Drug Interactions: Combinations That Can Kill Your Patients or "warnings"

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Introduction

- Common
  - 0.5-2.5% of hospitalized pts
- Only 1% clinically significant → fatal!
- Most are predictable and preventable

Definition of a Drug Interaction

- The pharmacological or clinical response to the administration of a drug combination, different from that anticipated from the known effects of the two agents when given alone.

Tatro, Drug Interaction Facts 1992

Multidisciplinary Medication Management
News, Articles, and Clinical Vignettes
Top 10 Drug Interactions
M3 Tool Kit
References
Background & Rationale
M3 Ad Hoc Committee
MedWatch (FDA) Safety Alerts

Clinical Corners
Acute Change of Condition
Altered Mental States
Anemia
COPD
Dementia
Depression

Top 10 Particularly Dangerous Drug Interactions in Long Term Care

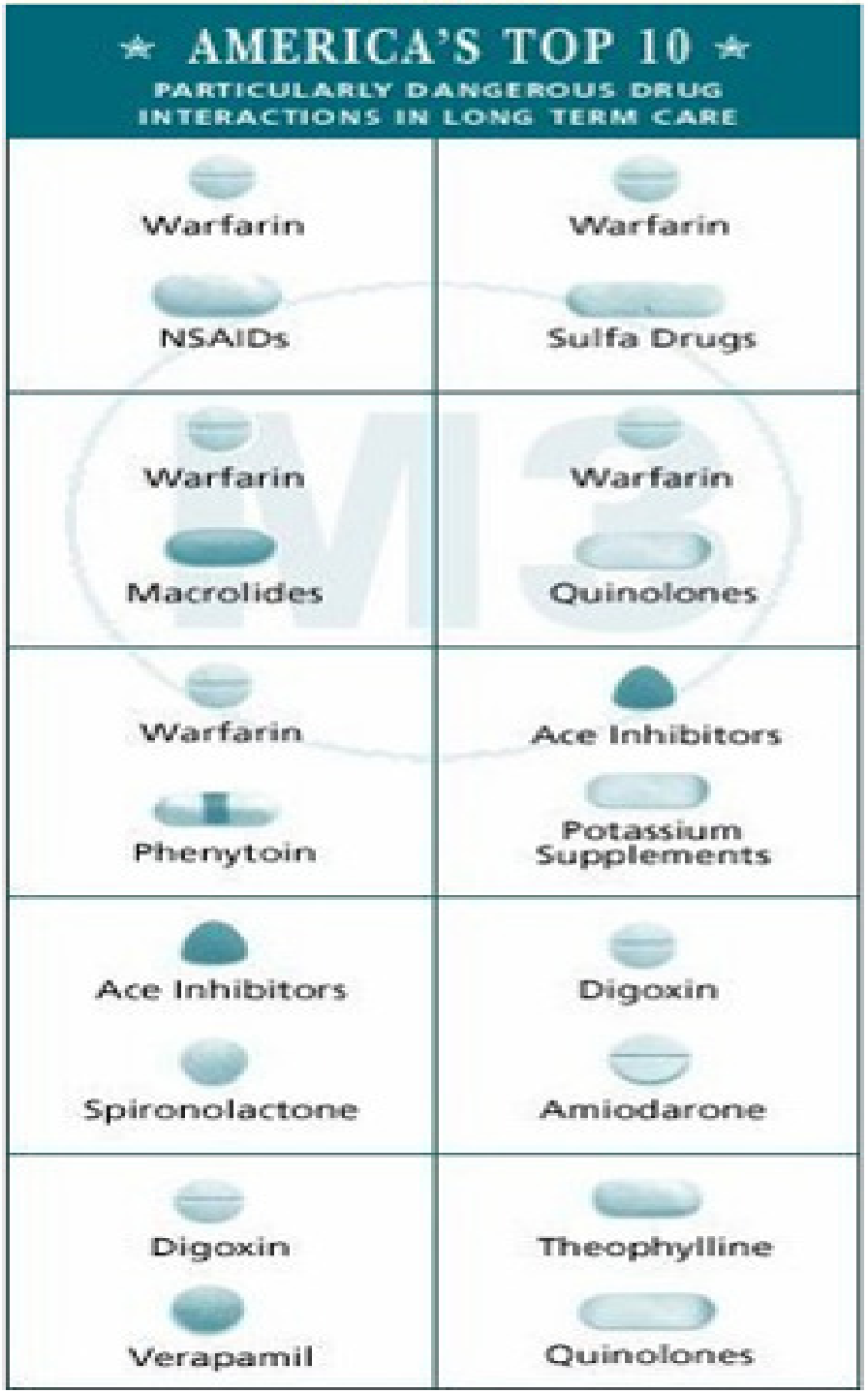
Recent studies have shown that adverse drug reactions (ADRs) are common among nursing home residents, and frequently go unrecognized or the symptoms attributed to another condition. Many ADRs are due to drug-drug interactions.

The occurrence of an interaction depends on many factors, including the inherent pharmacological properties of the drugs, the resident's medical condition and presence of co-morbidities, the dose of the drugs, and the presence of other drugs.

The severity and clinical significance of the interactions vary from mild and clinically unimportant to severe and life-threatening. Some combinations of drugs cause interactions more often than others.

The likelihood of an interaction is also increased for drugs that are more commonly prescribed in nursing homes. While most residents take various combinations of drugs without experiencing interaction-related ADRs, they nonetheless have a risk which is higher for certain combinations as discussed above.

Select any image below to learn more about interactions and treatment alternatives.


AMERICA'S TOP 10
PARTICULARLY DANGEROUS DRUG INTERACTIONS IN LONG TERM CARE
Warfarin
NSAIDs
Warfarin
Sulfa Drugs
Warfarin
Macrolides
Warfarin
Quinolones
Warfarin
Phenytoin
Ace Inhibitors
Potassium Supplements
Ace Inhibitors
Spironolactone
Digoxin
Amiodarone
Digoxin
Verapamil
Theophylline
Quinolones

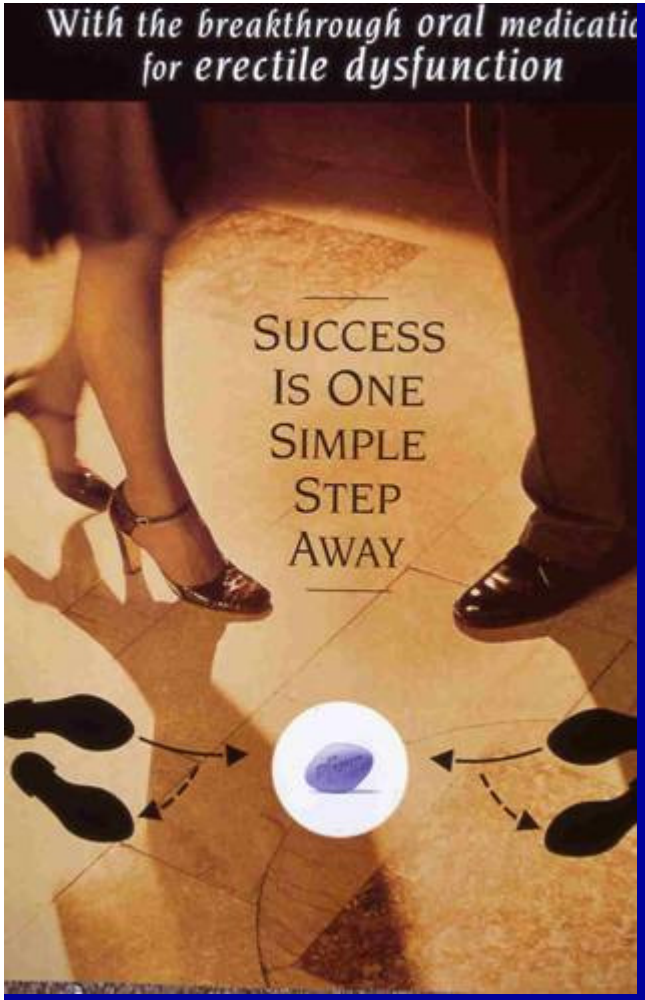
People don’t kill people, computers do

- Computerized physician order entry (CPOE) and decision support systems (DSS) can reduce certain types of error but often slow clinicians and may increase other types of error.

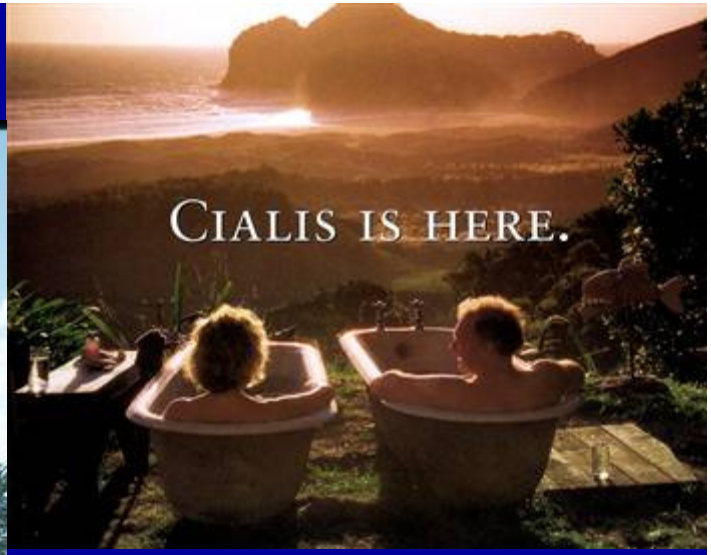
Acad Emerg Med. 2004 Nov;11(11):1135-41
Handler JA, et al

cc: Lightheadedness

- A 64 yr old male with a history of HTN, CAD, and stable angina became lightheaded and nauseated shortly after a dose of sildenafil (Viagra)
- Medications: ASA, captopril, isosorbide dinitrate (Isordil)

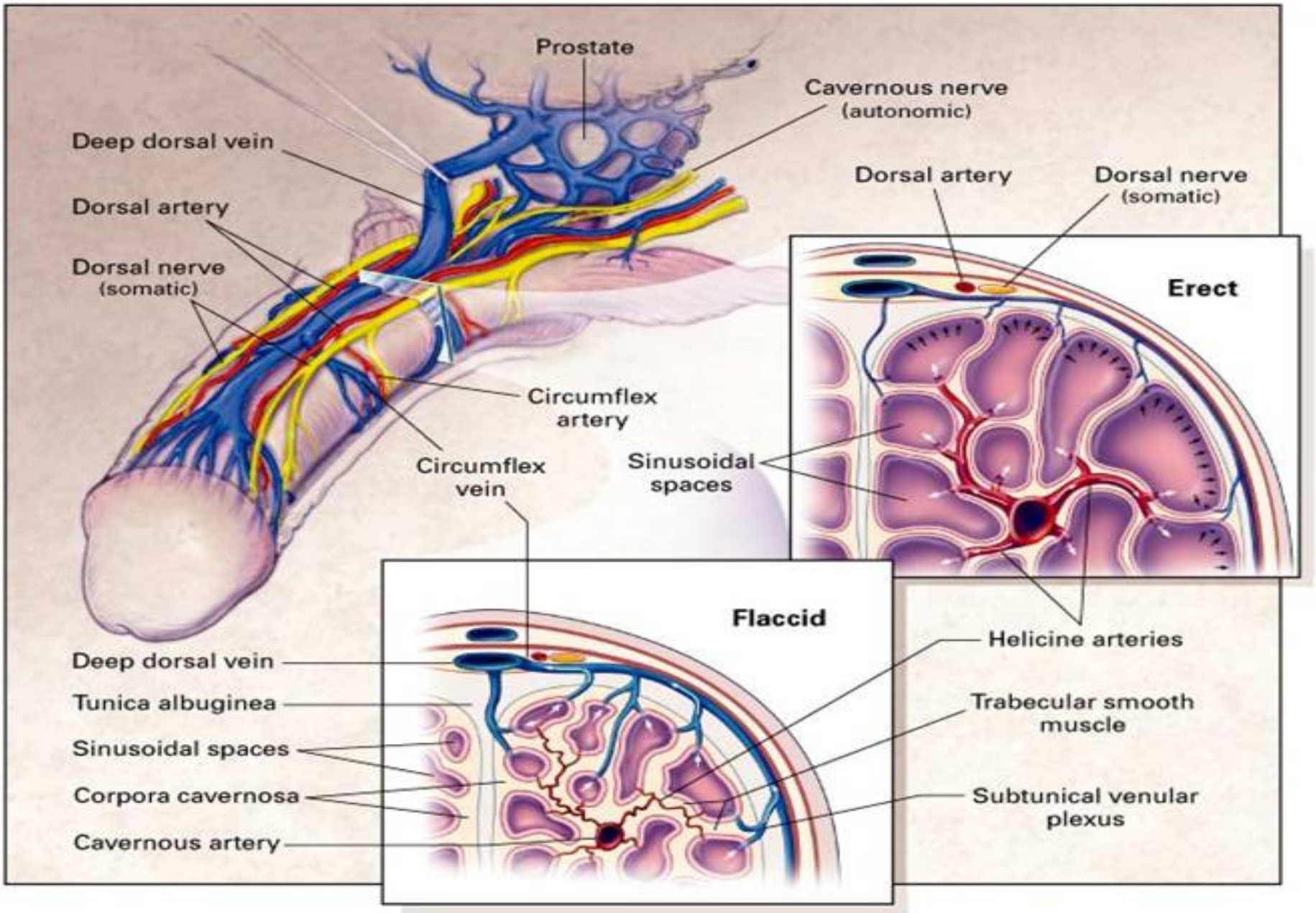

With the breakthrough oral medicatio
for erectile dysfunction
SUCCESS
IS ONE
SIMPLE
STEP
AWAY


Viagra


CIALIS IS HERE.

