



U.S. Food and Drug Administration

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Special cardiac safety concerns: QT prolongation and Valvulopathy

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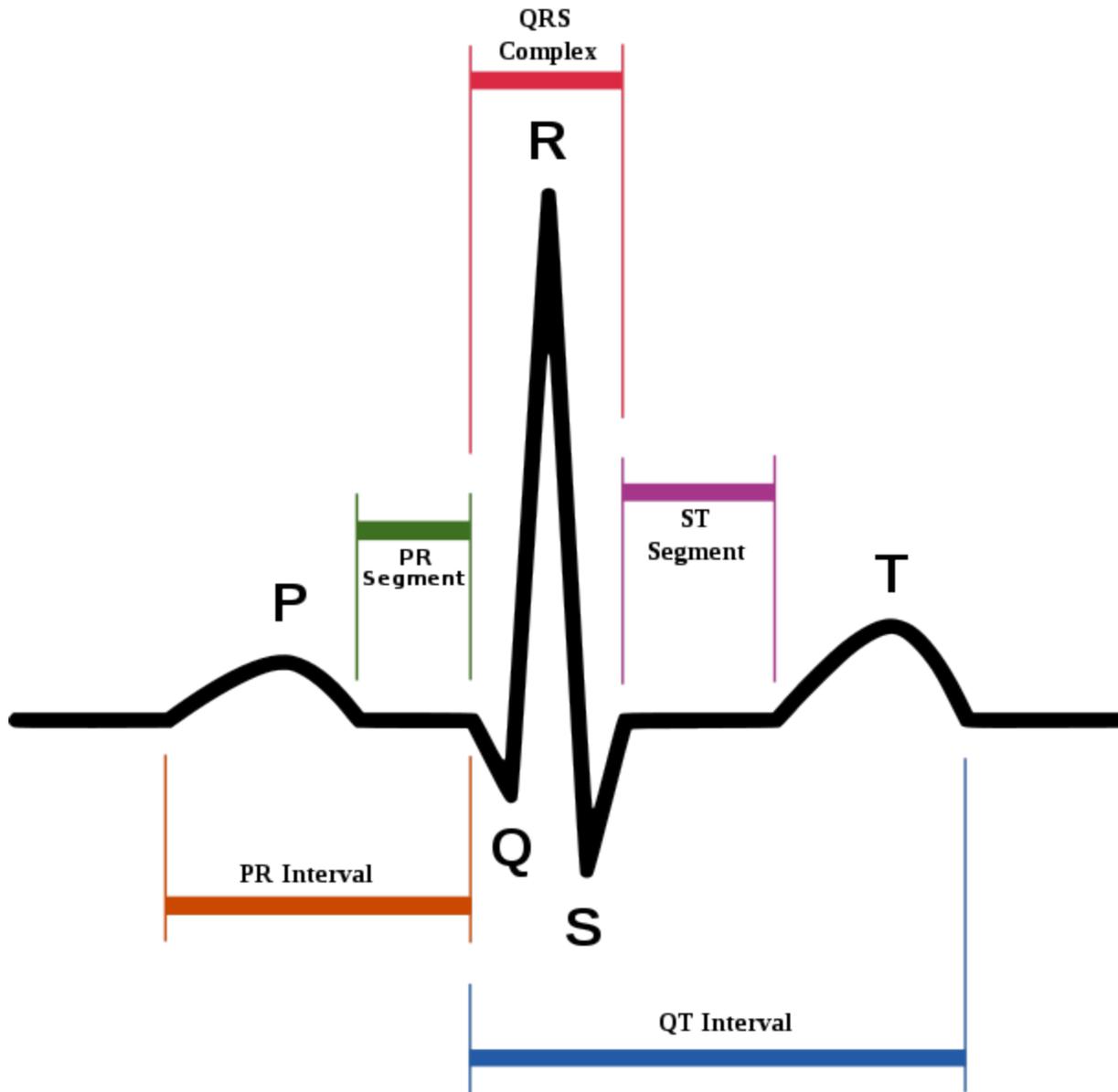
Detecting safety signals

- *Common, severe, drug-related*: can detect in controlled, clinical trials (size ~ what % can be ruled out)
- *Rare, severe, drug-related*: sometimes detected in clinical trials if single case interpretable (e.g., Stevens-Johnson) or via surrogate or biomarker (e.g., QT prolongation)
- *Spontaneous events* ↑ *rate with drug*: single event usually **not** interpretable;
 - large enough controlled trial or epidemiologic study (large hazard ratio) (e.g., valvulopathy)

