Common Drug Interactions

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Objectives

- Review the mechanisms of drug interactions
- Discuss the most common medications involved in drug interactions at BRRH
- Discuss other predispositions for drug interaction potential
- Review strategies to assist in minimizing drug interactions

Definition

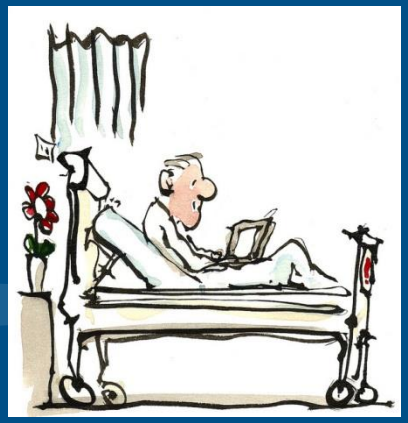
- Drug-Drug Interaction:
  - It is the modification of the effect of one drug (the object drug) by the prior or concomitant administration of another (precipitant drug).
  - May be unintended or intended
  - Various forms of interactions

Risk Factors for Drug Interactions

OTC Medications

Narrow Therapeutic Index Drugs

Polypharmacy



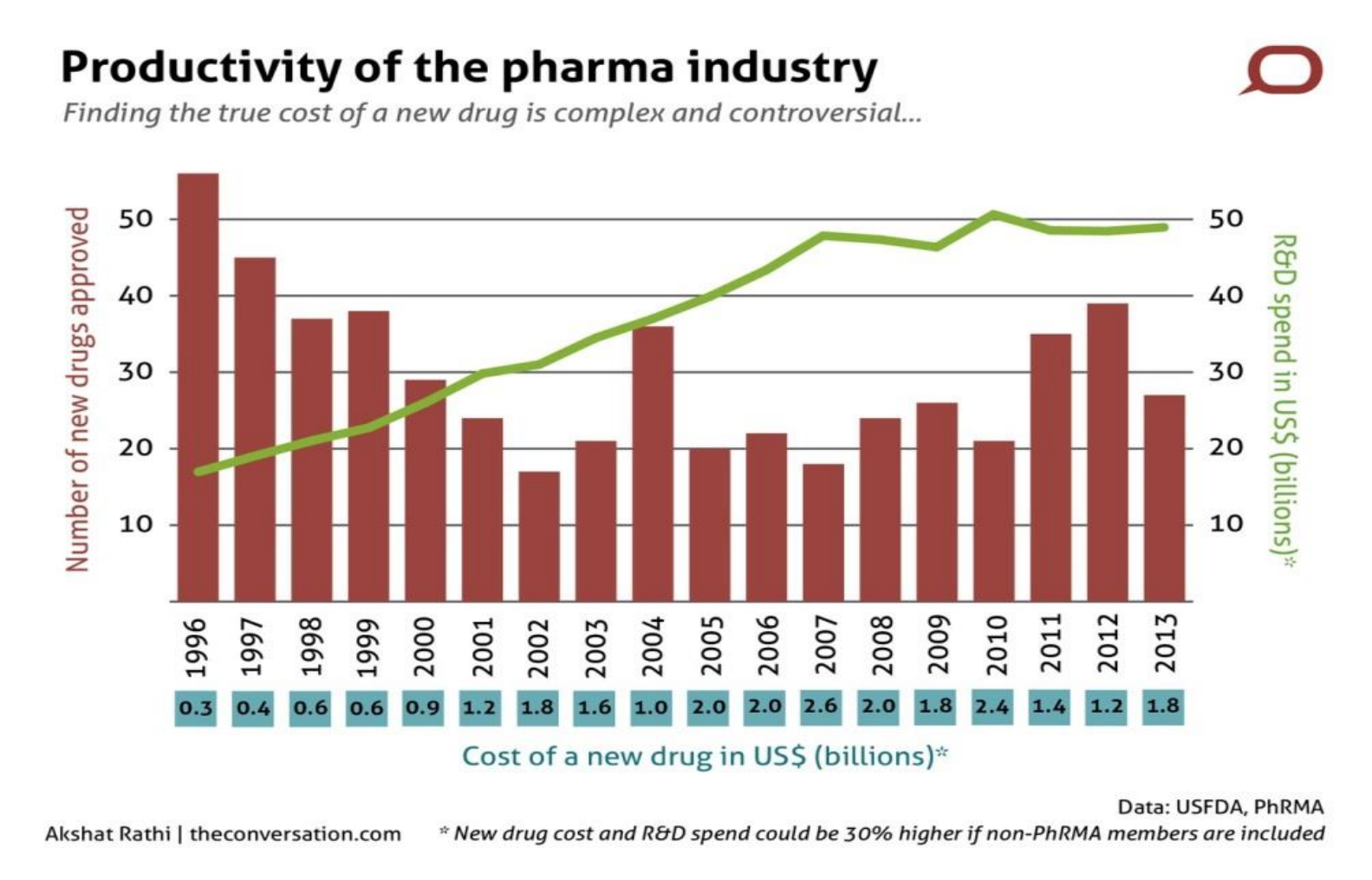
Genetic Disposition

Multiple Prescribers

Morbidity

Eur J Gen Practice 2008;14(1):23-9

Risk Factors for Drug Interactions



Drugs Withdrawn or Not Approved in the U.S. Because of Interactions

- Examples of Drugs Withdrawn
  - Terfenadine (Seldane)
  - Astemizole (Hismanal)
  - Cisapride (Propulsid)

- Examples of Drugs Not Approved
  - Domperidone

Mullins ME, et al, *JAMA*. 1998;280:157–8.

