COMPUTER ALERT FATIGUE – DON'T IGNORE THESE IMPORTANT DRUG-DRUG INTERACTIONS

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Disclosures

- I, Daniel Malone, have no financial relationships to disclose

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  - AHRQ U18 HS017001-01 – PI: Woosley;
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The Problem!

You wouldn't believe how many **BIG BAD** drug-drug interactions there are. Just ask your doctor about all the DDI alerts she gets!

Drug Interaction Knowledge and Information Sources

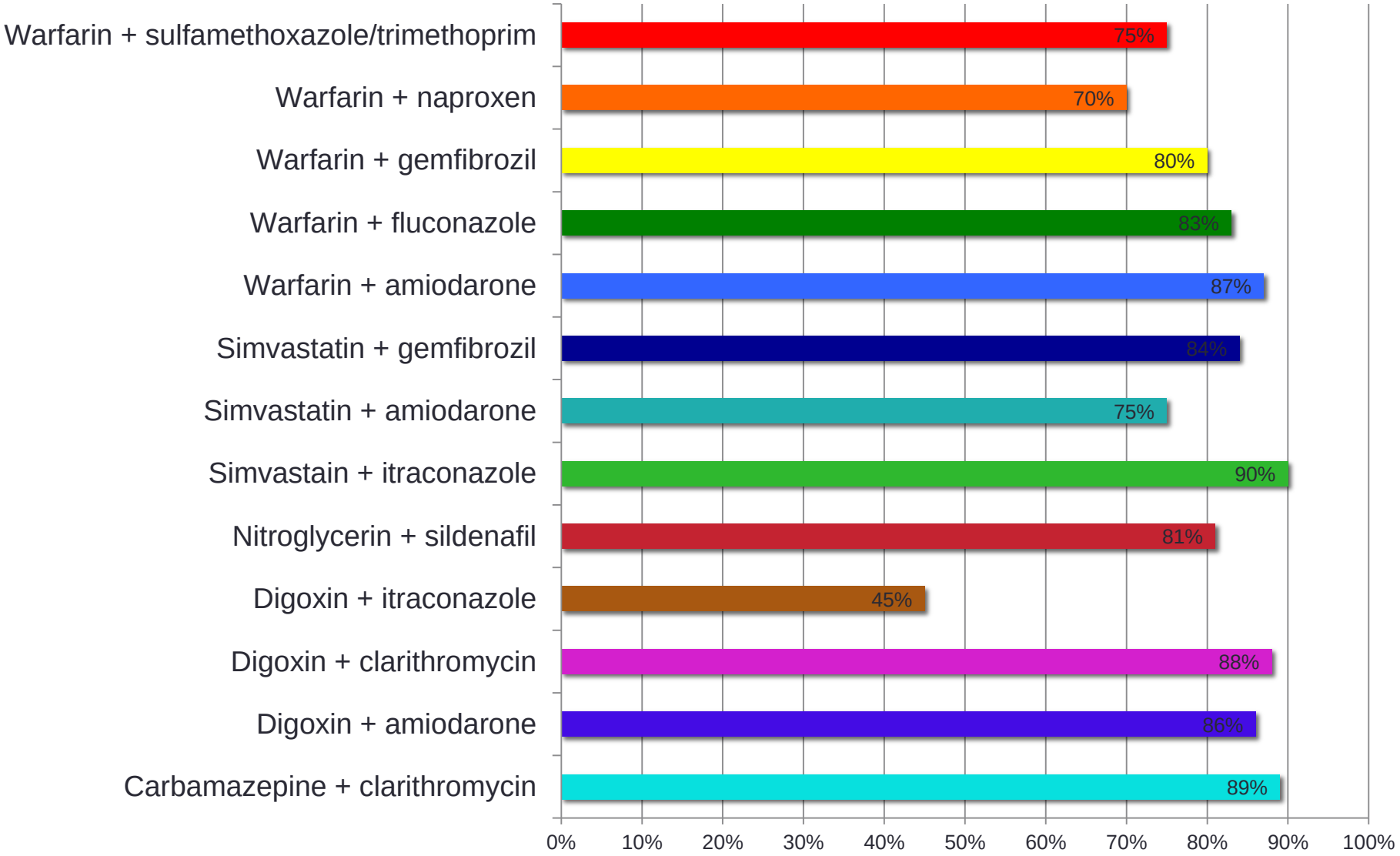
- Prescriber knowledge is lacking[1,2]
  - 42.7% of drug pairs correctly identified[1]
- Information sources use by prescribers for DDIs[3]
  - Pharmacists - 68.4% *also lacking knowledge[4]*
  - PDA - 15.8% *similar to online resources*
  - Alerts - 10.8% *known to be problematic*
  - Other sources - 5.1% *e.g., compendia, labeling*

1) Ko et al. *Drug Saf.* 2008;31(6):525-536. 2) Glassman. *Med Care.* 2002;40(12):1161-1171. 3) Ko et al. *Res Social Adm Pharm.* 2008;4(4):355-366. 4) Weideman et al. Am J Health Syst Pharm 1999 56: 1524-1529.

Terminology

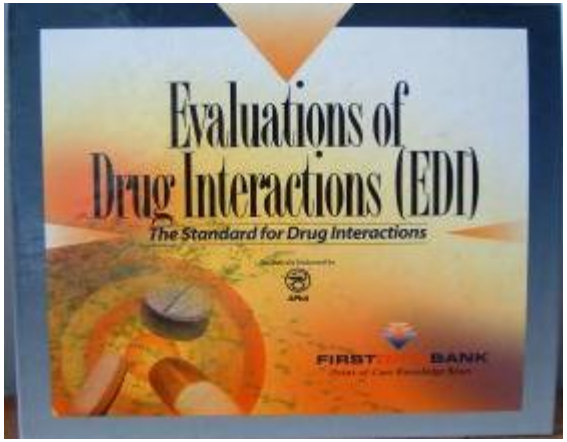
- **Drug-drug interaction (DDI):**
  Clinically meaningful alteration in the effect of one drug (*object*) as a result of co-administration of another (*precipitant*)
- **Potential drug-drug interaction (PDDI):**
  Co-prescription or co-administration of drugs known to interact, regardless of whether harm ensues

Sensitivity of Computer Software to Detect Drug Interactions in Arizona Pharmacies (N=64)



Saverno et al. JAMIA; 2011:18:32-37

Concordance Among DDI Compendia



DRUG-REAX® System

from MICROMEDEX

“Major” Drug Interactions Listed by Compendium

Compendium	**No.**
MicroMedex *DRUG-REAX®*	275
Evaluation of Drug Interactions	64
Drug Interactions: Analysis and Management	94
Drug Interaction Facts	141
Total	406*

* Sum of column exceeds total due to duplicate interactions.

