

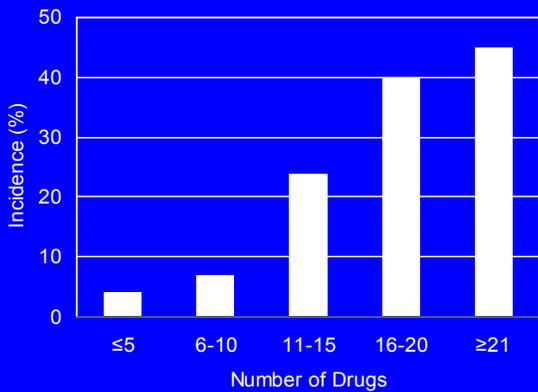
***PHARMACODYNAMICS OF AGING:
NARROWING OF THE THERAPEUTIC
INDEX IN THE FACE OF
THERAPEUTIC OPPORTUNITY***

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Pharmacodynamics of Aging

- Systemic Cardiovascular
- Local Cardiovascular
- Other Effector Systems



(Adapted from Cluff LE et al: JAMA 188:976, 1964)

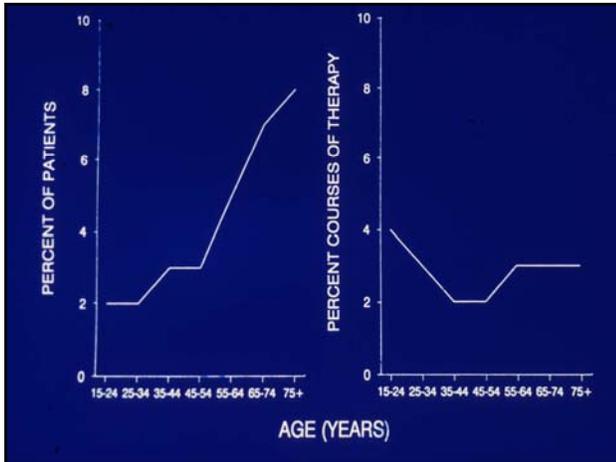


Table 1. Types of the 189 Side-Effects of Drug-Drug Interactions

Type of Effect	%
Neuropsychological disorder and/or cognitive impairment	44.1
Global or orthostatic arterial hypotension	21.8
Acute renal failure secondary to dehydration	15.7
Hypo/hyperkalemia	5.6
Impairment of heart automatism, conduction, or rhythm	4.5
Increased anticholinergic effects	3.3
Other side effects	5.0

Distribution of Office Visits by Number of Drugs Administered or Prescribed for Patients >85 Years of Age

Number of Drugs	Number*	Per Cent
0	2,168,000	32.1
1	1,431,000	21.2
2	797,000	11.8
3	1,084,000	16.0
4	530,000	7.8
5	363,000	5.4
6	160,000	2.4
7	117,000	1.7
8	14,000	0.2
9	73,000	1.1
≥10	27,000	0.4

* Total number of visits = 6,763,000, within rounding error.

Knapp, et al, J Amer Ger Soc. 1984;32:138-143.

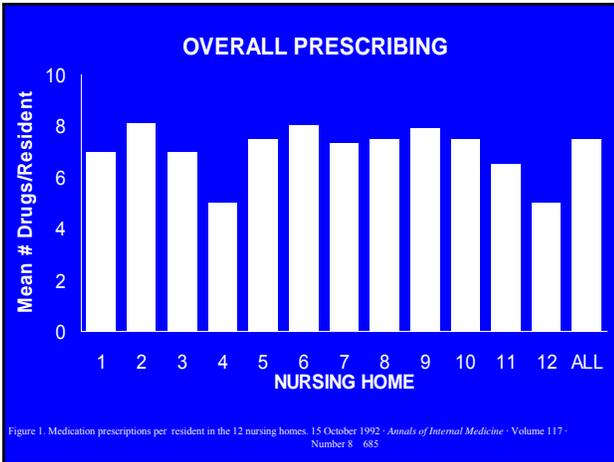
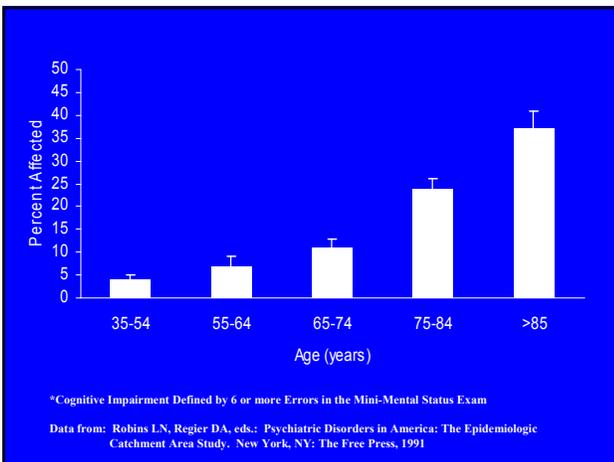