Not All Drug Interactions are Bad: Protease Inhibitors

Drug Affected	Ritonavir	Saquinavir*	Nelfinavir
Indinavir (IDV)	Levels: IDV ↑ 2-5x Dose: IDV 400 mg bid + RTV 400 mg bid, or IDV 800 mg bid + RTV 100 or 200 mg bid	Levels: IDV no effect, SQV ↑ 4-7x † Dose: Insufficient data	Levels: IDV ↑ 50%, NFV ↑ 80% Dose: Limited data for IDV 1,200 mg bid + NFV 1,250 mg bid
Ritonavir (RTV)	–	Levels: RTV no effect SQV ↑ 20x †† Dose: Invirase or Fortovase 400 mg bid + RTV 400 mg bid	Levels: RTV no effect NFV ↑ 1.5x Dose: RTV 400 mg bid + NFV 500-750 mg bid
Saquinavir (SQV)	–	–	Levels: SQV ↑ 3-5x, NFV ↑ 20%† Dose: Standard NFV Fortovase 800 mg tid or 1,200 mg bid
Nelfinavir (NFV)	–	–	–
Amprenavir (APV)	–	–	–

Not All Drug Interactions are Bad: Protease Inhibitors

Drug Affected	Amprenavir	Lopinavir + Ritonavir
Indinavir (IDV)	Levels: APV AUC↑33% Dose: no change	Levels: IDV AUC and Cmin increased. Dose: IDV 600 mg bid
Ritonavir (RTV)	Levels: APV AUC↑2.5-fold Dose: Limited data for APV 600-1,200 mg bid + RTV 100-200 mg bid	Lopinavir is co-formulated with ritonavir as Kaletra.
Saquinavir (SQV)	Levels: APV AUC↓32% Dose: insufficient data	Levels: SQV† AUC and Cmin increased Dose: SQV 800 mg bid, LPV/r standard
Nelfinavir (NFV)	Levels: APV AUC↑1.5-fold Dose: insufficient data	No data
Amprenavir (APV)	–	Levels: APV AUC and Cmin increased Dose: APV 600-750 mg bid, LPV/r standard

Evidence:
Most Common Drug-Drug Interactions

- Marengoni Study:
- Evaluated prevalence and characteristics of ADRs from drug interactions
- 1014 ADRs analyzed
- 912 of the ADRs had direct drug interactions
- 31% considered major
- Most were hemorrhages (54%)
- Warfarin was most common drug involved

Marengoni et al, Eur J Intern Med 2014 Nov; 25(9) 843-6

Evidence: How Much of an Impact are Drug – Drug Interactions?

- Becker et al – Evaluated the incidence of adverse patient outcomes due to drug interactions, ED visits and admissions
- Meta-analysis:
  - 23 clinical trials reviewed (>80,000 patients)
  - 0.054% of ED visits
  - 0.57% of hospital admissions
  - 0.12% re-admissions
  - Elderly pooled analysis: 4.8% hospital admissions
  - Most common drugs involved: NSAIDS and CV Drugs
  - Most common symptom from drug interactions: GIB, hypotension

Becker et al , Pharmacoepidemiology and Drug Safety 2007, Jun; 16(6): 641-561

Evidence: How Much of an Impact are Drug – Drug Interactions?

- Goldberg et al- Analyzed drug-drug and drug-disease interactions in the ER setting, both teaching facility and community hospital
  - 205 patients analyzed
  - 3 or more medications in patients over the age of 50
  - 47% potential interactions identified
  - 21% confirmed drug interactions
  - Risk of interactions rose from 13% for patients taking 2 meds to 82% for patients taking 7 or more medications

