Antipsychotics and QTc Prolongation

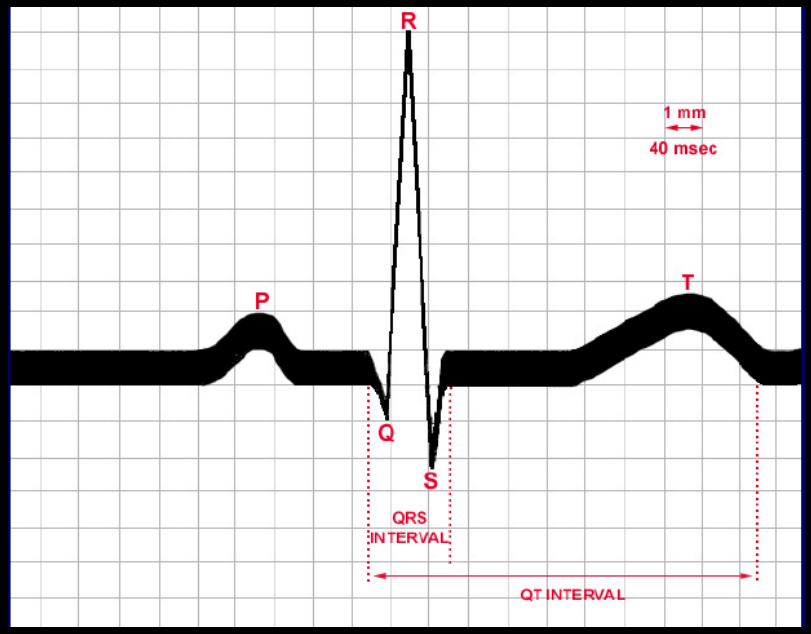
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Antipsychotics and QT Prolongation

Antipsychotic medications have long been known to have the potential to cause QTc interval prolongation and torsades de pointes (TdP). Retrospective and cohort studies have linked antipsychotic use with sudden cardiac death, and most antipsychotic medications have been shown to cause some degree of QT prolongation.

Arch Intern Med 2004; 164:1293–1297
Curr Drug Saf 2010; 5: 97–104.

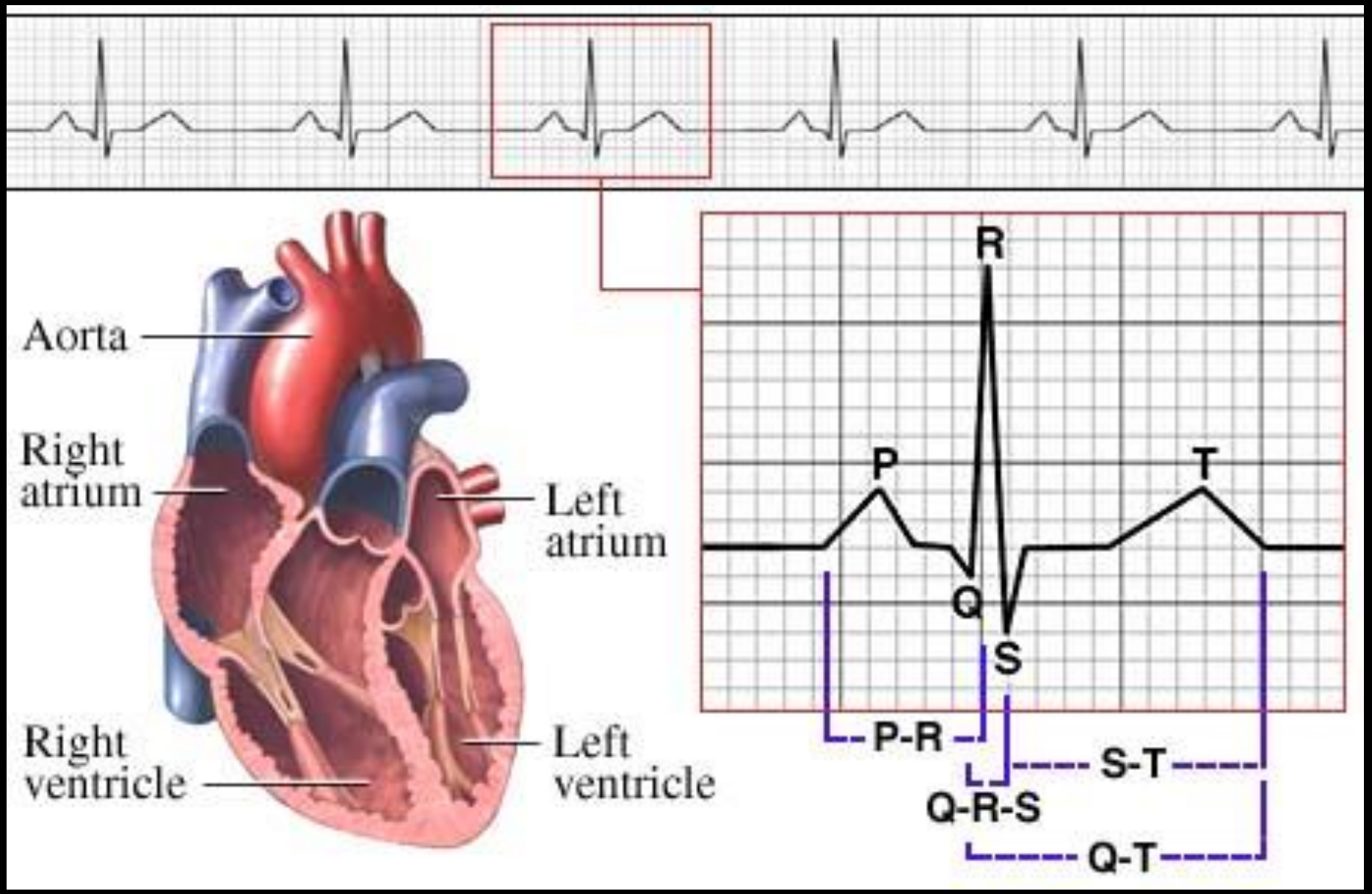
The QT Interval

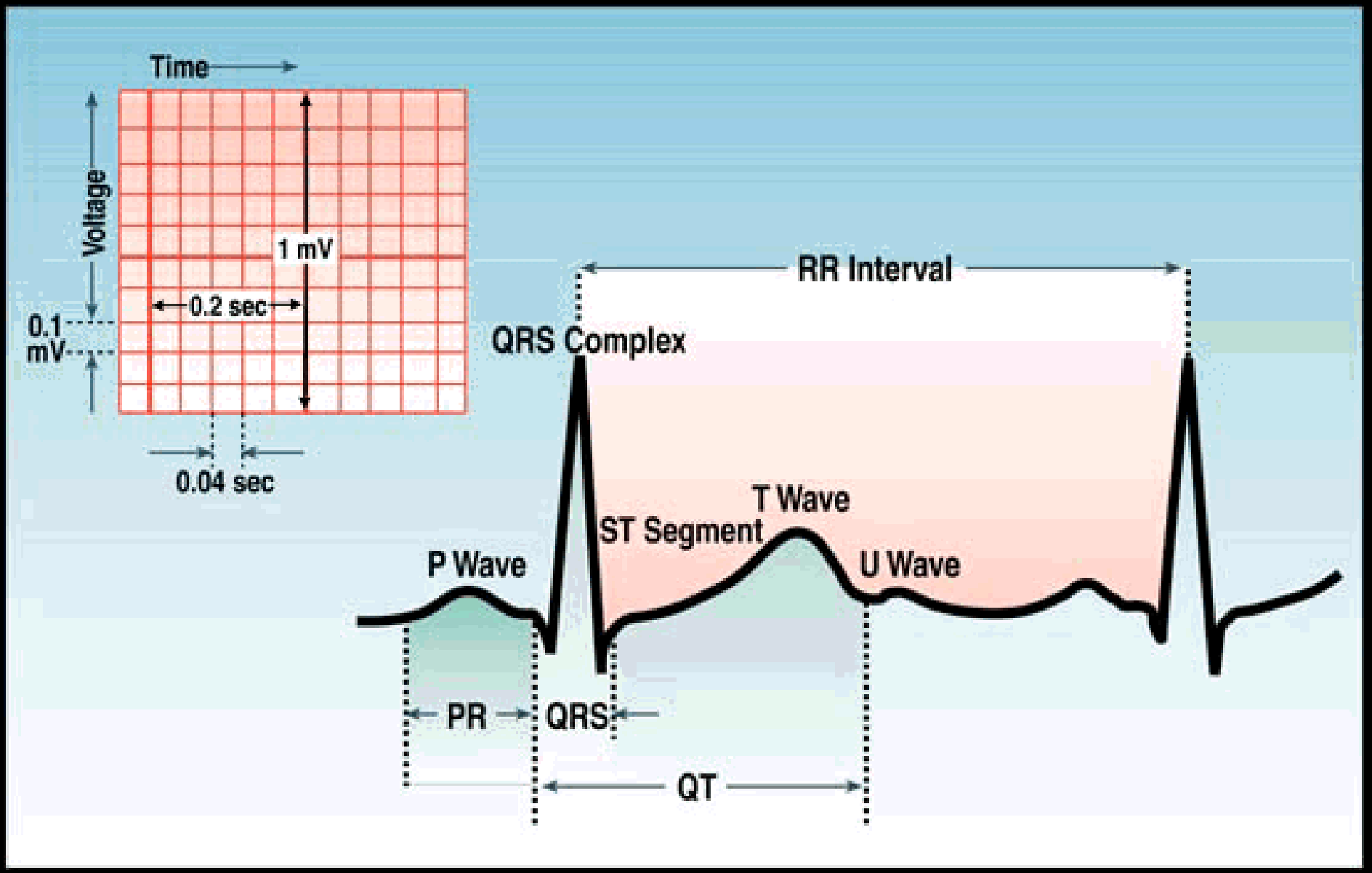


On the electrocardiogram (ECG), the QT interval reflects the time from the onset of ventricular depolarization to the end of repolarization.

QT Interval and Significance

- In cardiology, the time between the Q and T waves of an ECG is the QT interval
- Normal QT interval is 0.30 - 0.44 (0.46 for women) seconds
- If abnormally short or long, risk of developing various types of ventricular arrhythmias increases
- Some QT prolongation can cause *polymorphic ventricular tachycardia* with a characteristic twist of the QRS complex around the isoelectric baseline, this is called Torsades de pointes (TdP)


Aorta
Right atrium
Left atrium
Right ventricle
Left ventricle
R
P
T
Q
S
P-R
S-T
Q-R-S
Q-T


Time
Voltage
1 mV
0.2 sec
0.1 mV
0.04 sec
RR Interval
QRS Complex
T Wave
ST Segment
P Wave
U Wave
PR
QRS
QT

PQRST

- The **P-Wave** is caused by atrial contraction. The first upward deflection corresponds with the right atrium and the second downward deflection corresponds with the left atrium
- The **P-Q-time or PR-Interval** extends from the start of the P-wave to the very start of the QRS-complex. The excitation is decreased by the AV-node and led via the bundle of his to the left and right bundle branch (thus, conduction time).
- The normal duration is between 0.12 – 0.20 sec. A PR-interval of more than 0.20 sec may indicate a first degree an AV-block
- **The QRS- Complex:** The excitation is led via the left bundle branch and the ventricular septum and is visible as Q-wave n the ECG. During the R-phase most of the heart's muscles are activated. For this reason the ECG shows the great wave.
- Whereas during the S-phase the activation runs from the apex of heart to the base of the right and left ventricle

PQRST

- QRS demonstrates the duration of the depolarization of the heart's ventricles. A normal duration lies between 0.08 and 0.12 sec. If the duration is longer this may indicate a conduction abnormality as described before
- **The QT-interval** is measured from the beginning of the Q-wave to the end of the T-wave. ***The QT-interval represents the duration of activation and recovery of the ventricular muscles***. This duration is reciprocal to the pulse
- The ST-segment represents the period from the end of ventricular depolarization to the beginning of ventricular repolarization. Here all cells of the atria are depolarized. An isoelectric line is generated because in this segment there is no electrical current.
- The T-wave represents the repolarization of the ventricles and runs into the same direction as the R-wave.

