IMPACT OF OBESITY ON DRUG DISPOSITION AND RESPONSE

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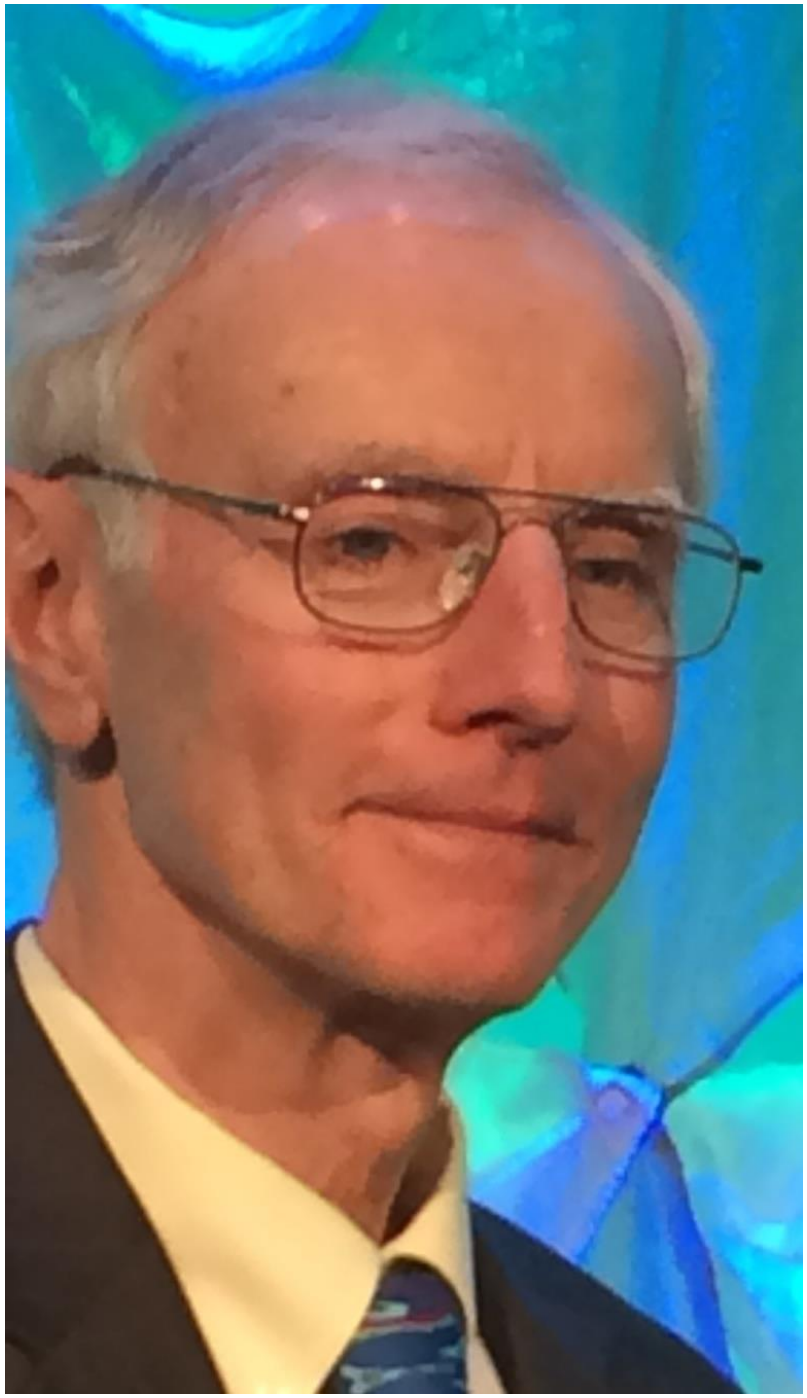
9 November 2022



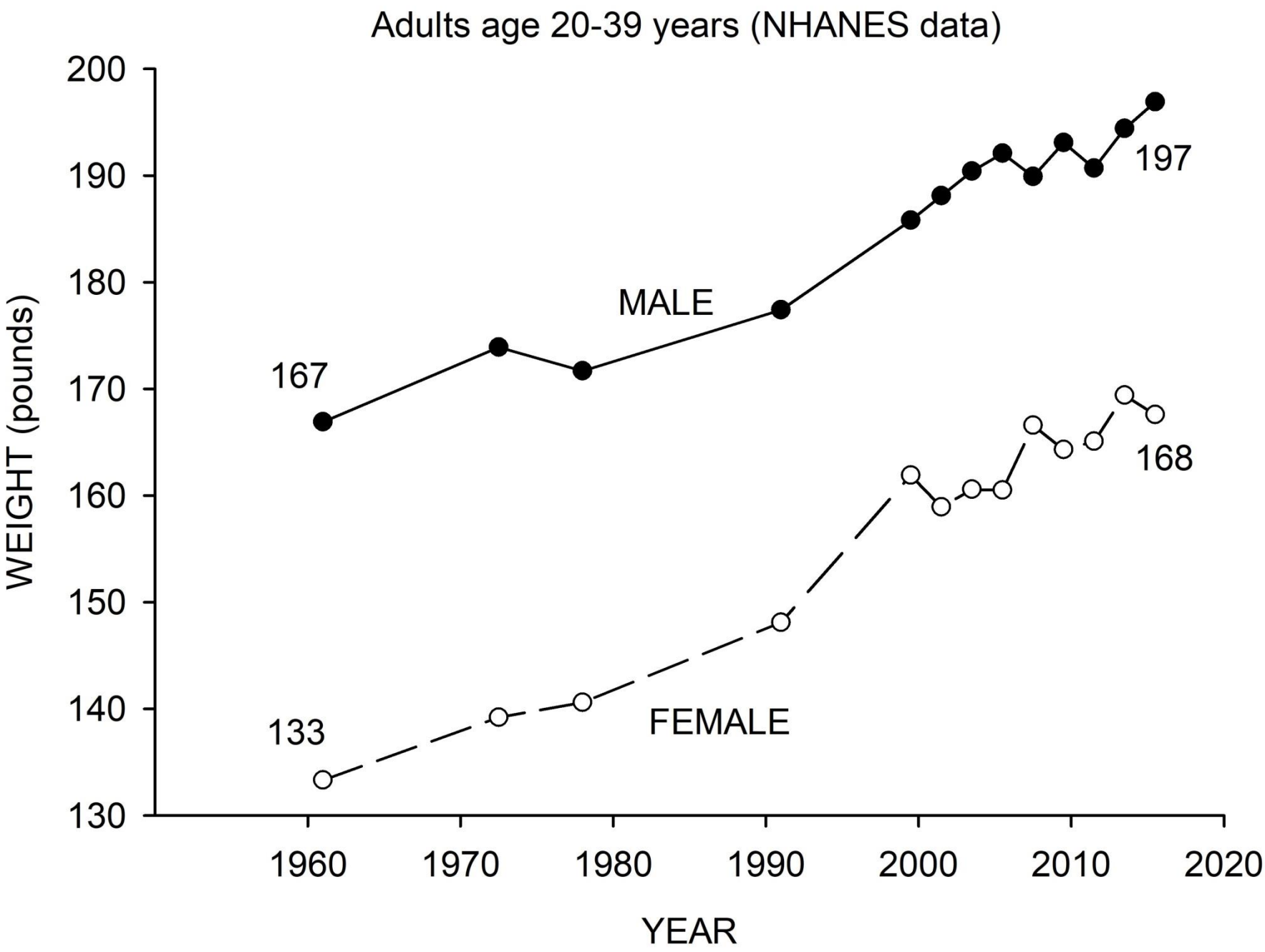
Darrell R. Abernethy
1949 - 2017

Tufts Post-Doc and Faculty
1979-1984

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

The Seventy-Kilogram Fantasy

Clinical Pharmacology
in Drug Development
2013; 2(2): 101–102


Adults age 20-39 years (NHANES data)
WEIGHT (pounds)
200
190
180
170
160
150
140
130
MALE
FEMALE
167
197
133
168
1960
1970
1980
1990
2000
2010
2020
YEAR