Goldberg et al, Am J Emergency Medicine 1996 Sep; 14(5): 447-50

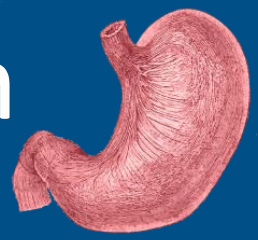
Types of Drug-Drug Interactions

Pharmacodynamic: Receptor Site Interaction

Pharmacokinetic: Based on change of drug shape

- Absorption
- Metabolism
- Excretion

Drug Interactions-Absorption



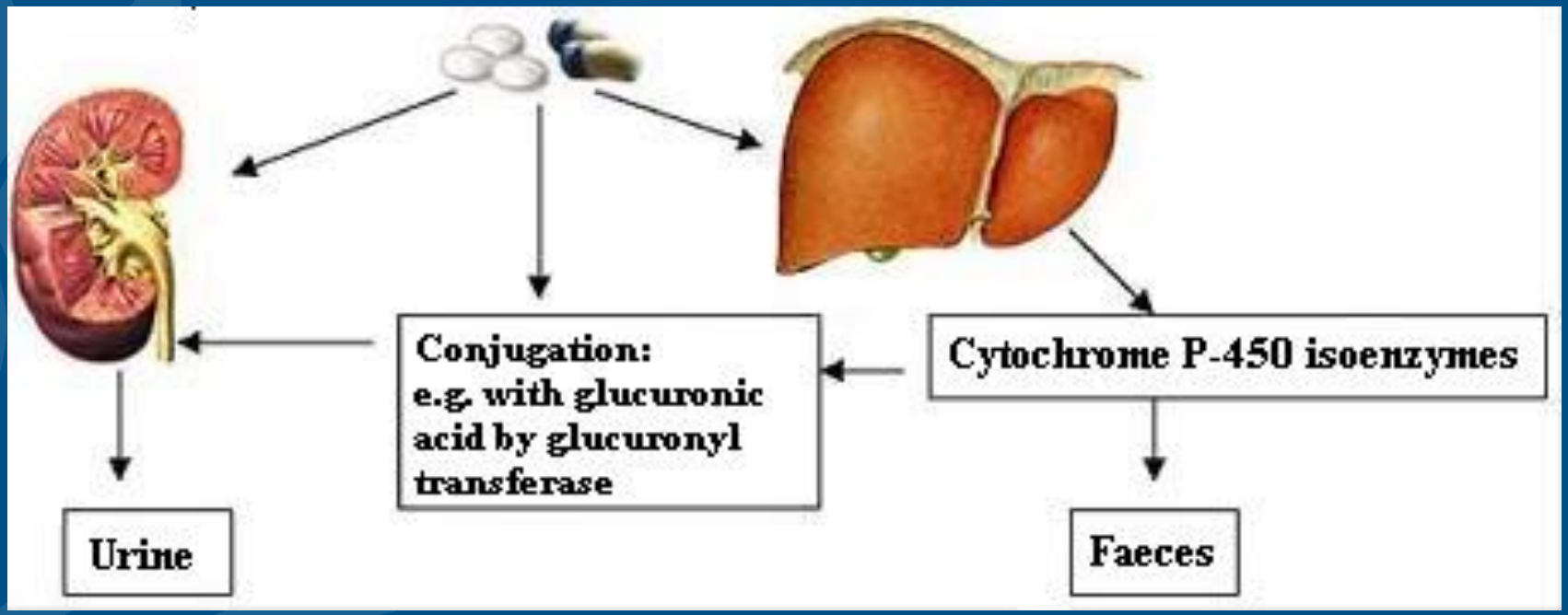
Concurrent therapy increases or decreases absorption of the drug

Suspect Drug	Affected Drug	Mechanism of Interaction
Pepcid	Saquinavir (Increase) Other HIV Meds	Increase of gastric pH
Proton Pump Inhibitors	Saquinavir (Increase) Other HIV Meds Pradaxa (decrease)	Increase of gastric pH
Cogentin Elavil Thorazine Bentyl Opioids	All Oral Drugs (decrease)	Slower absorption due to slower GI motility
Bile Acid Sequestrants (Questran)	Digoxin, Warfarin, Depakote, Amiodarone, SSRI's (decrease)	Bind to the affected drugs, affecting absorption

Clinical Pharmacokinetics
December 1994, Volume 27, pp 447-461

Drug Interactions-Metabolism

Concurrent therapy affects drugs metabolized by liver (CYTP450) increasing or decreasing effects of drugs



Drug Interactions-Metabolism

- Phase 1
  - Oxidation Metabolism
  - Enzymes act to introduce reactive and polar groups into their substrates
  - Cytochrome P450
  - Inactive metabolites
- Phase 2
  - Conjugation Metabolism
  - Active metabolites

Le, Jennifer, Merckmanual.com, updated 2016

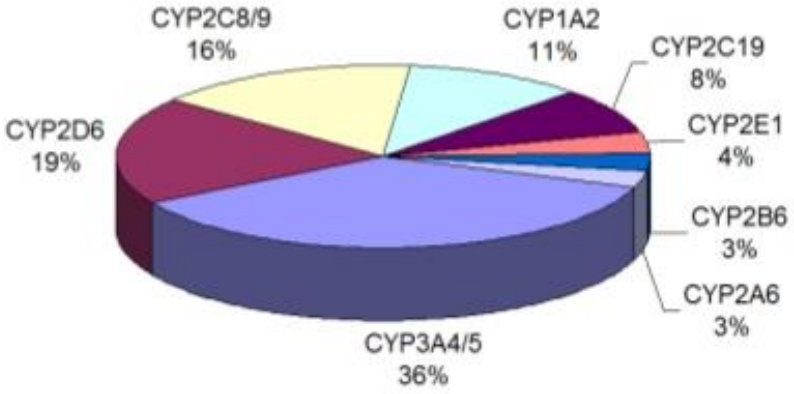
Drug Interactions-Metabolism

PGx Drug Metabolism Enzymes (DMEs)

DMEs catalyze reactions that affect the absorption, distribution, metabolism, excretion of drugs

Cytochrome P450 system

- Phase I metabolic system of the liver
- Metabolism of >85% of medications
- Genetic variability affects pharmacokinetics



life technologies

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Drug Interactions-Metabolism

- Object Drug:
  - Causative drug
  - Inducer or Inhibitor
- Substrate Drug:
  - Drug that is affected by the object drug
  - May be increased or decreased in effect depending on the object drug's action

Which CYTP450 Enzymes Impact The Most Medications?

