Pharmacology and the Elderly

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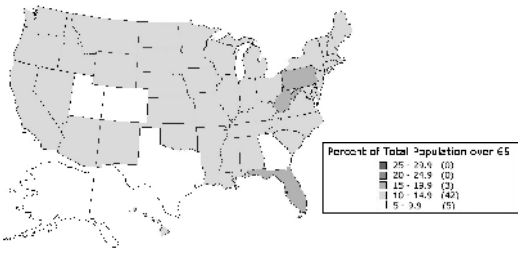
Population Changes

- According to US Census Bureau projections, the elderly population will more than double between 2000 and 2030, growing from 35 million to over 70 million.
- Much of this growth is attributed to the "baby boom" generation which will enter their elderly years between 2010 and 2030.
- The most populous States are also the ones with the largest number of elderly. However, the States with the greatest proportion of elderly are generally different from those with the greatest number.

Source of data: U.S. Census Bureau, "65+ in the United States: 2005," December 2005.
Prepared by the UNC Institute on Aging

The Graying of America

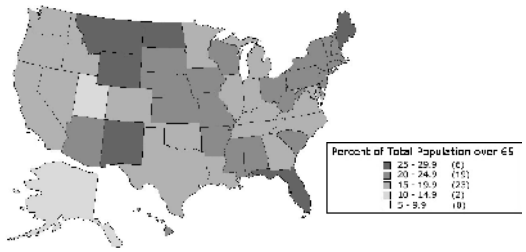
Percent of Total U.S. Population over 65 in 2000



Source of data: U.S. Census Bureau, State Interim Projections by Age and Sex: 2004-2030, 2005.
Prepared by the UNC Institute on Aging

The Graying of America

Percent of Total U.S. Population over 65 in 2030



Source of data: U.S. Census Bureau, State Interim Projections by Age and Sex: 2004-2030, 2005.
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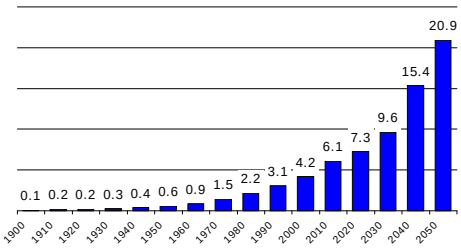
The Oldest Old

- The "oldest old" – those aged 85 and over – are the most rapidly growing elderly age group.
- The oldest old represented 12.1% of the elderly population in 2000 and 1.5% of the total population. In 2050, they are projected to be 24% of elderly Americans and 5% of all Americans.
- Centenarians – those aged 100 or more – represent a small but growing number of elderly Americans. The 1990 census reported 37,000 centenarians, while Census 2000 reported 50,000 centenarians in the United States.

Sources of data: U.S. Census Bureau, "65+ in the United States: 2005," December 2005; U.S. Census Bureau, U.S. Interim Projections by Age, Sex, Race, and Hispanic Origin, 2004.
Prepared by the UNC Institute on Aging

Increases in the Oldest Old

U.S. Population Aged 85+ (in millions)



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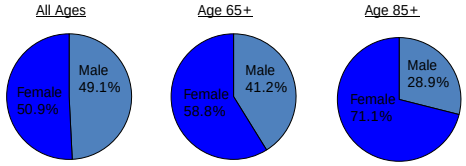
Women Live Longer

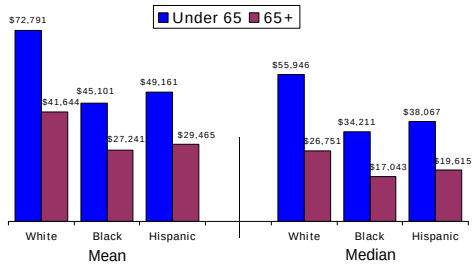
U.S. Population by Gender and Age (2000)



Source of data: U.S. Census Bureau, State Interim Population Projections by Age and Sex: 2004-2030, 2005.
Prepared by the UNC Institute on Aging

Income and Aging

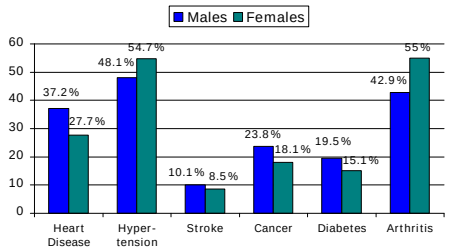
Total Money Income of U.S. Households (2005)