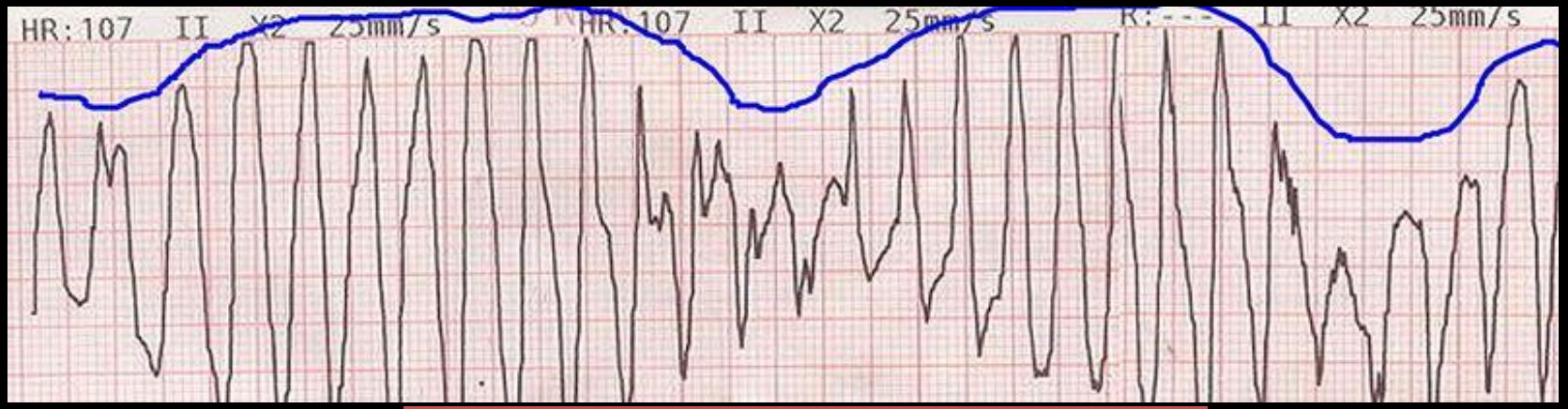
Calculation of the QT Interval

Automated QT and QTc Analysis on ECG

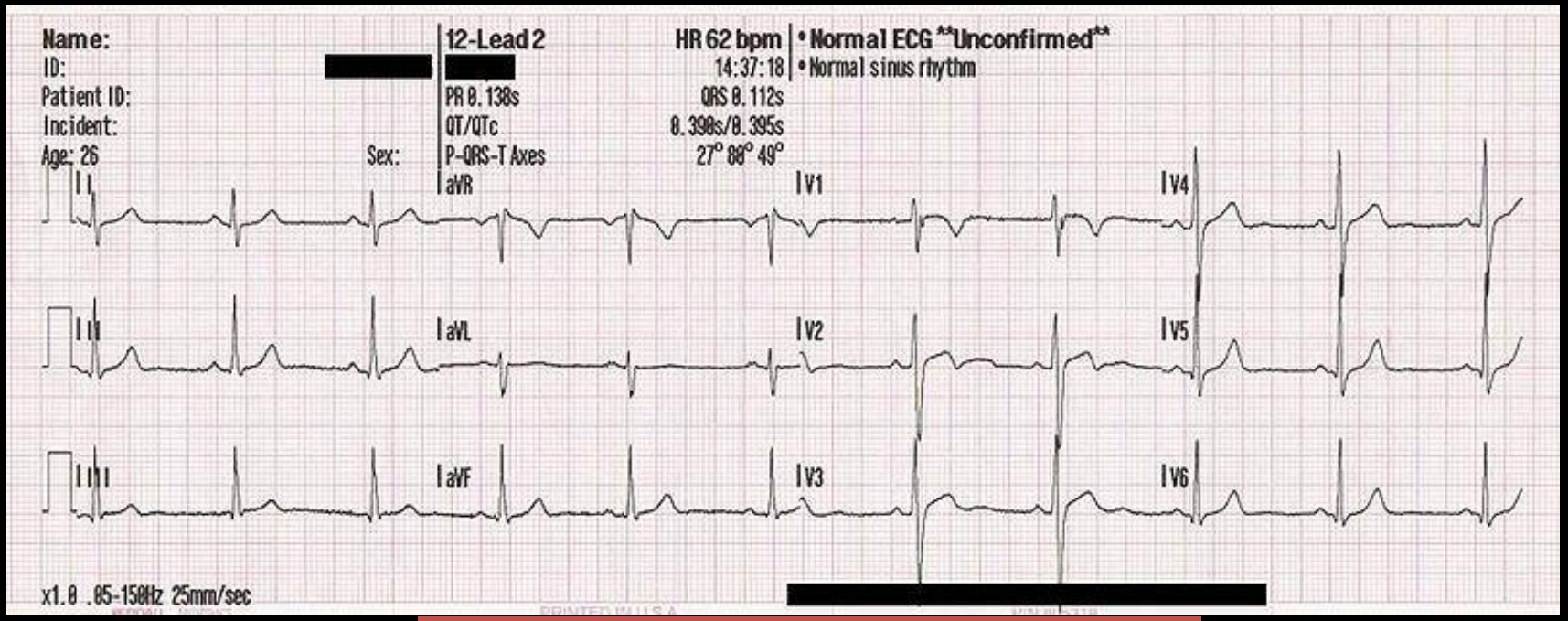
- Reliable with normal T waves at physiologic heart rates

Unreliable:

- High heart rates
- Abnormal T wave
- Prominent U waves
- T-U wave complex morphology



TdP



Normal ECG

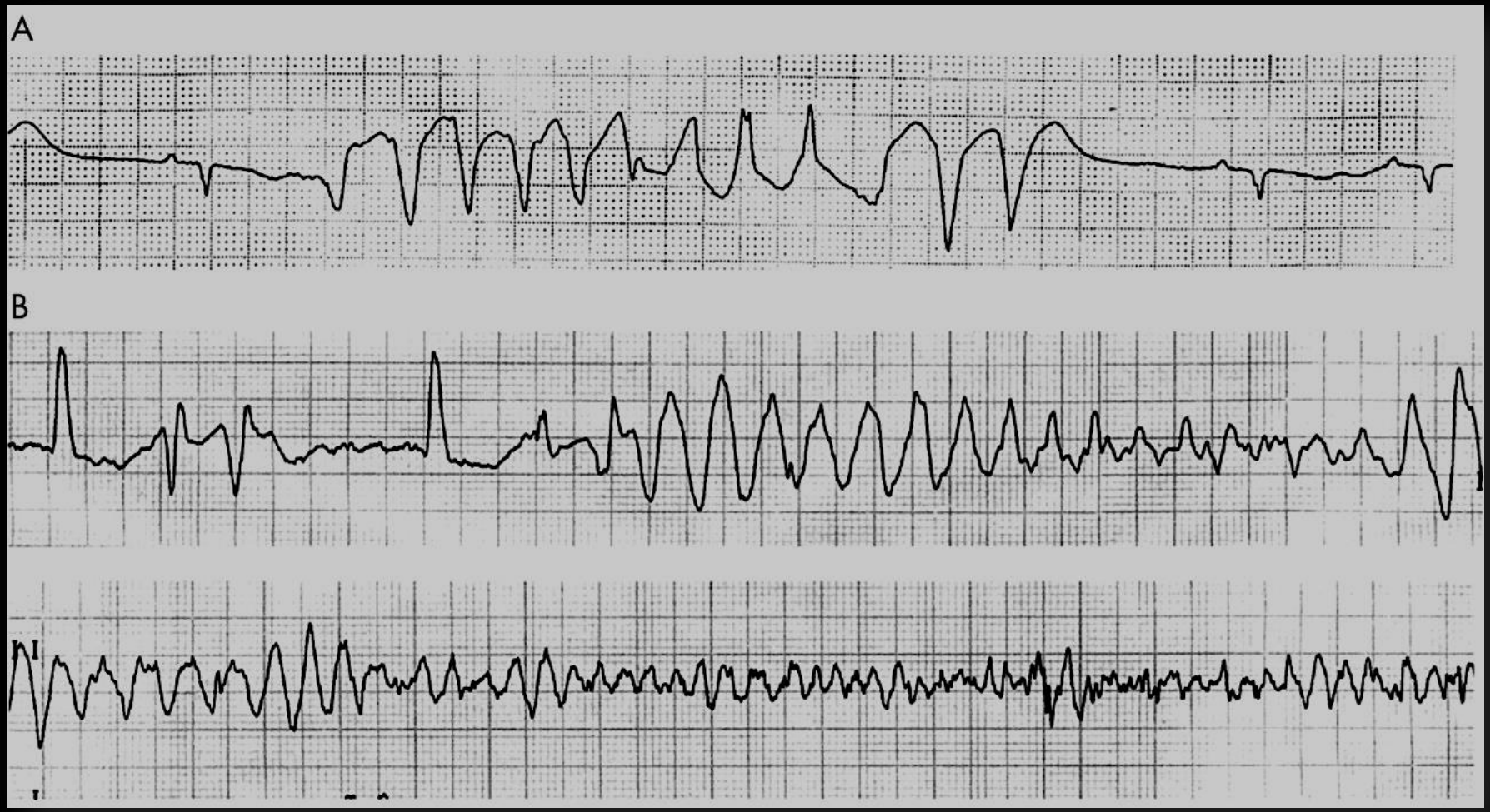
Causes of Torsades de pointes

- Many conditions may cause prolonged or abnormal repolarisation (that is, QT interval prolongation and/or abnormal T or T/U wave morphology), which is associated with Torsades de pointes (TdP)
- If TdP is rapid or prolonged, it can lead to ventricular fibrillation and sudden cardiac death
- Essentially, TdP may be caused by either congenital or acquired long QT syndrome (LQTS)
- In recent years, there has been considerable renewed interest in the assessment and understanding of ventricular repolarisation and TdP.

Why Interest in TdP?

1. The cloning of cardiac ion channels has improved the understanding of the role of ionic channels in mediating cardiac repolarisation, the pathophysiological mechanism of LQTS (congenital and acquired forms), and the pathogenesis of TdP
2. Modern molecular techniques have unravelled the mutations in genes encoding cardiac ion channels that cause long QT syndrome, although the genetic defects in about 50% of patients are still unknown
3. Development and use of class III antiarrhythmic drugs which prolong repolarisation and cardiac refractoriness
    i. Unfortunately, drugs that alter repolarisation have now been recognised to increase the propensity for TdP
4. Finally, an increasing number of drugs, especially non-cardiac drugs, have been recognised to delay cardiac repolarisation and to share the ability with class III antiarrhythmics to cause TdP occasionally

A. Self Limiting Torsades de pointes (TdP)
B. TdP Leading to Ventricular Fibrillation



Calculation of the QTc.Formulae

As repolarization is faster when the heart beats more rapidly, the QT interval should also be corrected for the heart rate.

- At least 17 unique QT correction formulas
- Bazett (QTc = QT/RR0.5)
- Fridericia (QTc = QT/RR0.33)
- Hodges (QTc = QT + 1.75[HR-60])

CNS Drugs 2011:25; 473–490.
Psychosomatics 2013:54:1–13

Correcting the QT Time for Heart Rate

- Bazett formula:

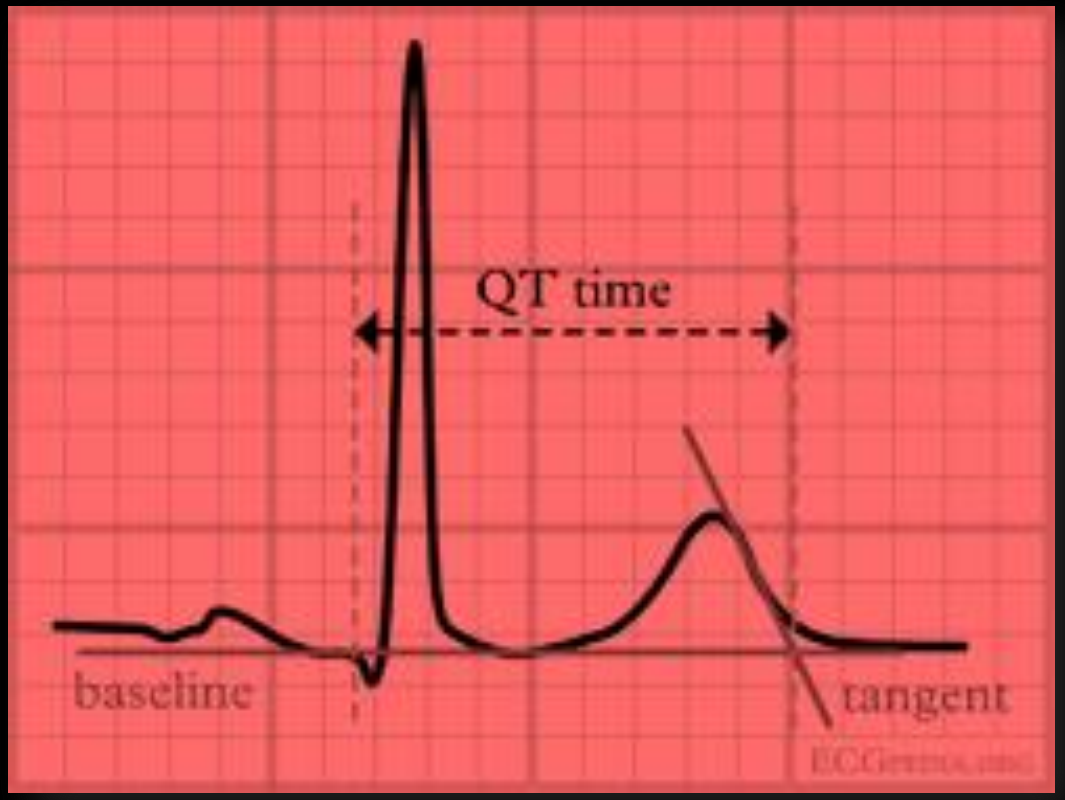
$$QTc = \frac{QT}{\sqrt{RR\ interval\ (sec)}}$$