Table 1. Age-related chronic medical conditions*

MEDICAL CONDITION	FREQUENCY PER 1000 PERSONS IN USA		
	Age <45 y	Age 46 - 64 y	Age > 65 y
Arthritis	30	241	481
Hypertension	129	244	372
Hearing impairment	37	141	321
Heart disease	31	134	295
Diabetes	9	57	99
Visual impairment	19	48	79
Cerebrovascular disease	1	16	63
Constipation	11	19	60

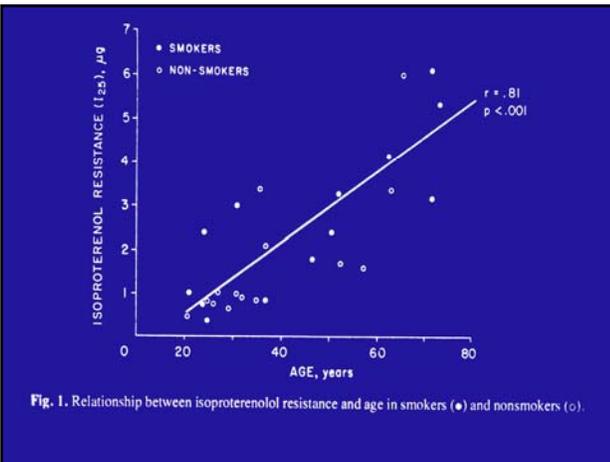
* From Zisook S, Downs NS. *J Clin Psych* 1998, 59 (suppl 4):80-91, data from Dorgan CA, editor. *Statistical record of health and medicine*. New York: International Thompson Publishing Co. 1995.

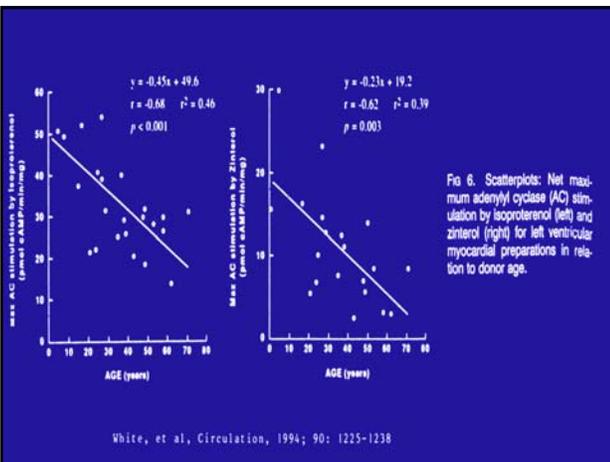


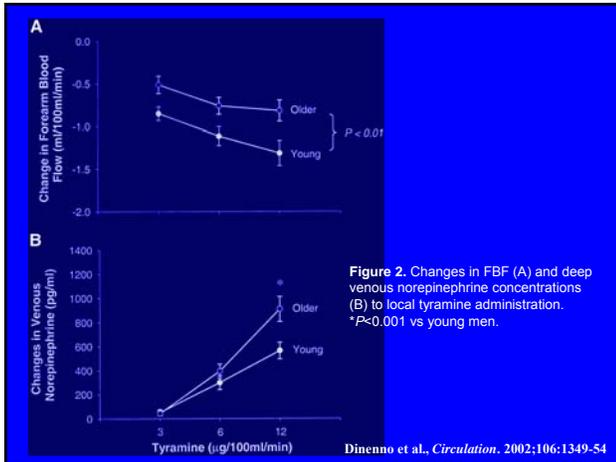
Alterations in the Cardiovascular System of the Elderly