Co-morbid conditions:

- Hypertension
- Diabetes
- Cardiovascular disease
- Metabolic disorders (cholesterol, lipids)
- Depression
- Osteoarthritis
- Sleep apnea

Dr. Abernethy's Research Questions:

- How do you measure obesity?
- How do you measure volume of distribution?
- What is the physiologic (not arithmetic) relation between volume of distribution, half-life, and clearance?
- How does obesity modify drug distribution? What is the relation to lipid solubility?
- How does obesity modify clearance?
- How does this influence pharmacologic treatment of the obese patient?

Additional questions: The influence of old age and gender

QUANTITATIVE MEASURES OF OBESITY

- Weight
- Weight-height combinations (Ponderal Index, BMI, etc.)
- Waist circumference
- Percent ideal body weight
- Skinfold thickness

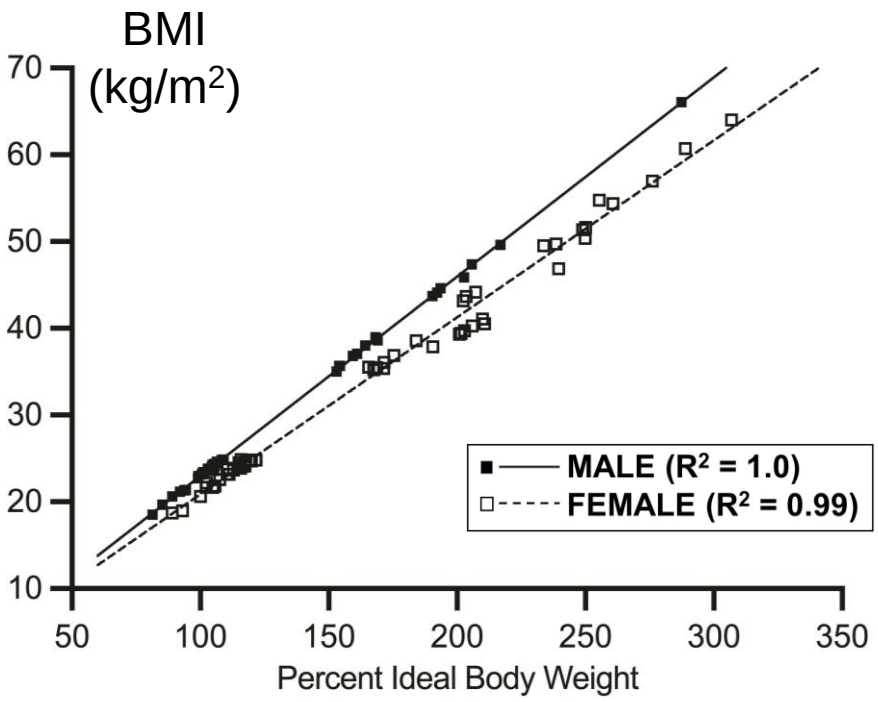
- Hydrostatic weighing
- Bioelectric impedance
- DXA (Dual-Energy X-Ray Absorptiometry)

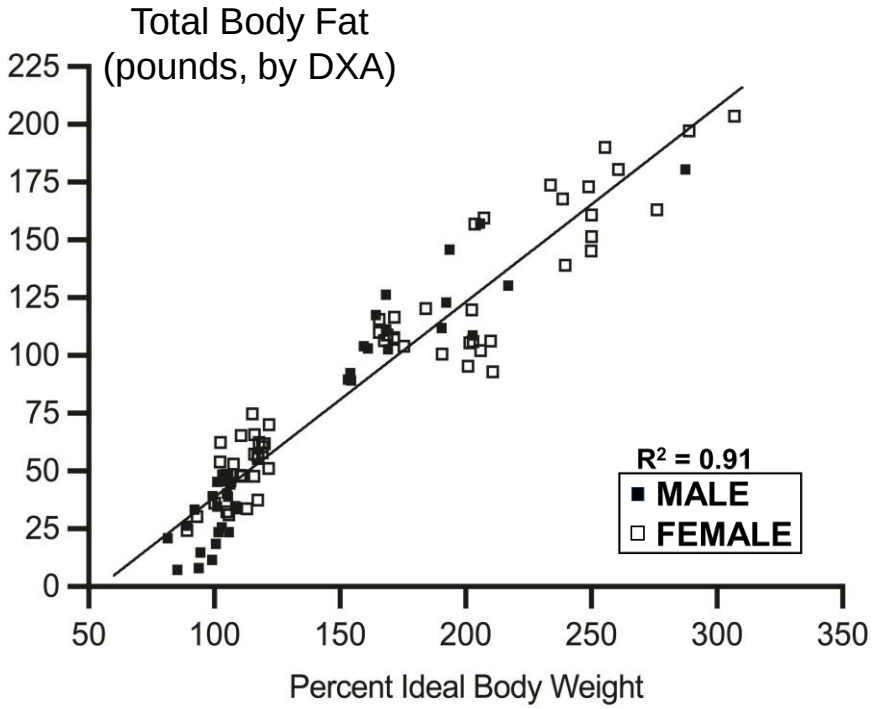
QUANTITATIVE MEASURES OF OBESITY

Percent ideal body weight

IBW (pounds) = 100 + 5 (Height – 60 inches) for women
110 + 5 (Height – 60 inches) for men

% IBW = [(actual weight) / IBW] x 100





J Clin Pharmacol. 2022; 62: 1350-1363

INITIAL CLINICAL QUESTION:

For a specific individual drug,
how does degree of obesity influence
drug distribution and clearance?

(Drug entity is fixed; degree of obesity is variable)

VOLUNTEER SUBJECTS

(1979-1984)

Category	Weight	% Ideal Weight
Healthy controls	65 kg (142 pounds)	99%
Obese	114 kg (251 pounds) (Max: 435 pounds)	179%

(Male and female mixed in both groups)

STUDY DESIGN

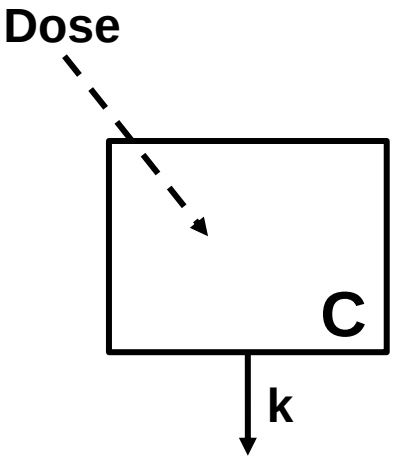
19 drugs studied;
N = 20 to 40 subjects per study;
More than 600 total trials!

