Unintended Cardiovascular Effects of Mood, Sleep and Pain Medications

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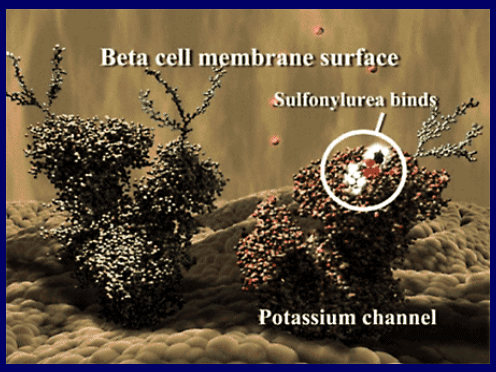
Objectives

- Review basic pharmacological principles as it pertains to medicinal chemicals used for common patient care
- Discuss some of the psychiatric-related medication classes that can lead to cardiac adverse effects
- Discuss environmental factors that may complicate or exacerbate cardiac complications associated with

Pharmacology 101

- Some things do not change; a leading pharmacology textbook in 1941 began: “The subject of pharmacology is a brodad one and embraces the knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate, and excretion, and therapeutic uses of drugs.” – Alfred Goodman Gilman

Sulfonylurea- Mechanism of Action



Gavin, S Medscape Image accessed 2/05

Sulfonylurea- Mechanism of Action

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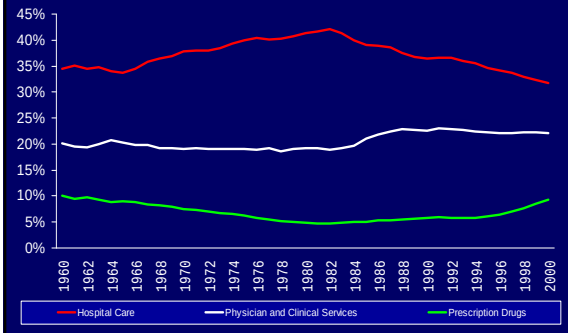
The Nation's Healthcare Dollar, 1960-2000

Share of National Health Care Spent on Each Category



Source: CMS at www.hcfa.gov/stats/nhe-oact/tables/nhe00.csv, 2002

MJ Case Study: First Visit

- 53 yr old male presents: office visit for a DMT2. It was scheduled by pt's spouse because pts father died at age 60 yrs due to an acute MI.
  - his father had not sought out the care of a physician except for acute care issues.
- The patient has not seen a doctor in 5 yrs, his last visit was for a sinus infection. At that visit he was told his blood pressure was elevated, the pt was unsure of that BP level and was given a card to check his BP outside the office and also given a lab slip –neither completed. He also reports some feelings of sadness at times, and does not sleep well.

MJ Visit One

- ROS: neg - CP, SOB, ankle swelling,
- ROS: + fatigue, trouble sleeping at times
- Social Hx: 10-15 cigs/day; 8-10 alcohol drinks/wk
- PE: Vitals: BP 148/86, P 82/min, R 18, afeb
- Weight : 238 lbs, Ht: 69 in. BMI: 34.6
- Waist Circumference: 41 in
- HEENT: neg; Neck: nl, no carotid bruits
- Lungs: clear Heart: NSR no murmur
- Abdomen: central obesity otherwise NL
- Ankles: no edema, good pulses

MJ Follow up visit #2

- 10 days later, labs completed
- BP: 146/84, Pulse: 84, Wt:239 lbs, Ht: 69 in
- CMP
  - Glucose: 124 –
  - Creatinine: 1.04 – nl ref (0.70-1.10)
  - Electrolytes normal
  - LFTs: ALT - 60 AST – 40
- CBC: completely normal

MJ Follow up visit #2

- Lipid panel –
  - Triglycerides: 190
  - Total cholesterol: 190
  - HDL: 38
  - Calculate the LDL?
    - LDL = TC – HDL - TG/5 Friedwald Formula
    - LDL = 190 - 38 - 190/5 (38)
    - LDL = 190 – 76 = 114
  - LDL: 114

Define “Adverse Drug Reaction”

- “…a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.”

