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)

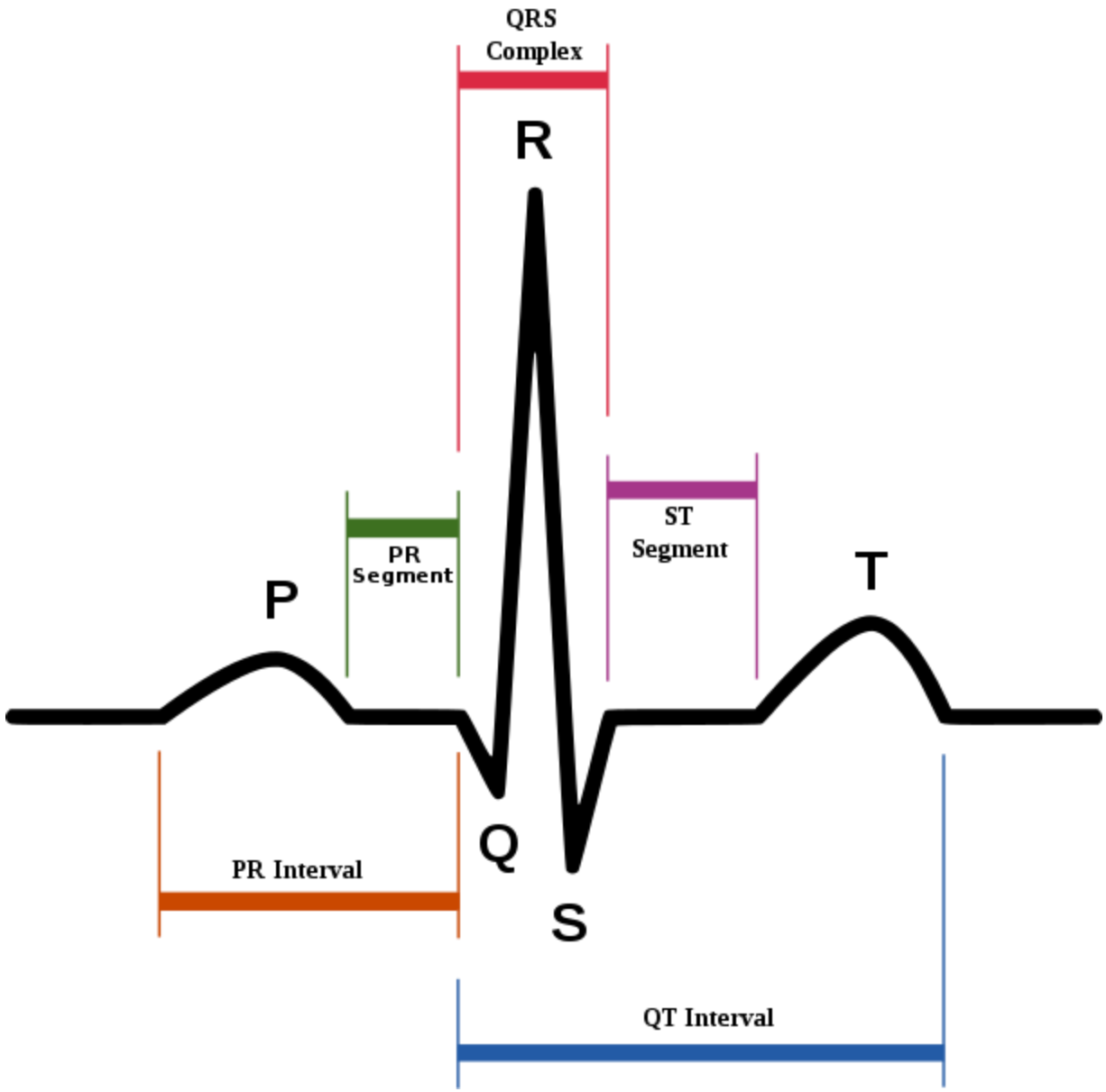
- *Rare, severe, drug-related*: sometimes detected in clinical trials if single case interpretable (e.g., Stevens-Johnson) or via surrogate or biomarker (e.g., QT prolongation)