At a heart rate of 60 bpm, the RR interval is 1 second and the QTc equals QT/1

- Fridericia Formula:

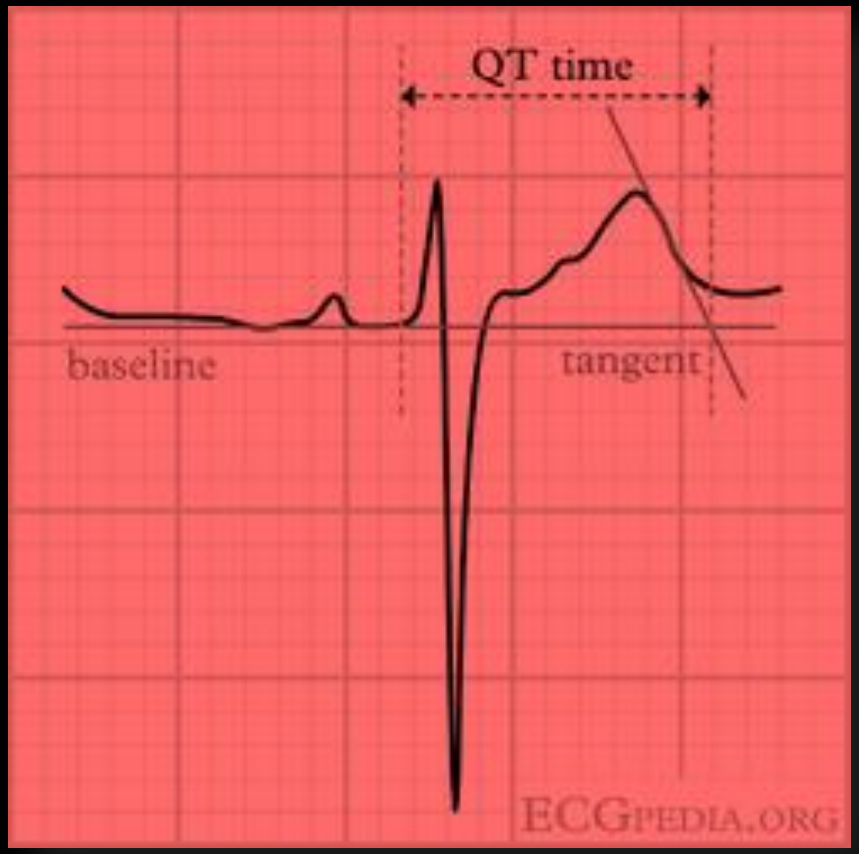
$$QTc_F = \frac{QT}{\sqrt[3]{RR\ interval\ (sec)}}$$

How to measure QT if the QT segment is abnormal



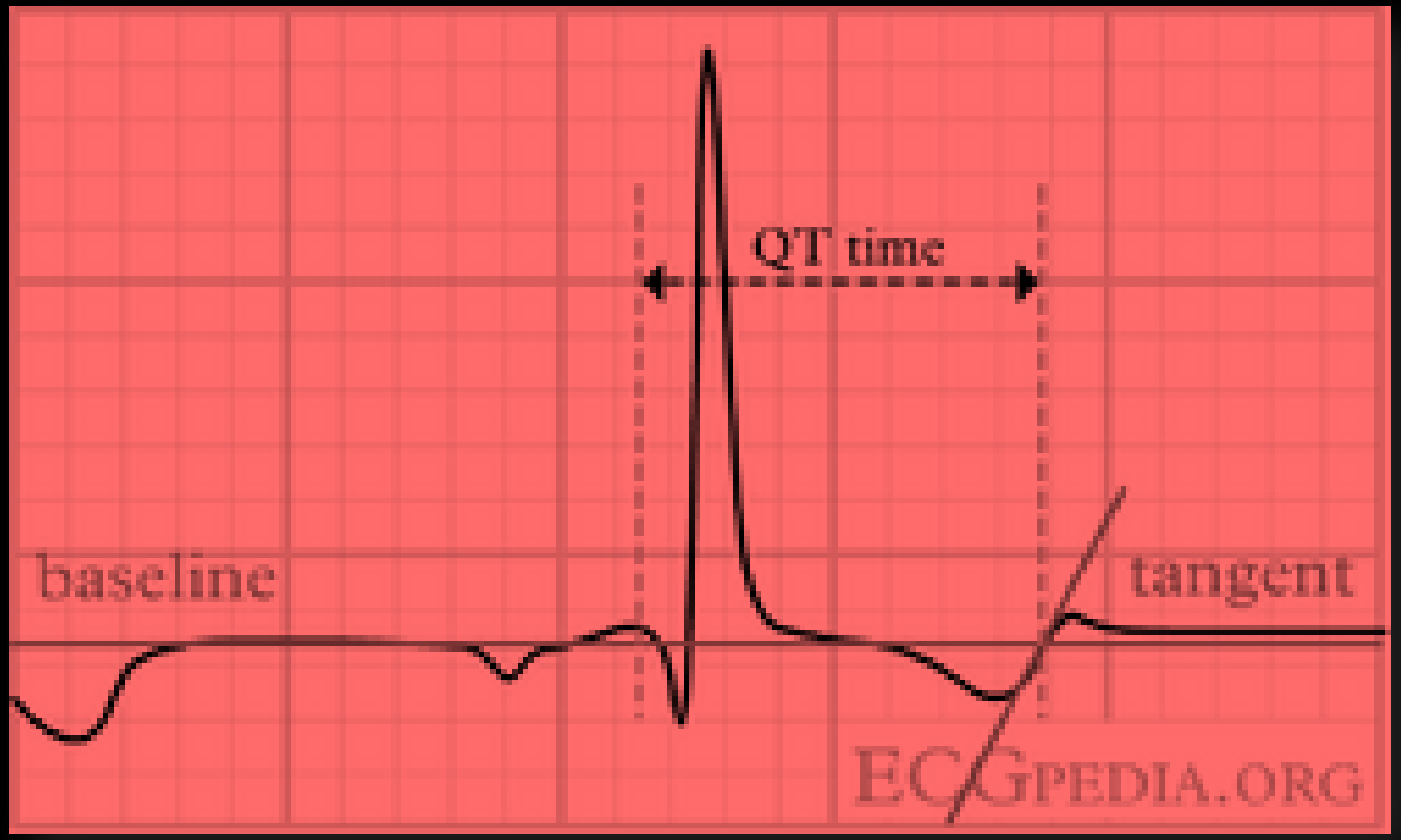
The T wave is broad, but the tangent crosses the baseline before the T wave joins the baseline. The QT interval would be overestimated when this last definition of the end of the T wave would be used.

How to measure QT if the QT segment is abnormal



The ECG does not meet the baseline after the end of the T wave. Still, the crossing of the tangent and baseline should be used for measurements

How to measure QT if the QT segment is abnormal



A bifasic T wave. The tangent to the 'hump' with the largest amplitude is chosen. This can change from beat to beat, making it more important to average several measurements.

R&A

Measuring QT Prolongation

QTc values for normal and prolonged QT interval after correction with Bazett's formula

	QTc values by age group and sex (ms)		
	1–15 years	**Adult males**	**Adult females**
Normal	<440	<430	<450
Borderline	440–460	430–450	450–470
Prolonged (top 1%)	>460	>450	>470

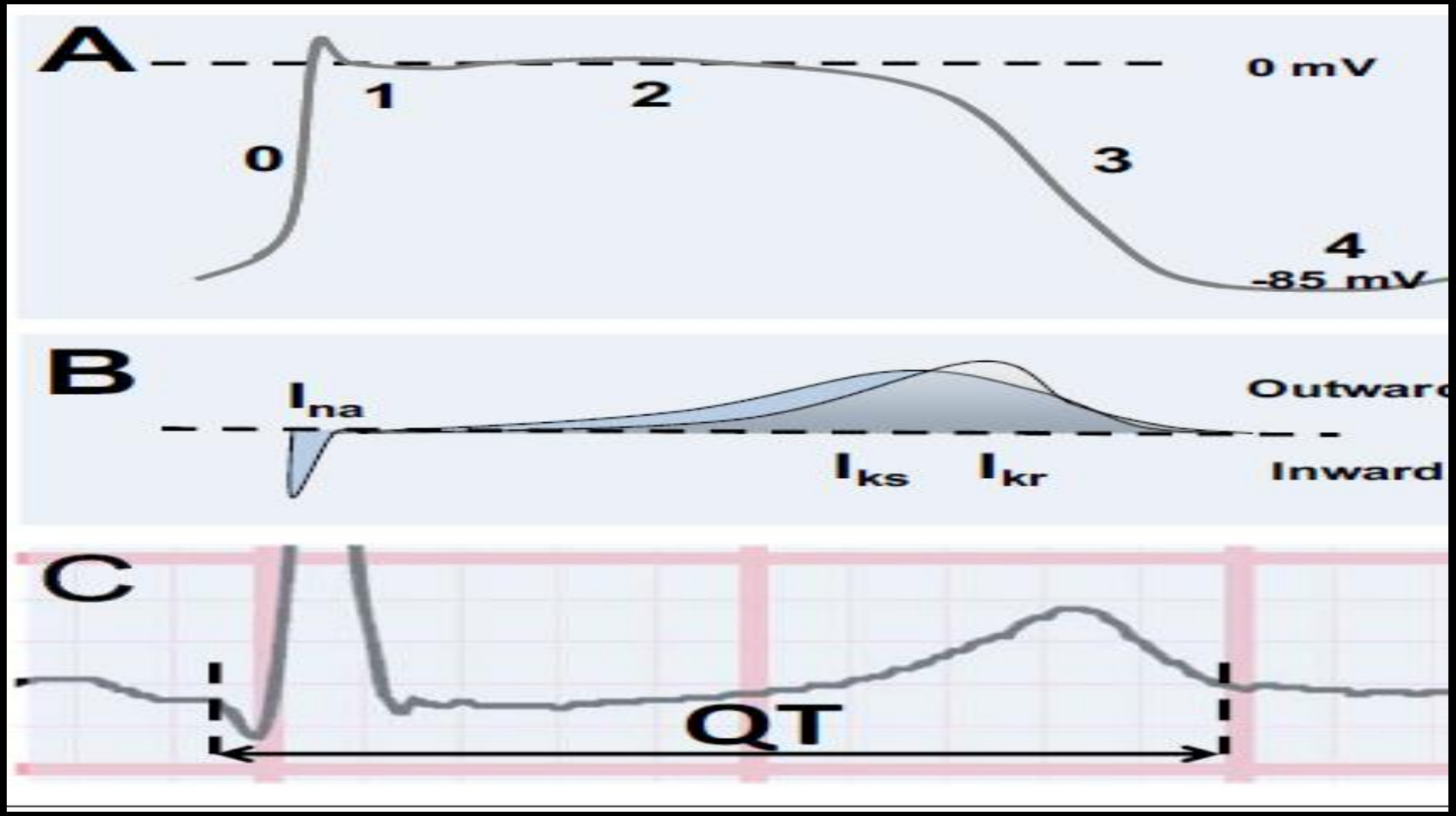
QTc Reference Values

QTc	Male (msec)	Female (msec)
Normal	≤430	≤450
Borderline	431-450	451-470
Prolonged	>450	>470

There is considerable intra- individual variability of the QTc: multiple studies have shown that it can vary by anywhere from 76 to 102 ms over the course of 24 hours. It has also been demonstrated that the QTc will increase during sleep and following a meal, by approximately 20 msec. ECG readings should be made at or near the maximum daily blood level of medications affecting the QT interval.