Medication Drug Disasters (Reference)

Xenobiotic	Location	Date	Significance
Thallium	US	1920s–1930s	Treatment of ringworm; 31 deaths
Diethylene glycol	US	1937	Elixir of sulfanilamide; renal failure
Thorotrast	US	1930s–1950s	Hepatic angiosarcoma
Phenobarbital	US	1940–1941	Sulfathiazole contaminated with phenobarbital; 82 deaths
Diethylstilbestrol (DES)	US, Europe	1940s–1970s	Vaginal adenocarcinoma in daughters
Stalinon	France	1954	Severe neurotoxicity from triethyltin
Clioquinol	Japan	1955–1970	Subacute myelooptic neuropathy (SMON); 10,000 symptomatic
Thalidomide	Europe	1960s	5000 cases of phocomelia
Isoproterenol 30%	Great Britain	1961–1967	3000 excess asthma deaths
Pentachlorophenol	US	1967	Used in hospital laundry; nine neonates ill, two deaths
Benzyl alcohol	US	1981	Neonatal gasping syndrome
Tylenol-cyanide	Chicago	1982	Tampering incident resulted in seven homicides
L-Tryptophan	US	1989	Eosinophilia myalgia syndrome
Diethylene glycol	Haiti	1996	Acetaminophen elixir contaminated; renal failure; >88 pediatric deaths
Diethylene glycol	Panama	2006	Cough preparation contaminated with DEG, causing 78 deaths
Diethylene glycol	Nigeria	2009	Teething formula contaminated with DEG, causing 84 deaths

Cardiotoxic drugs – A focus on Chemotherapeutic Agents

- **Chemotherapeutic agents have the most concern of resulting in cardiotoxicity for patients**
  - Physiologic challenges include
  - LV dysfunction (symptomatic and asymptomatic)
- Structural changes include valvular heart disease, **conduction disturbances**, or pericardial disease

Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. J Clin Oncol. 2012;45:2938.
beta-Adrenergic blockade for anthracycline- and trastuzumab-induced cardiotoxicity: is prevention better than cure?.
Nohria A. *Circulation: Heart Failure. 6(3):358-61, 2013 May.*

Problem Statement

- **Unintended Cardiovascular Effects of Mood, Sleep and Pain Medications occur with patients**
- **WHAT are the most prevalent**
- **ARE there co-morbidities associated with te use of these medications?**
- **WHAT does the future hold?**

What Cardiac Effects concern us with psychiatric-related meds?

- HTN
- Metabolic Effects
- Serotonin-like effects
- Orthostatic Hypotension
- **QT prolongation; arrythmias**
- **SUDDEN DEATH**

QT PROLONGATION – The one that REALLY concerns us!

QT PROLONGATION

- Can result from therapeutic use, combination or overdose
- Patients with QT prolongation are at increased risk of arrhythmias, particularly **Torsades de Pointes**, which in turn can devolve into life-threatening VF or asystole.
- Determining at what point the QT interval is long, and therefore a danger is controversial and poorly understood.

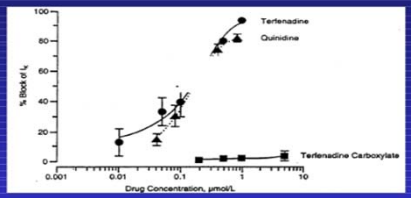
QT PROLONGATION – The one that REALLY concerns us!

QT PROLONGATION

- Likely the result of potassium-channel blockade
- Bradycardia
- Decrease potassium or magnesium

Classic example – Drug-induced Arrhythmia

Terfenadine and Quinidine
K+ channel blockade potency



Woosley JAMA 1993

Classic example – Metabolism Matters as potential causes of Arrhythmias

Inhibitors of P450 Enzymes

CYP 1A2	CYP 2C9	CYP 2C19
Fluvoxamine	Fluconazole	Fluoxetine
		Ketoconazole
		Omeprazole
		Ticlopidine
CYP 2D6	**CYP2E1**	**CYP 3A4**
Fluoxetine	Disulfiram	Erythromycin
Paroxetine		Grapefruit Juice
Propafenone		Itraconazole
Quinidine		Ketoconazole

