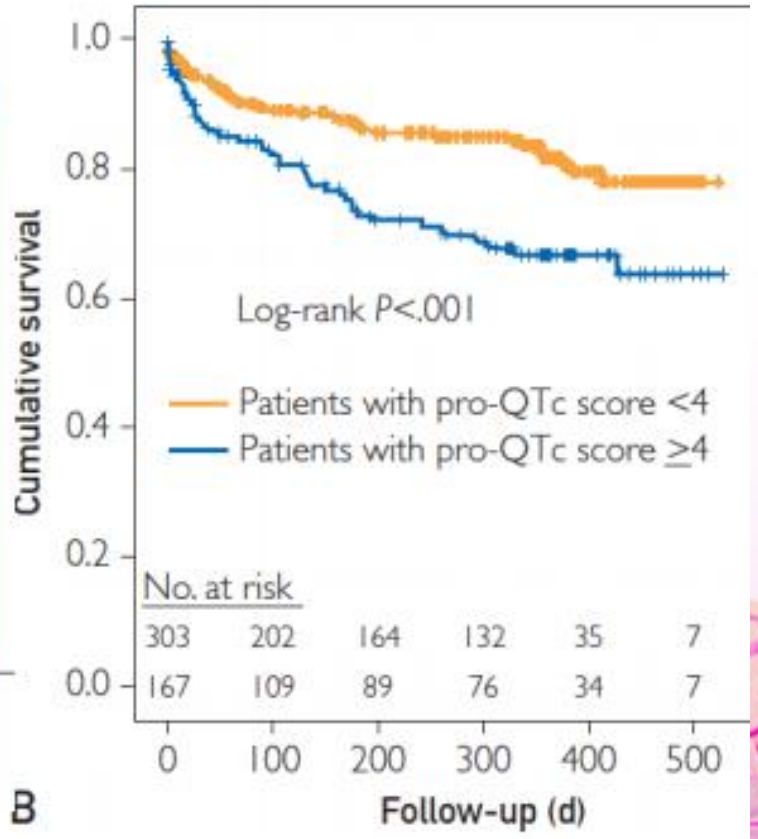
Mayo Clin Proc 2013;88(4):315-25

TABLE 1. QT-Prolonging Diagnoses and Conditions With a Pro-QTc Score of 1[a,b]

Diagnosis/condition	No. (%) of patients (n=470)
Acute coronary syndrome (≤7 d)	26 (6)
Anorexia nervosa or starvation	6 (1)
Bradycardia (heart rate <45 beats/min)	3 (<1)
Cardiac heart failure (EF <40%)	47 (10)
Diabetes mellitus (types 1 and 2)	88 (19)
Female sex	263 (56)
Hypertrophic cardiomyopathy	6 (1)
Hypoglycemia (documented and in the absence of diabetes)	1 (<1)
Intoxication with QT-prolonging drug (≤24 h)	8 (2)
Long QT syndrome	45 (10)
Pheochromocytoma	2 (<1)
Renal dialysis	25 (5)
Status after AF conversion (7 d after cardioversion, radio-frequency ablation, or the Maze procedure)	4 (1)
Status after cardiac arrest (24 h)	8 (2)
Status after syncope or seizure (24 h)	9 (2)
Stroke, SAH, head trauma (≤7 d)	16 (3)
Electrolyte disturbances	
Hypocalcemia (calcium <4.65 mg/dL)	131 (28)
Hypokalemia (potassium <3.6 mmol/L)	121 (26)
Hypomagnesemia (magnesium <1.7 mg/dL)	74 (16)
QT-prolonging medication	
≥1 Medication from CredibleMeds during the previous 7 d	310 (66)
Pro-QTc score ≥1	465 (99)

Pro-QTc Score





Mayo Clin Proc 2013;88(4):315-25

Pro-QTc Score

Strengths

- Developed to predict mortality
- Large database of hospitalized patients
- Accessible information