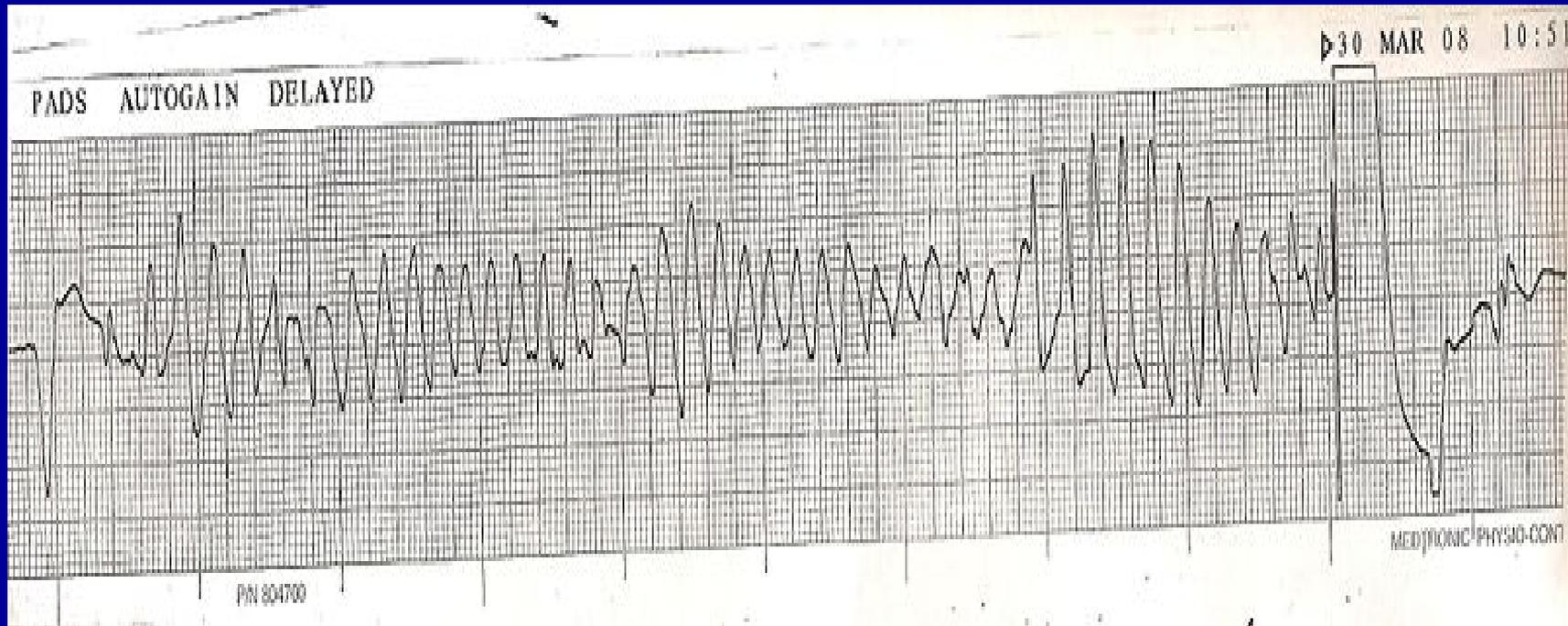
QT prolongation and valvulopathy—different issues: what do they share?

- Drug-related effects
- Associated with significant risk
- Both concerns have led to withdrawal of drugs from the market....
- Originally detected post-approval, now efforts to detect earlier in development...

QT Prolongation



Torsade de pointes: polymorphic ventricular tachycardia



Rare, but life-threatening. Associated with prolonged QT.

Background

Late 1990s-2005

- Drug withdrawals due to TdP (terfenadine, cisapride)
- Agency Working Group on QT prolongation
- Early Concept Paper, then joint effort with Health Canada, then ICH
- ICH E14 (final version: 2005): advanced the notion of a “thorough QT study” (TQT) for all New Molecular Entities

ICH E14/ S7B: Current FDA Policy

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

**THE CLINICAL EVALUATION OF QT/QTc INTERVAL
PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-
ANTIARRHYTHMIC DRUGS**

E14

Current *Step 4* version
dated 12 May 2005

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

**THE NON-CLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED
VENTRICULAR REPOLARIZATION
(QT INTERVAL PROLONGATION)
BY HUMAN PHARMACEUTICALS**