- *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


QRS
Complex
R
PR
Segment
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Segment
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T
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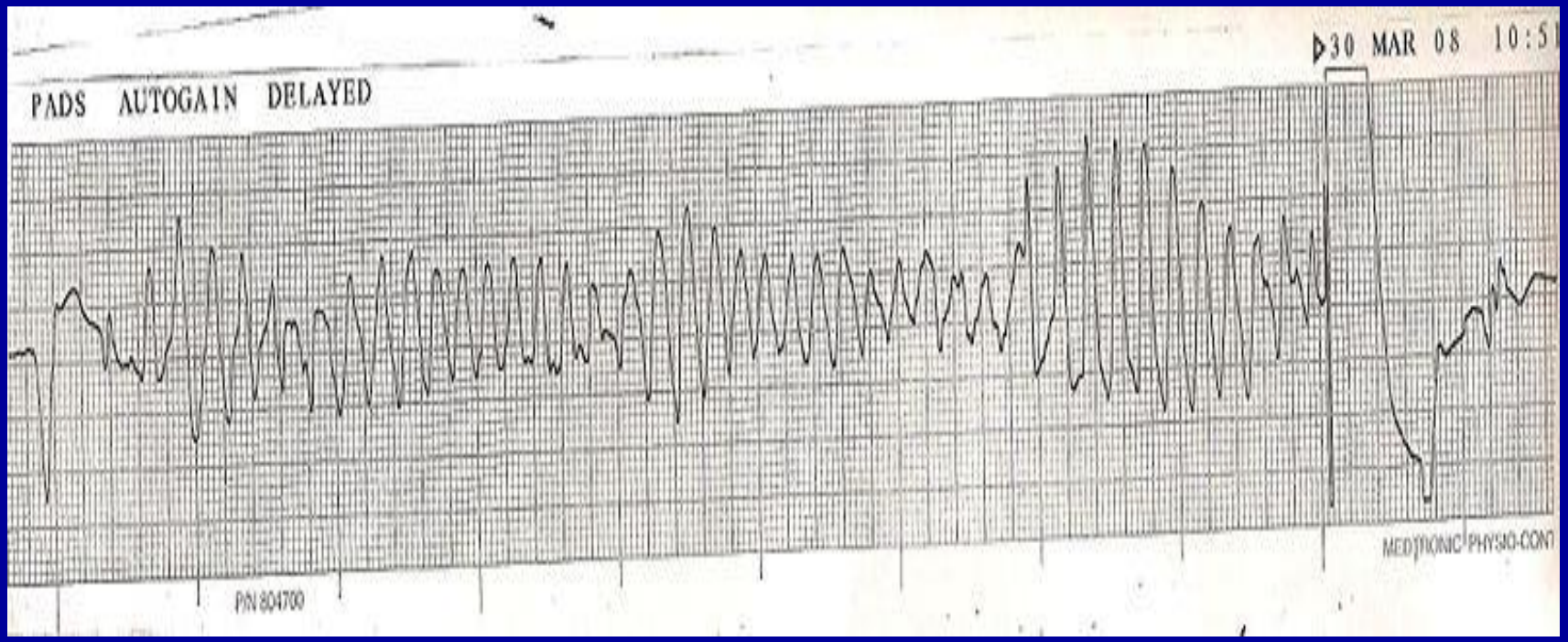
S
PR Interval
QT Interval

