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Clinical Review: Drug-Induced QT Interval Prolongation

Learning Objectives:

- Review medications with known risk for causing the potentially lethal ventricular arrhythmia, torsades de pointes (TdP) in some people.
- Describe risk factors for drug-induced QT interval prolongation, including TdP.
- Summarize best practices for responsible prescribing of QT-prolonging drugs.

Key Points:

- Even though drug-induced TdP is a relatively rare event, sudden cardiac death and TdP due to drug-induced QT interval prolongation are top reasons that prompt the U.S. Food and Drug Administration (FDA) from removing drugs from the U.S. market.
- Whenever possible, QT-prolonging drugs should be avoided in people with known risk factors for TdP or used at the smallest effective dose with close electrocardiogram (ECG) monitoring and patient vigilance for symptoms of TdP.
- Expert opinion should be sought before starting QT-prolonging medications if the patient has a prolonged rate-corrected QT interval (QTc) at baseline (>450 ms in men and >470 ms in women in the absence of interventricular conduction defects). Regular ECG monitoring is recommended for patients at high risk for QT interval prolongation and those taking additional concomitant QT-prolonging medications.
- In a study of 65,833 continuously eligible Medi-Cal fee-for-service beneficiaries with a diagnosis of schizophrenia and/or bipolar disorder, 61% had at least one paid claim for an antipsychotic medication with a known, possible, or conditional risk of developing TdP. Among beneficiaries with at least one paid claim for a known TdP risk antipsychotic medication, almost half (49%) had at least one paid claim for another non-antipsychotic medication with a known TdP risk during the same time period.

Background

Changes in the electrical activity that control contraction of the cells of the heart muscle can lead to a condition in which there is an abnormally long QT interval on the ECG, that may result in a rare, but potentially fatal, ventricular arrhythmia known as TdP.[1-3] The QT interval can be prolonged due to an inherited condition known as congenital long QT syndrome (LQTS), or acquired.[1-4] Acquired QT prolongation can be caused by medical conditions including cardiac disease or electrolyte imbalances, but it is most commonly drug-induced.[2-6] Even though drug-induced TdP is a relatively rare event, sudden cardiac death and TdP due to drug-induced QT interval prolongation are top reasons that prompt the U.S. FDA to remove drugs from the U.S. market.[2-6]

However, not all QT-prolonging drugs are associated with risk for TdP and the mechanisms for determining the association between a particular drug and TdP risk are not well established.[4] There is also no clear-cut consensus on the degree of drug-induced QT prolongation that should require drug discontinuation.[2,4]

In order to address these gaps in knowledge, the Arizona Center for Education and Research on Therapeutics (AZCERT) developed a standardized process to identify and categorize marketed drugs according to their ability to cause both QT prolongation and TdP.[7] This open-source list called *QTdrugs* is maintained on the CredibleMeds website, and categorizes drugs into one of three categories of TdP risk.[7,8] Table 1 includes the CredibleMeds definitions for each of the three categories, and includes the categorization of each antipsychotic medication.[7,8]

Table 1. Antipsychotic Medications with Known, Possible, or Conditional Risk of Torsades de Pointes (TdP)[7,8]

Risk of TdP	CredibleMeds Definition	Antipsychotic Medication	Drug Category
Known	There is substantial evidence to support the conclusion that these drugs prolong the QT interval and are associated with TdP when used as directed.	chlorpromazine*	First-Generation (Typical) Antipsychotic
		haloperidol*	
		pimozide	
		thioridazine*	
Possible	There is substantial evidence to support the conclusion that these drugs prolong the QT interval, but there is insufficient evidence at this time to indicate these drugs, when used as directed, are associated with TdP.	perphenazine*	
		aripiprazole*	Second-Generation (Atypical) Antipsychotic
		asenapine*	
		clozapine*	
		lioperidone*	
		paliperidone	
		pimavanserin	
		risperidone*	
Conditional	There is substantial evidence to support the conclusion that these drugs are associated with TdP, but only under conditions or circumstances of their use (e.g., excessive dose, or when given to a patient with a condition such as hypokalemia) or because the drug has shown the ability to create one or more conditions that facilitates induction of TdP (e.g., by inhibiting metabolism of QT-prolonging drugs or by causing an electrolyte disturbance that induces TdP).	olanzapine*	
		quetiapine*	
		ziprasidone*	

* As of the date of publication of this article, these drugs appear on the *Medi-Cal List of Contract Drugs*, although some medications may have additional restrictions on manufacturer codes. For current information, use the online Medi-Cal Formulary search tool available on the Formulary File web page of the Department of Health Care Services (DHCS) website.