Am J Psychiatry 2001; 158:1774–1782. Dtsch Arztebl Int 2011; 108(41): 687–93

The QT Interval



Mechanism of Drug Induced QT Prolongation and Torsades de pointes

- At the cellular level, the repolarisation phase of the myocytes is driven predominantly by outward movement of potassium ions
- A variety of different K^+ channel subtypes are present in the heart
- Two important K^+ currents participating in ventricular repolarisation are the subtypes of the delayed rectifier current
  - I_{Kr} ("rapid") and I_{Ks} ("slow")
  - Blockade of either of these outward potassium currents may prolong the action potential
  - I_{Kr} is the most susceptible to pharmacological influence. It is now understood that virtually without exception, the blockade of I_{Kr} current by these drugs is at least in part responsible for their pro-arrhythmic effect
- Blockade of the I_{Kr} current manifests clinically as a prolonged QT interval (and the emergence of other T or U wave abnormalities on the surface ECG)

Mechanism of Drug Induced QT Prolongation and Torsades de pointes contd…

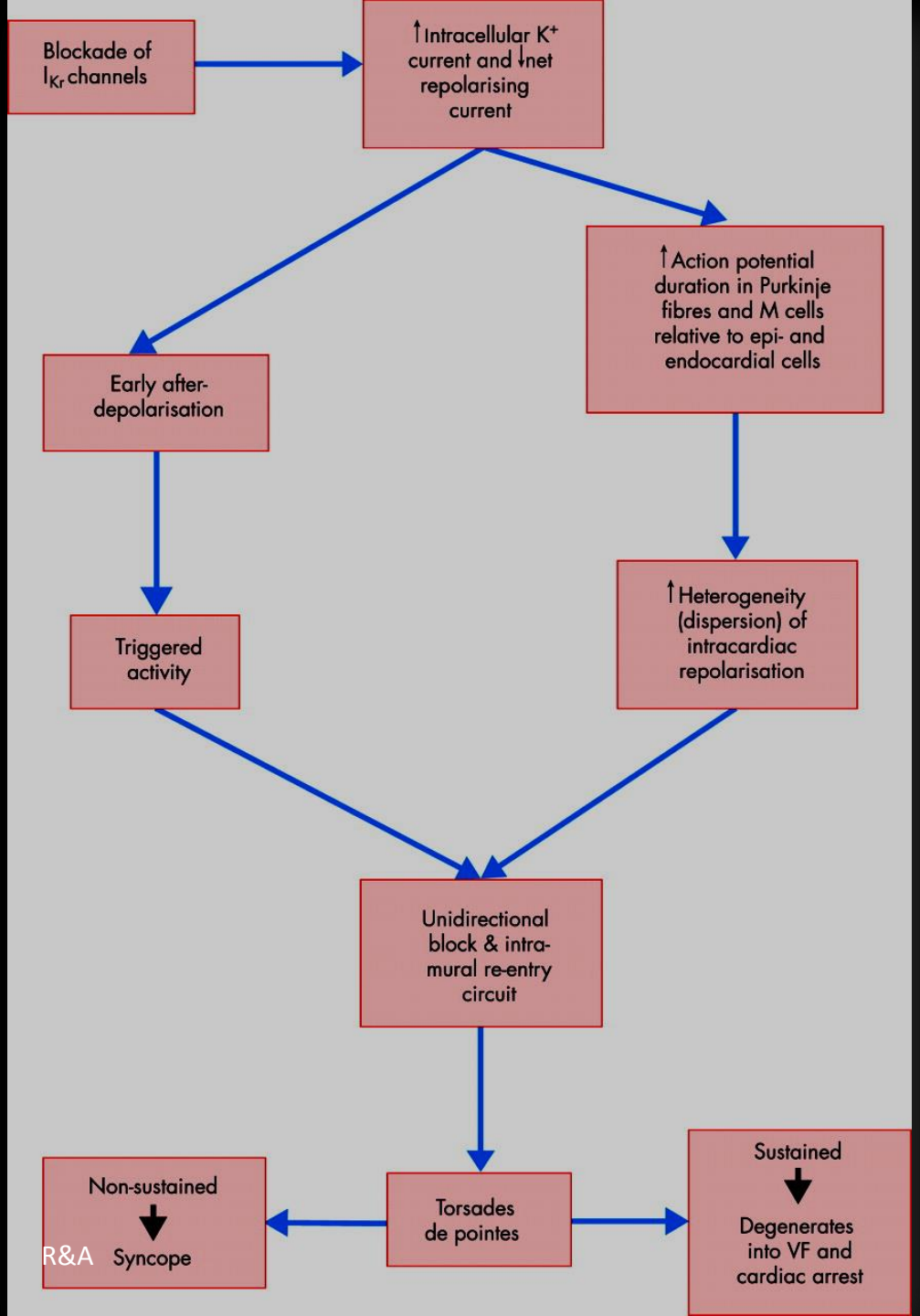
- The prolongation of repolarisation results in subsequent inward depolarisation current, known as an early after-depolarisation
  When accompanied by increased dispersion of repolarisation, TdP is provoked, which is sustained by further re-entry or spiral wave activity

- Such phenomena are more readily induced in the His-Purkinje network and also from a subset of myocardial cells from the mid ventricular myocardium, known as M cells

- Compared to subendocardial or subepicardial cells, M cells show much more pronounced action potential prolongation in response to I_{Kr} blockade.

  Resulting in a pronounced dispersion of repolarisation (that is, heterogeneous recovery of excitability), creating a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry that is sustaining the TdP.

Arrhythmogenesis of torsades de pointes

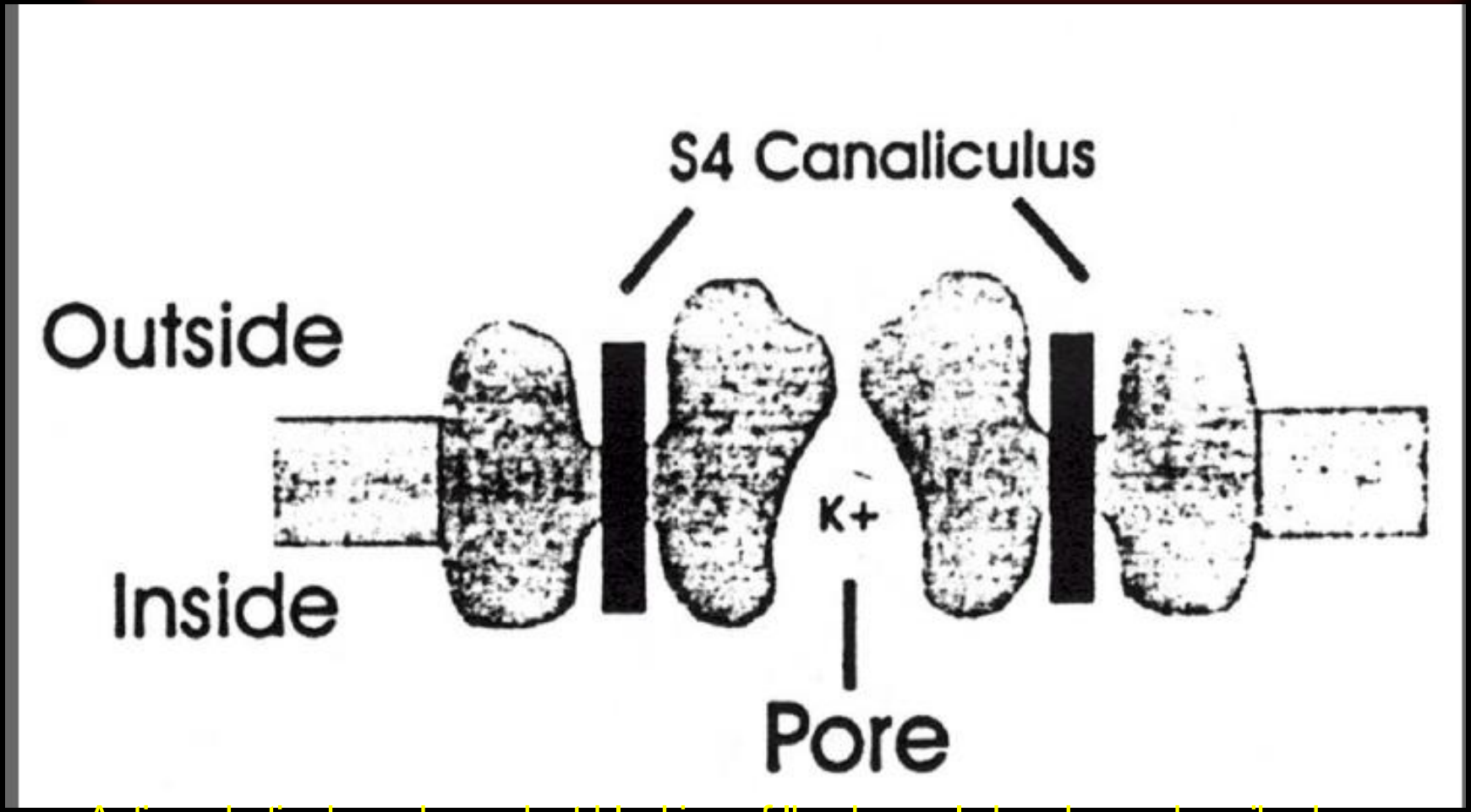


VF, ventricular fibrillation

Yap, Y. G. et al. Heart 2003;89:1363-1372

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The QT Interval
Ikr Channel: hERG controlled



Antipsychotic dose-dependent blocking of Ikr channels has been described.

(*Drolet1999,;TieH2000)*

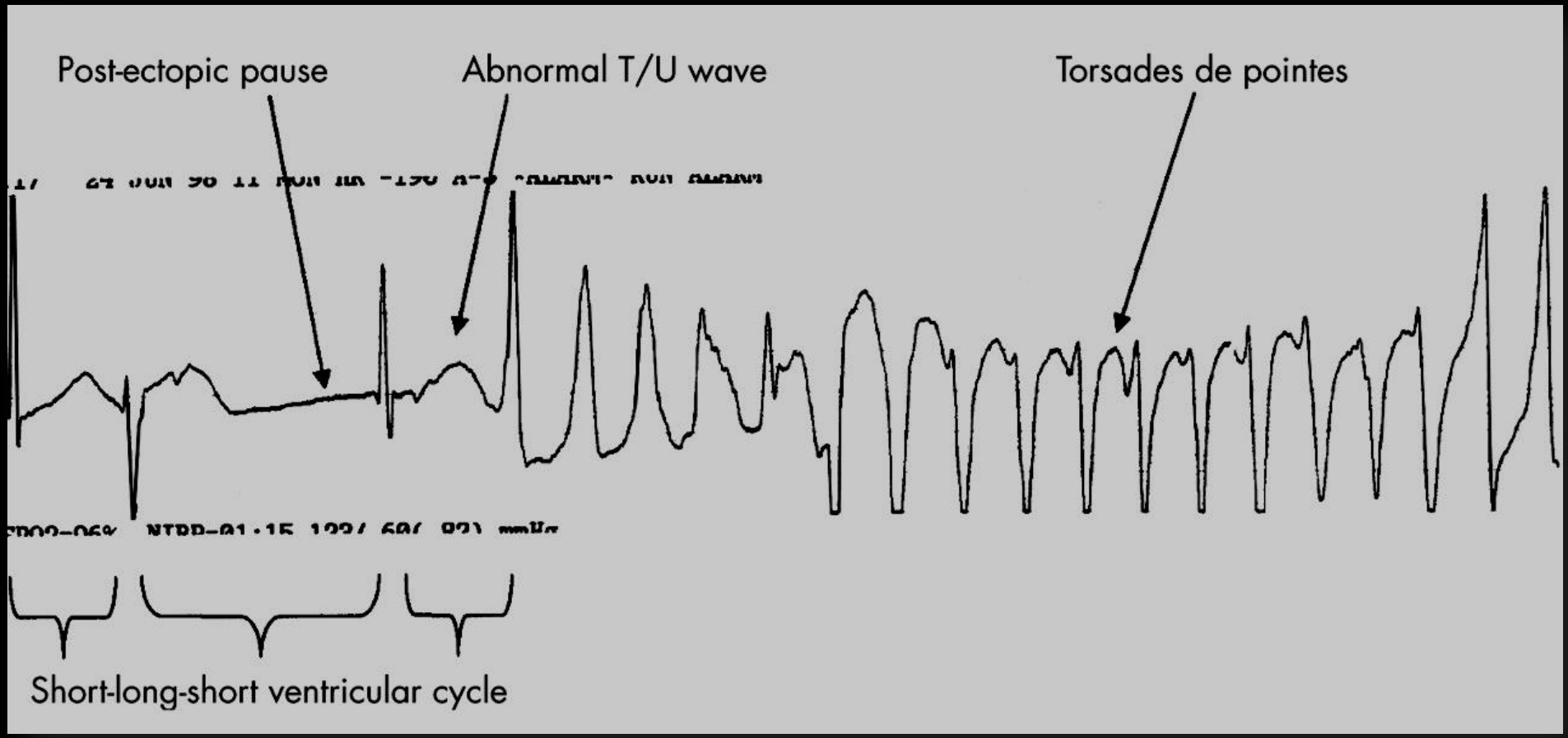
Generic Name	Brand Name	Class/Clinical Use	Comments
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Bepridil	Vascor®	Anti-anginal / heart pain	Females>Males
Chloroquine	Aralen®	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	Propulsid®	GI stimulant / heartburn	Restricted availability; Females>Males.
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Motilium®	Anti-nausea / nausea	Not available in the U.S.
Droperidol	Inapsine®	Sedative;Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	Erythrocin®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Erythromycin	E.E.S.®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence	
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia	
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence	Females>Males
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence	Females>Males
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females>Males
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic / Tourette's tics	Females>Males
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm	
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	
Terfenadine	Seldane®	Antihistamine / Allergic rhinitis	No longer available in U.S.
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia	

R&A

Characteristic Sequence before the Onset of TdP

- The first ventricular complex of the sequence is usually a ventricular ectopic beat or the last beat of a salvo of ventricular premature beats. This is then followed by a compensatory pause terminated by a sinus beat. The sinus beat frequently has a very prolonged QT interval and an exaggerated U wave. A ventricular extrasystole then falls on the exaggerated U wave of the sinus beat and precipitates the onset of TdP. It has been suggested that post-pause accentuation of the U wave, if present, may be a better predictor of drug induced TdP than the duration of QTc interval.

