

# Drug-induced QTc-prolongation: risk management in a community pharmacy

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## Educational aims

- To summarize basic information about the risk of QTc-prolongation
- To list recommended sources and provide a risk score and an algorithm to deal with the risk of QTc-prolongation in a community pharmacy
- To emphasize the role of a community pharmacist in this risk management

## Key words

QTc-prolongation, Torsade de Pointes, risk management, community pharmacy

## Abstract

**A prolonged QTc-interval can in rare cases lead to ventricular arrhythmias (Torsade de Pointes) and sudden cardiac death. Most cases of QTc-prolongation are associated with medication, as listed in the QT-drug lists of CredibleMeds. Beside QTc-prolonging drugs, other patient-specific risk factors are associated with this risk. Community pharmacists have an important role in the risk management of QTc-prolongation. The aim of this paper is to give an overview of the most important aspects in the risk of QTc-prolongation, to underline the relevance of this risk and to offer tools to help community pharmacists deal with this risk in clinical practice.**

## Introduction

The risk of QTc-prolongation has become an important issue in medication safety, as in rare cases it can lead to serious adverse events such as Torsade de pointes (TdP) and sudden cardiac death (SCD). In the last decade, several drugs have been removed from the market (e.g. cisapride) or restricted in use (e.g. domperidone, (es)citalopram) because of this risk.<sup>1</sup> At the moment, more than 170 drugs are linked with this risk of QTc-prolongation, as defined in the QT-drug lists of CredibleMeds.<sup>2</sup> Furthermore, a lot of other risk factors (e.g. age, female gender, electrolyte disturbances, cardiovascular and other comorbidities, congenital long QT-syndrome) can increase the risk.<sup>3</sup> Due to possible combinations of these factors with additive effect on the QTc-interval, a complex risk estimation is warranted for each individual patient who receives a QTc-prolonging drug. Community pharmacists play an important role in this risk management, especially in the detection of drug-drug interactions (DDI) with risk of QTc-prolongation.

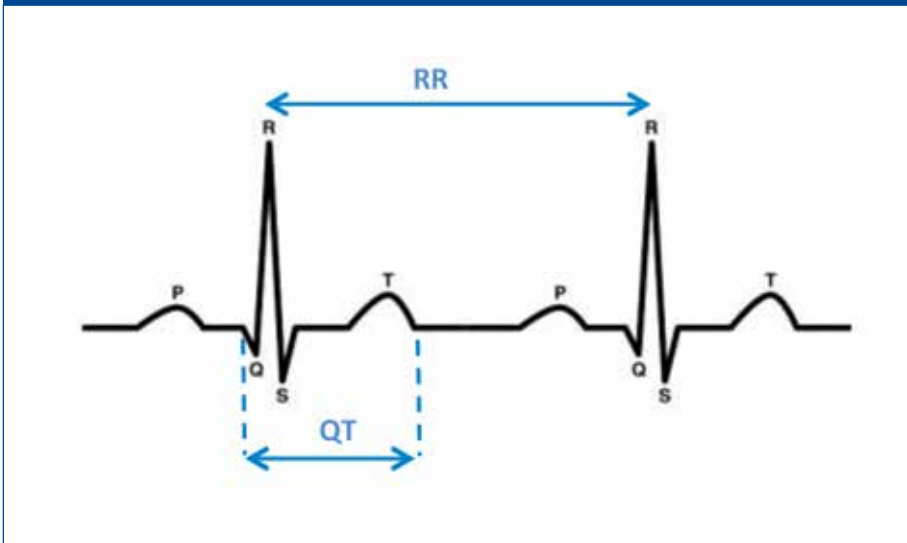
## Definition of a prolonged QTc-interval

The QT-interval is an important phase in an electrocardiogram (ECG); it is measured in milliseconds (ms) from the beginning of the QRS-complex until the end of the T-wave (see Figure 1). The QT-interval measures the ventricular depolarization followed by the ventricular repolarization. QT-prolongation is used as a marker for a prolongation of the ventricular repolarization time.<sup>4,5</sup>

