VASPEN Fall Meeting

Drug-Nutrition Interactions in Clinical Practice

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Objectives

Upon completion of this session, the participant will be able to:

- Define the term and describe classes of drug-nutrition interactions
- Provide specific examples that could be seen in clinical practice
- Explain the clinician's role in identifying and managing drug-nutrition interactions

Outline

- **Introduction**
- **Defining DNIs**
- **Clinical Examples**
- **Recommendations**
- **Conclusions**

Introduction

The Background

- History of Drug-Nutrient Interactions
  - Isolated reports and reviews
  - Focus on drug-food interactions
  - Memorize lists of interactions
  - Poor clinical relevance
  - Little mechanistic perspective

Proc Soc Exp Biol Med 1941;48:403 / *Vit Horm* 1943;1:59 / *JAMA* 1954;156:1549 / *Br Med J* 1970;4:532 / *J Pharmacokinet Biopharm* 1977;5:291 / *Clin Pharmacokinet* 1978;3:216 / *Trends Pharmacol Sci* 1979;1:67 / *Drug-Nutr Interact* 1985;4:117

The Background

Drug (Medication) Use
- Prescription medicines
- Non-prescription medicines
- Natural/traditional medicines

Nutrition Variability
- Nutrition status
- Dietary habits
- Food composition
- Dietary supplement use

Defining Drug-Nutrition Interactions

Journal of Clinical Pharmacy and Therapeutics, 2013, **38**, 269–271 doi: 10.1111/jcpt.12075

Commentary

Drug and nutrition interactions: not just *food* for thought

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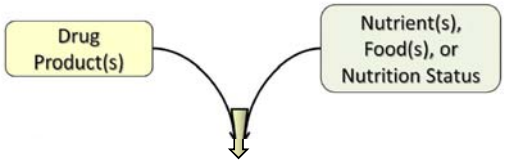
"… reintroducing the topic of drug and nutrition interactions."

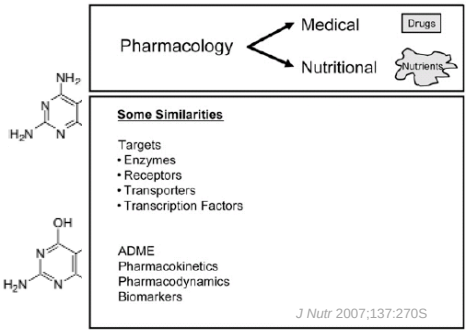
"Drug-Nutrition Interaction"

- An interaction resulting from:
  - A **physical**, **chemical**, **physiologic**, or **pathophysiologic** relationship
- Between:
  - A **drug**
- And:
  - A **nutrient**, **multiple nutrients**, **food** in general, **specific foods** or **components**, or **nutrition status**

Pharmacotherapy 2005;25:1789 / *J Acad Nutr Diet* 2012;112:506 / *J Clin Pharm Ther* 2013;38:269



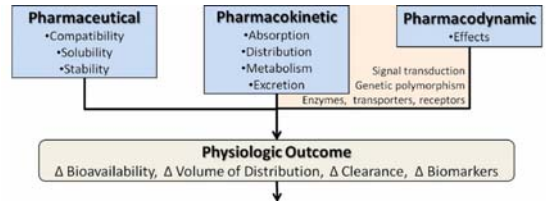
Why Does This Occur?

