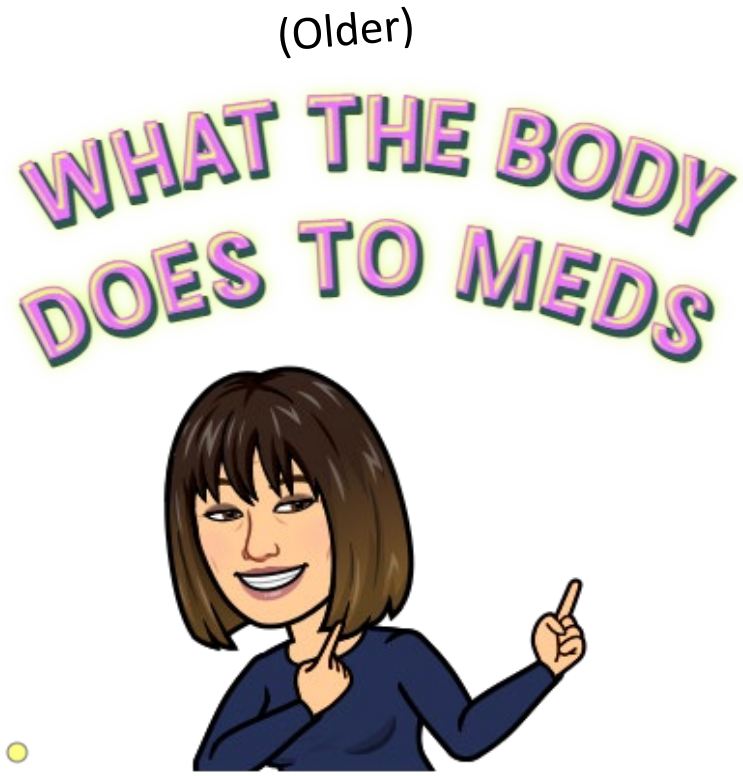

Pharmacokinetic Considerations in Older Adults

Presented by:
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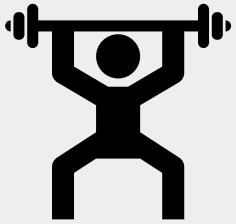
Schools of Public Health and Medicine
Director, Frazier Polypharmacy Program

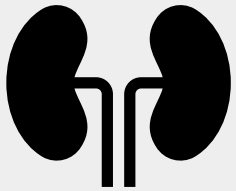
Demetra Antimisiaris has no relevant financial relationship to disclose.

Objectives

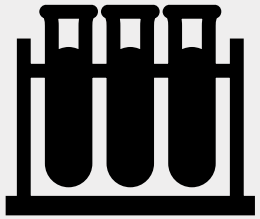
- Describe common age-associated physiologic changes impacting pharmacokinetics (PK).
- Discuss expected alterations in PK in older adults.
- Explain the influence of polypharmacy on PK.
- Apply principles older adult PK to clinical medication management.



Body Composition



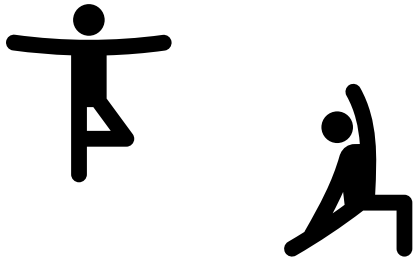
Organ Physiology



Biochemical Function

Polypharmacy

Major Components of PK Considerations in Older Adults



- Drug data from clinical trials typically excludes older adults.
- Interpretation of drug data for older adults is necessary.
- Large population studies sometimes reveal PK and PD in older adults.

The data described below reflect exposure in randomized, double-blind, placebo-controlled trials of sertraline in 3066 adults. These 3066 patients exposed to sertraline for 8 to 12 weeks represent 568 patient-years of exposure. The mean age was 40 years; 57% were females and 43% were males.

nce ID: 4867358

The most common adverse reactions (≥5% and twice placebo) in all pooled placebo-controlled clinical trials of all sertraline-treated patients (MDD, OCD, and other conditions) were nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido (see Table 2). The following are the most common adverse reactions in trials of sertraline (≥5% and twice placebo) by indication that were not mentioned previously.

- MDD: somnolence
- OCD: insomnia, agitation

Table 2: Common Adverse Reactions (Greater than 2% of Adults with MDD, OCD, and Other Conditions Treated with Sertraline Hydrochloride and Greater than or Equal to Twice the Incidence of Placebo) in Pooled Placebo-Controlled Trials*

	Sertraline Hydrochloride (N=3066) %	Placebo (N=2293) %
Cardiac disorders		
Palpitations	4	2
Eye disorders		
Visual impairment	4	2
Gastrointestinal Disorders		
Nausea	26	12
Diarrhea/Loose Stools	20	10
Dry mouth	14	9
Dyspepsia	8	4
Constipation	6	4
Vomiting	4	1
General disorders and administration site conditions		

Body Composition

Changes in Body Composition

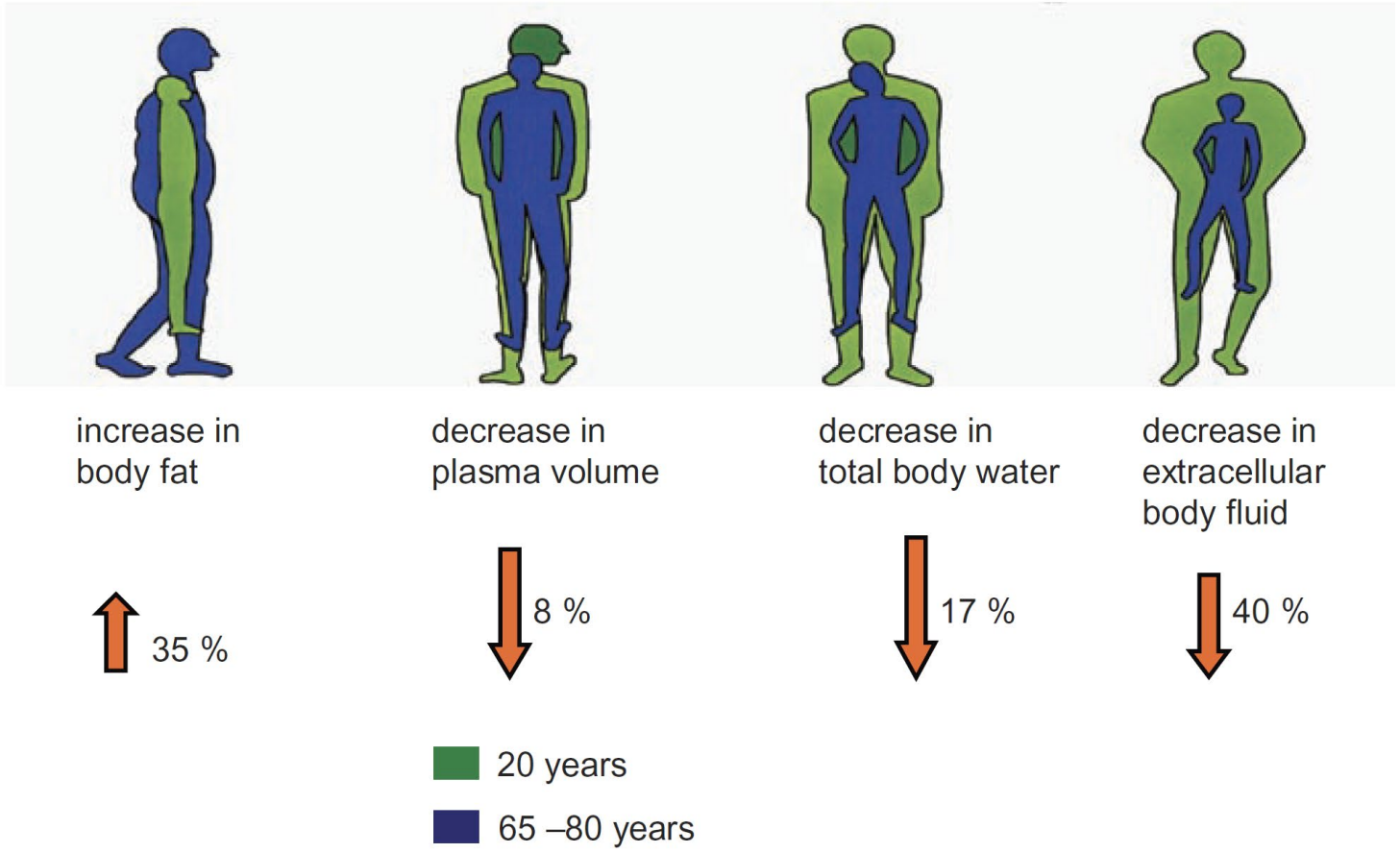
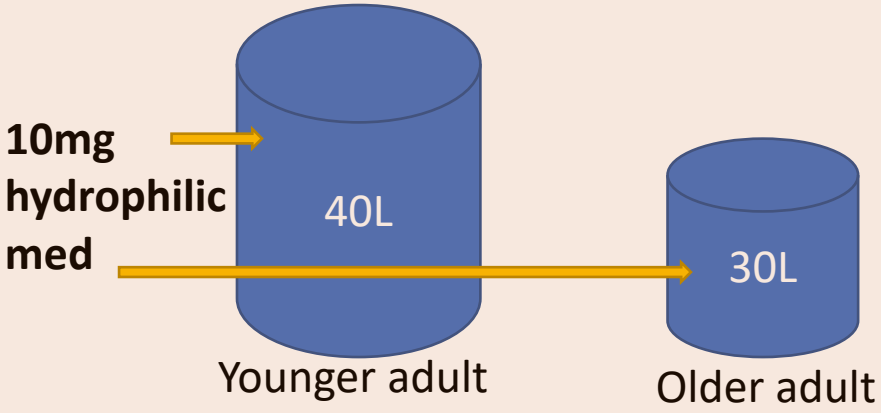