Because the QT-interval varies with the heart rate (HR), the corrected QT-interval (QTc-interval) should be used. Various correction formulas are available for this correction.<sup>6</sup> The Bazett formula is the easiest correction and most used in clinical practice. However, this is not an ideal correction; it results in an over-correction of the QT-interval at elevated heart rates and in an under-correction at heart rates below 60 beats per minute (bpm).<sup>4,7</sup> The Fridericia formula has been suggested to replace Bazett.<sup>4</sup>

A QTc-interval higher than 450 ms in adult males and higher than 470 ms in adult females is defined as prolonged. QTc-values higher than 500 ms are strongly prolonged and linked with a 2- to 3-fold higher risk for TdP (4;5;8). A delta QTc (difference in QTc between a baseline and follow-up ECG) higher than 30 ms and certainly higher than 60 ms must also be considered as a risk for TdP.<sup>7</sup>

Figure 1: QT-interval



### Torsade de Pointes

The term TdP, referring to the presentation of ‘twisting points’ on an ECG (see Figure 2), was introduced by the French cardiologist Dessertenne in 1966.<sup>1,4</sup> TdP is a ventricular polymorphic tachycardia, characterized by a change in amplitude and morphology of QRS-complexes, a short-long-short pattern at the start and a HR of 160 to 240 bpm. In most cases, it terminates spontaneously. However, in few cases, it will lead to ventricular fibrillation and SCD. Typical symptoms of TdP are dizziness and syncope. In case of non-spontaneously ending TdP or ventricular fibrillation, immediate cardioversion should be performed. Other treatments for TdP (including prevention of reoccurrence) consist of intravenous magnesium sulfate, repletion of potassium, isoproterenol ( $\beta$ -receptor agonist) to prevent bradycardia, stopping QTc-prolonging drugs and implanting a pacemaker in case of chronic bradycardia.<sup>4,8,9</sup>

The overall incidence of TdP in a general population was estimated at 50 per million person-years.<sup>10,11</sup> However, these numbers are probably an underestimation, because only a part of the patients reach the hospital alive. Furthermore, TdP-cases are often not recognized or not registered on an ECG. Also the proportion of SCD that are caused by TdP is unclear.<sup>4,12</sup> Approximately one-fifth of the TdP-cases will proceed in ventricular fibrillation of which approximately 85% will be fatal.<sup>11,13</sup>

Besides TdP and sudden cardiac death, QTc-prolongation is also linked with other serious outcomes. Pickham *et al.* reported

that patients in critical care units with a prolonged QTc-interval have a longer hospital stay and a 3-times higher overall in-hospital mortality than patients without QTc-prolongation.<sup>14</sup>

### Drugs with a risk of QTc-prolongation and TdP

Both cardiac and non-cardiac drugs are linked with QTc-prolongation and TdP. Different therapeutic classes are involved, e.g. antibiotics, antipsychotics, antidepressants, oncolytic agents and antihistamines. Antiarrhythmic drugs like quinidine and sotalol have the highest risk of causing TdP (in 1-5% of the exposed subjects). With non-cardiac drugs, the risk of TdP is considered to be lower (0.01-0.0001%).<sup>1,15</sup> Most frequently, QTc-

prolonging drugs inhibit the rapid component of the delayed potassium current by blocking the hERG-channels (regulated by the human ether-a-go-go-related gene (hERG)), which results in a prolongation of the repolarization phase and a prolongation of the QTc-interval.<sup>4,16</sup>

The American organization CredibleMeds<sup>(2)</sup> has created lists of QTc-prolonging drugs, based on the evidence per drug:

- List 1: drugs with a known risk for TdP (substantial evidence for causing TdP) e.g. haloperidol, escitalopram, domperidone, methadone, macrolides, moxi/levo/ciprofloxacin, sotalol
- List 2: drugs with a possible risk for TdP (substantial evidence for QTc-prolongation, but evidence for TdP is lacking) e.g. risperidone, venlafaxine, protein kinase inhibitors, tacrolimus, tamoxifen
- List 3: drugs with a conditional risk for TdP (risk of QTc-prolongation and/or TdP in certain conditions, e.g. overdose, cLQTS, interaction with other drugs) e.g. furosemide, indapamide, trazodone, pantoprazole, metronidazole
- List 4: drugs to be avoided by patients with congenital long QT-syndrome (all drugs in the previous lists and heart stimulants)

