AGE-RELATED CHANGES THAT IMPACT DRUG METABOLISM

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Disclosures

- NIA, NIAID
- PCORI
- Consultant to Janssen Pharma
- Consultant to Spring Discovery
- Consultant to ResTORBio
- Consultant to UpToDate

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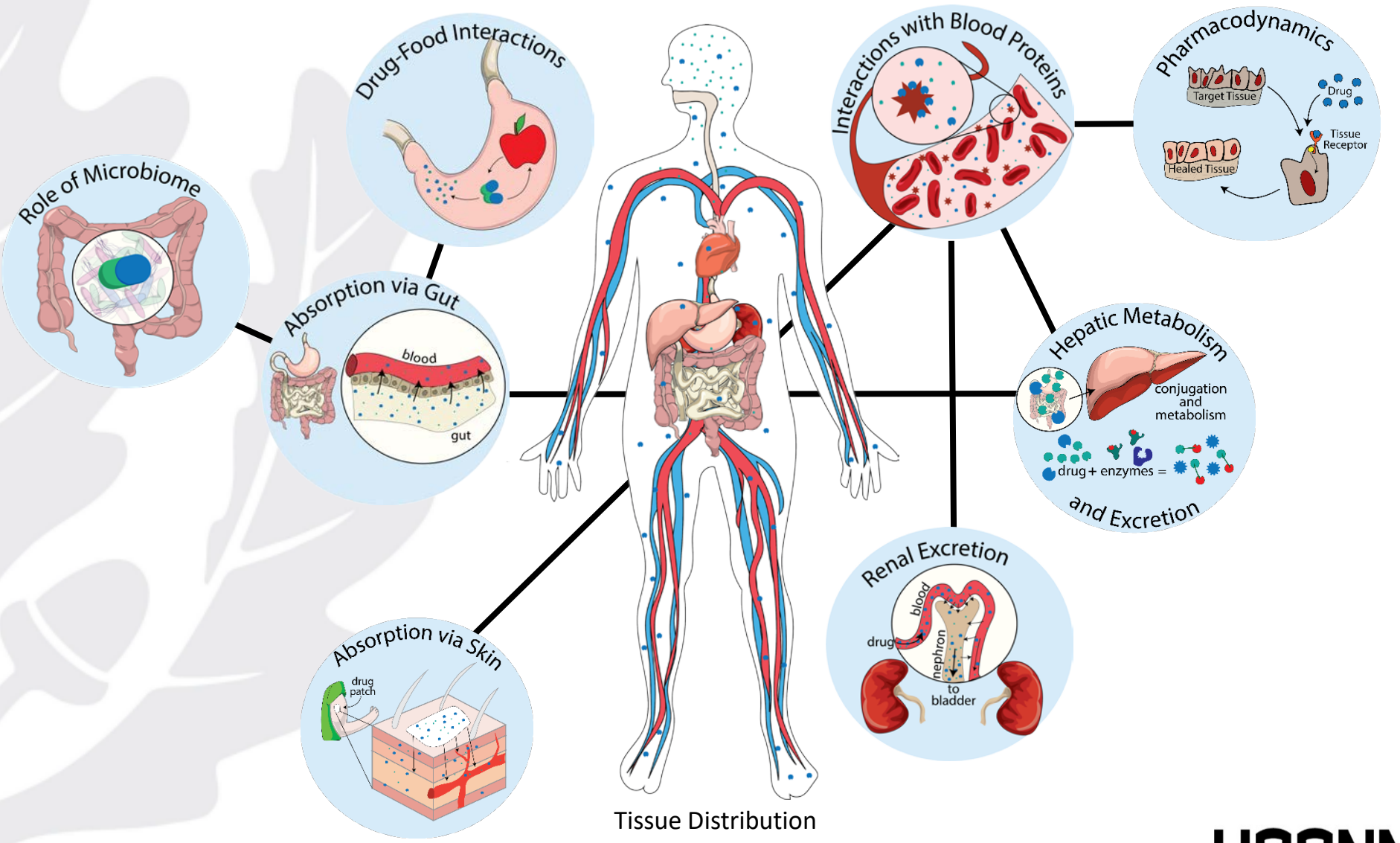
Systems-based approaches to drug metabolism



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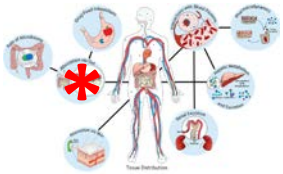
Drug Absorption with Aging



- Oral transmucosal fentanyl absorption unchanged
- GI absorption generally unchanged
- Decreased acid secretion plus use of PPIs and antacids can:
  - interfere with drug ionization
  - impair absorption of some meds
  - impair oxidation of ferric to more absorbable ferrous iron
  - impair liberation of vitamin B12 from food
  - contribute to iron, calcium and vitamin B12 deficiencies
- L-DOPA absorption is enhanced due to lower DOPA decarboxylase
- IM antibiotic absorption may be impaired
- Transdermal absorption may be enhanced from epidermal thinning