Figure 3. Age-dependent changes in body composition.

Eldosoky E.S. 2007; Meeuwsen et al. 2010; Pea F 2018

Altered lipophilic and hydrophilic drug volumes of distribution

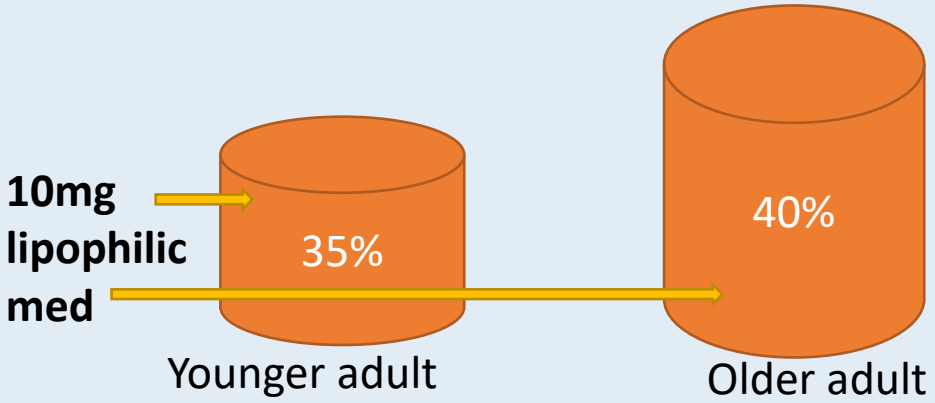
HYDROPHILIC DRUGS



Older Adult:

- Reach C_{max} faster at lower doses, higher peak plasma levels
- Drugs more "concentrated"

LIPOPHILIC DRUGS



Older Adult:

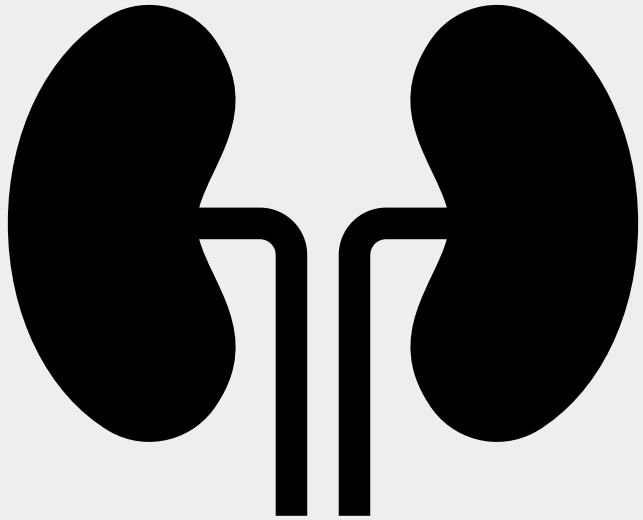
- Takes longer to distribute, longer to take effect
- Extended t ½ (longer elimination)

Examples

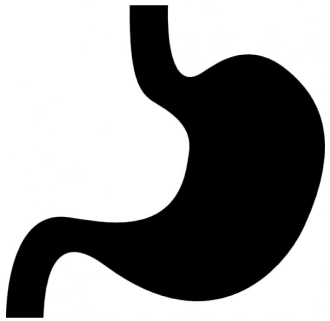
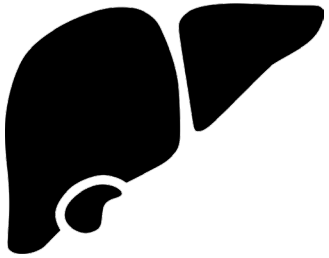
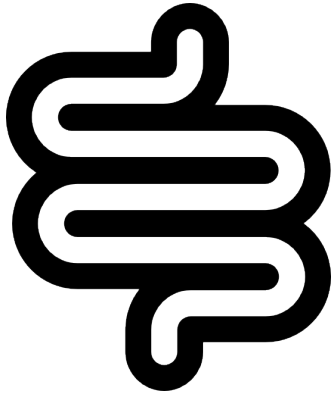
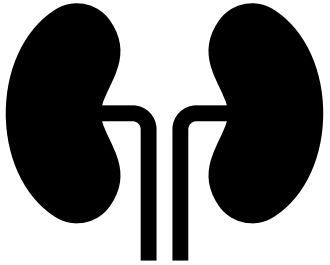
Fat Soluble Drugs/Products
Amiodarone
Diazepam
Verapamil
Any CNS active medication
Vitamin A, D, E, K
First generation antihistamines

Water Soluble Drugs/Products

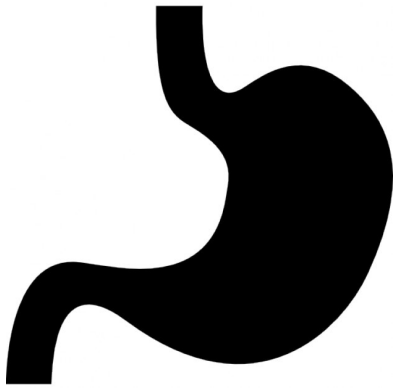
- Lithium
- Digoxin
- Most antibiotics
- B Vitamins
- Vitamin C
- Atenolol



Organ Physiology

Stomach



- Slower gastric emptying
  - Compounded by anticholinergic meds.
- Decreased acid production
- Smaller surface area for absorption
- Impact of PPI use
- Impact of food and slower gastric emptying

Absorption

- **Gastric motility**
  - can be slowed by polypharmacy and gastroparesis.