Agreement Among Four Drug Interaction Compendia

- DDIs in 4 of 4: 2.2% (9/406)
- DDIs in 3 of 4: 8.6% (35/406)
- DDIs in 2 of 4: 17.4% (71/406)
- DDIs in 1 of 4: 71.7% (291/406)

- Intra-class Correlation Coefficient: -0.092

Abarca J et al. J Am Pharmacist Assn 2003: 44:136-141.

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Market Removals Due to Drug-Drug Interactions

- Terfenadine (Seldane®) – 1998
- Mibefradil (Posicor®)- 1998
- Astemizole (Hismanal®) – 1999
- Cisapride (Propulsid®) – 2000
- Cerivastatin (Baycol®) – 2001

DDI Prevalence in Elderly

- Elderly veterans with new DDI at ED discharge:[1] **13%**
- Older adults exposed to a “major” DDI:[2] **4%**
- Medicare Part D enrollees exposed to certain DDIs: **7.3%**

1) J Am Geriatr Soc. 2008;56:875-80. 2) JAMA. 2008;300:2867-78.

Question: What factors contribute to patients being exposed to potential DDIs?

A. Evidence for DDIs is lacking
B. Conflicting information among DDI compendia
C. There are too many irrelevant DDI alerts
D. DDI knowledge is poor among health professionals
E. All of the above

Question: What factors contribute to patients being exposed to potential DDIs?

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E. All of the above

Health Systems Approach to DDIs

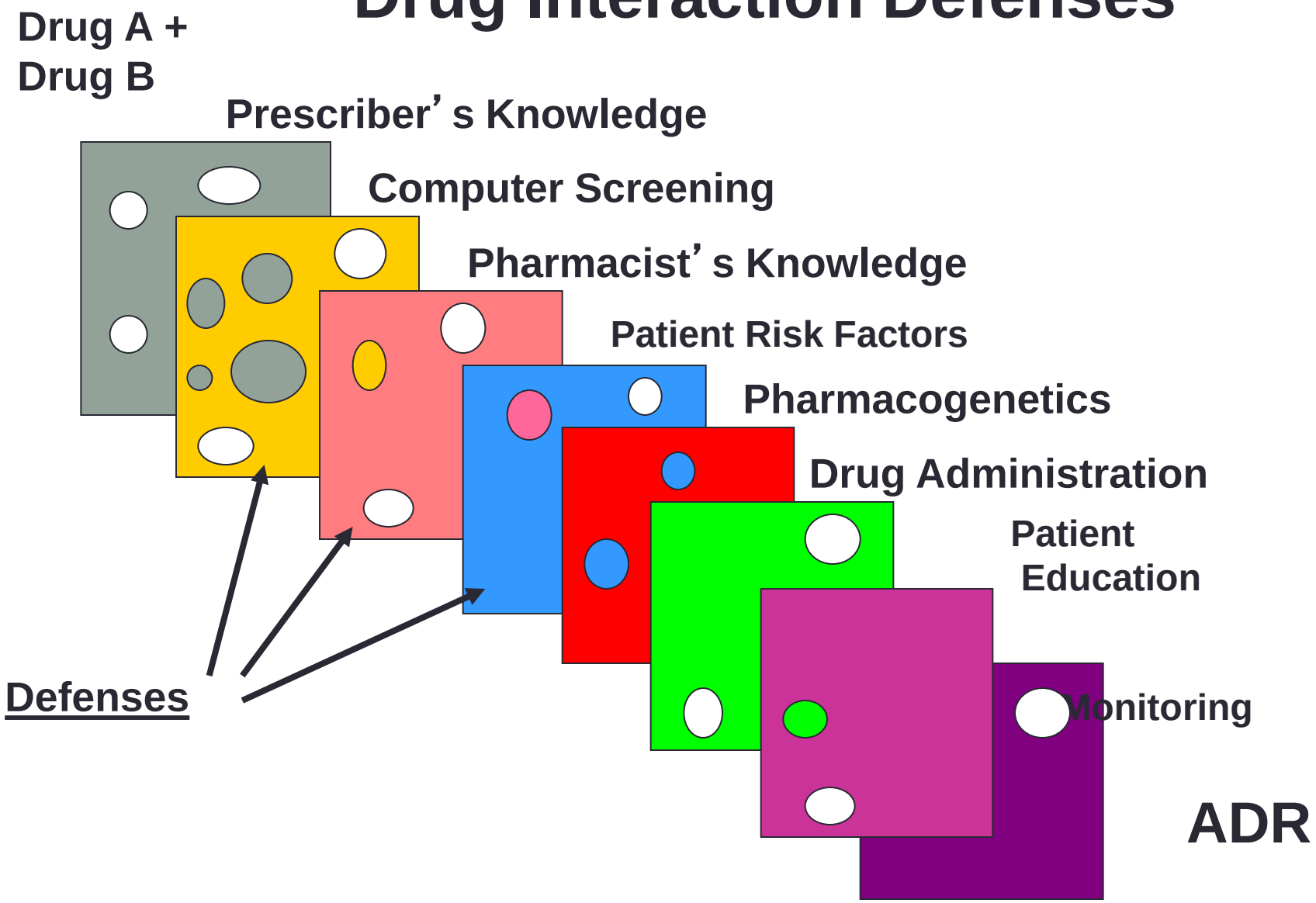
- Evidence for DDIs is lacking
  - Very few well-controlled studies
- Lack of concordance among DDI compendia[1]
  - Differing severity rating systems, terminology, methodologies
- Limitations of DDI clinical decision support[2-4]
  - "Alert fatigue"
  - High rates of alert override

1) Abarca et al. J Am Pharm Assoc (2003). 2004;44(2):136-141. 2) Grizzle et al. Am J Manag Care. 2007;13(10):573-578. 3) Murphy et al. Am J Health Syst Pharm. 2004;61(14):1484-1487. 4) Abarca et al. J Manag Care Pharm. 2006;12(5):383-389.