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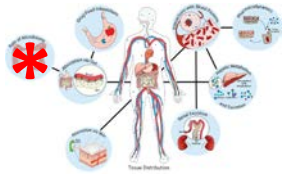
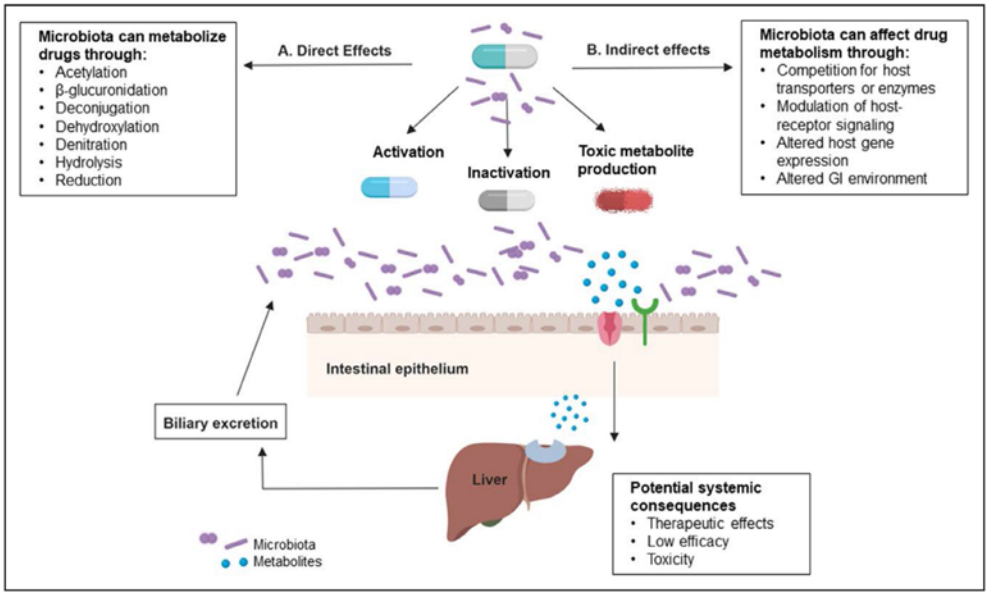
Microbiome & Drug Metabolism



- Medications have potent effects on GI microbiome
- Microbiome can:
  - Inactivate med (digoxin)
  - Activate med previously inactivated in liver (irinotecan)
  - Produce toxic metabolite (teratogenic nitrazepam form)
- Role of microbiome on geriatric pharmacology unknown



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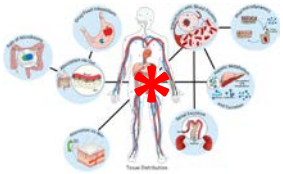
Body Distribution with Aging



- **Body fat** – increased
- **Muscle mass** – decreased
- **Total body water** – decreased

Volume of distribution:

- **For fat soluble drugs** - increased
- **For water soluble drugs** - decreased
- Data mostly cross-sectional with variable trajectories
- BMI poor fat measure

Calcified Tissue International
https://doi.org/10.1007/s00223-020-00679-2

ORIGINAL RESEARCH

Long-term rates of change in musculoskeletal aging and body composition: findings from the Health, Aging and Body Composition Study

Leo D. Westbury[1] · Holly E. Syddall[1] · Nicholas R. Fuggle[1] · Elaine M. Dennison[1,2] · Jane A. Cauley[3] · Eric J. Shiroma[4] · Roger A. Fielding[5] · Anne B. Newman[3] · Cyrus Cooper[1,6,7]

Received: 18 December 2019 / Accepted: 19 February 2020

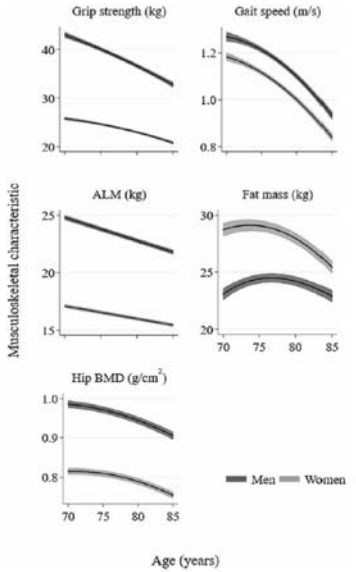


Fig. 2 Mean (95% CI) trajectories of characteristics among men and women. *ALM* appendicular lean mass, *BMD* bone mineral density. Mean trajectories were derived using linear mixed effects models with random intercepts and slopes. Quadratic and cubic age terms were included as fixed effects if significant ($p < 0.05$). For each characteristic, trajectories from participants with at least two observations were included