Risk factors for drug-induced TdP include underlying heart conditions, such as LQTS, older age, female sex, heart disease, electrolyte disorders (especially hypokalemia and hypomagnesemia), renal or hepatic dysfunction, bradycardia or rhythms with long pauses, treatment with more than one QT-prolonging drug, and genetic predisposition.[1,4,9] The presence of multiple risk factors increases the risk of TdP; thus, identifying and minimizing risk factors is important to reduce the risk of TdP. [1,2] Whenever possible, QT-prolonging drugs should be avoided in people with risk factors, or used at the smallest effective dose with close ECG monitoring and patient vigilance for symptoms of TdP. [1-3,10].

As an additional reference, non-antipsychotic medications with known TdP risk that are currently available in the U.S. market are shown in Table 2.[8]

Table 2. Current List of Non-Antipsychotic Medications with Known TdP Risk Available in the U.S. (as of August 14, 2017)[8]

Drug Category	Drug(s)
Anesthetic, general	propofol, sevoflurane
Antiarrhythmic	amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ibutilide, procainamide, quinidine, sotalol
Antibiotic	azithromycin, ciprofloxacin, clarithromycin, erythromycin, levofloxacin, moxifloxacin,
Anticancer	arsenic trioxide, vandetanib
Antidepressant	citalopram, escitalopram
Antiemetic	droperidol, ondansetron
Antifungal	fluconazole, pentamidine
Antimalarial	chloroquine
Antinausea	domperidone
Antineoplastic Agent	oxaliplatin
Cholinesterase inhibitor	donepezil
Local anesthetic	cocaine
Opioid agonist	methadone
Phosphodiesterase 3 inhibitor	anagrelide, cilostazol
Vasodilator, Coronary	papaverine (intra-coronary)

The risks (modifiable and non-modifiable) of each particular drug and each individual patient must be balanced against the potential benefit expected from that drug, as well as the availability and feasibility of alternative therapies that have not been shown to impact the QT interval.

QT Prolongation in the Medi-Cal Fee-for-Service Population

A retrospective cohort study was conducted in the Medi-Cal fee-for-service population in order to assess the utilization of QT-prolonging medications, the prevalence of medical conditions causing QT prolongation, and the incidence of potential adverse events that may be associated with QT prolongation. This study focused on beneficiaries with a diagnosis of schizophrenia and/or bipolar disorder because antipsychotic medications are recommended as first-line treatments for these conditions, and the benefits of treatment often outweigh the risks.

The initial study population included all Medi-Cal fee-for-service beneficiaries between 18 and 64 years of age with at least one paid medical claim with either schizophrenia or bipolar disorder listed as a primary or secondary ICD-10-CM diagnosis code during either the measurement year (between April 1, 2016, and March 31, 2017) or the year prior to the measurement year (between April 1, 2015, and March 31, 2016). Continuous, exclusive eligibility in the Medi-Cal fee-for-service program during the measurement year was also required for inclusion into the study population to ensure that complete medical and pharmacy claims data were available.