Improving Knowledge to Prevent Exposure to Potential DDIs

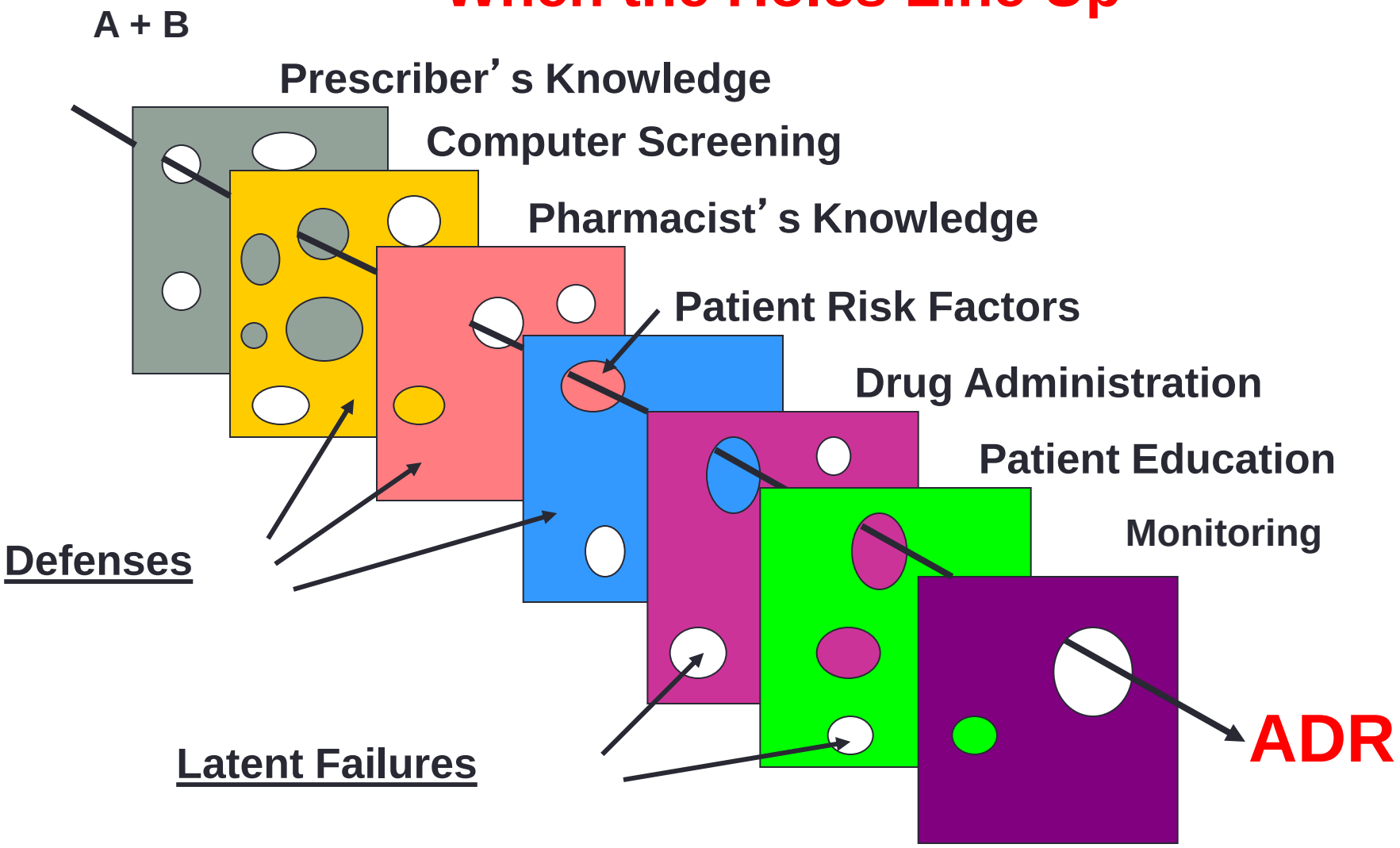
- Understanding basic concepts allows for more rationale DDI predictions
- Prevent adverse DDIs by making patient- and situation-specific assessments
- When appropriate:
  - Avoid concomitant administration
  - Implement alternative therapeutic strategies
  - Take precautionary measures

Drug Interaction Defenses



Hansten PD, Horn JR. Modified from: James Reason, Human Error, 1990

“When the Holes Line Up”



Hansten PD, Horn JR. Modified from: James Reason, Human Error, 1990

Pharmacokinetic Drug Interactions

- GI absorption
  - Drug binding in GI tract
  - Alterations in GI motility
  - Alterations in GI pH
- Plasma protein binding
  - ? clinical significance
- Cytochrome P450
  - Induction or inhibition
- Transport proteins
  - Induction or inhibition