Torsade de pointes: polymorphic ventricular tachycardia



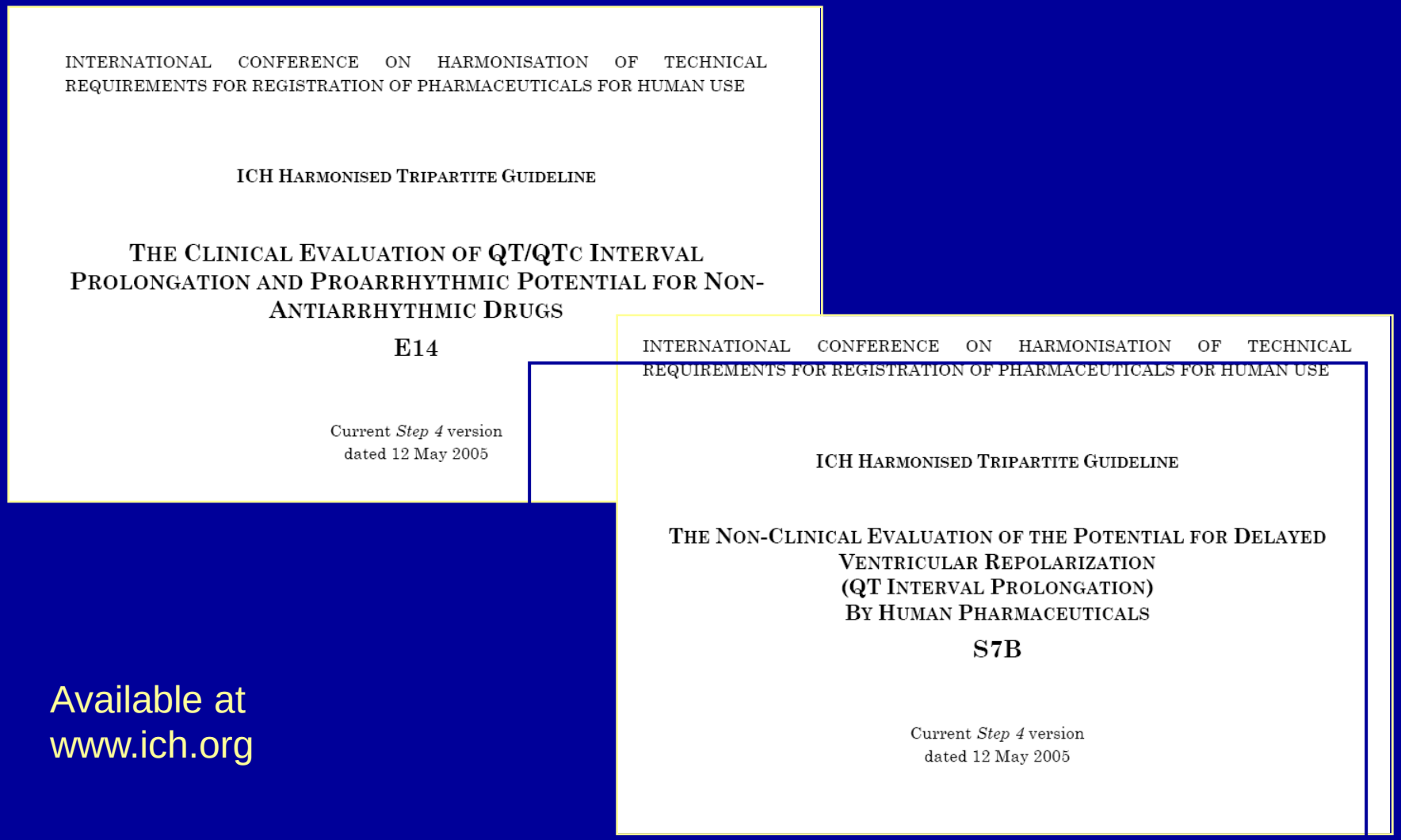
Rare, but life-threatening. Associated with prolonged QT.