- **Food-Drug Interactions are not easy to predict**
  - and not explicitly noted in drug databases.
  - *Pharmacodynamic food-drug interactions are robustly described.*
- Pharmacokinetic food-drug interactions linked to **narrow therapeutic index drugs are notable**.
  - Grapefruit juice's inhibition of CYP 3A4 pathway and inhibition of intake and efflux membrane transporters.

Absorption

Gastric pH Variation After FDA Standard Breakfast

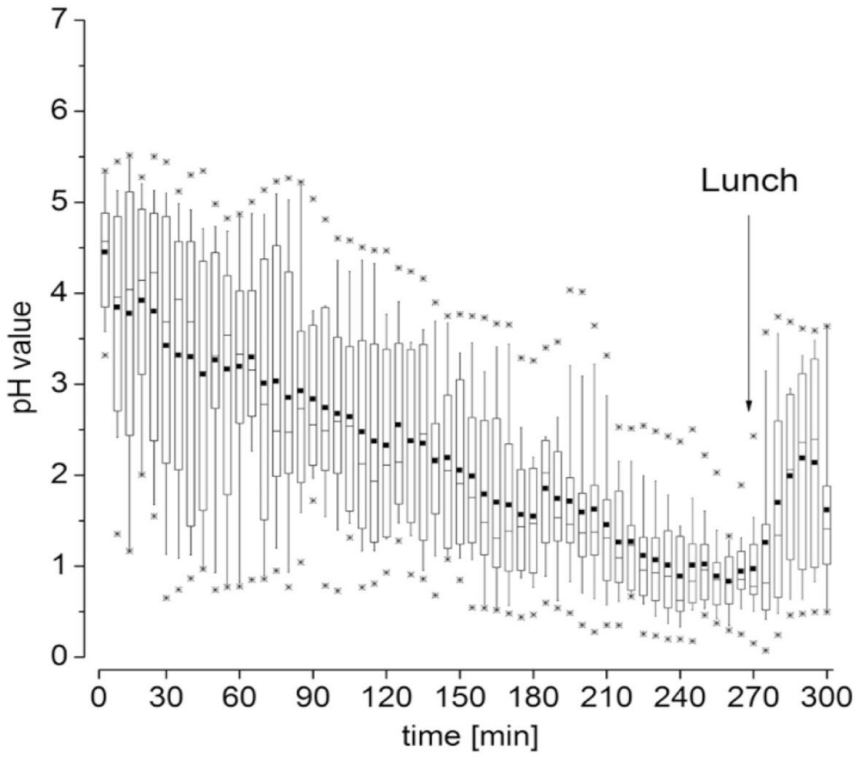
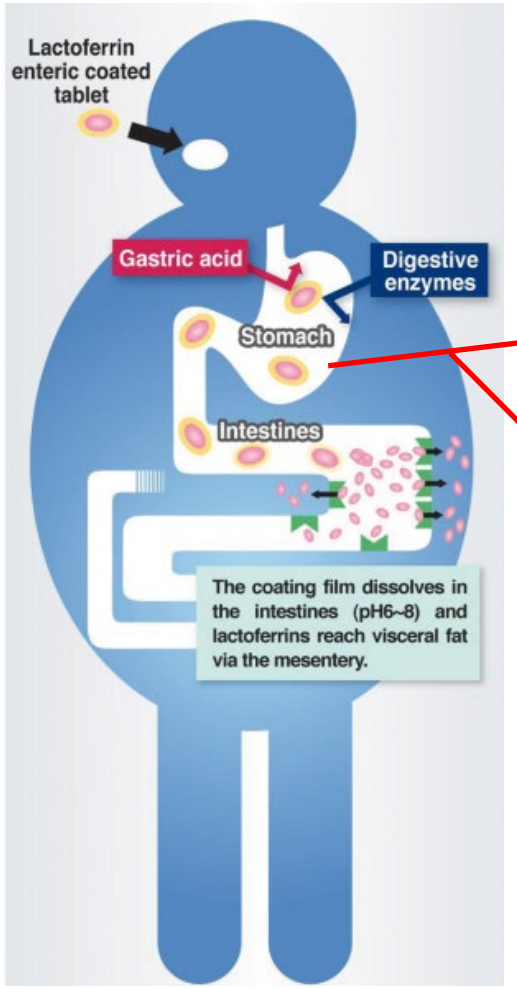


Fig. 6. Re-acidification of the stomach over a period of 5 h after intake of the FDA standard breakfast. Each box represents a 5 min interval. Box: 50%, whisker: 10–90%, square: mean, asterisks: max/min; n = 16.
Reprinted from Koziolek et al., 2015b, with permission from Elsevier.



Normally
pH=1

Acid Suppression Thx
pH=6-8

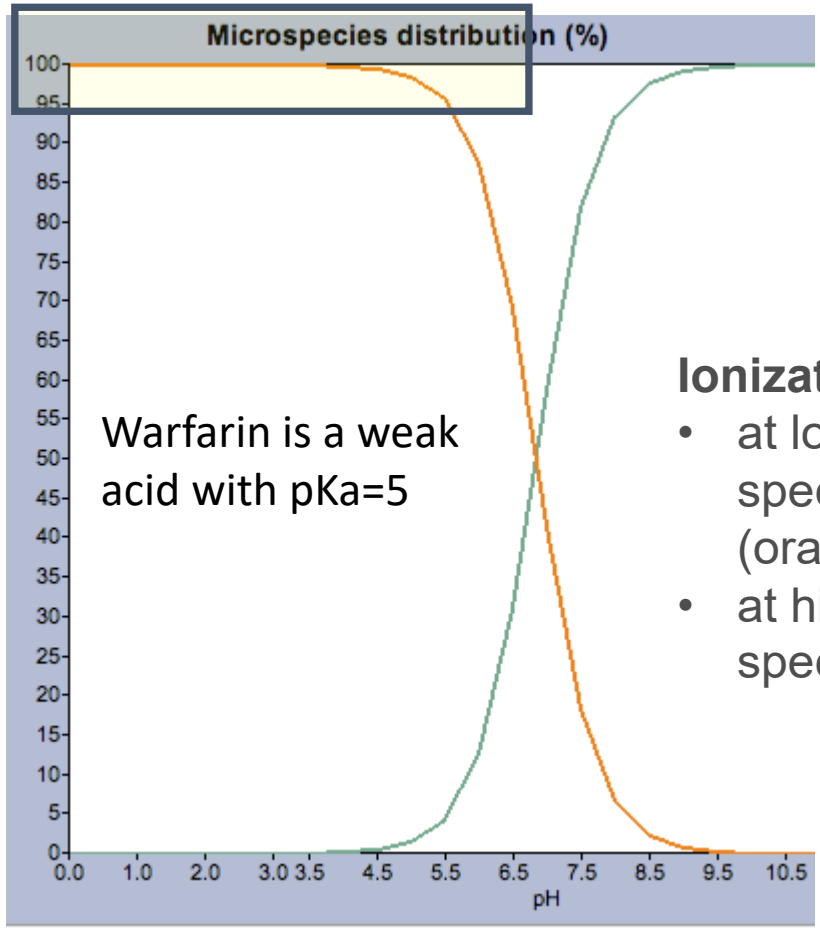
- Koziolek M., Alcaro S., Augustijns P., et. al. The mechanisms of pharmacokinetic food-drug interactions-A perspective from the UNGAP group. Eur J of Pharm Sciences 134 (2019) 31-59.
- Blonski W, Vela M, Catell D. Comparison of frequency during prolonged multichannel intraluminal impedance and pH monitoring on and off acid suppression therapy. J Clin Gastroent. 2009 Oct, 43(9): 816-20.