Source of data: U.S. Census Bureau, Current Population Survey: Annual Social and Economic Supplement, Table HINC-07, 2006.
Prepared by the UNC Institute on Aging

Chronic Health Problems

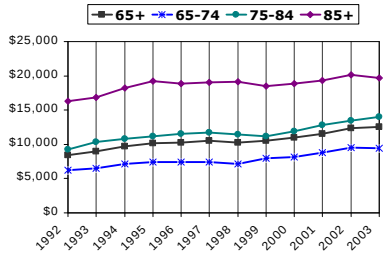
Percent of 65+ with selected conditions, 2003-2004



Source of data: U.S. Census Bureau, Older Americans Update 2006: Key Indicators of Well-Being, May 2006.
Prepared by the UNC Institute on Aging

Rising Health Care Costs

Average annual expenses for Medicare recipients



Source of data: U.S. Census Bureau, Older Americans Update 2006: Key Indicators of Well-Being, May 2006.
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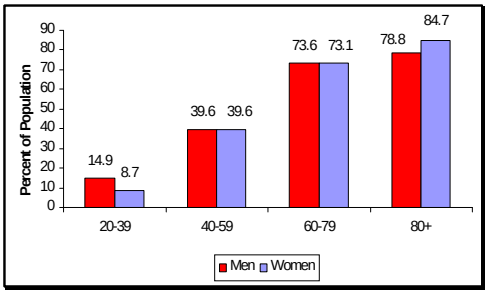
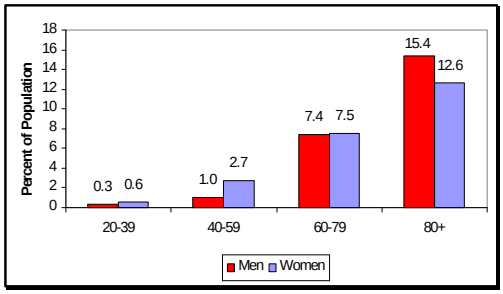
Prevalence of Cardiovascular Disease



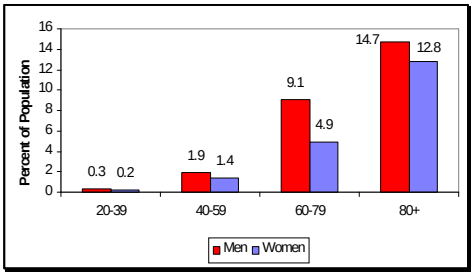
Prevalence of CVD in adults age 20 and older by age and sex (NHANES 2003-2006). Source: NCHS and NHLBI.
These data include coronary heart disease, heart failure, stroke and hypertension.

Prevalence of Stroke



Prevalence of stroke by age and sex (NHANES: 2003-2006).
Source: NCHS and NHLBI.

Prevalence of Heart Failure



Prevalence of heart failure by age and sex (NHANES: 2003-2006). Source: NCHS and NHLBI.

Drug Therapy in the Elderly: General Considerations

- **Decreased volume of distribution**
- **Decreased renal and hepatic clearance**
- **Altered drug pharmacodynamics**
- **Increased comorbidity**
- **Increased risk of drug interactions**
- **Paucity of data from clinical trials**

Effects of Aging on Absorption

- Rate of absorption may be delayed
  - Lower peak concentration
  - Delayed time to peak concentration
- Overall amount absorbed (bioavailability) is unchanged

Factors Affecting Absorption

- Route of administration
- What it taken with the drug
  - Divalent cations (Ca, Mg, Fe)
  - Food, enteral feedings
  - Drugs that influence gastric pH
  - Drugs that promote or delay GI motility
- Comorbid conditions
- Increased GI pH
- Decreased gastric emptying
- Dysphagia

Pharmacokinetics and Aging

- Metabolism:
  - Though liver function tests are unchanged with age, there is some overall decline in metabolic capacity.
  - Decreased liver mass and hepatic blood flow
    - Highly variable, no good estimation algorithm
    - Minimal clinical manifestations

Effects of Aging on Volume of Distribution (Vd)