Rhythm Strip in a Patient with Drug Induced TdP



Note the typical short-long-short initiating ventricular cycle, pause dependent QT prolongation, and abnormal TU wave leading to the classical "twisting of a point" of the cardiac axis during TdP.

R&A

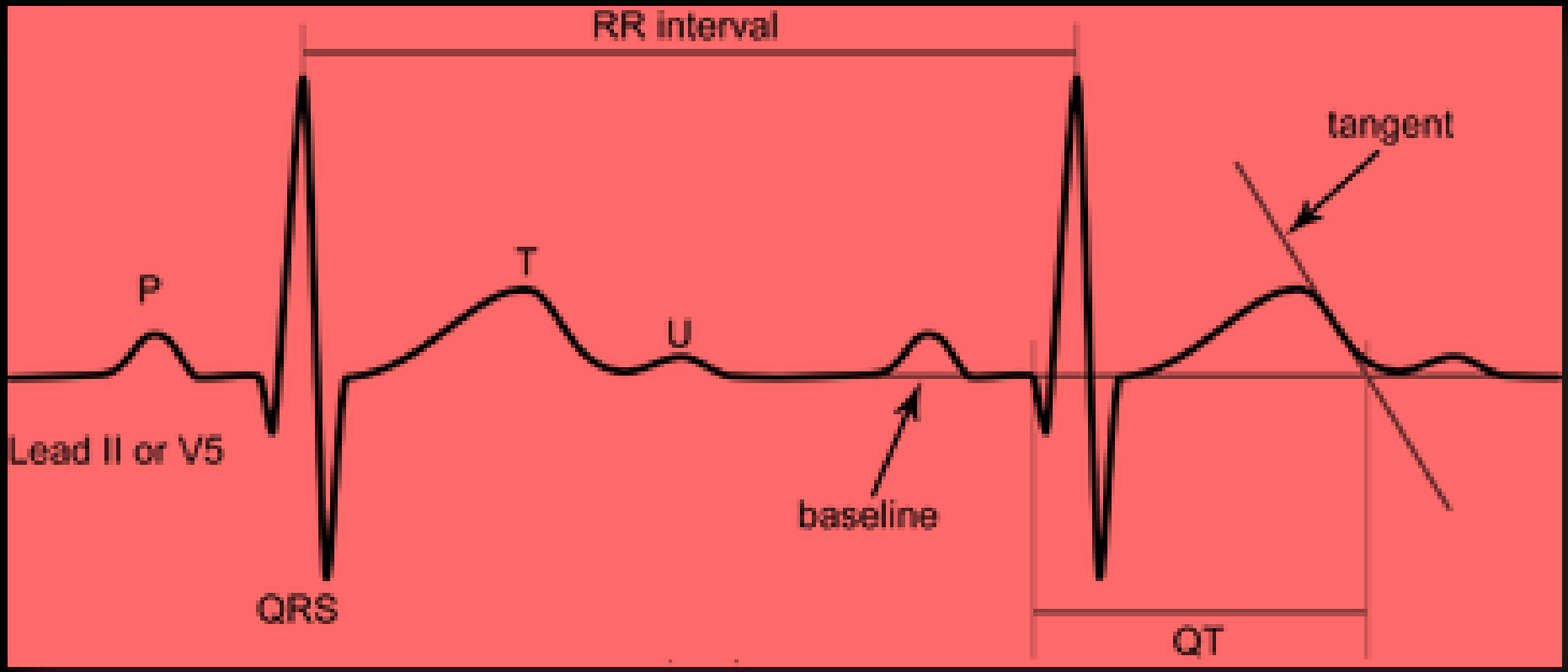
Yap, Y. G. et al. Heart 2003;89:1363-1372

Measuring QT Prolongation

- For QT, ECG is best recorded at a paper speed of 50 mm/s and at an amplitude of 0.5 mV/cm using a multichannel recorder capable of simultaneously recording all 12 leads
- A tangent line to the steepest part of the descending portion of the T wave is then drawn. The intercept between the tangent line and the isoelectric line is defined as the end of the T wave
- The QT interval is measured from the beginning of the QRS complex to the end of the T wave on a standard ECG
  - There are no available data on which lead or leads to use for QT interval measurement
  - Traditionally, lead II has been used for QT interval measurement because in this lead, the vectors of repolarisation usually result in a long single wave rather than discrete T and U waves

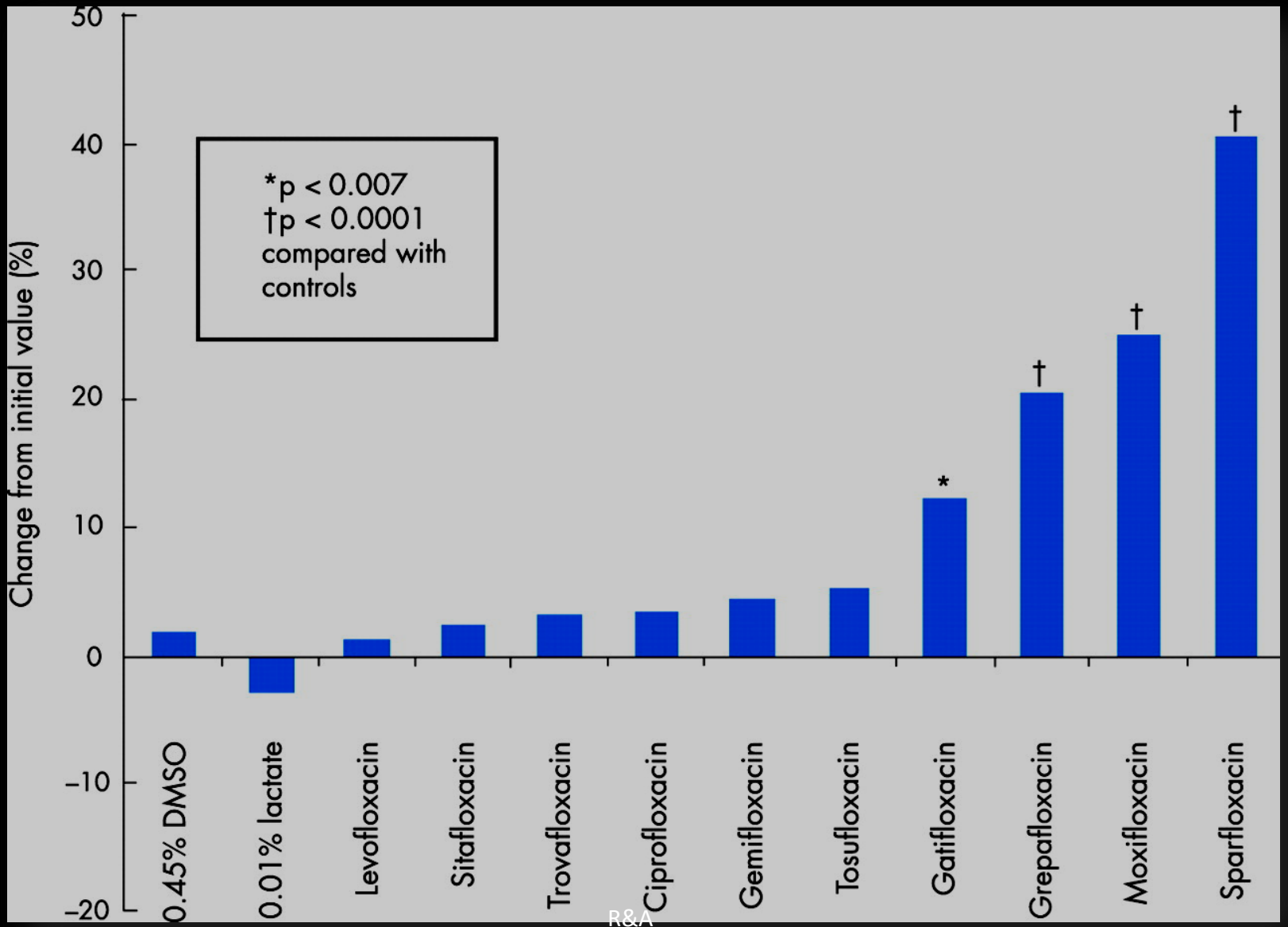
Measuring QT Prolongation

- Generally, QT prolongation is considered when the QTc interval is greater than 440 ms (men) and 460 ms (women), although arrhythmias are most often associated with values of 500 ms or more
- The severity of pro-arrhythmia at a given QT interval varies from drug to drug and from patient to patient. Unfortunately, the extent of QT prolongation and risk of TdP with a given drug may not be linearly related to the dose or plasma concentration of the drug because patient and metabolic factors are also important (for example, sex, electrolyte concentrations, etc)
- Furthermore, there is not a simple relation between the degree of drug induced QT prolongation and the likelihood of the development of TdP, which can occasionally occur without any substantial prolongation of the QT interval.



The QT interval start at the onset of the Q wave and ends where the tangent line for the steepest part of the T wave intersects with the baseline of the ECG. The normal value for QTc(orrected) is: below 450ms for men and below 460ms for women

Effect of Various Fluoroquinolones on Prolonging Action Potential Duration



R&A

Yap, Y. G. et al. Heart 2003;89:1363-1372

The QT Interval
hERG channel affinities for Antipsychotics

Comparison of QT_c changes, HERG IC_{50} and plasma concentrations for various antipsychotic drugs

Drug	ΔQT_c (ms)[b]	HERG IC_{50} (nM)	[Total plasma] (nM)	[Free plasma][c] (nM)	[Total plasma]/ HERG IC_{50}	[Free plasma]/ HERG IC_{50}
Thioridazine	29.6	191	2064	20.6	10.8	0.11
Ziprasidone	15.5	169	414	4.1	2.4	0.02
Quetiapine	4.8	5765	3329	566	0.6	0.10
Risperidone	3.0	167	143	14.3	0.9	0.09
Olanzapine	1.1	6013	176	12.3	0.03	0.002

In addition to HERG channel/receptor affinities, pharmacokinetic considerations will also determine the potential for a drug to prolong QTc interval. For this limited series of drugs, the ratio of total plasma concentration to HERG IC50 appeared to correspond well with the observed changes in QTc.

European Journal of Pharmacology 450 (2002) 37–41

The QT Interval.INa Channel

Evidence for a crucial modulating role of the sodium channel in the QTc prolongation related to antipsychotics

Abstract

Blockade of the cardiac hERG channel is recognized as the main mechanism underlying the QT prolongation induced by many classes of drugs, including antipsychotics. However, antipsychotics interact with a variety of other pharmacological targets that could also modulate cardiac function. The present study aims to identify those key factors involved in the QT prolongation induced by antipsychotics. The interactions of 28 antipsychotics were measured on a variety of pharmacological targets. Binding affinity (K_i), functional channel blockade (IC_{50}), and the corresponding ratios to total and free plasma drug concentration were compared with the corrected QT changes (QTc) associated with the therapeutic use of these drugs by multivariable linear regression analysis to determine the best predictors of QTc. Besides confirming hERG as the primary predictor of QTc, all analyses consistently show the concomitant involvement of $Na_V1.5$ channel as modulating factor of the QTc related to hERG blockade. In particular, the hERG/$Na_V1.5$ ratio explains the 57% of the overall QTc variability associated with antipsychotics. Since it is known that inhibition of late I_{Na} could offset the dysfunctional effects of hERG blockade, we hypothesize the inhibition of late I_{Na} as a crucial compensatory mechanism of the QTc associated with antipsychotics and hence an important factor to consider concomitantly with hERG blockade to appraise the arrhythmogenic risk of these drugs more accurately.