Absorption:

IN GENERAL:

At 2.0 pH units above the pKa, the conjugate base is at least 99% of the total.

At 2.0 pH units below the pKa, the conjugate acid is at least 99% of the total.



Warfarin is a weak acid with pKa=5

Ionization of Warfarin

- at low pH the neutral species predominates (orange line)
- at high pH it is the ionized species (green line).

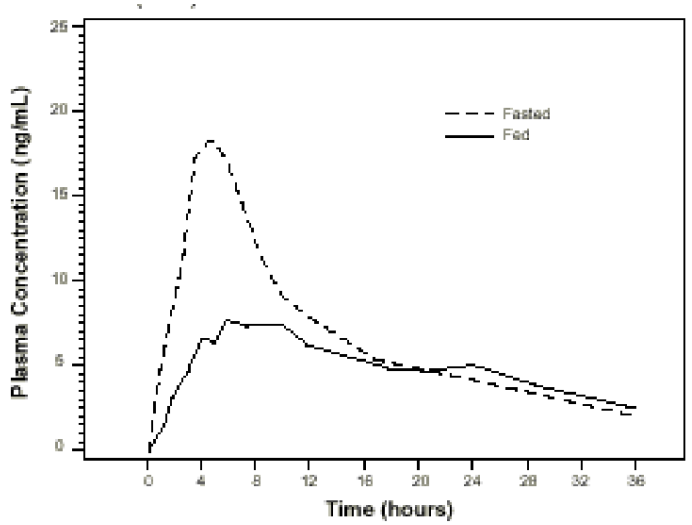
Location/pH	**Stomach/pH=2**	**Duodenum/pH=6**	**Jejunum/pH=7.5**	**Blood/pH=7.4**
Unionized (%)	100	88	18	25
Ionized(%)	0	12	82	75

Drugbank online : https://go.drugbank.com/drugs/DB00682

Effect of Food

The time to maximum concentration (T_{max}) is reached by 4 to 5 hours under fasting conditions and by 6 to 7 hours when FLOMAX capsules are administered with food. Taking FLOMAX capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions (Figure 1).

Figure 1 **Mean Plasma Tamsulosin Hydrochloride Concentrations Following Single-Dose Administration of FLOMAX Capsules 0.4 mg Under Fasted and Fed Conditions (n=8)**



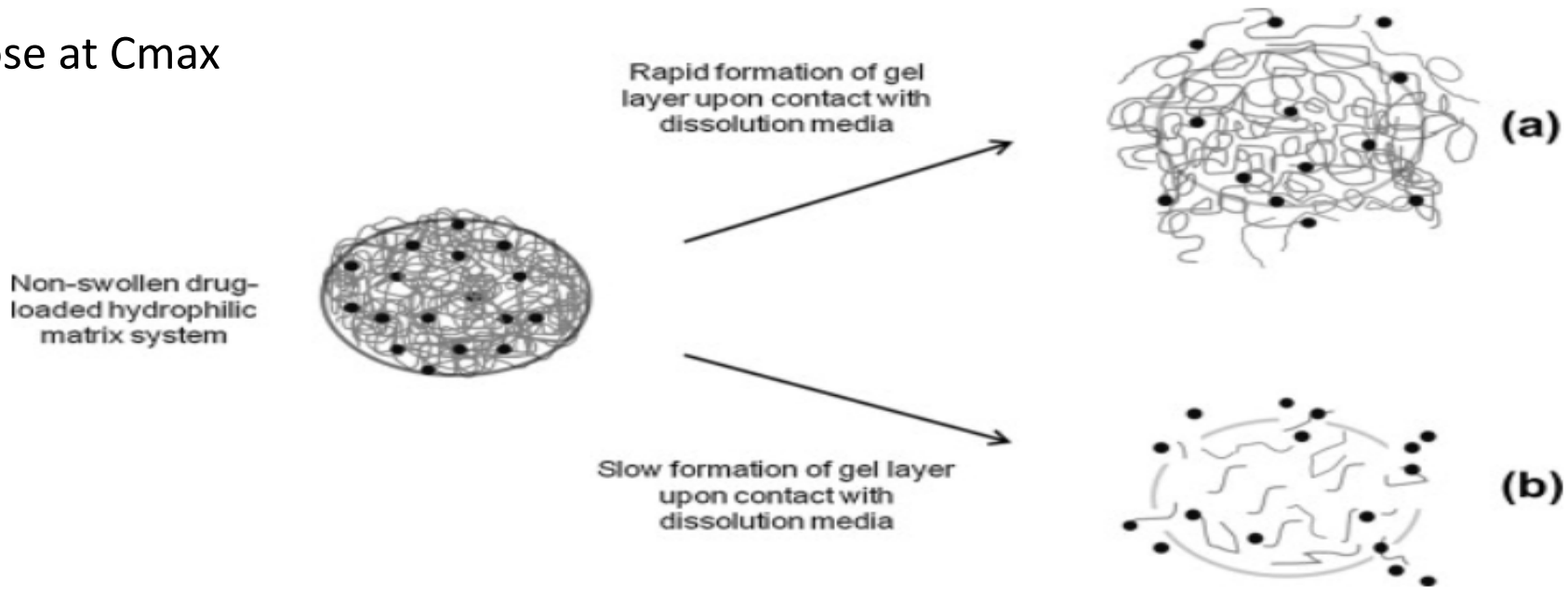
Dosing: "FLOMAX (tamsulosin) 0.4mg should be administered approximately one-half hour following the same meal each day.
For those patients who fail to respond to the 0.4 mg dose after two to four weeks of dosing, the dose of FLOMAX capsules can be increased to 0.8 mg once daily."

Flomax® Prescribing Information https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020579s016lbl.pdf

Alcohol and Dosage Forms

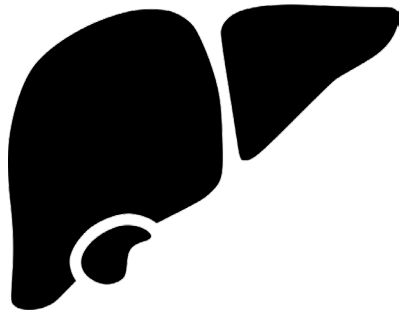
Controlled Release coated systems: EtOH dose dumping

- Tramadol ER is made with an alcohol soluble polymer which immediately dissolves in EtOH vs typical gastric contents.
- Multiple ER opioid formulations as well.
- 5-26-fold increase in dose at Cmax