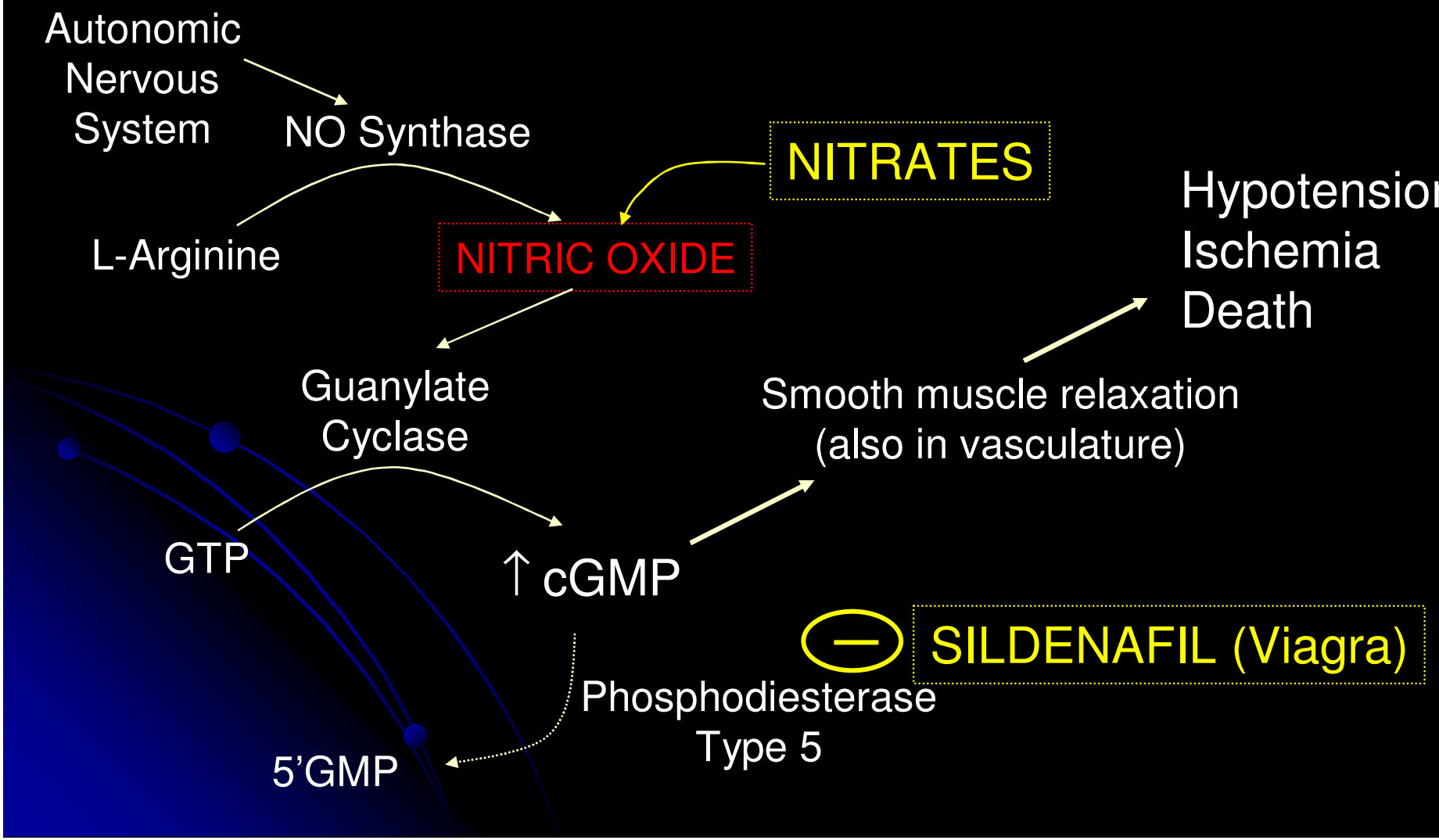
Sildenafil and Nitrates

- Released in March 1998
- Over 6 million Rx in first year
- 130 deaths reported to FDA, most cardiac
- Many cases of severe hypotension in pts taking nitrates $\Rightarrow$ 16 deaths



Lue TF, N Engl J Med 342(24):1802, 2000

Sildenafil and Nitrates Mechanism of Interaction



Pharmacodynamic Interactions

- The use of two agents which affect the same physiologic system
- Can be either synergistic or antagonistic
  - calcium channel blocker + beta blocker
  - furosemide + gentamicin

Pharmacokinetic Interactions

- Absorption
- Distribution
  - protein binding
- Metabolism
  - cytochrome p450
- Elimination
  - diuretics & lithium

Survey Says: History of epilepsy, rash and fever 5 days after dilantin

- The best agent to switch the patient to is?

A. Valpraote
B. Carbamazepine
C. Phenobarbital
D. Lamotrigine

Anticonvulsant Hypersensitivity Syndrome (AHS)

- Rare adverse event (1/1,000 to 1/10,000) characterized by fever, rash, and internal organ involvement (liver, kidney, CNS, lungs), usually with lymphadenopathy,
- 1-8 weeks after drug initiation
- It is not dose-related and can recur if the drug is re-started

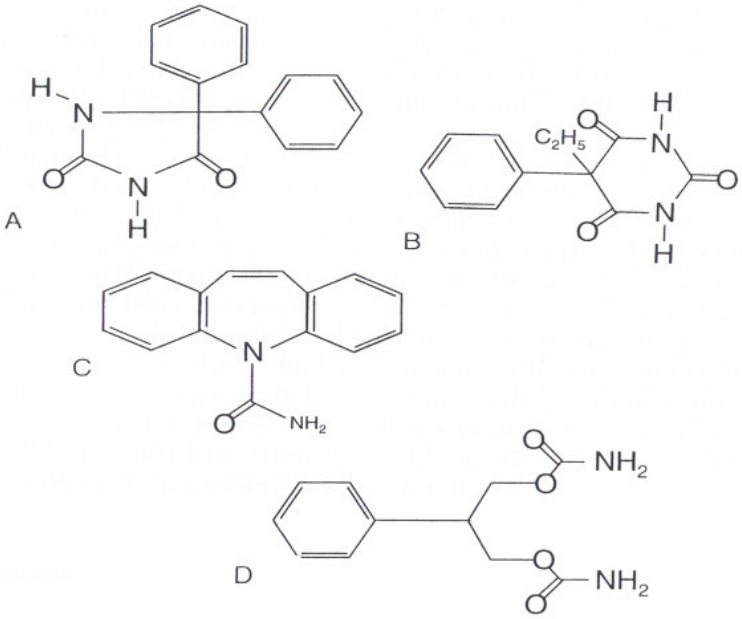
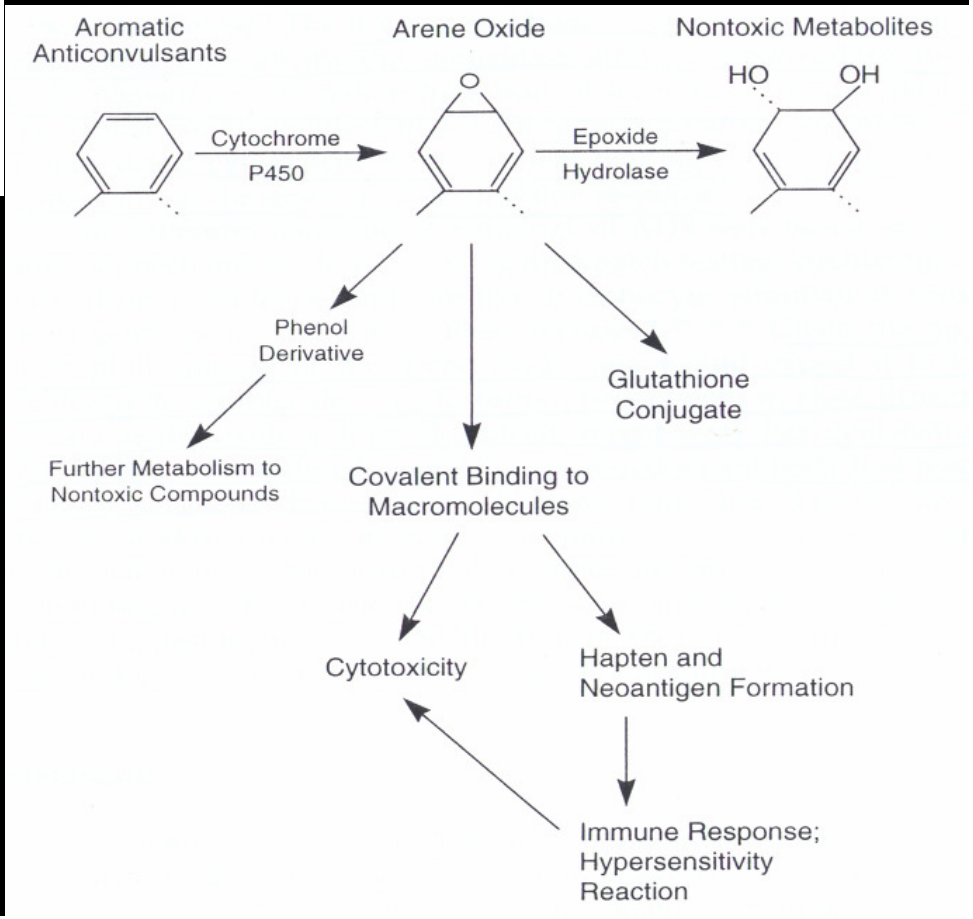


Figure 2. Similarities in the structure of phenytoin *(A)*, phenobarbital *(B)*, carbamazepine *(C)*, and felbamate *(D)*.

Crit Care Clin. 1997 Oct;13(4):727-39.
Anticonvulsant Hypersensitivity Syndrome.
Morkunas AR, Miller MB.



AHS: Clinical Findings

- Fever
- Rash, exfoliative suggests Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis
- Lymphadenopathy is seen in 2/3 of patients, has been associated with “pseudolymphoma”
- Liver involvement: mild transaminitis to fulminant hepatic necrosis
- Other findings in AHS include eosinophilia, hematologic abnormalities, and nephritis
- Less common findings include myalgias, arthralgias, rhabdomyolysis, pneumonitis, and thyroiditis, which results in hypothyroidism approximately 2 months after presentation.

