Drug Interactions

Bruce G. Pollock, M.D., Ph.D.

Professor of Psychiatry, Pharmacology and Nursing

Chief, Academic Division of Geriatrics and Neuropsychiatry

University of Pittsburgh Medical Center

Self Assessment Question 1

- Compared to the rate of ADRs among adults age 20-29, the rate among adults age 80+ is which of the following:

A. Similar

B. Twice as great

C. Greater than 5 x as frequent

D. Greater than 10 x as frequent

Self Assessment Question 2

- Commonly prescribed psychiatric medications are substrates of which of the following C450 enzymes?

A. 1A2

B. 2D6

C. 3A4

D. All of the above

Self Assessment Question 3

- Which of the following 3A inhibitors can be associated with significant drug/drug interactions when co-administered with a 3A substrate?

A. Ketoconazole

B. Erythromycin

C. Calcium antagonists

D. Any of the above

Self Assessment Question 4

- Which of the following medications has anticholinergic properties?

A. Furosemide

B. Warfarin

C. Ranitidine

D. Digoxin

E. All the above

Self Assessment Question 5

- The risk of drug/drug interactions is increased by which of the following?

A. Narrow therapeutic index of co-administered agent

B. Highly potent co-administered enzyme inducer or inhibitor

C. Greater sensitivity to adverse effects in elderly patients

D. Co-administration of multiple drugs

E. All the above

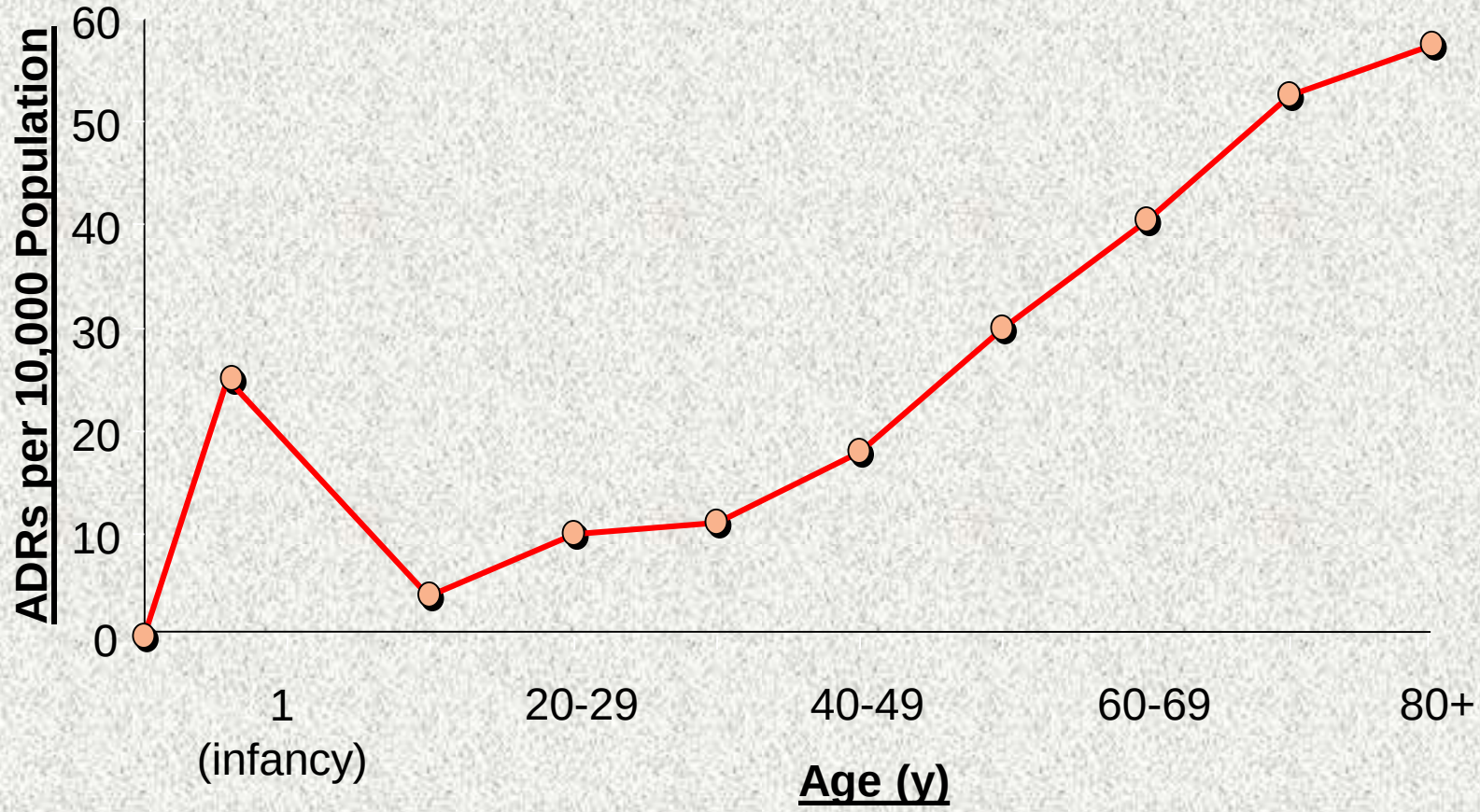
Major Teaching Points

- Elderly patients are highly vulnerable to drug/drug interactions
- Two important types of drug/drug interactions to understand and prevent are:
  - Pharmacokinetic interactions based on drug metabolism through the cytochrome P450 system
  - Pharmacodynamic interactions based on additive serum anticholinergicity

Brief Outline

- Adverse drug interactions' relationship to age, location, number of prescribed drugs
- Cytochrome P450 drug interactions
- Drug interactions based on additive serum anticholinergicity
- Coping with drug/drug interactions
- Suggested readings

Adverse Drug Reactions (ADRs) as a Function of Increasing Age



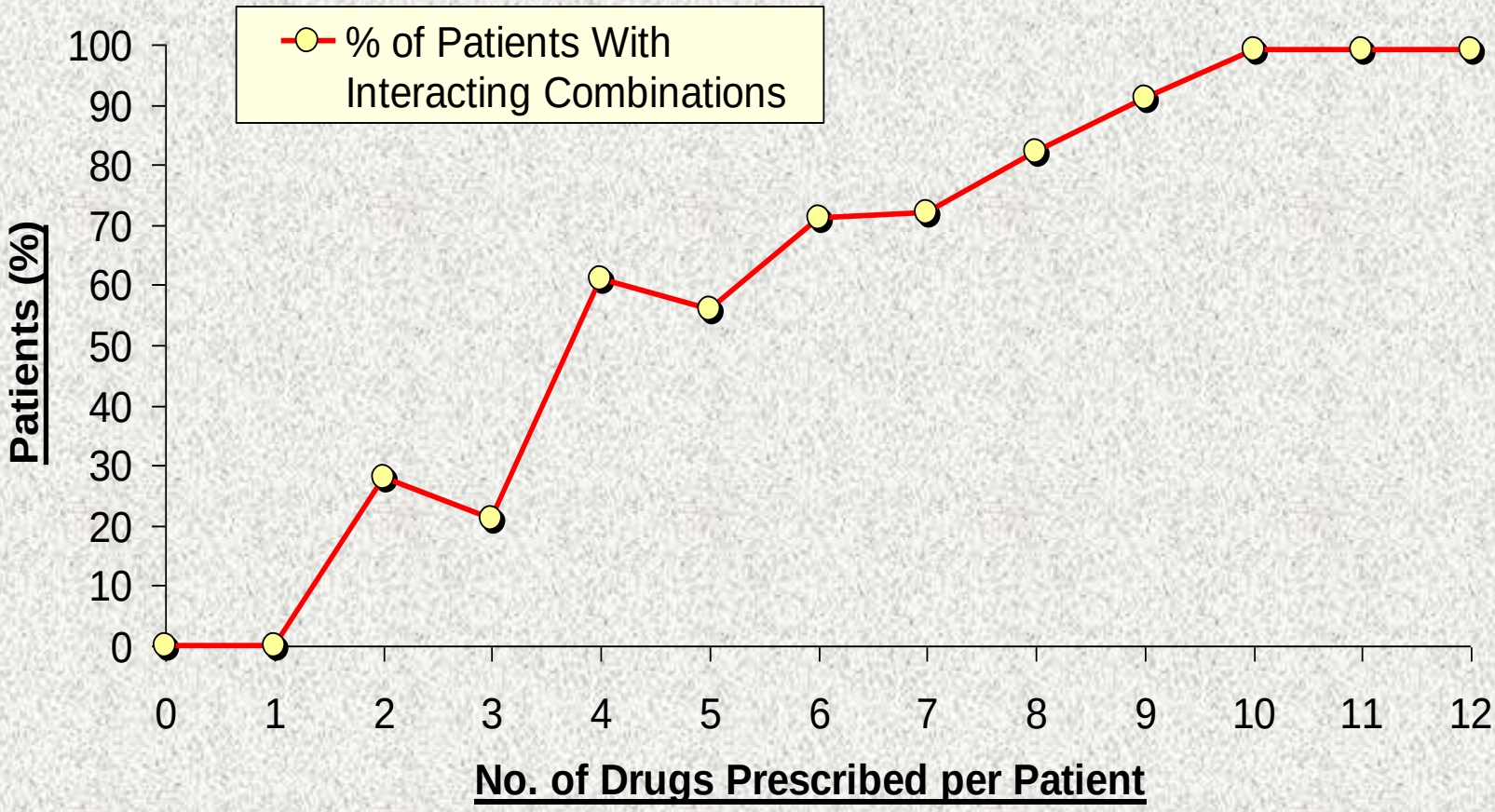
Ghose K. Drugs Aging. 1991;1:2-5.

