




The DDI Quiz Show:
Knowledge Test and A Quick Look
Behind the Curtain on The Evidence
for Drug Interactions

Daniel C. Malone, RPh, PhD
 Professor, The University of Arizona College of Pharmacy
 Tucson, AZ

DDIs – Fact or Fiction?


- Millions of patients exposed to DDIs each year^{1,2}
- Most DDIs clinically inconsequential BUT harm does occur^{3,4}
- DDIs are preventable medication errors



1) Malone et al. Am J Health Syst Pharm. 2005;62(19):1983-1991. 2) Lafata et al. Med Care. 2006;44(6):534-541. 3) Hamilton et al. Pharmacotherapy. 1998;18(5):1112-1120. 4) Juurlink et al. JAMA. 2003;289(13):1652-1658

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?

- 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



Health Systems Approach to DDIs

- o Evidence for DDIs is lacking
 - Very few well-controlled studies
- o Lack of concordance among DDI compendia¹
 - Differing severity rating systems, terminology, methodologies
- o Limitations of DDI clinical decision support²⁻⁴
 - “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.

Concordance Among Compendia

Research Question:

What is the level of agreement among commonly used drug-drug interaction (DDI) compendia with regard to the severity ratings of ‘major’ drug-drug interactions?

Abarca J, Malone DC, Armstrong EP, et al. J Am Pharm Assoc. 2004; 44:136-141. Malone DC, Abarca J, Hansten PD, et al. J Am Pharm Assoc. 2004; 44: 142-151. Malone DC, Hutchins DS, Hauptert H, et al. Am J Health-Sys Pharm. 2005; 62:1983-91.

Tertiary References for Drug-Drug Interactions



DRUG-REAX® System
from MICROMEDEX

Methods

- Study performed in Fall 2001
- Review compendia for "major" interactions
 - DDI listed in at least 3 compendia
 - Additional criteria:
 - Available in US for human use
 - Medications likely to be dispensed in community pharmacy
 - Medications likely captured in electronic database
 - Interacting medications not used for therapeutic benefit

Rating Systems & Selection Criteria

- Evaluation of Drug Interactions
 - Uses 4-item summary measure based on:
 - Potential harm to the patient
 - Frequency and predictability of occurrence
 - Degree and quality of documentation
 - Code 1: highly clinically significant
 - Code 2: moderately clinically significant
 - Code 3: minimally clinically significant
 - Code 4: not clinically significant
- Selected 'Code 1' interactions

Rating Systems & Selection Criteria

- Drug Interaction Facts
 - Uses 5-item summary measure based on:
 - Severity (i.e., major, moderate, minor)
 - Documentation (i.e., established, probable, suspected, possible, unlikely)
 - 1: major/established, probable, suspected
 - 2: moderate/established, probable, suspected
 - 3: minor/established, probable, suspected
 - 4: major, moderate/possible
 - 5: minor/possible or any/unlikely
- Selected 'major' interactions

Rating Systems & Selection Criteria

- Drug Interactions: Analysis and Management
 - Used 5-item summary measure based on:
 - Severity
 - Corresponding documentation
 - Availability of alternatives are considered
 - 1: Avoid combination
 - 2: Usually avoid combination
 - 3: Minimize risk
 - 4: No action needed
 - 5: No interaction
- Selected '1' and '2' interactions

Rating Systems

- Drug-REAX (MicroMedex)
 - Used 5-item severity scale
 - Major
 - Moderate
 - Minor
 - None
 - Not specified
 - No summary measure
- Selected 'major' interactions

Results

- DDI listed in at least 3 compendia
 - 62 'major' DDIs identified
- Additional criteria:
 - 18 'major' DDIs excluded :
 - 8 DDIs - not available in U.S. (e.g., terfenadine, mibefradil)
 - 4 DDIs – not dispensed from a community pharmacy
 - 4 DDIs – not likely to be captured in electronic database (e.g, ethanol, tyramine-containing foods)
 - 1 DDI – occurs upon discontinuation (clonidine-β blockers)
 - 1 DDI – used for therapeutic benefit (phenothiazine-SSRI)

Problems with Identifying Drug-Drug Interactions

"Major" Drug Interactions (at Medication Class Level) 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.

Which Drug-Drug Interaction Reference?

