# What a QT'ie! What We Know About Drug-induced QT Prolongation in Children

Brian K. Brown, Pharm.D., BCPS, BCPPS
CVICU/Cardiac Transplant Pharmacist
Johns Hopkins All Children's Hospital
St Petersburg, Florida

Gabriella Blyumin, Pharm.D., BCPPS
PICU Clinical Pharmacy Specialist
Nicklaus Children's Hospital
Miami, Florida

Bernard Ryan Lee, Pharm.D., BCPS, BCPPS
PGY2 Pediatrics Residency Program Director
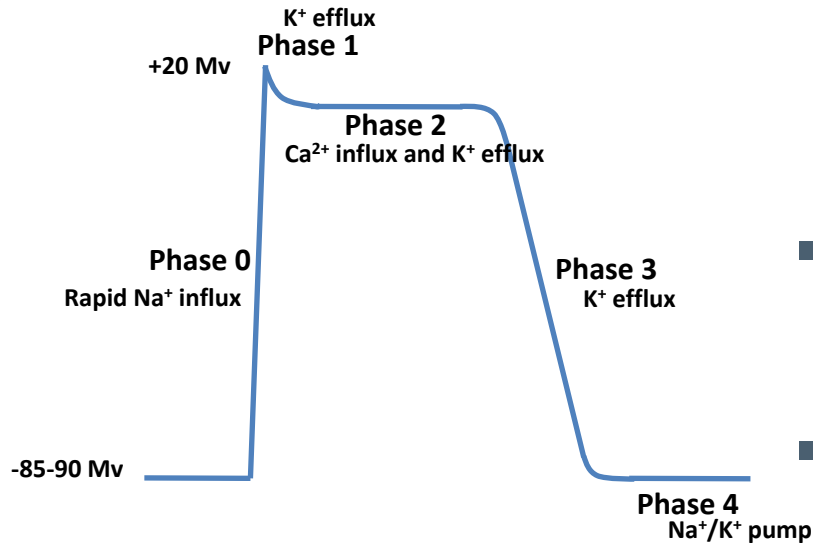Johns Hopkins All Children's Hospital
St Petersburg, Florida

# Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

# Objectives

- Differentiate the common etiologies of drug-induced QT prolongation in children.

- Analyze the current available literature regarding the significance and impact of combination drug-induced QT prolongation in children.

- Compare potential preventative tools and strategies to identify, risk stratify, and prevent drug-induced QT prolongation in children.

# Cardiac Action Potential



K$^+$ efflux
**Phase 1**

+20 Mv

**Phase 2**
Ca$^{2+}$ influx and K$^+$ efflux

**Phase 0**
Rapid Na$^+$ influx

**Phase 3**
K$^+$ efflux

-85-90 Mv

**Phase 4**
Na$^+$/K$^+$ pump

- Transmembrane potential of cardiac cells is determined by concentrations of several electrolytes

- Ions move across the lipid cell membrane through ion-specific channels

- Unable to generate a new action potential during the refractory period

Katzung BG, Trevor AJ. McGraw Hill Professional; 2014.

# Components of ECG
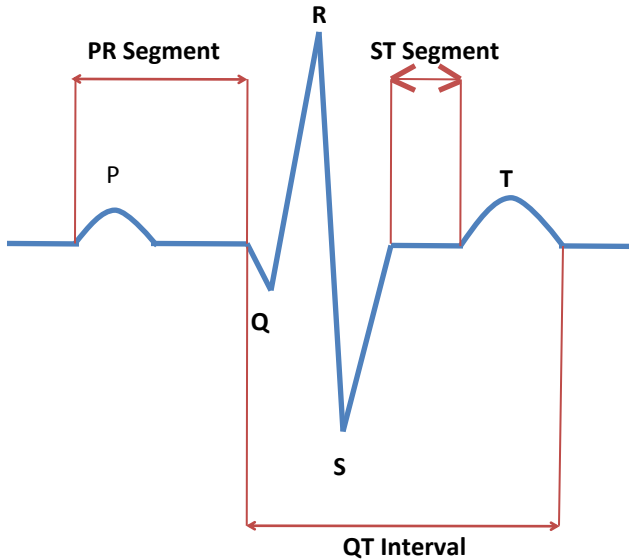


- An ECG is the manifestation of the depolarization and repolarization of the heart

- P wave = atrial depolarization

- PR segment = conduction from the atria to ventricles

- QRS interval = ventricular depolarization

- T wave = ventricular repolarization

Katzung BG, Trevor AJ. McGraw Hill Professional; 2014.