Drug Interactions-Metabolism

Cytochrome P540 1A2

Inhibitor	Substrates Affected	Inducer	Substrates Affected
Norvasc Tagamet Cipro Prozac Lopid Nizoral Procardia Primaquine Diprivan	↑ Effects of: Aminophylline Flexeril Clozaril Cymbalta Estrogens Zyprexa Inderal Ropivacaine Theophylline	Tegretol Phenobarbital Primidone Rifampin	↓ Effects of: Aminophylline Flexeril Clozaril Cymbalta Estrogens Zyprexa Inderal Ropivacaine Theophylline

Drug Interactions-Metabolism

Cytochrome P540 2C8/9

Inhibitor	Substrates Affected	Inducer	Substrates Affected
Amiodarone/Multaq Sustiva Plendil Statins (except pravastatin) Entresto Ibuprofen Avapro Nizoral Cozaar Cardene Norvir Rosiglitazone Sulfadiazine Bactrim Flagyl	↑ Effects of: Coreg Celebrex Prozac Lescol Fosphenytoin Glucotrol Amaryl Ketamine Cozaar Singulair Phenytoin Avandia Sulfadiazine Bactrim Demadex Warfarin	Carbamazepine Fosphenytoin Phenobarbital Phenytoin Primidone Rifampin	↓ Effects of: Coreg Celebrex Prozac Lescol Fosphenytoin Glucotrol Amaryl Ketamine Cozaar Singulair Phenytoin Avandia Sulfadizine Bactrim Demadex Warfarin

Drug Interactions-Metabolism

Cytochrome P540 2D6

Inhibitor	Substrates Affected	Substrates Affected
Amiodarone/Multaq Thorazine Tagamet Clozaril Cocaine Precedex Benadryl Cymbalta Prozac Haldol Nizoral Lidocaine Methadone Cardene Paxil	↑ Effects of: Elavil Abilify Capoten Coreg Thorazine Codeine DM Cymbalta Prozac Haldol Lidocaine Lopressor Bystolic Paxil Phenergan Diprivan Flomax	↓ Effects of: Ultram: Ultram is a prodrug, and its active metabolite cant be activated without 2D6

No Known Inducers of 2D6

Drug Interactions-Metabolism

Cytochrome P540 3A4

Inhibitor	Substrates Affected	Inducer	Substrates Affected
Amiodarone/Multaq Caffeine Tagamet Biaxin Cyclosporine Cardizem Erythromycin Diflucan Haldol Nizoral Lidocaine Cardene Noxafil Diprivan Flagyl	↑ Effects of: Xanax Amiodarone Norvasc Abilify Lipitor Ultram Tegretol Librium Klonopin Cyclosporine Dexamethasone Cardizem Sustiva Estrogens Fentanyl Mevacor / Zocor Bactrim Eliquis	Tegretol Dexamethasone Phenytoin Pentobarbital Phenobarbital Rifabutin Rifampin	↓ Effects of: Xanax Amiodarone Norvasc Abilify Lipitor Ultram Tegretol Librium Klonopin Cyclosporine Dexamethasone Cardizem Sustiva Estrogens Fentanyl Mevacor / Zocor Bactrim

Risk Factors for Drug Interactions

Newer Medications Being Produced Still Have Drug Interactions

Year	Drug	Used In	Effect of CYP450
2015	Genvoya	HIV	Substrate of 3A4 and 2D6
2015	Addyi	Hypoactive Sexual Desire Disorder in premenopausal women	Substrate of 3A4, 2D6, 2C9
2015	Entresto	CHF	Inhibitor of 2C9
2015	Corlanor	CHF	Substrate of 3A4
2015	Cresemba	Antifungal for IA, Mucormycosis	Inhibitor of 3A4, 2C19, 2C8/9 Substrate of 3A4, Induces 2C8/9
2015	Avycaz	Multi-Resistant Abx	Induces 2E1

Drug Interactions-Excretion

- **Five potential mechanisms exist for drug interactions at the renal level:**

✓ Displacement of bound drug resulting in an increase in drug excretion via an increase in glomerular filtration;

✓ Competition at a tubular secretion site resulting in a decrease in drug excretion;

✓ Competition at the tubular reabsorption site resulting in an increase in drug excretion;

✓ A change in urinary pH and/or flow that may increase or decrease drug excretion depending on the pKa of the drug; and

✓ Inhibition of renal drug metabolism.