R&A **Journal of Psychopharmacology 2014, Vol. 28(4) 329– 340**

Drug related factors inducing QTc Prolongation

Drug-Drug Interactions

- Farmacokinetic
- Farmacodynamic

Drug-Gene Interactions

- Genetic Polimorphisms

Drugs associated with QTc Prolongation and Antipsychotic PK and PD Interactions

- Antiarrhythmics
  - Class I
    - Qunidine
    - Disopyramide
    - Procainamide
  - Class III
    - Sotalol
    - Amiodarone
    - Dofetilide
- Antibiotics
  - Macrolides
    - Erythromycin
    - Clarithromycin
    - Azithromycin
  - Quinolones
    - Levofloxacin
    - Moxifloxacin
- Antifungals
  - Fluconazole
  - Ketoconazole
- Other Antibiotics
  - Pentamidine
- Antimalarials
  - Chloroquine
  - Halofantrine
- Other Medications
  - Tamoxifen
  - Vandetanib
  - Furosemide
  - Terfenadine (withdrawn
  - Cisapride (withdrawn du
  - Methadone

Table 3 Pharmacokinetic DDIs occurring more than once

Substrate + inhibitor (CYP450 enzyme)	N
Ondansetron + acetaminophen (1A2)	11
Tacrolimus + metronidazole (3A4)	9
Amiodarone + metronidazole (3A4)	8
Ondansetron + amiodarone (2D6)	7
Ondansetron + famotidine (1A2)	6
Risperidone + amiodarone (2D6)	5
Haloperidol + famotidine (1A2)	5
Ondansetron + lidocaine (1A2)	5
Voriconazole + metronidazole (3A4, 2C9)	5
Tacrolimus + voriconazole (3A4)	5
Haloperidol + acetaminophen (1A2)	3
Diphenhydramine + amiodarone (3A4, 2D6)	3
Haloperidol + amiodarone (3A4, 2D6)	3
Citalopram + pantoprazole (2C19)	3
Ondansetron + diltiazem (3A4)	3
Risperidone + haloperidol (2D6)	3
Amiodarone + diltiazem (3A4)	2
Nicardipine + amiodarone (3A4)	2
Trazodone + amiodarone (3A4, 2D6)	2
Verapamil + amiodarone (3A4, 1A2)	2
Diphenhydramine + venlafaxine (2D6)	2
Ondansetron + escitalopram (2D6)	2
Ondansetron + haloperidol (2D6)	2
Ondansetron + venlafaxine (2D6)	2

Table 4 Pharmacodynamic interactions occurring more than once

Medication combination	N
Amiodarone + ondansetron	8
Tacrolimus + voriconazole	7
Amiodarone + risperidone	4
Diphenhydramine + tacrolimus	4
Amiodarone + diphenhydramine	4
Amiodarone + haloperidol	3
Amiodarone + nicardipine	3
Diphenhydramine + ondansetron	3
Nicardipine + ondansetron	3
Ondansetron + risperidone	3
Amiodarone + azithromycin	2
Amiodarone + perflutren	2
Amiodarone + sulfamethoxazole/trimethoprim	2
Diphenhydramine + venlafaxine	2
Diphenhydramine + voriconazole	2
Fluoxetine + moxifloxacin	2
Haloperidol + ondansetron	2
Haloperidol + risperidone	2
Ondansetron + sulfamethoxazole/trimethoprim	2
Ondansetron + venlafaxine	2

Pharmacokinetic drug-drug interactions involving the cytochrome P450 (CYP) 3A4 and 2D6 enzymes occurred commonly. It is surprising to note that CYP450 1A2 nteractions were involved in 32/162 (19.8%) of the PK DDIs found in this study. Cardiac death occurs in a large number of patients and it is unknown how many of these deaths are due to unintended and unmonitored QTc prolongation from DDIs.

R&A

Journal of Critical Care (2013) 28, 243–249

Psychotropic drugs association and QTc Prolongation

In clinical practice, combination of psychotropic drugs that affect myocardial repolarization and prolong the QTc, is very frequent.

- Slow CYP2D6 metabolizers and patients concomitantly taking other drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, bupropion, duloxetine, venlafaxine and trazodone are at particularly elevated risk.
- Moreover combination of antipsychotics increase the risk of QTc Prolongation.

R&A

Journal of Critical Care (2013) 28, 243–249
Psychopharmacology (2013) 228:515–524

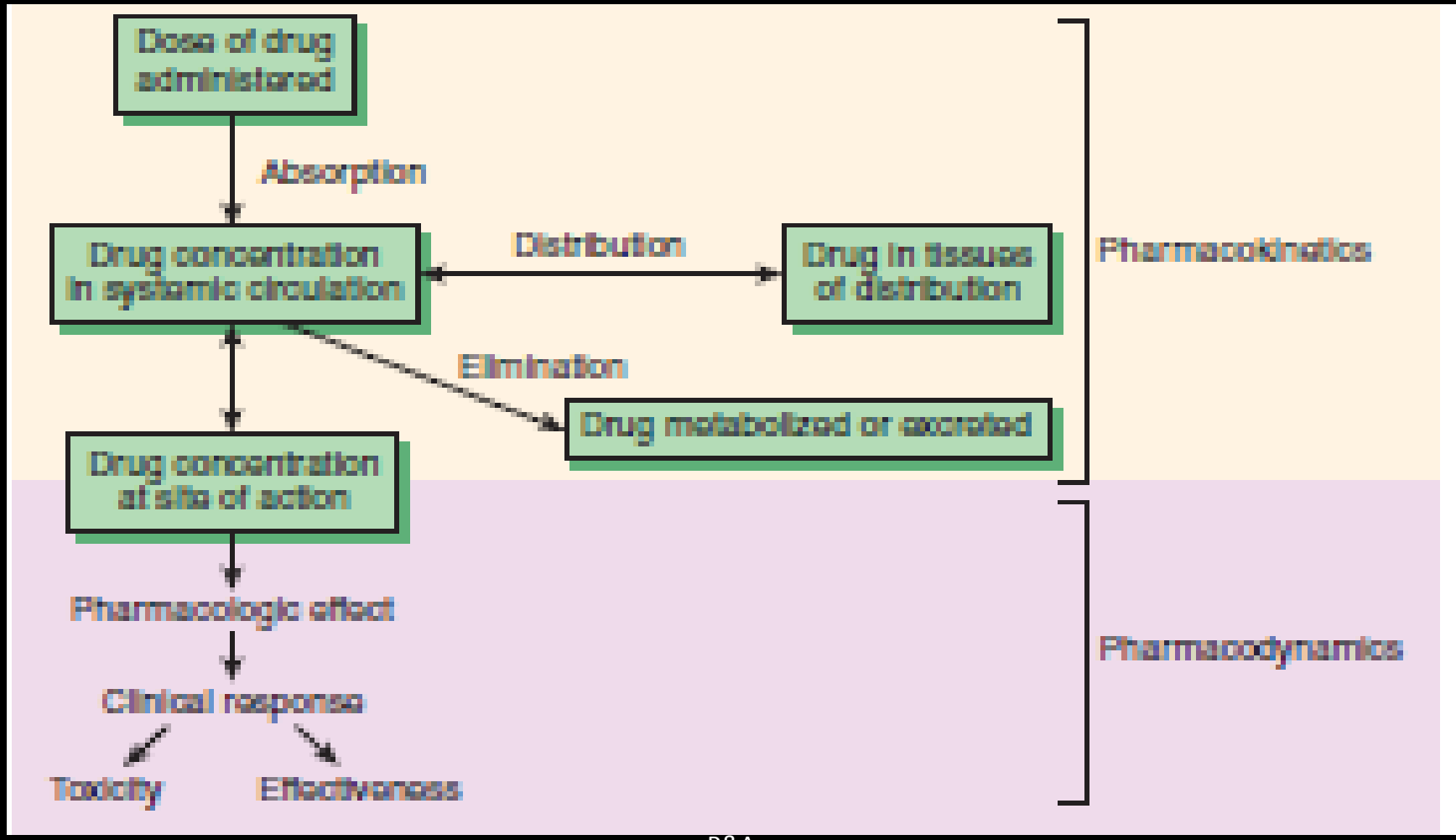
Psychotropic drugs association and QTc Prolongation

Substrati, inibitori e induttori dei principali farmaci che metabolizzano isoenzimi del citocromo P450 (CYP). (Spina E et al, 2008)

Enzima	Substrati	Inibitori	Induttori
CYP1A2	Antidepressivi: amitriptilina,* clomipramina,* duloxetina, fluvoxamina, imipramina,* mirtazapina - Antipsicotici: clozapina, aloperidolo, olanzapina - Miscellanea: caffeina, melatonina, fenacetina, tacrina, teofillina, R-warfarin	Ciprofloxacina Enoxacina Fluvoxamina	Barbiturici Carbamazepina Fenitoina Rifampicina Fumo di sigaretta
CYP2C9	FANS: diclofenac, ibuprofene, naprossene, piroxicam - Miscellanea: losartan, fenobarbital, fenitoina, tolbutamide, acido valproico, valsartan, S-warfarin	Fluconazolo Fluoxetina[2] Fluvoxamina[2] Sulfafenazolo	Barbiturici Carbamazepina Fenitoina Rifampicina
CYP2C19	Antidepressivi: amitriptilina,* citalopram, clomipramina,* escitalopram, imipramina* - Miscellanea: diazepam, lansoprazolo, omeprazolo, fenitoina, proguanil, propanololo	Fluvoxamina Omeprazolo Ticlopidina	Barbiturici Carbamazepina Fenitoina Rifampicina
CYP2D6	Antiaritmici: encainide, flecainide, propafenone - Antidepressivi: amitriptilina,[1] citalopram, clomipramina,[1] desipramina,[1] escitalopram, fluoxetina, fluvoxamina, imipramina,[1] mirtazapina, nortriptilina,[1] paroxetina, venlafaxina - Antipsicotici: aripiprazolo, clozapina, aloperidolo, olanzapina, perfenazina, risperidone, sertindolo, tioridazina - β-bloccanti: alprenololo, bufuralolo, metoprololo, propanololo, timololo - Miscellanea: atomoxetina, codeina, donepezil, galantamina, fenformina, tramadolo	Bupropione[3] Duloxetina[3] Fluoxetina Paroxetina Chinidina Tioridazina[5]	Nessuno conosciuto
CYP3A4	Antidepressivi: amitriptilina,* citalopram, clomipramina,* escitalopram, imipramina,* mirtazapina, nefazodone, sertralina, venlafaxina - Antipsicotici: aripiprazolo, clozapina, aloperidolo, pimozide, quetiapina, risperidone, sertindolo, ziprasidone - Benzodiazepine: alprazolam, clonazepam, diazepam, midazolam, triazolam - Calcio-antagonisti: diltiazem, felodipina, nifedipina, verapamil - Statine: atorvastatina, lovastatina, pravastatina, simvastatina - Immunosoppressori: ciclosporina, sirolimus, tacrolimus - Miscellanea: amiodarone, astemizolo,[5] carbamazepina, cisapride,[5] claritromicina, donepezil, eritromicina, etinil estradiolo, galantamina, levonorgestrel, metadone, chinidina, ritonavir, tamoxifene, terfenadina[5]	Eritromicina Succo di pompelmo Itraconazolo Ketoconazolo Nefazodone Ritonavir[6] Troleandomicina	Barbiturici Carbamazepina Fenitoina Rifampicina Ritonavir[6]

*Demetilazione.
[1]Enzimi inibitori meno potenti del fluconazolo e del sulfafenazolo.
[2]Idrossilazione.
[3]Ritirato dal mercato degli Stati Uniti.
[4]Un potente inibitore del CYP3A4 che induce l'enzima anche dopo qualche settimana.
Adattato da Cozza et al.

Drug Metabolism and QTc Prolongation



Katzung B.G.Basic and Clinical Pharmacology 2012.

