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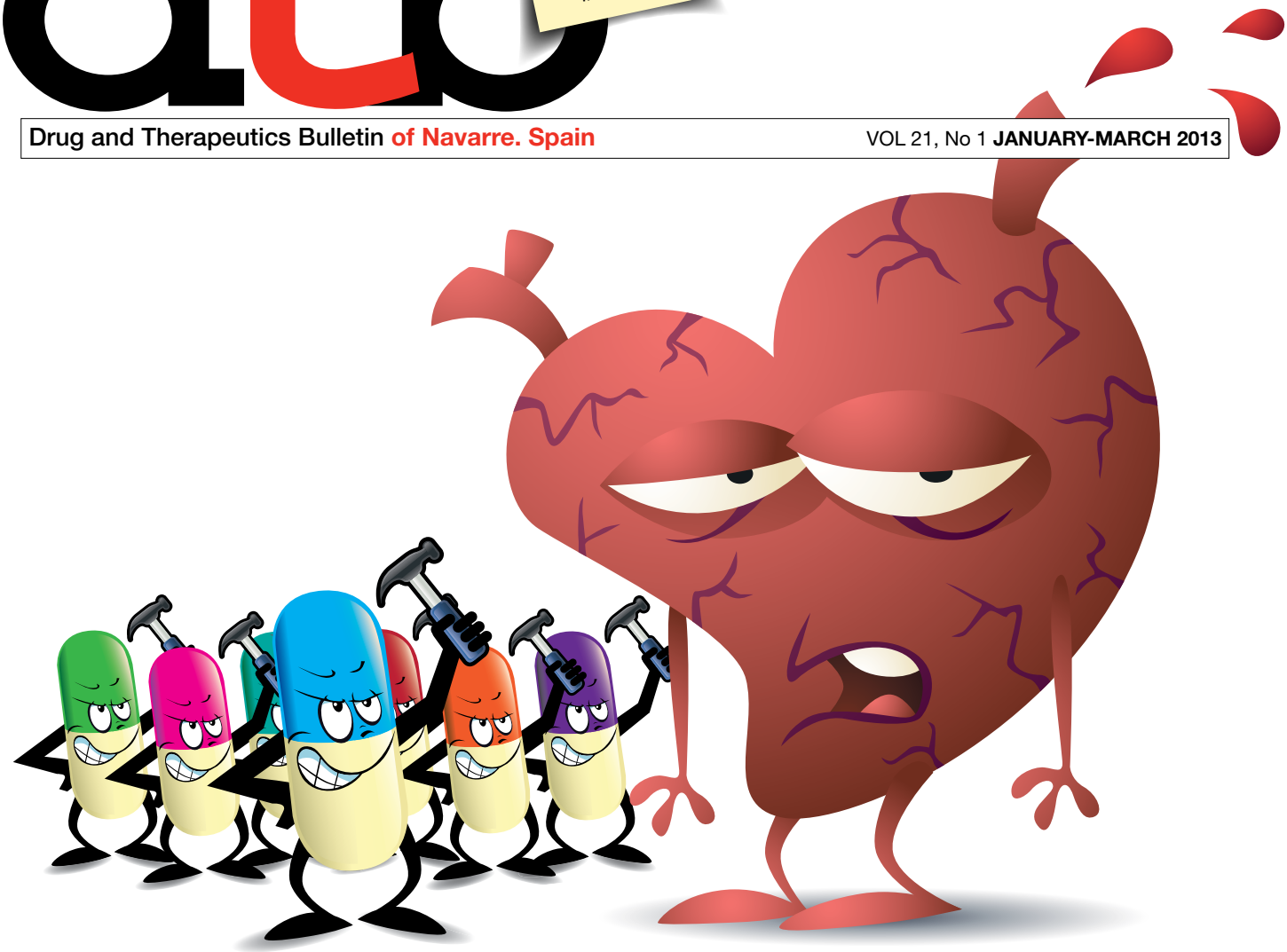

