

Age related changes in kinetics and dynamics

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The relevance

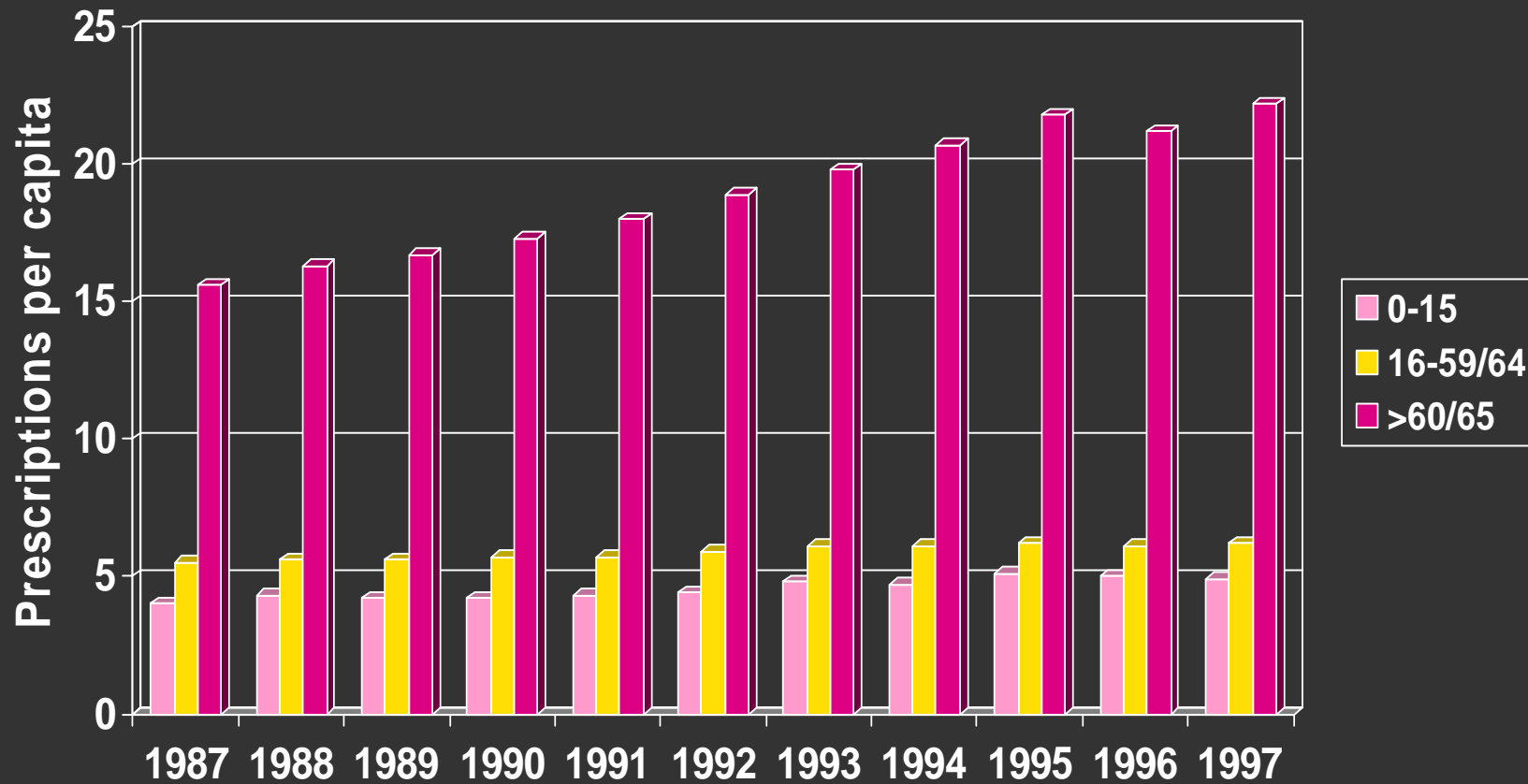


BNF 1976

The Time Span.

A great deal of treatment that is given to the young and middle aged is intended to prevent troubles in the distant future and some nuisance in the present may be accepted to obtain this end. The rigid control of hypertension and diabetes are examples. It is of course obvious that old people have no distant future, yet they are often continued on treatment which, however correct it might have been, can no longer benefit them.

Prescribing trends



Terminology

Pharmacodynamics:

φαρμακον = **medicine**

δυναμις = **power**

Pharmacokinetics:

φαρμακον = **medicine**

κινητικον = **movement**

Pharmacokinetics in elderly patients

Renal function

- **Reduced glomerular filtration**
 - Approximately 20 - 50% reduction in GFR
 - Important for drugs predominantly renally excreted
eg digoxin, lithium, aminoglycosides
- **Reduced tubular secretion**
 - Less important and less well documented
- **Therapeutic implications:**
 - Reduce dose for once daily regimens
 - Reduce dose interval

Pharmacokinetics in elderly patients

Hepatic function

- **Reduced liver volume (cf children)**
 - up to 30% reduction
- **Reduced liver blood flow**
- **Reduced enzyme activity (frail elderly)**
- **Reduced serum proteins (frail elderly)**
 - **Reduced protein binding**
 - **↑ Vd**