Treatment of AHS

- Discontinue offending drug and supportive care
- The use of systemic corticosteroids, IV immunoglobulins, and antihistamines is controversial
- Due to the high degree of cross-reactivity among the aromatic anticonvulsants, patients should not be switched to another medication in this class!!
- Family members of patients with AHS should be warned, and may want to undergo testing prior to starting any of the drugs in this class

?Survey Says

- 30 year old on Venlafaxine (Effexor) complains of severe ankle pain after a trauma. Obvious fracture is noted with good pulses. She requests analgesics. Which is potentially most harmful?

A. Ibuprofen
B. Meperidine
C. Morphine
D. Fentanyl

Serotonin Syndrome

- Acute increase in serotonin at the $5HT_{1A}$ receptor
- Produced by
  - 2 serotonergic drugs simultaneously
  - initiating serotonergic drug
  - increased dosing
  - overdose

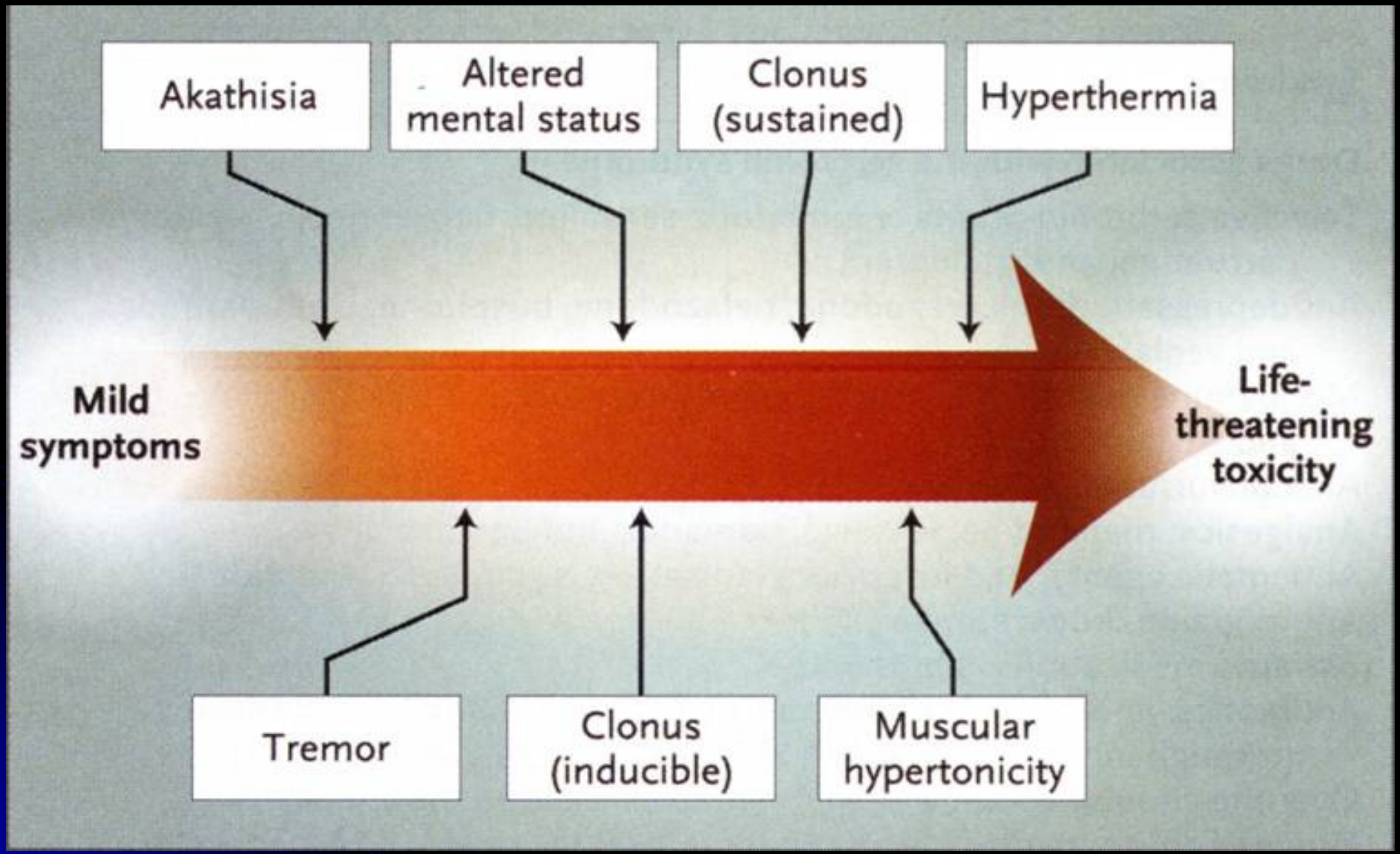
Serotonin Syndrome Medications Involved

- MAOI's, TCA's, SSRI's
- Venlafaxine, trazodone, nefazodone
- Meperidine, dextromethorphan
- Sumatriptan
- "Ecstasy"
- Lithium

Changing Antidepressants

- Stop MAOI
  - start SSRI in 2 weeks
- Stop SSRI
  - start MAOI in 2 weeks
  - if fluoxetine then 4 weeks

Spectrum of Clinical Findings



Boyer et al. N Engl J Med 352;11:1112-20, 2005

Serotonin Syndrome Clinical Presentation

- Cognitive and behavioral
  - dizziness, restlessness, agitation, delerium, seizures, coma
- Autonomic nervous system
  - diaphoresis, ↑ HR, ↑ BP, ↑ T
- Neuromuscular
  - hyperreflexia, muscle stiffness, rigidity
  - lower extremities

Mills, Critical Care Clinics 13(4):763-83, 1997

Serotonin Syndrome Treatment

- Stop all serotonergic agents
- Cyproheptadine (Periactin) 4-8 mg PO
- Benzodiazepines - titrate to effect
- Aggressive sedation/paralysis/cooling for critically ill but is rarely needed

A Few Other Causes of Drug-Induced Heat Illnesses

	ΔMS	Hot	Miscellaneous
MH	✔	✔	Post-anesthesia
NMS	✔	✔	Dopamine-blockers
SS	✔	✔	SSRI's "plus"
ACS	✔	✔	Dry skin, etc
ST	✔	✔	Moist skin

Safety Notices

FDA issues warning about CNS toxicity in patients taking antibacterial agent Zyvox with certain psychiatric drugs

July 27, 2011

ST LOUIS (MD Consult) - On July 26, 2011, the US Food and Drug Administration (FDA) issued a safety notice concerning use of the anti-infective agent *Zyvox* (linezolid) with serotonergic psychiatric mec
below). The FDA has received reports of serious central nervous system (CNS) reactions occurring when such medications are taken together. Some deaths were reported.

Although the exact mechanism of this drug interaction is unknown, linezolid inhibits the action of *monoamine oxidase A*, an enzyme responsible for breaking down serotonin in the brain. It is believed that
to patients receiving serotonergic psychiatric medications, high levels of serotonin can accumulate in the brain, leading to the development of serotonin syndrome. Signs and symptoms of serotonin syndrc
changes (confusion, hyperactivity, memory problems), muscle twitching, hyperhidrosis, shivering or shaking, diarrhea, trouble with coordination, and/or fever.

The FDA believes that some health care professionals and patients may not realize that linezolid has monoamine-oxidase inhibitor properties. Linezolid should generally not be given to patients taking ser
However, treatment with linezolid may be necessary in the presence of certain serious conditions including vancomycin-resistant *Enterococcus faecium* infections, and nosocomial pneumonia and complic
structure infections, including cases caused by methicillin-resistant *Staphylococcus aureus*.

In emergency situations requiring urgent treatment with linezolid, the availability of alternative interventions should be considered and the benefit of linezolid treatment should be weighed against the risk of
linezolid must be administered to a patient receiving a serotonergic drug, the serotonergic drug must be immediately stopped and the patient should be closely monitored for emergent symptoms of CNS t
weeks if fluoxetine [Prozac] was taken), or until 24 hours after the last dose of linezolid, whichever comes first.

In non-emergency situations when non-urgent treatment with linezolid is contemplated and planned, the serotonergic psychiatric medication should be stopped, to allow its activity in the brain to dissipate.
psychiatric drugs should be stopped at least 2 weeks in advance of linezolid treatment. Fluoxetine (Prozac), which has a longer half-life compared with similar drugs, should be stopped at least 5 weeks in
with the serotonergic psychiatric medication may be resumed 24 hours after the last dose of linezolid.

Treatment with serotonergic psychiatric medications should not be initiated in a patient who is receiving linezolid, but may be started 24 hours after the last dose of linezolid.

Patients should be educated to contact a health care professional immediately if they experience any symptoms of serotonin syndrome or CNS toxicity while taking serotonergic psychiatric medications c

The following tables contain lists of serotonergic psychiatric medications:

Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic name	Found in Brand name(s)
paroxetine	Paxil, Paxil CR, Pexeva
fluvoxamine	Luvox, Luvox CR
fluoxetine	Prozac, Sarafem, Symbyax

Survey Says: Which of the following is the most common side-effect of Neuroleptics / Antipsychotics?

a. Akathisia
b. Dystonia
c. Malignant Hyperthermia
d. Neuroleptic Malignant Syndrome

Antiemetics in the ED: a randomized controlled trial comparing 3 common agents

- This randomized, placebo-controlled, double-blind trial compares 1.25 mg droperidol, 10 mg metoclopramide, 10 mg prochlorperazine, and saline placebo.
- Droperidol (-54.5 mm) was significantly better than metoclopramide (-40.2 mm) or prochlorperazine (-40.5 mm) at reducing nausea at 30 minutes (P = .04).
- There were no significant differences in rescue medication or patient satisfaction; however, droperidol had significantly higher akathisia (71.4% vs 23.5%) at 24-hour follow-up.

Braude D, Soliz T, Crandall C, Hendey G, Andrews J, Weichenthal L.
Am J Emerg Med. 2006 Mar;24(2):177-82.

?Survey Says

- 24 year old on seldane for URI symptoms. You diagnosis sinusitis. You agree to prescribe and antibiotic. Which is the best choice?

A. Azithromycin

B. Erythromycin

C. Ofloxacin

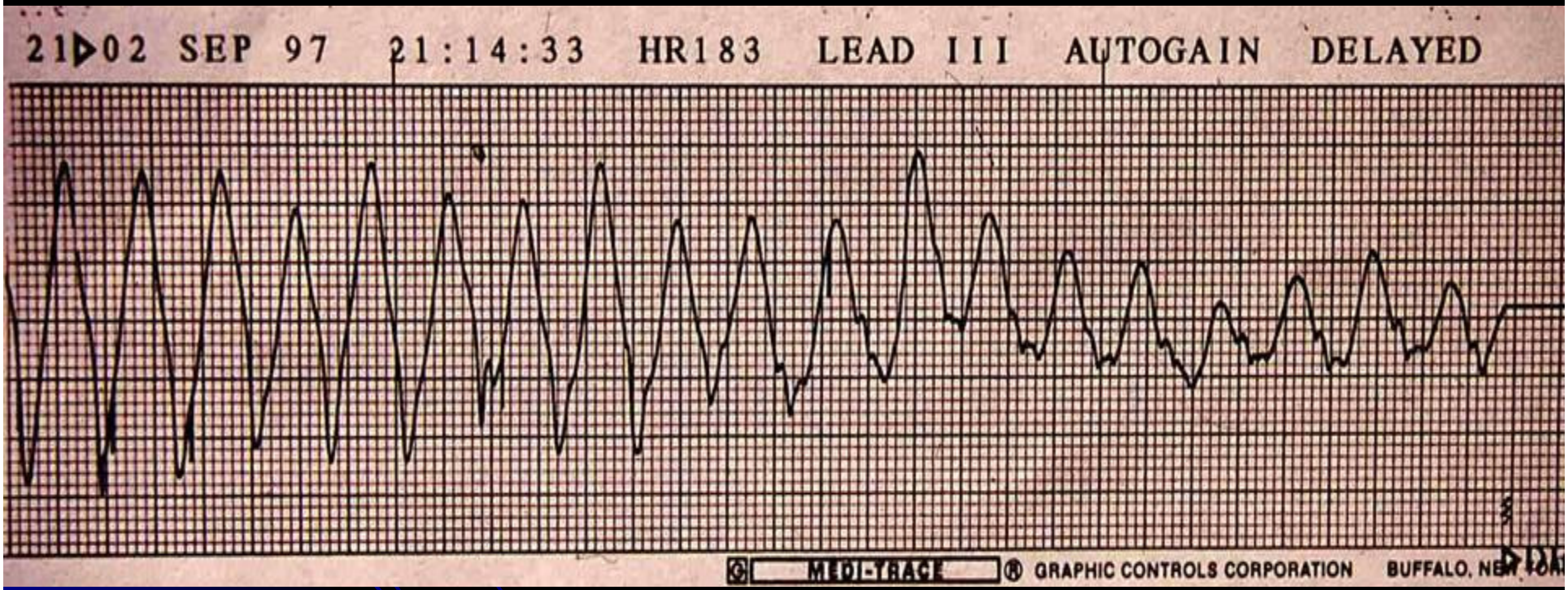
D. Flagyl

cc: Palpitations

- 24 yr old female returns now and complains of palpitations and dizziness. Recently diagnosed with bronchitis and treated with erythromycin.
- Pt also self-treating with OTC's acetaminophen and Propulusid (Cisapride)