Drugs and QT interval prolongation

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abstract

Objective: To describe the adverse effect of a prolonged QT interval, discuss the possible relationship beteween an increase in the risk of Torsade de Pointes (TdP) and establish recommendations to minimize risks. **Materials and methods:** A search on Medline was carried out for studies that evaluated this adverse effect, as well as for drug warnings and alerts from regulatory agencies, EMA, AEMPS and the FDA. The registry of the University of Arizona (www.azcert.org/) was consulted, which includes a list of drugs that may cause a prolonged QT interval. **Results and conclusions:** The long QT syndrome is a heart disorder characterized by a prolonged QT interval. The origin may be hereditary or caused by certain medications. Clinical manifestations may present with a syncope, dizziness, polymorphic ventricular tachycardia otherwise known as Torsade de Pointes, which may end spontaneously, though in some cases can produce ventricular fibrillation and be associated with sudden death of cardiac origin. The capacity to prolong the QT interval is measured to evaluate the risk a drug may have to produce TdP, although the correlation is not well established. The incidence of drug related TdP is low. However, the incidence can increase in cases where a drug that prolongs the QT interval is prescribed to a patient with predisposing factors. This article offers recommendations to reduce the incidence of this proarrhyhtmia. **Key words:** QT interval, drugs, long QT syndrome, Torsade de Pointes.

Introduction

The electrical activity of the heart is divided in two phases: depolarization and repolarization. Depolarization results from the net flow of positive charges (influx of sodium and calcium into the interior of the cell), which stimulates heart muscule contraction and represents the QRS interval on the electrocardiogram, ECG. Repolarization results from the efflux of positive charge (potassium) across the membrane to the exterior, which then causes the myocardial cell to restore itself to the original resting state where it can be stimulated again. Repolarization is represented in the ECG by the ST segment and T wave. The QT interval coincides in time with the ventricular systole, both in period of depolarization and in repolarization. It extends from the start of the QRS complex up to the end of the T wave (figure 1).

A prolonged QT interval can be the origin of a polymorphic ventricular tachycardia denominated 'Torsade de Pointes' (TdP) that can present as a syncope, dizziness or palpitations. Usually it resolves spontaneously but, in some cases, it can evolve into ventricular fibrillation and can be associated with sudden death of cardiac origin.[1]

This adverse effect that some drugs present may make the risk-benefit relationship unfavourable and should be taken into account when prescribing or authorizing a new drug. The regulatory agencies demand the identification of a possible risk of prolonged QT intervals during pre-clinical and clinical research.

Over the years, the capacity of prolonging the QT interval has been a motive for withdrawing drugs from the market given that their use imply greater risk than benefit as with the cases of astemizole, terfenadine, grepafloxacin, cisapride, etc. The Spanish Medicines Agency has published various safety alerts related to the risk of a prolonged QT interval of some drugs such as citalopram, escitalopram, ondansetron and domperidone. The risk of producing a prolonged QT interval increases especially in polymedicated patients and in cases where various factors concur, as we will see later in this article.

What is the long QT syndrome (LQTS) and torsades de pointes (TdP)?

The long QT syndrome (LQTS) is a disorder caused by an elongation of the repolarization phase of the ventricular action potential. It is characterized by the prolongation of the QT interval, with or without T wave alterations in the ECG, with an increased dispersion of the ventricular repolarization that is associated with the predisposal for malign ventricular arrhythmias (TdP) and in some instances, ventricular fibrillation that can cause sudden death of cardiac origin.[2,3] (Figures 2a and 2b)

The LQTS can be caused by genetic or acquired factors. Congenital LQTS is an hereditary disease caused by different mutations of genes that encode the proteins of the transmembrane channels of sodium or potassium, enlongating the ventricular repolarization, which produces a predisposition for the appearance of TdP. The congenital LQTS is characterized by a normal QT interval in occasions and with a predisposition for TdP in concurrence with other factors (bradycardia, electrolytic disorders,

Figure 1. Schematic representation of a normal ECG outline in sinus rhythm.

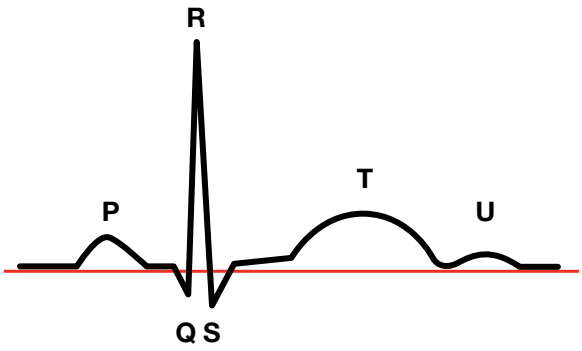


Figure 2a. Rhythm strip in a patient with a normal ECG.