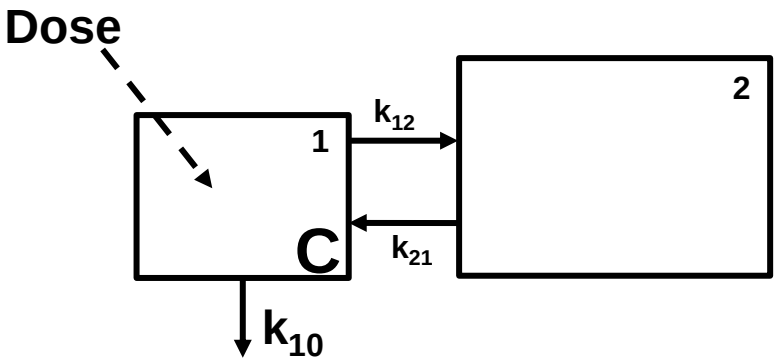
- Single intravenous dose, or
- Single oral dose, if F = 1
- Multiple blood samples
- Determine $T_{½}$, V_d, Clearance

Pharmacokinetic analyses done by Jerold S. Harmatz

How do you measure volume of distribution?

$$V_d = \frac{X}{C}$$



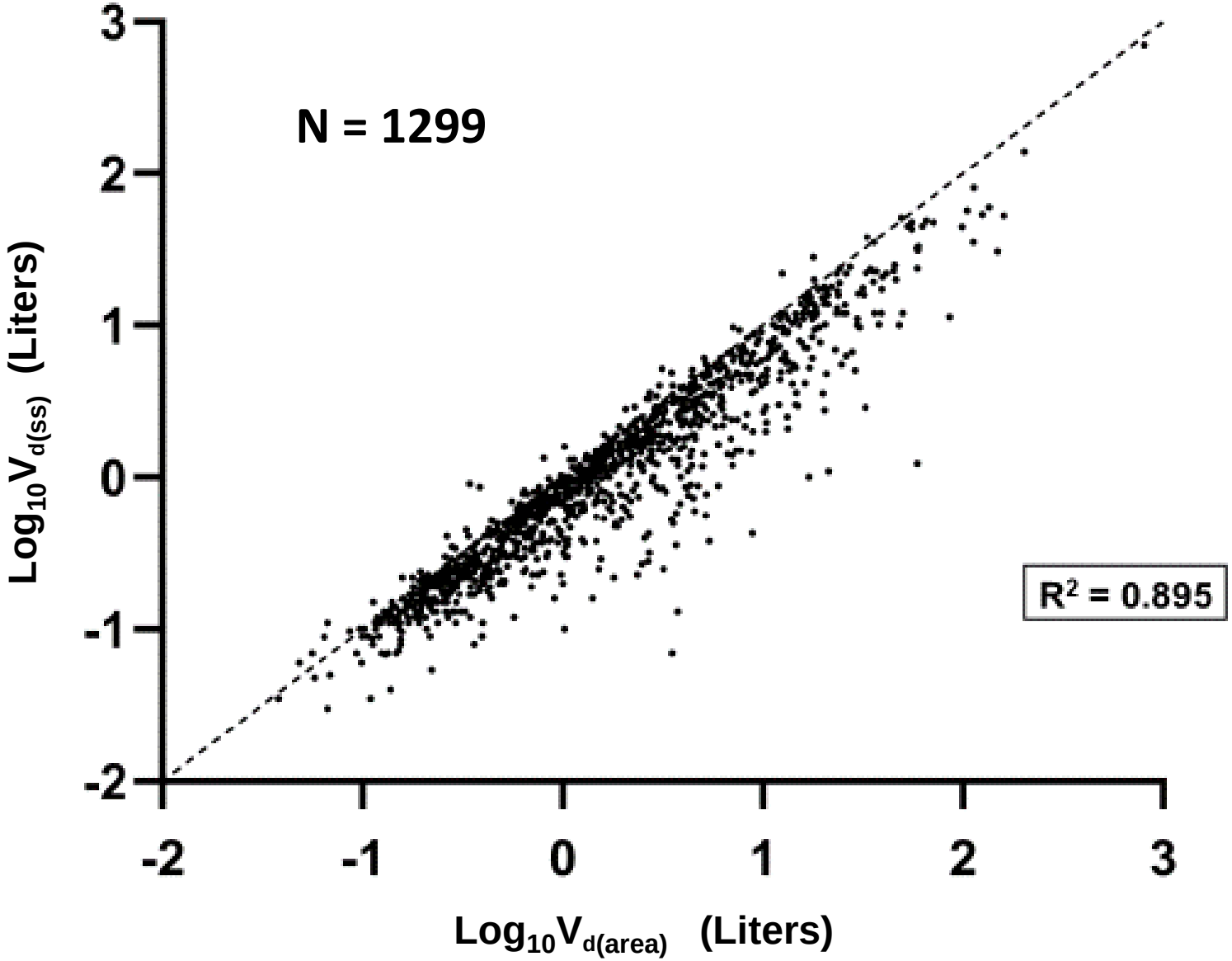


$V_{d(ss)}$ vs. $V_{d(area)}$?

Neither is "dependent" on elimination;
both are independent physiologic determinants of $T_{1/2}$

$V_{d(area)}$ used in all studies

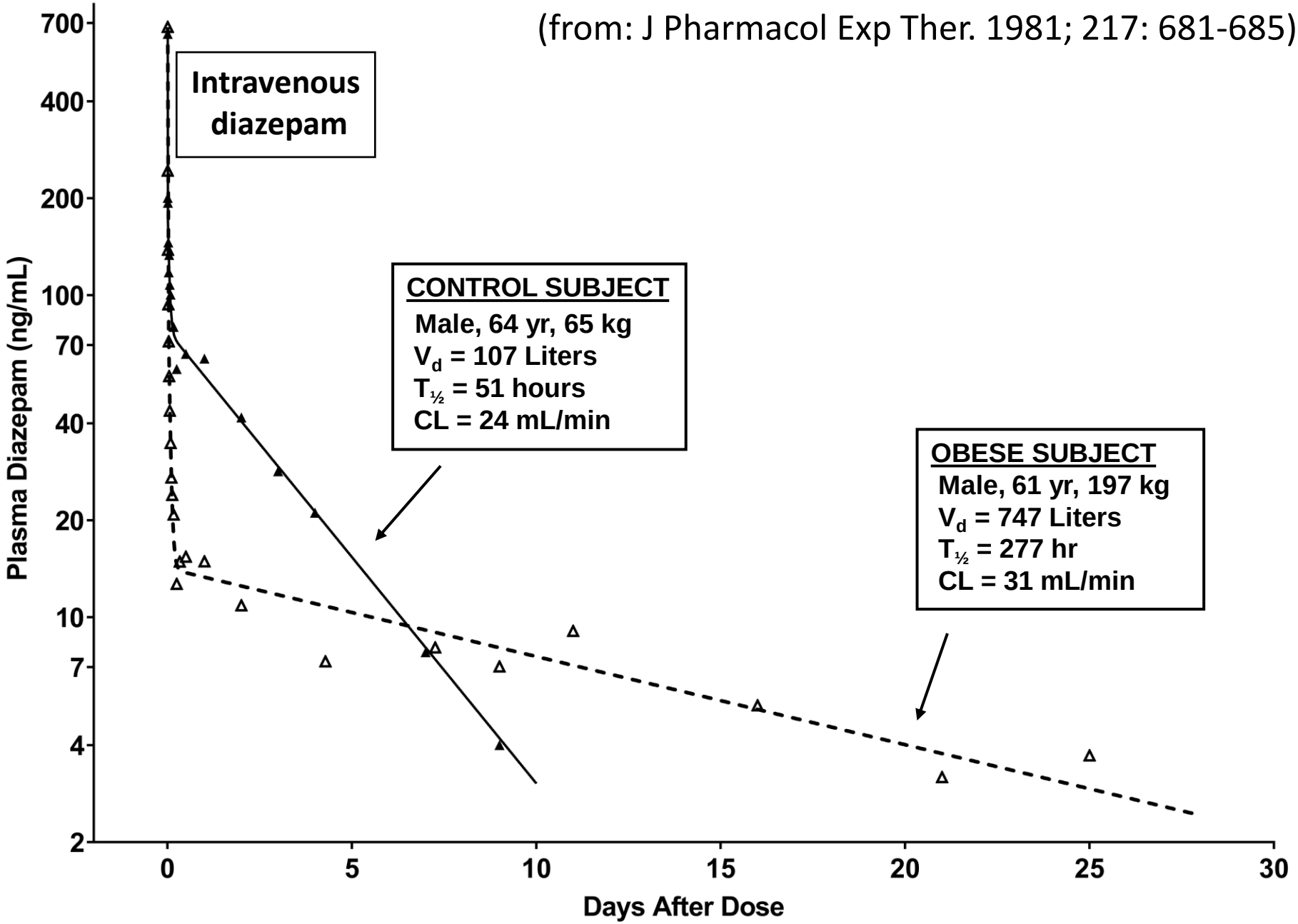
***J Pharm Sci* 1969; 58: 193-197 and 639-641**
***J Clin Pharmacol* 1983; 23: 391-400**
***Clin Pharmacol Drug Dev* 2014; 3: 419-420**
***J Clin Pharmacol* 2022; 62: 1350-1363**