Adverse Drug Reactions in the Nursing Home

- Psychoactive medications (antipsychotics, antidepressants, and sedatives/hypnotics) and anticoagulants were the medications most often associated with preventable ADRs

Gurwitz JH, et al. *Am J Med.* 2000;109:87-94.

Relationship Between Prescribing Rate and Prevalence of Potential Drug Interactions

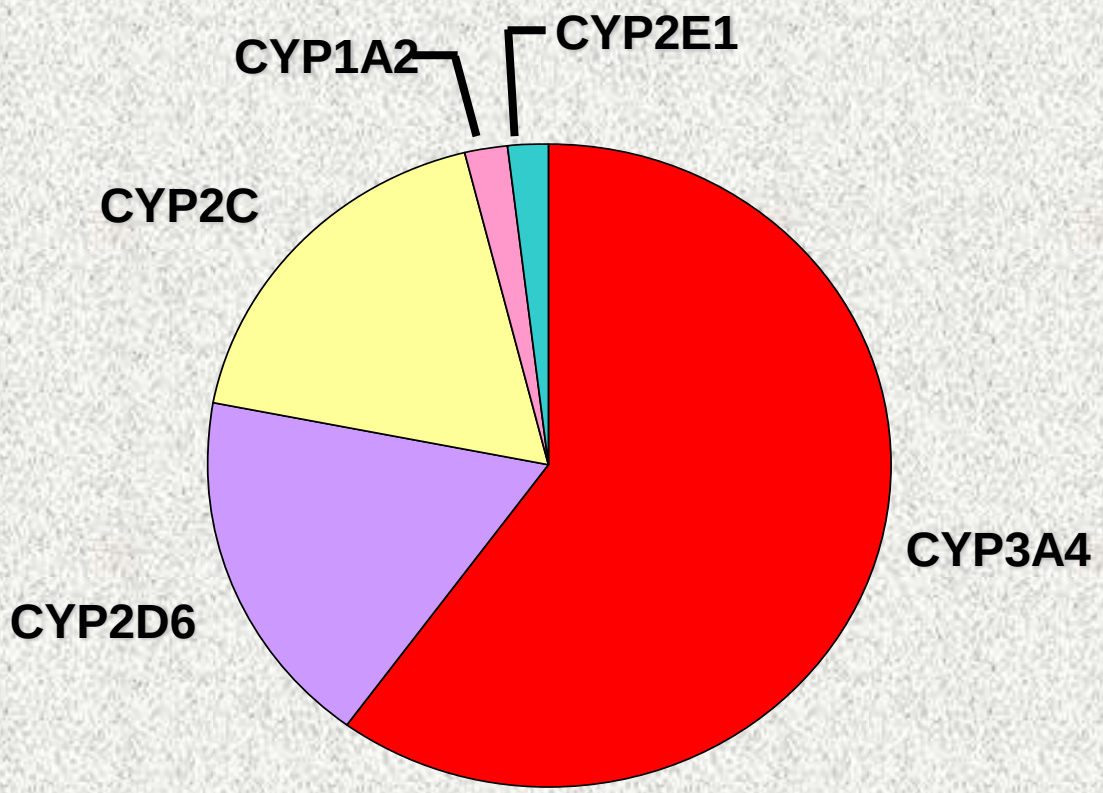


Nolan L, O'Malley K. *Age Ageing.* 1989;18:52-56.

Clinical Dilemma

- Number of possible drug interactions too large to memorize
- Difficult to determine which interactions are important
- Conflicting promotional claims

Cytochrome P-450 Enzyme Subtypes



CYP isoform	Representative substrates
1A2	Caffeine, theophylline, tacrine
2B6	Propofol, bupropion
2C9	Phenytoin, S-warfarin, tolbutamide, NSAIDs
2C19	Omeprazole (partial contributor to many)
2D6	Some CNS and cardiac drugs
2E1	Fluranes, chlorzoxane
3A	(many)

CYP3A

- High abundance
- Present in G.I Tract
- No polymorphism, but high individual variability