Demographic characteristics, including gender, age, race/ethnicity, and geographic region of residence, were reviewed for all beneficiaries in the study population. In addition, paid pharmacy claims for all antipsychotic medications during the measurement year were reviewed for each individual beneficiary and the cohort was stratified into the following five subgroups:

- Known TdP risk: The beneficiary had at least one paid claim for either chlorpromazine, haloperidol, pimozide, or thioridazine.
- Possible TdP risk: The beneficiary had at least one paid claim for either aripiprazole, asenapine, clozapine, iloperidone, paliperidone, perphenazine, pimavanserin, or risperidone.
- Conditional TdP risk: The beneficiary had at least one paid claim for either olanzapine, quetiapine, or ziprasidone.
- Other: The beneficiary had at least one paid claim for an antipsychotic medication; however the medication has not been classified as having a known, possible, or conditional TdP risk (as of August 14, 2017).
- None: The beneficiary had no paid claims for any antipsychotic medication during the measurement year.

In cases where beneficiaries had paid claims for multiple antipsychotic medications, subgroups were assigned based on the antipsychotic medication with the greatest risk (if any).

As the risk of QT prolongation may increase with the use of multiple QT-prolonging medications, paid pharmacy claims for any non-antipsychotic medications classified as having known TdP risk (see Table 2) were also reviewed for the study population during the measurement year. All other QT-prolonging drugs, including non-antipsychotic medications classified as "possible TdP risk" and "conditional TdP risk" were not included in this analysis in order to focus on drugs that have been shown to cause TdP in some people.[10]

In order to determine the prevalence of medical conditions that may cause QT prolongation,[1,9] all available medical claims data for each beneficiary were reviewed for a primary or secondary ICD-10-CM diagnosis code for any of the following:

- Cerebrovascular accident
- Complete atrioventricular block
- Encephalitis
- Hyperaldosteronism
- Hyperparathyroidism
- Hypocalcemia
- Hypokalemia
- Hypomagnesemia
- Hypothyroidism
- Myocardial ischemia or infarction
- Myocarditis
- Rheumatic fever
- Romano-Ward syndrome
- Severe bradycardia
- Sinus node dysfunction
- Subarachnoid hemorrhage

To assess the incidence of potential adverse cardiac events that may be associated with QT prolongation, medical claims data during the measurement year were reviewed for a primary or secondary ICD-10-CM diagnosis code for any of the following:

- Arrhythmia
- Cardiac arrest
- Long QT syndrome
- Syncope
- Ventricular fibrillation
- Ventricular tachycardia

Finally, although medical claims data do not contain information about ECG measurements or other clinical values, the data were reviewed in order to determine whether each individual beneficiary in the study population had at least one paid claim for an ECG during the measurement year.

Descriptive statistics were used to summarize beneficiary characteristics. Analysis of variance (ANOVA) was used to assess demographic differences in the use of non-antipsychotic QT-prolonging medications and the prevalence of medical conditions leading to QT prolongation. Significance level was determined using $\propto = .05$. Data analyses were performed using IBM® SPSS®, version 24.0 (Chicago, IL).

Results

The study population included a total of 68,533 continuously-eligible Medi-Cal fee-for-service beneficiaries between 18 and 64 years of age with at least one paid medical claim for either schizophrenia or bipolar disorder listed as a primary or secondary ICD-10-CM diagnosis code during either the measurement year (between April 1, 2016, and March 31, 2017) or the year prior to the measurement year (between April 1, 2015, and March 31, 2016).

Almost 25% (n = 17,094) of beneficiaries had no paid claims for any antipsychotic medication during the measurement year and another 4% (n = 3,014) had paid claims only for antipsychotic medications where the risk of TdP has neither been observed nor classified. Among the remaining 61% of the study population, 8% (n = 5,654) had at least one paid claim for an antipsychotic medication with a known TdP risk during the measurement year, 38% (n = 26,025) had at least one paid claim for an antipsychotic medication with a possible TdP risk (and no paid claims for an antipsychotic medication with a known TdP risk), and 24% (n = 16,746) had at least one paid claim for an antipsychotic medication with a conditional TdP risk (and no paid claims for either known or possible TdP risk antipsychotic medications). Clinical characteristics of the study population with at least one paid claim for a QT-prolonging antipsychotic medication during the measurement year are shown in Table 3.