Jedinger N, et al. 2014

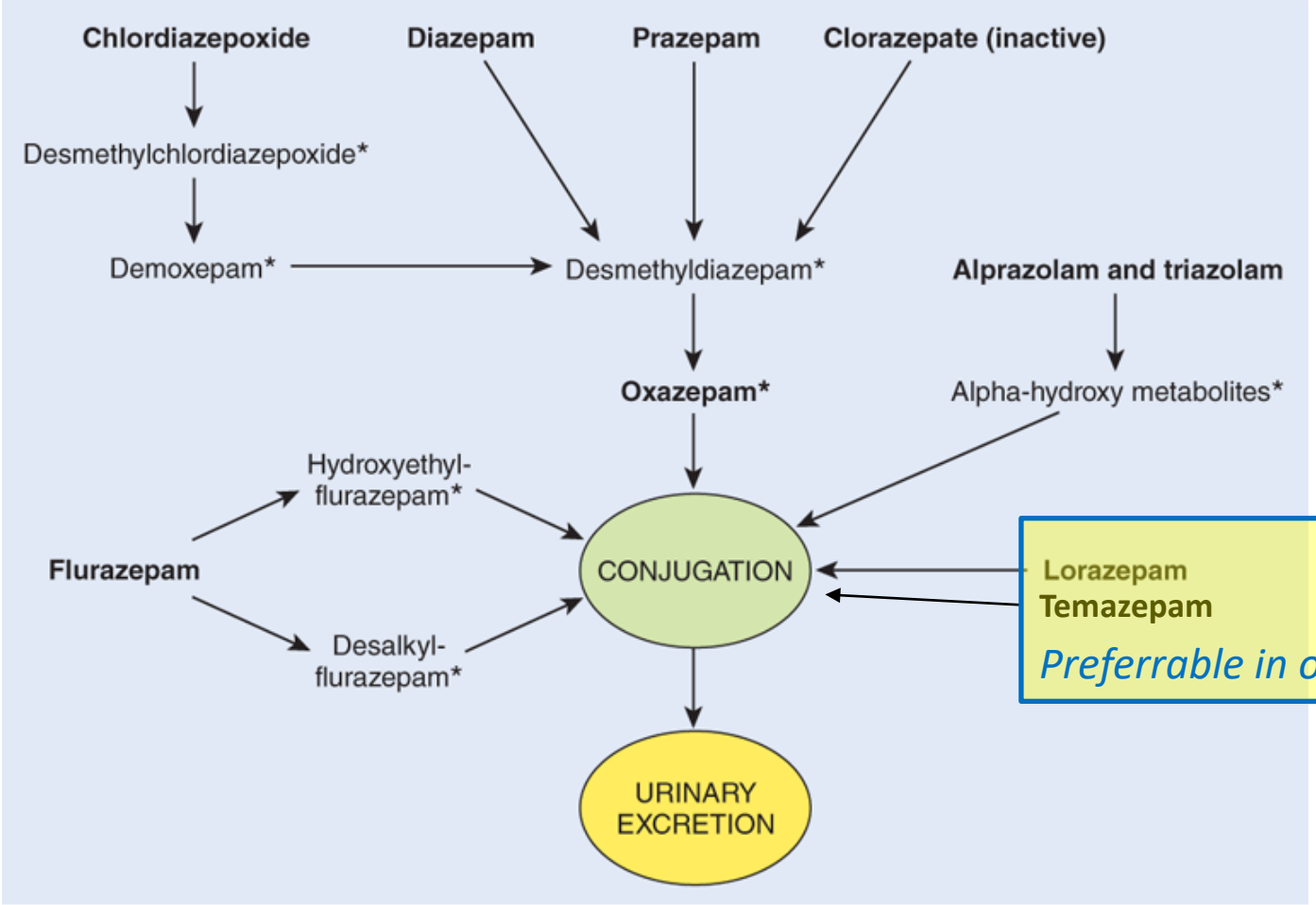
Liver



- Reduction in liver mass and reduced blood flow
- Phase I hepatic metabolism is more likely to be less efficient
  - Decreases about 1% per year after 40 years of age
  - CYP 450, aldehyde dehydrogenase, xanthine oxidase, etc.
- Phase II (glucuronidation/conjugation) is not significantly affected by age.
  - Olanzapine, Acetaminophen, Ezetimibe, Salicylic acid
- Induction or inhibition of CYP p450 enzymes
  - Inhibition: Frailty, Malnutrition
  - Induction: Alcohol, Smoking

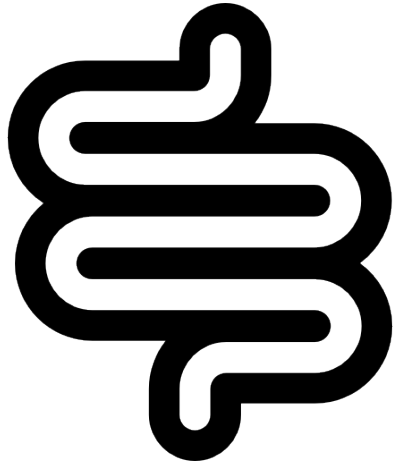
Metabolism:

Beware of active metabolites and slow Phase I activity



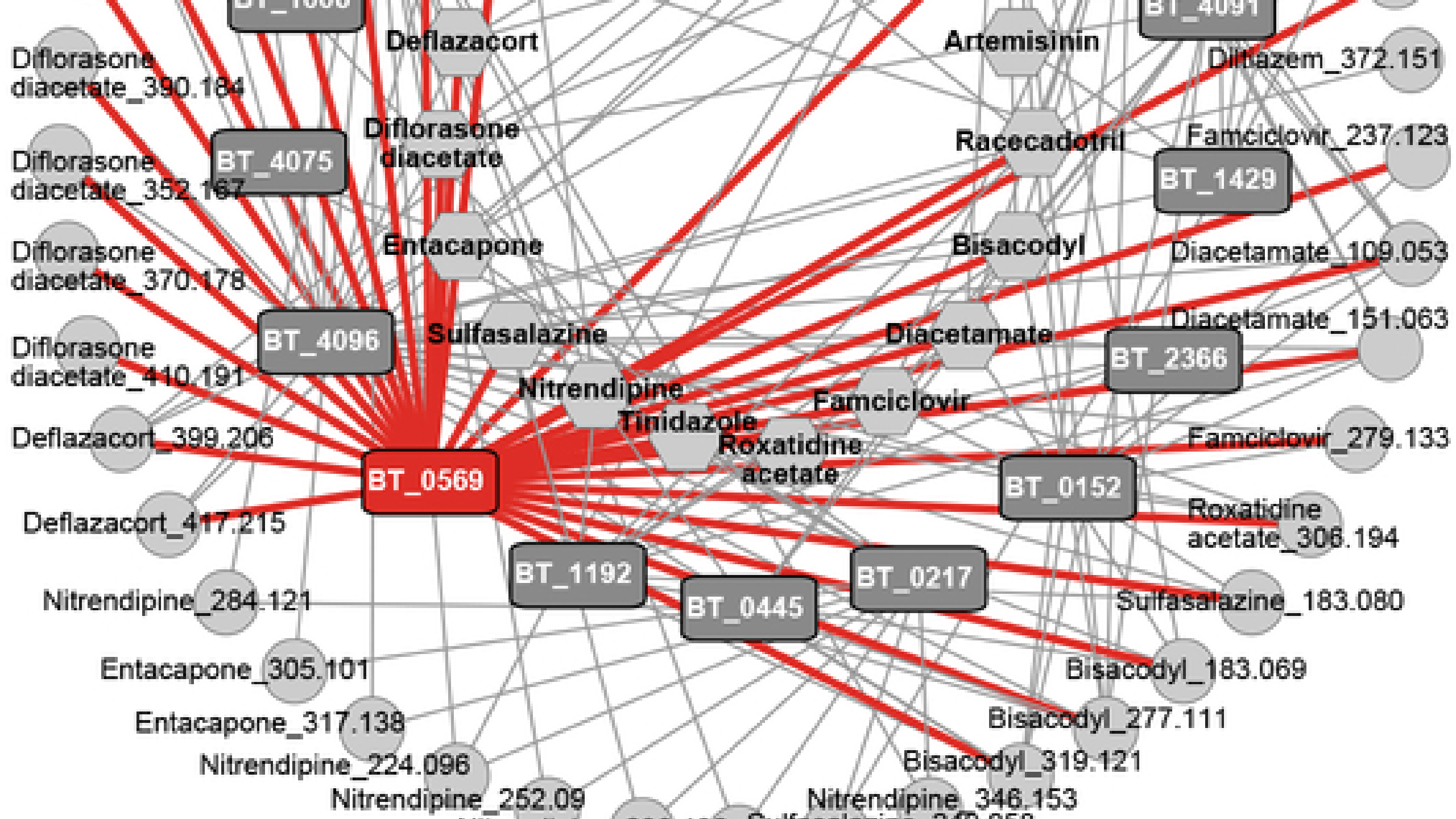
Restoril (temazepam) package insert. Mallinckrodt Inc. Hazelwood, MO 63042 USA. 2.25.08