P-glycoprotein (PGP): an efflux transporter

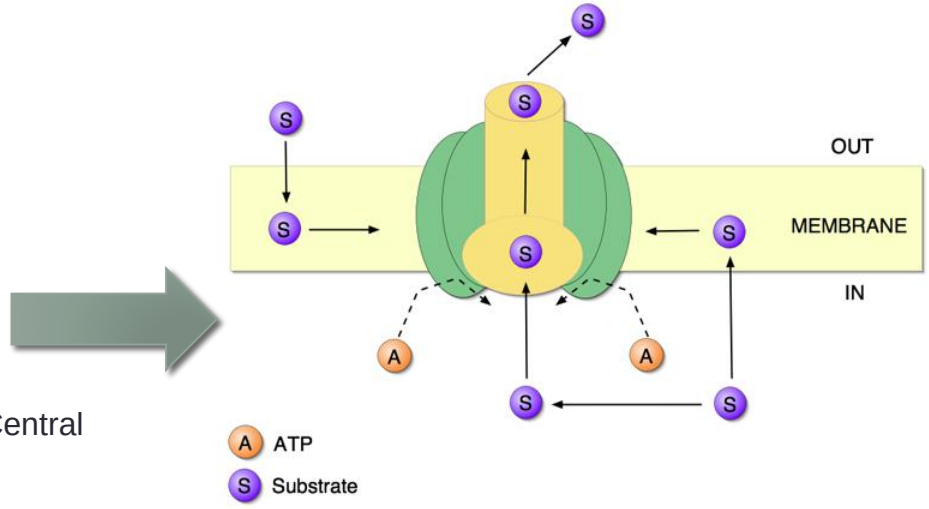


Figure reproduced with permission from BioMed Central (http://www.biomedcentral.com):
Edwards G. Filaria J. 2003;2(Suppl 1):S8.

Question: Which of the following is classified as a pharmacokinetic DDI?

A. Oral contraceptives-carbamazepine
B. Tadalafil-isosorbide dinitrate
C. Sotalol-levofloxacin
D. Spironolactone-ramipril
E. Benazepril-aspirin

Question: Which of the following is classified as a pharmacokinetic DDI?

A. Combination oral contraceptives-carbamazepine
B. Tadalafil-isosorbide dinitrate
C. Sotalol-levofloxacin
D. Spironolactone-ramipril
E. Benazepril-aspirin

Drug Interaction Mechanisms

- Pharmacodynamic
  - Additive or antagonistic pharmacologic effects
- Pharmacokinetic
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**xcretion

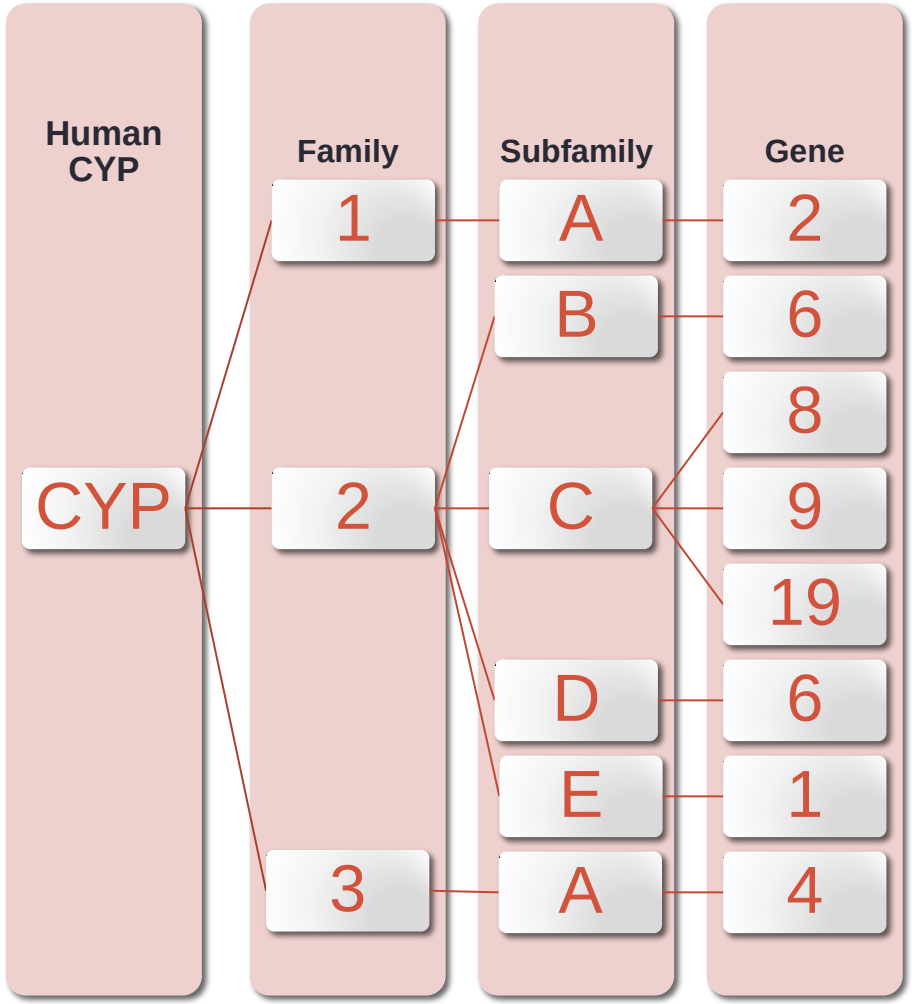
Altered drug elimination is the most common cause of adverse PK DDIs

Drug Interaction Mechanisms (continued)

Pharmacokinetic Interactions

- GI absorption
  - Drug binding in GI tract
  - Alterations in GI motility
  - Alterations in GI pH
- Plasma protein binding
  - Not clinically significant
- Cytochrome P450 (CYP)
  - Induction or inhibition
- Transport proteins (P-glycoprotein [PGP])
  - Induction or inhibition