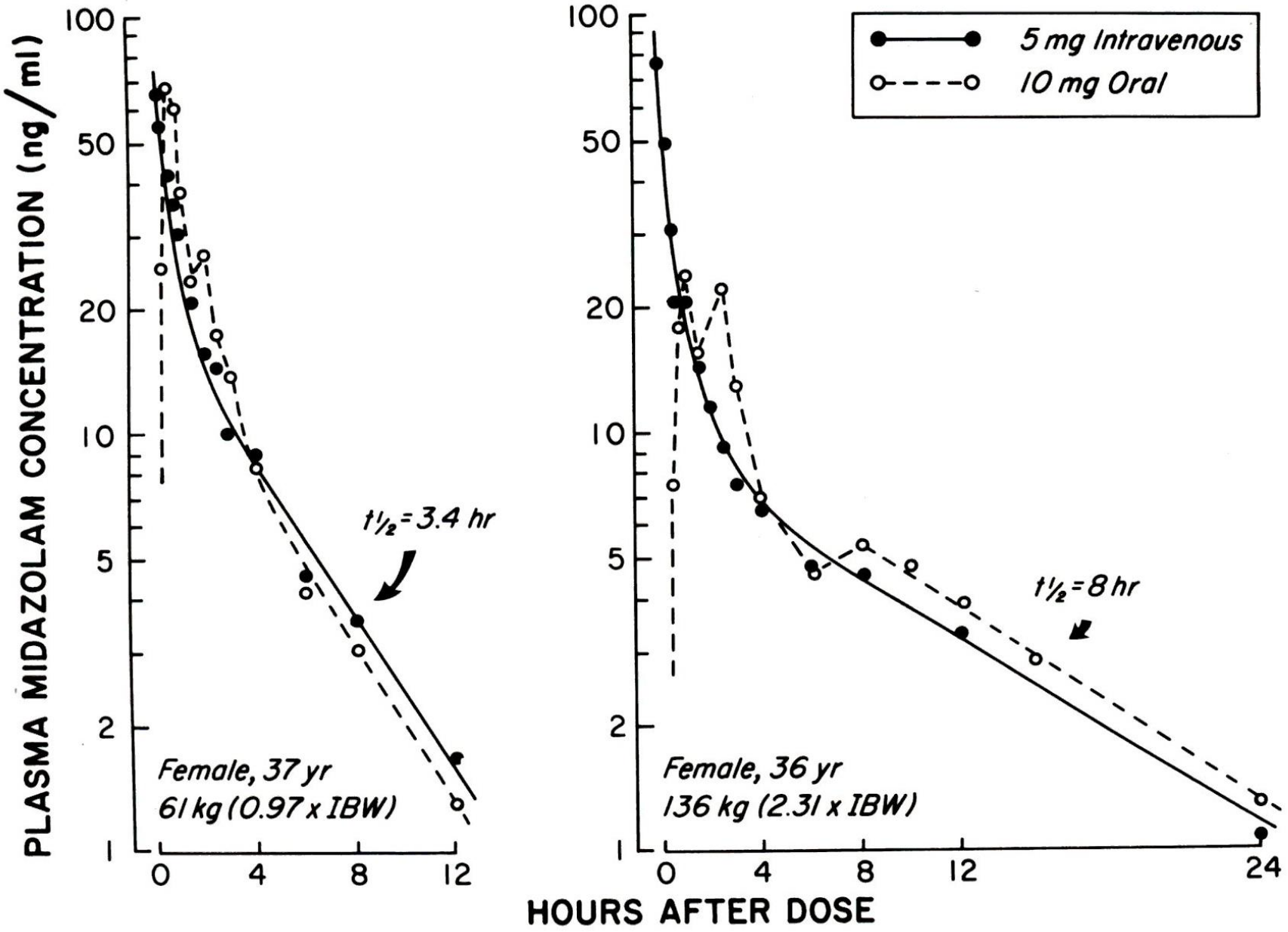


J Clin Pharmacol. 2022; 62: 1350-1363

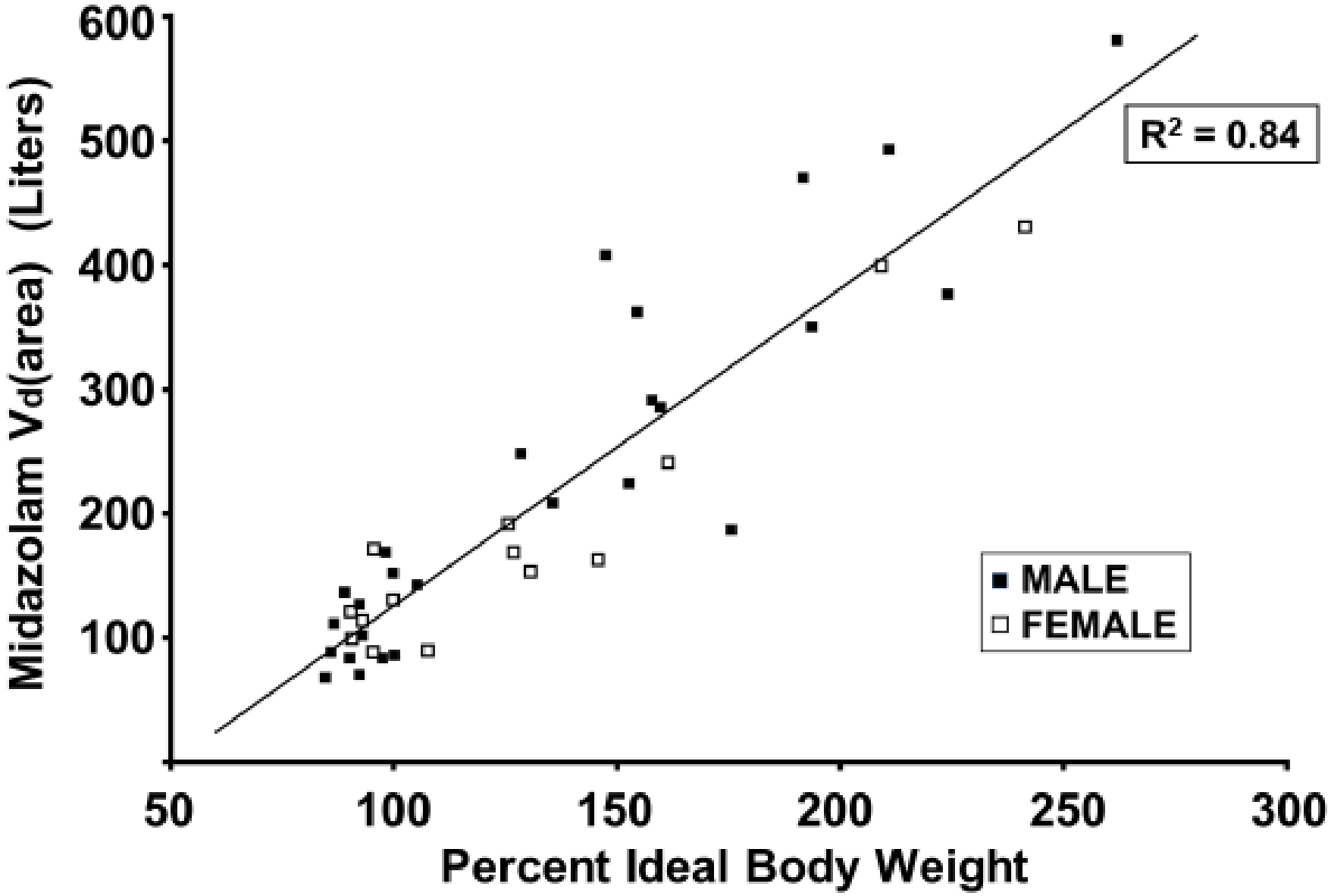
From: Lombardo F, et al. Drug Metab