# ECG and Action Potential
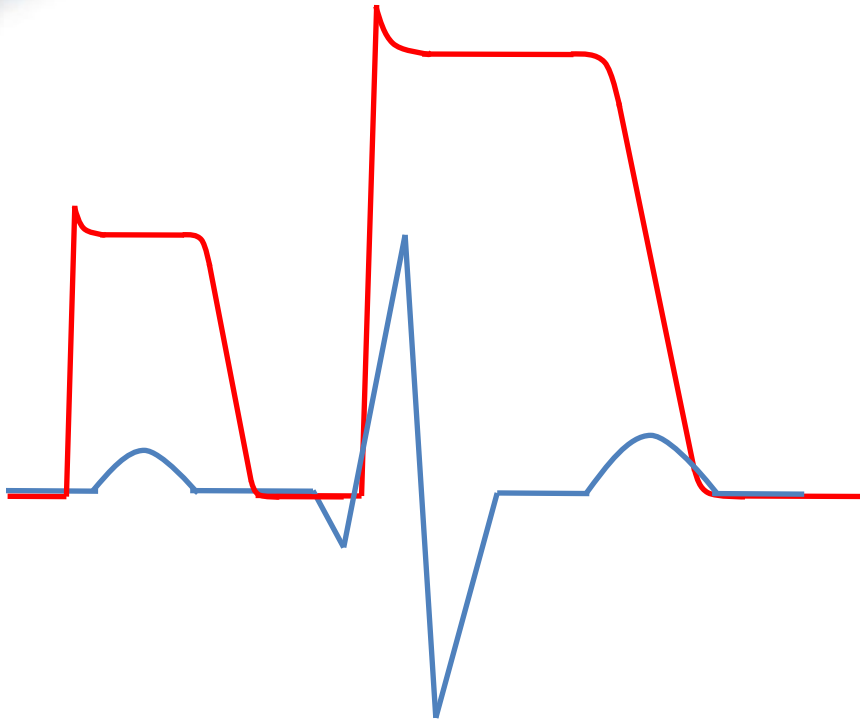


- P wave = atrial depolarization

- QRS interval = ventricular depolarization

- T wave = ventricular repolarization

# QT/QTc Interval

- Measure of total duration of ventricular activation and recovery
- Begins at QRS complex and ends at T wave
- Corrected QT (QTc) formulas: Bazett, Fridericia, Framingham, Hodges
  - Shared limitations:
    - QT does not adapt to changes in heart rate immediately
    - No studies have investigated the correlation between QTc and patients outcomes

Am Heart J. 2007 Jun;153(6):891-9.
Heart. 2003 Nov;89(11):1363-72.

# QTc Values

| | 1-15 years of age | Adult Males | Adult Females |
|---|---|---|---|
| Normal | <440 | <430 | <450 |
| Borderline | 440-460 | 430-450 | 450-470 |
| Prolonged (top 1%) | >460 | >450 | >470 |

Heart. 2003 Nov;89(11):1363-72.

# Contributory Factors

- Gender
- **Genetic predispositions**
- Cardiac structural abnormalities
- Electrolyte abnormalities
- Altered oral intake
- Hypothyroidism
- Hypothermia
- HIV infection
- **Drug interactions**

Am Heart J. 2007 Jun;153(6):891-9.
Heart. 2003 Nov;89(11):1363-72.

# Etiologies of QT prolongation

- Effects on ion channels

- Genetic involvement

- Medication characteristics and drug interactions

# Ion Channels

- Net decrease in repolarization current (increased inward current or reduced outward current)

- Myocardial repolarization is primarily mediated by efflux of potassium ions

  - Two important ion channels include: $I_{Kr}$, $I_{ks}$
- Inward sodium currents (sodium-calcium exchanger, sodium channel)
- Inward calcium currents (L-type calcium channels)

Am Heart J. 2007 Jun;153(6):891-9.
Heart. 2003 Nov;89(11):1363-72.
Curr Opin Cardiol. 2007 Jan;22(1):39-43.

# Early Afterdepolarization

- Depolarizing oscillations in membrane voltage during phases 2 and 3 of the action potential

- His-Purkinje network and mid ventricular myocardium (M cells)

- May result in ectopic beats if occurring in a large enough region of the heart
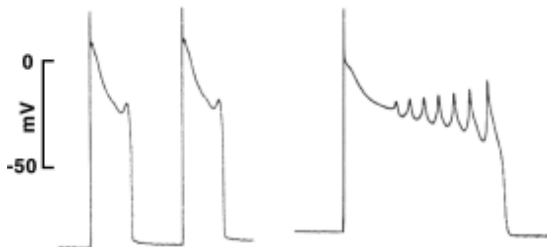
- Inward depolarizing currents, most likely L-type calcium channels or sodium-calcium exchange current

Am Heart J. 2007 Jun;153(6):891-9.
Heart. 2003 Nov;89(11):1363-72.
Curr Opin Cardiol. 2007 Jan;22(1):39-43.

# Genetic Involvement

- KCNQ1 – encodes the pore-potassium channel subunit (Kv7.1)

  - KCNE1 –function modifying subunit

- **KCNH2 / HERG**- encodes the Kv11.1 potassium channel

  - Pore-forming subunits of channels

- SCN5A – cardiac sodium channels

# KCNH2 / HERG Gene

- Encodes the Kv11.1 potassium channel
  - Major drug target in drug induced QT prolongation
- Binding occurs in the pore
- Many classes of medications interact with Kv11.1
  - Wide interior
  - Multiple aromatic groups

J Physiol. 2016 May 1;594(9):2459-68.
Proc Natl Acad Sci U S A. 2000 Oct 24;97(22):12329-33.