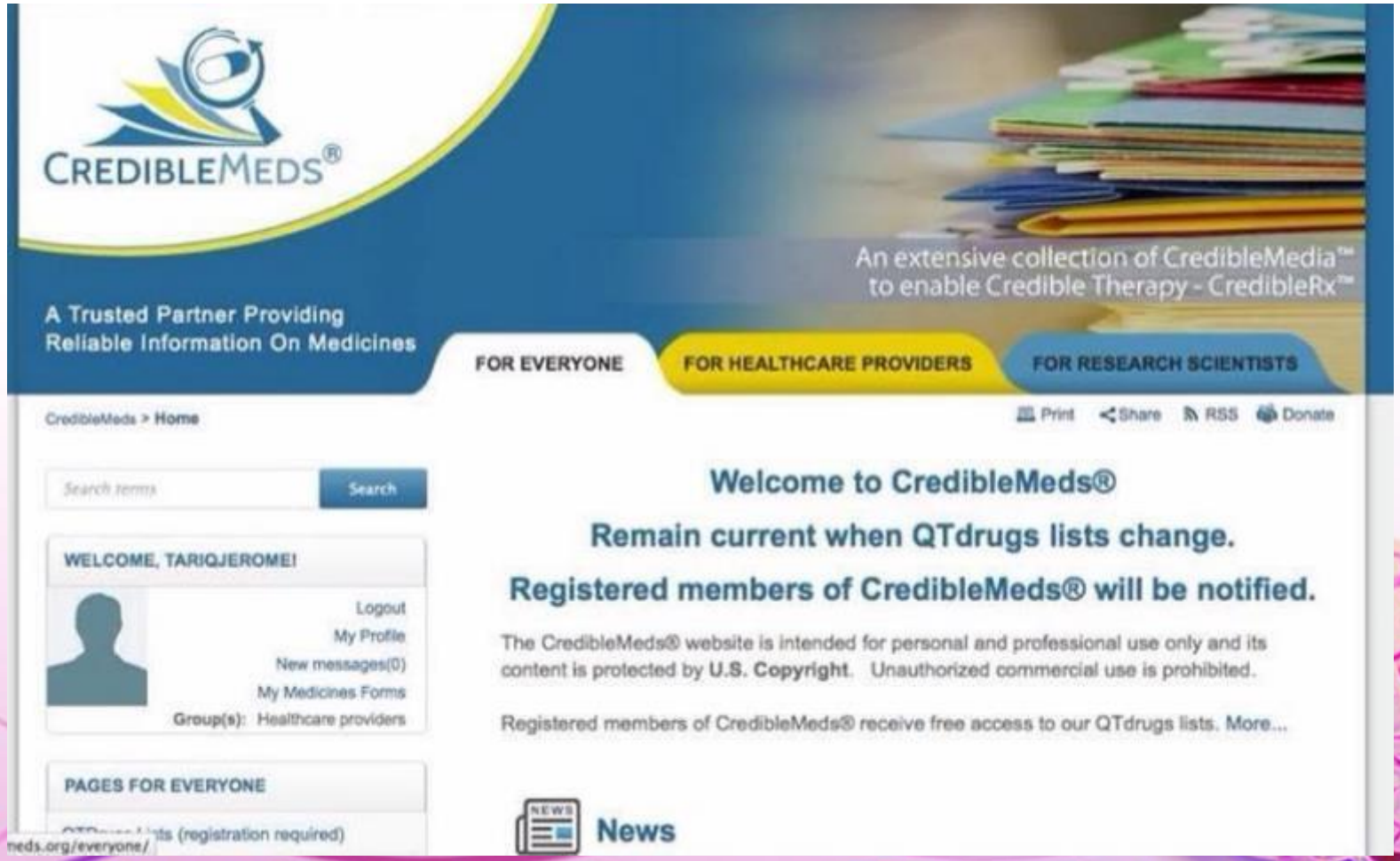
Limitations

- Only applicable to those with already prolonged QT interval
- Not validated
- Each risk factor considered equipotent