cc: Palpitations

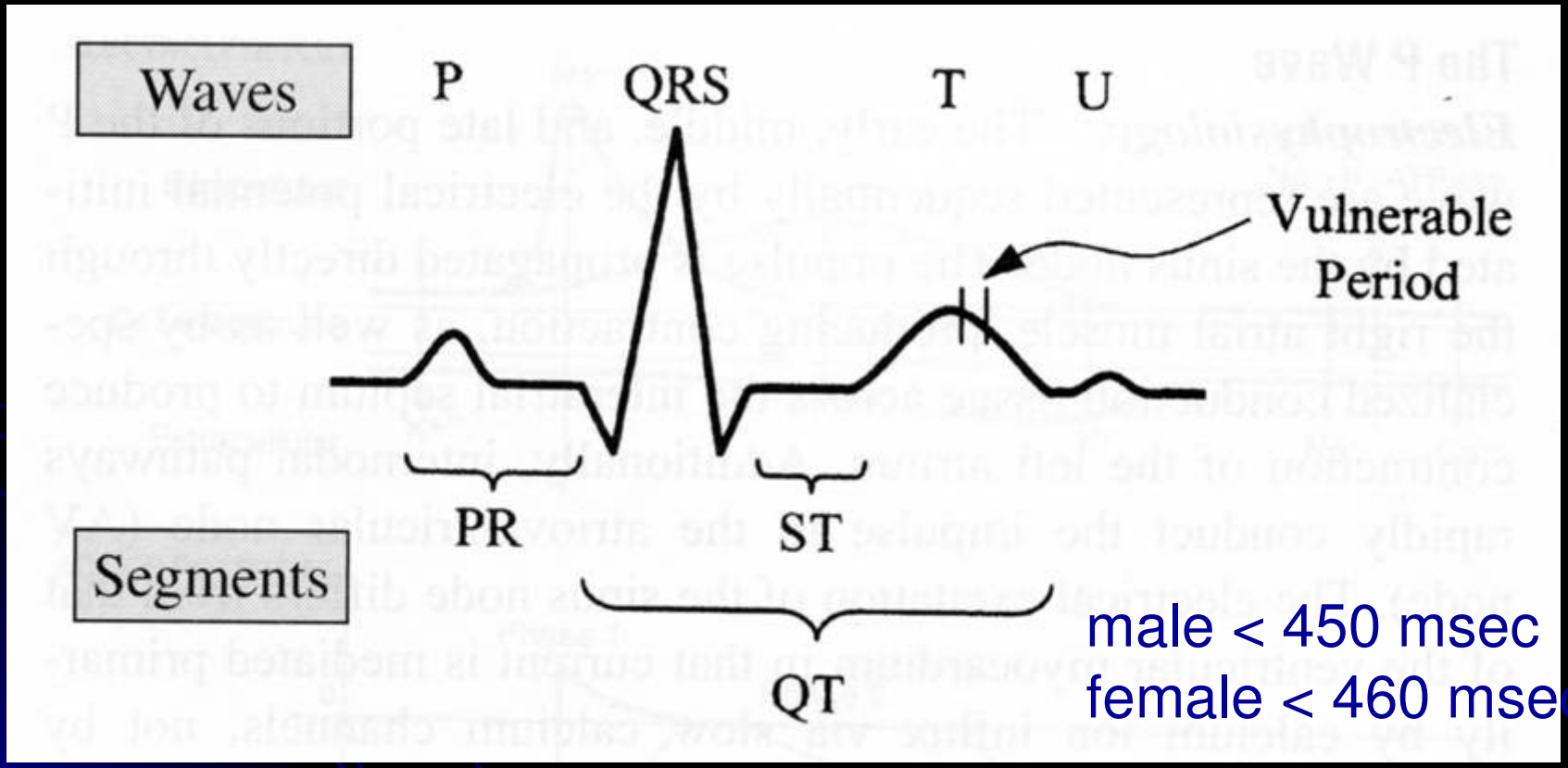
- Vitals, physical examination unremarkable
- Hx of palpitations >> monitor



FDA Withdrawals/Restrictions Due to Prolongation of the QT Interval

- Withdrawn
  - Terfenadine (Seldane) - 1998
  - Astemizole (Hismanal) - 1999
  - Grepafloxin (Raxar) – 1999
- “Black box”
  - Cisapride (Propulsid) - 2000
  - Levomethadyl (Orlaam) - 2001
  - Droperidol (Inapsine) - 2002

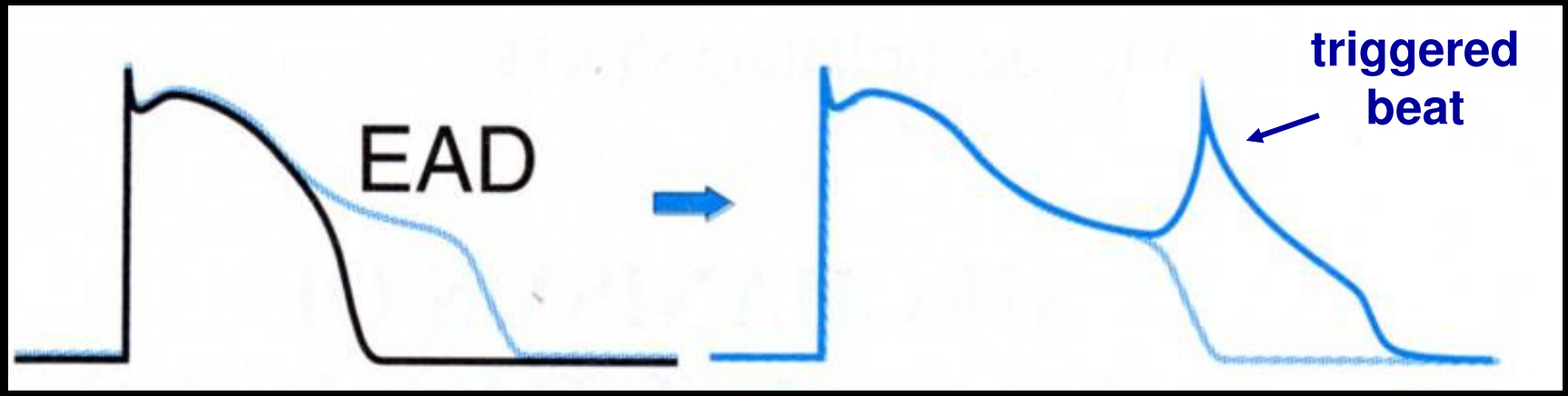
The QT Interval



male < 450 msec
female < 460 msec

Goldfranks Toxicologic Emergencies 7th ed

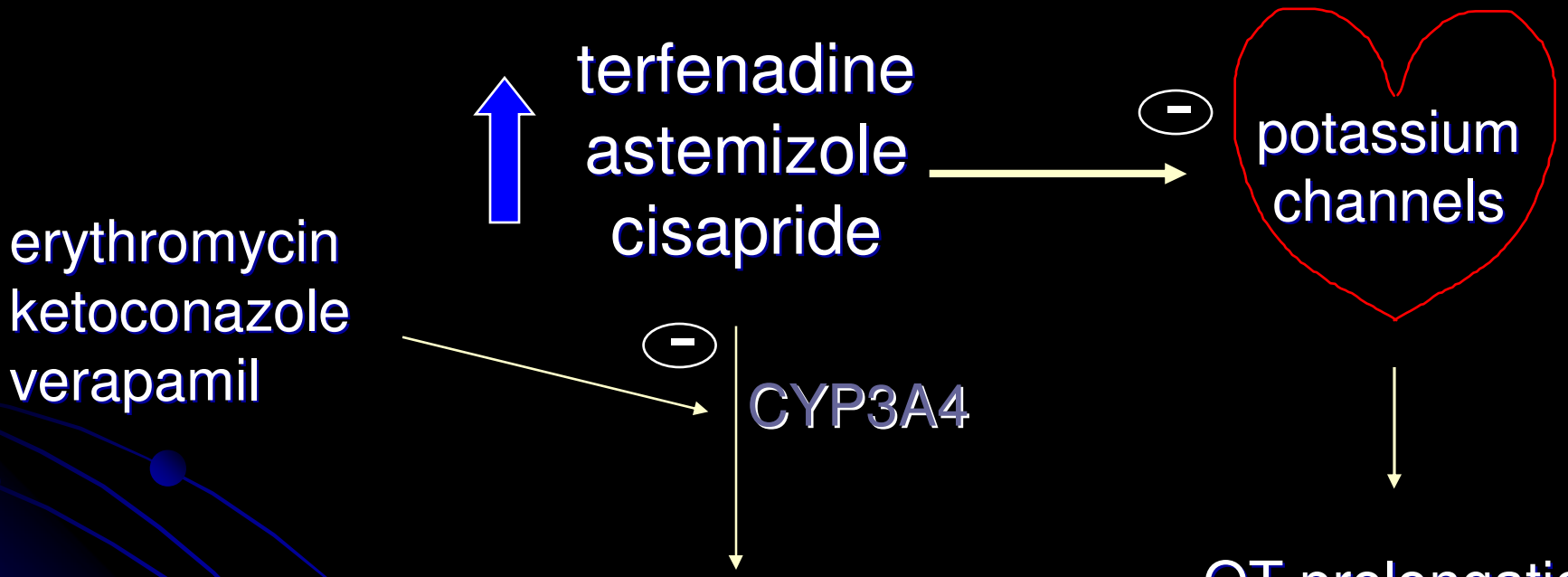
Early After-depolarization Triggering a Dysrhythmogenic Beat



Early after-depolarization (EAD) interrupting phase 3 repolarization.
Under some conditions, a triggered beat can arise from an EAD (black arrow, right)

Goodman & Gilman 9th ed

Pharmacokinetic Interaction



Woosley, JAMA 269;1532-6, 1993

Available Drugs Associated w/ QT prolongation

- Disopyramiide, procainamide, quinidine, sotalol, bepridil, amiodarone
- Erythromycin, clarithromycin, sparfloxacin
- Droperidol, haloperidol, mesoridazine, thioridazine, chlorpromazine, quetiapine
- Methadone

Drugs associated with prolonged QTC and Torsades

- Amantadine
- Arsenic
- Astemizole
- Bepridil
- Butyrophenones
- Chloral hydrate
- Chloroquine
- Cisapride
- Citalopram
- Emetine
- Fluoride (secondary to hypocalcemia)
- Fluoxetine
- Ketoconazole
- Erythromycin
- Mercury (organic)
- Organophosphates
- Pentamidine
- Phenothiazines (particularly thioridazine, mesoridazine)
- Phosphorus
- Pimozide
- Scorpion venom
- Terfenadine
- Tetracyclic antidepressants
- Tricyclic antidepressants
  - Disopyramide
  - Procainamide
  - Quinidine
- Encainide
  - Flecainide
  - Lorcainide
  - Moricizine
  - Propafenone
- Amiodarone
  - Bretylium
  - N-Acetylprocainamide
  - Sotalol

Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

Wayne A. Ray, Ph.D., Cecilia P. Chung, M.D., M.P.H., Katherine T. Murray, M.D., Kathi Hall, B.S., and C. Michael Stein, M.B., Ch.B.