The evidence per drug is collected in the medical literature (Pubmed search), the FDA label, summary of approval on the FDA website, cases in the FDA’s Adverse Event reporting System and reports to CredibleMeds. Subsequently, this evidence is reviewed by the CredibleMeds review team with the help of the Bradford-Hill criteria, and finally allocated to the different lists. The QT-drug lists are freely available on the website [www.crediblemeds.org](http://www.crediblemeds.org)

Table 1: Risk score for QTc-prolongation, score  $\geq 5$  defined as high risk

Risk factors for QTc-prolongation	Points
▪ Use of $\geq 1$ potassium-lowering diuretic *	3 points
▪ Use of $\geq 1$ anti-arrhythmic drug	3 points
▪ Age $\geq 65$ years	2 points
▪ Female gender	2 points
▪ Thyroid disturbances	2 points
▪ Cardiovascular comorbidities **	1 point
▪ Diabetes mellitus	1 point
<b>TOTAL RISK SCORE</b>	<b>Maximum 14 points</b>

\* No points if used in combination with potassium-sparing diuretics

\*\* Including antihypertensive drugs, beta-blocking agents, nitrates, calcium-channel blockers, agents acting on the renin-angiotensin system and lipid-modifying agents

for registered users and are continuously updated based on new information.<sup>2,17</sup>

### Other risk factors for QTc-prolongation

Besides QTc-prolonging drugs, a lot of other patient-specific risk factors are mentioned in the literature<sup>1,4,18,19</sup> including:

- Demographic factors (e.g. age  $\geq 65$  years, female gender, smoking, alcohol use, over- and underweight)
- History of a prolonged QTc-interval
- Cardiovascular comorbidities (e.g. rhythm disturbances, heart failure, hypertension)
- Other comorbidities (e.g. thyroid disturbances, diabetes, liver- or kidney failure, infections)
- Electrolyte disturbances (e.g. hypokalemia, hypocalcemia, hypomagnesemia)
- Genetic predisposition

To understand the interplay between genetic mutations, the use of QTc-prolonging drugs and other risk factors, the term 'repolarization reserve' was introduced by Roden *et al.* in 1998. This framework explains that there are physiological mechanisms available that maintain the normal cardiac repolarization and that this can vary among patients. These mechanisms are a protection (reserve) against factors

that may distort the normal ventricular repolarization. The more risk factors present, the more susceptible a person becomes for developing QTc-prolongation and TdP (reduced reserve). Consequently, multiple risk factors are needed to overcome this barrier. However, one should be aware that one additional factor can suddenly lead to QTc-prolongation and TdP.<sup>4,9,20</sup>

A recent systematic review of Vandael *et al.* summarized and assessed the evidence on different risk factors for QTc-prolongation.<sup>3</sup> Based on this review, a preliminary risk score for QTc-prolongation (the RISQ-PATH score) was developed.<sup>21</sup> This risk score is mainly useful for the hospital setting, as it needs a lot of clinical information, including recent lab results. For community pharmacists, we developed a simplified QT risk score based on the information that is usually available in a community pharmacy (see Table 1).<sup>22</sup> A QT risk score  $\geq 5$  points is defined as a high risk for QTc-prolongation. Moreover, an algorithm (see Figure 3) was developed to help community pharmacists decide when the prescribing physician should be contacted in case of a QTc-prolonging DDI, taking into account the number of QTc-prolonging drugs, the classification in CredibleMeds and the risk score.<sup>22</sup> In Table 2, some additional recommendations for clinical practice are listed.

### An example in clinical practice

Andrew (70 years old) enters the pharmacy with a prescription for levofloxacin (indication: prostate infection). You notice in his medication history that he also takes donepezil for Alzheimer disease. On your screen, an alert for a QTc-prolonging DDI pops open.