S7B

Current *Step 4* version
dated 12 May 2005

Available at
www.ich.org

QT policy

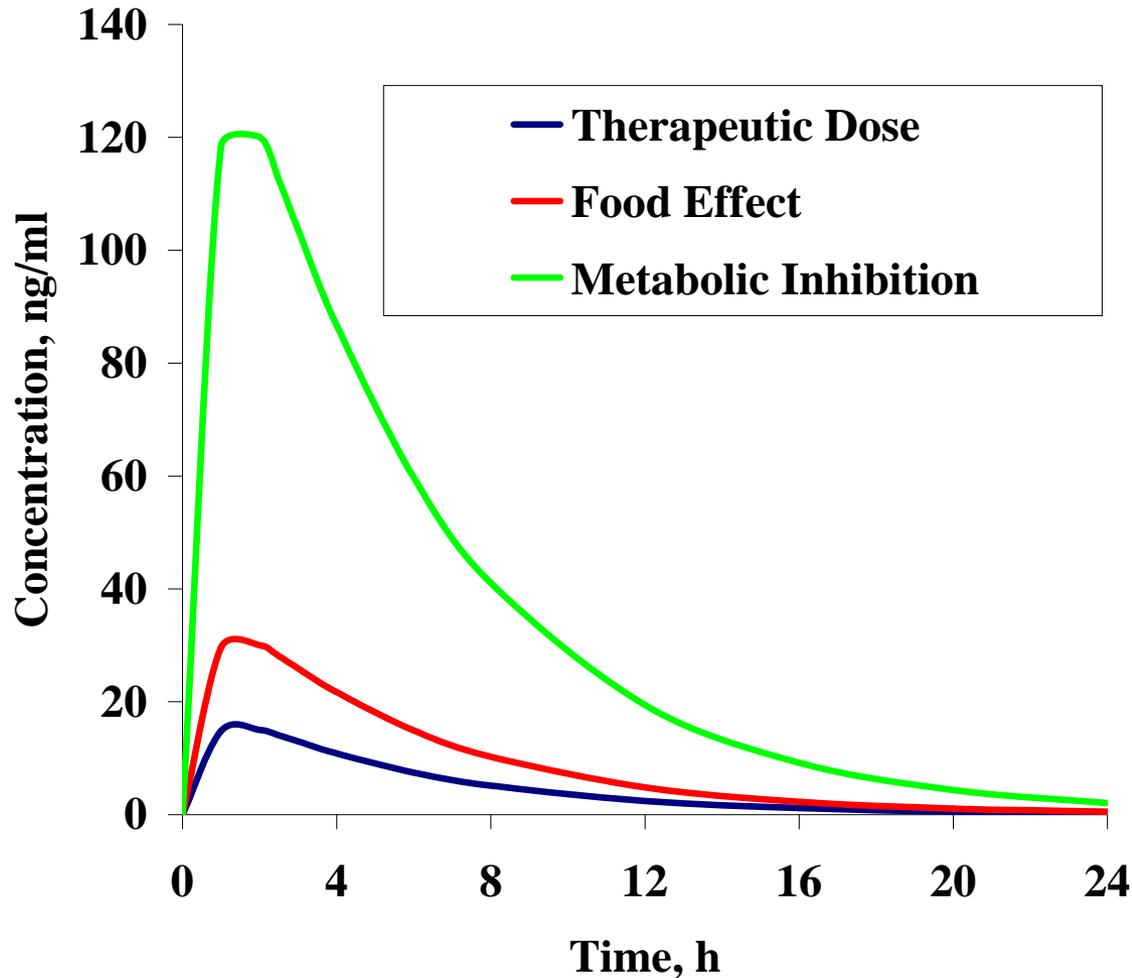
- Pre-clinical studies not considered adequate to rule out risk
- Most systemically available drugs need a “thorough QT” study
- Threshold for potential clinical importance set very low (10 ms; a few percent of normal)
- Failure to rule out 10 ms leads to heightened monitoring during phase 3—and approval or labeling implications

Thorough QT Study Purpose

- Characterize the concentration-response relationship
- Characterize QT effects of the drug under near “worst case” scenario
 - ECG sampling at peak concentrations (drug/metabolites)
 - Exposure at supratherapeutic concentrations
 - Sufficient duration of dosing/sampling to characterize effects

Dose Selection

How to define a suprathreshold dose



What if the study is positive?

- Need to explore further (examine adverse events, explore vulnerable populations)
- More intensive monitoring
- Might alter development (choose a different dose, different target population, etc.)
- Look for benefits that might offset risk

Problems with this approach...