Intestine



- Place where most medication absorption occurs
- Reduced blood flow
- Highly complex site of drug absorption and metabolism, as well as elimination.
  - Zimmerman et al. reported microbiome induced alterations in 2/3rds of 271 drugs resulting in:
    - Activation (sulfasalazine), inactivation (digoxin) or toxification (sorivudine)
  - Microbiome can influence bioavailability

Zimmerman et al. 2019


Deflazacort
Artemisinin
Diltiazem_372.151
Diflorasone diacetate_390.184
Diflorasone diacetate
Racecadotril
Famciclovir_237.123
BT_4075
BT_1429
Diflorasone diacetate_352.167
Entacapone
Bisacodyl
Diacetamate_109.053
Diflorasone diacetate_370.178
Diacetamate_151.063
BT_4096
Sulfasalazine
Diacetamate
BT_2366
Diflorasone diacetate_410.191
Nitrendipine
Famciclovir
Tinidazole
Deflazacort_399.206
Roxatidine acetate
Famciclovir_279.133
BT_0569
BT_0152
Deflazacort_417.215
Roxatidine acetate_306.194
BT_1192
BT_0217
BT_0445
Nitrendipine_284.121
Sulfasalazine_183.080
Entacapone_305.101
Bisacodyl_183.069
Entacapone_317.138
Bisacodyl_277.111
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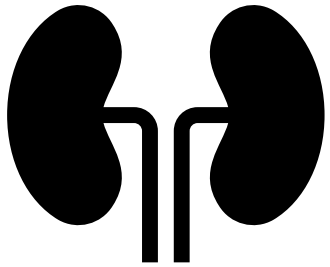
Bisacodyl_319.121
Nitrendipine_252.09
Nitrendipine_346.153

Kidney



- Reduced number of nephrons
- Reduced renal blood flow
- Renal elimination decreases an average of 8 mL/min/1.73 m^2/decade after the age of 40.
- Serum creatinine often remains “normal”

Nearly 100% of >85-year-olds = Moderate to Severe renal impairment

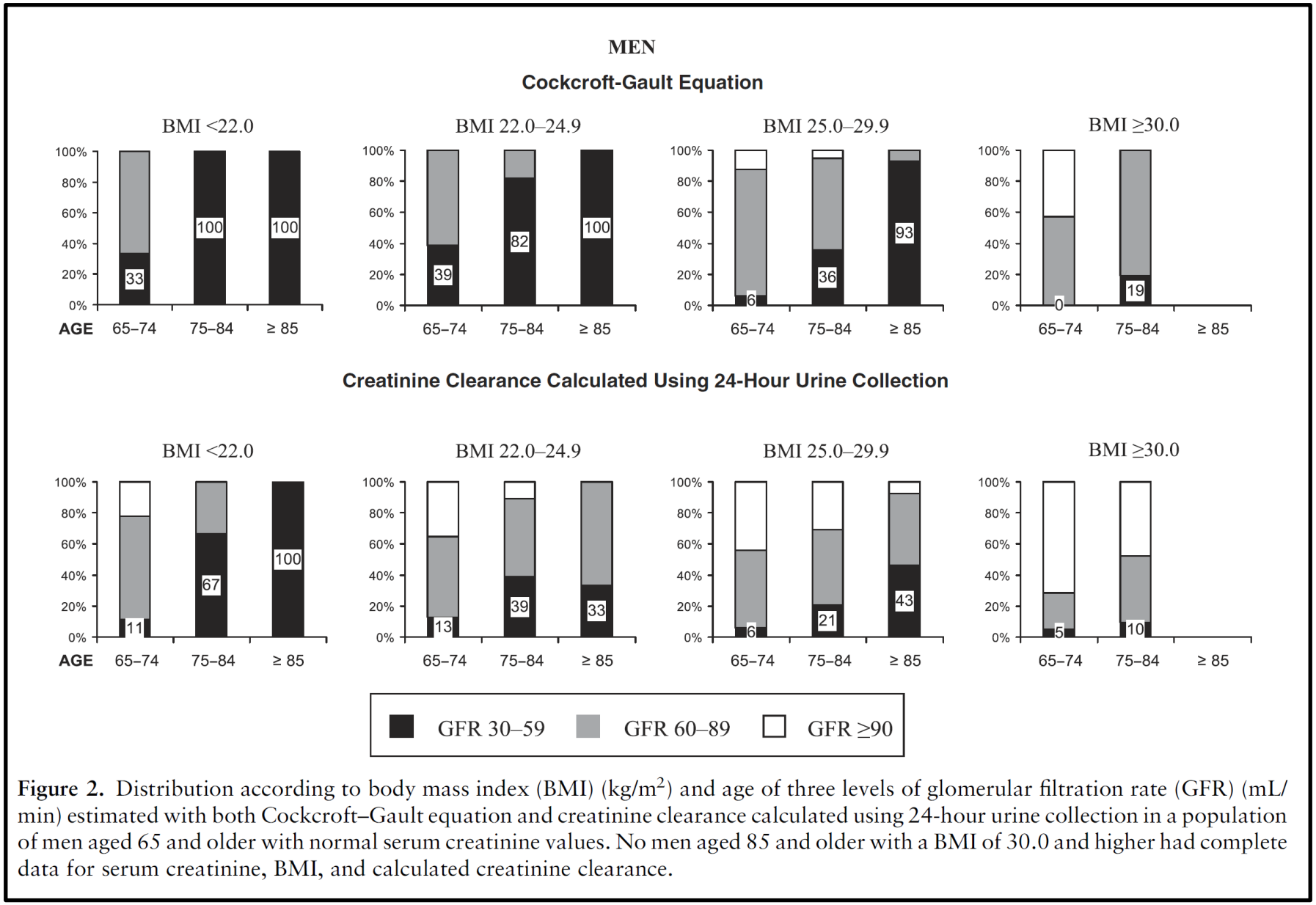


Figure 2. Distribution according to body mass index (BMI) (kg/m^2) and age of three levels of glomerular filtration rate (GFR) (mL/min) estimated with both Cockcroft–Gault equation and creatinine clearance calculated using 24-hour urine collection in a population of men aged 65 and older with normal serum creatinine values. No men aged 85 and older with a BMI of 30.0 and higher had complete data for serum creatinine, BMI, and calculated creatinine clearance.

Giannelli SV., Kushang PV., Windham G., et. al. Magnitude of Underascertainment of Impaired Kidney Function in Older adults with Normal Serum Creatinine. J Am Geriatr Soc 55: 816-823, 2007. (INCHIANTI study)

Attention: New FDA monographs might specify eGFR

Severe Renal Impairment — Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (estimated creatinine clearance <30 mL/min) *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.10)]*.

Cockcroft and Gault Equation :

FDA historically standardized C&G.

$$CrCl_{men} = \frac{(140 - Age) \times LBW}{Scr \times 72}$$

$$CrCl_{women} = CrCl_{men} \times 0.85$$

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of JARDIANCE

- Assess renal function before initiating JARDIANCE and as clinically indicated *[see Warnings and Precautions (5.2)]*.
- In patients with volume depletion, correct this condition before initiating JARDIANCE *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage

The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food. In patients tolerating JARDIANCE, the dose may be increased to 25 mg for additional glycemic control.