ABSTRACT

BACKGROUND

Users of typical antipsychotic drugs have an increased risk of serious ventricular arrhythmias and sudden cardiac death. However, less is known regarding the cardiac safety of the atypical antipsychotic drugs, which have largely replaced the older agents in clinical practice.

METHODS

We calculated the adjusted incidence of sudden cardiac death among current users of antipsychotic drugs in a retrospective cohort study of Medicaid enrollees in Tennessee. The primary analysis included 44,218 and 46,089 baseline users of single typical and atypical drugs, respectively, and 186,600 matched nonusers of antipsychotic drugs. To assess residual confounding related to factors associated with the use of antipsychotic drugs, we performed a secondary analysis of users of antipsychotic drugs who had no baseline diagnosis of schizophrenia or related psychoses and with whom nonusers were matched according to propensity score (i.e., the predicted probability that they would be users of antipsychotic drugs).

RESULTS

Current users of typical and of atypical antipsychotic drugs had higher rates of sudden cardiac death than did nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 (99% confidence interval [CI], 1.68 to 2.34) and 2.26 (99% CI, 1.88 to 2.72), respectively. The incidence-rate ratio for users of atypical antipsychotic drugs as compared with users of typical antipsychotic drugs was 1.14 (99% CI, 0.93 to 1.39). Former users of antipsychotic drugs had no significantly increased risk (incidence-rate ratio, 1.13; 99% CI, 0.98 to 1.30). For both classes of drugs, the risk for current users increased significantly with an increasing dose. Among users of typical antipsychotic drugs, the incidence-rate ratios increased from 1.31 (99% CI, 0.97 to 1.77) for those taking low doses to 2.42 (99% CI, 1.91 to 3.06) for those taking high doses ($P<0.001$). Among users of atypical agents, the incidence-rate ratios increased from 1.59 (99% CI, 1.03 to 2.46) for those taking low doses to 2.86 (99% CI, 2.25 to 3.65) for those taking high doses ($P=0.01$). The findings were similar in the cohort that was matched for propensity score.

CONCLUSIONS

Current users of typical and of atypical antipsychotic drugs had a similar, dose-related increased risk of sudden cardiac death.

From the Division of Pharmacoepidemiology, Department of Preventive Medicine (W.A.R., K.H.), the Divisions of Rheumatology (C.P.C., C.M.S.), Cardiology (K.T.M.), and Clinical Pharmacology (K.T.M., C.M.S.), Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine; and the Geriatric Research, Education, and Clinical Center, Nashville Veterans Affairs Medical Center (W.A.R.) — both in Nashville. Address reprint requests to Dr. Ray at the Department of Preventive Medicine, Village at Vanderbilt, Suite 2600, 1501 21st Ave. South, Nashville, TN 37212, or at cindy.naron@vanderbilt.edu.

N Engl J Med 2009;360:225-35.

Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

Table 2. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death, According to Use or Nonuse of Antipsychotic Drugs.*

User Status	No. of Person-Years	No. of Sudden Deaths	Incidence-Rate Ratio (95% CI)	P Value
Nonuser	624,591	895	Reference group	
Former user	189,981	311	1.13 (0.98–1.30)	0.08
Current user†				
Typical agent				
Any	86,735	255	1.99 (1.68–2.34)	<0.001
Haloperidol	21,728	58	1.61 (1.16–2.24)	0.005
Thioridazine	15,715	65	3.19 (2.41–4.21)	<0.001
Atypical agent				
Any	79,589	223	2.26 (1.88–2.72)	<0.001
Clozapine	4,654	19	3.67 (1.94–6.94)	<0.001
Olanzapine	27,257	75	2.04 (1.52–2.74)	<0.001
Quetiapine	17,355	40	1.88 (1.30–2.71)	<0.001
Risperidone	24,589	85	2.91 (2.26–3.76)	<0.001

FDA examining risk of cardiovascular death with use of antibiotic Zithromax

May 18, 2012

ST LOUIS (MD Consult) - On May 17, 2012, the US Food and Drug Administration (FDA) issued a statement concerning the safety of the macrolide antibacterial a cardiovascular death. This statement was prompted by the agency's preliminary review of a study published in the May 17, 2012, issue of *The New England Journa*

The study compared the risks of cardiovascular death in patients treated with azithromycin (Zithromax), amoxicillin, ciprofloxacin (Cipro), levofloxacin (Levaquin), an increase in cardiovascular deaths, and in the risk of death from any cause, in persons treated with a 5-day course of azithromycin compared with persons treated w cardiovascular death associated with levofloxacin treatment were similar to those associated with azithromycin treatment.

The use of macrolides has previously been associated with cardiovascular effects; specifically, prolongation of the QT-interval. Prolongation of the QT-interval can le not address the use of other macrolide antibacterial drugs, such as clarithromycin (Biaxin) and erythromycin, regarding the potential for cardiovascular death.

The Warnings and Precautions section of the drug label for the azithromycin extended-release oral suspension formulation was revised in March 2012 to include ne which appears to be low. The FDA is in the process of updating risk information in the drug labels for additional macrolide antibacterial drugs.

The FDA plans to communicate any new information on azithromycin and the potential risk of QT-interval prolongation after it has completed its review. The FDA is for QT-interval prolongation and cardiac arrhythmias when prescribing or administering antibacterial drugs.

Safety Notices

FDA ups warnings about prolonged QT intervals in patients taking antiemetic Zofran

September 15, 2011

ST LOUIS (MD Consult) - On September 15, 2011, the US Food and Drug Administration (FDA) issued a safety notice concerning use of the antiemetic Zofran (onc possible increased risk of cardiac electrical disturbances. The FDA previously noted cardiovascular safety concerns that suggested that use of Zofran could cause fatal arrhythmia known as *Torsade de Pointes*. The agency is now adding a new warning to avoid the use of ondansetron in patients with congenital long QT syndro experiencing Torsade de Pointes.

Zofran is used prevent nausea and vomiting related to cancer chemotherapy, radiation therapy, and surgery.

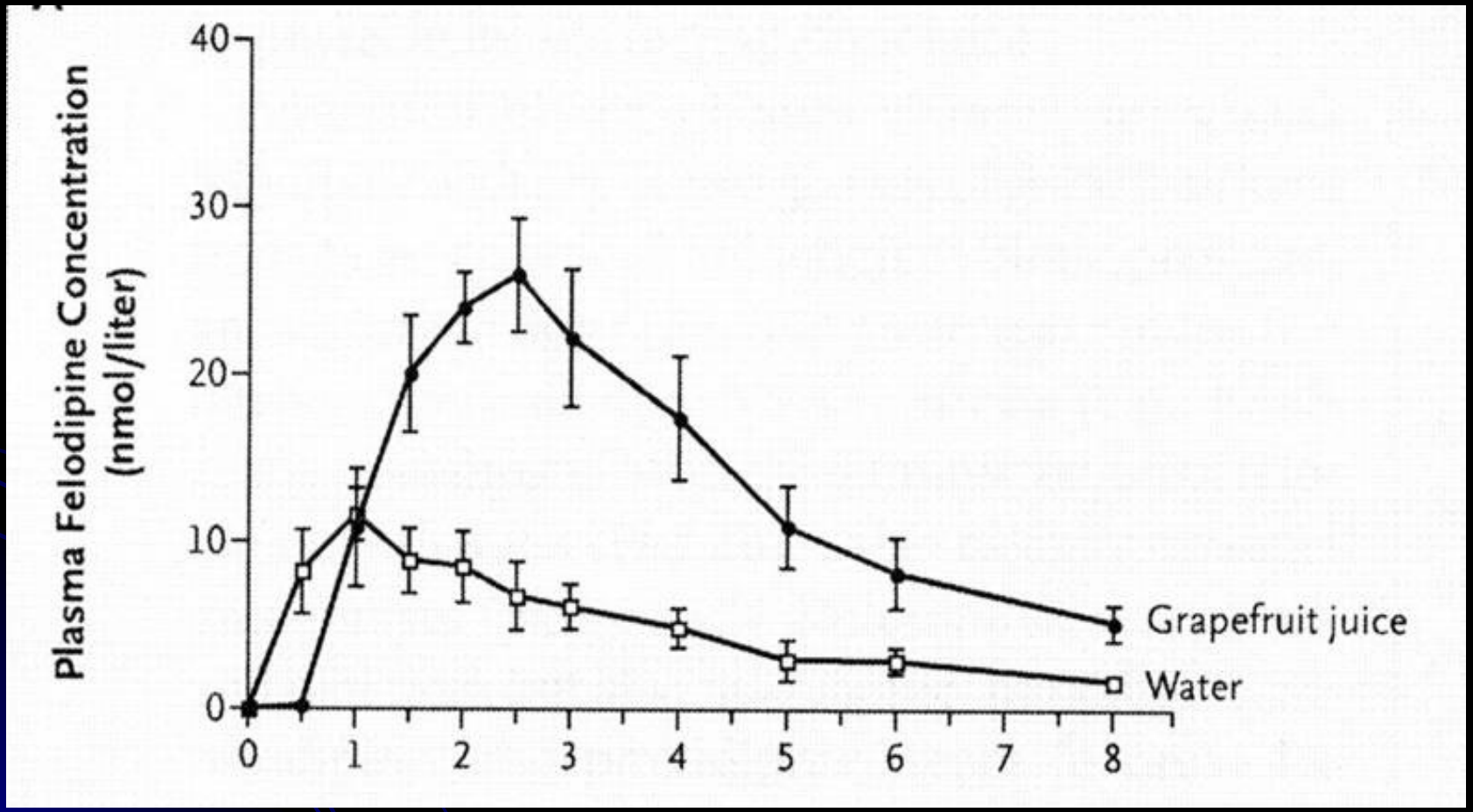
In certain patients receiving Zofran, electrocardiographic monitoring is recommended. Such patients include those with electrolyte abnormalities (eg, hypokalemia o and in patients taking concomitant medications that prolong the QT interval. Patients should be advised to contact a health care professional immediately if they ex rhythm while taking Zofran.

The FDA has reviewed all available information and is making interim changes to the ondansetron drug labels. The manufacturer of Zofran (GlaxoSmithKline) is bein potential for the drug to prolong QT intervals.

Potent Inhibitors of CYP3A

- Erythromycin, clarithromycin, ciprofloxacin
- Azole antifungals (ketoconazole, fluconazole)
- Diltiazem, verapamil
- SSRI's (footnote), nefazodone
- Protease inhibitors (ritonovir, indinavir)
- Cimetidine (not as potent but very common)

Time Plasma Concentration Curve



Bailey et al. Br J Clin Pharmacol 46:101-110, 1998

Common Drugs Metabolized Significantly/Exclusively by CYP3

- Antidepressants
  - Amitriptyline, venlafaxine imipramine
- Calcium channel blockers
- Protease inhibitors
- Cyclosporine, tacrolimus
- Midazolam

Wilkerson, N Engl J Med 352;21:2211-21

? Survey says

- Your next patient presents on Dipyridamole (Persantine®) and has SVT. The best drug at this time is?

A. Adenosine 6 mg

B. Adenosine 12 mg

C. Adenosine 3 mg

Adenosine drug Interactions

- Carbamazepine may increase heart block.
- Dipyridamole potentiates effects of adenosine; reduce dose of adenosine.
- Theophylline and caffeine (methylxanthines) antagonize adenosine's effects; may require increased dose of adenosine.

Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Sarah Meredith, M.B., B.S., Sukumar Suguna Narasimhulu, M.B., B.S., M.P.H., Kathi Hall, M.S., and C. Michael Stein, M.B., Ch.B.