# Medication & Interactions

- Medication properties
  - Medication specific cause
  - Dose-dependent manner
- Interactions
  - Medications metabolized by CYP3A4
  - Hepatic/Renal dysfunction
  - Decreased elimination

Am Heart J. 2007 Jun;153(6):891-9.
Heart. 2003 Nov;89(11):1363-72.

# What subunit that encodes a potassium channel is the major target in drug induced QT prolongation?

A. Kv11.1

B. SCN5A

C. Kv7.1

D. KCNQ1

# ADECA

- Adverse Drug Event Causality Analysis
  - Model for evaluation
  - Bradford Hill criteria
  - Thee categories of certainty

# Categories of Certainty

- Known risk of Torsades de pointes (TdP)

- Possible risk of TdP

- Conditional risk of TdP



Drug Saf. 2017 Jun;40(6):465-474.

Drug Saf. 2017 Jun;40(6):465-474.
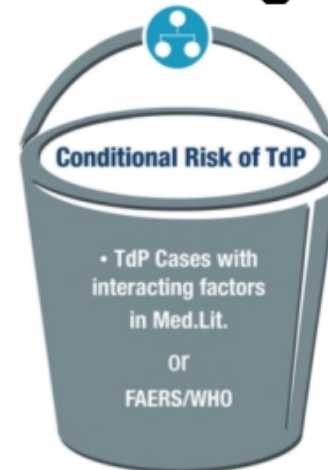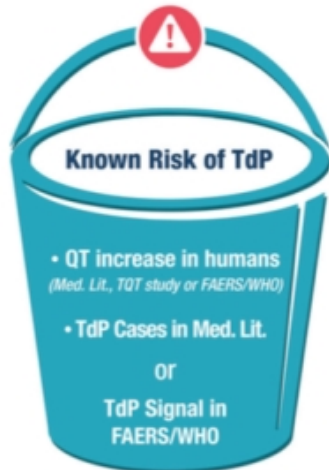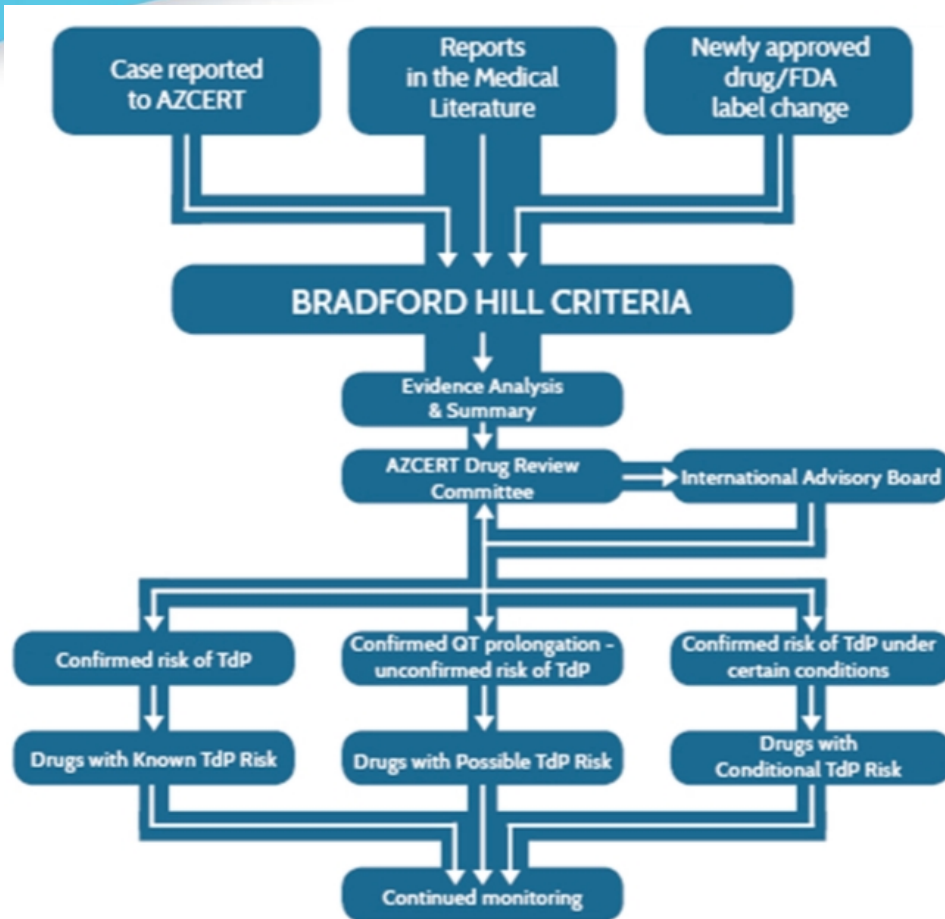
# Number of Medications with Risk of QT Prolongation
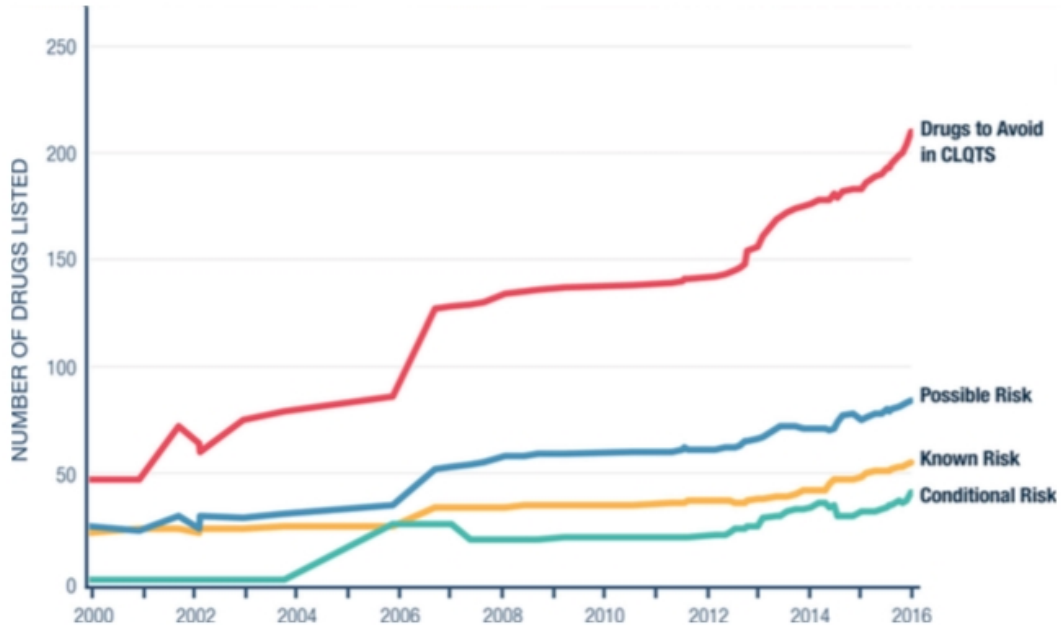
# What literature exists regarding drug induced QT prolongation in children?

