

# Drug Interactions in Clinical Practice

Focus on Cardiology

## EMR

- “ Failure to incorporate EMR into a practice may, in the not-too-distant future, be considered a deviation from recognized standard of care. “
- “ As the EMR technology becomes pervasive, failure to use it to avoid medical errors may also lead to malpractice claims. “
- Medicare incentives are also present for EMR use

<http://www.medscape.com/viewarticle/589724>

## EMR

- Is the information easily available?
- Are the alerts meaningful?
- Is there too much information of low relevance presented to the user too frequently?

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## EMR and Drug Alerts

- Alert fatigue
  - Show me only what's important
- Four commonly used references (which?) identify 406 major drug interactions
  - Only 9 of these are considered major by all four
- Recent article in Archives of Internal Medicine showed that a majority of ambulatory medication alerts were overridden

Thomas Isaac, MD, MBA, MPH, et al. Overrides of Medication Alerts in Ambulatory Care. *Arch Intern Med.* 2009;169(3):305-311

Abarca J, Malone DC, Armstrong EP, et al. Concordance of severity ratings provided in four drug interaction compendia. *J Am Pharm Assoc* 2004;44:136-41

## EMR and Drug Alerts

- Cerner: drug alerts turned OFF for order entry
  - 9295 drug interactions were flagged as major
- Used Hansten and Horn as our reference for thinning alerts.
- Computer can give you valuable information, but it can't tell you what's important in that particular clinical situation

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## Our Focus

- As technology becomes more pervasive, the ability to determine clinical relevance becomes more important
- Common patient populations visiting a cardiology practice
- What are our options when faced with these interactions
  - Class effect or switch to safer alternative?
  - Risk vs Reward of therapy

## Outline

- Look closely at 2 currently debated interactions
  - Develop a strategy that can be used for addressing other interactions
- Utilize this strategy and add to it
  - Common interactions (highly prescribed drugs) and susceptible populations
  - Interactions with primary care meds and OTCs

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## Pharmacokinetic vs Pharmacodynamic

- PK
  - Absorption, Distribution, **Metabolism**, Excretion
  - Plasma Drug Concentrations
- PD
  - Pharmacologic activity is altered
  - Synergistic or Antagonistic
- Effects are magnified in drugs with a narrow therapeutic window: digoxin, warfarin, amiodarone.

## Debated

- PPIs vs clopidogrel
- ASA vs ACE-I
  
- Look at the evidence
- Use knowledge of the mechanism to help manage or avoid the problem
- Look at other options in same class, or perhaps eliminating the causative drug

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## ACE-I vs ASA

- GUSTO-1 and EPILOG trials
  - inc mortality and non-fatal MI with combo
  - ...retrospective evaluation
  - some more data from this....
- Can we design a trial to examine this?
  - Unethical, unfeasible
    - Very few pts with vascular disease which would not get both ASA and ACE-I

## PPIs and Plavix

- PPI's used in Plavix pts to attenuate risk of GI bleed
- Possible interaction which reduces the effectiveness of clopidogrel
  - mechanism possibly inhibition of Cyp 2C19
- Evidence?

## PPIs and Plavix

- Randomized double-blind placebo controlled trial in 140 pts undergoing coronary artery stent placement
  - All receive ASA and clopidogrel
  - Randomized to omeprazole 20mg vs placebo x 7d
  - Initial mean PRI similar for both groups (83.9% vs 83.2%, active/placebo)
  - Day 7: PRI found to be significantly higher in those receiving omeprazole (51.4% vs 39.8%)
    - PRI >50%: 60.9% vs 26.7%

Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. *J Am Coll Cardiol* 2008;51:256-60.

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## PPIs and Plavix

- Aetna claims review (retrospective)
  - 1000 patients taking clopidogrel with PPI (non-specific)
    - 2 groups: low exposure <6 mos, high exposure >6mos
  - 1yr MI rates significantly higher in clopidogrel pts receiving PPI vs not
    - No PPI: 1.38%, Low exposure: 3.08%, High exposure: 5.03%.  $p < 0.05$
    - Adjusted for comorbidities

Pezalla E, Day D, Pulliath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. *J Am Coll Cardiol* 2008;52:1038-9.