Pharmacokinetics in elderly patients

Body content

- Physiology

- Increased proportion of body fat
- Decreased proportion of body water

- Implications

- ↑ Vd of lipid soluble drugs
- ↓ Vd of water soluble drugs

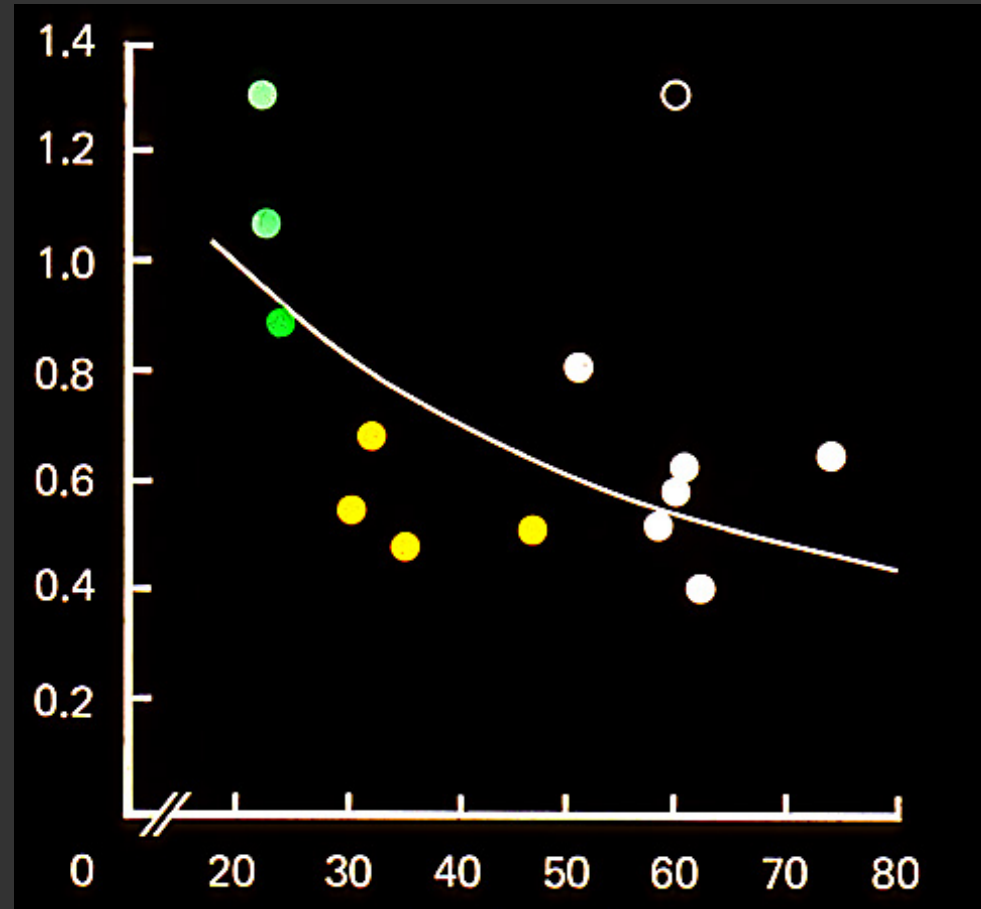
NB: $t_{1/2} \propto Vd / CL$

Pharmacokinetics in elderly patients

- **Reduced glomerular filtration**
- **Reduced tubular secretion**
- **Reduced liver volume (cf children)**
- **Increased proportion of body fat**
- **Reduced enzyme activity (frail elderly)**
- **Reduced protein binding ($\uparrow V_d$)(frail elderly)**
- **Reduced liver blood flow (\downarrow clearance)**