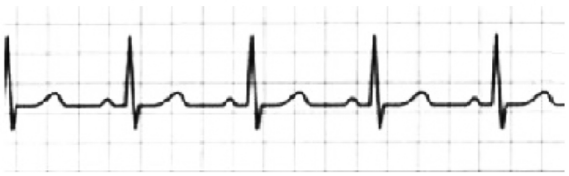


Figure 2b. Rhythm strip in a patient with LQTS.

drugs that prolong the QT interval, etc.). In the case of acquired LQTS, the most frequent cause is the use of drugs that prolong the QT interval.

Acquired LQTS is usually classified as 'pause-dependent' because the associated TdP generally occurs at low heart rates or in response to sequences of short-long-short RR intervals. On the other hand, the congenital LQTS is usually adrenalin-dependent, as it appears with increases in adrenergic activity or sympathetic tone. Sometimes both processes can be superimposed.

TdP is a polymorphic ventricular tachycardia characterized by the presence of QRS complex with axis changes (contortion of the tips), of variable amplitude, and ondulating shapes that turn around the isoelectric baseline. This type of arrhythmia develops in the framework of a prolonged QT interval over time, which reflects that there is some delay in ventricular repolarization and prolongation of the duration of the heart action potential.[4] The TdP is a rare and characteristic ventricular tachyarrhythmia, but not exclusive of hereditary or acquired LQTS, nearly always greater than 500 ms.

The electrographic characteristics of the TdP include:[4]
· A marked prolongation of the QT interval in the last sinus beat before the start of TdP.
· Progressive contortion of polarity of the QRS complexes around the isoelectric baseline.
· Complete 180° turn of QRS complexes in 10-12 beats.
· Change of amplitude of the QRS complexes in each sinosoidal cycle.
· Heart rate between 150-300 beats per minute.
· Irregular RR intervals.

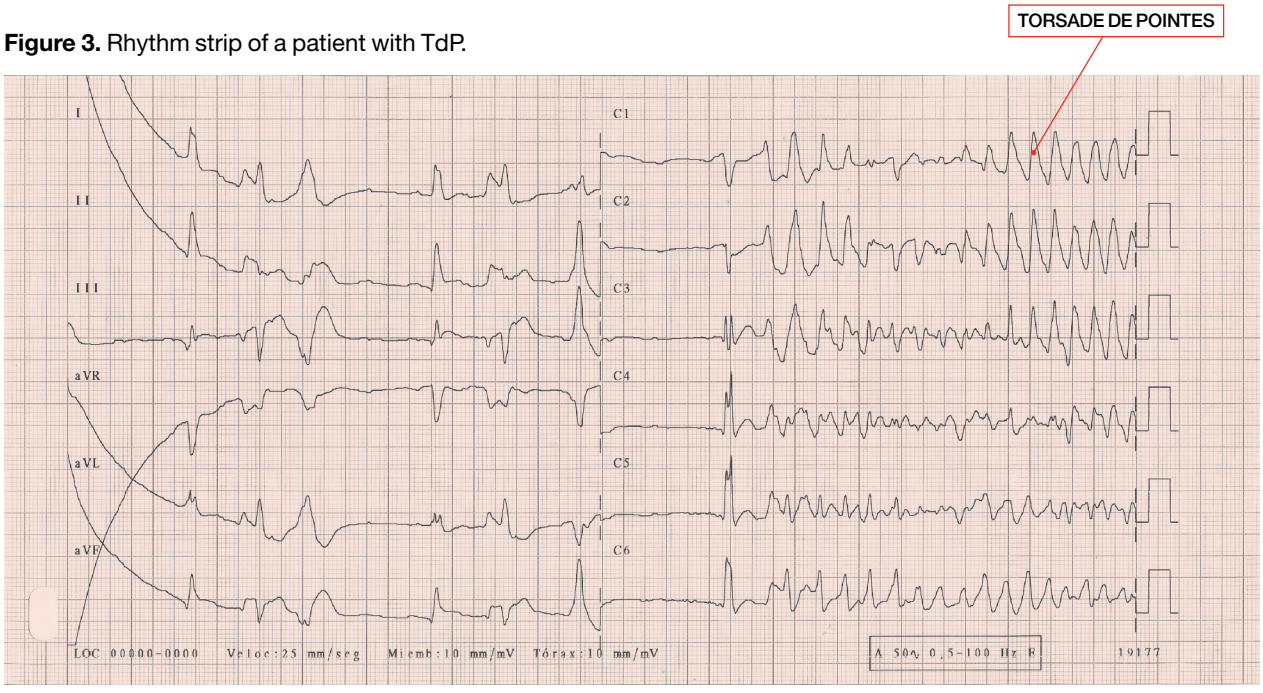
The initiation of TdP in acquired LQTS generally depends on a pause in electrical activity created by the prolongation of a long cycle, which could result from bradycardia or an extrasystole.