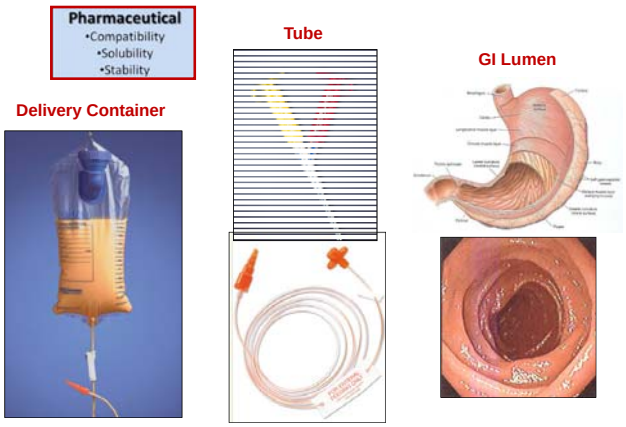


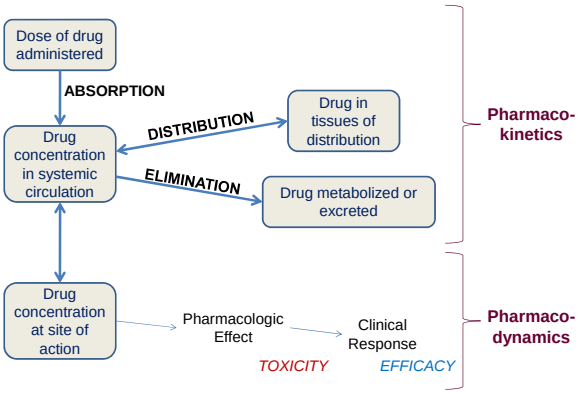
Mechanisms of Interaction

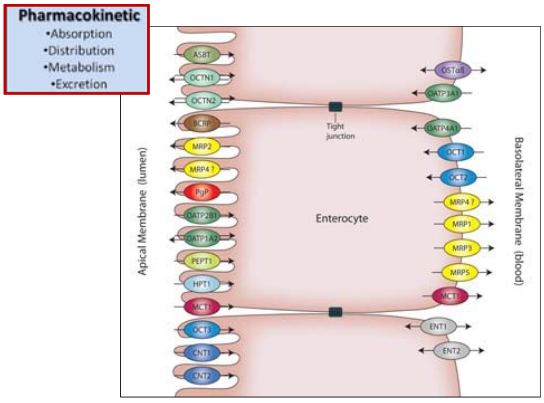
- Related to:
  - Physico-chemical attributes
  - Environmental matrix
  - Location
- Viewed as:
  - Pharmaceutical
  - Pharmacokinetic
  - Pharmacodynamic

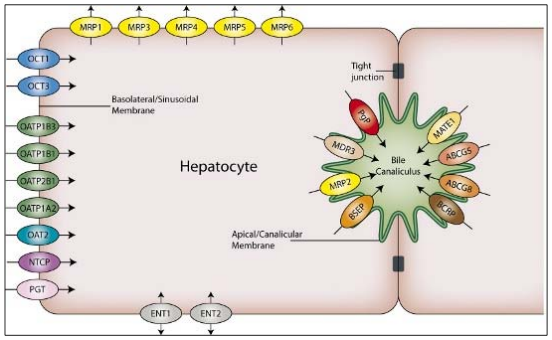
How Does This Occur?