#### STEP 1: Check which drugs are involved in the QTc-prolonging DDI

In this case, levofloxacin and donepezil are linked with a risk of QTc-prolongation. Both drugs are classified in list 1 of CredibleMeds (known risk of TdP).

#### STEP 2: Check if the patient has other risk factors for QTc-prolongation

Andrew is older than 65 years and he also uses two cardiovascular drugs (perindopril and bumetanide). If we calculate the simplified QT risk score (Table 1), Andrew has a score of 6 points which correlates with a high risk.

#### STEP 3: Consider if an action is needed

Taking into account that 2 drugs of list 1 are involved in the QTc-prolonging DDI (see algorithm in Figure 3), that Andrew has a high risk score for QTc-prolongation and that it is a new prescription for an antibiotic treatment in which case it is still possible to suggest an alternative, it is in this case recommended to contact the physician.

#### STEP 4: Consider which physician should be contacted

The best choice is to contact the physician who prescribed the new treatment. It is possible that it was prescribed by a specialist who was not aware of the other medications of Andrew. If the specialist cannot be reached, you can also contact the general practitioner (GP). In this case levofloxacin was prescribed by the GP, so we will contact him.

#### STEP 5: Try to suggest an alternative drug

For a prostate infection, amoxicillin in combination with an enzyme inhibitor is the second-line choice besides levofloxacin and is not included in the lists of CredibleMeds. We can suggest this as an alternative treatment for Andrew.

#### STEP 6: Contacting the physician

The GP agrees with your suggestion to replace levofloxacin with amoxicillin in combination with clavulanic acid.

**Table 2: Additional recommendations for clinical practice**

#### If you need to contact the prescribing physician concerning a QTc-prolonging DDI:

- Specify the type of DDI and the involved QTc-prolonging drugs.
- Specify the other risk factors for QTc-prolongation (see risk score in Table 1).
- Ask if a recent ECG is available.
- Try to propose an alternative drug.

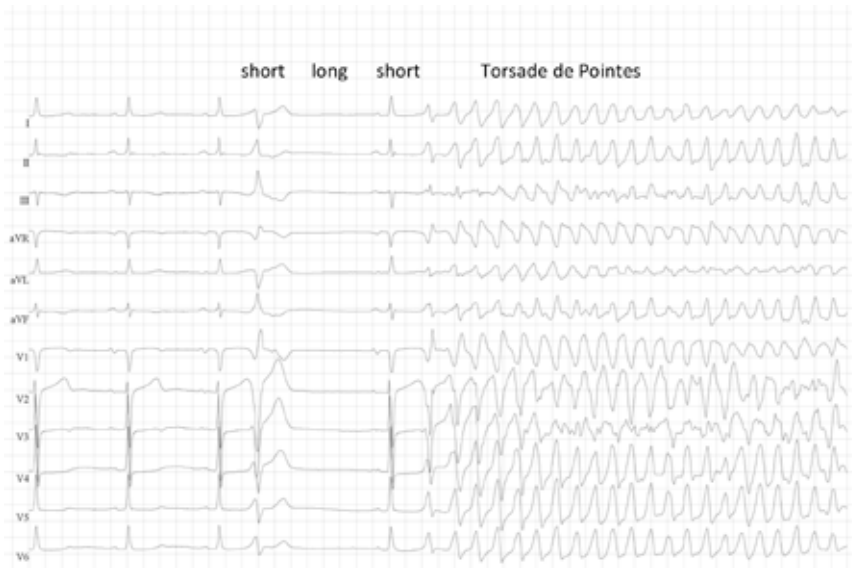
#### Recommendations to find an alternative drug:

- Focus on the QTc-prolonging drug that is started.
- Try to find an alternative which is not listed in the CredibleMeds lists.
- If such an alternative is not available, a drug of list 3 or 2 of CredibleMeds should be preferred.
- Still no alternative? Ask the physician if it is possible to plan a follow-up ECG and/or if you can warn the patient for the symptoms of TdP.