Cytochrome P450 (CYP) Enzymes



Clopidogrel

Tamoxifen

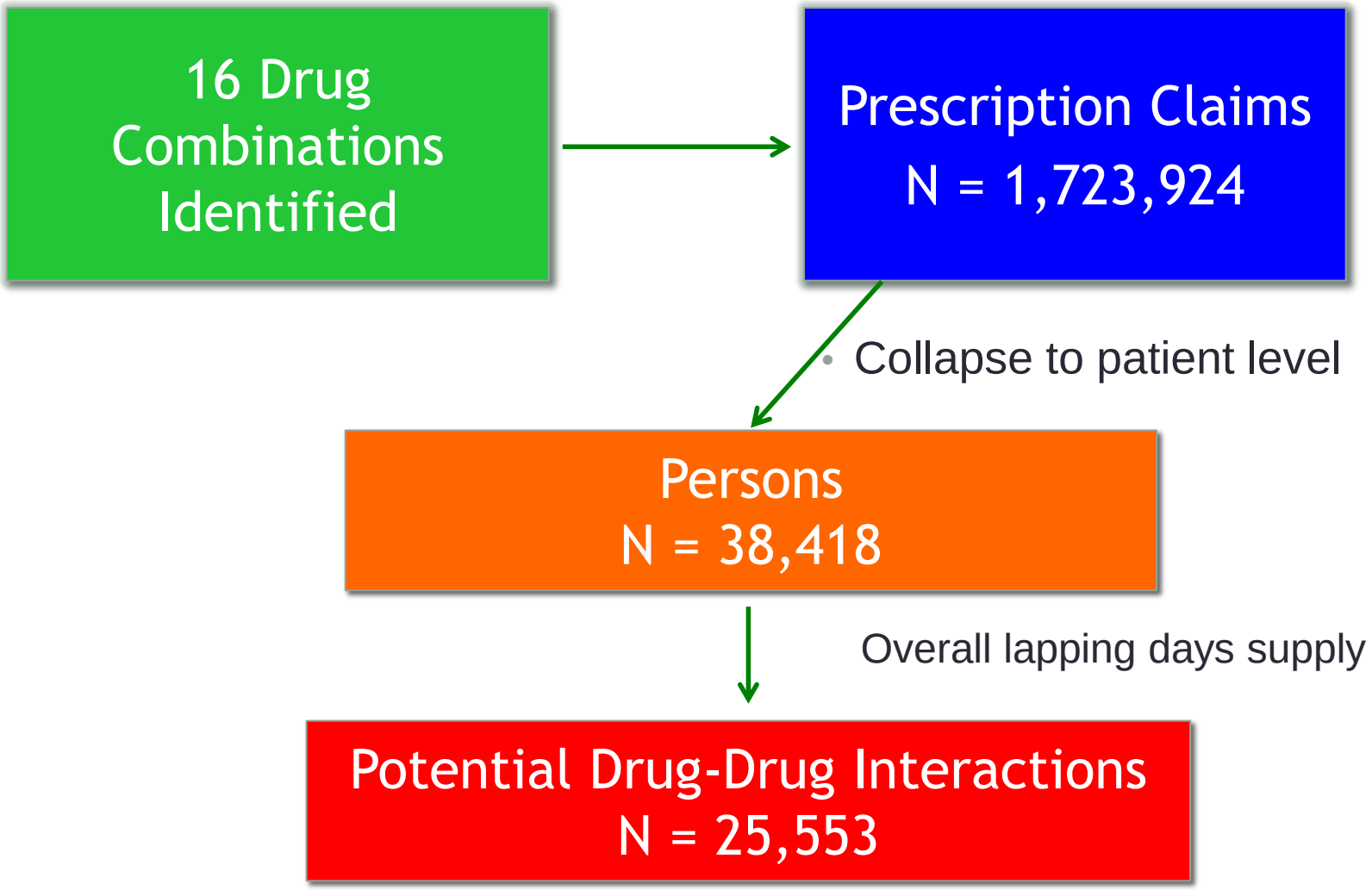
Macrolides, Azole antifungals

THE LAB WHERE
THEY STUDY DRUG INTERACTION

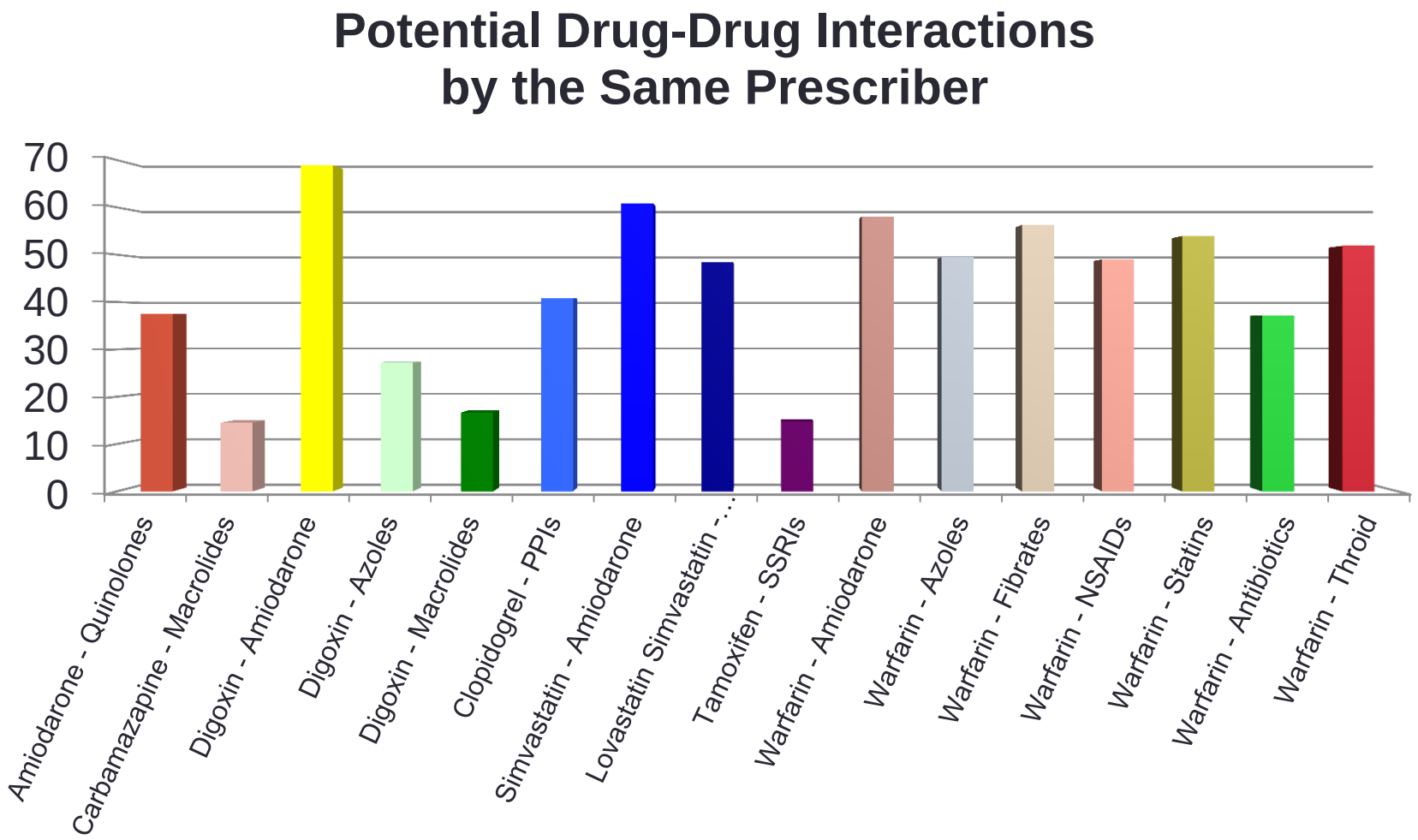
Most Drug-Drug Interactions Are Due to Different Prescribers!