CYP3A Substrates

Complete	Partial
Benzodiazepines (short $t_{1/2}$)	Zolpidem
Buspirone	Amitriptyline
Trazodone	Imipramine
Nefazodone	Sertraline
Cyclosporine	Citalopram
Statins	Diazepam
Calcium antagonists	Clozapine
Quinidine	
Protease Inhibitors	
Sildenafil	

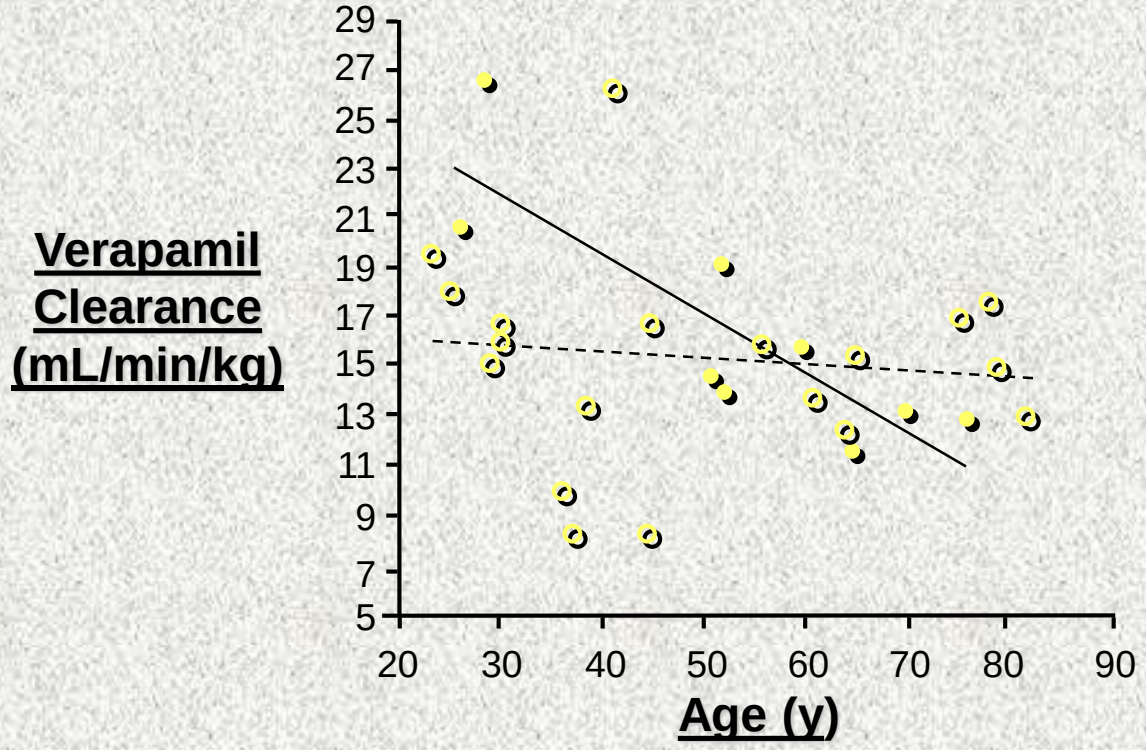
CY3A Inhibitors

High Risk	Moderate Risk
Ketoconazole	Fluconazole
Itraconazole	Fluvoxamine
Nefazodone	Fluoxetine
Ritonavir (acute)	Grapefruit juice
Erythromycin	Other HIV PIs
Clarithromycin	Delavirdine
Calcium Antagonists	Cimetidine

CYP3A Inducers

- Rifampin
- Barbiturates
- Carbamazepine
- Ritonavir (chronic)
- Nevirapine
- Hypericum perforatum
  (St. John's Wort)

CYP3A4: Verapamil



Racemic verapamil clearance data are plotted versus age for women (*solid circles*) and men (*open circles*). The *solid line* represents the regression of clearance versus age relationship in women (*P* < .004) and the *broken line* represents the regression of clearance versus age in men (regression not significant).