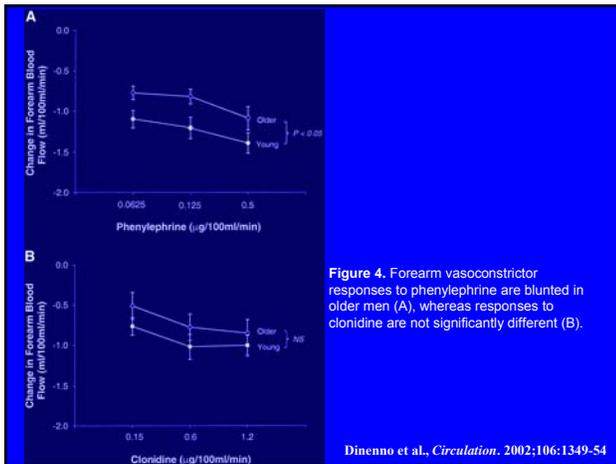
Cardiovascular hemodynamics

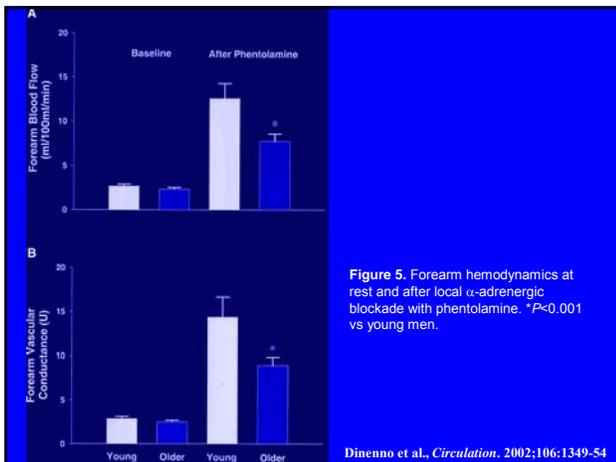
- Tendency to contracted intravascular volume
- Increased peripheral vascular resistance
- Tendency to lowered cardiac output
- Decreased baroreceptor sensitivity
- Increased blood pressure variability
- Suppressed plasma renin activity
- Decreased vascular endothelium production of nitric oxide