Bonate et al; Clinical Pharmacokinetics; 1998; May 34(5) pp375-404

Drug Interactions-Excretion

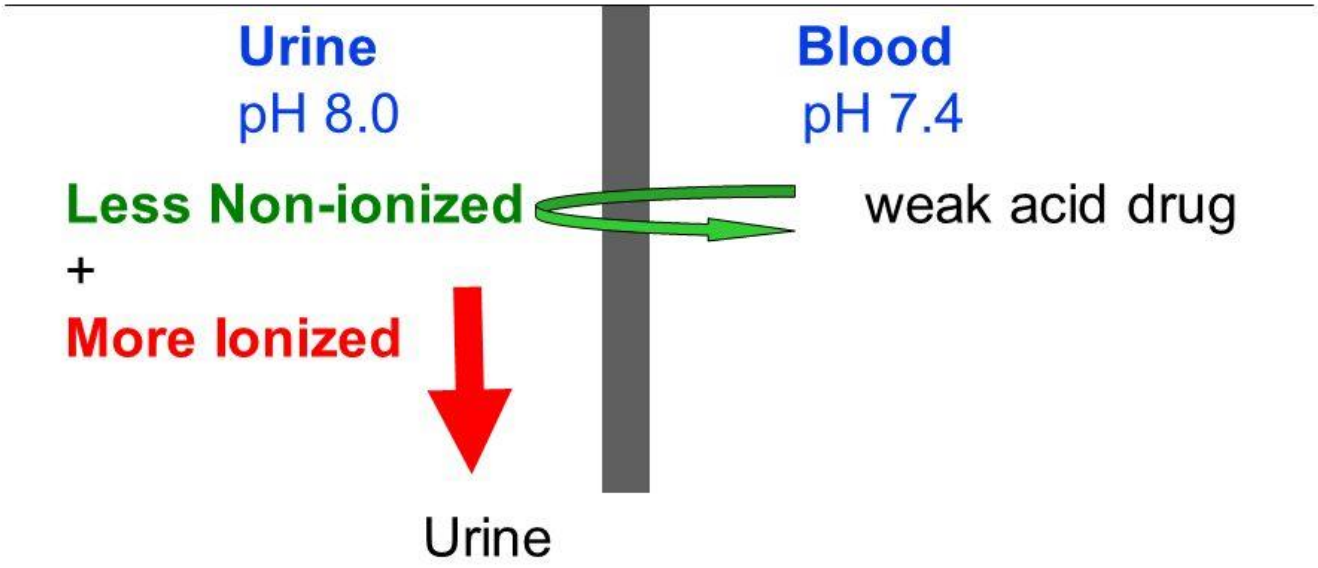
Drug	Effect on Substrate	Mechanism
Thiazide Diuretics	Decrease lithium elimination, increase lithium levels and effect	Competition at tubular site reabsorption
NSAIDs	Decrease lithium elimination, increase lithium levels and effect	Inhibit prostaglandins, leading to decreased glomerular filtration of lithium
Acetazolamide	ASA	Inhibits tubular excretion of ASA
Urinary Alkalizers (NaBicarb, thiazides, Na or K citrate)	Increase ASA, PCN, cephalosporin, acyclovir elimination (acid drugs), decrease elimination of weak base drugs (cocaine)	These drugs require low pH for reabsorption, higher pH for elimination

Clinical Pharmacokinetics
December 1994, Volume 27, pp 447-461

Drug Interactions-Excretion

Ion trapping

In presence of sodium bicarbonate, urine is alkaline and more excretion of acidic drug into urine



Most of acidic drug will be eliminated into urine.

Drug Interactions-Excretion

Weak Acids	pKa	Weak Bases	pKa
Amoxicillin	2.4	Alprenolol	9.6
Acetazolamide	7.2	Allopurinol	9.4, 12.3
Ampicillin	2.5	Amphetamine	9.8
Aspirin	3.5	Atropine	9.7
Chlorothiazide	6.8, 9.4*	Chlorpheniramine	9.2
Ciprofloxacin	6.1, 8.7*	Cocaine	8.5
Cephalexin	3.6	Codeine	8.2
Ethacrynic acid	2.5	Diazepam	3.0
Furosemide	3.9	Diphenhydramine	8.8
Ibuprofen	4.4, 5.2*	Amoxicillin	7.4
Levodopa	2.3	Ephedrine	9.6
Methotrexate	4.8	Epinephrine	8.7
Methyldopa	2.2, 9.2*	Imipramine	9.5
Penicillamine	1.8	Lidocaine	7.9
Pentobarbital	8.1	Methadone	8.4
Phenobarbital	7.4	Methamphetamine	10.0
Phenytoin	8.3	Methyldopa	10.6
Propylthiouracil	8.3	Metoprolol	9.8
Salicylic acid	3.0	Morphine	7.9
Sulfadiazine	6.5	Nicotine	7.9, 3.1*
Sulfapyridine	8.4	Norepinephrine	8.6
Theophylline	8.8	Phenylephrine	9.8
Tolbutamide	5.3	Pilocarpine	6.9, 1.4*
Warfarin	5.0	Pseudoephedrine	9.8

* denotes more than one ionizable group

Remingtons, 20th ed

BRRH Impact to Physicians? Most Common Medications Prescribed

Most Common Drugs Prescribed at BRRH – Summary of Specific Medications

Drug	Increase or Decreases:	Possible Effects:
Amiodarone Or Multaq	**Inc levels of** class 1A, III antiarrhythmics Canabis Digoxin Coreg Vaprisol Pradaxa Cerebyx / Dilantin “Statins”, except prava Claritin Bystolic Warfarin **Dec levels of** Ultram Plavix	Inc QTC prolongation Inc effects of canabis Inc side effects Bradycardia, hypotens Inc sodium rapidly Bleeding Inc levels Myopathy, rhabdo Inc QTC prolongation Bradycardia, hypotens Inc INR Increased pain / failed effic Failed anti-platelet tx
Flagyl	**Inc the effects of** Ethanol Warfarin	Disulfiram-effects Increased INR