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

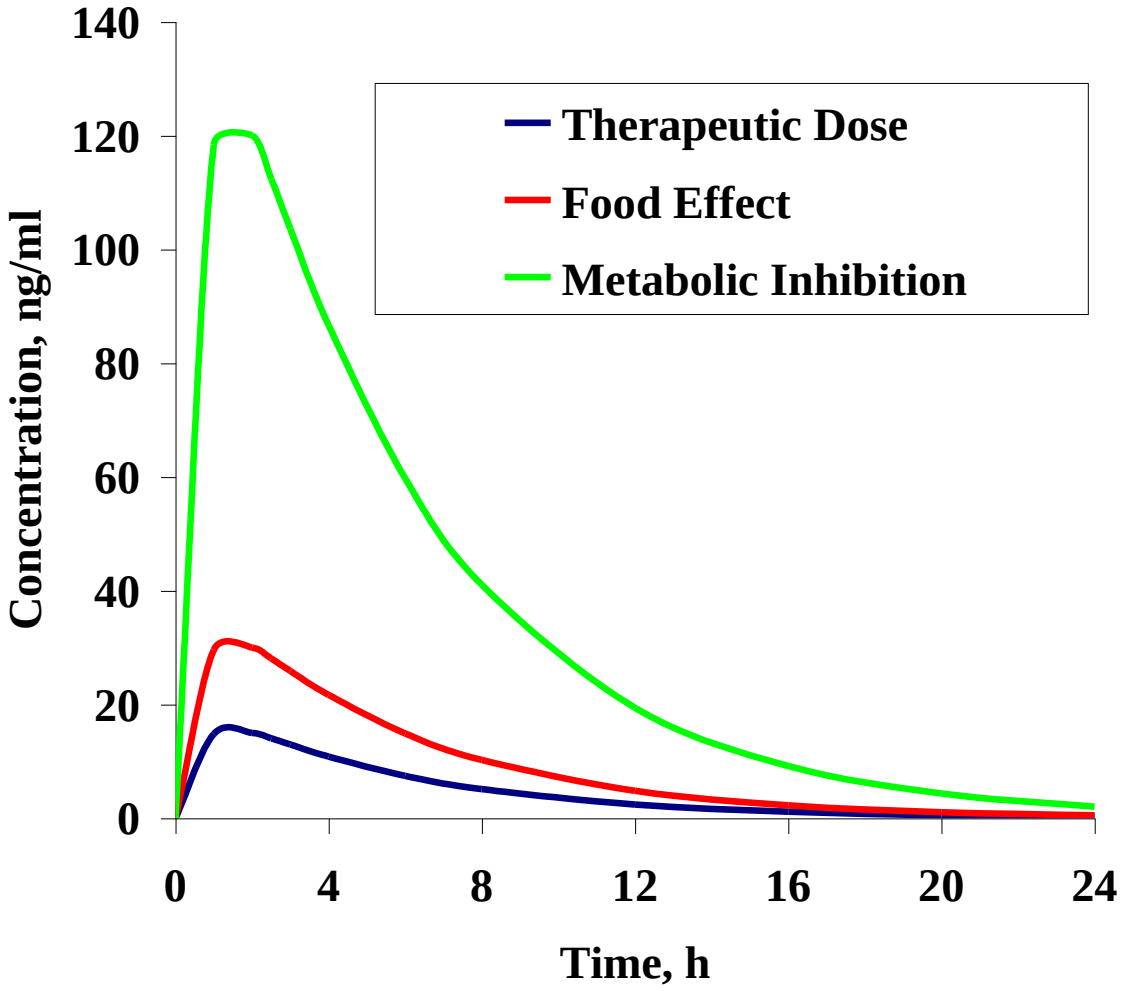
- Pre-clinical studies not considered adequate to rule out risk
- Most systemically available drugs need a “thorough QT” study
- Threshold for potential clinical importance set very low (10 ms; a few percent of normal)
- Failure to rule out 10 ms leads to heightened monitoring during phase 3—and approval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

VOLUME 335 AUGUST 29, 1996 NUMBER 9

APPETITE-SUPPRESSANT DRUGS AND THE RISK OF PRIMARY PULMONARY HYPERTENSION

LUCIEN ABENHAIM, M.D., YOLA MORIDE, PH.D., FRANÇOIS BRENOT, M.D.,* STUART RICH, M.D., JACQUES BENICHOU, M.D., XAVIER KURZ, M.D., TIM HIGENBOTTAM, M.D., CELIA OAKLEY, M.D., EMIL WOUTERS, M.D., MICHEL AUBIER, M.D., GÉRALD SIMONNEAU, M.D., AND BERNARD BÉGAUD, M.D., FOR THE INTERNATIONAL PRIMARY PULMONARY HYPERTENSION STUDY GROUP†