- QT studies difficult and expensive
- Relationship to risk (arrhythmia) not constant
- Unknown public health consequences of compounds removed from pharmaceutical pipeline

Valvulopathy

Obesity and weight loss

- Big public health problem today
- Long recognized problem in society
- Weight loss medication as solution?

Background

- Appetite suppressants in the management of obesity
 - Fenfluramine (1973): racemic mixture* - increased serotonin, associated with depression
 - Dexfenfluramine (1996)* thought to be safer
 - Phentermine (1959) still in use
- Combination (fen-phen) was never FDA approved

*withdrawn in 1997

Case-control study in Europe: odds ratio 23.1 associated with use > 3 months.

The New England Journal of Medicine

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VOLUME 335

AUGUST 29, 1996

NUMBER 9



APPETITE-SUPPRESSANT DRUGS AND THE RISK OF PRIMARY PULMONARY HYPERTENSION

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24 women, no prior heart disease, mean rx duration 11 months.

The New England Journal of Medicine

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VOLUME 337

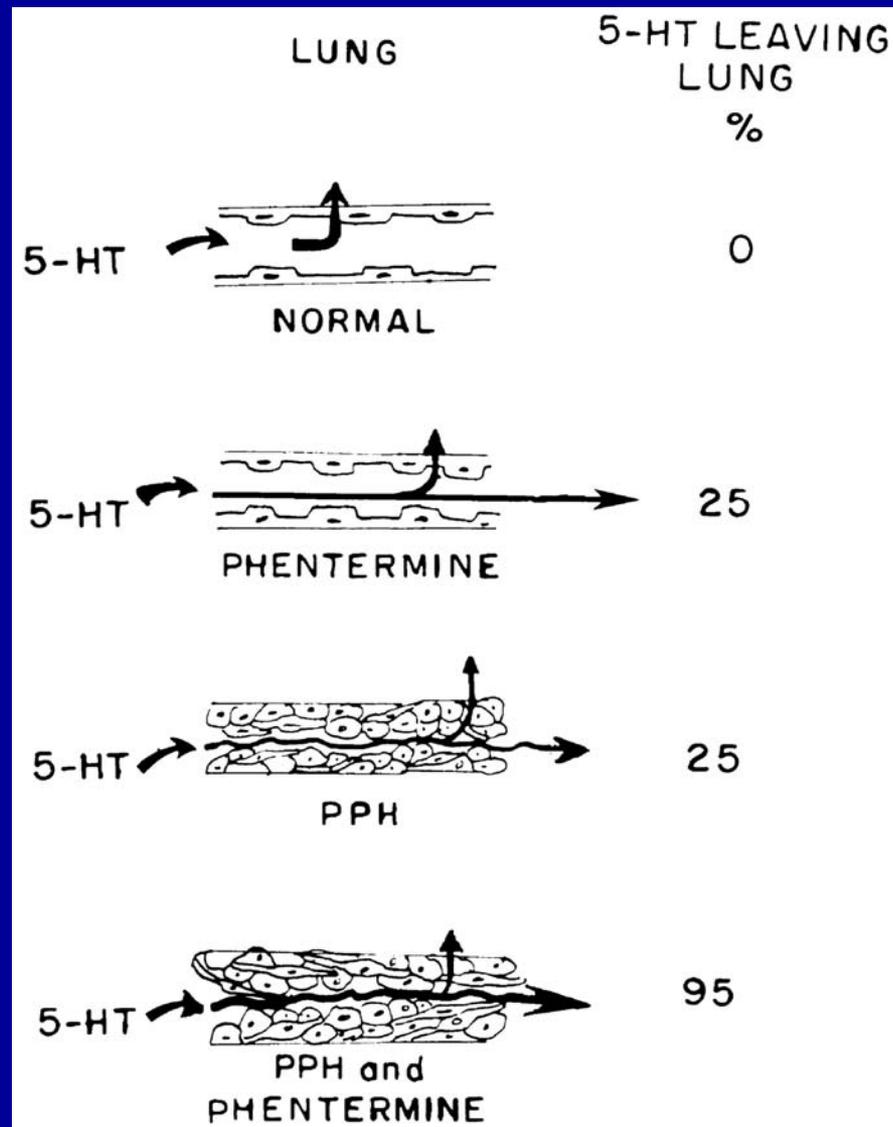
AUGUST 28, 1997

NUMBER 9

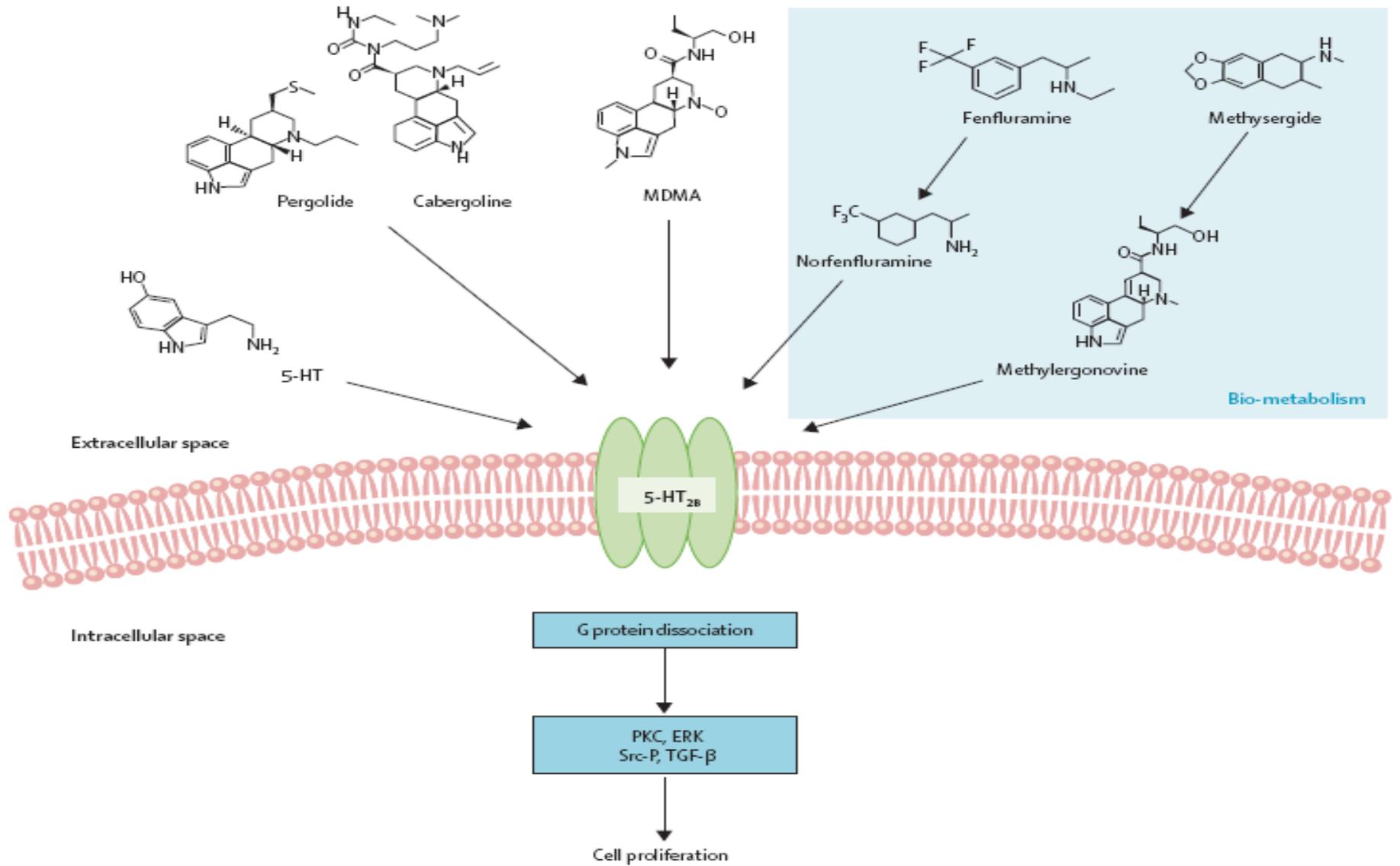


VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE- PHENTERMINE

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Fishman A P Circulation 1999;99:156-161



Source: Bhattacharyya et. al. Lancet 2009; 374: 577-85

Summary

- Concerns about QT prolongation and valvulopathy have led to drug withdrawals.
- Torsade de pointes is a rare, life-threatening ventricular tachycardia. QT prolongation is measured with pharmacokinetic data in TQT studies as part of risk assessment.
- Drug-associated valvulopathy has been detected post-approval, via cases and epidemiologic studies. Common mechanism appears to be 5HT-2B receptor.

Thank you

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