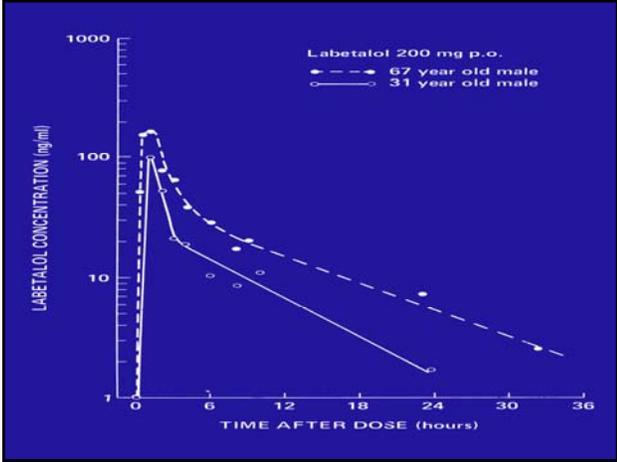


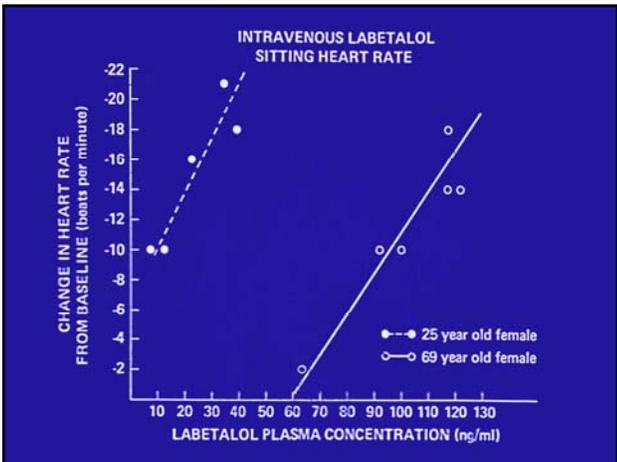


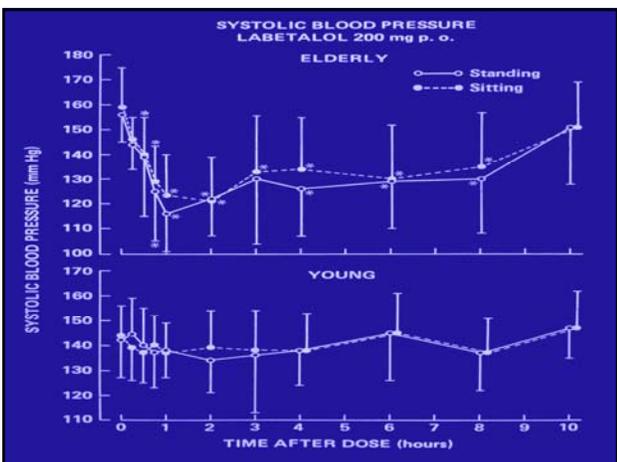


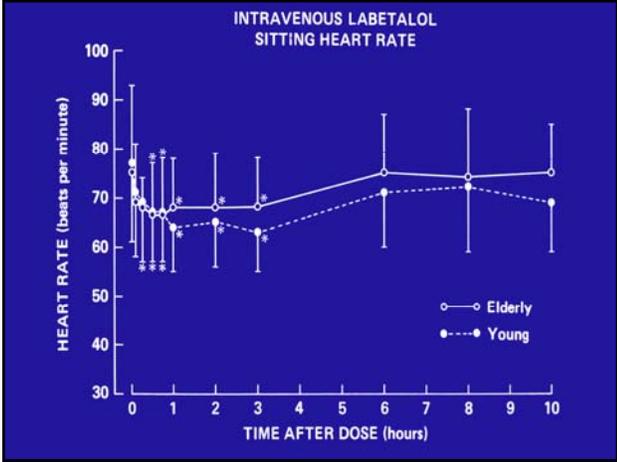






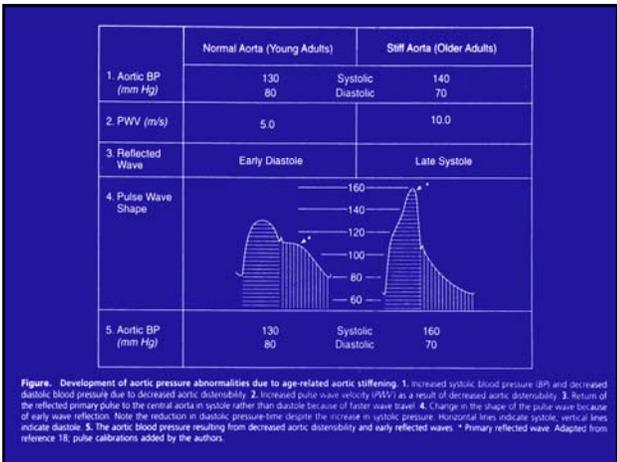


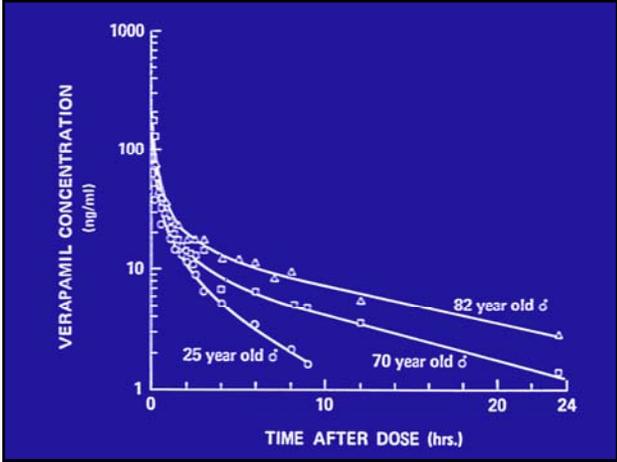


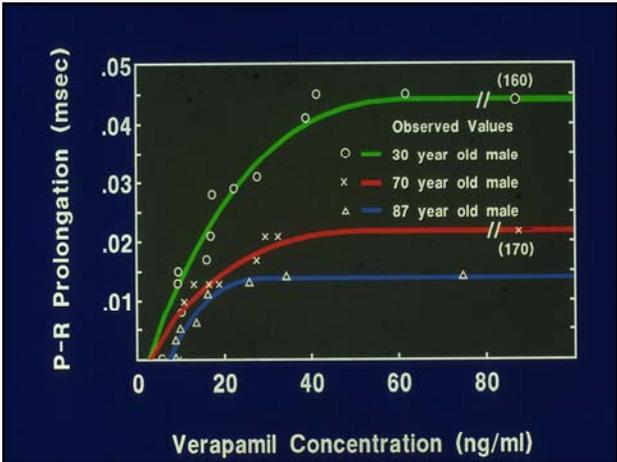


