SPECIAL CARDIAC SAFETY CONCERNS

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Importance of Cardiac Safety Evaluation

- Several non-cardiac drugs withdrawn from market due to cardiac safety issues
- Characterize safety earlier in development?
- Do not want to delay development of promising therapies….

Detecting the problem

- Observation of events often precedes understanding

  -- mechanism of action (the “why” and “how”)
- Helpful to characterize mechanism (risk mitigation)
- You are the front line.

Detecting a safety signal

- *Common events*:
  - Detect in clinical trials
- *Rare events*: sometimes detect in clinical trials (e.g., Stevens-Johnson) or via
  - Risk biomarkers
  - Epidemiologic studies (e.g., case-control)

Detecting a safety signal (cont.)

- *Spontaneous events ↑ rate with drug*: single event usually ***not*** interpretable; detect via:
  - adequately powered controlled trial
  - compare to background rate
  - epidemiologic study (large hazard ratio)
- Include vulnerable populations

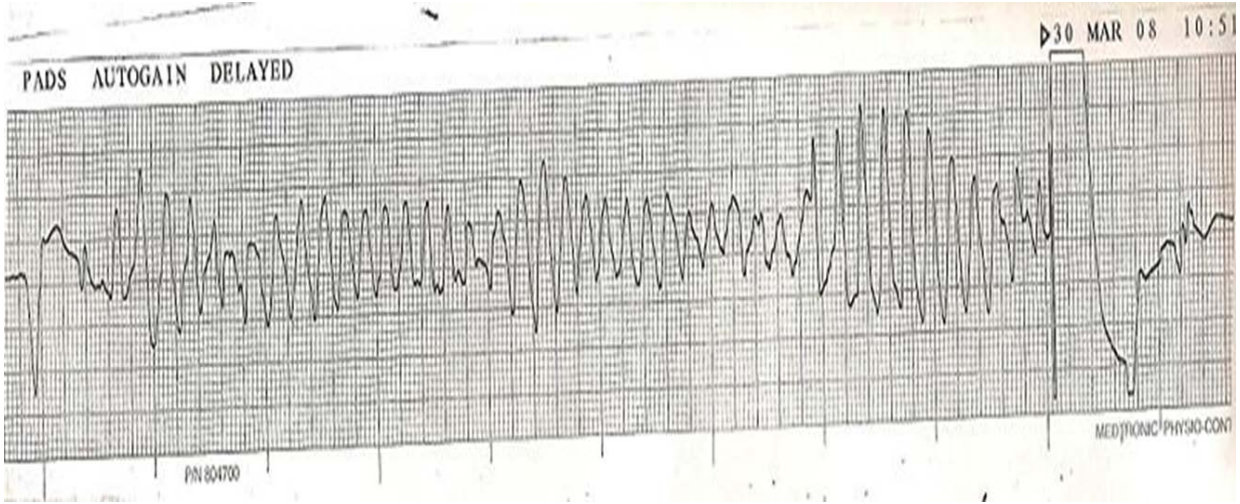
DRUG-INDUCED QT PROLONGATION AND PROARRHYTHMIA

QT Interval

- Highly variable (time of day, autonomic tone)
- Can be prolonged because of:
  - Heart disease
  - Electrolyte abnormalities
  - Drugs

Torsade de Pointes (TdP)

- Rare, life-threatening; might not be detected in a development program



QT interval: safety biomarker

- “Thorough QT” study
- Threshold for potential importance set low (10 msec prolongation)
- “Negative study”—routine phase 3 monitoring
- Failure to rule out 10 msec—heightened phase 3 monitoring

Era of Thorough QT studies

Pro:

- No further drug withdrawals due to TdP risk

Con:

- Expensive
- Relationship to risk crude and not constant
- Interest in alternative approaches to assess risk of proarrhythmia

DRUG-INDUCED VALVULAR DISEASE

Weight Loss and Appetite Suppressants

- Fenfluramine (1973): approved for short-term use
  - Increased serotonin, associated with depression
- Dexfenfluramine (1996) thought to be “safer”
- Fen-Phen: never approved, used off-label for long-term management