Theophylline clearance and age

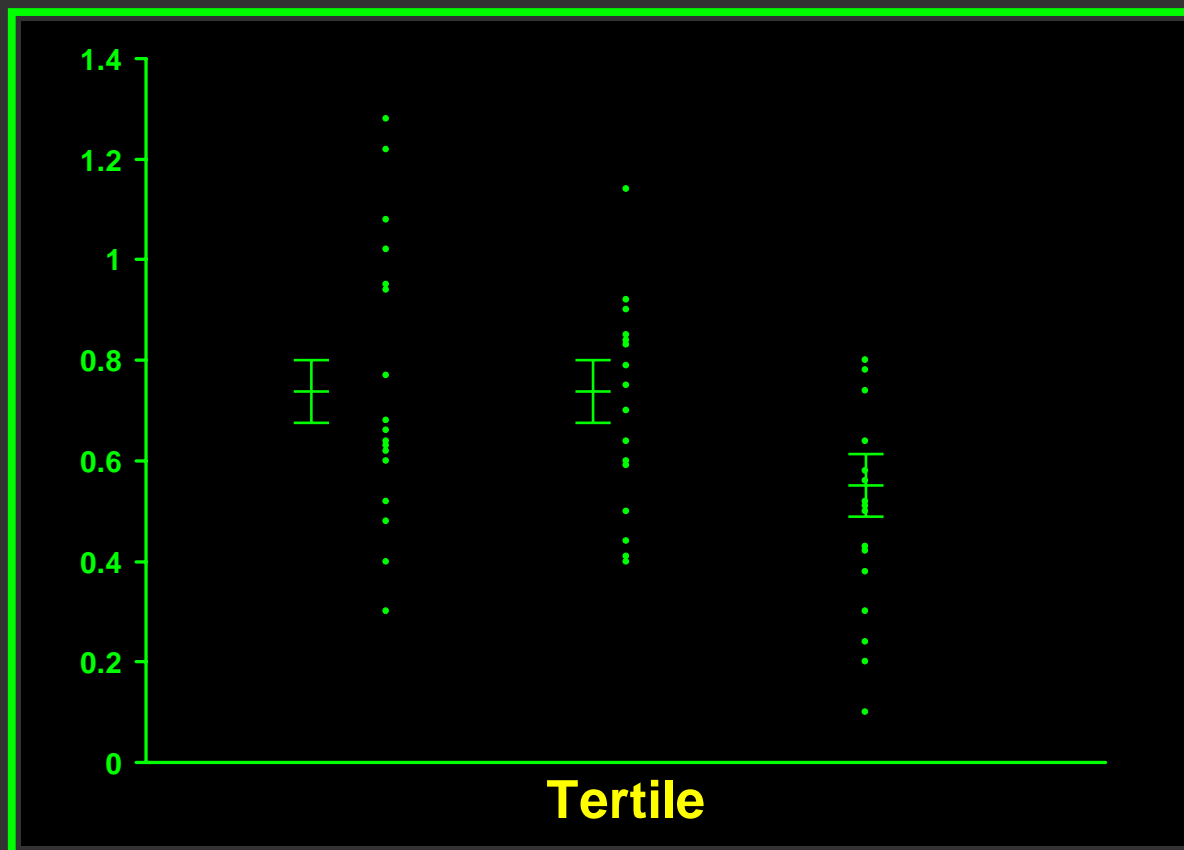
Theophylline clearance



Age

Theophylline clearance and age

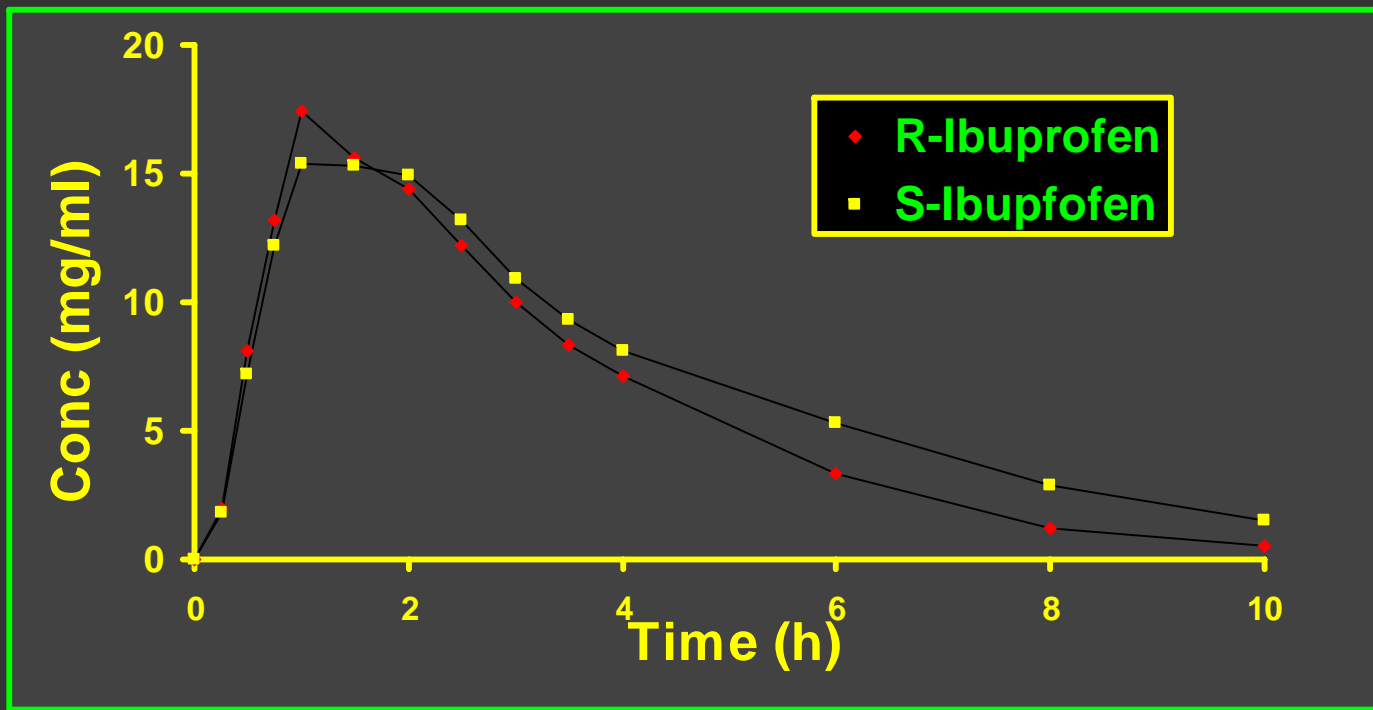
Theophylline clearance
(mL/min/kg CBW)



Lower Middle Upper

(age range 20 - 87 years)