## PPIs and Plavix

- Case control, 734 patients, readmitted with MI or died within 90 days of being admitted for MI
  - 2057 controls, matched for age, receipt of PCI, date of hospital discharge, predicted probability of short term mortality
  - Cases were however noted to be sicker (HF, diabetes, renal insufficiency)
- Current PPI use associated with 30% inc in mortality
  - lansoprazole, omeprazole, rabeprazole, pantoprazole
  - pantoprazole had no associations while others combined showed a 40% increase in mortality
  - 7-14% of readmissions associated with PPI

Juurink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713-8.

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## PPIs and Plavix

- 8205 VA patients, filled clopidogrel Rx after treatment for acute MI or unstable angina
  - Primary endpoint is all-cause mortality or readmission for ACS
  - Patients followed for median of 521 days
- 5244 of these were also prescribed PPI
  - 2/3 omeprazole, 3% rabeprazole, <1% lansoprazole and pantoprazole (remaining had tried >1 PPI)
  - These were older and had more co-morbidities
- 30% of clopidogrel+PPI vs 21% of clopidogrel+no PPI readmitted for ACS or died
- In patients not receiving clopidogrel, PPI use was not associated with increase in adverse outcomes

Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301:937-44.

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## PPIs and Plavix

- Medco insurance claims review, 15,000 patients
  - 9862 with no PPI use, 6828 filled a PPI Rx
- Risk for adverse cardiac events 25.1% in those who used PPI vs 17.9% in those who didn't ( $p < 0.0001$ )
- Looked at individual PPIs.
  - Omeprazole and lansoprazole: hazard ratio 1.39, pantoprazole: hazard ration 1.61
  - Evidence of class effect?

Wood S. Possible "class effect" for proton-pump inhibitors on top of clopidogrel therapy. May 6, 2009. 22. *Heartwire*. <http://www.theheart.org/article/967075.do>. (Accessed June 9, 2009).

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## PPIs and Plavix

- So where does this leave us?
- Study weaknesses
  - Not controlled for polymorphism of CYP2C19, pts receiving PPI are sicker, not controlled for clopidogrel resistance
- Is the mechanism CYP2C19 inhibition
  - If not, is this a class effect?
- Can we avoid this entirely?
  - who needs a PPI?
  - what about other platelet inhibitors?

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## Issues with Commonly Prescribed Drugs

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## Elderly

- CDC, CPSC, and FDA set up monitoring system at ER visits attributed to ADEs.
- 701,574 patient visits to ER for ADE.
  - 2.4 for every 1000, 1/4 were elderly
  - 1/3 of these are hospitalized
- 1/3 of all these ADEs caused by 3 drugs.
  - Warfarin, insulin, and digoxin.
- This risk holds for all patients, but the elderly are particularly susceptible.

Budnitz DS, Pollock DA, Weidenbach KN, et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006;296:1858-66. 19

## Statins and amiodarone

- Myopathy: >65 years of age, impaired renal or hepatic function, untreated hypothyroidism, low muscle mass, diabetes, or female gender
- 2002, simvastatin PI was updated
  - Inc risk of rhabdomyolysis when amiodarone is used w simvastatin at doses >20mg
  - Still happening, FDA 'reminder' in 2008
- Compared to other statins, risk is greater with simvastatin
  - Amiodarone inhibits CYP3A4, which increases concentrations of simvastatin...lovastatin...and to a lesser extent, atorvastatin.

Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

## Statins and Interactions

- Some statins are not metabolized by the Cytochrome P450 system
  - Pravastatin metabolized through Phase II (conjugative) mechanism, difficult to inhibit
  - Rosuvastatin not metabolized by Cyt P450
    - But levels of both can be increased by cyclosporin and gemfibrozil (likely due to transporter inhibition)
- Are these better options?
- Hydrophilic vs Lipophilic

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## Statins and Interactions

- Plenty of evidence to support intensive therapy
  - Using pravastatin, for example, may not be sufficient to reach LDL goals
- Start looking at the other side of the interaction
  - Can we lose the fibrates, or switch off of gemfibrozil?