- 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)

- Agreement on Severity Ratings for Major Drug-Drug Interactions Among Compendia
 - Intraclass Correlation Coefficient: -0.092

Health Systems Approach to DDIs (continued)

- DDI knowledge is lacking
 - 42.7% of drug pairs correctly identified in a postal survey of prescribers¹
 - Pharmacist knowledge also poor²



1) Ko et al. Drug Saf. 2008;31(6):525-536. 2) Weideman et al. Am J Health Syst Pharm. 1999;56(15):1524-1529.

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

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



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

- o Pharmacodynamic
 - Additive or antagonistic pharmacologic effects
- o Pharmacokinetic
 - Absorption
 - Distribution
 - Metabolism
 - Excretion



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

Drug Interaction Mechanisms (continued)

Pharmacokinetic Interactions

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



Case

- o 67-year-old woman
- o Diagnosed with pneumonia after mitral valve repair
- o 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

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

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

Question: Which of the following is associated with the lowest risk of TdP and/or QTc prolongation?

- A. Clarithromycin
- B. Erythromycin
- C. Ciprofloxacin
- D. Levofloxacin
- E. Moxifloxacin

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

Question: Which of the following is associated with the lowest risk of TdP and/or QTc prolongation?


- A. Clarithromycin
- B. Erythromycin
- C. Ciprofloxacin
- D. Levofloxacin
- E. Moxifloxacin

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

QT Drug Lists by Risk Groups

Risk of Torsades	Possible Risk of Torsades	Conditional Risk of Torsades
<ul style="list-style-type: none"> • Disopyramide • Procainamide • Quinidine • Amiodarone • Dofetilide • Ibutilide • Sotalol • Clarithromycin • Erythromycin 	<ul style="list-style-type: none"> • Flecainide • Gemifloxacin • Levofloxacin • Moxifloxacin • Ofloxacin • Azithromycin 	<ul style="list-style-type: none"> • 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

- 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

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

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)

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

?

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



Usually Avoid This Combination

Warfarin-NSAID

- o Additive risk of bleeding
 - Some NSAIDs may also alter warfarin PK
- o Considerable increased risk of GI bleeding¹
 - 13-fold higher risk hospitalization for hemorrhagic PUD vs. neither drug; 4-fold higher risk with either drug alone
- o 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.

Usually Avoid This Combination

Warfarin-NSAID (continued)

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

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



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



Take Precautions with This Combination

Warfarin-Carbamazepine

- o Carbamazepine induces warfarin metabolism
- o The warfarin dose was likely previously increased to adjust for enzyme induction
- o Stopping the enzyme inducer would increase the warfarin concentration
- o The warfarin dose would be then excessive if not adjusted
- o 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



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



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



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



Take Precautions with this Combination

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

- 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



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



Take Precautions with this Combination

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

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

Past Medical History

- Hypertension
- Hyperlipidemia

Medications

Chronic medications:


- Simvastatin
- Lisinopril
- Aspirin

New medication:

- Itraconazole


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



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



Usually Avoid this Combination

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



Usually Avoid this Combination

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

Stepwise Approach to DDIs

1. Take a thorough medication history
 - Remember OTC and herbal agents
2. Focus on high-risk patients
 - Polypharmacy, renal, or hepatic impairment
3. Focus on high-risk drugs
 - Object drugs (e.g., warfarin, digoxin)
 - Precipitant drugs (e.g., amiodarone, clarithromycin, azole antifungals)
4. Keep a short list of top DDIs
 - Learn interactions with the drugs you frequently encounter
5. Use multiple resources
 - Check software programs
 - Check pocket reference

Acknowledgments

- This work is supported by the Agency for Healthcare Research and Quality (RL Woosley, PI; award U18 HS017001-01)
- The Arizona Center for Education & Research on Therapeutics (AZ CERT) is a collaboration between The Critical Path Institute and the University of Arizona College of Pharmacy
 - Raymond L. Woosley, PhD, MD, PI, and Director
 - Daniel C. Malone, RPh, PhD, Co-Director
 - University of Arizona Investigators: Ed Armstrong, PharmD, Amy Grizzle, PharmD, Lisa Hines, PharmD, John Murphy, PharmD, Sally Reel, PhD, RN, CS, FNP, Duane Sherrill, PhD, Grant Skrepnek, RPh, PhD, Terri Warholak, PhD