# Pediatric Literature Review

- QT prolongation or TdP associated with therapeutic doses in children
  - Crediblemeds.org → PubMed Search → 🔗 LINK
    - Case reports
    - Observational cohorts/cross sectional studies
    - Retrospective analyses
    - Systematic reviews

# Medication Classes

- **Psychotropics**
  - Antidepressants
  - Antipsychotics
  - ADHD medications
- **Antimicrobials**
  - Antibiotics
  - Antifungals

- **Anti-emetics**
- Prokinetics
- Antiarrhythmics
- **Anesthetics**
- Miscellaneous
  - **Methadone**
  - Doxapram

# Antidepressants

| Class | Agent | Risk Category | Pediatric Data Available |
|---|---|---|---|
| **Tricyclic antidepressants (TCAs)** | **Desipramine Imipramine Clomipramine** Nortriptyline | Possible | Case reports (>5) Observational cohort Systematic review |
| | Amitriptyline | Conditional | Secondary analysis from RCT |

# Antidepressants

| Class | Agent | Risk Category | Pediatric Data Available |
|-------|-------|---------------|--------------------------|
| **SSRIs** | Citalopram Escitalopram | **Known** ⚠️ 🛑 | Retrospective chart review Observational cohort |

# Antidepressants

| Class | Agent | Risk Category | Pediatric Data Available |
|-------|-------|---------------|--------------------------|
| **SNRI** | Venlafaxine | **Possible** | Observational cohort |

# Antidepressants

| Class | Agent | Risk Category |
|-------|-------|---------------|
| **SSRIs** | Sertraline<br>Paroxetine<br>Fluoxetine<br>Fluvoxamine | Conditional |

# Antidepressants

| Study | Methods | Results |
|-------|---------|---------|
| **Uchida M, et al 2015** | Retrospective chart review<br>n = 297 children prescribed **antidepressant** with EKG within 14-90 days of Rx | Highest mean QTc associated with **escitalopram**: 436 ms<br><br>Significantly lower QTC associated with sertraline: 10.6 ms less than other drugs |

# Antidepressants

| Study | Methods | Results |
|-------|---------|---------|
| **Uchida M, et al 2017** | Observational cohort of 49 children (6 - 17 years old) treated with **non-TCA antidepressants**<br><br>Evaluated effects between dose and cardiac parameters (QTc, EKG, BP) | No associations between total or weight-corrected dose of any antidepressant and any cardiac parameter |

# Antipsychotics

| Class | Agent | Risk Category | Pediatric Data Available |
|---|---|---|---|
| **Second Generation Anti-Psychotics (SGAs)** | Risperidone | **Possible** ❓ ⊗CLQT | Meta analysis<br>Observational cohort study (3)<br>Prospective cross-sectional (1)[c] |
| | Aripiprazole | **Possible** ❓ ⊗CLQT | Meta analysis<br>Observational cohort study (2)<br>Prospective cross-sectional (1) |

[c] denotes concomitant QT-prolonging medications described

# Antipsychotics

| Class | Agent | Risk Category | Pediatric Data Available |
|-------|-------|---------------|--------------------------|
| **SGA** | Paliperidone | **Possible** | Meta analysis |

# Antipsychotics

| Class | Agent | Risk Category |
|-------|-------|---------------|
| SGAs | Quetiapine Olanzapine Ziprasidone | **Conditional** |