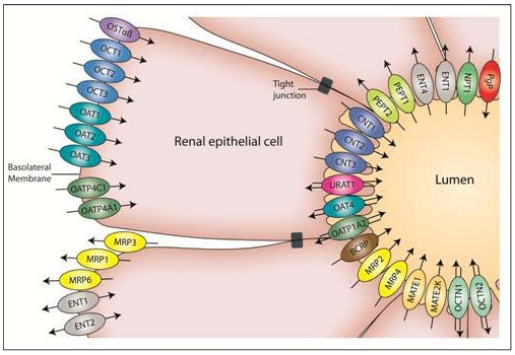








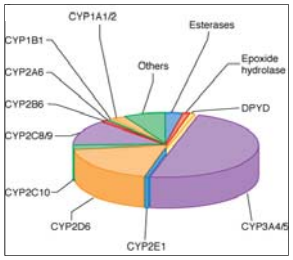




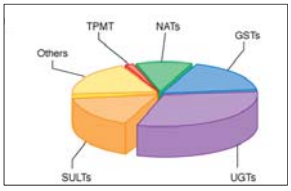
Transporters

Gene Family	Protein	Substrate
ABCB1	MDR1 (Pgp)	Cyclosporine, digoxin
ABCC1	MRP1	Folate, glutathione, adefovir, indinavir
ABCC2	MRP2	Ampicillin
ABCC3	MRP3	Folate, etoposide, methotrexate
ABCG2	BCRP	Cimetidine
SLC5	SMVT	Biotin, lipoic acid, pantothenic acid
SLC6	SERT	Sertraline
SLC15	PEPT	Ampicillin, captopril, cephalexin, valacyclovir
SLC16	MCT	Aromatic amino acids, atorvastatin, salicylate
SLC19	RFC, THTR	Folate, thiamin, methotrexate
SLC21	OATP	Digoxin, prostaglandins
SLC22	OAT, OCT	Acyclovir, salicylates, carnitine
SLC23	SVCT	Ascorbic acid
SLC27	FATP	Fatty acids
SLC31	hCtr	Copper, cisplatin

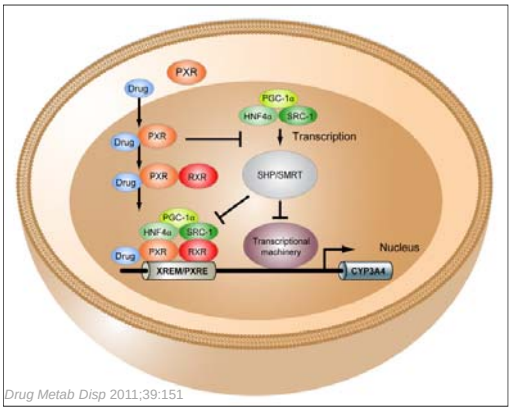
Drug-Metabolizing Enzymes



Phase I



Phase II



Drug Metab Disp 2011;39:151

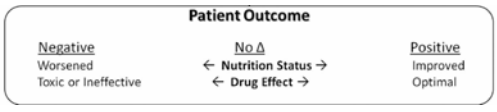
Clinical Consequences

- Altered *disposition* of drug and/or nutrient
  - Absorption, distribution, elimination
- Altered *effect* of drug and/or nutrient
  - Physiologic action at the cellular level

Pharmacotherapy 2005;25:1789 / *J Acad Nutr Diet* 2012;112:506 / *J Clin Pharm Ther* 2013;38:269

The End Result

- Clinically significant
  - Compromises nutrition status
  - Alters therapeutic drug response



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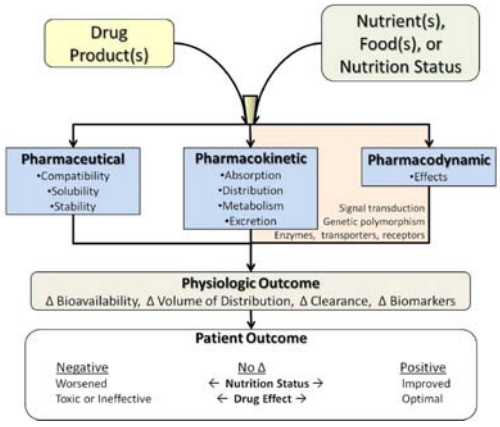


Classification

Precipitating Factor → Object of Interaction

Pharmacotherapy 2005;25:1789 / *J Acad Nutr Diet* 2012;112:506 / *J Clin Pharm Ther* 2013;38:269

Classification

Precipitating Factor →	Object of Interaction
• Nutrition status	Drug
• Food or food component	Drug
• Specific nutrient	Drug
• Drug	Nutrition status
• Drug	Specific nutrient

Pharmacotherapy 2005;25:1789 / *J Acad Nutr Diet* 2012;112:506 / *J Clin Pharm Ther* 2013;38:269

Classification System

- Recognize the *object* of the interaction
- Identify the *precipitating* factor

- Explain the likely *location* and *mechanism*
- Describe potential *consequences*