Disp. 2018; 46: 1466-1477

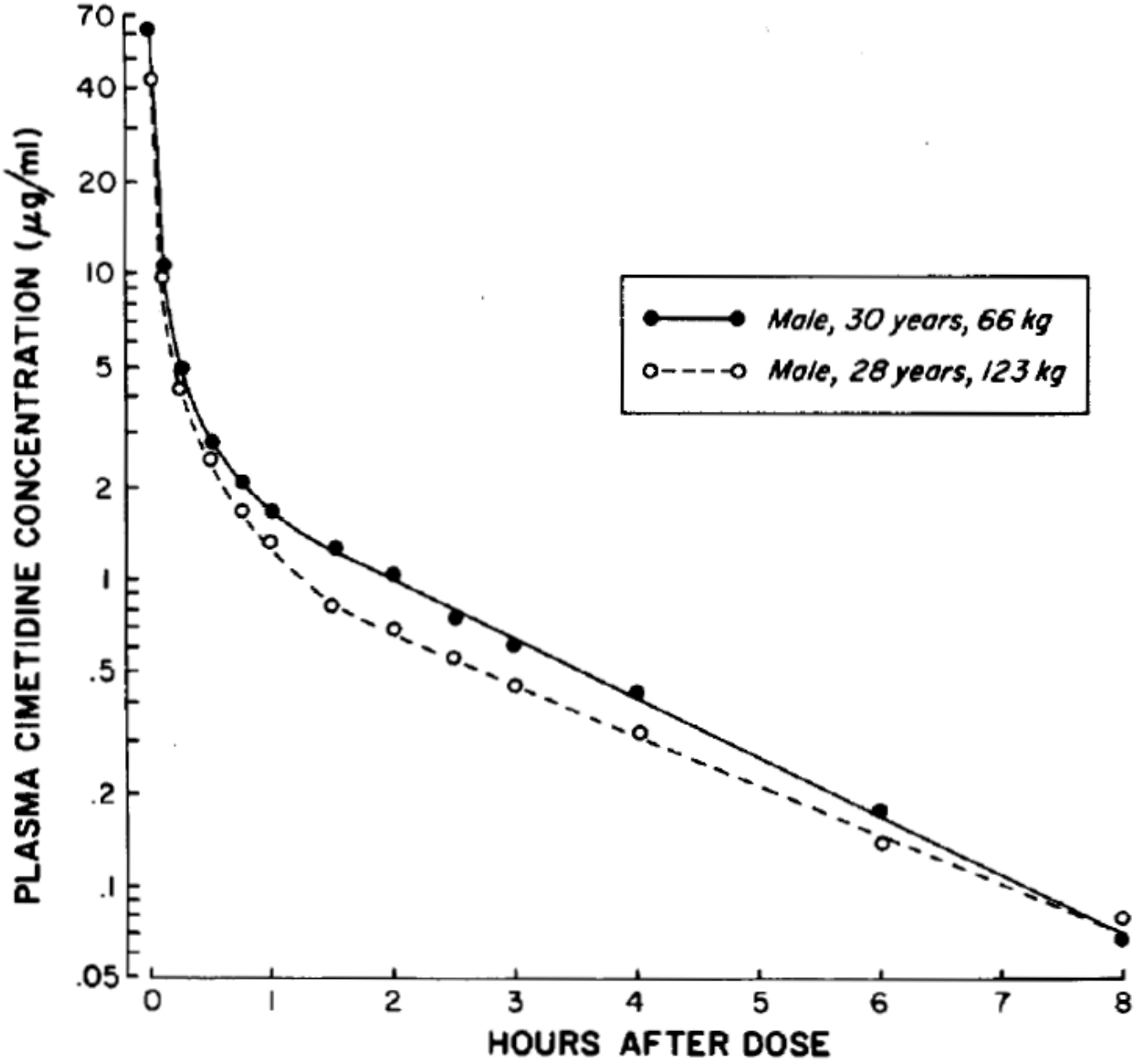
J Clin Pharmacol. 2022; 62: 1350-1363
(from: J Pharmacol Exp Ther. 1981; 217: 681-685)