# Antipyschotics

| Class | Agent | Risk Category | Pediatric Data Available |
|---|---|---|---|
| First Generation Anti-Psychotics (FGAs) | Haloperidol | **Known** ⚠️ ⊗CLQT | Meta analysis Prospective randomized |
| | Chlorpromazine | **Known** ⚠️ ⊗CLQT | Nested case-control |

# Antipsychotics

| Study | Methods | Results |
|-------|---------|---------|
| **Jensen K, et al 2015** | Meta analysis evaluating effects of **FGAs and SGAs** on QTc<br><br>N = 5,423 children/adolescents; mean age 12.8 ± 3.6 years | Risperidone (+1.68 ms) and ziprasidone (+8.74 ms) significantly **increased** QTc<br><br>Aripiprazole significantly **decreased** QTc (-1.44 ms) |

# Antipsychotics

| Study | Methods | Results |
|-------|---------|---------|
| **Alda J, et al 2016** | Prospective cohort evaluating effects of **risperidone**, **olanzapine** and **quetiapine** effects on QT<br><br>N = 216 children and adolescents; mean age 14.27 ± 3.09 years | No differences in QTc rates between any SGA<br>No QTc >500 ms<br>9 patients with QTc >450 ms |

J Child Adolesc Psychopharmacol. 2016 ;26(5):449-57.

# Antipsychotics

| Study | Methods | Results |
|-------|---------|---------|
| **Palanca-Maresca I, et al 2017** | Observational cohort evaluating children treated with **SGA antipsychotics**<br><br>N = 101 children/adolescents; mean age 11.5 years (range: 4-17 yrs) | 4 aripiprazole (8.7% of exposed) and 3 risperidone (5.7% of exposed) patients with abnormal EKGs (QTc >450 ms) No QTc >500, no TdP or arrhythmia |

# Antipsychotics

| Study | Methods | Results |
|-------|---------|---------|
| **Correll C, et al 2011** | Prospective observational study evaluating ECG changes associated with **ziprasidone**<br><br>N = 29 children, mean age 15.3 ± 2.9 years | 5 patients with peak QTc duration > 500 ms<br><br>Baseline-to-peak QTc duration increased significantly by 22.9 ms<br><br>No TdP or arrhythmia |

# ADHD Medications

| Class | Agent | Risk Category | Pediatric Data Available |
|-------|-------|---------------|--------------------------|
| **NE Reuptake Inhibitor** | Atomoxetine | **Possible** | Case report (2)<br>Clinical trials - pooled analyses<br>Observational cohort (2) |

# ADHD Medications

| Class | Agent | Risk Category |
|---|---|---|
| **Stimulants** | Methylphenidate<br>Dexmethylphenidate<br>Lisdexamfetamine<br>Amphetamine | Avoid in CLQT  |

# ADHD Medications

| Study | Methods | Results |
|---|---|---|
| **Sert A, et al 2012** | Prospective observational study evaluating ECG changes associated with **atomoxetine**<br><br>N = 40 children; mean age 8.6 ± 2.3 years | Maximum QT interval increased significantly compared to baseline (p = 0.046)<br><br>QTc not significantly increased from baseline (+5 ms) |

# ADHD Medications

| Study | Methods | Results |
|-------|---------|---------|
| **Tanidir I, et al 2015** | Prospective observational study evaluating ECG and Holter monitor changes associated with **atomoxetine**<br><br>N = 41 children; mean age 10 ± 2.3 years in ADHD group vs. 11 ± 3.5 years in control group | No statistically significant change in QT, QTc, QT interval dispersion<br><br>Statistically significant increase in HR |

Pediatr Int. 2015;57(6):1078-85.

# Antimicrobials

| Class | Agent | Risk Category | | | Pediatric Data Available |
|---|---|---|---|---|---|
| Macrolide Antibiotics | Clarithromycin | **Known** | ⚠️ | ⊗CLQT | Case report<br>Observational cohort |
| | Azithromycin | **Known** | ⚠️ | ⊗CLQT | Observational cohort[c] (2)<br>Case report |
| | Erythromycin | **Known** | ⚠️ | ⊗CLQT | Observational cohort[c]<br>Case report (2) |

# Macrolide Antibiotics

| Study | Methods | Results |
|-------|---------|---------|
| **Germanakis I, et al 2006** | Observational cohort evaluating effect of **clarithromycin** 15 mg/kg BID on QTc interval<br><br>N = 28 children; mean age 7.5 years (0.5 – 14 years) | Average increase in QTc 24 h after administration: 22 ms (-4 – 75 ms, p < 0.001)<br><br>7 patients (25%) with QTc >440 ms, 1 QTc >460 ms<br>No arrhythmias |

# Macrolide Antibiotics

| Study | Methods | Results |
|-------|---------|---------|
| **Lenehan P, et al 2016** | Observational cohort evaluating effect of chronic **azithromycin** on QTc interval<br><br>N = 56 pediatric CF patients; 33 children, 23 adolescents | Average change in QTc: 1 ± 18 ms Adolescent males significantly increased QTc: + 12 ms, p = 0.047 No patients with clinically prolonged QTc, 4 with borderline prolonged QTc >440 ms |