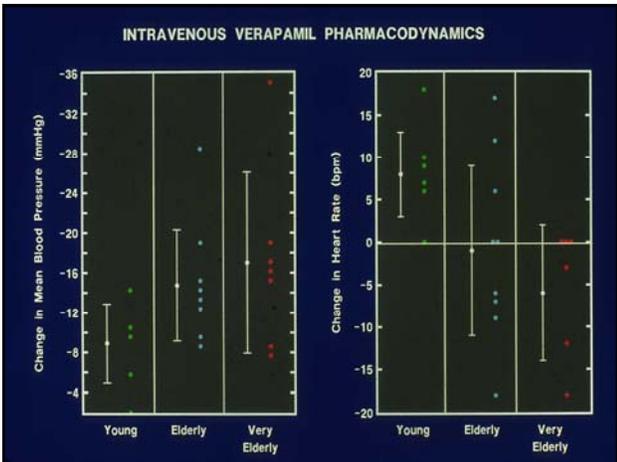
Arterial Changes Related to Aging

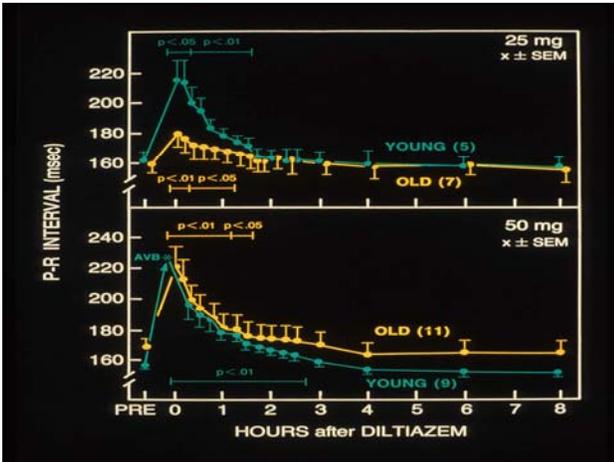
- Increased Calcium and Collagen
- Reduces Elasticity and Compliance
- Increased Pulse Pressure
- Decreased Baroreceptor Sensitivity
- Hyaline Thickening in Arterioles, Small Arteries
- Increased Peripheral Resistance