Relationship between QT interval prolongation and the risk of TdP

In 2005, the International Conference on Harmonization elaborated a guideline[5] to evaluate the prolongation of the QT interval and the proarrhythmic potential of all non-anti-arrhythmic medication, an indispensable requisite in the process of authorizing new drugs. Traditionally the QT interval is measured to evalute the risk of producing TdP ventricular tachycardia as a side effect of certain drugs. The correlation between the QT interval and the risk for TdP[6] is not well established because not all drugs that prolong the QT interval are proarrhythmic and not prolonging the QT interval is no guarantee that any proarrhythmia will not occur. The prolongation of the QT interval is not a good predictive parameter of ventricular arrhythmia, and presents a limited value in drug safety with regard to cardiac affectation.[6-11]

The QT interval is an electrocardiographic parameter that measures the amount of time required for ventricular depolarization and repolarization, from the start of the QRS complex up to the end of the T wave. That is, it reflects the action potential duration in myocytes. Measurement is normally carried out with the 12 lead[5] electrocardiogram. A Holter is not necessary on a routine basis, although it can be useful when a long QT interval baseline is suspected in a patient with no clinical manifestations.

Figure 3. Rhythm strip of a patient with TdP.

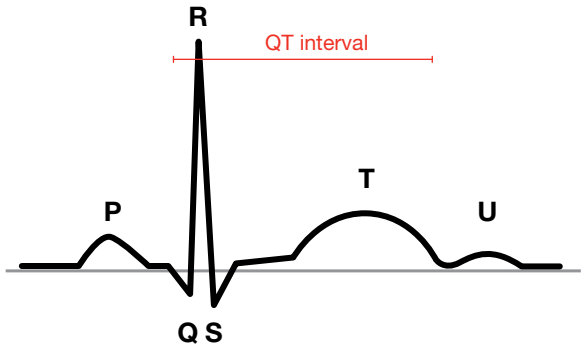


The QT interval depends on age, gender, and heart rate. In cases of bradycardia it tends to be longer while it is shorter in the presence of tachycardia. The higher the rate the lower the interval.[1] It is also subject to diurnal variations. Thus, it increases during sleep, and it is at its longest during the early hours of the morning and during the postprandial period. Various formulas have been proposed to adjust, correct and normalize the QT interval with the heart rate. The most common include the Bazett, Fridericia and Framingham formulas. There is no comparison of the three formulas to determine which is the most effective in predicting what patients have a greater risk to suffer from TdP.[4]

The standard correction uses the Bazett formula, $QTc = QT/RR^{1/2}$ where QTc is the corrected QT interval for the heart rate whereas RR represents the interval from the start of one QRS complex to the start of the next QRS complex, measured in seconds. However, this formula is not usually exact, overestimating at high heart rates and underestimating at lower rates.

Fredericia formula presents greater precision at physiological extremes of heart rate, $QTc = QT/RR^{1/3}$.

The normal value of the QTc interval is up to 440 ms in men and <450 in women. The QTc is considered to be prolonged if greater than 450 ms in men or 470 ms in women (table 1).[12] However, the arrhythmias are associated with values higher than 550 ms.[11-13]



What are the factors that increase the possibility of LQTS and TdP?

Often, multiple risk factors appear that can produce a prolonged QT interval and cause TdP. The main risk factors[1,6,14,15] are listed in table 2.

Women present a longer QT interval than men, and a higher susceptibility for a prolonged QT interval induced by drugs.

Bradycardia also favours the prolongation of the QT interval, which suggests that the prolonging effect of the QT interval caused by drugs is increased in patients with low heart rates or problems in atrioventricular conduction.

Other known factors are electrolyte disturbances, such as hypocalcemia, hypokaliemia and hypomagnesemia which favour the prolongation of the QT interval.

Myocardial infarction and left ventricle hypertrophy also favour greater elongation of the QT interval, just as heart failure by prolonging repolarization. Renal and liver perfusion can be reduced in cases of heart dysfunction, a condition that favours lower systemic elimination of drugs and produce a higher risk of proarrythmia with drugs that may prolong the QT interval.

The subclinical long QT syndrome presents a normal or slighlty prolonged QT interval and patients are more susceptible to present prolongation when exposed to drugs with that capacity.