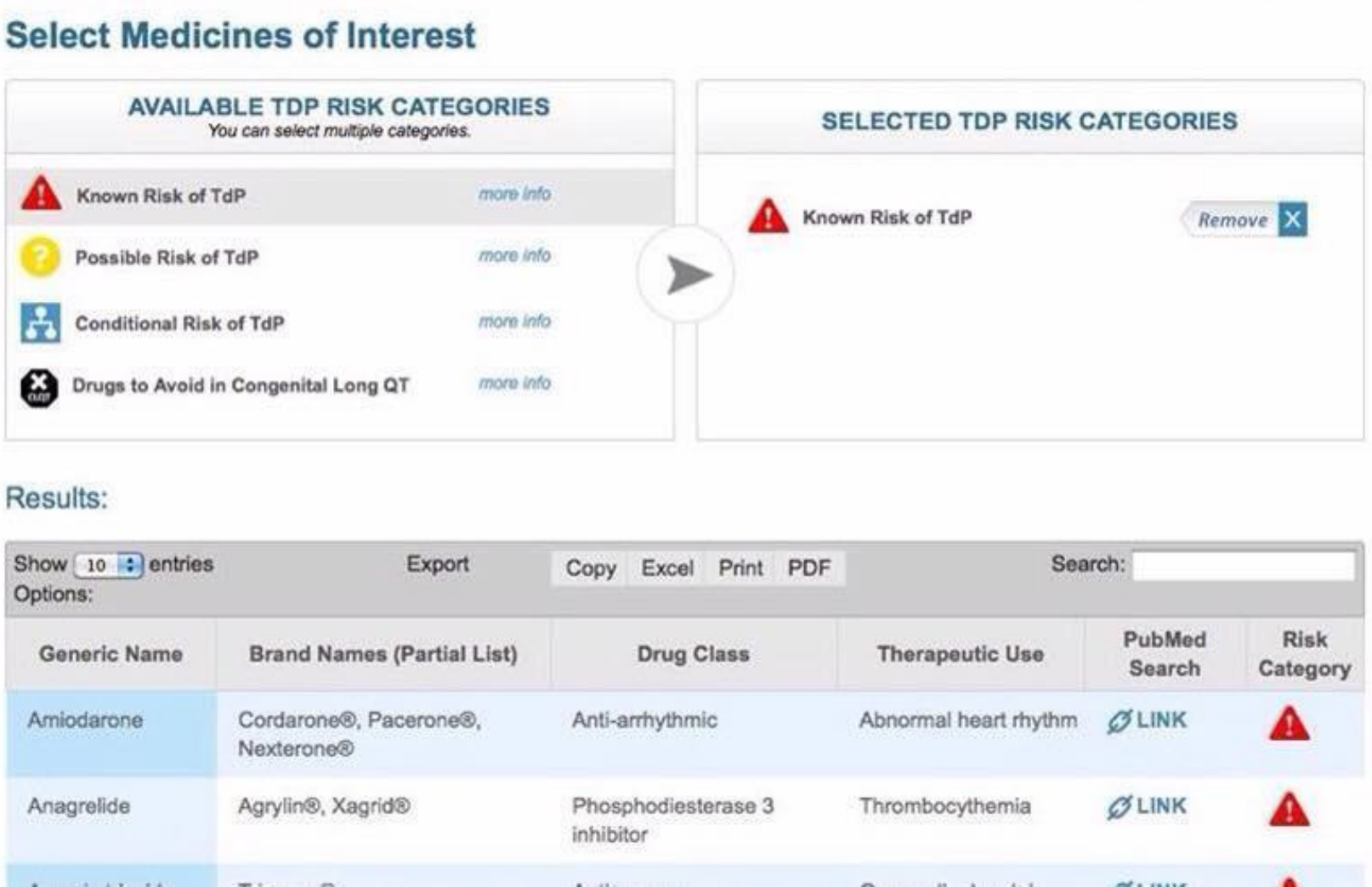
Drugs

- More than 50 commonly prescribed medications can lead to drug-induced QT prolongation…
- With so many drugs that can cause QT prolongation how do we go about stratifying risk of potential drug-induced QT prolongation?

Stratification of Risk Factors



Stratification of Risk Factors



Stratification of Risk Factors

Drugs with “Known risk of TdP”

- On the Canadian Market: 33
  - Ex: macrolides, flouroquinolones, Citalopram, Domperidone, Ondansetron, Sotalol, Amiodarone

Drugs with “Possible risk of TdP”

- On the Canadian Market: 52
  - Ex: Quetiapine, Lithium, Nortriptyline, Tolterodine, Verdenafil, Venlafaxine

Drugs with “Conditional Risk of TdP”

- On the Canadian Market: 26
  - Ex: Amitriptyline, fluoxetine, furosemide, HCTZ, Pantoprazole

High Risk QT Prolonging Medications

High Risk Medications	
Antiarrhythmics:	*Miscellaneous:*
• amiodarone • disopyramide • dofetilide • ibutilide • procainamide • quinidine • sotalol	• arsenic • cisapride • droperidol • thioridazine • pentamidine

Table 2: High risk QTc prolonging medications

2007. University of Illinois College of Pharmacy**Drug-induced QT prolongation (Part 2): a focus on select medications**.http://dig.pharm.uic.edu/faq/2013/Feb/faq2.aspx