Site of Interaction	Mechanism of Interaction	Consequence[a]
In drug (or nutrient) delivery device or gastrointestinal lumen	Physicochemical reaction and inactivation	Reduced bioavailability
Gastrointestinal mucosa	Altered transporter and/or enzyme function	Altered bioavailability
Systemic circulation or tissues	Altered transporter, enzyme, or other physiologic function	Altered distribution/effect
Organs of excretion	Antagonism, impairment, or modulation of elimination	Altered clearance

Clinical Examples

Nutrition Status → Drug

- Obesity
  - Lower drug concentration (ertapenem)
  - Higher toxicity (acyclovir)
- Micronutrients
  - Vitamin C deficiency prolongs drug action (pentobarb)
  - Zinc deficiency increases drug toxicity (aspirin)

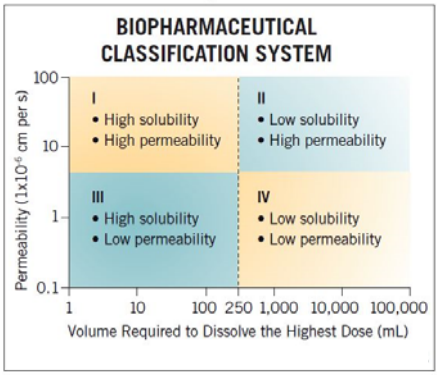
Antimicrob Agents Chemother 2006;50:1222 / *Am J Health-Syst Pharm* 2009;66:1288 / *Proc Soc Exp Biol Med* 1941;48:403 / *Biol Trace Elem Res* 1988;16:43

Food Component → Drug

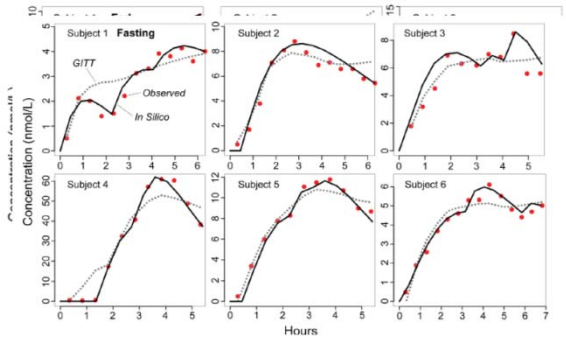
- Enteral nutrition
  - Impairs drug absorption (ciprofloxacin)
- Food
  - Interferes with drug absorption (alendronate)
  - Improves drug absorption (gabapentin-enacarbil)

Int Care Med 1998;24:1047 / *Int J Clin Pharmacol Ther* 2010;48:120 / *J Clin Pharmacol* 2010;50:188 / *J Clin Pharmacol* 2009;49:1403