Aging Effect	Vd Effect	Examples
⇓ body water	⇓ Vd for hydrophilic drugs	ethanol, lithium
⇓ lean body mass	⇓ Vd for for drugs that bind to muscle	digoxin
⇑ fat stores	⇑ Vd for lipophilic drugs	diazepam, trazodone
⇓ plasma protein (albumin)	⇑ % of unbound or free drug (active)	diazepam, valproic acid, phenytoin, warfarin
⇑ plasma protein (α_1-acid glycoprotein)	⇓ % of unbound or free drug (active)	quinidine, propranolol, erythromycin, amitriptyline

Principal Effects of Aging on Cardiovascular Structure and Function

- **Increased vascular + myocardial stiffness**
- **Decreased β-adrenergic and baroreceptor responsiveness**
- **Impaired sinus node function**
- **Impaired endothelial function**

Net effect **-** Large reduction in CV reserve

CV Changes: Max Exercise - Ages 20 and 80 Years

Oxygen consumption	Reduced ~ 50%
AV oxygen difference	Reduced ~ 25%
Cardiac output	Reduced ~ 25%
Heart rate	Reduced ~ 25%
LV stroke volume	Reduced ~ 15% to 25%
LV end diastolic volume	No change or small decrease
LV end systolic volume	Increased ~ 150%
LV ejection fraction	Reduced ~ 15%

Conduction System

- **Increased elastic tissue, collagen and fat, especially in the SA node with marked reduction in SA node pacemaker cells**
- **Calcification of cardiac skeleton**
- **Slowed conduction throughout the heart**
- **Hypertension, CAD, and amyloid infiltration amplify conduction abnormalities**

Arrhythmias

- **Marked increase in frequency of supra-ventricular and ventricular ectopic beats**
- **Short runs of SVT occur in 1/3 of healthy older subjects on Holter studies**
- **Ventricular couplets occur in ~11% and short runs of ventricular tachycardia occur in ~4% of normal persons > 60 yr**
- **In the absence of heart disease, none of these arrhythmias are associated with an adverse prognosis**

Source: Am J Cardiol 1992:70:748-51

Clinical Implications

- **Increased systolic BP and pulse pressure**
- **Increased prevalence of atrial fibrillation, heart failure, especially heart failure with preserved LV function**
- **Increased prevalence of bradyarrhythmias and "sick sinus syndrome"**
- **Worse prognosis associated with all CV diseases**

Other Factors Affecting Drug Metabolism

- Gender
- Comorbid conditions
- Smoking
- Diet
- Drug interactions
- Race
- Frailty

Concepts in Drug Elimination

- Half-life
  - time for serum concentration of drug to decline by 50% (expressed in hours)
- Clearance
  - volume of serum from which the drug is removed per unit of time (mL/min or L/hr)
- Reduced elimination ⇒ drug accumulation and toxicity

Effects of Aging on the Kidney

- Decreased kidney size
- Decreased renal blood flow
- Decreased number of functional nephrons
- Decreased tubular secretion
- Result: ⇓ glomerular filtration rate (GFR)
- Decreased drug clearance: atenolol, gabapentin, H2 blockers, digoxin, allopurinol, quinolones

Estimating GFR in the Elderly

- Creatinine clearance (CrCl) is used to estimate glomerular rate
- Serum creatinine alone not accurate in the elderly
  - ⇓ lean body mass ⇒ lower creatinine production
  - ⇓ glomerular filtration rate
- Serum creatinine stays in normal range, masking change in creatinine clearance

Determining Creatinine Clearance

- Measure
  - Time consuming
  - Requires 24 hr urine collection
- Estimate
  - Cockroft Gault equation

$$\frac{(\text{IBW in kg}) \times (140 - \text{age})}{72 \times (\text{Scr in mg/dL})} \times (0.85 \text{ for females})$$

Example: Creatinine Clearance vs. Age in a 5'5", 55 kg Woman

Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Limitations in Estimating CrCl

- Not all persons experience significant age-related decline in renal function
- Some patient's muscle mass is reduced beyond that of normal aging
  - Suggest using 1 mg/dL if serum creatinine is less than normal (<0.7 mg/dL)
  - Not precise, may underestimate actual CrCl

Pharmacodynamics and Aging

- "What the Drug Does to the Body"
- Generally, lower drug doses are required to achieve the same effect with advancing age.
  - Receptor numbers, affinity, or post-receptor cellular effects may change.
  - Changes in homeostatic mechanisms can increase or decrease drug sensitivity.