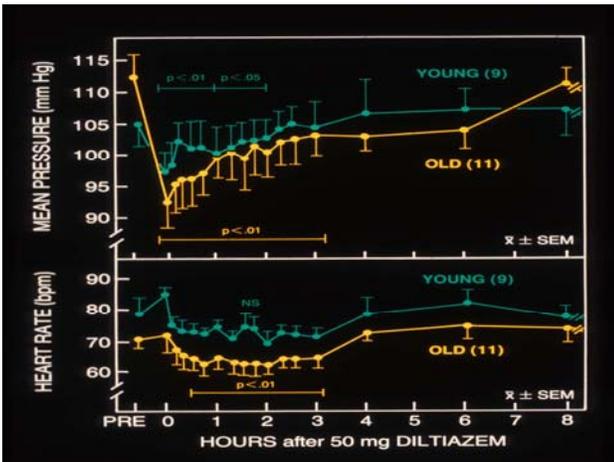






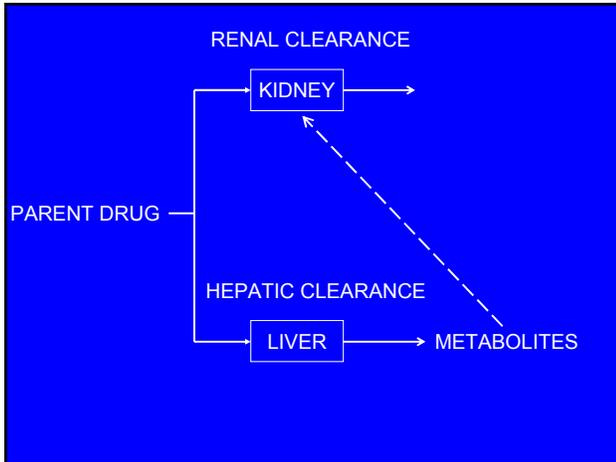


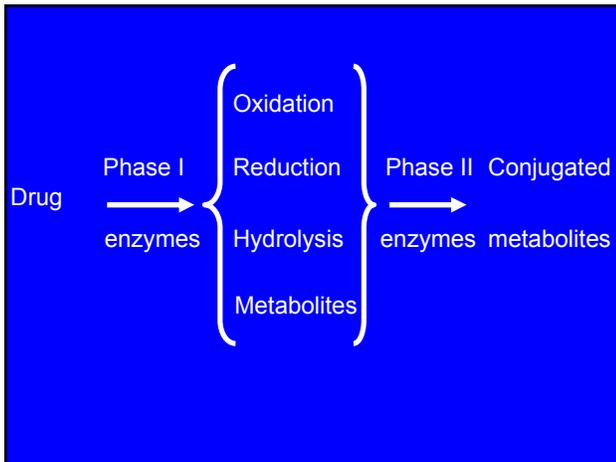




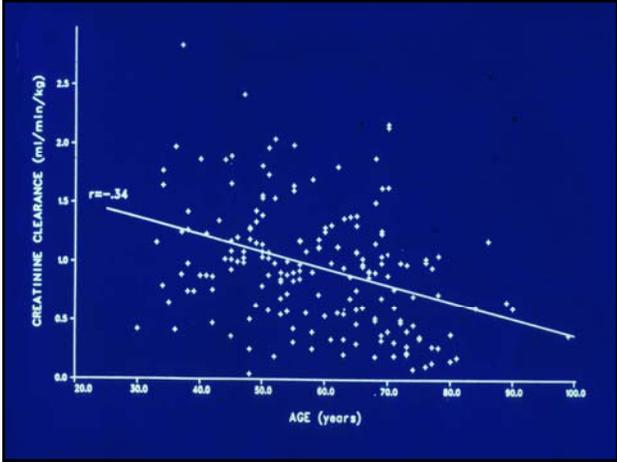
HEART RATE RESPONSES

- DECREASED RATE RESPONSES
 - Parasympathetic
 - Sympathetic
- DIFFERING SENSITIVITY TO CALCIUM CHANNEL BLOCKADE OF THE SINUS NODE