# Macrolide Antibiotics

| Study | Methods | Results |
|-------|---------|---------|
| **Espadas D, et al 2016** | Observational cohort evaluating effect of chronic **azithromycin** 10 mg/kg TIW on QTc interval<br><br>N = 86 pediatric patients with chronic lung disease; mean age 6 years | Mean duration of treatment: 5 months<br><br>Mean QTc: 381.5 ms (326 – 430 ms)<br><br>No arrhythmias |

# Fluoroquinolone Antibiotics

| Class | Agent | Risk Category | | | Pediatric Data Available |
|---|---|---|---|---|---|
| Fluoroquinolone Antibiotics | Ciprofloxacin | **Known** | ⚠️ | ✖CLQT | Case report |
| | Levofloxacin | **Known** | ⚠️ | ✖CLQT | None |
| | Moxifloxacin | **Known** | ⚠️ | ✖CLQT | None |

# Fluoroquinolone Antibiotics

| Study | Methods | Results |
|---|---|---|
| **Knorr J, et al 2008** | Case report | Treated with **ciprofloxacin** IV 400 mg BID |
| | 16-year old male with acute Crohn's disease flare | Developed bradycardia and discomfort within 48 hours, QTc: 486 mS |
| | No known risk factors for long QT syndrome | Upon discontinuation, QT interval decreased to 368 ms within 7 days |

# Antimicrobials

| Class | Agent | Risk Category | | | Pediatric Data Available |
|-------|-------|---------------|--|--|--------------------------|
| Azole Antifungals | Fluconazole | **Known** | ⚠️ | ⊗ CLQT | Case report<br>Observational cohort[c] |
| | Voriconazole | **Conditional** | 🔗 | ⊗ CLQT | Case report[c]<br>Case series[c] |

# Antimicrobials

| Class | Agent | Risk Category | | Pediatric Data Available |
|---|---|---|---|---|
| **Antifungal/ antiprotozoal** | Pentamidine | **Known** | ⚠️ ⊗CLQT | Case report (2) |

# Azole Antifungals

| Study | Methods | Results |
|-------|---------|---------|
| **Esch J, et al 2008** | Case report<br><br>11 year old male with neurofibromatosis, perforated gastric volvulus, sepsis<br><br>No cardiac history or baseline EKG | Given **fluconazole** 150 mg IV BID<br>Day 11: recurrent PVCs with normal QTc (422 ms)<br>Day 13: ventricular bigeminy and tachycardia, QTC 467 ms<br>Day 14: ventricular bigeminy, pulseless monomorphic vtach, **TdP,** QTc: 490 ms |

Pediatr Cardiol. 2008 Jan;29(1):210-3.

# Azole Antifungals

| Study | Methods | Results |
|-------|---------|---------|
| **Alkan Y, et al 2004** | Case report<br><br>15 year old female with ALL and *Fusarium* infection<br><br>Baseline EKG normal | Treated with **voriconazole** 6 mg/kg IV and PO BID; on concomitant ciprofloxacin, SMZ/TMP, dexamethasone, diphenhydramine, and ondansetron<br>Day 22 of voriconazole: patient developed bradycardia, QTc prolongation (570 ms), asymptomatic TdP<br>Upon re-challenge, QTc prolongation recurred |

Clin Infect Dis. 2004;39(6):e49-52.

# Azole Antifungals

| Study | Methods | Results |
|-------|---------|---------|
| **Aypar E, et al 2011** | Case series | Case 1: 15 yo male with fungal endocarditis; baseline QTc 400 ms, developed TdP with one dose of **voriconazole** 6 mg/kg, QTc 500 mS, no concomitant meds<br><br>Case 2: 12 yo female with ALL and pulmonary aspergillosis on **voriconazole** and **ciprofloxacin**, developed ventricular bigeminy and trigeminy with QTc 570 mS |

# Pentamidine

| Study | Methods | Results |
|-------|---------|---------|
| **Miller H, 1993** | Case report<br><br>7 month old with congenital HIV and *Pneumocystis*<br><br>Baseline EKG normal | Treated with IV **pentamidine** isothionate 4 mg/kg/day<br>During 3rd dose, patient became pulseless, TdP on EKG; found to be hypokalemic and hypomagnesemic<br>Electrolytes corrected, infusion discontinued, no further clinical instability |

Pediatr Infect Dis J. 1993;12(8):694-6.

# Pentamidine

| Study | Methods | Results |
|-------|---------|---------|
| **Harel Y, et al 1993** | Case report<br><br>11 year old boy with ALL, *Pneumocystis* and *Candida* respiratory infections | Treated with IV **pentamidine** isothionate 4 mg/kg/day; day 3 QTc: 430 ms with HR 110 bpm<br>Day 4: QTc prolongation to 490 ms, then 620 mS with HR 70 bbpm → subsequent asymptomatic ventricular bigeminy and intermittent TdP |

# Antiemetic Agents

| Agent | Risk Category | | | Pediatric Data Available |
|-------|---------------|---|---|--------------------------|
| Ondansetron | **Known** | ⚠️ | ❌CLQT | Observational cohort (4)[c]<br>Case report (5+)[c]<br>Systematic review<br>Prospective interventional (3)[c] |
| Granisetron | **Possible** | ❓ | ❌CLQT | Prospective randomized |
| Palonosetron | **Possible** | ❓ | ❌CLQT | None |