Most Common Drugs Prescribed at BRRH – Summary of Specific Medications

Drug	Increase or Decreases:	Possible Effects:
Ultram	**Inc effects of** Tegretol Zyvox warfarin SSRIs	Inc CNS depression Serotonin syndrome Inc INR Serotonin syndrome
NSAIDs	**Inc effects of** Aminoglycosides Digoxin Lithium MTX Quinolones Vancomycin	 Inc risk of nephrotoxicity Inc levels, side effects Inc lithium levels, effects Inc levels, risk of toxicity QTC prolongation, neuro Inc levels
PPIs – Prilosec	**Inc effects of** Coreg Celexa Cerebyx Warfarin **Dec effects of** Plavix Pradaxa	Hypotension, bradycardia QTC prolongation CV events Inc INR CV events Bleeding

Most Common Drugs Prescribed at BRRH – Summary of Specific Medications

Drug	Increase or Decreases:	Possible Effects:
Quinolones	**Inc levels of** Tegretol Cymbalta MTX Theophylline Warfarin **Dec levels of** Cerebyx/Phen	 Inc CNS depression Inc risk of MTX toxicity Toxicy Inc INR Dec levels
Diflucan	**Inc effects of** Eliquis Statins, except pravastatin Pulmicort Calcium Channel Blockers Coreg Fentanyl	 Bleeding Rhabdo, myopathy Bradycardia, hypotension Bradycardia, hypotension Inc CNS/resp depression

Most Common Drugs Prescribed at BRRH – Summary of Specific Medications

Drug	Increase or Decreases:	Possible Effects:
Macrolide Antibiotics ? Azithromycin?	**Inc effects of** Statins Eliquis, Pradaxa, and Xarelto Pulmicort Calcium channel blockers Digoxin Fentanyl and Versed Theophylline Warfarin	 Rhabdo, myopathy Bleeding Bradycardia, hypotension Inc levels, side effects Inc CNS depression Inc levels, toxicity Inc INR
Statins	**Inc effects of** warfarin	 Inc INR

Gender Disposition for Drug Interaction Potential

Women and men are not equal in :

- ✓ % of body fat
  - Affects lipophilic drug interaction potential, involving opiods and benzodiazepines
- ✓ Drug Metabolism
  - Hepatic elimination of drugs is variable, and more likely to cause drug interactions

Table 1. CYP450 Enzymes and Their Sex-Dependent Activity

CYP Enzyme	Enzyme Activity	Example Drugs	Other Characteristics
1A2	M > W	Clozapine, olanzapine	Suppressed activity during pregnancy
2A6	W > M	Nicotine, coumarin	Increased activity in female users of oral contraceptives
2B6	W > M	Bupropion, tamoxifen	Activity: Hispanic women > Caucasian or African-American women
2C9	M = W	Imipramine, phenytoin	Increased activity during pregnancy
2C19	M = W	Imipramine, topiramate	Decreased activity during pregnancy or use of oral contraceptives
2D6	Mostly W > M	Codeine, fluoxetine, haloperidol	Increased activity during pregnancy
3A4	Mostly W > M	Cyclosporine, erythromycin, nimodipine	Increased activity during pregnancy

M: men; W: women. Source: References 16-24.

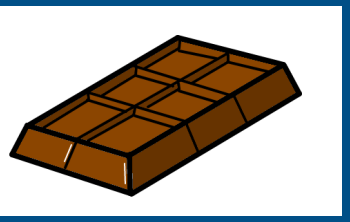
Chu, Teresa, U.S. Pharmacist, Sept 2014 40-43

Genetic Disposition for Drug Interaction Potential

CYP450 Sub Enzyme	Substrate	% Clearance From Norm
CYP2C9, genetics leading to intermediate or poor metabolizers	Celebrex Phenytoin Avapro Warfarin	-30% to -70% -33% to -88% -39% -42% to -90%
CYP2C19, genetics leading to intermediate or poor metabolizers	Prilosec Plavix	-37% to -76% -40% to -66%
CYP2D6, genetics leading to poor metabolizers or even ultrametabolizers	Lopressor Ultram	-32% to +160% -31% to -87%

POTENTIAL DRUG INTERACTIONS INCREASE BASED ON GENETICS

Westervelt, Paul et al P&T Sept 2014, Vol. 39 No. 9 630-638



Food-Drug Interactions

Food	Increase or Decreases:	Possible Effects:
Grapefruit	Inc effects of drugs metabolized by CYP3A4	Toxicity!
Tyramine Products: wine, chocolate, cheese, hotdogs, draft beer (bottle or canned ok),	Increase effects of MAOinhibitors by inhibiting breakdown of tyramine: Zyvox, Nardil, Parnate, etc	Increased hypertension
Green Leafy Vegetables	Dec effects of warfarin by increased Vit K enriched contents	Decreased INR
Natural Black Licorice (Glycyrrhiza)	Incr effects of digoxin by decreasing K+ levels and Inc Na+	Dig toxicity
Salt Substitutes	Dec effects of digoxin by increased K+ from salt substitutes	Lack of dig efficacy, exacerbation of CHF

Academy of Nutrition and Dietetics, 2014

A Word About Herbals

A Word About Herbals

Table 4. Possible Herb-Drug Interactions.