Medium Risk QT Prolonging Medications

Medium Risk Medications		
Psychotropics: Phenothiazines: - chlorpromazine - fluphenazine - mesoridazine - perphenazine - trifluoperazine Atypicals - clozapine - paliperidone - quetiapine - risperidone - ziprasidone Others: - haloperidol - venlafaxine - pimozide	*Antimicrobials:* Quinolones (ranked from highest to lowest risk) • moxifloxacin • levofloxacin • ofloxacin Azoles: • voriconazole Antimalarials: • chloroquine • halofantrine • mefloquine Macrolides (ranked from highest to lowest risk) • clarithromycin • erythromycin • telithromycin	*Tyrosine kinase inhibitors:* • dasatinib • lapatinib • nilotinib • sunitinib *Miscellaneous:* - alfuzosin - flecainide - fosphenytoin - indapamide - methadone - ranolazine - tacrolimus - vardenafil

Table 3: Medium risk QTc prolonging medications

2007. University of Illinois College of Pharmacy**Drug-induced QT prolongation (Part 2): a focus on select medications**.http://dig.pharm.uic.edu/faq/2013/Feb/faq2.aspx

Low Risk QT Prolonging Medications

Low Risk Medications		
Psychotropics: SSRIs (ranked from highest to lowest risk): • citalopram • escitalopram • fluoxetine • paroxetine • sertraline TCAs • amitriptyline • clomipramine • desipramine • doxepin • imipramine • nortriptyline • protriptyline • trimipramine	*Antimicrobials:* Azoles (ranked from highest to lowest risk): • itraconazole • ketoconazole • Fluconazole Miscellaneous: • atazanavir • azithromycin • ciprofloxacin • SMX/TMP	*Antiemetics:* • dolasetron • palonosetron • ondansetron • granisetron *Miscellaneous:* • mexiletine • propafenone • solifenacin

Table 4: Low risk QTc prolonging medications

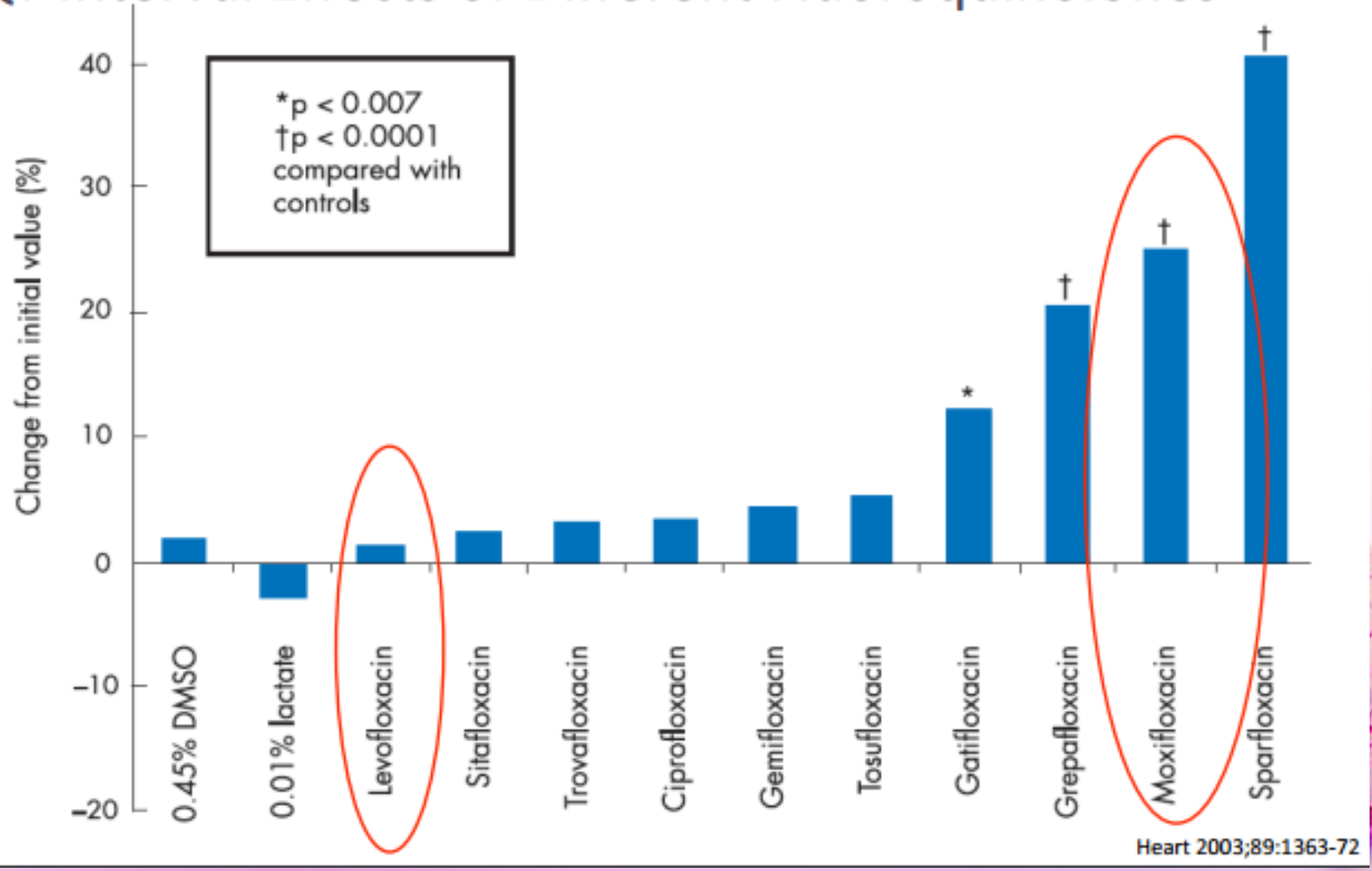
2007. University of Illinois College of Pharmacy**Drug-induced QT prolongation (Part 2): a focus on select medications**.http://dig.pharm.uic.edu/faq/2013/Feb/faq2.aspx