Ibuprofen

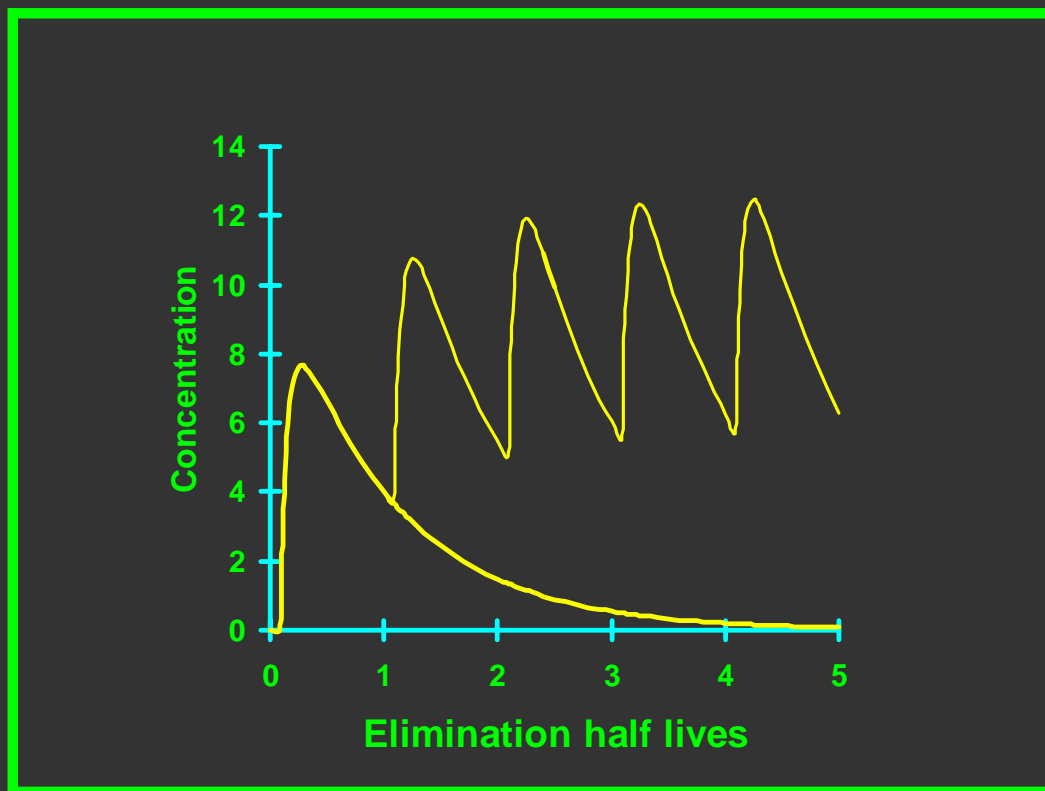


Age associated ↓ intrinsic CL of S ibuprofen

Disease states

- Migraine
 - ↓ rate of absorption
- Renal failure
 - ↓ renal CL
 - ↓ protein binding
 - ± Na and H₂O retention (↑ V → ↑ t_{1/2})
- Cardiac failure
 - Na and H₂O retention
 - Hepatic congestion (↓CL)
- Hepatic impairment
 - Na and H₂O retention
 - Hepatic congestion (↓CL)
 - ↓ protein binding (↑ V → ↑ t_{1/2})
 - ↓ presystemic metabolism
- Acute phase response
 - ↑ α₁ acid glycoprotein (↓V → ↑ t_{1/2})
- Small bowel disease
 - ↓ extent of absorption

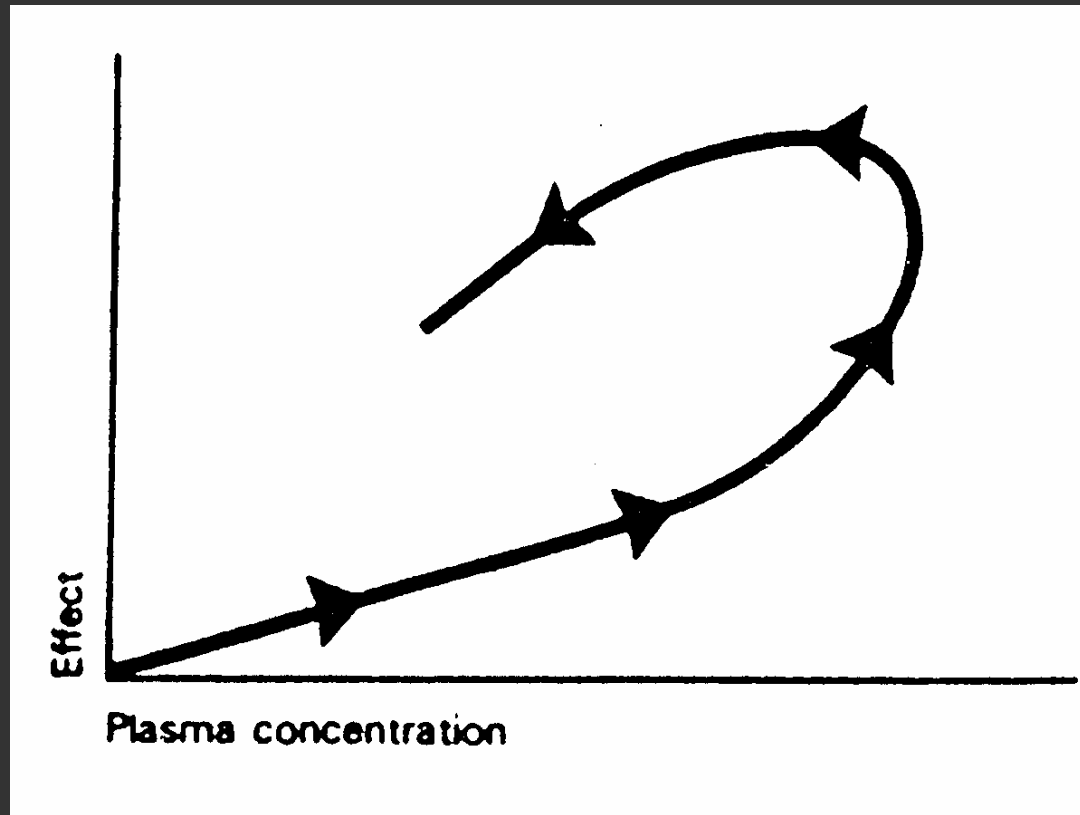
Chronic dosing



Accumulation

- **Steady state conc > single dose conc**
- **Occurs when dosing interval < 5 half lives
(ie almost always)**
- **Extent of accumulation determined by dosing interval and elimination half life**
- **4 - 5 half lives to reach steady state**
- **4 - 5 half lives to reach new steady state if half life changes**

Hysteresis loop



Pharmacodynamics in elderly patients

Age related changes in sensitivity (1):

- Benzodiazepines (↑)
- Warfarin (↑)
- β_1 modulators in cardiac tissue (↓)
- α modulators (↓)
- Hypotensives (↑)

Pharmacodynamics in elderly patients

Age related changes in sensitivity (2):