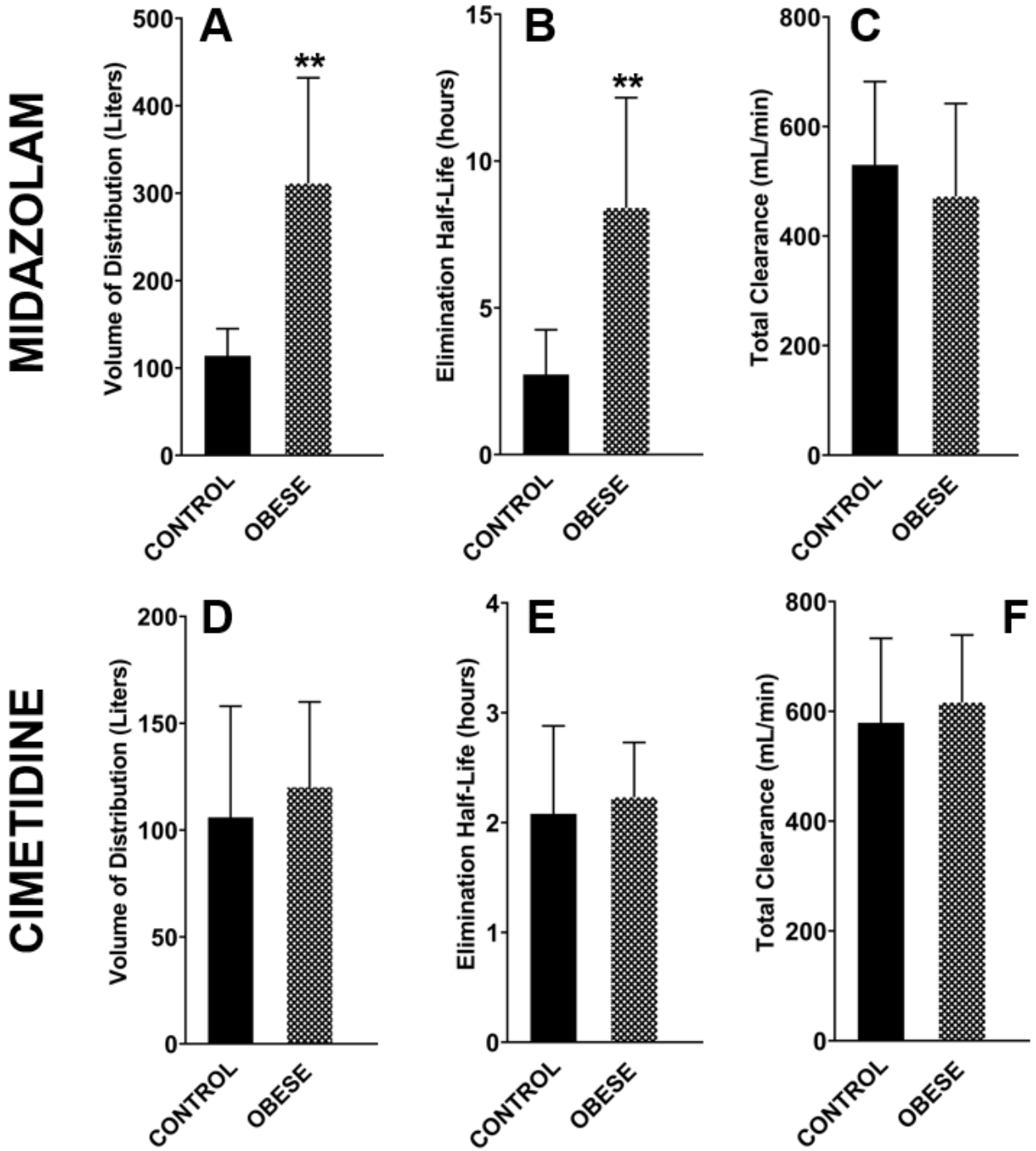


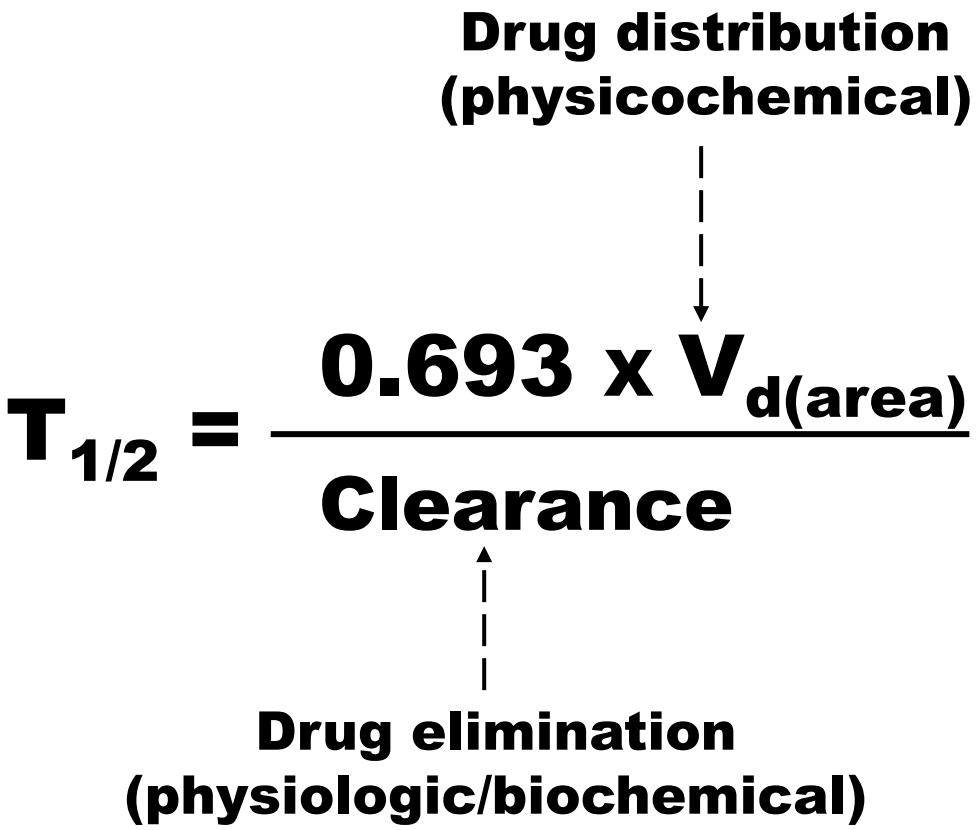
Anesthesiology 1984; 61: 27-35


Midazolam V_d(area) (Liters)
600
500
400
300
200
100
50
100
150
200
250
300
Percent Ideal Body Weight
R^2 = 0.84
MALE
FEMALE



Abernethy DR. Am J Gastroenterol. 1984;79:91-94

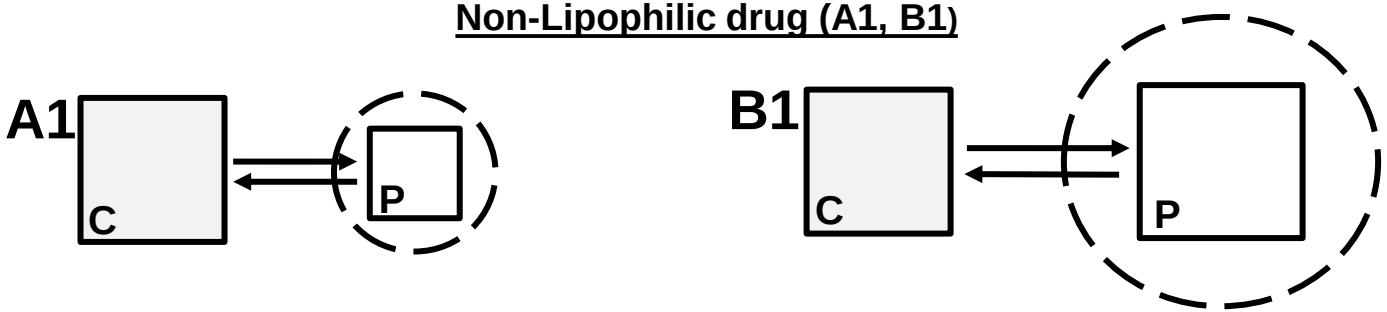

MIDAZOLAM
CIMETIDINE
A
B
C
D
E
F
Volume of Distribution (Liters)
Elimination Half-Life (hours)
Total Clearance (mL/min)
**
**
CONTROL
OBESE
0
100
200
300
400
500
5
10
15
600
800
50
150
1
2
3
4