Antibiotics

- Fluoroquinolones and Macrolides with known risk of QT prolongation and TdP
  - Moxifloxacin, Levofloxacin, Ciprofloxacin, Azithromycin, Clarithromycin, Erythromycin
- Typical uses:
  - Pneumonia
  - Acute exacerbation of COPD
  - Urinary tract infection

Antibiotics

QT Interval Effects of Different Fluoroquinolones



Heart 2003;89:1363-72

Antibiotics

- Pneumonia/AECOPD
  - Consider if atypical coverage is warranted
    - If low risk of atypicals – beta lactam alone will provide good coverage of likely organisms (S.pneumoniae)
    - If risk of atypicals – doxycycline offers atypical coverage without causing QT prolongation. Consider doxycycline +/- beta lactam
  - If fluoroquinolone or macrolide is necessary, choose lowest risk of QT prolongation

Table 6. Most common etiologies of community-acquired pneumonia.

Patient type	Etiology
Outpatient	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* Respiratory viruses[a]
Inpatient (non-ICU)	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella* species Aspiration Respiratory viruses[a]
Inpatient (ICU)	*S. pneumoniae* *Staphylococcus aureus* *Legionella* species Gram-negative bacilli *H. influenzae*

Clin Infect Dis 2007;44:S27-72

Antibiotics

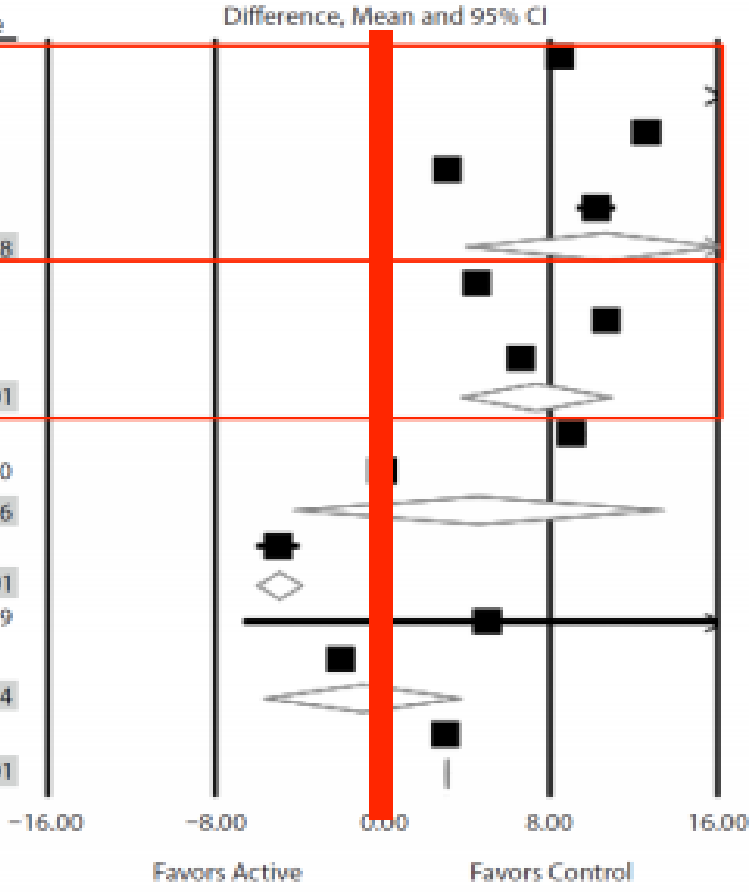
Urinary tract infections:

- E.coli is most common causative organism
- Nitrofurantoin, beta lactams and SMX-TMP not associated with QT prolongation

SSRIs

Figure 4. Effects of Individual Selective Serotonin Reuptake Inhibitors (SSRIs) on QTc When Compared to Placebo

SSRI	Study	N	Mean Difference in QTc, ms	Standard Error	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Citalopram	FDA-1[8]	120	8.50	0.09	8.33	8.67	< .001
Citalopram	FDA-2[8]	120	18.50	0.09	18.33	18.67	< .001
Citalopram	FDA-3 (modeled)[8]	120	12.60	0.09	12.43	12.77	< .001
Citalopram	Lesperance et al[25]	284	3.10	0.02	3.06	3.14	< .001
Citalopram	Slavicek et al[24]	52	10.20	0.48	9.25	11.15	< .001
Citalopram		696	10.58	3.39	3.93	17.23	.0018
Escitalopram	FDA-4[26]	120	4.50	0.09	4.33	4.67	< .001
Escitalopram	FDA-5[26]	120	10.70	0.09	10.53	10.83	< .001
Escitalopram	FDA-6 (modeled)[26]	120	6.60	0.09	6.43	9.74	< .001
Escitalopram		360	7.27	1.82	3.78	10.83	< .0001
Fluoxetine	Roose et al[19]	81	9.00	0.38	8.26	13.32	< .001
Fluoxetine	Strik et al[16]	54	0.00	0.31	−0.61	−3.95	1.0000
Fluoxetine		135	4.50	4.50	−4.32	13.32	.3176
Fluvoxamine	Robinson ad Doogan[12]	27	−5.00	0.53	−6.05	16.69	< .001
Fluvoxamine		27	−5.00	0.53	−6.05	−3.95	< .0001
Paroxetine	Edwards et al[17]	20	5.00	5.96	−6.69	3.68	.4019
Paroxetine	Nelson et al[21]	1,466	−2.00	0.00	−2.00	3.05	< .001
Paroxetine		1,486	−1.04	2.41	−5.76	3.68	.6654
Sertraline	Glassman et al[23]	369	3.00	0.02	2.95		< .001
Sertraline		369	3.00	0.02	2.95	3.05	< .0001



J Clin Psychiatry 2014;75(5):e441-9

Prokinetic Agents

Domperidone and pro-arrhythmic risk

Table 2: Case control studies of domperidone and VA or SCD

Study Population	Control Population	Number of Cases on Domperidone	OR (95% CI)
Electronic primary care record with 1 million patients [van Noord C, et al, 19]	Patients without VA or SCD	10 with domperidone 3 with domperidone > 30mg/24 h	3.72 (1.7.2–8.08) 11.4 (1.99–65.2)
Single institution database of cardiac arrest and SCD over 8 years [De Bruin ML, et al, 20]	Patients with cardiac arrest or SCD not on any QTc prolonging medications	140 cases on a QTc prolonging drug 7 cases on domperidone	4.7 (1.4–16)
Electronic database of approximately 1 million patients [Johannes CB, et al, 21]	Patients without VA or SCD with or without PPI	69 cases on domperidone	1.44 (1.12– 1.86) compared to PPI 1.59 (1.28– 1.98) compared to no exposure to either domperidone or a PPI

Antipsychotics

All antipsychotics have the ability to prolong the QT interval; however some have a higher risk of TdP than others.

Antipsychotics From highest to lowest QTc prolongation in ms

ANTIPSYCHOTICS	
Thioridazine	25-30
Ziprasidone	5-22
Pimozide	13
Clozapine	8-10
Iloperidone	9
Haloperidol	7
Quetiapine	6
Risperidone	0-5
Olanzapine	2
Asenapine	2-5
Aripiprazole	0

Gören JL, Dinh TA. Psychotropics and sudden cardiac death. R I Med J (2013). 2013;96(3):38-41.