Simultaneous use of drugs that prolong the QT interval increases the risk of proarrythmia. The prologation of the QT interval by a drug can be increased by the concommitant admnistration of another drug that presents the same pharmaceutical property and in cases where the drug used reduces the levels of potassium (thiazide diuretics, loop diuretics, glucocorticoids, and beta adrenergic agonists).

Other facors have been identified that predispose drugs to prolong the QT interval, and include the administration of high doses and rapid infusions of drugs that prolong the QT interval, and thyroid related disorders.

What drugs present risk for LQTS and TdP?

The mechanism by which certain drugs prolong the QT interval is generally due to blocking of the potassium channels of the heart1. The incidence of TdP produced by drugs is not established although supposedly it is very low.[15]

Of the most known drugs that frequently prolong the QT interval we find the antiarrhythmic agents. However, other drugs have been observed to produce this adverse effect such as some antibiotics, antihistamine agents, antiviral agents, antimycotics, antiemesis agents, neuroleptics, and antidepressants among others. The prolongation of the QT interval can occur at higher doses than recommended or at recommended doses of a drug administered concommitantly with other drugs that inhibit P450 cytochrome enzymes.

The existence of the described risk factors in the previous section potentiate the prolongation of the QT interval by drugs.

Table 1. QTc values (ms) according to the Bazett formula.

QTc value	1-15 years	Adult male	Adult woman
Normal	< 440	< 430	< 450
Limit	440-460	430-450	450-470
Prolonged	> 460	> 450	> 470

Table 2. Risk factors for LQTS and TdP.

Risk factor	Observations
Gender	Higher in women 2-3:1
Bradycardia (abrupt slowing down of heart rate or slowing down of the heart rate after a maintained period of tachycardia)	With heart rates < 60 bpm
Hypocalcemia	
Hypokaliemia	Serum potassium < 3.5 mg/dL
Hypomagnesemia	Serum magnesium < 1.5 mg/dL
Recent cardioversion of atrial fibrillation especially with drugs that prolong the QT intervalo (antiarrhythmic agents)	Incidence: 1-3%
Congestive heart failure	
Myocardial infarction	
Left ventricle hypertrophy	
Renal or liver failure	
Subclinical long QT syndrome	
Pharmacological interaction:	
Drugs that prolong the QT interval	
Concommitant admistration of a drug that prolongs the QT interval with an inhibitor of its metabolism	
High doses and rapid infusions of drugs that prolong the QT interval	This can increase the QT interval by 50 ms compared to the standard dose
Hyperthyrodism / hypothyrodism	

The AzCERT[16] (Center for Education and Research in Therapeutics of the University of Arizona) www.azcert.org has a website that contains lists of drugs that prolong the QT interval and the risk of producing TdP classified in three groups according to the available evidence. These lists are updated periodically as more clinical evidence and notifications become available from the regulatory agencies or published in PubMed.

Risk of TdP
The available evidence supports the conclusion that these drugs increase QT intervals and present a risk for TdP when employed for the authorized indications.

Possible risk of TdP
The available evidence supports the conclusion that these drugs can cause a prolongation of the QT interval, but there is no sufficient evidence that these drugs, when used in authorized indications, increase the risk of producing TdP.

Conditional risk of TdP
The available evidence supports the conclusion that these drugs increase the QT interval and present a risk of developing TdP but only when risk factors concur.

There is also a list of drugs that should be avoided, if possible, for those patients with congenital LQTS. This list includes all those drugs in the above mentioned three classified groups, and some heart stimulants (atomoxetine, methylphenidate and lisdexanphetamine).[16]

Drugs not included in these groups should not be considered risk free with regard to prolonging the QT interval or TdP, given that not all drugs have been adequately evaluated to measure this potential risk.

The Spanish Medicines Agency has published alerts on citalopram,[17] escitalopram,[18] ondansetron,[19] and doperidone[20] related to the dose-dependent risk of prolonging the QT interval with the following recommendations:

Citalopram
In the management of depression, panic disorder, and obsessive-compulsive disorder, the maximum recommended dose in adults is 40 mg daily. In elderly patients and those with liver dysfunction, the maximum recommeded dose is 20 mg daily.

Escitalopram
In the management of major depression, panic disorder with or without agoraphobia, generalized anxiety disorder and obsessive-compulsive disorder in patients over 65 years, the maximum dose is 10 mg daily.

Ondansetron
One single maximum intravenous dose of 16 mg (infusion in at least 15 minutes) to prevent nausea and vomiting induced by chemotherapy.