Pharmacodynamics (PD)

- Definition: the time course and intensity of pharmacologic effect of a drug
- Age-related changes:
  - ⇑ sensitivity to sedation and psychomotor impairment with benzodiazepines
  - ⇑ level and duration of pain relief with narcotic agents
  - ⇑ drowsiness and lateral sway with alcohol
  - ⇓ HR response to beta-blockers
  - ⇑ sensitivity to anti-cholinergic agents
  - ⇑ cardiac sensitivity to digoxin

PK and PD Summary

- PK and PD changes generally result in decreased clearance and increased sensitivity to medications in older adults
- Use of lower doses, longer intervals, slower titration are helpful in decreasing the risk of drug intolerance and toxicity
- Careful monitoring is necessary to ensure successful outcomes

Consequences of Overprescribing

- Adverse drug events (ADEs)
- Drug interactions
- Duplication of drug therapy
- Decreased quality of life
- Unnecessary cost
- Medication non-adherence

Adverse Drug Events (ADEs)

- Responsible for 5-28% of acute geriatric hospital admissions
- Greater than 95% of ADEs in the elderly are considered predictable and approximately 50% are considered preventable
- Most errors occur at the ordering and monitoring stages

ADE Risk Factors

- Six drugs or > 12 doses a day
- Female
- Low BMI
- High # of comorbidities (Charleson Index Score)
- > 85 years old
- Low Cr. Cl.

Most Common Medications Associated with ADEs in the Elderly

- Opioid analgesics
- NSAIDs
- Anticholinergics
- Benzodiazepines
- Also: cardiovascular agents, CNS agents, and musculoskeletal agents

Adverse Drug Reaction Risk Factors in Older Outpatients. Am J Ger Pharmacotherapy 2003;1(2):82-89.

Patient Risk Factors for ADEs

- Polypharmacy
- Multiple co-morbid conditions
- Prior adverse drug event
- Low body weight or body mass index
- Age > 85 years
- Estimated CrCl <50 mL/min

Drug Reactions

- Drug reactions in the elderly often produce effects that simulate the conventional image of growing old:

unsteadiness	drowsiness
dizziness	falls
confusion	depression
nervousness	incontinence
fatigue	malaise
insomnia	

Drug Reactions

- Drugs most frequently associated with adverse reactions in the elderly:
  - psychotropic drugs-benzodiazepines
  - anti-hypertensive agents
  - diuretics
  - digoxin
  - NSAIDS
  - corticosteroids
  - warfarin
  - theophylline

The Beers Criteria

High Potential for Severe ADE	High Potential for Less Severe ADE
amitriptyline	antihistamines
chlorpropamide	diphenhydramine
digoxin >0.125mg/d	dipyridamole
disopyramide	ergot mesyloids
GI antispasmodics	indomethacin
meperidine	muscle relaxants
methyldopa	
pentazocine	
ticlopidine	

Drug-Drug Interactions (DDIs)

- May lead to adverse drug events
- Likelihood ⇑ as number of medications ⇑
- Most common DDIs:
  - cardiovascular drugs
  - psychotropic drugs
- Most common drug interaction effects:
  - confusion
  - cognitive impairment
  - hypotension
  - acute renal failure

Concepts in Drug-Drug Interactions

- Absorption may be ⇑ or ⇓
- Drugs with similar effects can result additive effects
- Drugs with opposite effects can antagonize each other
- Drug metabolism may be inhibited or induced

Common Drug-Drug Interactions

Combination	Risk
ACE inhibitor + potassium	Hyperkalemia
ACE inhibitor + K sparing diuretic	Hyperkalemia, hypotension
Digoxin + antiarrhythmic	Bradycardia, arrhythmia
Digoxin + diuretic Antiarrhythmic + diuretic	Electrolyte imbalance; arrhythmia
Diuretic + diuretic	Electrolyte imbalance; dehydration
Benzodiazepine + antidepressant Benzodiazepine + antipsychotic	Sedation; confusion; falls
CCB/nitrate/vasodilator/diuretic	Hypotension

Doucet J, Chassagne P, Trivalle C, et al. Drug-drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients. J Am Geriatr Soc 1996;44(9):944-948.