Antipsychotics & QTc Prolongation

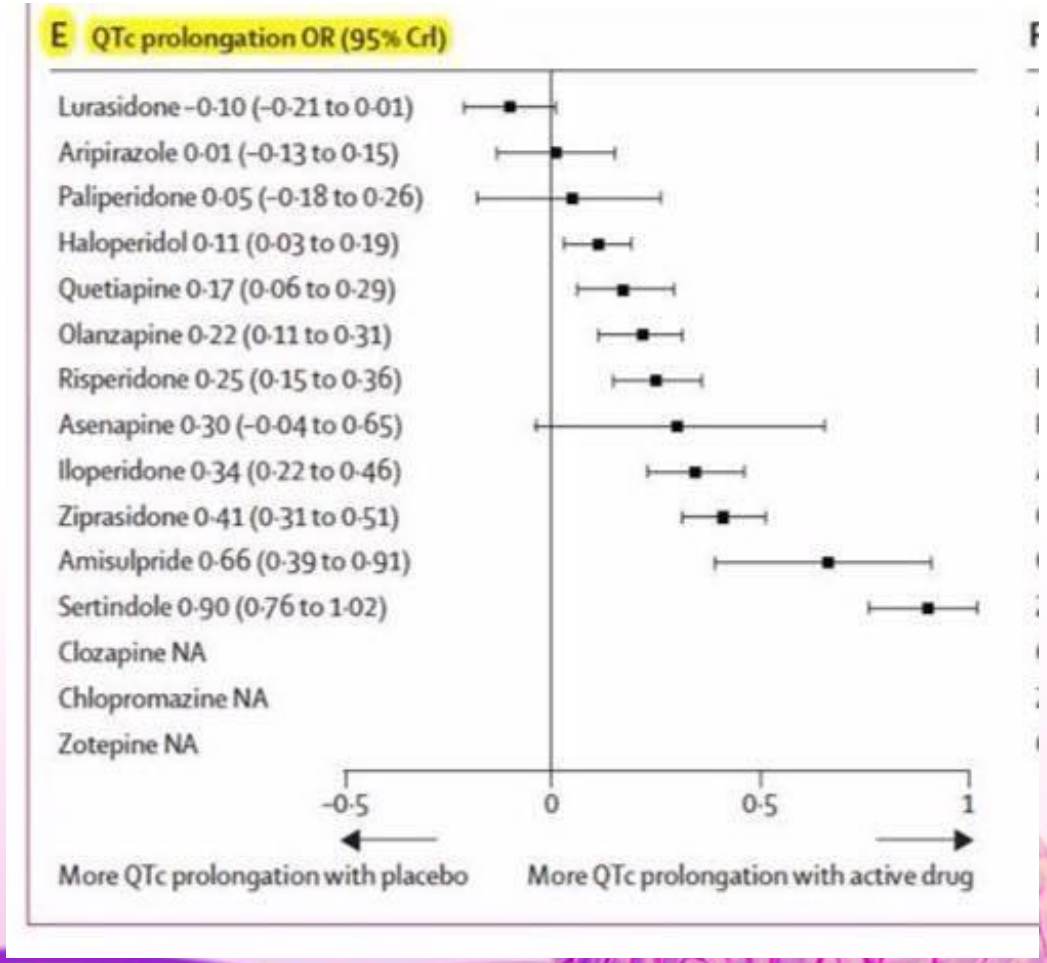
Drug	QTc Prolongation	QTc (Bazett) prolongation compared to baseline in ms (n)	Reported cases of TdP in FDA database
Ziprasidone	++	+9.7 (n=3095)	+++
Quetiapine	+++	-2 to +19.7 (n=312)	++
Risperidone	++	+2 to 11.6 (n=185)	+
Clozapine	++	+10 (n=13)	+
Paliperidone ER	0	+1.7 to 3.7 (n=1300)	Not Reported
Olanzapine	+	-4.5 to +8.4 (n=1342)	Not Reported
Aripiprazole	0	-4 to -3.5 (n=828)	Not Reported

Table 6:Relative risk of QTc prolongation, the ranges reported in the literature and the relative incidence of QTc prolongation in the literature.

Wenzel-Seifert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of torsades de pointes. Dtsch Arztebl Int. 2011; 108(41): 687-93.