Abstract BACKGROUND: Antipsychotic agents have been associated with a prolonged QT interval. Data on the effects of ziprasidone and haloperidol on the QTc interval are lacking. OBJECTIVE: This study aimed to characterize the effects of 2 **high-dose intramuscular injections of ziprasidone and haloperidol** on the QTc interval at T(max). METHODS: This randomized, single-blind study enrolled patients with schizophrenia or schizoaffective disorder in whom long-term antipsychotic therapy was indicated. Patients were randomized to receive 2 high-dose intramuscular injections of ziprasidone (20 and 30 mg) or haloperidol (7.5 and 10 mg) separated by 4 hours. The primary outcome measure was the mean change from baseline in QTc at the T(max) of each injection. Each dose administration was followed by serial ECG and blood sampling for pharmacokinetic determinations. Twelve-lead ECG data were obtained immediately before and at predetermined times after injections. ECG tracings were read by a blinded central reader. Blood samples were obtained immediately before and after injections. Point estimates and 95% CIs for mean QTc and changes from baseline in QTc were estimated. No between-group hypothesis tests were conducted. For the assessments of tolerability and safety profile, patients underwent physical examination, including measurement of vital signs, clinical laboratory evaluation, and monitoring for adverse events (AEs) using spontaneous reporting. RESULTS: A total of 59 patients were assigned to treatment, and 58 received study medication (ziprasidone, 31 patients; haloperidol, 27; age range, 21-72 years; 79% male). **After the first injection, mean (95% CI) changes from baseline were 4.6 msec (0.4-8.9) with ziprasidone (n = 25) and 6.0 msec (1.4-10.5) with haloperidol (n = 24). After the second injection, these values were 12.8 msec (6.7-18.8) and 14.7 msec (10.2-19.2), respectively.** Mild and transient changes in heart rate and blood pressure were observed with both treatments. None of the patients had a QTc interval >480 msec. Two patients in the ziprasidone group experienced QTc prolongation >450 msec (457 and 454 msec) and QTc changes that exceeded 60 msec (62 and 76 msec) relative to the time-matched baseline values. With haloperidol, QTc interval values were <450 msec with no changes >60 msec. Treatment-emergent AEs were reported in 29 of 31 patients (93.5%) in the ziprasidone group and 25 of 27 patients (92.6%) in the haloperidol group; most events were of mild or moderate severity. Frequently reported AEs were somnolence (90.3% and 81.5%, respectively), dizziness (22.6% and 7.4%), anxiety (16.1% and 7.4%), extrapyramidal symptoms (6.5% and 33.3%), agitation (6.5% and 18.5%), and insomnia (0% and 14.8%).

CONCLUSIONS: In this study of the effects of high-dose ziprasidone and haloperidol in patients with schizophrenic disorder**, none of the patients had a QTc interval >480 msec, and changes from baseline QTc interval were clinically modest with both drugs.** Both drugs were generally well tolerated.

Clin Ther. 2010 Mar;32(3):472-91. **Effects of high-dose ziprasidone and haloperidol on the QTc interval after intramuscular administration: a randomized, single-blind, parallel-group study in patients with schizophrenia or schizoaffective disorder.** Miceli JJ, Tensfeldt TG, Shiovitz T, Anziano RJ, O'Gorman C, Harrigan RH.

Case Report American Journal of Emergency Medicine (2012) 30, 837.e1–837.e2

Single-dose ziprasidone associated with QT interval prolongation

Abstract

Ziprasidone has been rarely associated with QT prolongation especially in patients (1) with no underlying cardiac or metabolic disorders, (2) who are receiving no concomitant medications known to prolong the QT interval, and (3) whom therapy is being initiated at a low dose. We report a 47-year-old patient who was agitated with suicidal ideation. He had a history of cocaine use, the last time being 72 hours before emergency department (ED) presentation. His electrocardiogram (ECG) on arrival in the ED showed a QT of 484 milliseconds and a QTc of 475 milliseconds with a pulse of 58 beats per minute. The patient was given 20 mg intramuscular (IM) ziprasidone for agitation. He reported feeling palpitations and weakness 45 minutes after receiving ziprasidone. His QT interval was prolonged on ECG and returned to baseline after 72 hours. Clinicians should consider obtaining an ECG before ziprasidone administration.

J Hosp Med. 2010 Apr;5(4):E8-16.

The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond?

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Abstract

BACKGROUND: **In September 2007, the Food and Drug Administration (FDA) strengthened label warnings for intravenous (IV) haloperidol regarding QT prolongation (QTP) and torsades de pointes (TdP) in response to adverse event reports.** Considering the widespread use of IV haloperidol in the management of acute delirium, the specific FDA recommendation of continuous electrocardiogram (ECG) monitoring in this setting has been associated with some controversy. We reviewed the evidence for the FDA warning and provide a potential medical center response to this warning.

METHODS: Cases of intravenous haloperidol-related QTP/TdP were identified by searching PubMed, EMBASE, and Scopus databases (January 1823 to April 2009) and all FDA MedWatch reports of haloperidol-associated adverse events (November 1997 to April 2008).

RESULTS: A total of 70 of IV haloperidol-associated QTP and/or TdP were identified. There were 54 reports of TdP; 42 of these events were reportedly preceded by QTP. When post-event QTc data were reported, QTc was prolonged >450 msec in 96% of cases. Three patients experienced sudden cardiac arrest. **Sixty-eight patients (97%) had additional risk factors for TdP/prolonged QT, most commonly receipt of concomitant proarrhythmic agents.** Patients experiencing TdP received a cumulative dose of 5 mg to 645 mg, patients with QTP alone received a cumulative dose of 2 mg to 1540 mg.

CONCLUSIONS: While administration of IV haloperidol can be associated with QTP/TdP, this complication most often took place in the setting of concomitant risk factors. **Importantly, the available data suggest that a total cumulative dose of IV haloperidol of <? mg can safely be administered without ongoing electrocardiographic monitoring in patients without concomitant risk factors.**

The QTc Prolongation and Antipsychotics

Table III. Mean change in QTc and heart rate from baseline to steady state. Results of Pfizer Study 054[8]

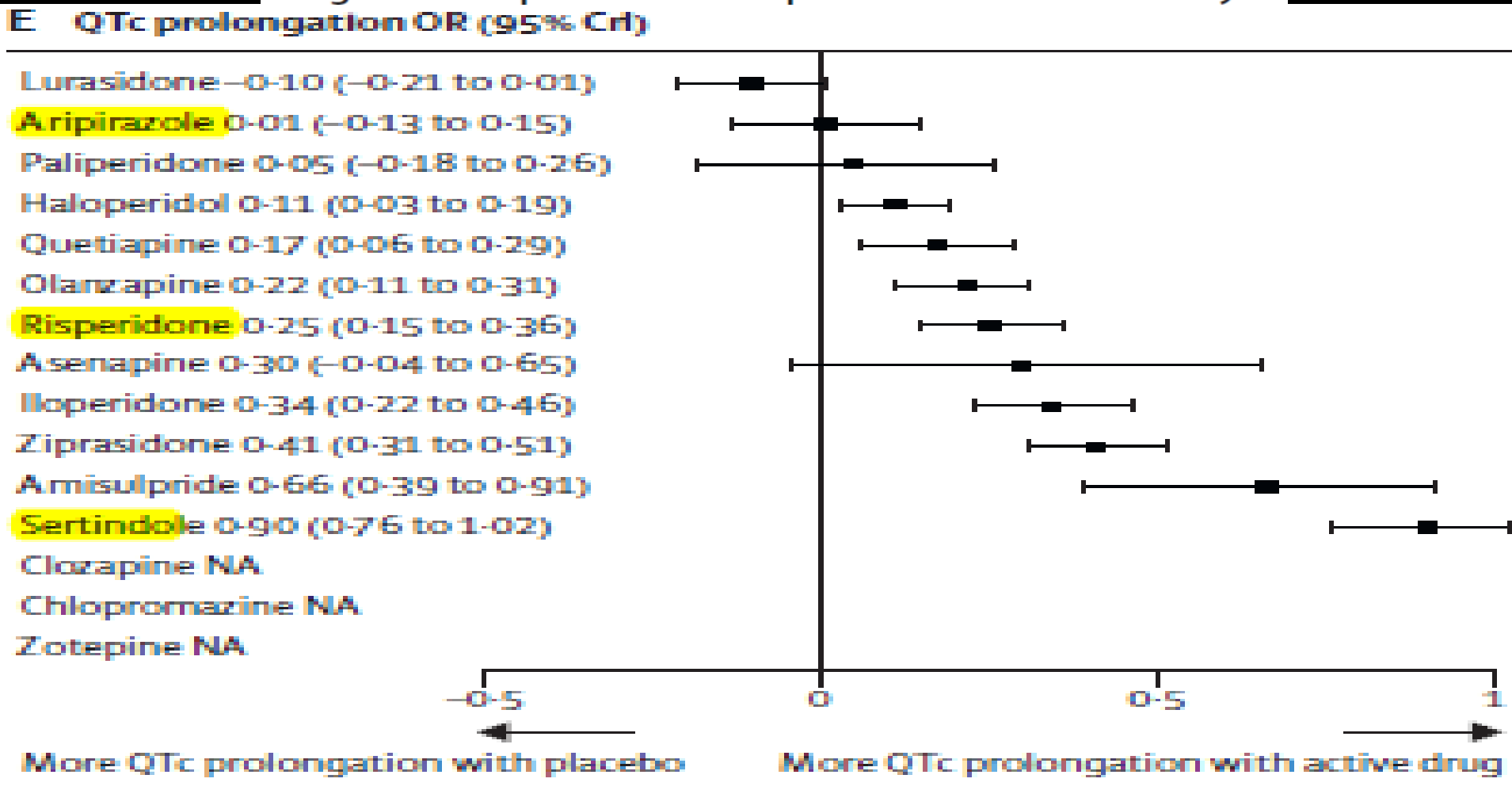
Drug	QTc (Bazett)[msec]	QTc (Fridericia)[msec]	Heart rate (beats per min)
Thioridazine	+35.8	+29.6	+5.7
Ziprasidone	+20.6	+15.6	+4.6
Quetiapine	+14.5	+4.8	+11.2
Risperidone	+10.0	+3.0	+6.4
Olanzapine	+6.4	+1.1	+6.5
Haloperidol	+4.7	+7.3	–2.9

- Individual changes of less than 30 msec unlikely to be of concern
- > 60 msec over baseline or an absolute QTc of greater than 500 msec, or at lower heart rates uncorrected QT > 500msec of concern

J Clin Psychopharmacol.2004. 24:62–69

The QTc Prolongation and Antipsychotics

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis



The Lancet 2013:382;951-962

The QTc Prolongation and Antipsychotics

Changes in the Metabolic Parameters and QTc Interval After Switching From Olanzapine to Aripiprazole in Japanese Patients With Stable Schizophrenia

TABLE 1. Changes in the Clinical and Metabolic Parameters After Switching From OLZ to ARP Treatment (N = 19)

	OLZ Treatment	ARP Treatment	*P*
Dose, mg	14.6 ± 9.2	20.8 ± 8.1	
BPRS	27.7 ± 8.0	26.5 ± 7.2	NS
Body weight, kg	62.5 ± 13.5	59.6 ± 13.3	0.02
WC, cm	53.7 ± 24.7	54.5 ± 25.9	NS
Electrolyte, mEq/L			
Na	140.3 ± 1.7	140.1 ± 1.7	NS
K	4.1 ± 0.3	4.2 ± 0.3	NS
Cl	104.3 ± 1.8	103.7 ± 1.9	NS
Mg	2.3 ± 0.1	2.3 ± 0.2	NS
QTc, milliseconds	403.8 ± 20.8	390.7 ± 22.8	0.00
Fasting plasma glucose, mg/dL	92.0 ± 10.3	92.4 ± 8.3	NS
HOMA-IR	2.5 ± 2.7	2.0 ± 2.3	NS
HbA1c, %	4.8 ± 0.4	4.8 ± 0.2	NS
Prolactin, mg/dL	34.3 ± 42.2	5.6 ± 4.8	0.00
TC, mg/dL	207.5 ± 46.5	200.1 ± 29.6	NS
TGs, mg/dL	142.0 ± 128.1	104.5 ± 94.1	0.00
HDL, mg/dL	51.3 ± 17.6	59.5 ± 18.5	<0.00
LDL, mg/dL	124.8 ± 40.8	117.3 ± 36.7	NS
Leptin, ng/mL	10.6 ± 13.0	7.7 ± 10.7	0.07
Adiponectin, μg/mL	9.2 ± 5.7	11.2 ± 6.3	0.04
TNF-α, pg/mL	1.6 ± 0.4	1.2 ± 0.4	<0.00

All values are expressed as mean ± SD.
NS indicates not significant.