Table 3. Clinical Characteristics of the Medi-Cal Fee-for-Service Study Population during the Measurement Year, Stratified by Risk of TdP from Antipsychotic Medications

	Known TdP Risk n = 5,654	**Possible TdP Risk n = 26,025**	**Conditional TdP Risk n = 16,746**
Percentage with ≥1 paid claim for non-antipsychotic medications with known TdP risk	49.4%	42.1%	44.9%
Percentage with ≥12 paid claims for non-antipsychotic medications with known TdP risk	19.2%	22.0%	22.5%
Percentage with ≥1 medical conditions that may cause QT prolongation	11.9%	10.0%	9.9%
Percentage with ≥1 paid claim for an ECG	10.1%	7.9%	8.8%
Percentage with any potential adverse cardiac event	1.6%	1.5%	1.6%

Almost half of the study population with at least one paid claim for a QT-prolonging antipsychotic medication during the measurement year had at least one paid claim for an additional, non-antipsychotic medication categorized as a known TdP risk (azithromycin was the most common). Within the cohort with at least one paid claim for an antipsychotic medication with known TdP risk, 49% also had a paid claim for another non-antipsychotic medication with a known TdP risk, 12% had at least one medical condition that may cause QT prolongation, and only 10% of this group had a paid claim for an ECG during this same time period.

As expected, during a single measurement year, the incidence rate for potential adverse cardiac events was very low and, as a result, all potential adverse cardiac events were aggregated in Table 3. Due to the limitations inherent in claims data, causality of these adverse events cannot be determined and there are no QT interval measurements available to provide objective outcome measures.

While not shown in Table 3, the percentage of the stratified study population with at least one potential adverse cardiac event during the measurement year was evaluated in both the group without a paid claim for any antipsychotic medication during the measurement year (1.3% incidence rate) and the group with only paid claims for antipsychotic drugs not categorized as having known, possible, or conditional TdP risk (also a 1.3% incidence rate). These incidence rates were slightly lower than in the cohorts with at least one QT-prolonging medication shown in Table 3.

In addition, despite epidemiological evidence showing females have an increased sensitivity to many of the drugs that prolong the QT interval,[1,4] when stratified by sex, the study population did not show any statistically significant differences in the incidence of potential adverse cardiac events that may be associated with QT prolongation.

Table 4 highlights the use of non-antipsychotic QT-prolonging medications and the prevalence of medical conditions that may cause QT prolongation in the study population, stratified by demographic characteristics.

Table 4. Measurement Year Utilization of Non-Antipsychotic Medications Categorized as Known TdP Risk and the Prevalence of Medical Conditions that may Lead to QT Prolongation, Stratified by Demographic Characteristics

Study population n = 68,533	**Total number of non-antipsychotic medications categorized as known TdP risk (Mean ± S.D.)**		**Total number of paid claims for non-antipsychotic medications categorized as known TdP risk (Mean ± S.D.)**		**Total number of medical conditions that may lead to QT prolongation (Mean ± S.D.)**	
Sex						
• Female (n = 34,180)	1.5 ± 2.1	*p < 0.001*	9.9 ± 9.1	*p < 0.001*	0.2 ± 0.2	
• Male (n = 34,353)	1.2 ± 1.7		8.8 ± 9.4		0.2 ± 0.1	*n.s.*
Age Group						
• 18 – 49 years of age (n = 47,008)	1.4 ± 1.9	*n.s.*	8.5 ± 8.2	*p < 0.001*	0.1 ± 0.1	*p < 0.001*
• 50 – 64 years of age (n = 21,525)	1.4 ± 2.4		10.2 ± 9.4		0.6 ± 0.3	
Race/Ethnicity						
• White/Caucasian, non-Hispanic (n = 27,781)	1.5 ± 2.2	*p < 0.001*	9.5 ± 9.1	*p < 0.001*	0.2 ± 0.1	*p < 0.01*
• All other races/ethnicities (n = 40,752)	1.2 ± 1.4		9.1 ± 9.0		0.1 ± 0.2	
California Region of Residence						
• Los Angeles County (n = 17,904)	1.4 ± 2.1	*n.s.*	9.4 ± 9.1	*n.s.*	0.2 ± 0.1	*n.s.*
• All other regions/counties (n = 50,629)	1.4 ± 2.0		9.3 ± 9.3		0.2 ± 0.2	

Women and those with white/Caucasian, non-Hispanic race/ethnicity had greater use of non-antipsychotic QT-prolonging medications. When compared to the age group between 18 and 49 years of age, the age group between 50 and 64 years of age had more medical conditions that may lead to QT prolongation and more paid claims for non-antipsychotic medications categorized as known TdP risk. There were no differences observed based on geographic region within California.