# Antiemetic Agents

| Agent | Risk Category | | | Pediatric Data Available |
|-------|---------------|---|---|--------------------------|
| Chlorpromazine | **Known** | ⚠️ | ⬛ CLQT | Nested case-control |
| Promethazine | **Possible** | 🟡? | ⬛ CLQT | None |

# Antiemetic Agents

| Agent | Risk Category | Pediatric Data Available |
|-------|---------------|--------------------------|
| Metoclopramide | **Conditional** | Prospective randomized |

# Antiemetic Agents

| Study | Methods | Results |
|---|---|---|
| **Moeller J, et al 2016** | Observational cohort evaluating rate of ventricular arrhythmias within 24 hours of **ondansetron** N = 37,794 patients age 1-19 years | Average ondansetron dose 0.13 mg/kg 7 children with ventricular arrhythmia: **0.003% annual incidence**, all with major cardiac diagnoses; prolonged QT in 3 patients, TdP in 1 2 with other QT prolonging meds: tacrolimus, nicardipine |

# Antiemetic Agents

| Study | Methods | Results |
|-------|---------|---------|
| **Trivedi S, et al 2016** | Retrospective observational cohort evaluating effects of **ondansetron** on QT interval in PICU patients<br><br>N = 107 pediatric patients, mean age 10.5 ± 4.8 years | Overall incidence of QTc > 460 ms: 40%<br>QTc > 500 ms in 11% of administrations<br>Mean difference from baseline: 5.2 ms<br>No episodes of TdP<br><br>Groups with higher QTc associated significantly with electrolyte abnormalities |

# Antiemetic Agents

| Study | Methods | Results |
|-------|---------|---------|
| **Buyukavci M et al, 2005** | Prospective randomized trial evaluating effects of **granisetron** 40 mcg/kg and **ondansetron** 0.1 mg/kg on EKG in children with ALL<br><br>N = 22 children on HD-MTX | Granisetron significantly decreased HR at 1 and 3 hours post-administration and prolonged mean QT and QTc dispersions at 1 hour; all measurements resolved at 3 hours<br><br>Ondansetron showed no changes |

# Methadone

| Risk Category | | | Pediatric Data Available |
|---|---|---|---|
| **Known** | ⚠️ | ⊗ CLQT | Observational cohort[c] (4) Case report |

# Methadone

| Study | Methods | Results |
|-------|---------|---------|
| **Parikh R, et al 2011** | Observational cohort evaluating effect of maternal **methadone** use on infant EKG at DOL 1, 2, 4 and 7<br><br>N = 26 infants, mean gestation 38 weeks | 4 methadone exposed infants (15%) with QTc > 460 ms in first two days of life<br>All QTC < 460 mS on DOL 7<br><br>All patients asymptomatic during study period |

# Methadone

| Study | Methods | Results |
|---|---|---|
| **Anghelescu D, et al 2016** | Observational cohort evaluating effect of **methadone** on QTc in pediatric oncology patients<br><br>N = 37 patients age 0.9-27.4 years | Mean QTc during treatment longer than baseline (+8.95 ms)<br><br>No correlation between dose, duration, electrolyte abnormalities and concomitant QT prolonging medications |

# Methadone

| Study | Methods | Results |
|---|---|---|
| **Madden K, et al 2017** | Observational cohort to determine frequency of QT prolongation in pediatric patients with cancer pain<br><br>N = 25 patients; mean age 11.6 ± 6.8 years | 5/25 (20%) patients had prolonged QTc > 470 ms, 1 with QTc >500 ms<br>Mean change in QTc -9 ms<br>No association found between methadone dose and increased QTc<br>No arrhythmias observed |

# Methadone

| Study | Methods | Results |
|-------|---------|---------|
| **Rasmussen V, et al 2015** | Observational cohort evaluating extreme doses of **methadone** (>10 mg/kg/day) on QTc in pediatric oncology patients N = 2 (11 years old and 17 years old) | Case 1: Doses up 32.7 mg/kg/day methadone; no cardiac toxicities Case 2: Doses up to 24.8 mg/kg/day, >10 mg/kg/day for 207 days; asymptomatic prolonged QTc observed once (510 ms) with concurrent use of fluconazole and TCA |

Pediatr Blood Cancer. 2015 ;62(6):1087-90.