Drug-Disease Interactions

- Obesity alters Vd of lipophilic drugs
- Ascites alters Vd of hydrophilic drugs
- Dementia may ⇑ sensitivity, induce paradoxical reactions to drugs with CNS or anticholinergic activity
- Renal or hepatic impairment may impair metabolism and excretions of drugs
- Drugs may exacerbate a medical condition

Common Drug-Disease Interactions

Combination	Risk
NSAIDs + CHF Thiazolidinediones + CHF	Fluid retention; CHF exacerbation
BPH + anticholinergics	Urinary retention
CCB + constipation Narcotics + constipation Anticholinergics + constipation	Exacerbation of constipation
Metformin + CHF	Hypoxia; increased risk of lactic acidosis
NSAIDs + gastropathy	Increased ulcer and bleeding risk
NSAIDs + HTN	Fluid retention; decreased effectiveness of diuretics

NUTRACEUTICALS

- Plants used as medicines for thousands of yrs
- Used by all major cultures
  - Saw palmetto used in Egypt in the 15th century BC
  - Hippocrates used SJW for mood ailments in the 5th century BC
  - The Greek physician Galen (AD 129–200) devised the first pharmacopoeia describing the appearance, properties and use of many plants of his time
  - Herbal medicines flourished in Europe until the 17th century declined with the scientific revolution
  - European immigrants brought herbal traditions to America and acquired Native American influences
- After~1920, standardized synthetic pharmaceutical drugs replaced herbal therapies, felt to have larger pharmacological effects and more profitable
- Estimated more than 40% of Americans use alternative medical therapies, nutraceuticals (herbals/botanicals) account for a significant proportion
- >120 conventional drugs derived from plant sources

Examples of Conventional Medications with Plant Origins

Drug	Herb common name (Latin name)	
Atropine	Belladona (Atropa belladonna)	
Codeine	Poppy (Papaver somniferum)	
Colchicine	Autumn crocus (Colchicum autumnale)	
Digoxin	Foxglove (Digitalis purpurea)	
Ephedrine	Ephedra (Ephedra sinica)	
Reserpine	Rauwolfia (Rauvolfia serpentine)	
Salicylic acid	Willowbark (Salix purpurea)	
Scopolamine	Jimson weed (Datura stramonium)	
Taxol	Pacific yew (Taxus brevifolia)	
Vincristine	Madagascar periwinkle (Catharanthus roseus)	

Herbs are Drugs

- Though not classified so legally
- Have pharmacological potency and individualized pharmacokinetics
- Have a mixture of ingredients, some active, some "inactive" which yield effects
- Think about them as drugs and you will have less difficulty in counseling

The nutraceutical industry in the US is about $86 billion. This figure is slightly higher in Europe and, in Japan, represents approximately a quarter of their $6 billion total annual food sales - 47% of the Japanese population consume nutraceuticals

Definitions/nomenclature

- Definition of a Nutraceutical: "Food, or parts of food, that provide medical or health benefits, including the prevention and treatment of disease."Dr Stephen DeFelice (Foundation for Innovation in Medicine)-coined the term "Nutraceutical" from "Nutrition" and "Pharmaceutical" in 1989. The term nutraceutical is commonly used in marketing but has no regulatory definition.
  - "nutraceutical"is an umbrella term in the general vernacular to define herbs, supplements, vitamins or, at times, supplements that are actually illegally used FDA-approved drugs bought for specific uses and may cause severe drug interactions and/or death (*e.g.,* dextromethorphan products).
- Dietary supplements-can be "extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders." These substances may be found in preparations such as fresh decoctions (chopped) or whole herbs (steeped as teas), tinctures (fresh or dried herbs preserved in alcohol), vinegar extracts, syrups, glycerites (in vegetable glycerin), miels (in honey), freeze-dried or powdered (which may come in bulk, tablet, troche, paste, capsule, or concentrate forms), suppositories, creams, gels liniments, oils, or compresses.
- Functional foods are foods or food ingredients that may have health benefits in addition to providing traditional nutrients such as protein, carbohydrate, vitamins and minerals.