Conclusion/Discussion

While a retrospective study using claims data to evaluate drug-induced prolongation of the QT interval has multiple limitations, several areas for improvement within the Medi-Cal fee-for-service population were identified that may have the potential to improve patient safety, quality of care, and provider education concerning QT-prolonging medications. For example, provider education efforts could focus on increasing the percentage of Medi-Cal fee-for-service beneficiaries at high risk for TdP who have at least one paid claim for an ECG each year.

A prolonged QT interval can result in rare, but life-threatening cardiac events such as TdP. High utilization of QT-prolonging medications among Medi-Cal beneficiaries with a diagnosis of schizophrenia and/or bipolar disorder and the presence of additional medical conditions that may lead to QT prolongation may substantially increase risk for adverse cardiac events. Prescribers must increase their vigilance regarding QT prolongation and TdP risk and use risk-mitigation strategies when considering any change in medication regimen.

Clinical Recommendations

- Risk for QT interval prolongation should be assessed for every patient who is about to begin taking a QT-prolonging medication. Currently, the most comprehensive and up-to-date reference for QT-prolonging drugs can be found on the CredibleMeds website.
- QT-prolonging medications should be avoided in elderly patients, patients with pre-existing heart disease, history of ventricular arrhythmias, or with metabolic abnormalities such as hypokalemia, except for cases in which the benefits of treatment clearly outweigh the risks.
- Concomitant administration of drugs that inhibit the cytochrome P450, especially imidazole antifungals, macrolide antibiotics, or drugs that cause electrolyte disturbance should be avoided in patients taking QT-prolonging medications. Grapefruit juice should also be avoided, due to similar inhibition of cytochrome P450 enzymes.
- Health care providers should always discuss the risks of QT-prolonging medications with their patients. Patients at risk for QT interval prolongation should be educated to go directly to the emergency room if they experience palpitations, shortness of breath, lightheadedness, dizziness, or fainting.
- Health care providers should pay careful attention to potential electrolyte loss caused by diarrhea, vomiting, profuse sweating, undernourishment, diuretic therapy, alcohol and/or drug use, and eating disorders in patients at high risk for QT interval prolongation.
- In patients with a diagnosis of schizophrenia and/or bipolar disorder who have either concomitant medical conditions that may cause QT prolongation or risk factors for drug-induced TdP, the selection of an antipsychotic medication should include an ECG assessment of the QT interval and evaluation of the risk profile of all potential first-line treatment options.
- An ECG should be routinely checked before and after starting QT-prolonging medication. Expert opinion should be sought before starting QT-prolonging medications if the patient has a prolonged QTc at baseline (>450 ms in men and >470 ms in women in the absence of interventricular conduction defects). Regular ECG monitoring is recommended for patients at high risk for QT interval prolongation and those taking additional concomitant QT-prolonging medications.

- Routine monitoring of electrolytes is recommended for patients who start QT-prolonging medications, especially for patients taking concomitant medications that may cause hypokalemia or hypomagnesemia.
- If the ECG shows signs of impending TdP development, treatment options may include immediately discontinuing the QT-prolonging drug, replacing potassium, administering intravenous magnesium, considering temporary pacing to prevent bradycardia and long pauses, and transferring the patient to a hospital unit with the highest level of ECG monitoring surveillance where immediate defibrillation is available.
- If drug-induced QT interval prolongation has occurred, a careful review of the patient's personal and family history should be obtained in order to identify the possibility of a congenital LQTS. Where congenital LQTS is suspected, ECG screening is recommended for all of the patient's first-degree relatives.

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