A. Yes
B. No
C. Sometimes
D. Don’t know

Analysis of Arizona Medicaid Claims



Who Prescribes Drug-Drug Interactions?



Case

- 67-year-old woman
- Diagnosed with pneumonia after mitral valve repair
- Developed the following on electrocardiogram...

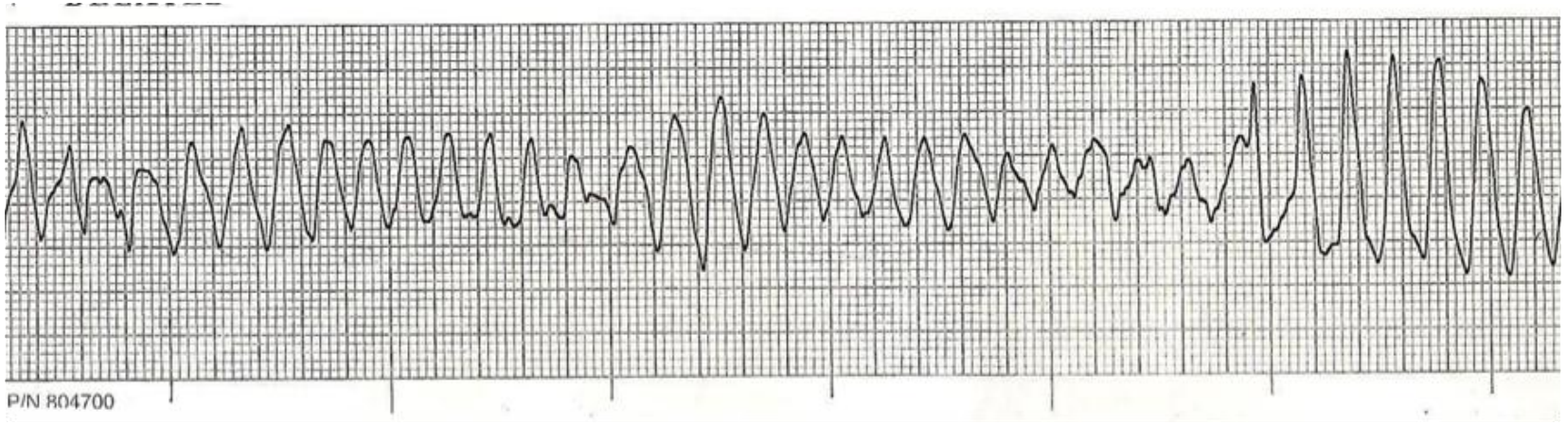
Past Medical History

- Chronic atrial fibrillation
- Heart failure
- Hypertension
- Hypothyroidism
- Obesity

Medications

New medications:

- Amiodarone
- Levofloxacin



Case adapted from: Proc (Bayl Univ Med Cent). 2006;19(4):345-6.

Question: What risk factors for TdP did this patient have?

A. Concomitant QT-prolonging drugs
B. Female sex
C. Advancing age
D. Cardiac disease
E. All of the above

QTc=rate-corrected QT interval on electrocardiogram; TdP=torsades de pointes

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Usually Avoid This Combination

Amiodarone-Levofloxacin

- Additive risk of QTc prolongation
- Potentially fatal
- Data limited regarding arrhythmogenic risk of drugs alone or in combination

Risk Factors for TdP

- Concomitant QTc-prolonging drugs
- Female
- Advancing age
- Cardiac disease
- Bradycardia
- Familial history long QT syndrome
- Electrolyte disturbances (e.g., low K^{+}, Mg^{++}, Ca^{++})

QTc=rate-corrected QT interval on electrocardiogram; TdP=torsades de pointes

Prolonged QT Risk Groups

Risk of Torsades	Possible Risk of Torsades	Conditional Risk of Torsades
• Disopyramide • Procainamide • Quininidine • Amiodarone • Dofetilide • Ibutilide • Sotalol • Clarithromycin • Erythromcyin	• Flecainide • Gemifloxacin • Levofloxacin • Moxifloxacin • Ofloxacin • Azithromycin	• Ciprofloxacin

QT drug lists by risk groups. Arizona Center for Education and Research on Therapeutics. Available at: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm

Case 2

- 77-year-old woman
- Presented with episodes of vomiting bright red blood and passing bloody stools
- INR 2.1 (target 2.5-3.5)
- Severe dyspnea due to aspiration
- Expired from hypotension and multisystem failure

Past Medical History
- Aortic valve replacement
- Atrial fibrillation
- Heart failure
- Hypertension
- Ischemic heart disease

Medications

Chronic medications:
- Warfarin
- Furosemide
- Lisinopril
- Metoprolol

New medication:
- Ibuprofen (OTC)

Case adapted from: Med J Aust. 1996;164(11):700-1.

Question: Which of the following are appropriate treatments for a patient on chronic warfarin therapy who requires an analgesic in order to minimize the risk of GI bleeding?