Figure 1



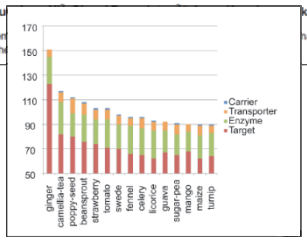
Felodipine ER



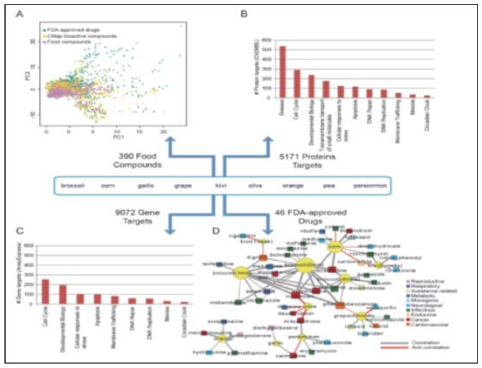
PLoS One 2014;9(9):e108392

RESEARCH ARTICLE

Developing a Molecular Roadmap of Drug-Food Interactions



PLoS Comput Biol 2015;doi:10.1371/journal.pcbi. 1004048

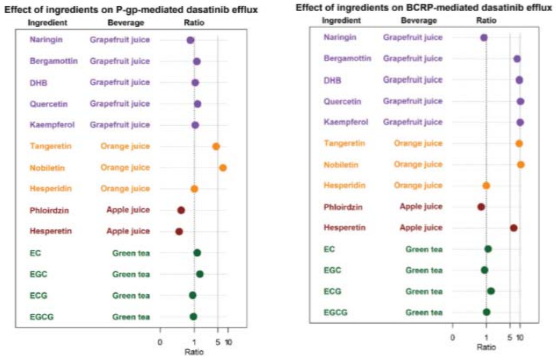


PLoS Comput Biol 2015;doi:10.1371/journal.pcbi. 1004048

Food Component → Drug

- Grapefruit juice
  - Increases drug bioavailability (atorvastatin, dasatinib, sildenafil, simvastatin) and risk for drug toxicity
  - Decreases drug bioavailability (etoposide, levothyroxine)

Int Care Med 1998;24:1047 / *Clin Pharmacol Ther* 2002;71:21 / *Br J Clin Pharmacol* 2005;60:494 / *Br J Clin Pharmacol* 2005;60:494 / *Clin Pharmacol Ther* 2007;81:362 / *Int J Clin Pharmacol Ther* 2010; 48:120 / *J Clin Pharmacol* 2010;50:188 / *J Clin Pharmacol* 2009;49:1403



J Pharm Sci 2015;104:266

Specific Nutrient → Drug

- Iron
  - Reduces drug concentration (doxycycline)
- Vitamin C
  - May reduce drug activity (fluconazole)
- Vitamin D
  - Reduces drug concentration (atorvastatin)
- Daidzein
  - Increases drug bioavailability (theophylline)

J Pharmacokinet Biopharm 1977;5:291 / *Clin Exp Pharmacol Physiol* 2009;36:e40 / *Clin Pharmacol Ther* 2009;85:198 / *Eur J Clin Pharmacol* 2003;58:237

Dietary Supplement → Drug

- ω3 Fatty Acids
  - Improves drug response (irinotecan) or reduces toxicity (paclitaxel)
- St John's wort
  - Reduces drug concentrations (imatinib, irinotecan)
- Ginseng
  - Increases toxicity (imatinib)

JNCI 2002;94:1247 / *Clin Cancer Res* 2003;9:3589 / *Br J Cancer* 2004;91:1651 / *Clin Pharmacol Ther* 2004;76:323 / *Pharmacother* 2004;24:1508 / *Clin Cancer Res* 2007;13:7146 / *Ann Pharmacother* 2010;44:926 /

Influence of 'Polypharmacy' on Nutrition

Key Points:

- About 82-91% of adults use at least one medication on a regular basis many taking five or more
- Medication use is a significant, seldom recognized, factor for altering nutrition status that is not routinely assessed prior to marketing
- Drug-induced poor nutrition status can be manifest by changes in body mass or composition, in metabolic function, or in nutrient biomarkers
- Mechanistically, drugs can impact food preparation/intake, gastrointestinal structure/function, nutrient absorption, distribution, metabolism or elimination

Drug → Nutrition Status

- Quetiapine
  - Alters body weight (weight gain)
- Sorafenib
  - Associated with altered body comp (sarcopenia)
- Capecitabine
  - May cause metabolic disorder (hypertriglyceridemia)
- Many medications
  - Alter GI tract function (taste change, anorexia, stomatitis, nausea, vomiting, diarrhea)

Ann Pharmacother 2006;40:328 / *Pharmacotherapy* 2010;30:1011 / *J Clin Oncol* 2010;28:1054 /

Drug → Specific Nutrient Status

- Carbamazepine
  - Lowers nutrient (vitamin D, biotin) status
- Ezetimibe
  - Reduces nutrient (vitamin E) absorption
- Isoniazid
  - Impairs nutrient (vitamin B_6) status
- Ribavirin + peginterferon-α2b
  - Impairs nutrient (vitamin B_{12}) status