Antipsychotics

Forest plot for effect sizes of antipsychotic drugs compared with placebo for QTc prolongation



Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-62.

Systematic Approach To Managing Potential QTc Prolongation

(AHA 2010) Indications for QTc monitoring

(1) Initiation of a drug known to cause TdP

(2) Overdose from potentially proarrhythmic agents

(3) New-onset bradyarrhythmias

(4) Severe hypokalemia or hypomagnesemia

(5) Intentional overdose situation

Systematic Approach To Managing Potential QTc Prolongation

(AHA 2010) Continuous QTc monitoring

Continuous QTc monitoring is appropriate for drugs deemed most at risk to cause not only QT prolongation but also TdP.

- After administration of an at-risk drug, if the QTc exceeds 500 ms or there has been an increase of at least 60 ms compared with the pre-drug baseline value
- How long QTc measurement should be continued depends on
  - Drug half-life or how long it takes for the drug to be eliminated from the body
  - How long it takes for the QTc to return to the baseline, and whether the ECG shows QT-related arrhythmias.

Systematic Approach To Managing Potential QTc Prolongation

Initiation of Drug with Risk of QTc prolongation or QTc > 500 ms or > 60ms increase

Risk assessment - the patient
What risk factors are present in the patient?
What are past ECG QTc intervals?

Risk assessment - the drug(s)
What are each drug and the overall risks of QT prolongation and TdP with?
Which of the patient's other medications are of concern? (Renal, hepatic, drug interactions)

What is my patient's Global risk, taking in consideration all risk factors?

Risk minimization
Address all modifiable risk factors (Potassium, Magnesium, Calcium)
Drugs: Within the same class, utilize drugs that carry the lowest risk of TdP
Consider alternative treatments with lower or no TdP-inducing potential
Use lower doses, Use other routes than IV, Consider drug-drug, liver, kidney interactions
Consider stopping drugs without indications, evaluate risk benefit of balance of drugs

Monitoring
ECG at baseline and after drug administration (12-24 hours)
Investigate if there is drug specific monitoring (Methadone, domperidone)
Continued risk factor monitoring minimization such as electrolyte disturbances dosage adjustments and drug interaction avoidance

ECG signs of TdP and Management

Recommended actions when ECG signs of impending TdP develop are to:

- Discontinue the offending drug
- Replace potassium IV
- Administer 2 g IV magnesium
- Consider temporary pacing to prevent bradycardia and long pauses, and transfer the patient to a hospital unit with the highest level of ECG monitoring surveillance where immediate defibrillation is available.

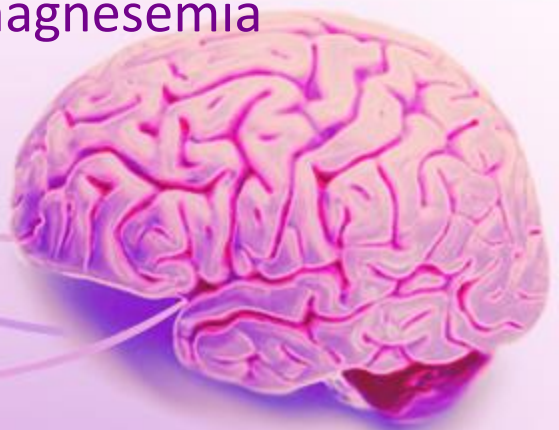
ECG signs of TdP and Management

- Repletion of potassium to supratherapeutic levels of 4.5 to 5 mmol/L may also be considered, although there is little evidence to support this practice (Class IIb, Level of Evidence: C).[34]

- An increase in heart rate to prevent pauses that may trigger TdP may be attempted with temporary transvenous atrial or ventricular pacing at rates >70 beats per minute.

Summary

- The ECG wave is constituted from the synchronous opening and closing of cardiac ion channels
- If you block the channels that cause electrical recovery of cardiac tissue, you get a QTc prolongation on the ECG
- Many unrelated drugs classes used in cardiac and non-cardiac condition cause QT prolongation
- Start to monitor more closely when QTc progressively increases beyond 450 ms
  - Really get worried if in hypokalemia and hypomagnesemia



Summary

- QT prolongation leading to TdP is a relatively rare potential side effect of many drugs.
- Most common affiliated classes of drugs include: antiarrhythmics, antidepressants, antibiotics, and antipsychotics.
- It is important to consider patient risk factors as well as specific properties of the drugs.
  - i.e. patients with 2 or more risk factors and 2 or more drugs with the risk of TdP