2.3 Dosage Recommendations in Patients with Renal Impairment

JARDIANCE is not recommended for use in patients with an eGFR less than 30 mL/min/1.73 m^2 and contraindicated in patients on dialysis *[see Indications and Usage (1), Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

Until 2008 FDA only recommended C&G

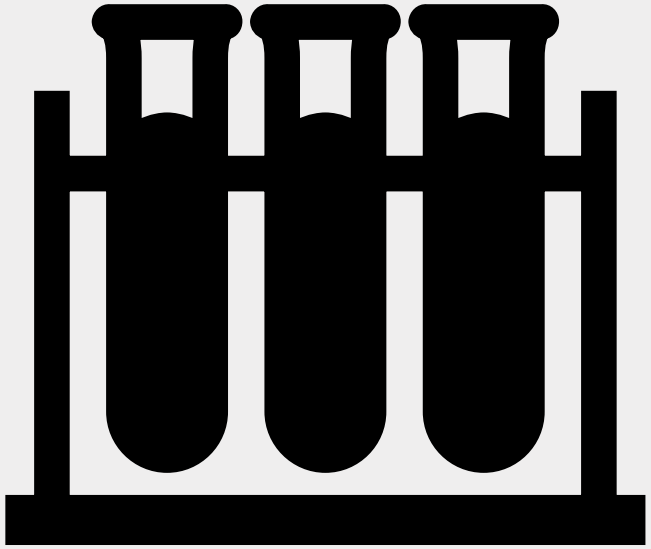
Hart L A, et al. 2018; NIDDK [Determining Drug Dosing in Adults with Chronic Kidney Disease - NIDDK (nih.gov)]

TABLE 6 2023 American Geriatrics Society Beers Criteria® for medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults.

Drug	CrCl (mL/min) at which action is required	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Anti-infective					
Ciprofloxacin	<30	Increased risk of CNS effects (e.g., seizures, confusion) and tendon rupture.	Dosages used to treat common infections typically require reduction when CrCl <30 mL/min.	Moderate	Strong
Nitrofurantoin	<30	Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use. (See	Avoid if CrCl <30 mL/min	Low	Strong

Beers Criteria 2023 and previous, highlight renal dose adjustment

By the 2023 AGS Beer Criteria® Update Expert Panel. JAGS May 4, 2023



Biochemical Function

Plasma Protein Binding

Albumin

Decreases with age, disease and malnutrition.

Increased free fraction of highly protein bound acidic drugs

Such as: digoxin, warfarin, naproxen, benzodiazepines, valproic acid

A-1 glycoprotein

Increases with inflammation and aging

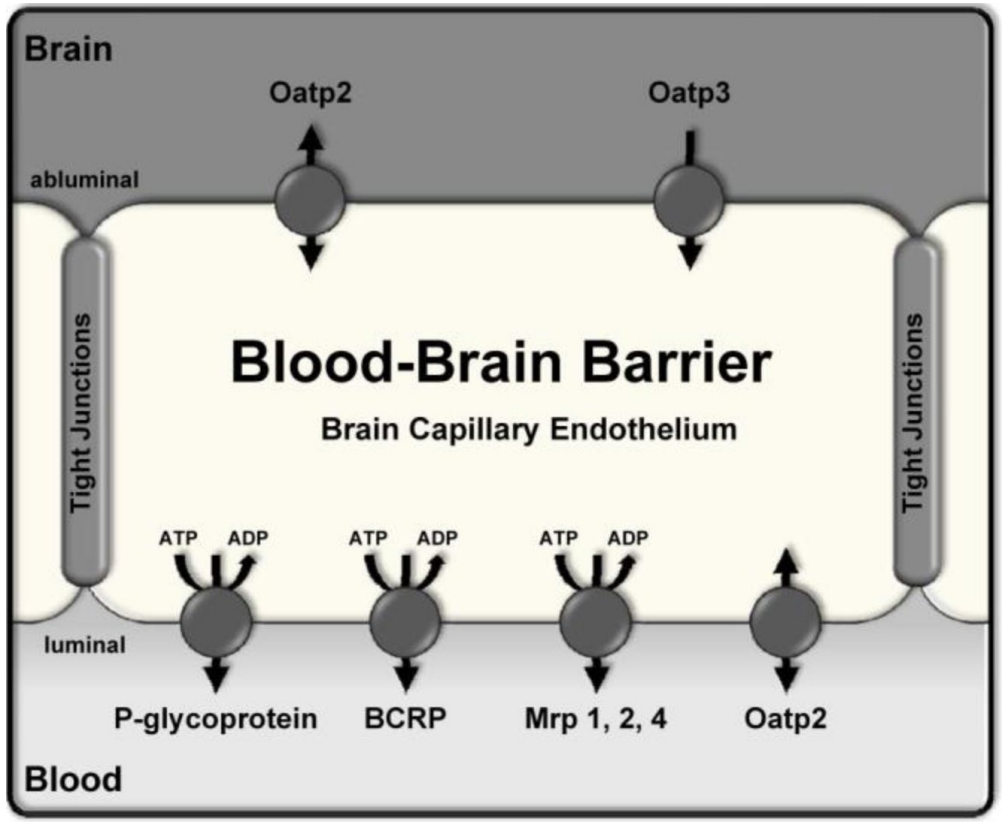
Decreased free fraction of basic drugs

Such as: propranolol, TCAs, warfarin

Smith SA, Waters NJ. 2018; Miller DS, et al. 2008

P-glycoprotein & Blood Brain Barrier

- A membrane protein that transports various substrates across the cell membrane.
- Studies have shown lower levels in brain and intestinal tissue in older adults, especially persons with dementia.
- Keeps hydrophilic medications out of CNS normally.
- Older adults can experience confusion and CNS impairment with medications not intended for CNS when BBB weakens



Smith SA, Waters NJ. 2018; Miller DS, et al. 2008

Polypharmacy

Co-occurrence: multimorbidity & polypharmacy

- Multimorbidity will increase. By 2035 87% of people will live with 2 or more conditions *(highest increase for cancer and diabetes).*
  - Multimorbidity can impair medication handling and administration.
  - Contributes to PK misadventure

Drug-Drug PK Interactions

67-year-old male

(+) Fluoxetine 20mg and Tramadol

HTN & CHF controlled on metoprolol, losartan (last BP 126/72, HR 64).

*He was prescribed **fluoxetine** for depression, and **tramadol** for his back pain.*

What happened?

<u>One week later</u> he returned to clinic with dizziness, lightheadedness upon standing. His BP is 90/60, HR 53.

ECG showed 2nd degree AV block which hadn't been present in the past.

And tramadol didn't work.

67-year-old

and Fluoxetine = 90/60, 53, dizzy, still in pain

Metoprolol
Losartan
Tramadol
Fluoxetine

Fluoxetine Inhibits CYP 2D6

Metoprolol and Tramadol are 2D6 substrates

<u>Inhibit CYP 2D6:</u> Fluox *, Parox, Dulox, Burprop > Sert, Cital, Escital

<u>Substrates</u>: B-Blockers, Narcotics (codeine, tramadol, oxycodone, hydrocodone), TCAs

<u>Inhibit CYP 3A4:</u> Norfluoxetine

<u>Substrates:</u> CCB, estrogen, corticosteroids, statins (atorvastatin, lovastatin, simvastatin not pravastatin), narcotics (methadone, fentanyl, oxycodone), protease inhibitors, alprazolam, triazolam, buspirone, sildenafil, 'z' drugs (zolpidem, eszopiclone)

<u>Opioid Pro Drugs:</u> Codeine, Tramadol, Oxycodone, Hydrocodone. Require CYP 2D6 metabolism to more active species. O-desmethyltramadol is 200x more potent than tramadol.