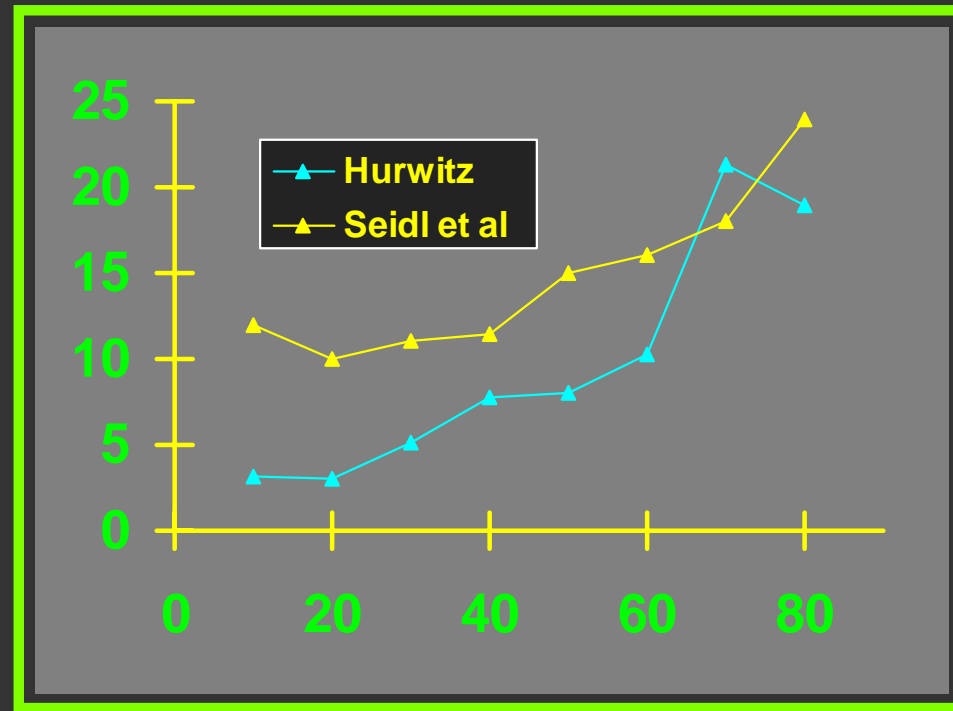
- Most effects of phenothiazines (↑)
- Calcium channel blocking effect on PR interval (↓)
- GI effects of NSAIDs (↑)
- Central effects of anticholinergics (↑)

Homeostatic mechanisms

- **Baroreflex**
- **Thermoregulation**
- **Posture**
- **GI integrity**
- **Volume/electrolyte homeostasis**

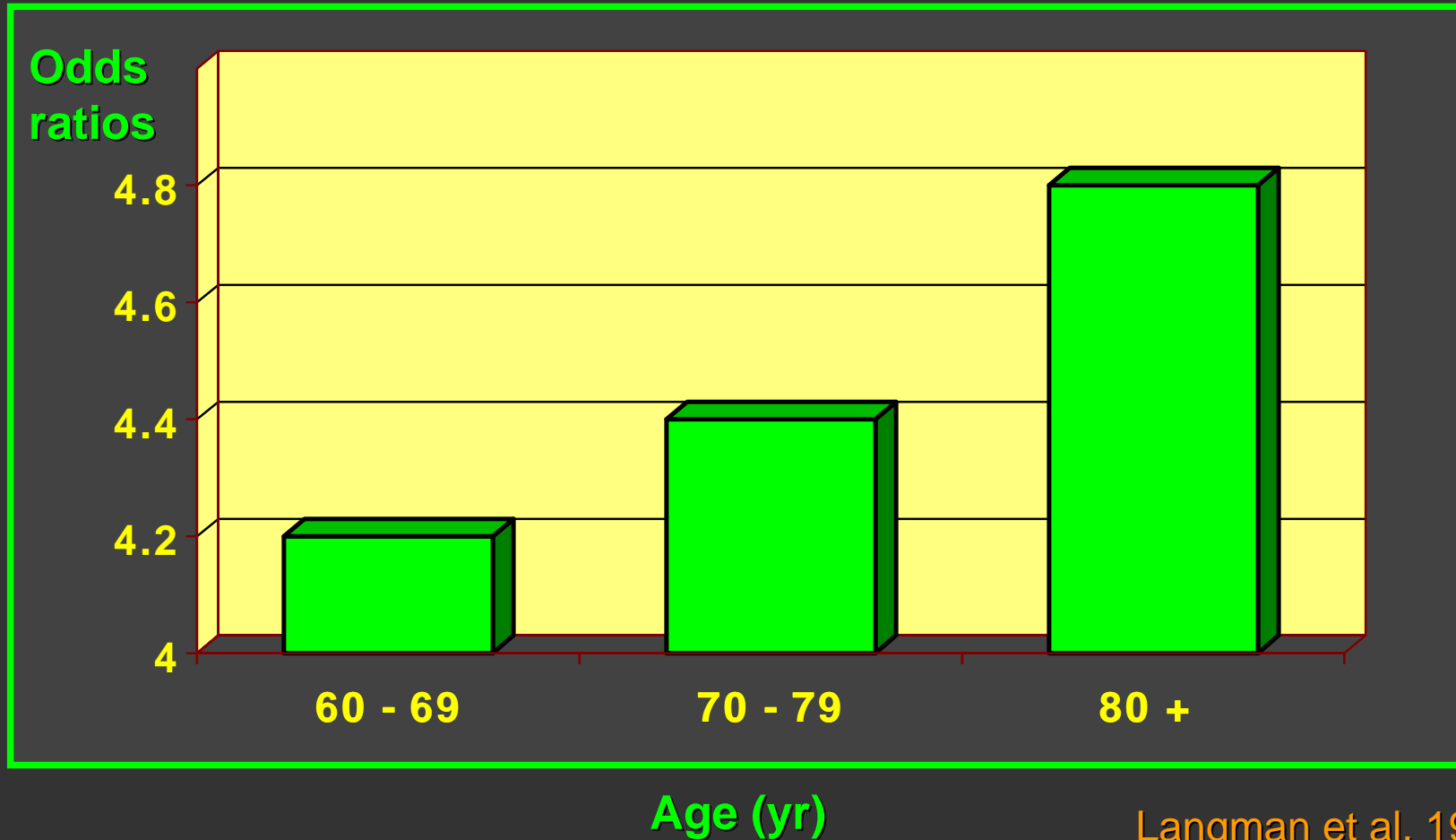
Adverse drug reactions

Prevalence (%)