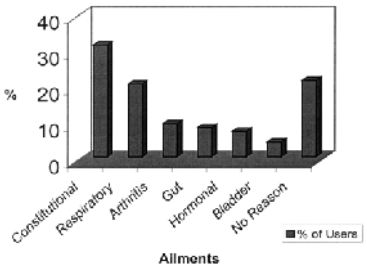
Nutraceutical Categories:

- **Dietary Supplements including botanicals:**
  - Vitamins, minerals, co-enzyme Q, carnitine Ginseng, Gingko Biloba, Saint John's Wort, Saw Palmetto
- **Functional Foods:**
  - Oats, bran, psyllium and lignin's for heart disease and colon cancer
  - Prebiotics - oligofructose for control of intestinal flora
  - Omega-3 milk in prevention of heart disease
  - Canola oil with lowered triglycerides for cholesterol reduction
  - Stanols (Benecol) in reduction of cholesterol adsorption
- **Medicinal Foods:**
  - Health bars with added medications

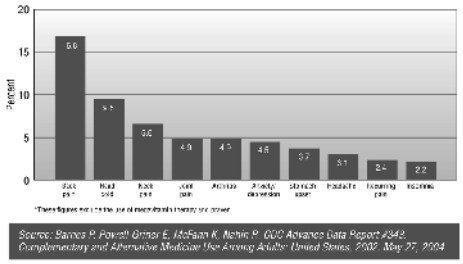
Patients most likely to use Nutraceuticals

- Middle-aged women
- Patients with college education
- Patients with higher income
- Caucasians
- Patients diagnosed with cancer
- The elderly with chronic medical conditions

Reasons for herbal medicine use



Disease/Condition for Which CAM Is Most Frequently Used*



1 Barnes P, Powell-Griner E, McFann K, Nahin R. *CDC Advance Data Report #343*. Complementary and Alternative Medicine Use Among Adults: United States, 2002. May 27, 2004.

10 Top Best Selling Botanicals

According to market reports the top 10 best selling herbs in 2007 were, in rank order:

- Garlic
- Echinacea
- Saw palmetto
- Ginkgo
- Cranberry
- Soy isoflavones
- Ginseng
- Black cohosh
- St. John's wort
- Milk thistle

http://takingcharge.csh.umn.edu

Dennis McKenna, PhD

Drug-Herb Interactions

- Types of Drug Interactions

- – Decreased bioavailability of drug
  - – ↓ Absorption (fibers, mucilage herbs, ↑ p-glycoprotein)
  - – ↑ Metabolism (↑ CYP 450)
  - – ↑ Elimination (laxative or diuretic herbs)
- – Increased bioavailability of drug
  - – ↑ Absorption (Ginger, Cayenne, Black Pepper)
  - – ↓ Metabolism (↓ CYP 450, eg. Grapefruit Juice)
  - – ↓ Elimination (Licorice- anti-diuretic)

St. John's Wort

- Suggested mechanism of antidepressant effect: inhibit reuptake of serotonin, dopamine, and norepinephrine, inhibition of monoamine oxidase, etc
- Has CNS effects on serotonin, NE, DA, COMT
- Possible serotonin syndrome with SSRI's
- No in vivo MAOI effects
- Main concern is drug-herb interactions. Affects cytochrome P450 isoforms increasing metabolic activity

St. John's Wort

- Can reduce levels of cyclosporine (transplant rejection), indinavir (HIV inhibitor), OCP's, digoxin (P-glycoprotein transporter), many others.
- Can also affect coagulation factors
- Half-life 43.1 hrs (hypericin) and 9 hrs (hyperforin)
- Possible prolongation of anesthesia
- Stop at least 5 days before surgery

Echinacea

- Caution: in pts with asthma, atopy, allergic rhinitis, esp ragweed allergy
- Caution: in pts w liver dysfx(↑hepatic microsomal enzymes) or transplants/ immuno-supression
- D/C prior to surgery(↑levels of sedation when taken with midazolam)
- Acts on CYP3A?

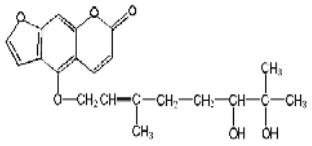
Garlic

- Allicin main ingredient
- Platelet aggregation inhibition
- Also has anti-hypertensive, anti-neoplastic, antilipemic, antibiotic effects
- Like St. John's wort, SOME garlic preparations also induce CYP3A4. Many of the same interactions caused by St. John's wort can also be caused by garlic. But not all garlic preparations seem to cause these interactions- depend on allicin content.
- D/C ~7 days before surgery

Grapefruit Juice: What's the Story?