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## Fibrates

- Gemfibrozil inc blood conc of most statins by partially inhibiting metab (glucorinidation) of the statin acid byproduct
- Fenofibrate doesn't use this pathway and shows no significant effect on PK of statins.
- Still all fibrates carry risk due to additive effects
- Isomers!
  - Trilipix (fenofibric acid) is only fibrate approved to use with statin
  - No proof it's better than fenofibrate

## Fibrates and Warfarin

- Fibrates may decrease warfarin metabolism and displace warfarin from protein binding sites
- Again, not a problem when stable on both medications but upon start, dosage adjustment, or discontinuation of fibrate, use caution
  - Upon initiation, suggested to decrease warfarin dose by half

Ahmad S: Gemfibrozil interaction with warfarin sodium (Coumadin) (letter). Chest 1990; 98:1041-1042.

Rindone JP & Keng HC: Gemfibrozil-warfarin drug interaction resulting in profound hypoprothrombinemia. Chest 1998; 114:641-642. 24

## General Practice

- Other commonly prescribed medications written for by other physicians
- Educate patients
  - On drugs with narrow therapeutic window
  - At-risk patients
    - elderly
    - comorbidities/polypharmacy
    - reduced kidney or liver function

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## Antibiotics

- Common short term treatment which can precipitate significant changes in the metabolism of other drugs
- Some drugs such as statins can be safely held during antibiotic treatment
- Other times the best option is to choose an antibiotic that won't interact

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## Warfarin vs Corticosteroids

- Many references list this as low severity or not at all
- Average INR increase of 1.2
  - Timeframe 2-10 days
- Mechanism is likely CYP3A4 inhibition or possible transient increase in serum pH which decreases warfarin protein binding
- Can not decrease warfarin dose empirically due to possibility of decreased INR.
- Monitor

## Patients who Smoke

- It's the smoke, not the nicotine
- Induction of CYP1A2
- Thus, issues most likely to occur when patient quits or transitions to nicotine products.

## Smokers and Beta Blockers

- Nicotine mediated sympathetic activation may necessitate higher doses in smokers
  - Patients who are quitting may need dose decrease, transitioning to nicotine products can mediate this
- Smoking can increase the clearance of propranolol by 77%
  - Patients on propranolol will likely need a dose reduction

<http://www.ashp.org/Import/PRACTICEANDPOLICY/PublicHealthResourceCenters/TobaccoCessation/DrugInteractionsWithSmoking.aspx>

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## Bupropion and Varenicline

- No significant interactions with Chantix at all...
- Bupropion can interact with other medications
  - Concurrent use of bupropion and metoprolol may increase metoprolol exposure and events of bradycardia have been reported in a clinical setting (McCollum et al, 2004).  
CYP2D6

## OTCs, Herbals, and Food

- Perhaps the most worrisome
  - Perceived as safe or natural
    - Thanks Oprah
  - Patients often start, stop, and change without notice, and frequently
- Question your patients
- Educate your patients

## Loop diuretics vs food

- Decreased absorption with food
- Drug concentrations in blood drive the transport pathway in the proximal tubule to secrete drug
- Several studies show that food decreases absorption, thus decreasing rate of tubular secretion and effect

# Alcohol

- Alpha-1-adrenergic blockers
  - prazosin, but theoretically any (doxazosin, terazosin...)
  - Hypotension
  - Asians more susceptible, more likely to be deficient in aldehyde dehydrogenase - acetaldehyde accumulation.
- Verapamil
  - Inhibits alcohol metabolism, 1st pass metabolism
  - Incr alcohol concentrations and prolongs intoxication
- Warfarin
  - Acute intox: Enhanced anticoag effect, mech??
  - Chronic use: reduced anticoag effect, alcohol induced stimulation of hepatic enzymes
  - Acute excessive intake: reduce warfarin metab. Check reference here

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# Conclusions