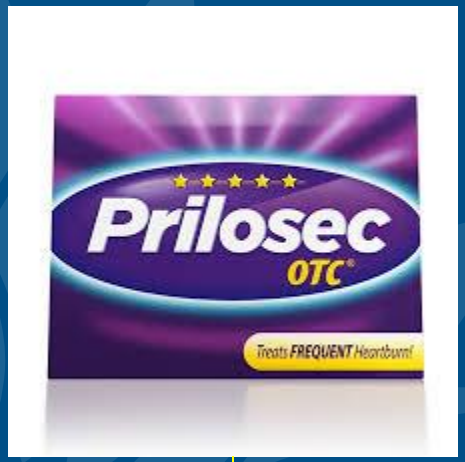
Herbal agent	Interacting drugs	Clinical effect
Danshen (*Salvia miltiorrhiza*)	Warfarin	Bleeding
Dong quai	Warfarin	Bleeding
Ephedra	Caffeine, decongestants	Sympathomimetic toxidrome (hypertension, tachycardia, CNS, CVS stimulation)
Garlic	Warfarin	Lowers blood levels
	Chlorpropamide	Hypoglycemia
Ginkgo biloba	Aspirin, clopidogrel, dipyridamole, ticlopidine, warfarin, heparin	Bleeding
	Thiazide diuretic	Elevated blood pressure
	Trazodone	Coma
	Morphine	Lack of effect
Ginseng	Warfarin, ethanol	Lowers blood levels
	Phenelzine	Induces mania
Kava	Benzodiazepines, sedative-hypnotics	CNS depression
	Levodopa	Increased "off" periods
St. John's wort	Antidepressants	Serotonergic stimulation (theoretical)
	Cyclosporin	Decreased effect (cytochrome p450 inducer)
	Digoxin	Decreased serum level
Valerian	Anxiolytics	CNS sedation

What Can We Do?

- 1. Minimize prescriptions (decrease polypharmacy)
- 2. Accurate medication history
- 3. Discourage OTC medications that are on this list
- 4. Caution with herbal medications

What Can We Do?