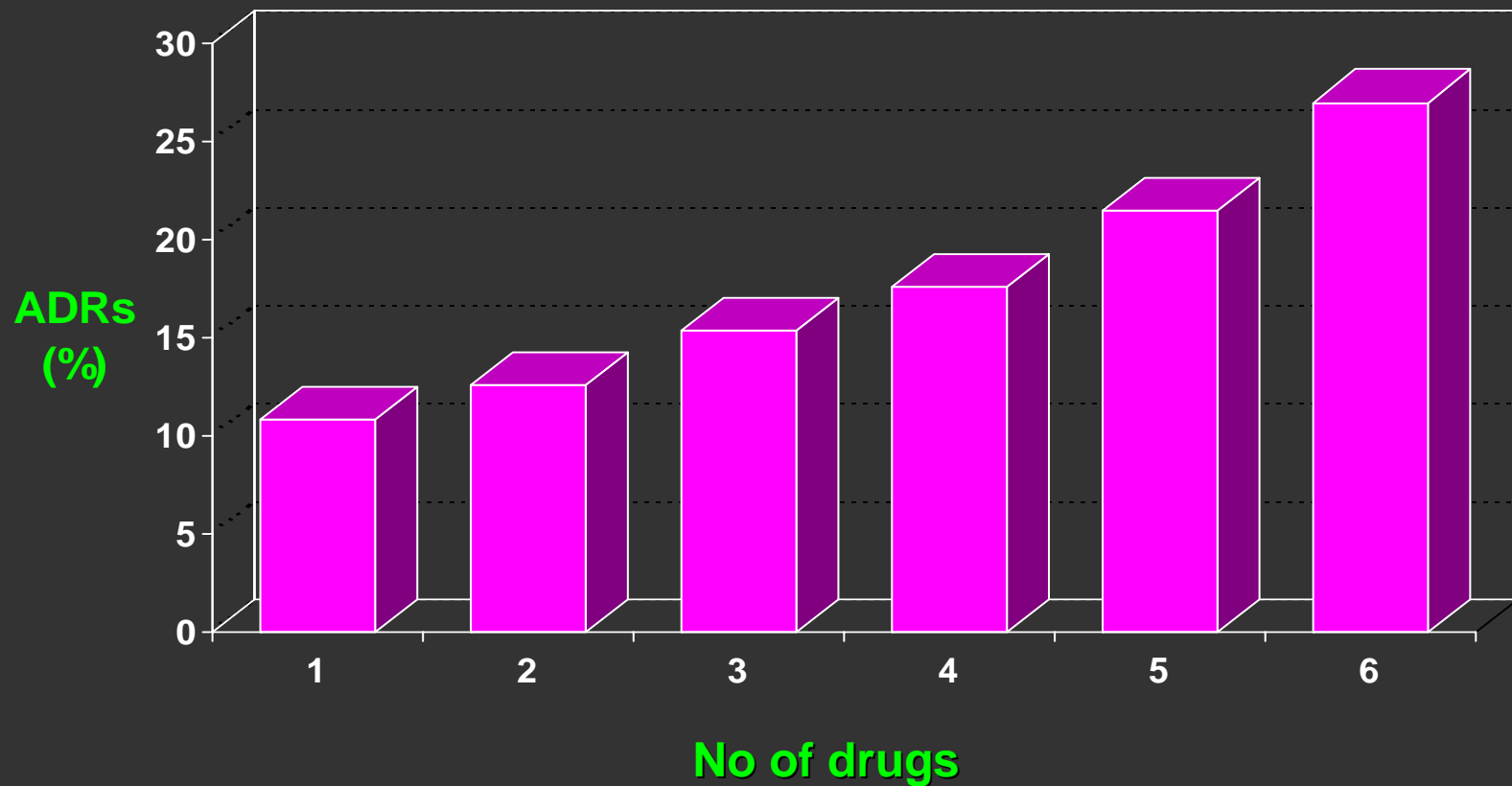
Age (years)

Odds ratios and ulcer complications



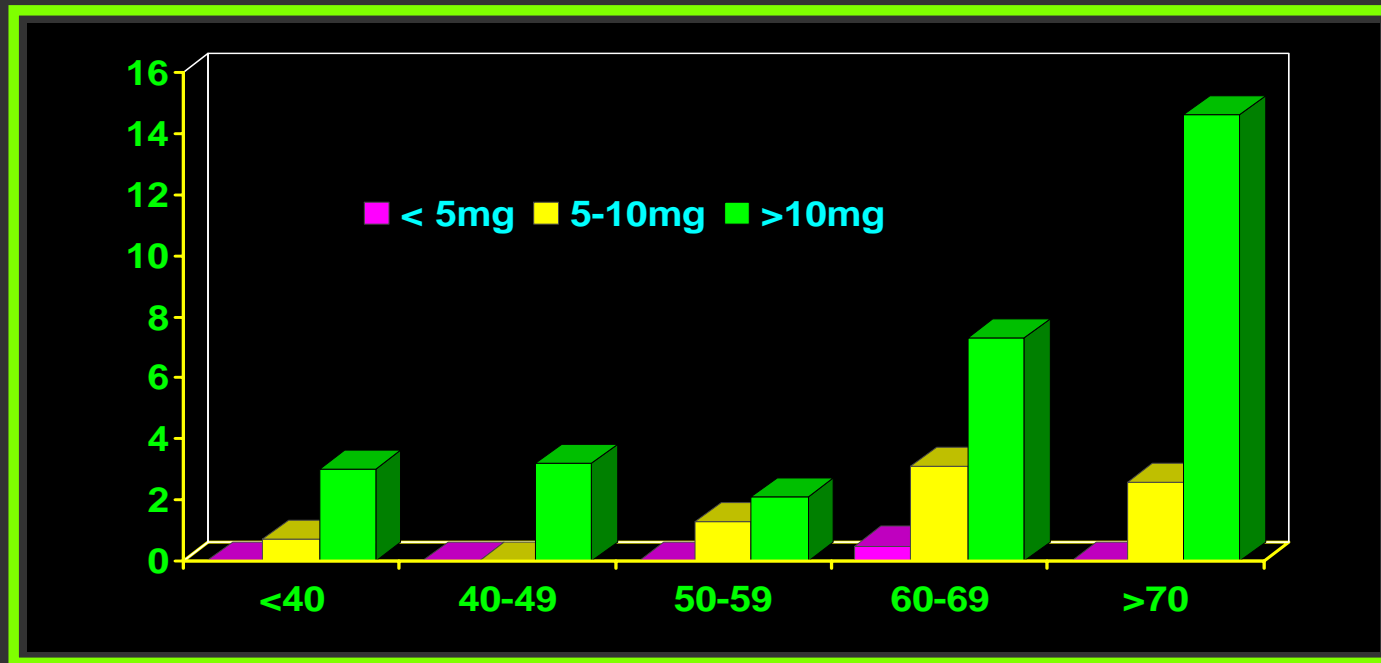
Langman et al, 1994

Adverse Drug Reactions



Adverse reactions to nitrazepam

Frequency of ADR (%)