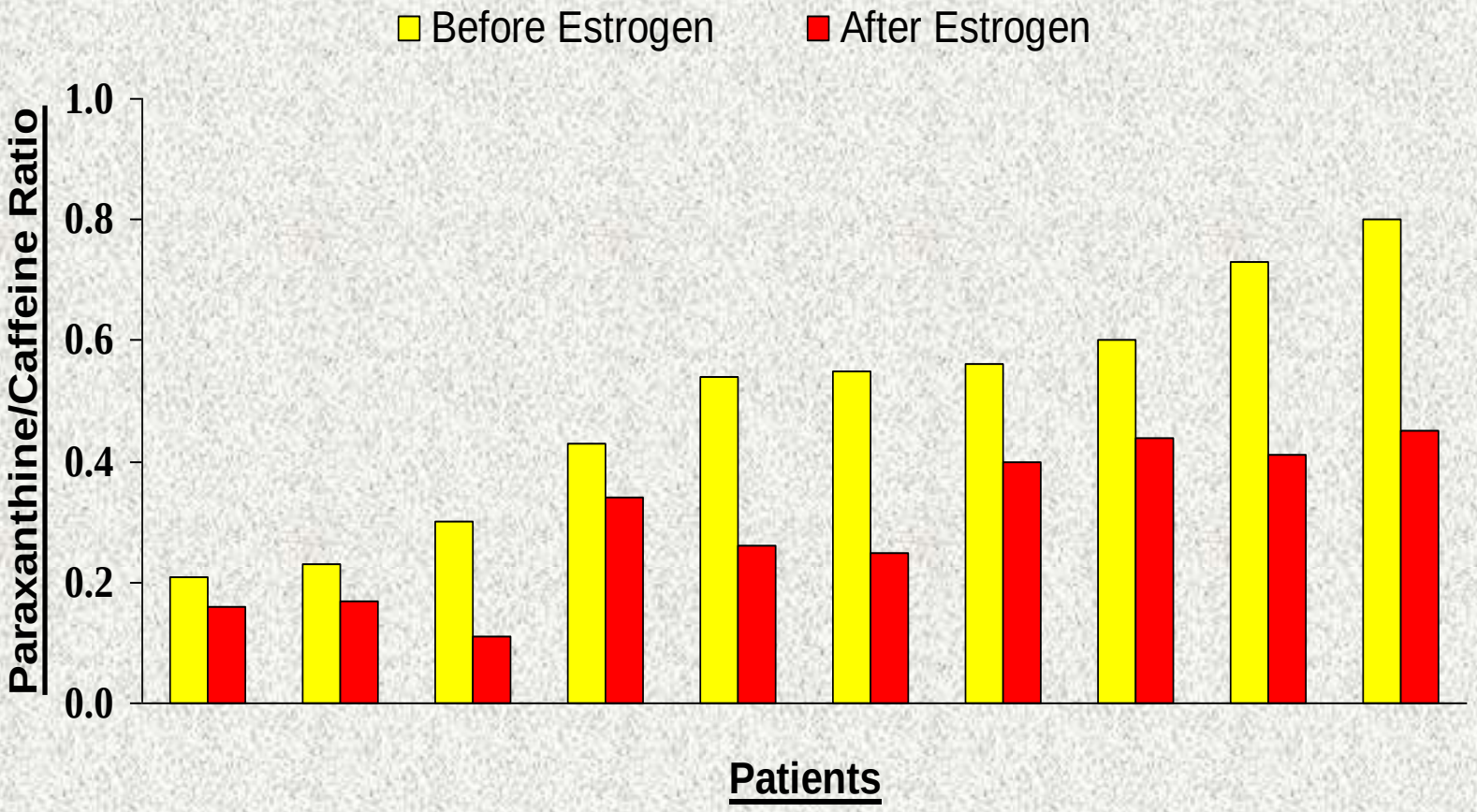
Schwartz JB, et al. *Clin Pharmacol Ther*. 1994;55:509-517.

St. John's Wort

- **Induces P-glycoprotein**
  - **↓ Digoxin by 30%**
- **Induces CYP3A4**
  - **↓↓ Indinavir**
  - **↓↓ Cyclosporine**
  - **↓ Statins**

Ruschitzka F, et al. *Lancet.* 2000;355(9203):548-549.
Piscitelli SC, et al. *Lancet.* 2000;355(9203):547-548.

CYP1A2 Phenotyping (Caffeine) Results Before and After Estrogen Treatment of Healthy Postmenopausal Women



Pollock BG, et al. *J Clin Psychopharmacol.* 2000;20:137-140.

Cytochrome P-450: Enzymes and Selected Substrates

1A2	2C	2D6	3A4
Theophylline	Phenytoin	Codeine	Antihistamines
Warfarin	Warfarin	Venlafaxine	Calcium channel blockers
Antipsychotics	Amitriptyline	Trazodone	Carbamazepine
Benzodiazepines	Clomipramine	Risperidone	Cisapride
Fluvoxamine	Omeprazole	Haloperidol	Corticosteroids
		Tramadol	Cyclosporine
		β-Blockers	Fentanyl
			Protease inhibitors
			Statins
			Triazolo-benzodiazepines

Michalets EL. *Pharmacotherapy*. 1998;18:84 -112.
Cupp MJ, Tracy TS. *Am Fam Physician.* 1998;57:107-116.