Beware of OTCs

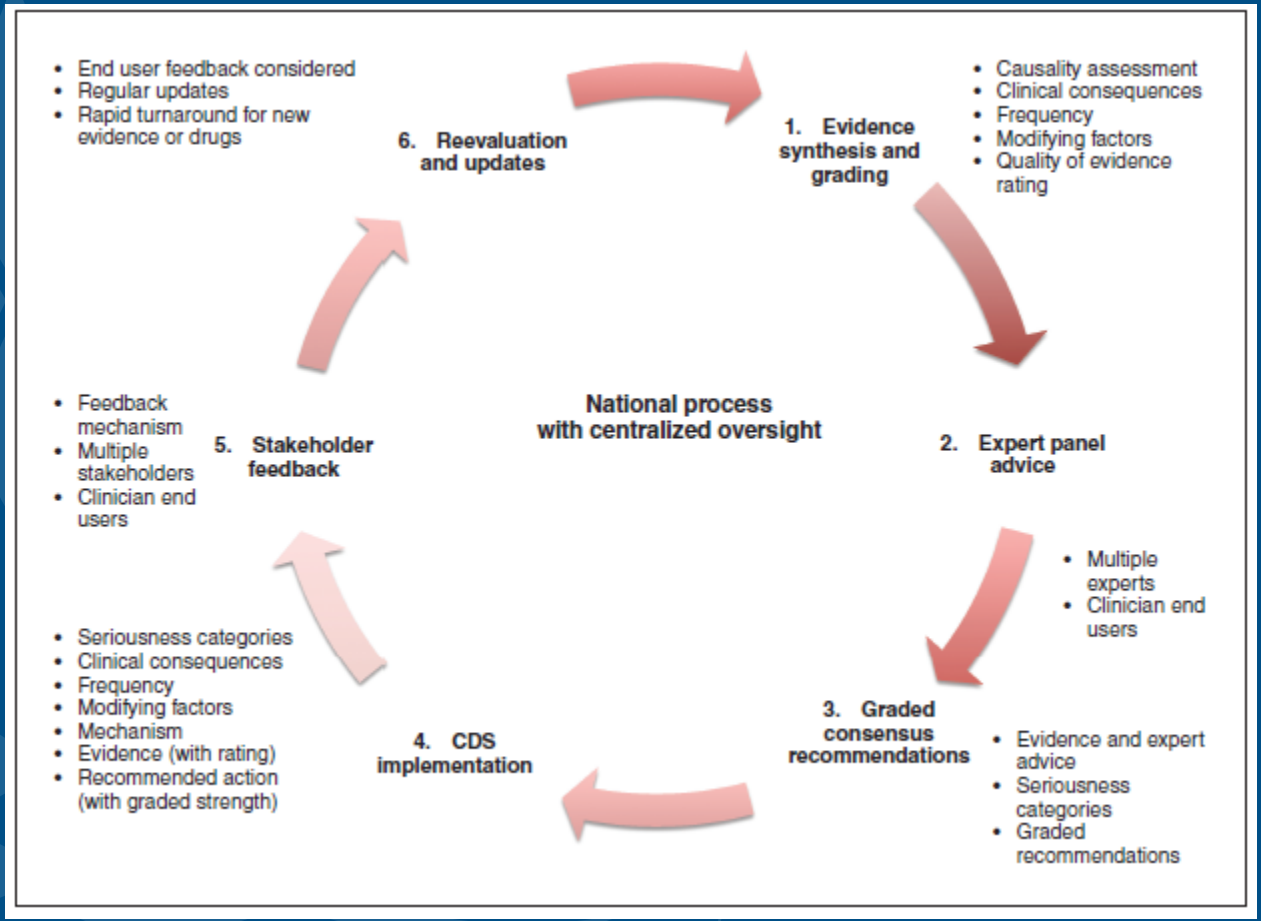


What Can We Do?

- Electronic Medical Record Utilization
  - BRRH currently uses First Data Bank for pharmacy review of drug interactions
  - Physicians see absolute contraindications upon order entry (decision made by Medical Staff)
  - Develop a systematic process for development of standard set of drug drug interactions for clinical decision support

What Can We Do?

- Electronic Medical Record Utilization



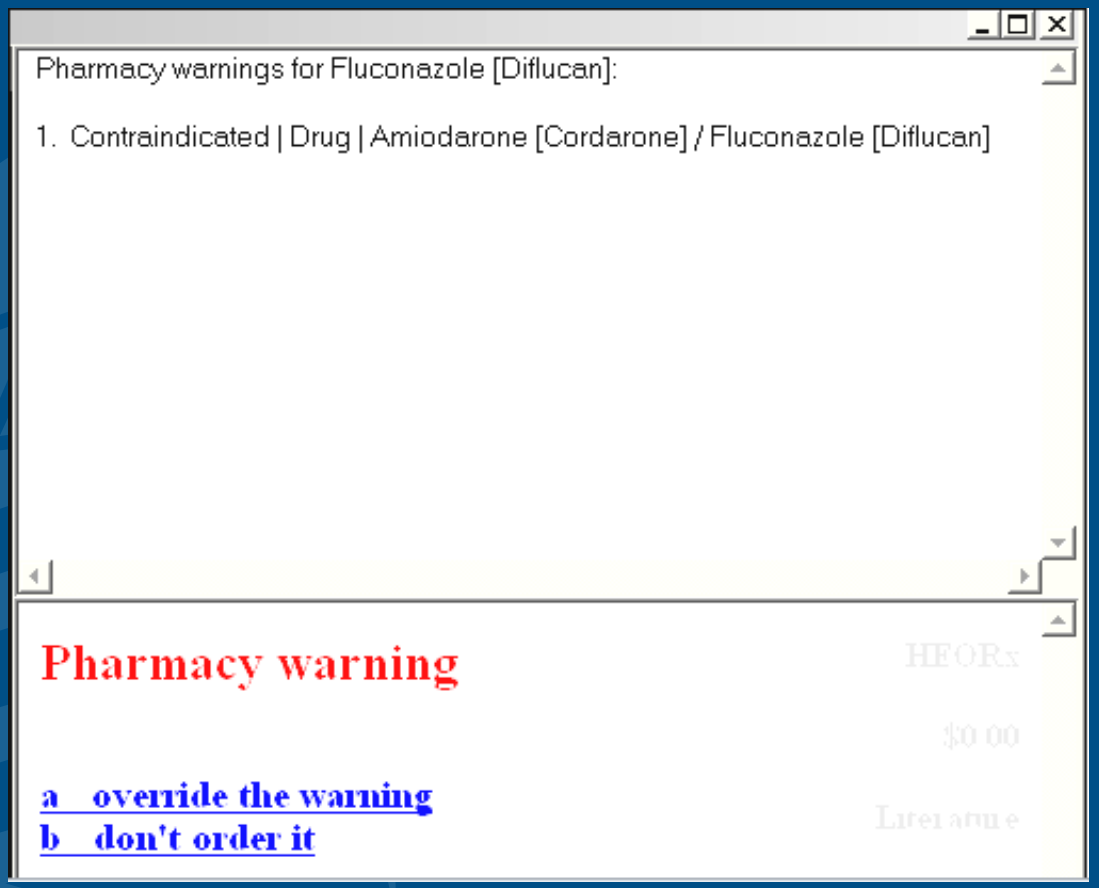
Each institution decides which levels of drug interactions to be set

Drawbacks: Alert fatigue!

Physicians only see grade X contraindications in current CPOE

Tilson et al Am J Health-Syst Pharm ; April 2016; Vol 73, No 8 576-585

BRRH Drug Interaction Notification to Physicians



Local Drug Interactions References for Physicians

- Phone / Pad devices – Epocrates, Micromedex
- BRRH Intranet – Pharmacy Tab Lexicomp
  - Direct drug input with all possible interactions
- Up to Date – More focused on the complications of the interaction, some more common drug-drug

Thank You