Age (years)

Greenblatt & Allen, 1978

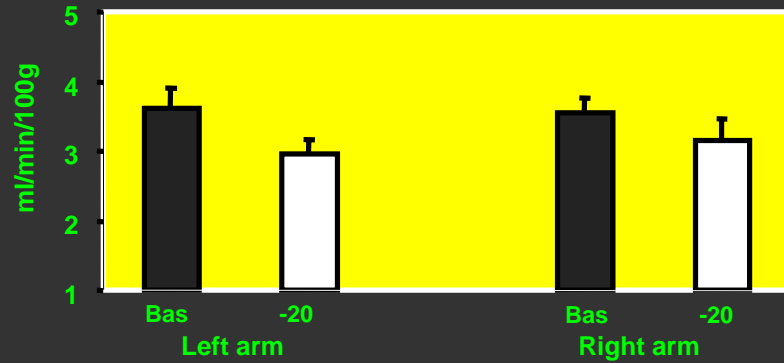
Adverse drug reactions

Excess prevalence in older patients

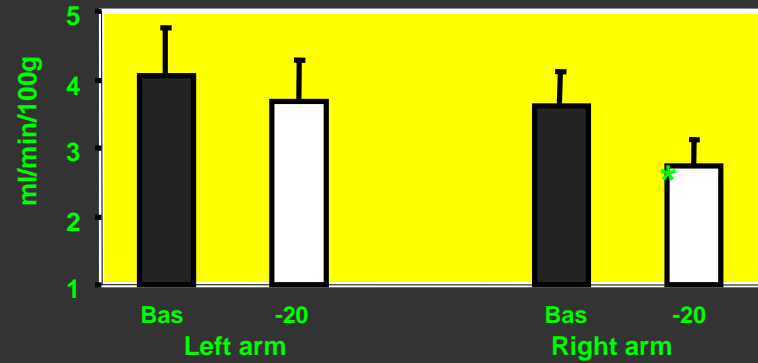
- **Pharmacokinetic changes**
 - distribution
 - renal function
 - liver volume
- **Changes in sensitivity to drugs**
 - impaired functional reserve eg BP homeostasis
 - change in “primary” sensitivity eg β receptor sensitivity
- **Higher prevalence of disease**
- **Concomitant drug consumption**

FABF during LBNP

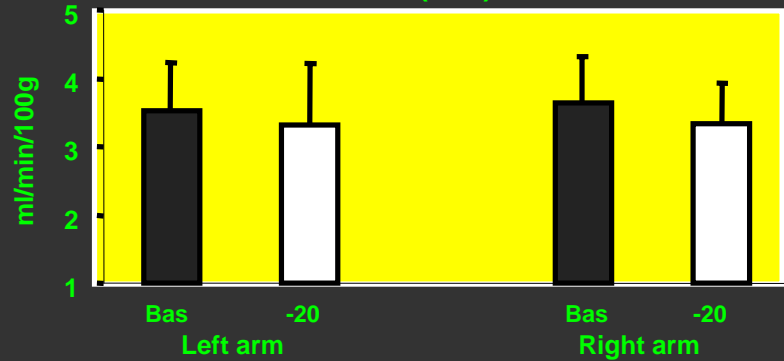
HYV (n=11)



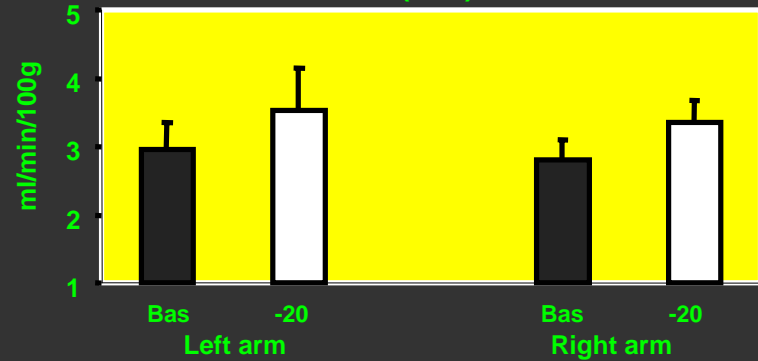
HEV (n=8)