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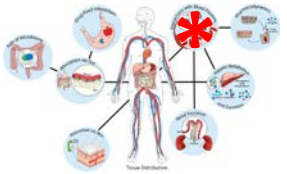
Interactions with blood proteins



- Decrease in serum albumin
- Acidic highly albumin-bound drugs most affected
- Even small protein binding reduction may result in a clinically significant increase in free drug concentration
- Slight increase in α1-acid glycoprotein can affect free drug concentrations, particularly of lipophilic basic drugs

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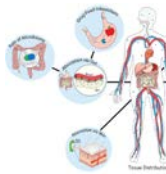
Renal Excretion with Aging



- Declines in renal perfusion and GFR in most patients
- Impact ability to eliminate renally-excreted meds
- This results from well-defined cellular and physiologic changes
- Chronic diseases and aging increase heterogeneity
- GFR does not decline in all older adults over time
- Cannot rely on serum creatinine value alone

Longitudinal Studies on the Rate of Decline in Renal Function with Age

Robert D. Lindeman, MD, Jordan Tobin, MD,† and Nathan W. Shock, PhD*

Serial creatinine clearances (5 to 14 studies) were obtained for 446 normal volunteers in the Baltimore Longitudinal Study of Aging followed between 1958 and 1981. When those subjects with possible renal or urinary tract disease and subjects on diuretics and antihypertensives were removed from the study, leaving a group of 254 "normal" subjects, the mean decrease in creatinine clearance was 0.75 ml/min/year. The slopes of the creatinine clearance vs. time fell into a normal (Gaussian) distribution around this mean. One third of all subjects followed had no absolute decrease in renal function (positive slope of creatinine clearance vs. time) and there was a small group of patients who showed a statistically significant increase ($P < 0.05$) in creatinine clearance with age. *J Am Geriatr Soc 33:278, 1985*

Serum creatinine of 1.6 may indicate normal GFR in muscular young athlete, while reflecting major decline in GFR for frail 85 year old woman

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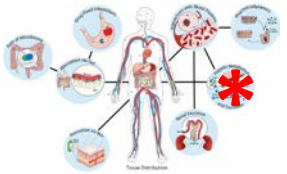
Hepatic metabolism & excretion



- Hepatic blood flow declines by 10% per decade
- Liver mass decreases by 20-40% with aging
- Drugs metabolized by cytochrome P450 most affected
- Reduction in clearance of flow-limited drugs by 30-40%
- This reflects declines in hepatic flow
- No alteration for capacity-limited drugs

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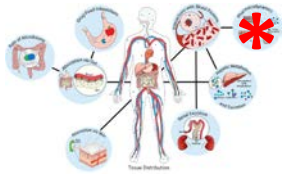
Changes in Pharmacodynamics



- Examples of decreased responsiveness with aging (e.g. isoproterenol)
- Examples of increased responsiveness (e.g. propofol)