- ### DRUGS METABOLIZED BY KNOWN P450s
- 3A (4)
 - Loratadine (in part)
 - Terfenadine
 - Astemizole
 - Verapamil
 - Nifedipine
 - Diltiazem
 - Felodipine
 - Nimodipine
 - Diazepam
 - Midazolam
 - Triazolam
 - Cyclosporine
 - Tacrolimus
 - Lovastatin
 - Progesterone
 - Testosterone
 - Cisapride
 - Lansoprazole
- Modified from Flockart. *J Psychopharm.*



**PARTIAL LIST OF DRUGS THAT UNDERGO
SIGNIFICANT RENAL EXCRETION IN
HUMANS**

- Amantadine
- Aminoglycoside antibiotics
- Cimetidine
- Digoxin
- Furosemide
- Lithium
- Nitrofurantoin
- Ouabain
- Penicillin antibiotics
- Phenobarbital
- Quinidine
- Sulfonamides
- Tetracycline

COCKCROFT & GAULT EQUATION

$$CL_{Cr} = \frac{(140 - \text{age}) (\text{weight in kg})}{72 (\text{serum Cr in mg/dL})}$$

[reduce estimate by 15% for women]

Terms in red estimate creatinine synthesis rate.

Table 2. Some drugs with decreased clearance in the elderly

ROUTE OF CLEARANCE	REPRESENTATIVE DRUGS
Renal	All aminoglycosides Vancomycin Digoxin Procainamide Lithium Sotalol Atenolol Dofetilide Cimetidine
Single Phase I metabolic pathway CYP3A	Alprazolam Midazolam Triazolam Diltiazem Dihydropyridine calcium channel blockers Lidocaine
CYP2C	Diazepam Phenytoin Celecoxib
CYP1A2	Theophylline

Table 2. Some drugs with decreased clearance in the elderly cont.

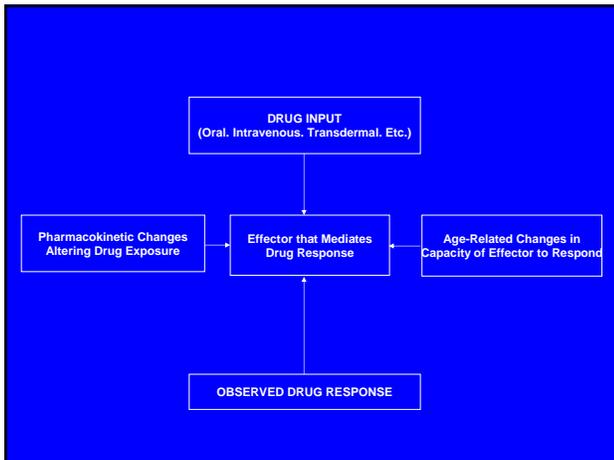
ROUTE OF CLEARANCE	REPRESENTATIVE DRUGS
Multiple Phase I metabolic pathways	Imipramine Desipramine Trazodone Hexobarbital Flurazepam

PHARMACOKINETIC CHANGES IN THE ELDERLY

PROCESS	CHANGE WITH AGE
Gastrointestinal Absorption	none
Drug Distribution	
Central Compartment Volume	none or ▼
Peripheral Compartment Volume	
Lipophilic Drugs	▲▲
Hydrophilic Drugs	▼▼
Plasma Protein Binding	
Binding to Albumin	▼
Binding to α_1 -acid Glycoprotein	none or ▲

PHARMACOKINETIC CHANGES IN THE ELDERLY

Process	Change with Age
Drug Elimination	
Renal Elimination	▼▼
Hepatic Elimination	
Phase I Reactions	▼
CYP3A	▼
CYP1A2,2D6,2C9,2C19,2E1	↔ or ▼
Phase II Reactions	
Glucuronidation	↔
Sulfation	↔
Acetylation	↔



The Goals for Treating the Older Patient

- ↓ Morbidity & Mortality
- Avoid or Minimize Drug-Related Problems
- Improve the Quality of Life

By the time a man gets well into the seventies,
his continued existence is a mere miracle

R.L. Stevenson: AES Triplex

**“Come grow old along with me,
the best of things are yet to be.”**

“Rabbi Ben Ezra,”
Robert Browning (1812 – 1889)