Journal of Clinical Psychopharmacology 31; 4, August 2011

The QTc Prolongation and the Risk of Torsade de Pointes

Prolonged QTc may be associated with dizziness, lightheadedness, palpitations, presyncope or syncope, and ventricular tachyarrhythmias including polymorphic ventricular tachycardia or torsades de pointes (TdP). While most cases of TdP resolve spontaneously, some may degenerate into ventricular fibrillation and sudden cardiac death if not treated promptly with cardiopulmonary support and cardioversion.

The QTc Prolongation and the Risk of Torsade de Pointes

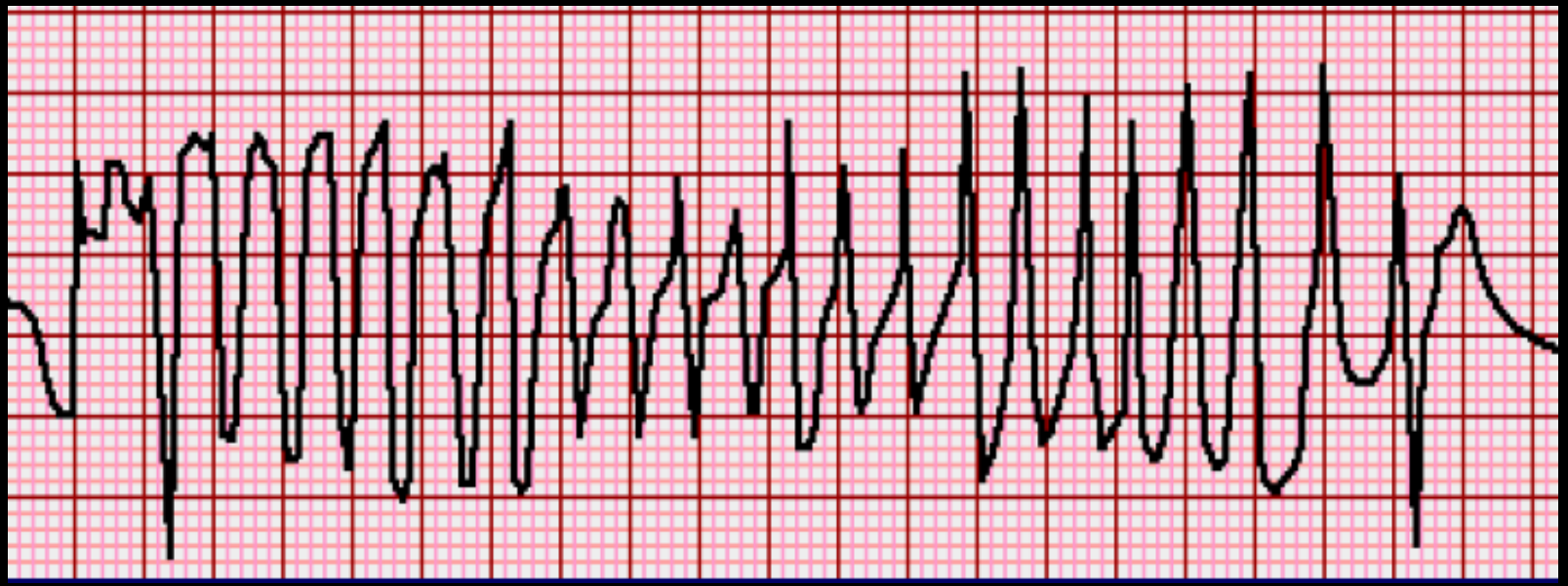
TABLE 1. Risk Factors for Prolonged QT[1–4,9]

- Female
- Increased age
- Congenital LQTS
- Electrolyte abnormalities
  - Hypokalemia
  - Hypocalcemia
  - Hypomagnesemia
- Anorexia nervosa*
- Diuretic use*
- Heart conditions
  - Bradycardia
  - Left ventricular dysfunction
  - Heart failure
  - Mitral valve prolapse
  - Myocardial infarction
- Other medical conditions
  - Renal dysfunction*
  - Hepatic dysfunction
  - Hypoglycemia*
  - Hypertension**
  - Diabetes*
  - Hypothyroidism*
  - Pituitary insufficiency*
  - CNS injury (stroke, trauma, tumor, infection)*
  - AIDS
  - Malnutrition*
  - Obesity (including acute weight gain)*

LQTS = Long QT syndrome.
* Causes QTc prolongation via effects on electrolytes.
** Causes QTc prolongation via diastolic dysfunction.

Psychosomatics 2013:54:1–13

Torsade de Pointes and Antipsychotics



A QTc above 500 ms represents a risk factor for TdP. Although a link exists between QTc and TdP, this link is neither linear nor straightforward.

Curr Drug Saf 2010; 5:97–104

Prog Cardiovasc Dis 2003; 45:415–427

Torsade de Pointes and Antipsychotics

- TdP is rare.
- Many TdP cases escape clinical detection because no ECG is recorded.
- When interpreting TdP case numbers, one must bear in mind the frequency with which different antipsychotics are prescribed.
- For some drugs, in fact, there have been no relevant studies or reports at all.

Effects of psychotropic drugs on QTc and the occurrence of torsade de pointes (TdP)

Drug	QTc prolongation	QTc (Bazett) prolongation compared to baseline in ms (n); reference no.	Reported cases of TdP	TdP risk (Arizona CERT)
Typical high-potency antipsychotic drugs				
Thioridazine[1]	+++	+28 to 36.6 (n = 60); 10	+++	1
Haloperidol[1]	+	+3.8 to 8.9 (n = 147; 4–15 mg); 4	+++	1
Pimozide[1]	+++	+19 to 24 (n = 97); 10	+	1
Perphenazine[1]	+	-55 to -16.6 (-35.7; n = 4); 7	+	
Fluphenazine[1]	+		+	
Flupentixole[1]	+		N.R.	
Benperidol[1]	Ø	-17.1 (n = 1); 7	N.R.	
Bromperidol[1]	+	-15.6 to 19.2 (+1.8; n = 5); 7	N.R.	
Zuclopenthixole[1]	Ø	-25.5 to 1.1 (-12.2; n = 9); 7	N.R.	
Perazine[1]	N.R.		N.R.	
Fluspirilene	N.R.		N.R.	
Typical low-potency antipsychotic drugs				
Chlorpromazine[1]	++		++	1
Melperone[1]	+++	+30 (n = 23); e32	+	
Levomepromazine[1]	++	+18 to 11.8 (-31; n = 6); 7	N.R.	
Promethazine[1]	+		+	
Pipamperone[1]	+	-10.8 to 9.6 (-0.6; n = 15); 7	+	
Prothipendyl[1]	Ø		N.R.	
Chlorprothixene[1]	Ø		N.R.	
Newer antipsychotic drugs				
Ziprasidone[1]	++	+9.7 (n = 3095); 13	+++	2
Sertindole[1]	+++	+11 to 30 (n = 510); 10	+	2
Quetiapine[1]	+++	-2 to +19.7 (n = 312); 10	++	2
Risperidone[1]	++	+2 to 11.6 (n = 185); 10	+	2
Clozapine	++	+10 (n = 13); 10	+	2
Paliperidone[1] ER	Ø	+1.7 to 3.7 (n = 1300); e4	N.R.	2
Sulpiride[1]	++		+	
Amisulpride[1]	+	-5.9 (n = 12); 13	++	
Zotepine[1]	+	+8.3 (n = 537); 13	N.R.	
Olanzapine[1]	+	-4.5 to +8.4 (n = 1342); 10	N.R.	
Aripiprazole	Ø	-4 to -3.5 (n = 828); 10	N.R.	

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2011; 108(41): 687–93

Conclusions

- Drug induced QT prolongation and torsades de pointes are an increasing public health problem
- The blockade of I_{Kr} potassium current by these drugs is responsible for their pro-arrhythmic effect
- Measurement of QT interval should be corrected for heart rate
- Antiarrhythmic drugs, non-sedating antihistamines, macrolides antibiotics, antifungals, antimalarials, tricyclic antidepressants, neuroleptics, and prokinetics have all been implicated in causing QT prolongation and/or torsades de pointes
- Co-administration of multiple drugs, especially with other QT prolonging drug(s) and/or hepatic cytochrome P450 CYP3A4 isoenzyme inhibitors, must be avoided

Conclusions

- The risk of QT prolongation is increased in females, patients with organic heart disease (for example, congenital long QT syndrome, myocardial infarction, congestive heart failure, dilated cardiomyopathy, hypertrophic cardiomyopathy, bradycardia), hypokalaemia, and hepatic impairment

- The treatment of drug induced torsades de pointes includes identifying and withdrawing the offending drug(s), replenishing the potassium concentration to 4.5–5 mmol/l, and infusing intravenous magnesium (1–2 g). In resistant cases, temporary cardiac pacing may be needed

Pharmacovigilance Working Party Public Assessment Report on Neuroleptics and Cardiac safety, in particular QT prolongation, cardiac arrhythmias, ventricular tachycardia and torsades de pointes

Treatment Recommendation

1)Baseline ECG prior to treatment and under steady –state conditions afterward.

2)Regular ECG monitoring of patients at high risk and those taking additional medications that can prolong the QTc interval.

3) Slow dose escalation and adaptation of the dose in case of altered elimination or concurrent medication sharing the same metabolic pathway.

4)Periodic electrolyte monitoring.In particular,in case of diarrhea, vomiting, profuse sweating, undernourishment, alcohol/drug use and Diuretic therapy

5) Administration of magnesium sulfate (orally or intravenously) if the QTc interval is markedly prolonged.

6) Discontinuation of medication if the QTc is longer than 500 ms, the potassium concentration is normal, and the QRS is of normal duration, even if the patient has no symptoms.

Antipsychotics ,QTc Prolongation and the Elderly

In the Elderly

- High Rates of Psychotic Depression.
- High Rates of Anxiety Disorders Refractory to Standard Treatment.
- Increased risk of Delirium.
- Behavior Abnormalities due to Dementia.

J Clin Psychopharmacol 2014; 34: 109-123

Psychiatry and Cardiovascular Disease : 2009; 17 ;-5

Risk Stratification

A. Mild Risk for QTc Interval Prolongation (Patients Who Are in Relatively Good Physical Health)

a) No current cardiovascular symptom or disease, and no history of severe CVD

b) Normal EKG with pretreatment QTc interval less than 450 milliseconds

c) Absence of other diseases that are known to predispose to QTc interval prolongation (Table I)

d) No concurrent cardiac or noncardiac medication that could increase QTc interval

B. Moderate Risk for QTc Interval Prolongation (Patients Who Have a Few Risk Factors i)

a) Current stable cardiovascular function: no current cardiovascular symptoms or disease but with past history of CVD

b) EKG abnormalities from past cardiovascular events that have little or no current clinical significance .

c) Presence of noncardiac diseases that could impact QTc interval, or two or more diseases listed in Table I

d) Concurrent use of at least one noncardiac medication known to prolong QTc interval

e) History of stroke with residual neurological deficits

f) a, b, c, and d or mildly elevated QTc interval of 450-470 milliseconds

C. High Risk for QTc Interval Prolongation

a) Presence of active cardiac disease or symptoms

b) Presence of multiple other risk factors listed in Table I

Psychiatry and Cardiovascular Disease 17 -;5 : 2009

R&A

Treatments Guidelines

A. Mild Risk for QTc Interval Prolongation (Patients Who Are in Relatively Good Physical Health)

a) For these patients, a baseline EKG prior to initiation of antipsychotic therapy and annual reassessment of QTc interval prolongation risk will suffice.

b)Regarding choice of antipsychotic medication, those known to have lower QTc interval prolongation are generally preferred.

c) Ziprasidone may be used in these patients, but only as a third-line option and with regular EKG monitoring.

B. Moderate Risk for QTc Interval Prolongation (Patients Who Have a Few Risk Factors i)

a) In these patients with moderate risk of QTc prolongation, alternative psychotropic medications should be considered (eg, mood stabilizers or antidepressants).

b)Cardiology consult is recommended for joint management.

c) Ziprasidone and all low- and mid-potency traditional antipsychotic medications are not recommended.

d)Prior to initiating antipsychotic medication, baseline EKG, optimum management of preexisting diseases, and alternatives to noncardiac medications capable of prolonging QTc interval should considered.

e)A much lower dose and very slow titration of antipsychotic medications is recommended.

g)Serial EKG's recordings may be helpful to adjust for daily variations in the QTc interval.

h) In patients with moderate risk, any upward trending of QTc interval prolongation is an indication to discontinue antipsychotic therapy.

Websites Resources

www.qtdrug.org

www.torsade.org

THANK YOU