Clin Pharmacol Ther 2006;80:440 / *J Clin Invest* 2005;115:177 / *Mol Pharmacol* 2006;69:56 / Am J Clin Nutr 1989;49:127 / *Neurology* 1997;49:1444 / *Drug Metab Disp* 2010;38:939 / *Eur J Gastroenterol Hepatol* 2009;21:593

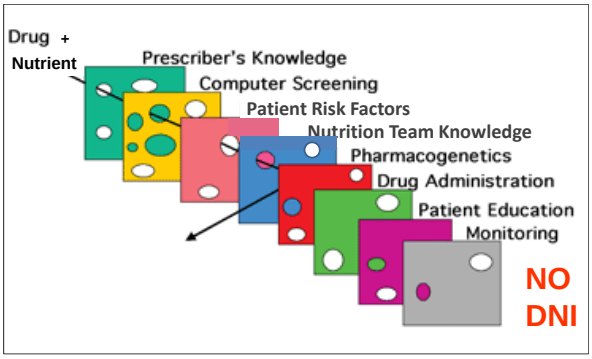
Recommendations

Clinician's Role

- Use the framework to optimize patient outcome
- Clinical observation, analysis, and documentation

Is my patient's *change in nutrition status* related to an interaction?

Is my patient's *unexpected drug effect* related to an interaction?



Risk Factors

- Factors that influence risk for developing a clinically significant drug-nutrient interaction:
  - Age
  - Disease status
  - Genetic variants
  - Medication
  - Nutrition status

Expectation

- *LEAST* Significant
  - Acute use of one drug in a patient with good nutrition status
- *WORST* Scenario
  - Elderly patient, with poor nutrition status, requiring multiple chronic medications

Policy & Procedures

- TJC
  - Less prescriptive than in the past
  - Suggests performing evaluation of DN interactions
- P&T subcommittee or work group
  - High-risk meds (AEDs, antimicrobials, warfarin)
  - High-risk patients (elderly, obese, ICU)
  - Identify patients, assign responsibility, document interventions
  - Periodically review P&P and interventions

Patient Approach

- Who
  - Coordinated, interdisciplinary, team-based approach is considered critical to managing patients with potential drug-nutrition interactions
- How
  - Decision support systems integrated into screening tools and ordering systems could be valuable

Patient Approach

- Thorough patient assessment
  - History and physical examination
- Identify risk potential for interaction
  - Based on risk factors
- Plan to manage
  - Close monitoring
  - Adjust regimen
  - Document

The Drug Interaction Probability Scoring System and Scale

Question	Reply		
	Yes	Unknown or N/A	No
• Are there previous *credible* reports of this interaction in humans?	+1	0	−1
• Is the observed interaction consistent with the known interactive properties of the precipitating factor?	+1	0	−1
• Is the observed interaction consistent with the known interactive properties of the object?	+1	0	−1
• Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	0	−1
• Did the interaction remit upon dechallenge of the precipitating factor with no change in the object?	+1	0	−2
○ If so, did the interaction reappear when the precipitating factor was readministered in the presence of continued use of the object?	+2	0	−1
• Are there reasonable alternative causes for the event?†	−1	0	+1

Question	Reply		
	Yes	Unknown or N/A	No
• Was the object of the interaction detectable in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
• Was the drug interaction confirmed by any objective evidence consistent with the effects on the object (other than concentrations from the previous question)?	+1	0	0
• Was the interaction greater when the precipitating factor was increased or less when the precipitating factor was decreased?	+1	0	−1

Total Score _____

Score	Probability
<2	Doubtful
2-4	Possible
5-8	Probable
>8	Highly Probable

Adapted from: *Ann Pharmacother* 2007;41:674

Conclusions

Conclusions

Drug-Nutrition Interactions

- Relevant to every day clinical practice
- Requires a systematic patient assessment
- Much more research is still needed (mechanisms, management)
- Better incorporate into the process of drug development, regulation, and review

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