A. Acetaminophen with codeine
B. Celecoxib
C. Naproxen
D. All of the above
E. None of the above

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D. All of the above
E. None of the above

Usually Avoid This Combination

Warfarin-NSAID

- Additive risk of bleeding
  - Some NSAIDs may also alter warfarin PK
- Considerable increased risk of GI bleeding[1]
  - 13-fold higher risk hospitalization for hemorrhagic PUD vs. neither drug; 4-fold higher risk with either drug alone
- Co-prescribing common despite risks[2,3]
  - Most common among top 25 clinically significant outpatient DDIs (242.7 per 1,000 warfarin recipients)

1) Shorr et al. Arch Intern Med. 1993;153(14)1665-70. 2) Malone et al. J Am Pharm Assoc (2003). 2004;44(2):142-51. 3) Malone et al. Am J Health Syst Pharm. 2005;62(19):1983-91.

Warfarin-NSAID (continued)

- Acetaminophen or opioids preferred
  - Limit acetaminophen & monitor
- COX-2 inhibitors
  - No conclusive evidence for lower risk
- Aspirin
  - Antiplatelet aspirin therapy increases minor bleeding risk
- If combined use necessary
  - Monitor for bleeding
  - Consider prophylaxis for NSAID-associated GI injury

Case 3

Question: A 50-year-old man with chronic atrial fibrillation and a history of epilepsy is stabilized on warfarin and carbamazepine. His neurologist wants to discontinue the carbamazepine. What is the primary concern regarding his anticoagulation if the carbamazepine is stopped?

A. Increased risk of thromboembolism
B. Excessive anticoagulation
C. There are no major concerns with this decision
D. None of the above

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C. There are no major concerns with this decision
D. None of the above

Warfarin-Carbamazepine

- Carbamazepine induces warfarin metabolism
- The warfarin dose was likely previously increased to adjust for enzyme induction
- Stopping the enzyme inducer would increase the warfarin concentration
- The warfarin dose would be then excessive if not adjusted
- Consider effects of stopping the precipitant drug – generally not detected by software

Question: What is the mechanism of the interaction between carbamazepine and clarithromycin?

A. Carbamazepine inhibits the metabolism of clarithromycin by CYP3A4
B. Clarithromycin inhibits the metabolism of carbamazepine by CYP3A4
C. Carbamazepine induces the metabolism of clarithromycin by CYP2D6
D. Clarithromycin induces the metabolism of carbamazepine by CYP2D6

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D. Clarithromycin induces the metabolism of carbamazepine by CYP2D6

Question: Which of the following would be appropriate alternatives to clarithromycin for a patient taking carbamazepine in order to avoid an interaction?

A. Azithromycin
B. Cefdinir
C. Levofloxacin
D. All of the above
E. None of the above

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E. None of the above

Carbamazepine-Clarithromycin

- Clarithromycin inhibits carbamazepine metabolism by CYP3A4
- Consider alternatives
  - Azithromycin or non-macrolide depending on infection and susceptibilities
- If combined use necessary, adjust and monitor
  - Temporarily decrease carbamazepine dosage (30%-50%) and monitor concentrations
  - Warn patients of toxicity symptoms

Case 4

- 45-year-old postmenopausal woman
- Underwent surgery, chemotherapy, and radiation therapy, followed by 6 months tamoxifen
- Pharmacogenetic testing for CYP2D6: extensive metabolizer
- Developed recurrence of depressive symptoms

Past Medical History

•ER+ invasive breast cancer

•Major depressive disorder

Medications

Chronic medications:

•Tamoxifen

Case adapted from: Am J Psychiatry. 2008;165(10):1251-5.

Question: Which of the following agents is thought to compromise the efficacy of tamoxifen?

A. Citalopram
B. Fluoxetine
C. Sertraline
D. Venlafaxine
E. All of the above

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E. All of the above

?

Tamoxifen-Fluoxetine

- Fluoxetine inhibits conversion of prodrug tamoxifen by CYP2D6 to its primary active metabolite
- Concern regarding increased risk breast cancer recurrence
- Alternative antidepressants
  - Citalopram, sertraline, and venlafaxine do not significantly inhibit CYP2D6
  - Bupropion, duloxetine, and paroxetine also inhibit CYP2D6
- Reasonable to avoid known CYP2D6 inhibitors based on current data

Case 5

Past Medical History
- Hypertension
- Hyperlipidemia

Medications

Chronic medications:
- Simvastatin
- Lisinopril
- Aspirin

New medication:
- Itraconazole

- 74-year-old man
- Started treatment for toenail infection
- 3 weeks later, lower extremity pain while golfing
- Pain progressed to upper extremities and neck, urine turned brown
- CK 22,800,000 U/L (reference range: 32-267)

CK=creatine kinase

Case Adapted from: Ann Pharmacother. 2006;40(4):753-7.

Question: Which of the following would be appropriate strategies to avoid an interaction between simvastatin and itraconazole?

A. Use an alternative antifungal (e.g., terbinafine)
B. Temporarily stop the simvastatin during short-term itraconazole therapy
C. Switch to an alternative statin during long-term itraconazole therapy
D. All of the above
E. None of the above

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D. All of the above
E. None of the above

Simvastatin-Itraconazole

- Itraconazole inhibits simvastatin metabolism by CYP3A4
- Antifungal alternatives
  - Consider terbinafine (not CYP3A4 inhibitor) or ciclopirox nail lacquer (not absorbed)
  - Avoid azole antifungals (inhibit CYP3A4)
- Hold simvastatin (short-term)
  - NOT in unstable angina or immediately post-MI
- Statin alternatives
  - Consider fluvastatin, rosuvastatin or pravastatin (not CYP3A4 substrates)
  - Avoid lovastatin and atorvastatin (to a lesser extent)

Question: Which of the following would be preferred therapeutic alternatives to simvastatin for a patient on chronic amiodarone therapy in order to avoid an interaction?

A. Atorvastatin
B. Lovastatin
C. Rosuvastatin
D. All of the above
E. None of the above – this is a class effect

Question: Which of the following would be preferred therapeutic alternatives to simvastatin for a patient on chronic amiodarone therapy in order to avoid an interaction?