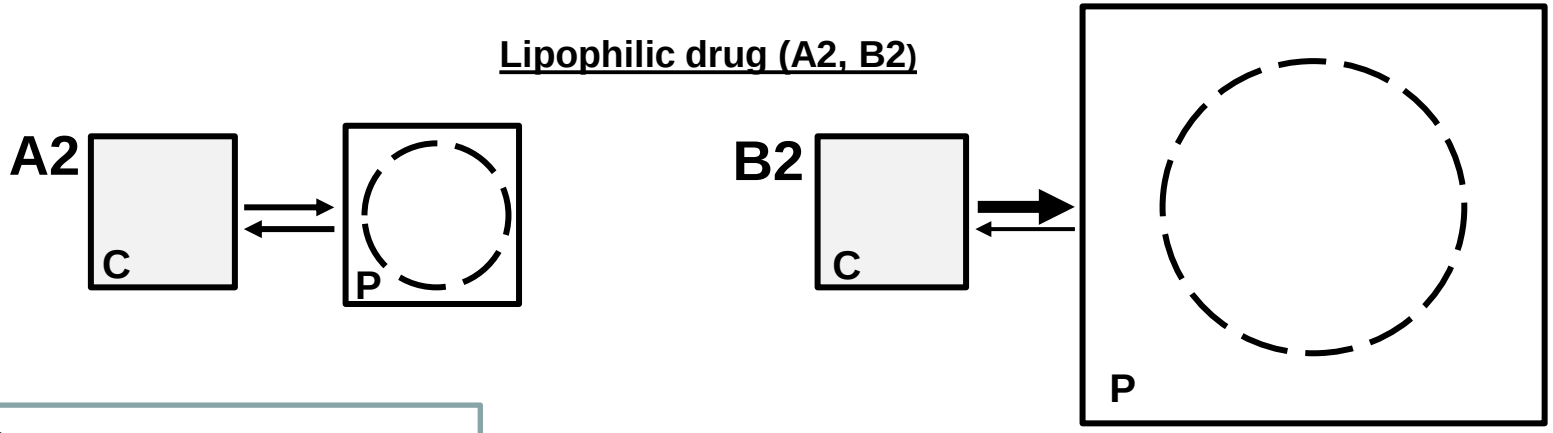
Clearance and volume of distribution are independent of each other.

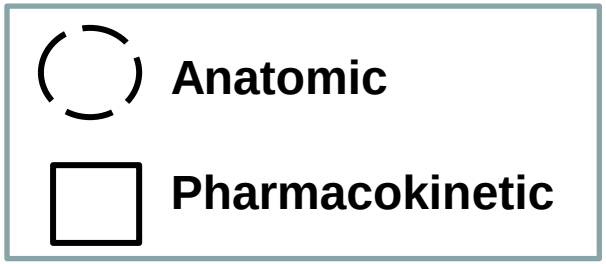
NORMAL-WEIGHT SUBJECT (A1, A2) **OBESE SUBJECT (B1, B2)**

Non-Lipophilic drug (A1, B1)



Lipophilic drug (A2, B2)



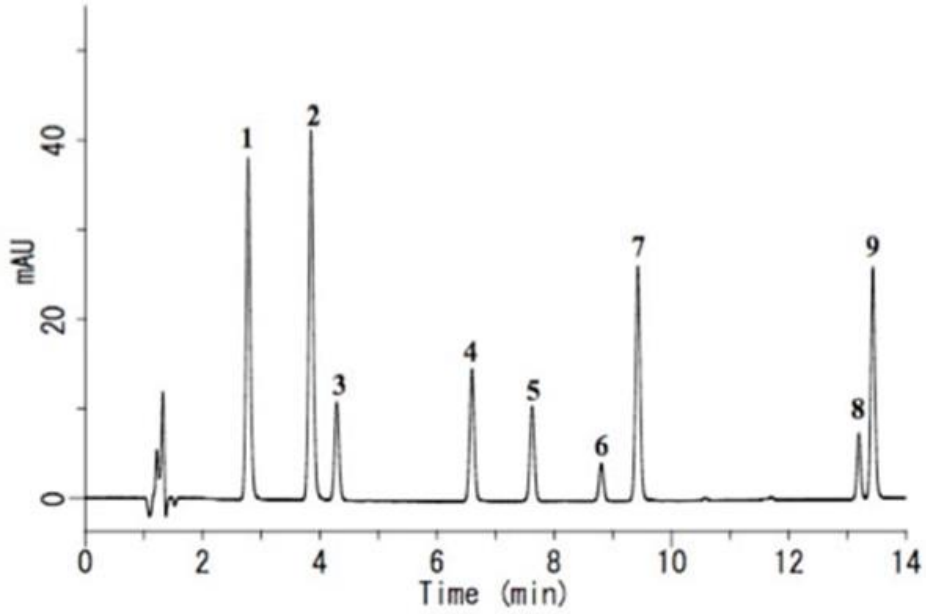


How do you measure lipid solubility?

PARTITION COEFFICIENTS

- octanol:water
- $Log_{10}P$

REVERSE-PHASE HPLC RETENTION TIME



- Log_{10} HPLC retention

NEXT CLINICAL QUESTION:

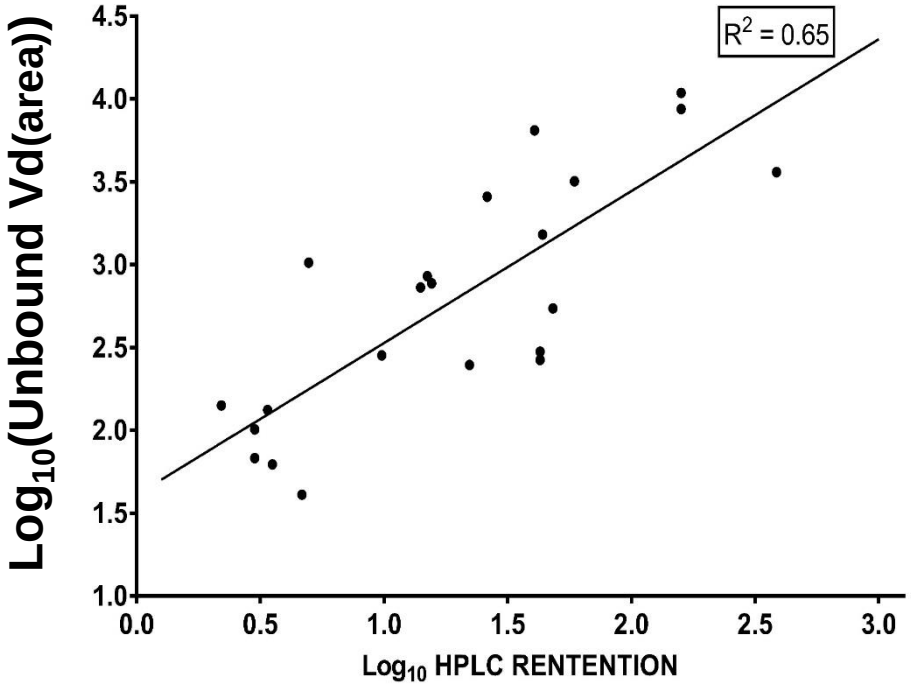
For a specific degree of obesity, how does lipid solubility across a series of drugs influence drug distribution and clearance?