Table 1 Antidepressants and CYP enzymes

Antidepressants	Major elimination pathway	Other elimination pathways	Inhibitory effect on CYP isoenzyme
SSRI			
Citalopram	CYP2C19	CYP3A4, CYP2D6	CYP1A2, CYP2B6, CYP2C19, CYP2D6
Escitalopram	CYP2C19	CYP3A4, CYP2D6	CYP2D6, CYP2C9
Fluoxetine (active metabolite norfluoxetine)	CYP2D6	CYP2C9, CYP2C19, CYP3A4	CYP2D6,** CYP2C9,* CYP2C19,* CYP3A4,* CYP1A2
Fluvoxamine	CYP1A2, CYP2D6		CYP1A2,** CYP2C19,** CYP2C9,* CYP3A4,* CYP2D6
Paroxetine	CYP2D6	CYP3A4	CYP2D6,** CYP1A2, CYP2C9, CYP2C19, CYP3A4
Sertraline	CYP2B6	CYP2C19, CYP2C9, CYP3A4, CYP2D6	CYP2D6,* CYP1A2, CYP2C9, CYP2C19, CYP3A4
SNRI			
Desvenlafaxine	Renal	UGT, CYP3A4	None
Duloxetine	CYP1A2	CYP2D6	CYP2D6*
Levomilnacipran	Renal	CYP3A4, CYP2C8, CYP2C19, CYP2D6, CYP2J2, UGT	None
Milnacipran	Renal	UGT, CYP3A4	CYP3A4
Venlafaxine (active metabolite desvenlafaxine)	CYP2D6	CYP3A4	CYP2D6, CYP3A4
Others			
Agomelatine	CYP1A2	CYP2C9, CYP2C19	None
Bupropion (active metabolite hydroxybupropion)	CYP2B6		CYP2D6*
Mirtazapine	CYP2D6, CYP3A4	CYP1A2, UGT	None
Reboxetine	CYP3A4		None
Vilazodone	CYP3A4	CYP2C19, CYP2D6, carboxylesterase	CYP2C8[?]
Vortioxetine	CYP2D6	CYP3A4, CYP2C19, CYP2C9, CYP2A6, CYP2C8, CYP2B6	None

Notes: **Potent; *moderate; [?]undetermined; no symbol, weak. Data from Flockhart,[33] Gelenberg et al,[23] and Spina et al.[34]
Abbreviations: CYP, cytochrome P450; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin-reuptake inhibitor; UGT, uridine diphosphate glucuronosyltransferases.

Preferred SSRIs include:
Sertraline
Citalopram
Escitalopram

Table 3. CYP450 Isoenzyme Inhibition by the SSRIs

	1A2	2C9	2C19	2D6	3A4
Citalopram	+	0	0	+	0
Escitalopram	0	0	0	0	0
Fluoxetine	+	++	+ to ++	+++	++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+ to ++	+	+

Note: 0 = minimal or weak inhibition; +, ++, +++ = mild, moderate, or strong inhibition
Von Moltke et al., 2001; Greenblatt et al., 2002 ; Greenblatt et al., 1998.

Don't forget St. John's Wort: **INDUCES CYP 3A4** and can make common drugs cleared by 3A4 **drop serum levels.**

CBD is a potent inhibitor of 2C9 and 2C19 pathways as well a CYP 3A isoforms including 3A4

Markowitz J, Donovan J, DeVane C, et al. Effect of St. John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA 2003 Sept 17; 290 (11): 1500-4.
Low Y, Setia S, Lima G. Drug-drug interactions involving antidepressants: focus on desvenlafaxine. J Neuropsychiatric Disease and Treatment, February 2018, Vol 2018:14, 567-580.
Tamaori S., Ebisawa J., Okishima Y., et al. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of pheolic hydroxyl groups in the resorcinol moiety. 2011 Apr 11; Life Sci 88 (15016): 730-6.
Epidiolex® package insert, 2020. Greenwich Bioscience, Inc., Carlsbad, CA 92008, USA

Transdermal Dosage Forms

TD formulations do not absorb in older persons the same as in younger because of **decreased dermal blood flow**,(also true for SC and IM routes of administration), dehydration, and altered stratum corneum.

Medication	% Absorbed in non older adults	% absorbed in older adults
Estradiol	7.1	5.4
Hydrocortisone	1.5	0.54
Testosterone	19.0	16.6
Acetylsalicylic Acid	31.2	13.6
Benzoic Acid	36.2	19.5
Caffeine	48.2	25.2

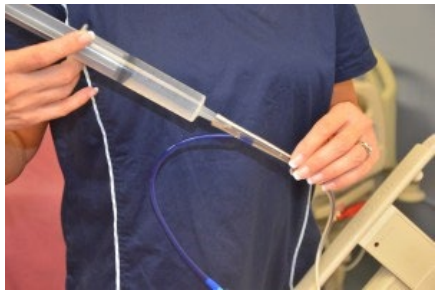
Roskos KV., Maibach HI., Guy RH. The effect of aging on percutaneous absorption in man. J Pharmacokinet Biopharm. 1989 Dec; 17 (6): 617-30
Turnheim K. When drug therapy gets old: Pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol, 2003; 38: 843-53.

G-Tube & warfarin failure

- **Warfarin binding to plastic surfaces** is dependent on pH, temperature, and concentration of warfarin in solution.

- Lower concentration of the drug will increase the exposure time and contact of the drug to the tubing surface.

- Separating enteral feeding product and just giving warfarin with water, **flushing the tube with water before and after markedly increases level delivered to the stomach for absorption.**



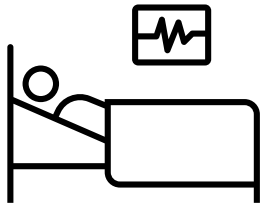
Klang M et al. Warfarin Bioavailability With Feeding Tubes and Enteral Formula *Journal of Parenteral and Enteral Nutrition* / Vol. 34, No. 3, May 2010

Geriatrics Hospitalists

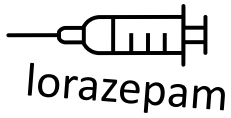
Be there in 15 ‘
“don’t do anything”

ICU

79 y.o. lives alone, confused, nausea

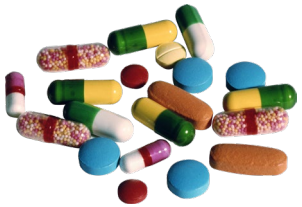


ED



lorazepam

home meds set up by daughter: "daily dosing” lisinopril, rivaroxaban, digoxin, hydrocodone-apap



Why?

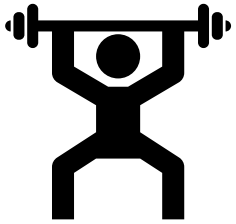
- 1 mg lorazepam given
- Opioid toxic already
- Dig toxic
- digi immune fab could have possibly avoided lorazepam

Lorazepam= ICU

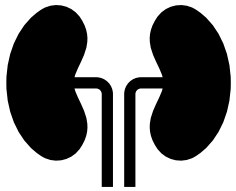
Dig Toxic

Why?

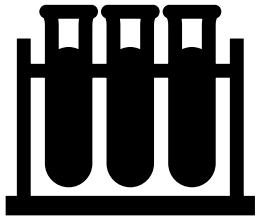
- Renal impairment (29 mL/min)
- Daily Dig vs QOD
- ACE + Diuretic more renal impairment
- Cognitive impairment + high risk medications



Body Composition



Organ Physiology



Biochemical Function

Polypharmacy

“Start Low and Go Slow”

Thank You
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