#### How to warn a patient for the risk of QTc-prolongation and TdP?

- Underline that it is a very rare risk.
- Mention the most common symptoms of TdP: sudden dizziness, fainting and palpitations.
- Tell the patient that if these symptoms occur, the physician should be contacted as soon as possible.
- Emphasize that the patient can always contact you in case of questions or worry.

Figure 2: An example of a TdP



**STEP 7: Explanation to the patient**

Carefully explain the potential risk of QTc-prolongation to Andrew. Underline that it concerns a very rare side effect, but that you discussed it with his GP that it is a safer option to use an alternative antibiotic treatment.

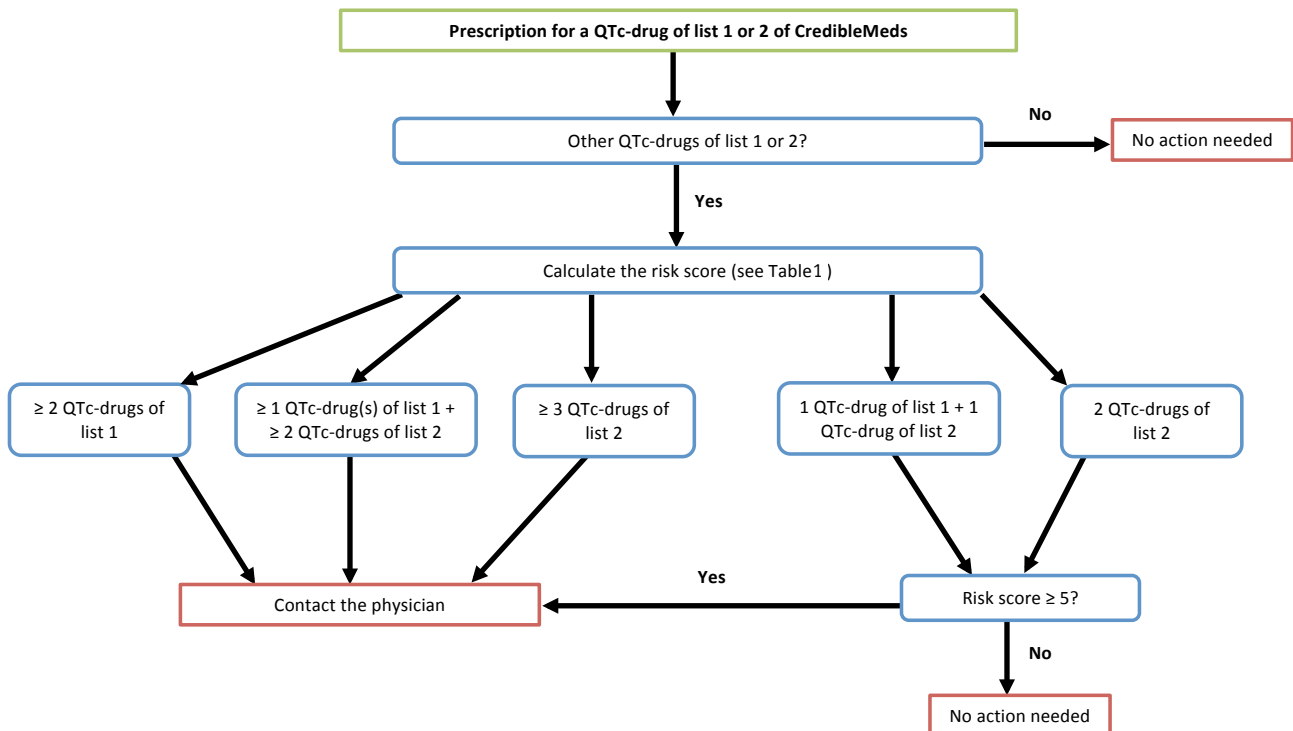
**STEP 8: Register in the pharmaceutical file of the patient how you handled the DDI**

By registering the performed action in the pharmaceutical file of Andrew, you can always look back how you handled this QTc-prolonging DDI.

**Conclusion**

Drug-induced QTc-prolongation can in rare cases lead to serious life-threatening outcomes. Pharmacists have an important role in the risk management of QTc-prolongation. They should be cautious for QTc-prolonging DDI, especially if drugs of list 1 of CredibleMeds or other patient-specific risk factors are involved.