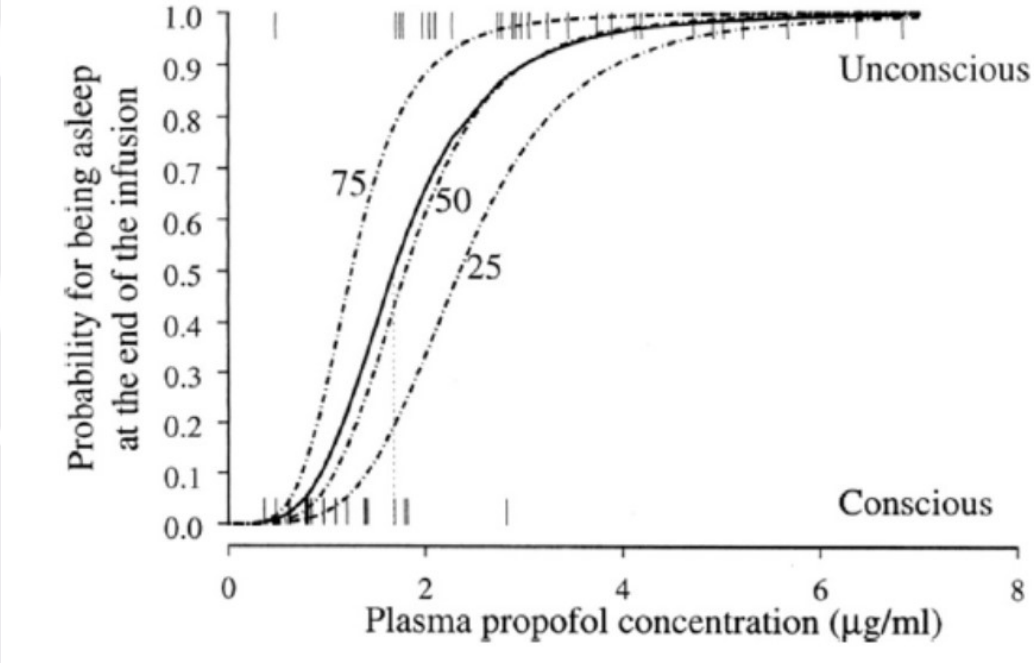


Fig. 1. Effect of age on propofol pharmacodynamics. This logistic regression shows the age-related probability of being asleep after a 1-hour infusion of propofol. A 75-year-old patient is 30% to 50% more sensitive to propofol than is a 25-year-old patient. (*From* Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90(6):1510; with permission.)

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Heterogeneity of Aging, Frailty, Multimorbidity

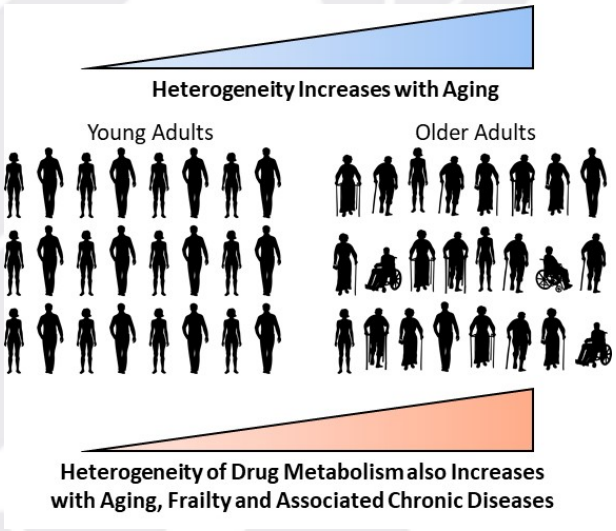

Table 1
Impact of biology of frailty on pharmacokinetics: theoretical and empirical data.

Pharmacokinetic parameter	Biological change in aging, which may be exaggerated in frailty	Impact of change on pharmacokinetic parameter	Direct empirical data comparing frail and non-frail older adults
Absorption	Reduced gastric motility and reduced hepatic metabolism	Delayed absorption and increased bioavailability of some orally administered drugs	Increased bioavailability of oxybutynin in frailty^ (Hughes et al., 1992)
Distribution	Sarcopaenia and increased relative body fat Reduced plasma albumin	Increased volume of distribution of lipophilic drugs and decreased volume of distribution of hydrophilic drugs Decreased protein binding of acidic drugs	No reduced volume of distribution of gentamicin in frailty* (Hilmer et al., 2011; Johnston et al., 2014)
Metabolism	Reduced hepatic volume and hepatic blood flow	Some reduced phase I clearance	No reduced CYP3A4 and P-glycoprotein metabolism in frailty according to erythromycin breath test results** (Schwartz, 2006) No reduced CYP2D6 metabolism in frailty** (Opdam et al., 2015) Reduced esterase activity in frailty ^(Hubbard et al., 2008) No reduced clearance of acetanilide in frailty ^(Wynne et al., 1989) No reduced metabolism of N-desthyl oxybutynin in frailty^ (Hughes et al., 1992)
		Reduced phase II clearance	Reduced clearance of metoclopramide via sulfation in frailty ^(Wynne et al., 1993) Reduced clearance of paracetamol in frailty via glucuronidation ^(Wynne et al., 1990)
Elimination	Reduced glomerular filtration rate	Reduced renal clearance	Reduced gentamicin clearance in frailty*(Hilmer et al., 2011; Johnston et al., 2014)

^ indicates studies that used a definition of frailty based on clinical impression and/or care setting.
* indicates studies that used an objective definition of frailty based on cumulative deficit model.
** indicates studies that used an objective definition of frailty based on phenotype model.

Mechanisms of Ageing and Development 181 (2019) 22–28
Contents lists available at ScienceDirect
Mechanisms of Ageing and Development
journal homepage: www.elsevier.com/locate/mechagedev

Biology of frailty: Implications for clinical pharmacology and drug therapy in frail older people

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Summary and Knowledge Gaps

- Average impact of aging on drug metabolism is well understood
- Yet, heterogeneity of aging "effect" is seen in terms of:
  - specific drugs within broader classes
  - inter-individual aging differences (health, frailty, co-morbidities)
  - prediction of hepatic changes is especially problematic
  - role of nutrition? alcohol? lifestyle? microbiome?
- We are much better at predicting population vs. individual changes
- Need "point of care" predictors of individual's drug metabolism
- Need "point of care" predictors of individual's drug response

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