Citalopram, escitalopram and ondansetron are contraindicated in patients with a history of prolonged QT interval or congenital syndrome of long QT segment, just as in the case of the concommitant use of medication with the capacity to prolong the QT interval. Precaution is advised in patients with co-existence of other risk factors for developing TdP such as patients with congestive heart failure, myocardial infarction, bradyarrhythmia or predisposition for disease-related hypokaliemia or hypomagnesemia or caused by concommitant medication.

The notification on **domperidone**[20] concludes that there may be a slight association with an increase in the risk of severe ventricular arrhythmia or sudden death of cardiac origin, in particular patients over 60 years, or those under a daily dose of over 30 mg. It is recomended to use the lowest effective dose possible, both in adults and children. Caution is advised in patients with a history of prolonged QT interval, with significant electrolyte imbalance, underlying heart disease such as congestive heart failure, and patients of advanced age.

The absence of consistent data regarding **azithromycin** leads to think that it presents a safer cardiotoxic profile than erythromycin and clarithromycin.[22,23] However, in March 2013, the FDA released an alert informing of azithromycins potential to prolong the QT interval and produce TdP.[24]

In table 3 the main drugs that can increase TdP risk are listed according to therapeutic subgroup.

Acknowledgements
We thank Dr Clint Jean Louis, of the Emergency Department of the Navarre Regional Health Service in Spain, for translating the original manuscript into English.

Table 3. Main drugs that can increase TdP risk according to therapeutic subgroup.

Cardiovascular drugs

Amiodarone(1)
Disopiramide(2)
Dronedarone
Flecainide
Indapamide
Nicardipine
Procainamide
Ranolazine
Sotalol(2)

Gastrointestinal drugs

Domperidone
Famotidine
Granisetron
Octreotide
Ondansetron

Neuropsychiatric drugs

Amisulpride(3)
Amitriptiline(3)
Clorpromazine
Citalopram
Clomipramine
Clozapine
Desipramine(3)
Escitalopram
Felbamate
Fluoxetine
Galantamine
Haloperidol(5)
Imipramine(3)
Lithium
Mirtazapine
Olanzapina
Paliperidone
Paroxetine
Pimozide(2)
Quetiapina
Risperidone
Sertindol
Sertraline
Tioridazina
Tizanidine
Trazadone
Venlafaxine
Ziprasidone

Antibiotics

Azithromycin
Ciprofloxacin(4)
Clarithromycin
Erithromycin(2)
Levofloxacin
Moxifloxacin
Ofloxacin
Roxithromycin
Trimethroprim/ sulfamethoxazole

Antifungal drugs

Fluconazol(4)
Itraconazol(4)
Ketoconazol(4)
Voriconazol

Antiviral drugs

Amantadine
Atazanavir
Foscarnet
Pentamidine(2)
Ritonavir
Saquinavir

Other drugs

Alfuzosin
Fingolimod
Lapatinib
Metadone(2)
Nilotinib
Oxitocin
Solifenacin
Sunitinib
Tacrolimus
Tamoxifen
Terfenadine
Tolterodine
Vardenafil

■ Risk of TdP ■ Possible risk of TdP ■ Conditional risk of TdP
(1) Risk: women > men. Low risk of TdP. **(2)** Risk women > men (> 2-fold higher). **(3)** Risk of TdP if overdose. **(4)** Risk of interaction - enzyme Inhibitor. **(5)** Risk of TdP if IV vial or overdose.

Recommendations for a safe prescription of drugs that prolong the QT interval

Before prescribing any drug that has the potential to prolong the QT interval it is important to:

- Evaluate the possible risk factors that may be present (bradycardia, eletrolyte imbalance, heart and endocrine related diseases, etc.) because the prescription may prove of greater risk than benefit and therefore contraindicated.
- Ensure that the drug to be prescribed in combination with other drugs does not prolong the QT interval nor produces an inhibition of the drug metabolism as it may potentiate the capacity to prolong the QT interval or the risk of TdP.
- Not exceed the recommended dose.
- Measure the QT interval on a previous ECG before administering the drug that can prolong the QT segment and avoid its prescription in patients with a slighlty prolonged QT interval.

Once a drug that can prolong the QT interval is prescribed it is recommendable to:

- Evalute the possible incidence of risk factors that can potentiate the risk of arrhythmia.
- Take into account the risk of prolonging the QT interval, the risk of metabolic inhibition or an increase in the risk of developing TdP in cases when it is necessary to introduce new treatments.

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