Figure 3: Algorithm to handle QTc-prolonging DDI in a community pharmacy



## 10 multiple choice evaluation questions

- Which length of the QTc-interval is correlated with a significant higher risk for TdP?**
  - A. QTc  $\geq$  100 ms
  - B. QTc  $\geq$  400 ms
  - C. QTc  $\geq$  500 ms
- A prolonged QTc-interval will always result in TdP.**
  - A. Correct
  - B. Not correct
- Most of the times, QTc-prolonging drugs will prolong the QTc-interval by:**
  - A. Blockage of calcium channels
  - B. Activation of calcium channels
  - C. Blockage of potassium (hERG) channels
  - D. Activation of potassium (hERG) channels
- Which are typical symptoms of a TdP?**

A. Dizziness | B. Paresthesia  
C. Chest pain | D. Syncope | E. Palpitations

  - A. Only symptom e
  - B. Symptoms b and e
  - C. Symptoms a, d and e
  - D. None of the mentioned symptoms
- Which of the following drugs have a clear risk for TdP (list 1 CredibleMeds)?**

A. Erythromycin | B. Ranitidine  
C. Levetiracetam | D. Doxycycline | E. Donepezil

  - A. Drugs a and e
  - B. Only drug a
  - C. Drugs b, d, and e
  - D. All mentioned drugs
- Citalopram is classified in list 1 of CredibleMeds.**
  - A. Correct
  - B. Not correct
- Which of the following risk factors are all linked with QTc-prolongation?**
  - A. Age, female gender, dementia, hyperkalemia
  - B. Age, female gender, diabetes, hypokalemia
  - C. Age, dementia, diabetes, hypercalcemia
  - D. Age, female gender, hypocalcemia, gout
- The use of diuretics is a risk factor for QTc-prolongation.**
  - A. Correct
  - B. Not correct
- Hanna (24 years) enters the pharmacy with a prescription for ciprofloxacin 250mg for a bladder infection. You know that she also suffers from a depression and that she is treated with escitalopram 10mg. Besides escitalopram, paracetamol is also included in her medication history. Based on the provided algorithm (see Figure 3), which action will you take?**
  - A. There is no risk for QTc-prolongation. No action is needed
  - B. There is an increased risk for QTc-prolongation and you decide to contact the physician.
  - C. There is increased risk for QTc-prolongation. However, you decide to only warn the patient for the symptoms of TdP.
- Thomas (35 years) suffers from a bipolar disorder and, for already 10 years, he is treated with lithium 500mg. Lately, his disorder deteriorated and his psychiatrist decided to additionally start levomepromazine. Thomas does not use other chronic medication. Based on the provided algorithm (see Figure 3), which action will you take?**
  - A. There is no risk for QTc-prolongation. No action is needed
  - B. There is an increased risk for QTc-prolongation and you decide to contact the physician.
  - C. There is increased risk for QTc-prolongation. However, you decide to only warn the patient for the symptoms of TdP.

Answers may be found on page 41

## Key points

- A QTc-interval  $\geq$ 500 ms is severely prolonged and correlated with a 2 to 3 times higher risk of TdP
- Typical symptoms of TdP are sudden dizziness, fainting and palpitations
- More than 160 drugs of different therapeutic classes are currently linked with a risk of QTc-prolongation and listed in the QT-drug lists of CredibleMeds (list 1: known risk of TdP, list 2: possible risk of TdP, list 3: conditional risk of TdP)
- Besides QTc-prolonging drugs, a lot of other patient-specific risk factors should be taken into account in the risk estimation
- The risk score and algorithm proposed in this paper can be used in clinical practice to deal with the risk of QTc-prolongation



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## Abbreviations

**bpm** = beats per minute

**DDI** = drug-drug interactions

**ECG** = electrocardiogram

**GP** = general practitioner

**hERG** = human ether-a-go-go-related gene

**HR** = heart rhythm

**ms** = milliseconds

**SCD** = sudden cardiac death

**TdP** = Torsade de Pointes

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