Caraco TDM 1998

Cardiotoxic drugs – A focus on QT interval disruption

- **The most common drugs that prolong QRS and QT intervals and cause conduction block are**
- Tricyclic antidepressants
- Antipsychotics (Typical vs. Atypical)
- Antihistamines
- Anticonvulsants
- Dextropropoxyphene
- Antimalarial drugs (chloroquine, quinine)
- Calcium channel blockers
- Beta blockers (propranolol, sotalol)
- Digoxin
- Antiarrhythmic drugs

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Potential for TCA Cardiotoxicity

- QRS > 100 milliseconds or more in a limb lead
- Ventricular arrhythmia
  - Sensitivity 0.79 (95% CI 0.58- 0.91)
  - Specificity 0.46 (95% CI 0.35- 0.59)
- Seizures
  - Sensitivity 0.69 (95% CI 0.57- 0.78)
  - Specificity 0.69 (95% CI 0.58- 0.78)

Bailey et al J Tox ClinTox 2004

TCA Cardiovascular toxicity

- Tachycardia:
  - Good indicator of TCA ingestion
  - Caused by cholinergic blockade
  - Catecholamine
  - Anxiety
- Hypotension
  - Vasodilation, hypovolaemia, alpha receptor blockade
  - Serious myocardial depression (normally wide QRS)
- Bradycardia:
  - generally associated major conduction block
  - **severe toxicity**

SSRIs, SNRI – Gain More with (LESS)

- SSRIs- have replaced TCAs for depressive symptoms and treatment
- More favorable side effect profile, in particular with cardiotoxic effect (less anticholinergic effect)
- As with many medications, sensitivity and/or specificity may decrease with increasing dosages of SSRIs

Cardiotoxic effects from Medications

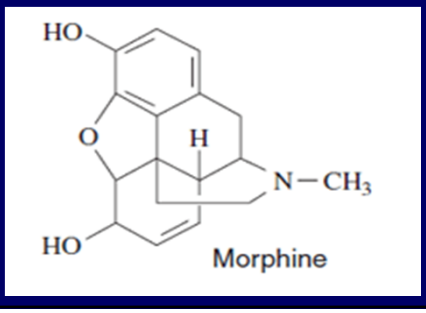
- Long cardiac toxicity can manifest as ventricular dysfunction and clinical heart failure.

Antidepressant medication take Center of QT controversy

- FDA issues warning that citalopram "can cause abnormal changes to the electrical activity of the heart."
- Believed to be dose related (now restricted to 40mg/ day upper limit dosing)
- "Patients at particular risk for developing prolongation of the QT interval include those with **underlying heart conditions** and those who are predisposed to low levels of potassium and magnesium in the blood,"

FDA MedWatch release, Aug 2011

What about Pain Medications and Toxicity?



Morphine

Pain Medication – Opioid Cardiovascular Toxicity

- Propoxyphene – most notorious recent cause of opioid cardiovascular toxicity
- Results in wide-complex dysrhythmias and negative contractility
  - Primarily through SODIUM channel antagonism (IA antiarrhthmics)

Pain Medication – Focus on Propoxyphene Cardiovascular Toxicity

- Withdrawn from the market in 2010-11
- Concerns of fatality in overdose and adverse cardiac effects, including prolongation of the QT interval
- Based upon case reports, summary vital statistics, and surrogate endpoint studies

Ray WA. Murray KT. Kawai V. Graham DJ. Cooper WO. Hall K. Stein CM. *Pharmacoepidemiology & Drug Safety. 22(4):403-12, 2013 Apr.*

Pain Medication – Focus on Propoxyphene Cardiovascular Toxicity

- Authors used a Tennessee Medicaid database (1992-2007),
  - Retrospective cohort study that compared risk of sudden cardiac, medication toxicity, and **total out-of-hospital death**
  - **Compared propoxyphene** users, comparable nonusers of any prescribed opioid analgesic, and users of hydrocodone.