A. Atorvastatin
B. Lovastatin
C. Rosuvastatin
D. All of the above
E. None of the above – this is a class effect

Simvastatin-Amiodarone

- Amiodarone inhibits simvastatin metabolism by CYP3A4
- Statin alternatives
  - Consider fluvastatin, rosuvastatin, pravastatin (not metabolized by CYP3A4)
  - Avoid lovastatin and atorvastatin (to a lesser extent)
- If combined use necessary
  - Maximum simvastatin dose: 20 mg/day
  - Warn patients to report muscle pain, tenderness, or weakness

Risk Factors for Rhabdomyolysis

- Advanced age (>65 years)
- Uncontrolled hypothyroidism
- Renal impairment

Clinically Relevant Interactions

Object Medications	Precipitant Medication	DDI-Specific Hospitalization: Odds Ratio 95% CI	DDI-Specific Medical Outcome: Odds Ratio 95% CI	Total Healthcare Cost Difference in Follow up Period
Amiodarone and/or Sotalol	Macrolides or quinolones	1.13 (0.94-1.36)	**1.52 (1.40-1.66)**	**$1923 ($1348 - $2497)**
Amiodarone	Macrolides	1.21 (0.60-2.46)	**1.84 (1.32-2.55)**	**$2784 ($1509 - $4059)**
Amiodarone	Quinolones	1.16 (0.94-1.42)	**1.57 (1.43-1.74)**	**$2756 ($2011 - $3500)**
Carbamazepine	Azole Antifungals	**3.00 (1.09-8.25)**	**2.40 (1.57-3.67)**	**$785 ($382 - $1187)**
Carbamazepine	Macrolides	**10.00 (1.28-78.12)**	**2.00 (1.23-3.27)**	**$1181 ($722 - $1640)**

Clinically Relevant Interactions

Object Medication	Precipitant Medication	DDI-Specific Hospitalization: Odds Ratio 95% CI	DDI-Specific Medical Outcome: Odds Ratio 95% CI	Total Healthcare Cost Difference in Follow up Period
Lovastatin or Simvastatin	Azole Antifungals	2.00 (0.50-8.00)	1.33 (0.46-3.84)	**$994 ($810 - $1177)**
Lovastatin or Simvastatin	Macrolides	-	**9.00 (1.14-71.04)**	**$872 ($781 - $962)**
Lithium	NSAIDS	2.00 (0.37-10.92)	**3.22 (1.90-5.47)**	**$681 ($491 - $870)**

Warfarin Interactions

Object Medication	Precipitant Medication	DDI-Specific Hospitalization: Odds Ratio 95% CI	DDI-Specific Medical Outcome: Odds Ratio 95% CI	Total Healthcare Cost Difference in Follow up Period
Warfarin	Amiodarone	**2.26 (1.89-2.70)**	**2.24 (2.02-2.48)**	**$1656 ($1382 - $1930)**
Warfarin	Sulfamethox-azole	**3.40 (2.53-4.57)**	**2.87 (2.42-3.41)**	**$3252 ($2869 - $3634)**
Warfarin	Metronidazole	**4.72 (3.22-6.91)**	**7.70 (6.03-9.83)**	**$4533 ($4043 - $5022)**
Warfarin	Fluconazole or Voriconazole	**2.37 (1.70-3.31)**	**3.62 (2.90-4.53)**	**$6130 ($5377 - $6883)**
Warfarin	Fenofibrate or Gemfibrozil	**1.41 (1.00-1.99)**	**1.67 (1.39-2.02)**	**$467 ($288 - $646)**
Warfarin	Statins	**1.61 (1.37-1.89)**	**1.83 (1.67-2.00)**	**$515 ($424 - $606)**
Warfarin	NSAIDS	**3.26 (2.49-4.26)**	**2.45 (2.09-2.87)**	**$1940 ($1763 - $2117)**

Other Interactions to Avoid Sildenafil and Nitrates

- Pharmacodynamic interaction: additive hypotensive effects
  - flushing, dizziness, headache, death

- Predisposing factors:
  - > 65 years old
  - Hepatic impairment
  - Severe renal impairment

- Patient Management:
  - Co-administration of nitrates with sildenafil may be appropriate under certain conditions.

Drug	ACC/AHA Recommendations for nitrate administration
sildenafil	24 hours
tadalafil	48 hours
vardenafil	24 hours (not in guideline)

Statins and Gemfibrozil (Fibrates)

- Proposed mechanism of interaction:

- Displacement of protein binding
- Atypical enzyme interaction
- Direct action on myocytes
- Interference with multiple drug resistance protein (MDRP)

- Risk of co-administration:

Severe myopathy, Rhabdomyolysis, Acute renal failure

- Evidence:

- PK studies and reviews of FDA Adverse Event Reporting databases
- Overall incidence is rare but serious
  - **>80% of reported rhabdomyolysis cases resulted in hospitalization for renal failure**
- Risk is higher for gemfibrozil than fenofibrate (15x)
- Simvastatin has highest reporting rate (4/100,000)

Colchicine-Clarithromycin

- Colchicine is substrate for CYP3A4 and PGP
  - Clarithromycin is potent inhibitor of both
- FDA database: 60 fatalities (as of 2010)
- Retrospective case series of 88 patients
  - 9 expired
- Adverse outcomes
  - Pancytopenia
  - GI effects: diarrhea, N/V, pain
  - Myopathy
  - Multi-organ failure
- Onset
  - Time to symptoms – approximately 4 days
  - Time to death (< 2 weeks)

Summary

- Drug interaction knowledge is poor among health professionals
- Many DDIs result from multiple prescribers – but not all
- Interactions can be harmful
  - ↑ Hospitalization
  - ↑ Morbidity
  - ↑ Costs

RED Flag Medications

- Warfarin
- Macrolide antibiotics
  - Clarithromycin / erythromycin
- Azole antifungals
- Anti-epileptic medications
- Amiodarone
- Colchicine

Questions?