ABSTRACT

BACKGROUND

Oral erythromycin prolongs cardiac repolarization and is associated with case reports of torsades de pointes. Because erythromycin is extensively metabolized by cytochrome P-450 3A (CYP3A) isozymes, commonly used medications that inhibit the effects of CYP3A may increase plasma erythromycin concentrations, thereby increasing the risk of ventricular arrhythmias and sudden death. We studied the association between the use of erythromycin and the risk of sudden death from cardiac causes and whether this risk was increased with the concurrent use of strong inhibitors of CYP3A.

Ray, et al. N Engl J Med 351;11:1089-96, 2004

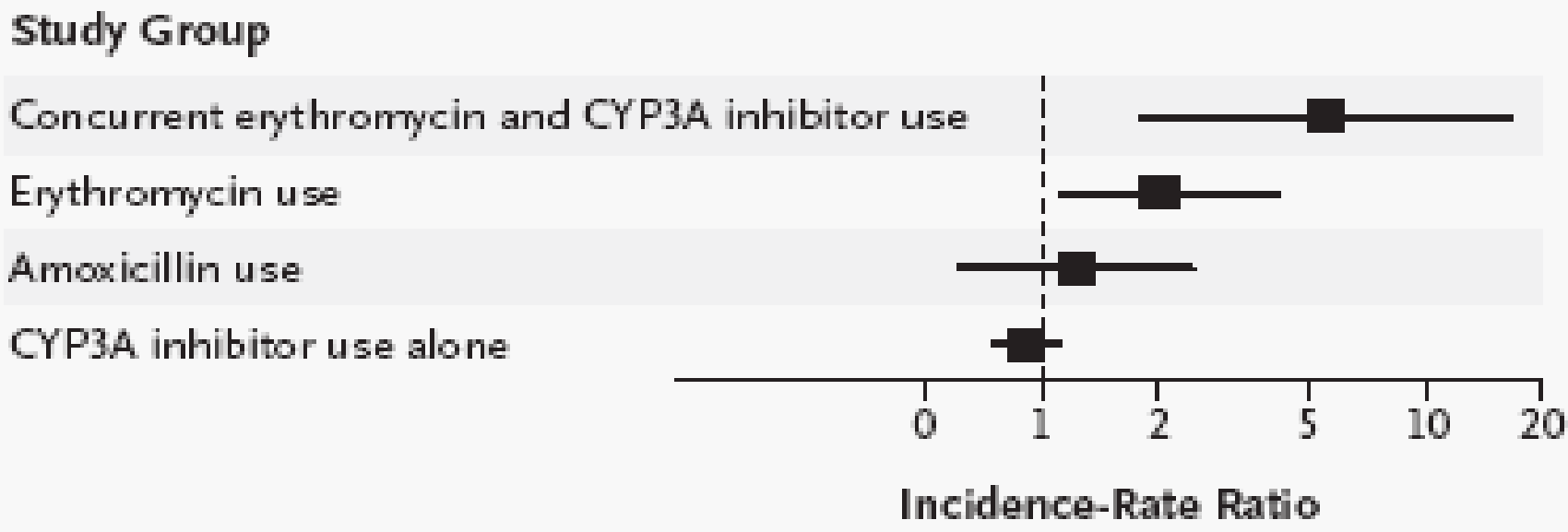


Figure 1. The Incidence-Rate Ratio for Sudden Death from Cardiac Causes According to the Current Use of the Study Antibiotic Medications and CYP3A Inhibitors.

The bars indicate 95 percent confidence intervals. The reference group for the incidence-rate ratio associated with the concurrent use of erythromycin and CYP3A inhibitors and with the use of CYP3A inhibitors alone is the patients who used none of these medications; that for the incidence-rate ratio associated with the use of erythromycin and use of amoxicillin, regardless of the use of CYP3A inhibitors, is the patients who used neither of these antibiotic medications.

Ray, et al. N Engl J Med 351;11:1089-96, 2004

Inducers of CYP450

- Increase the metabolism of drugs
  - subtherapeutic dosing
- Lipid soluble
- Gradual onset - days to weeks
- If stopped, the effect will disappear

Inducers of CYP450

- Rifampin, isoniazid
- Phenobarbital, phenytoin, carbamazepine
- Cigarette smoke (PAH's)
- Chronic ethanol

Lower Doses of Ambien ?

Impaired morning-after alertness concerns prompt labeling update for insomnia products containing zolpidem

January 10, 2013

ST LOUIS (MD Consult) - On January 10, 2012, the US Food and Drug Administration (FDA) issued a safety announcement concerning the insomnia drug *zolpidem*. The FDA now recommends that the bedtime dose be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Zoldipem is marketed in generic form and under the brand names Ambien, Ambien CR, Edluar, and Zolpimist.

The FDA urges health care professionals to caution all patients who use these zolpidem products about the risks of next-morning impairment for activities that require complete mental alertness, including driving. For zolpidem products, data show the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men.

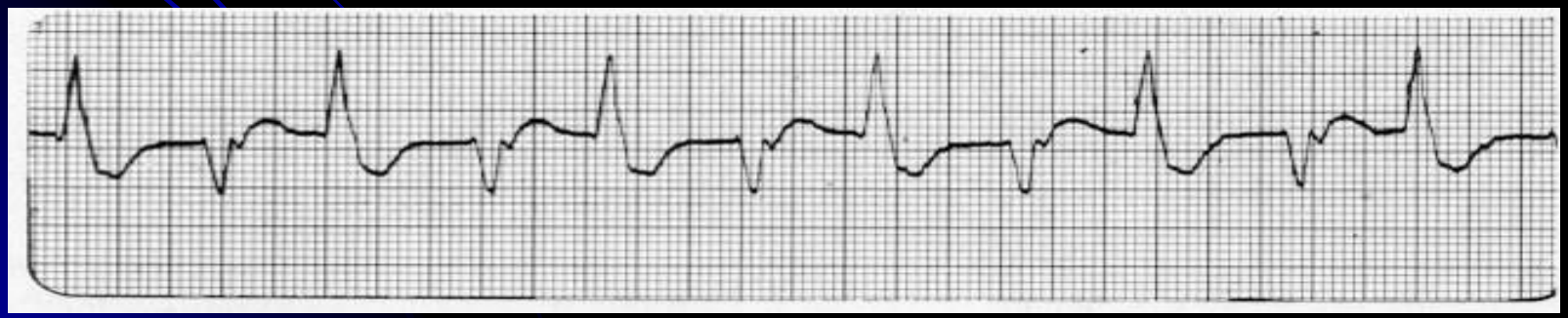
Because use of lower doses of zolpidem will result in lower blood levels in the morning, the FDA is requiring the manufacturers of Ambien, Ambien CR, Edluar, and Zolpimist to lower the recommended dose. The recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). For men, the FDA is requiring that labeling recommend that health care professionals consider prescribing the lower doses of zoldipem (ie, 5 mg for immediate-release products and 6.25 mg for extended-release products).

The drug labeling for immediate-release products should also include a statement that, for both men and women, the 5 mg dose could be increased to 10 mg if needed, but the higher dose is more likely to impair next-morning driving and other activities that require full alertness. For extended-release products, the drug labeling should include a statement that, for both men and women, the 6.25 mg dose can be increased to 12.5 mg if needed, but the higher dose is more likely to impair next-morning driving and other activities that require full alertness. Prescribers should select the lowest dose that treats the patient's symptoms.

The recommended doses of Intermezzo, a lower-dose zolpidem product approved for middle-of-the-night awakenings, are not changing. At the time of Intermezzo's approval in November 2011, the label already recommended a lower dosage for women than for men.

Survey Says?

- Your next patient has peaked t waves and a potassium of 6 meq/L. You administer calcium and they die shortly after
- Which drug were they on?
  - A. Digitalis
  - B. Verapamil
  - C. Potassium supplements



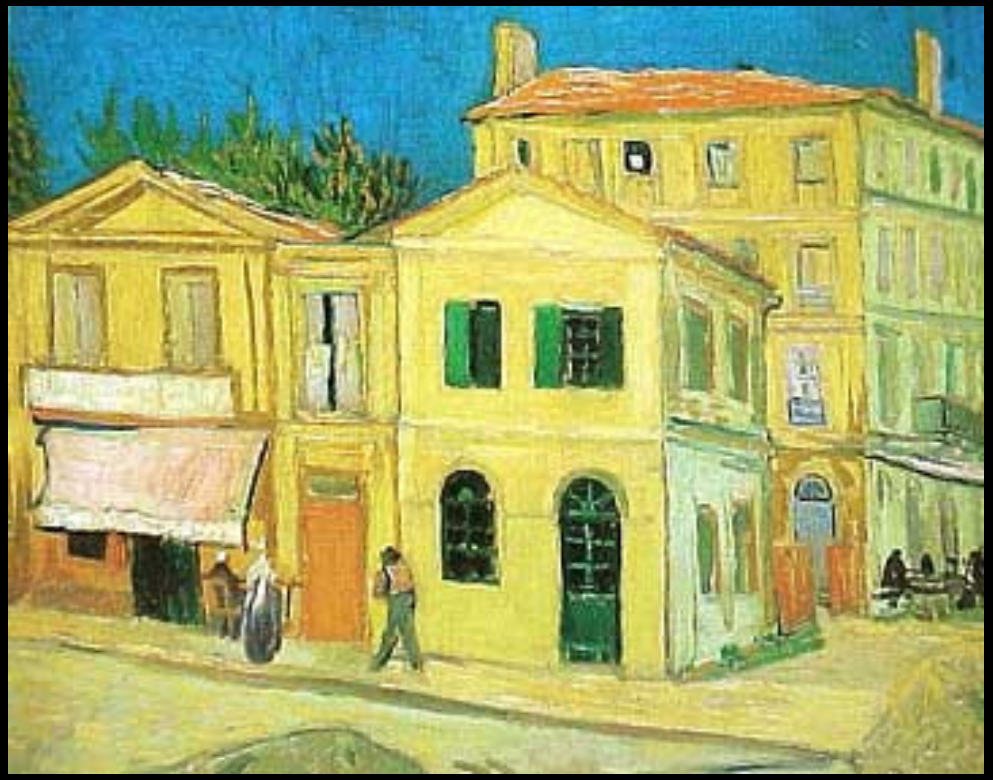
SCIENTIFIC AMERICAN August 1990, pages 11-12.