Ray WA. Murray KT. Kawai V. Graham DJ. Cooper WO. Hall K. Stein CM. *Pharmacoepidemiology & Drug Safety. 22(4):403-12, 2013 Apr.*

Pain Medication – Focus on Propoxyphene Cardiovascular Toxicity

- RESULTS
- No increased risk for sudden cardiac death
  - versus nonusers: hazard ratio [HR] = 1.00 [0.81-1.23];
  - versus current hydrocodone users: HR = 0.91 [0.68-1.21])
- Increased risk for medication toxicity deaths
  - versus nonusers: HR = 1.85 [1.07-3.19], p = 0.027;
  - versus current hydrocodone users: HR = 2.10 [0.87-5.10], p = 0.100)
- CONCLUSIONS: Supported the concern that **propoxyphene** has greater toxicity in overdose

Ray WA, Murray KT, Kawai V, Graham DJ, Cooper WO, Hall K, Stein CM. *Pharmacoepidemiology & Drug Safety. 22(4):403-12, 2013 Apr.*

Pain Medication – Opioid Cardiovascular Toxicity

- Other opioids at therapeutic concentrations, such as methadone, may interfere with normal cardiac repolarization and result in QT prologation
- Separate from propoxyphene, which likely and specifically disrupts Na+ channel function

So What does the Future Hold?

Toxicogenomics and Nanotoxicology

- Constitute the toxicologic responses to rapid advances in genetics and material sciences.
- Toxicogenomics combines toxicology with genomics dealing with how genes and proteins respond to toxic substances.
  - Goal is to better decipher the molecular events underlying toxicologic mechanisms,
  - develop predictors of toxicity through the establishment of better molecular biomarkers,
  - understand genetic susceptibilities that pertain to toxic substances such as unanticipated idiosyncratic drug reactions.

Toxicogenomics and **Nanotoxicology**

- Nanotoxicology refers to the toxicology of engineered tiny particles.
  - Typical barriers at portals of entry may not prevent absorption or may themselves be adversely affected by the nanoparticles.
  - Target sites are the central nervous system or bone marrow.

Cardiotoxicity…What about Cardioprotection?

- RAAS – still a gold-standard with regards to cardioprotection
- Novel Biomarkers – microRNA biomarkers for early assessment of myocardial injury
- Herbal/ CAM methods for cardioprotection- can nutrition deliver?

Currently Prescribed Medications create harm…Why???

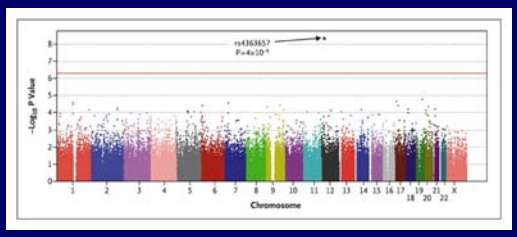
What We Do Know

What We Don't Know

CLINICIANS DON'T KNOW WHAT WE DON'T KNOW

CVD Patient

Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genomewide Association Study



the SEARCH Collaborative Group. N Engl J Med 2008;359:789-799

The NEW ENGLAND JOURNAL of MEDICINE

A New Way to Provide Medications to Patients…Pharmacogenomics!?

- Currently, medications are prescribed through "Trial and Error" methods
- Pharmacogenomics may provide the opportunity to individualize prospective medicine in order to
  - Maximize efficacy
  - Minimize adverse effects
  - Achieve therapeutic outcomes

Medications- Variable Effects on Patients

CONDITION	DRUG CLASS	RESPONSE RATE*
ASTHMA	BETA AGONIST	40% - 75%
HYPERTENSION	VARIOUS	30%
DEPRESSION	SSRI, Tricyclics	20% - 40%
DIABETES	Sulfonyureas, others	30% - 50%
CANCER	VARIOUS	Upto 70%

* = POOR RESPONSE RATE

MJ Follow up visits #4 – 8

- Patient complains of "skipping heart beat at times"
  - "I don't eat that much."
  - Increased fatigue: TSH/CBC levels nl
  - What other disorder could be causing fatigue for this pt?
- blood pressure became hypertensive
  - an ACEI was started 2 yrs ago

MJ Follow up visit #22
5 years from initial diagnosis

- Labs:
  - glucose: 280
  - HgbA1C: 9.0%
  - creatinine: 1.55
  - urine for microalbumin/creatinine: 69
  - TC: 216
  - HDL: 33
  - TG: 240
  - LDL: 135

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