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

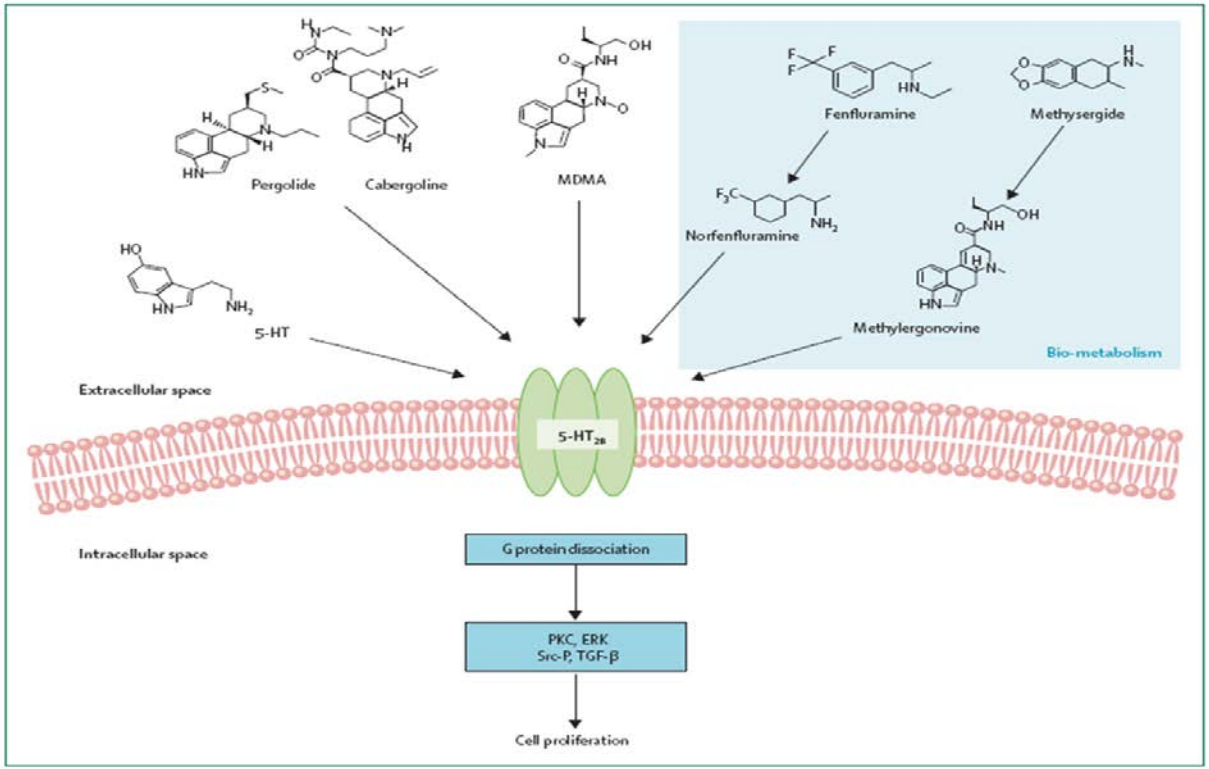
The New England
Journal of Medicine

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.

5-HT 2B Receptor Pathway



Source: Bhattacharyya 2009

RISK OF MYOCARDIAL INFARCTION

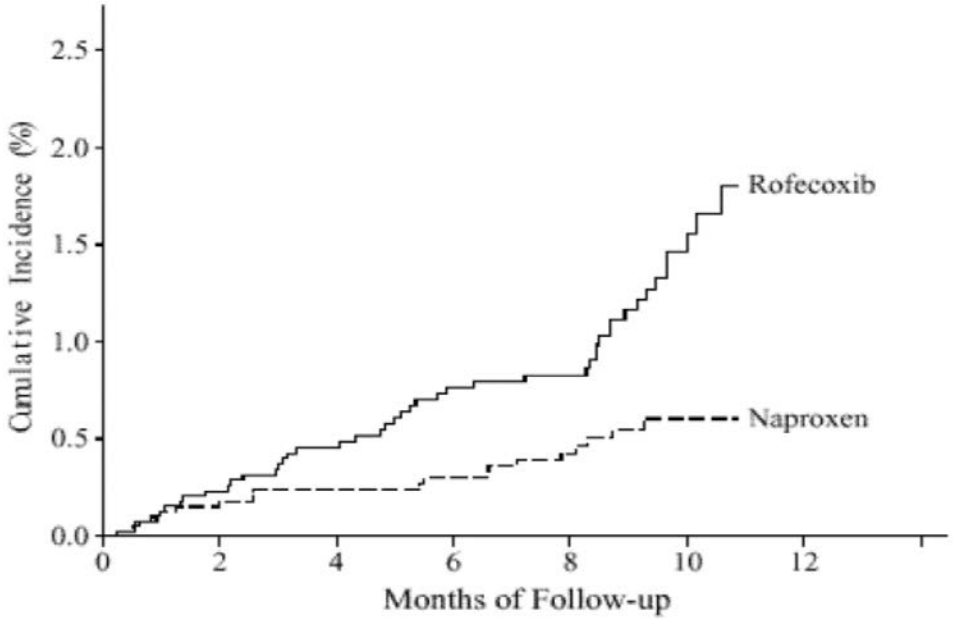
Rofecoxib (Vioxx)

- Originally approved (1999) for acute pain (up to 5 days), dysmenorrhea, and osteoarthritis (12.5 mg and 25 mg/day).
- COX-2 inhibition premise: analgesia with less GI toxicity
- Dose-related hypertension and edema
- No cardiovascular signal observed at approval.
- Controlled studies were short-term

VIGOR Study

- Large, randomized double-blind trial
- Vioxx 50 mg/day or Naproxen 500 mg twice/day
  – no placebo arm
- Primary endpoint was **GI events**
- Rheumatoid arthritis, mostly < 65 years
  – Population at ↑ risk of cardiovascular events

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
in Rheumatoid Arthritis Patients in the VIGOR Study
Time-to-Event Plot (All Patients Randomized)
Updated Application Data



at Risk						
tofecoxib	n=4047	3643	3405	3177	2806	1067 531
laproxen	n=4029	3647	3395	3172	2798	1073 514

APPROVe Study

- Three-year, placebo-controlled study
- Primary endpoint: prevention of colorectal polyps
- Terminated early--↑ incidence of cardiovascular events in subjects treated with Vioxx
- Vioxx withdrawn (2004)

Diabetes drugs and cardiac risk

- Guidance evaluating CV risk in new therapies to treat type 2 diabetes (2008)
  - Design 2/3 trials to allow meta-analysis
  - Blinded endpoint adjudication committee
  - Include higher risk subjects
  - Prespecified upper bound

Groups interested in cardiac safety

- Cardio-Oncology (American College of Cardiology, American Society of Clinical Oncology)
- Cardiac Safety Research Consortium

Final Thoughts

- Much has been learned; much work remains
- How best to screen? Monitor? Reduce risk?
- Can testing be done earlier and/or at less cost?

Contact Information

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FDA Headquarters

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