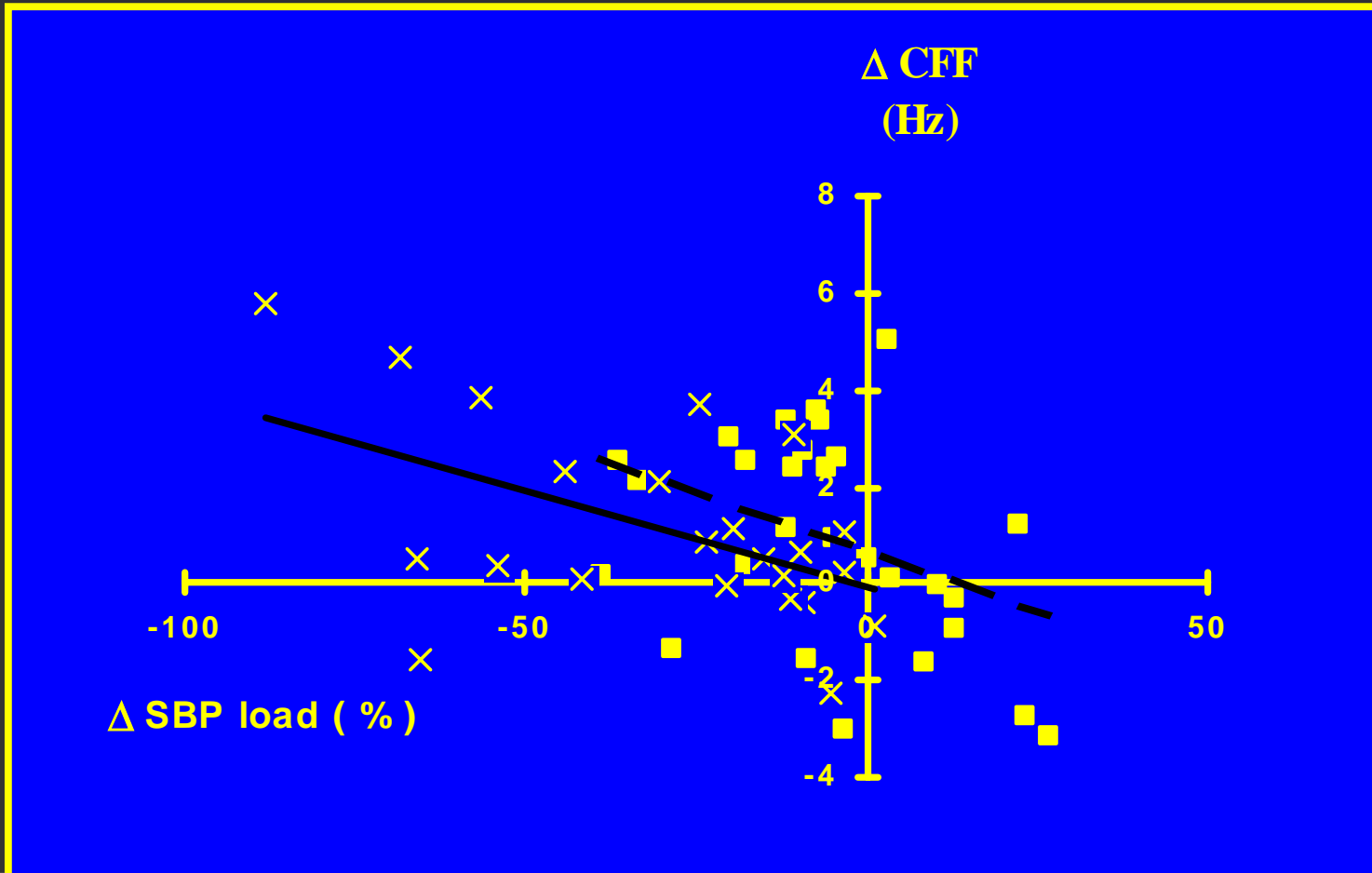
CI (n=3)



VD (n=5)



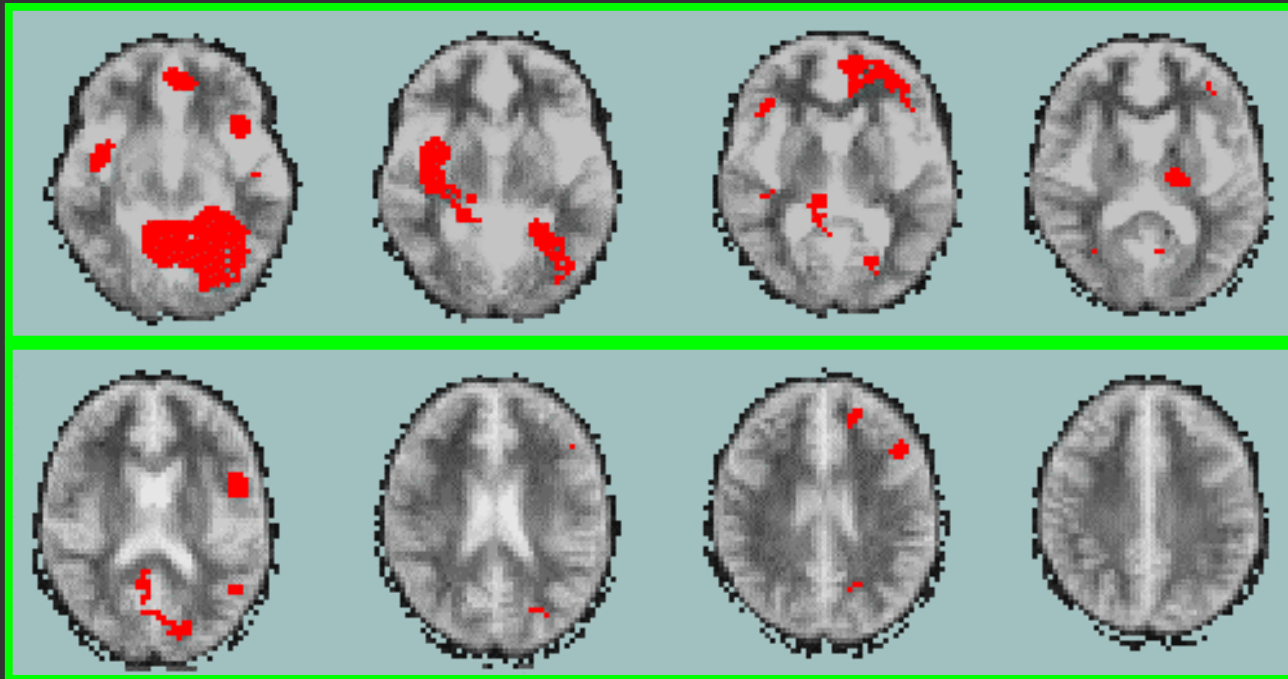
HT treatment and PP performance



Hypertension

Verbal working memory

Placebo



Active