# Anesthetics

| Agent | Risk Category | | | Pediatric Data Available |
|-------|---------------|---|---|--------------------------|
| Propofol | **Known** | ⚠️ | ⊗ CLQT | Prospective randomized (2)[c] |

# Additive Exposures

- Pharmacodynamic interactions
  - Cumulative effects of 2+ QTc prolonging agents
- Pharmacokinetic interactions
  - CYP inhibitors and substrate interactions → increased exposure
- Organ dysfunction
- Identifiable and modifiable risk factors

# QT-Prolonging Drug-Drug Interactions

| Medication | Example Interaction Leading to Prolonged QTc |
|---|---|
| Methadone | Decreased clearance with fluconazole (CYP 3A4, 2C9, 2C19) |
| Ciprofloxacin | Additive effects with concomitant amiodarone |
| Lithium | Decreased excretion with thiazide diuretics |
| Venlafaxine | Decreased metabolism with fluconazole (CYP3A4) |
| TCAs | Decreased clearance with fluoxetine (CYPD6, 1A2, 2C19) |

# Patient Case 1

CR is a 12 year old 60 kg male with no significant past medical history who was involved in a severe MVA requiring a prolonged 13 day PICU stay intubated and sedated on fentanyl and midazolam. He has stabilized by day 14, been extubated and initiated on an opioid and benzodiazepine taper with methadone 10 mg IV q6h and lorazepam 4 mg IV q6h and is resting comfortably.

# Patient Case 1 continued

On day 17, he is transferred to the floor on methadone 8 mg PO q6h and lorazepam 3 mg PO q6h, complains of significant nausea on arrival and soon discovered has developed a fungal UTI. The hospitalist team orders fluconazole 400 mg IV q24h and ondansetron 4 mg IV q6h PRN, which come to the pharmacist's pending verification queue.

# Recognition and ADR Prevention

- Screen for physiologic/pathologic risk factors
- Identify potential iatrogenic risks factors
  - Medications: conditional/possible/known risk stratify
  - Electrolytes disturbances
  - Systems based trigger tools
- Obtain a baseline ECG if indicated
- Monitor and reassess when indicated

# Patient Case 2

PR is a 13 year old 34 kg female with a past medical history significant for aortic coarctation corrected during newborn period, prolonged QT syndrome stabilized for the last 5 years on propranolol currently dosed at 10 mg PO BID. She presents to the pediatric and adolescent clinic with signs of depression and is referred to Psychiatry who diagnoses major depressive disorder.

# Patient Case 2 continued

The prescriber strongly considers antidepressant therapy with an SSRI or SNRI but is very hesitant and seeks additional recommendations and guidance from a clinical pharmacist.

# Assess Risk and Mitigate Harm

- Establish a baseline – obtain an ECG
- Identify and mitigate foreseeable risks factors
  - Therapeutic interchange
  - Medications: conditional/possible/known risk stratify
  - Dose titration to the lowest effective dose
  - Avoid/Prevent against electrolyte disturbances
- Monitor routinely and sequentially with interventions
- Prepare adequate 2$^{nd}$, even 3$^{rd}$ line alternatives

# Patient Case 3

KR is a 9 year old 33 kg female with past medical history significant for cystic fibrosis and is currently receiving azithromycin 250 mg qMWF and is admitted for a pulmonary exacerbation for the 3$^{rd}$ time in 6 months and requires an extended course of moxifloxacin and the pulmonologist requests assistance with guidance on dosing and cautions with the patient's polypharmacy.

# Monitoring
# Acutely vs Chronically

- Establish a baseline – obtain an ECG
- Identify all potential risks factors
  - Therapeutically interchange high potential agent(s) with lower potential alternatives
  - Dose reduce all essential, potential agents to the lowest effective dose
  - Monitor and preemptively correct all pertinent electrolyte anomalies
- Monitor progress with each major intervention
- Prepare adequately for emergence of QT prolongation
- Discuss plan for chronic monitoring and management

# Patient Case 4

TP is a is a 7 year old 27 kg female with no significant past medical history who developed an acute respiratory infection, which progressed to develop into atypical HUS, complicated by sepsis with acute decompensation, respiratory failure requiring intubation and severe AKI necessitating CRRT support.

During day 31 of a prolonged PICU stay, TP, has been extubated and on an opioid and benzodiazepine taper with methadone 6 mg IV q6h and lorazepam 3 mg IV q6h. The patient has been stabilized, on eculizumab and ciprofloxacin 250 mg BID prophylaxis.

# Patient Case 4 continued

On day 32 the patient transitioned from CRRT to PD, and on day 35 as the patient is weaned to methadone 3 mg PO q6 becomes faint, with weak pulses, unstable blood pressures and has a rapid response activated, which the decentralized pharmacist responds to.

# ADR Management

- Obtain an ECG immediately

- Identify and eliminate all potential risks factors
  - Discontinue all suspected agent(s) with the highest potential
  - Dose reduce all essential, potential agents to the lowest effective dose
  - Correct all pertinent electrolyte anomalies

- Serially monitor progress with each major intervention

- Prepare adequately for deterioration

- Stabilize and discuss potential 2$^{nd}$, 3$^{rd}$ line interventions for acute management

# Key Takeaways

- Key Takeaway #1
  - There are multiple different etiologies of drug induced QT prolongation which range from medication effects on ion channels, genetic involvement, medication characteristics, and drug interactions.
- Key Takeaway #2
  - Data describing drug-induced QT prolongation in pediatrics is scarce in comparison to adult data; similar principles relating to additive exposures, drug-drug interactions, and monitoring apply for children, particularly those with identifiable risk factors.
- Key Takeaway #3
  - Patients must be carefully evaluated on a case by case basis, assessing predisposition to and ultimately the summation of drug induced QT prolongation risk beginning with identification of potential agents, a baseline ECG and subsequent follow-up.