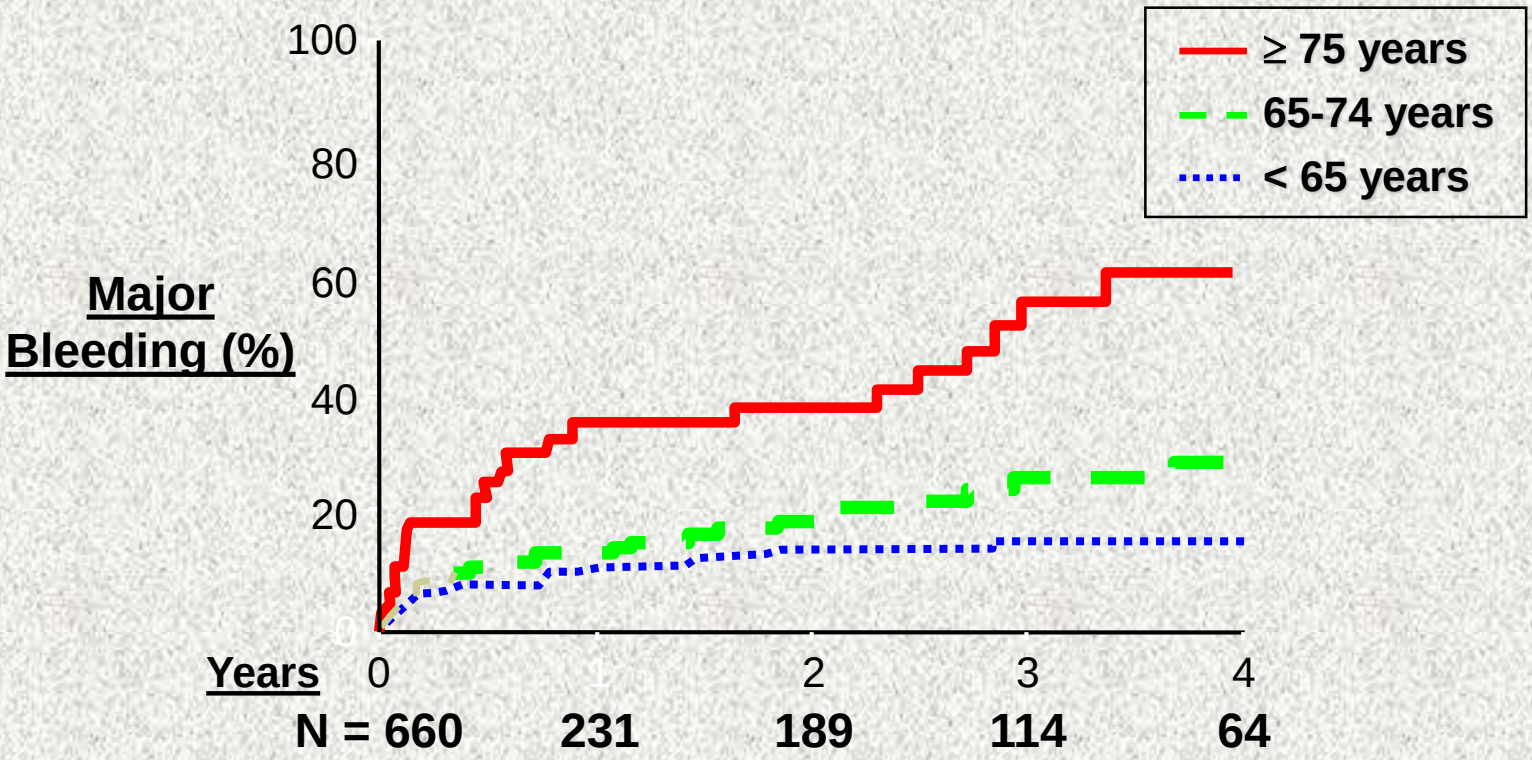
Inhibition of Human Cytochrome P-450 Isoenzymes by Newer Antidepressants

	Cytochrome P-450 Isoenzyme					
Antidepressant	**1A2**	**2C9**	**2C19**	**2D6**	**2E1**	**3A**
Fluoxetine	+	++	+ to ++	+++	—	+
Norfluoxetine	+	++	+ to ++	+++	—	++
Sertraline	+	+	+ to ++	+	—	+
Desmethylsertraline	+	+	+ to ++	+	—	+
Paroxetine	+	+	+	+++	—	+
Fluvoxamine	+++	++	+++	+	—	++
Citalopram	+	0	0	0	0	0
R-Desmethylcitalopram	0	0	0	+	0	0
Escitalopram	0	0	0	0	0	0
S-Desmethylcitalopram	0	0	0	0	0	0
Nefazodone	0	0	0	0	—	+++
Triazoledione	0	0	0	0	—	+
Hydroxynefazodone	0	0	0	0	—	+++
Venlafaxine	0	0	0	0	—	0
***O*-Desmethylvenlafaxine**	0	0	0	0	—	0
Mirtazapine	0	—	—	+	—	0

0 = minimal or zero inhibition.
\+ = mild inhibition.
++ = moderate inhibition.
+++ = strong inhibition.
— = no data available.