Bufo Abuse

A toxic toad gets licked, boiled, teed up and tanned

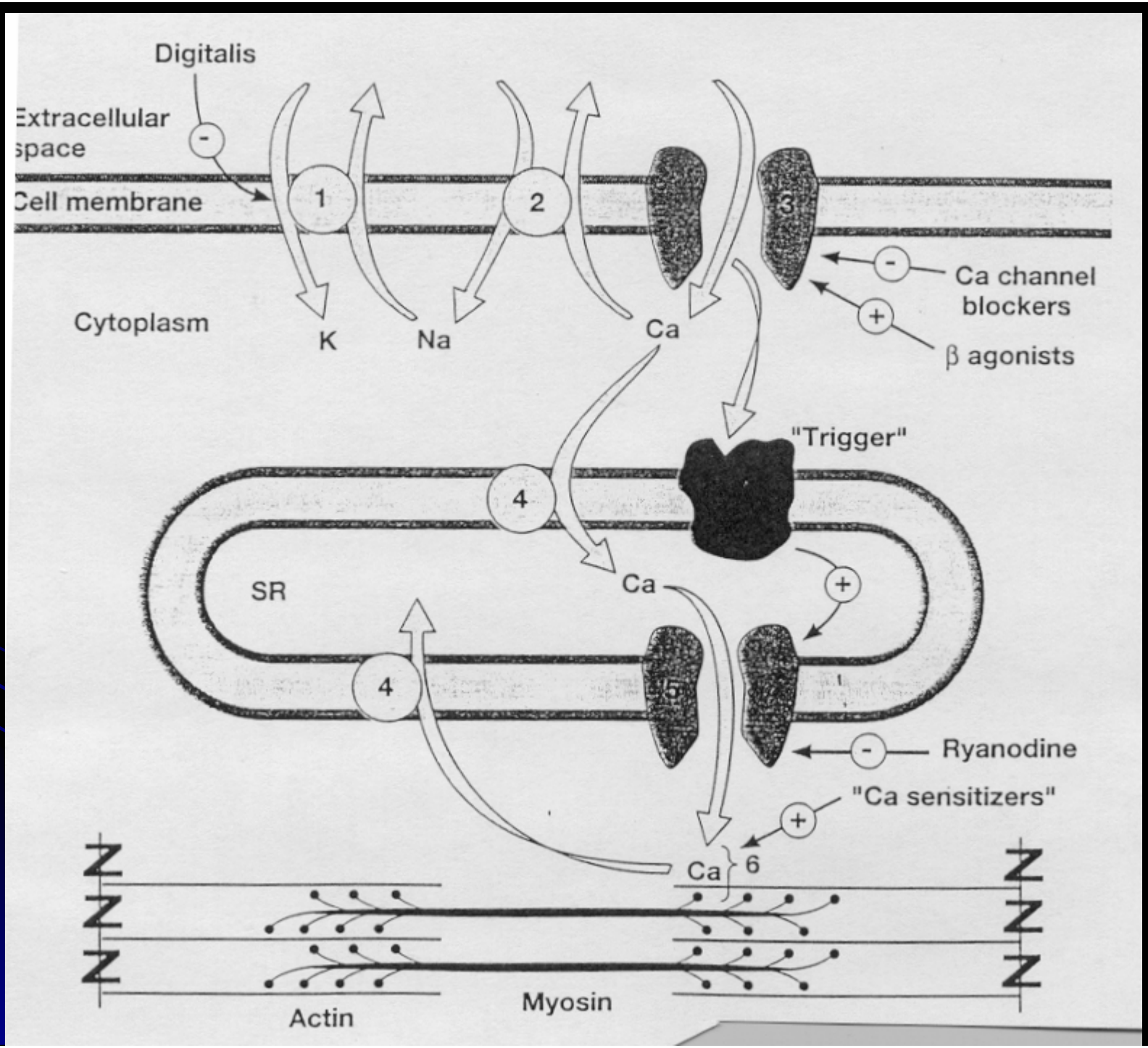
Plump, greenish-yellow and pebbly in texture, it is not much to look at. It can be nuisance, too, poisoning dogs and squishing noisily under automobile tires. But Bufo Marinus, also known as the cane toad, has become an international celebrity of late, inspiring drug-war hysteria in the U.S. and trade talks in the Far East. Here is its tale, warts and all.

Digoxin Toxicity



Drug Interactions:

- **Quinidine**
- **Verapamil**
- **Diltiazem**
- **Amiodarone**
- **Spironolactone**
- **Macrolides and tetracyclines (reversal of inactivation of digoxin by enteric bacterium *Eubacterium lentum*)**


Digitalis
Extracellular space
Cell membrane
Cytoplasm
1
2
3
K
Na
Ca
Ca channel blockers
β agonists
"Trigger"
4
SR
Ca
4
5
1
Ryanodine
"Ca sensitizers"
Ca
6
Actin
Myosin

cc: Bruising

- 67 yr old female w/ multiple medical problems sent in by her neurologist complaining of lightheadedness and a bruise on her thigh.
- Medications:
  gyburide, nifedipine, enalapril, aspirin, timolol, warfarin, cimetidine, colace.

cc: Bruising

- Gen: pale, slightly diaphoretic female
- Vitals: HR 105 irregular, BP 120/75
- Skin: several ecchymosis on legs w/ largest 7 x 10 x 4 cm on L thigh
- Abd: nontender, melanic stool

cc: Bruising

- Laboratory
  - hemoglobin = 8 g/dL (baseline 13 g/dL)
  - platelets = 280,000
  - PT > 50 sec

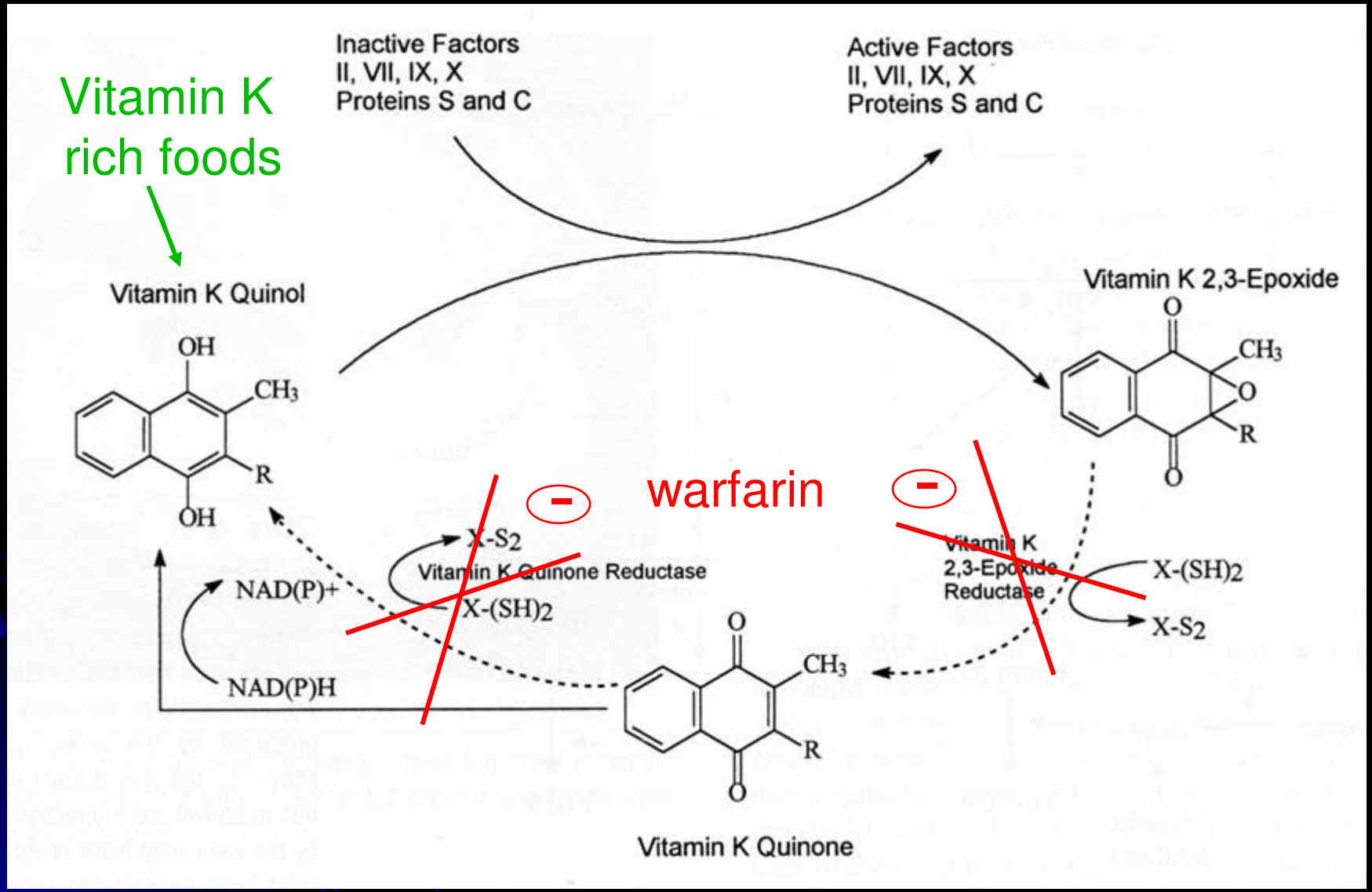
Warfarin

- Frequently involved in drug interactions
- Low therapeutic index
- Bleeding is a significant complication

Holbrook et al. Arch Int Med 165:1095-1106, 2005

Warfarin
Mechanism of Interaction

- Altered CYP metabolism (1A2, 2E1, 3A4)
  - inhibited, induced
- Drug synergism
  - heparin, NSAIDS, ticlodipine
- Drug antagonism
  - high vit K foods, enteral nutrition


Vitamin K rich foods
Inactive Factors
II, VII, IX, X
Proteins S and C
Active Factors
II, VII, IX, X
Proteins S and C
Vitamin K Quinol
Vitamin K 2,3-Epoxide
warfarin
X-S2
Vitamin K Quinone Reductase
X-(SH)2
NAD(P)+
NAD(P)H
Vitamin K
2,3-Epoxide
Reductase
X-(SH)2
X-S2
Vitamin K Quinone

cc: Bruising

- Because the patient was started on warfarin a few weeks prior by her cardiologist for atrial fibrillation, her family physician began cimetidine to prevent GI bleeding.

FDA review of bleeding risks associated with Pradaxa allays some earlier concerns

November 5, 2012

ST LOUIS (MD Consult) - On November 2, 2012, the US Food and Drug Administration (FDA) announced results of an investigation concerning bleeding risks asso the approval of Pradaxa, the FDA received a large number of post-marketing reports of bleeding among Pradaxa users. Prompted by these reports, the FDA decide intracranial hemorrhage for new users of Pradaxa, compared with new users of warfarin.

The risk assessment was performed using insurance claims and administrative data from the FDA's Mini-Sentinel pilot of the Sentinel Initiative. The *Sentinel Initiati* pre-existing electronic healthcare data from multiple sources as a means of assessing the safety of approved drugs and other medical products. The results of the I indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consis approve Pradaxa.

The FDA has not changed its recommendations regarding Pradaxa. Health care professionals who prescribe Pradaxa should carefully follow the dosing recommenc impairment) to reduce the risk of bleeding. Patients should be made aware of the signs and symptoms of bleeding, and should be instructed about concerns that re

The FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue. As part of this ongoing review, the FDA is conducting 2 additic Sentinel data. In addition, the FDA continues to monitor post-market reports for evidence of inappropriate dosing, use of interacting drugs, and other clinical factors

FDA issues safety update on risk of cardiovascular events with use of smoking cessation drug Chant

December 12, 2012

ST LOUIS (MD Consult) - On December 12, 2012, the US Food and Drug Administration (FDA) announced results of a meta-analysis that was performed to further
drug *Chantix* (varenicline). Because of earlier concerns about the drug's cardiovascular safety, the FDA required Pfizer, the manufacturer of the drug, to perform this
patients (4190 assigned to Chantix and 2812 assigned to placebo) that were enrolled in 15 Pfizer-sponsored, randomized, double-blind, placebo-controlled clinical t

A higher occurrence of major adverse cardiovascular events (a combined outcome of cardiovascular-related death, nonfatal myocardial infarction, and nonfatal strok
placebo. These events were uncommon in both the Chantix and placebo groups, and the increased risk was not statistically significant. However, the data were ana
occurrence of events in patients receiving Chantix, which makes it seem more likely that it is related to the drug and not purely a chance finding.

It should be noted that the incidence of cardiovascular mortality and all-cause mortality was lower in the Chantix group compared with the placebo group, though th

Patients receiving Chantix should be advised to contact their health care professional if they experience new or worsening symptoms of cardiovascular disease, suc
or sudden onset of weakness, numbness, or difficulty speaking.