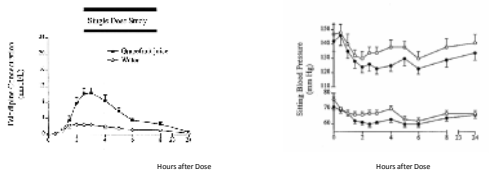
AN INGREDIENT IN GRAPEFRUIT JUICE INHIBITS CYP3A4

6',7', - Dihydroxybergamottin



•Inactivates metabolizing intestinal enzymes resulting in enhanced activity and possible toxicity

Effects of grapefruit juice on felodipine pharmacokinetics and pharmacodynamics.



Dresser GK et al *Clin Pharmacol Ther* 2000;68(1):28–34

Food/Nutrient Effects on Drug Action: Warfarin

- Warfarin (anticoagulant) acts by preventing the conversion of vitamin K to a usable form
- Ingestion of vitamin K in usable form will allow production of more clotting factors, making the drug less effective
- Pts must achieve a balance or steady state between dose of drug and consumption of vitamin K; recommend steady intake of K
- Other foods with anticlotting qualities may also have an effect (garlic, onions, vitamin E in large amounts, and ginseng)

Food/Nutrient Effects on Drug Action: Alcohol

- In combination with some drugs will produce additive toxicity
- With CNS-suppressant drugs may produce excessive drowsiness, incoordination
- Acts as gastric irritant; in combination with other irritants such as NSAIDs may increase chance of GI bleed

Malnutrition Effect on Drugs

- Low albumin levels can make drugs more potent by increasing availability to tissues
  - Lower doses often recommended for persons with low albumin
  - Warfarin and phenytoin are highly protein bound in blood; ↓ albumin can result in poor seizure control (phenytoin) or hemorrhage (warfarin)
- Body composition: obese or elderly persons have a higher ratio of adipose tissue; fat soluble drugs may accumulate in the body ↑ risk of toxicity

Drug-Herb Interactions (HDI)

- **Marked lack of clinical data**
- **HDI Difficult to predict**
  - **Cannot assume no interaction**
  - **Cannot simply ignore patient use**
  - **Cannot blindly recommend against general use**
  - **Cannot ignore potential benefits**

JCAHO Mandate

- The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) issued requirements regarding medication listed in hospital medical record (2005 National Patient Safety Goals FAQs)
- Requires that herbs/supplements/nutraceuticals-includes "alternative and complementary interventions" that may be used individually, in combinations of alternative or complementary interventions, or in combination with medications." be documented in the medical record

Non-Adherence

- Rate may be as high as 50% in the elderly
- Factors in non-adherence
  - Financial, cognitive, or functional status
  - Beliefs and understanding about disease and medications

Polypharmacy and Non-adherence

Factors contributing to Polypharmacy

- Underreporting symptoms
- Use of multiple providers
- Use of others' medications

- Limited time for discussion, diagnostics
- Limited knowledge of geriatric pharmacology
- The power of inertia

Factors contributing to Non-adherence

- Large number of medications
- Expensive medications
- Complex or frequently changing schedule
- Adverse reactions
- Confusion about brand name/trade name
- Difficult-to-open containers
- Limited patient understanding

Prescribing Appropriately

- Review medications regularly and each time a new medication started or dose is changed
- Maintain accurate medication records
- "Brown-bag"-inventory every visit
  - Prescription
  - Over the counter meds
  - Vitamins
  - Herbal supplements

Prescribing Appropriately

- Simple
  - Use least frequent dosing needed
  - Tie to scheduled daily activities, meals, sleep/wake
- Support
  - Educate
  - Medication Flowsheet
  - Encourage use of one pharmacist
  - Enlist family, friends as needed
  - Medication organization equipment
- Survey
  - Periodic review

Prescribing Appropriately

- Determine therapeutic endpoints and plan for assessment
- Consider risk vs. benefit
- Avoid prescribing to treat side effect of another drug
- Use 1 medication to treat 2 conditions
  - Ca++ channel blocker or beta-blocker to treat HTN and angina
  - ACEi to treat HTN, heart failure, renal protection in DM
- Consider drug-drug and drug-disease interactions
- Use simplest regimen possible
- Adjust doses for renal and hepatic impairment
- Avoid therapeutic duplication
- Use least expensive alternative
- Consider non-pharmacologic alternatives

In Summary for Elderly Patients

- Successful pharmacotherapy means using the correct drug at the correct dose for the correct indication in an individual patient
- Age alters PK and PD
- ADEs are common among the elderly
- Risk of ADEs can be minimized by appropriate prescribing
- Start low, go slow,
- . . . (but get to therapeutic levels)