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

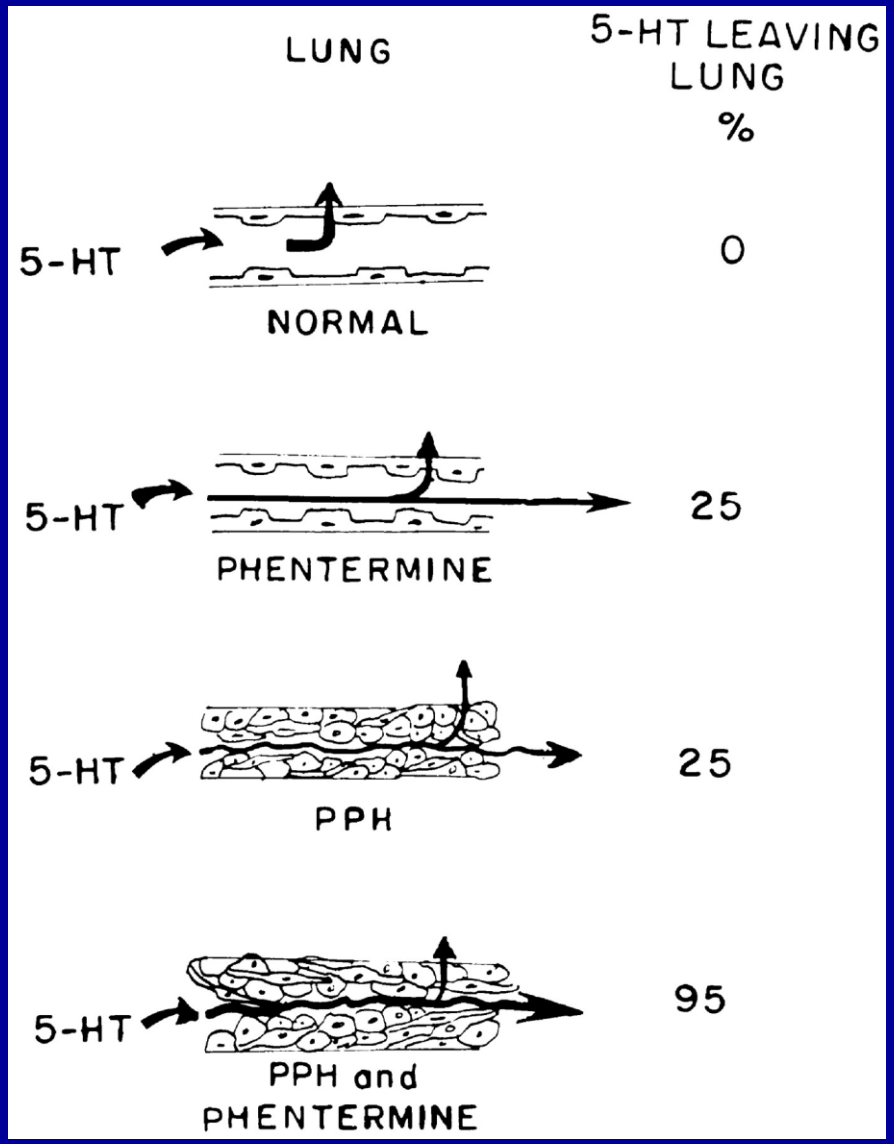
The New England Journal of Medicine

VOLUME 337 AUGUST 28, 1997 NUMBER 9

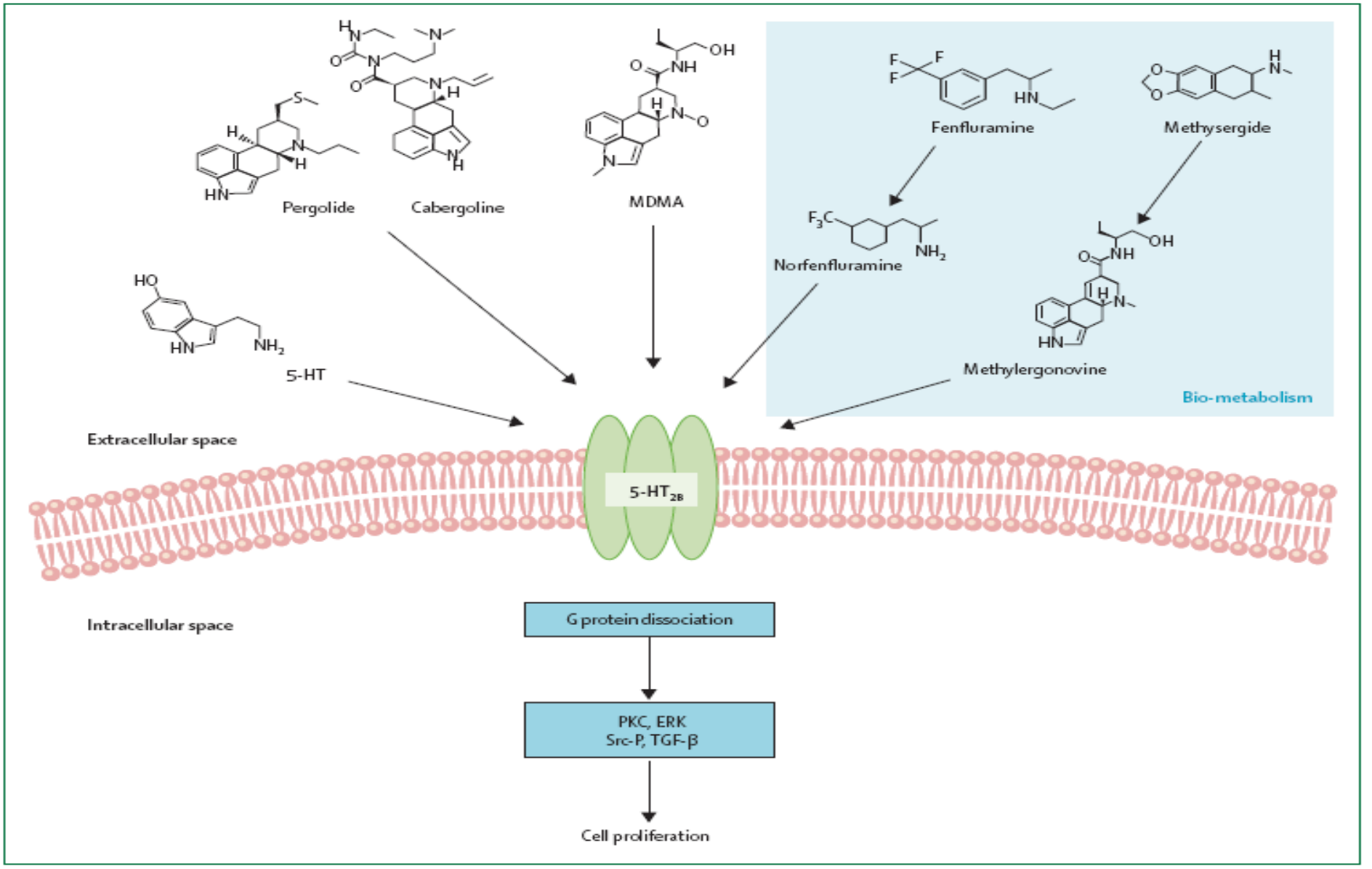
VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE–PHENTERMINE

HEIDI M. CONNOLLY, M.D., JACK L. CRARY, M.D., MICHAEL D. MCGOON, M.D., DONALD D. HENSRUD, M.D., M.P.H., BROOKS S. EDWARDS, M.D., WILLIAM D. EDWARDS, M.D., AND HARTZELL V. SCHAFF, M.D.

Fenfluramine and dexfenfluramine voluntarily withdrawn on Sept. 15, 1997



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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