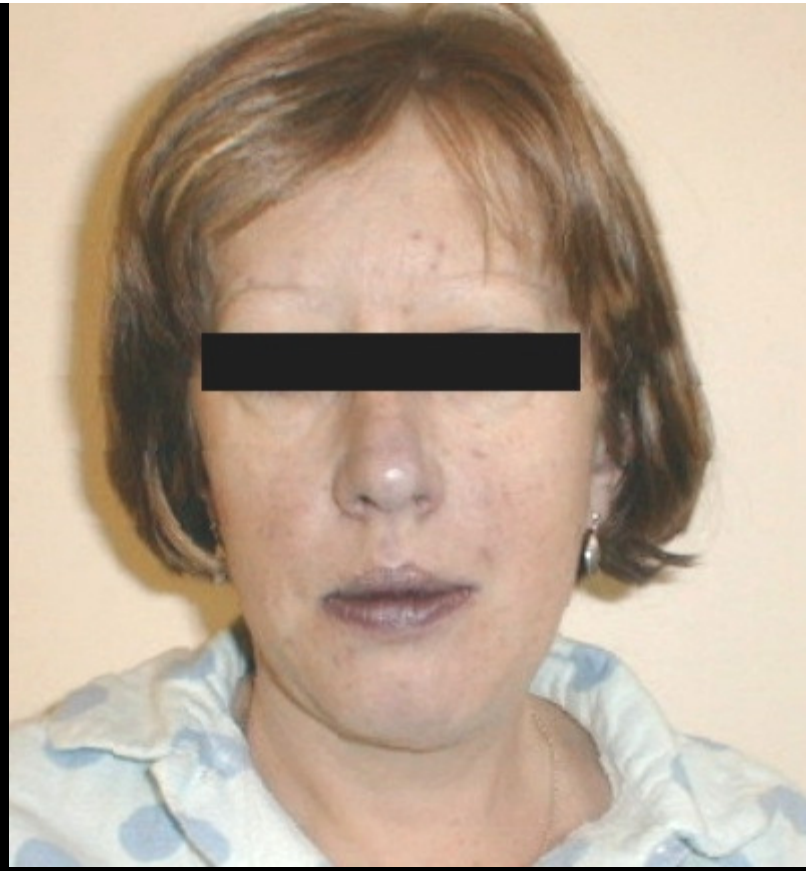
Health care professionals are advised to weigh the risks of Chantix against the benefits of its use. It is important to note that smoking is a major risk factor for cardi
to quit smoking and abstain from it for as long as 1 year. The health benefits of quitting smoking are immediate and substantial.

Case of Big Girl Blue

- A patient presents with a laceration to her scalp. No LOC. You administer Lidocaine with epinephrine and are called to the room.
- She is complaining of dizziness, headache, and dyspnea. The triage RN calls a medical alert because the patient is obviously cyanotic.
- In the resuscitation room, you find an alert patient with: BP 120/50 P 120 R24 T99 pulse ox 85% (on 70% FIO_2 by mask) and this appearance

Blue Lady

- What's going on?
  - A. pulmonary embolism
  - B. aortic dissection
  - C. Cyanide poisoning
  - D. Methemoglobinemia
  - E. pneumothorax



Methemoglobinemia

- Cyanosis in the setting of adequate oxygen delivery and a pulse oximeter ~ mid-80% range is suggestive of methemoglobinemia (oxidized hemoglobin)
- Commonly occurring from excessive exposure to oxidizing agents, such as benzocaine, dapsone, nitrobenzene;
- G6PD deficiency – and more frequently associated with significant hemolysis.
- Rx is administration of oxygen and methylene blue
  - Methylene blue will not be effective and will induce hemolysis in those with G6PD deficiency

High Risk Drugs

- Warfarin
- Theophylline
- Cyclosporine
- MAOI's
- Lithium
- Digoxin

- Frequently prescribed
- Significant toxicity
- Low therapeutic window
- One major route of elimination

Reviewed on 4/8/97

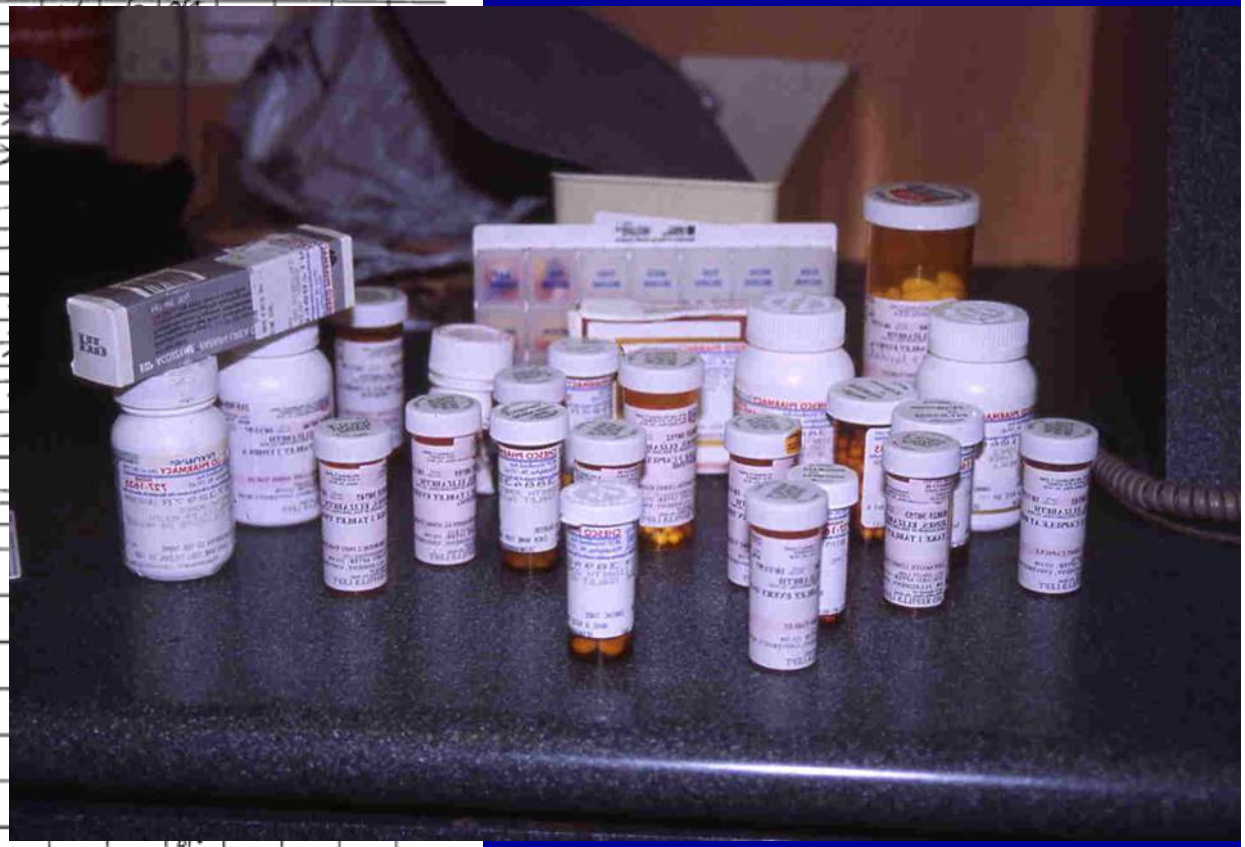
HOME MEDICATIONS LIST VRC-427-C

ALLERGIES: NKA

PATIENT NAME: Gloria Benjamin | MR NUMBER | YEAR: 1997

MEDICATIONS	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
Docusate ½ cap Bid					→	6/2 97	7/2 SA	8/8 SA				
Catapres 0.3 mg ½ PO Bid					→	6/2 SA	7/2 SA	8/8 SA				
Prilosec ½ cap (20mg) PO Bid												
Propec 20mg ½ cap PO qd.												
Procardia XL 90 mg PO Daily												
Haldol ½ mg PO H.S.												
Toprol XL 50mg ½ PO Daily												
Synthroid 0.75 mcg ½ tab QD												
Trazodone Hcl 50mg ½ tab H.S.												
Combivir 150mg ½ tab PO BID												
Lisinopril ½ cap Daily												
Darvon ½ q 4° PRN pain												
Ventolin inhaler 2 puffs Q10 PRN												
Cephalexin 500mg PO TID												
Zantac 150 mg BID												
Bactrim DS mg BID x 10 days												
Diltiazem 100mg PO Tid												
2/14 Restoril 30mg PO q HS PRN												
2/14 Amoxicillan 250 mg PO TID x 10 Days												
7/28 Claritin 10mg daily x 10												
Ecotrin 81mg PO Daily												
Seroquel 25mg BID												
NTG 0.3 mg SL PRN												
7/28/97 Cipro 500 mg PO BID x 10 days												

SIGNATURE - JANUARY	SIGNATURE - FEBRUARY	SIGNATURE - MARCH	SIGNATURE - APRIL
SIGNATURE - MAY	SIGNATURE - JUNE J. Arostegui RN	SIGNATURE - JULY S. Arostegui RN	SIGNATURE - AUGUST S. Arostegui RN
SIGNATURE - SEPTEMBER	SIGNATURE - OCTOBER	SIGNATURE - NOVEMBER	SIGNATURE - DECEMBER



High Risk Patients

- Elderly
  - altered metabolism, multiple medications
- Complex medical hx/multiple MD's
- Specific medical conditions
  - HIV/AIDS
  - transplant

HIV + Patient

- 5-20% incidence
  - multiple meds
  - meds w/ high interaction potential
  - meds w/ significant toxicity (risk/benefit)
  - MD’s unfamiliar w/ meds

Pharmacodynamic

- Bone marrow suppression
  - ganciclovir, TMP-SMZ, zidovudine
- Peripheral neuropathy
  - isoniazid, didanosine (ddI), stavudine, zalcitabine
- Pancreatitis
  - didanosine (ddI), pentamidine

Pharmacokinetic

- Protease inhibitors (inhibitors)
- Antifungals (inhibitors)
- Antituberculous (inducers)
- Anticonvulsants (inducers)


Vejiga, cistitis.
Té para la Sangre
Purifica la sangre.
Activa la circulación.
Alergias, várices.
espinillas, acné.
Té Medicinal
Estómago
Acidez, ardor, gases
higado, vesícula.
Indigestiones.
Té para los Nervios
Ahogos, dolor de ca-
bezas, jaquecas.
Estados depresivo
Insomnio.
Regula presión.
Prostasan
Próstata, riño-
nes y vejiga.
Ardores al orinar.
Venéreas.
Wine-Wine
Retarda la vejez
prematura, artrosis.
Cura la artritis.
Reumatismo.
Catarros.
Diabetisan
Chanca Piedra
Cálculos biliares y re-
nales. Vesícula.
Ulceras al higado.
Cólicos de la matriz.
Riñosan
Dolor de riñones
Cálculos renales,
orina turbia, sangre
Hipús en la orina.
Bronquisan
Resfrios, gripes.
Bronquios, tos,
catarros, asma.
300.
Té Machitén N°48
Adelgazante
Para combatir
el exceso de
peso.
Formula 26
Elimina ácido urico
reumatismo, artritis,
artereosclerosis.

St Johns Wort

- Depression

- CYP inhibitor
- MAO inhibitor
- Serotonin syndrome

Ginko Biloba

- Dementia
- Hemorrhage
  - warfarin, aspirin, rofecoxib

Recognizing Drug/Drug Interactions

- Obtain complete medication history
- Identify high risk patients
- Identify high risk drugs
  - QT prolongers
- Identify inhibitors/inducers of CYP

My Rules

1. Limit the total number of drugs, dose and duration (The more problems, the more problems)
2. Extremes of age deserve caution
3. If you are giving IV contrast, check medications and hydrate, consider bicarbonate
4. Never use Meperidine
5. Consider Ondansetron (now low dose)
6. Love P450
7. Know high risk drugs
8. If in doubt avoid, succinylcholine
9. If in doubt, use benzo's
10. Consider help prn

Recent References

- Roden, Drug-induced prolongation of the QT interval. N Engl J Med 350;10:1013-1022, 2004
- Ray et al, Oral erythromycin and the risk of sudden death from cardiac causes. N Eng J Med 351;11:1089-1096, 2004
- Wilkinson, Drug metabolism and variability among patients in drug response. N Engl J Med 352;21:2211-21, 2005
- Liu, Drugs and the QT interval – Caveat Doctor. N Engl J Med 351;11:1053-56, 2004
- Holbrook et al. Systematic overview of warfarin and its drug and food interactions. Arch Int Med 165:1095-1106, 2005
- Boyer et al. The serotonin syndrome. N Engl J Med 352:1112-20, 2005
- Barrett, B.J. and P.S. Parfrey, Preventing Nephropathy Induced by Contrast Medium. N Engl J Med, 2006. 354(4): p. 379-386