Greenblatt DJ, et al. *J Clin Psychiatry*. 1998;59(suppl 15):19-27.
von Moltke LL, et al. *Drug Metab Disposition.* 2001;29:1102-1108.

Incidence of Bleeding During Anticoagulant Therapy



Beyth RJ, Schorr RI. *Drugs Aging*. 1999;14:231-239.

American Medical Directors Association "Top 10" Drug Interactions

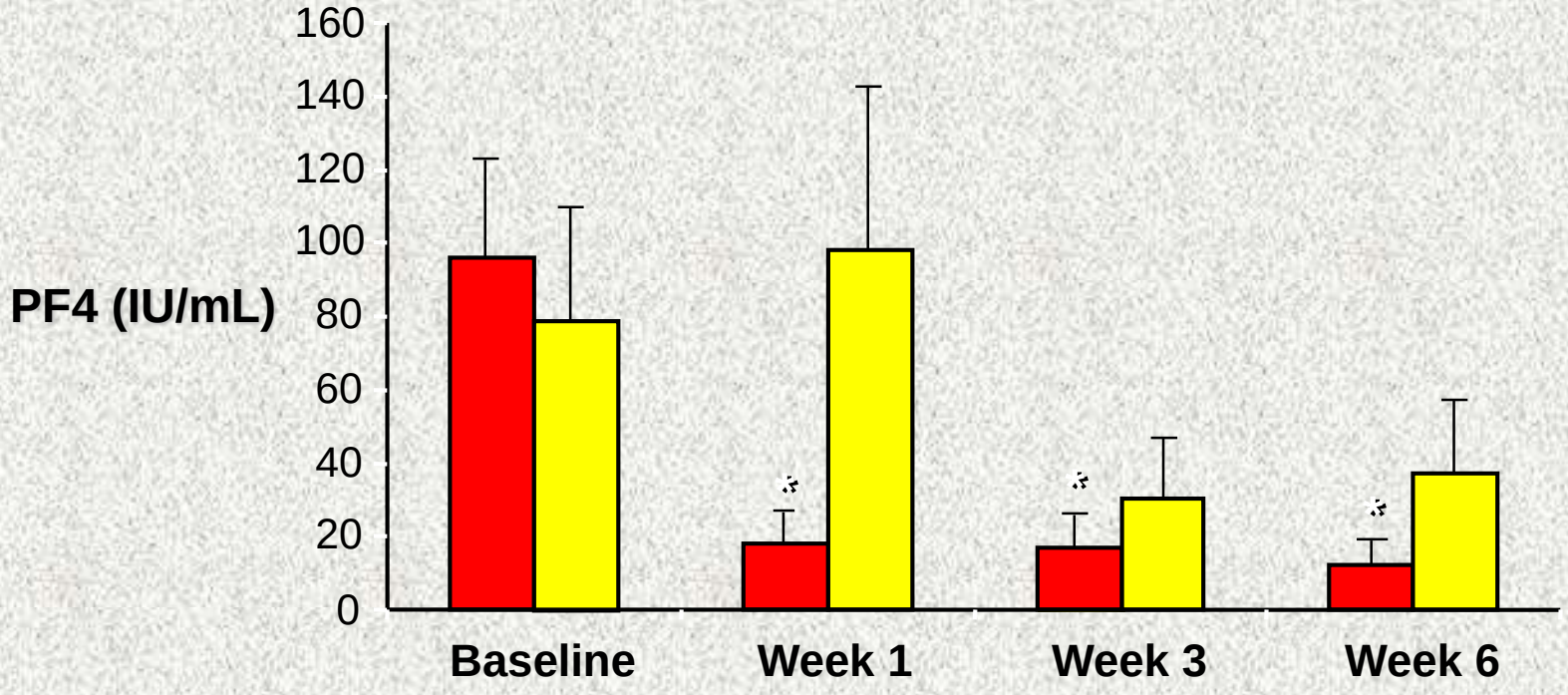
Warfarin with:

- NSAIDs
- Macrolides
- Phenytoin
- Sulfa Drugs
- Quinolones

Warfarin Metabolism

***S*-warfarin**	**CYP2C9**	**Fluoxetine** **Fluvoxamine** **(Sertraline)** **(Paroxetine)**
***R*-warfarin** **(major pathway)**	**CYP1A2**	**Fluvoxamine** **(Fluoxetine)** **(Sertraline)** **(Paroxetine)**
***R*-warfarin** **(minor pathway)**	**CYP2C19** **& CYP3A4**	

Platelet Activation in Depressed Patients With Ischemic Heart Disease After Paroxetine or Nortriptyline Treatment



- Effect of paroxetine ( ) and nortriptyline ( ) on PF4 plasma levels in depressed patients with ischemic heart disease. Data presented are mean ± SEM

****P* < .05 versus baseline levels.**

PF4 = platelet factor 4.

Pollock BG, et al. *J Clin Psychopharmacol.* 2000;20:137-140.

Anticholinergic Medications Commonly Prescribed in the Elderly

Commonly Prescribed in the Elderly

- Furosemide
- Digoxin
- Theophylline
- Warfarin
- Prednisolone
- Triamterene and hydrochlorothiazide
- Nifedipine
- Isosorbide
- Codeine
- Cimetidine
- Captopril
- Ranitidine
- Dipyridamole

Tune L, et al. *Am J Psychiatry.* 1992;149:1393-1394.

Age, Sex, Education, Number of Medications, MMSE score, and SA (N = 201)

Mean (SD) Age	78.2 (5.2)
Female (N, %)	122 (60.7%)
Education (< high school)	38.3 %
Number of Medications	5.2 (3.4)
Number of Anticholinergic Medications	0.91 (1.23)
MMSE	26.8 (3.5)
SA (pmol/mL) — Mean (SD)	1.45 (1.10)
Median (Range)	1.25 [0-5.70]

MMSE = Mini-Mental State Examination.
SA = serum anticholinergicity.

Mulsant BH, Pollock BG, et al. *Am J Ger Psychiatry.* 2002;10(suppl):58.

Logistic Regressions: SA as a Continuous Variable

		OR	95% CI
Age		1.20	(1.09, 1.32)
Sex	Male	1.00	---
	Female	1.15	(0.37, 3.57)
Education	< high school	1.00	---
	≥ high school	0.39	(0.13,1.21)
# of Rx	0-3	1.00	---
	4-6	1.46	(0.39,5.44)
	> 6	1.21	(0.29,5.05)
SA		16.71	(2.02, 138.29)

SA = serum anticholinergicity.

Mulsant BH, Pollock BG, et al. *Am J Ger Psychiatry.* 2002;10(suppl):58.

Elderly Are More Difficult to Treat Safely

- Pharmacokinetic changes result in higher and more variable drug concentrations
- The elderly often take multiple medications
- Greater sensitivity exists to a given drug concentration
- Homeostatic reserve may be impaired

When To Worry About Drug Interactions

- Narrow therapeutic index of victim
- Highly potent inducer or inhibitor

Coping With Drug Interactions

- Anticipation and prevention
  - Highly potent inducer/inhibitor
  - Narrow therapeutic index of victim
  - Victims dependent on one metabolic enzyme/transport protein

Coping With Drug Interactions

- Recognize interaction potential of "nondrugs" (herbals)
- Keep knowledge base current
- Consider interactions whenever the clinical picture unexpectedly changes

Suggested Readings

- **Pollock BG: Geriatric Psychiatry: Psychopharmacology: General Principles. In: Sadock BJ, Sadock VA, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry/VII. Baltimore: Williams & Wilkins 2000 pp 3086-3090.**

- **DeVane CL, Pollock BG: Pharmacokinetic considerations of antidepressant use in the elderly. J Clin Psychiatry 60[suppl 20]:38-44, 1999.**

Self Assessment Question 1

- Compared to the rate of ADRs among adults age 20-29, the rate among adults age 80+ is which of the following:

A. Similar

B. Twice as great

C. Greater than 5 x as frequent

D. Greater than 10 x as frequent

Self Assessment Question 2

- Commonly prescribed psychiatric medications are substrates of which of the following C450 enzymes?

A. 1A2

B. 2D6

C. 3A4

D. All of the above

Self Assessment Question 3

- Which of the following 3A inhibitors can be associated with significant drug/drug interactions when co-administered with a 3A substrate?

A. Ketoconazole

B. Erythromycin

C. Calcium antagonists

D. Any of the above

Self Assessment Question 4

- Which of the following medications has anticholinergic properties?

A. Furosemide

B. Warfarin

C. Ranitidine

D. Digoxin

E. All the above

Self Assessment Question 5

- The risk of drug/drug interactions is increased by which of the following?

A. Narrow therapeutic index of co-administered agent

B. Highly potent co-administered enzyme inducer or inhibitor

C. Greater sensitivity to adverse effects in elderly patients

D. Co-administration of multiple drugs

E. All the above

Self Assessment Question Answers

- 1. C
- 2. D
- 3. D
- 4. E
- 5. E