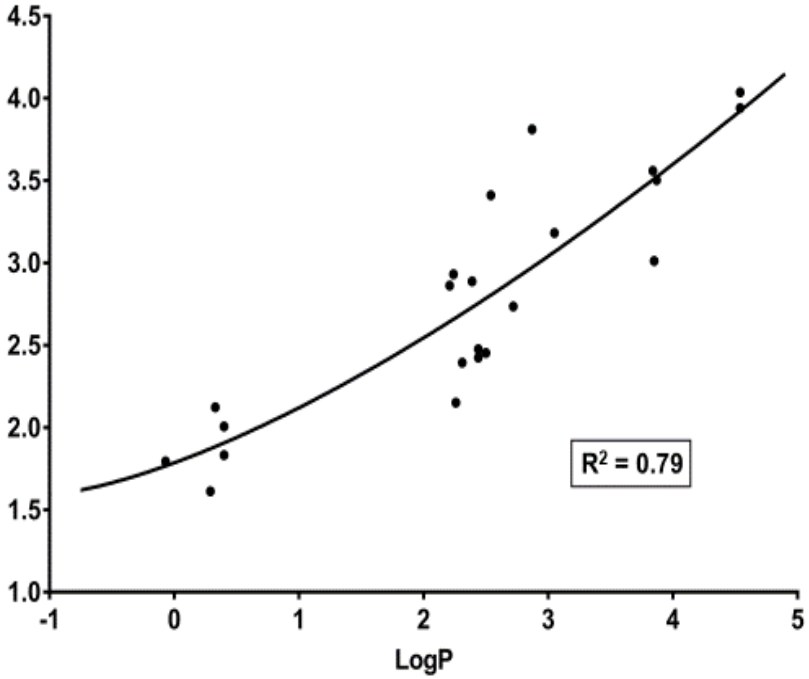
(Degree of obesity is fixed; drug lipid solubility is variable)

Category of lipophilicity based on Log_{10} of high-pressure liquid chromatographic retention		
Low (≤0.95)	**Intermediate (0.96–1.35)**	**High (≥1.36)**
Acetaminophen	Alprazolam	Desmethyldiazepam
Antipyrine	Lorazepam	Diazepam
Caffeine	Nitrazepam	Imipramine
Cimetidine	Oxazepam	Lidocaine
Ibuprofen	Phenytoin	Midazolam
Salicylate		Propranolol
		Trazodone
		Verapamil

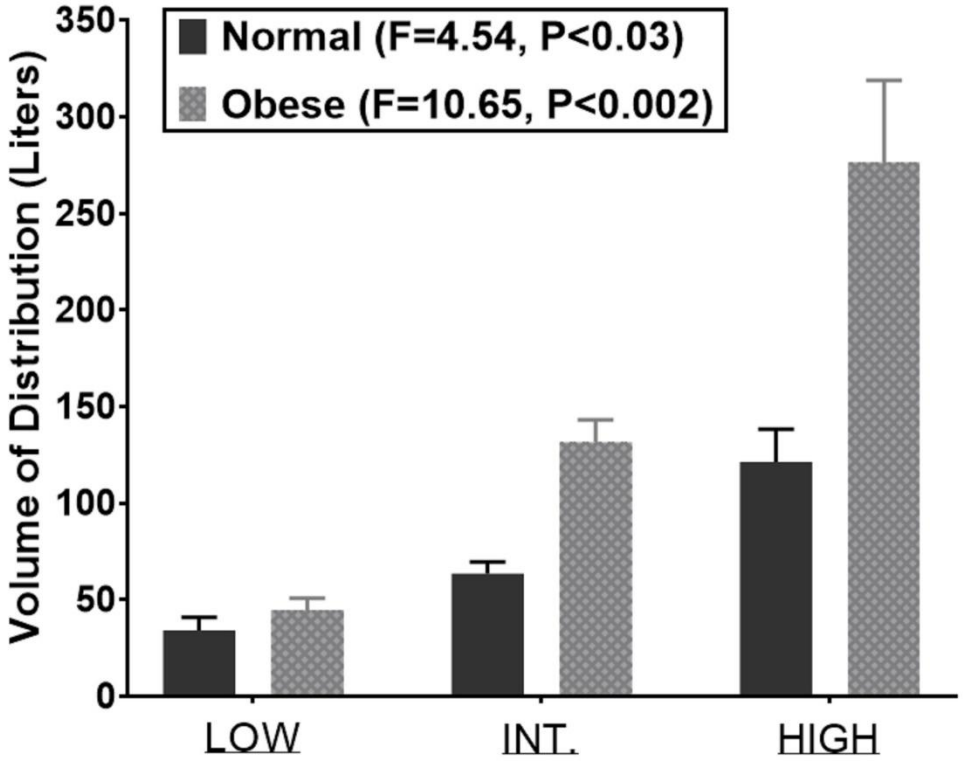
Bruno CD et al. Br J Clin Pharmacol. 2021; 87: 3197-3205

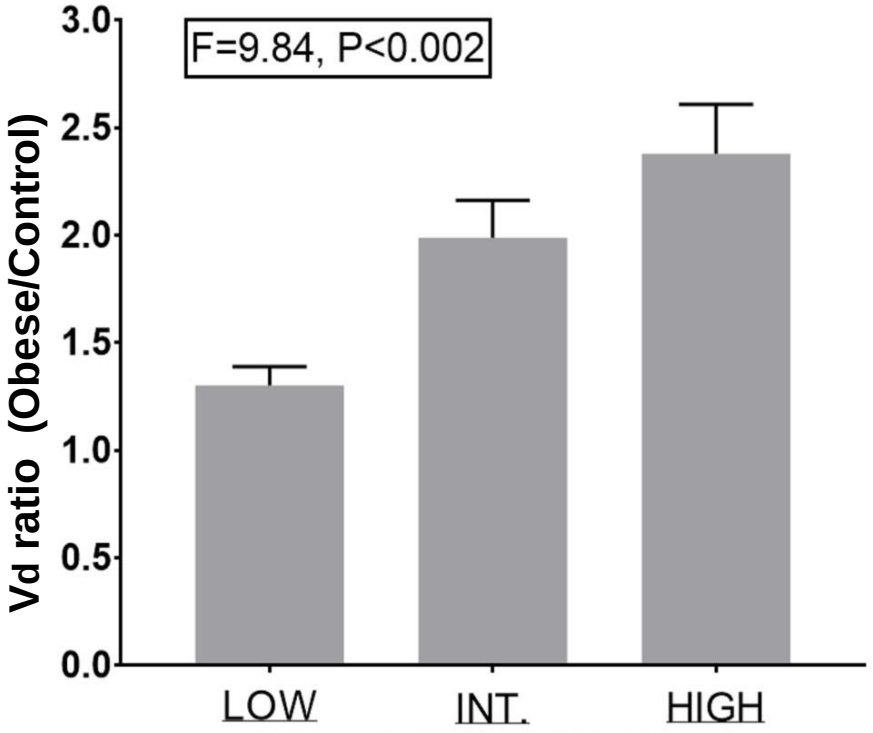
Non-obese control subjects





Bruno CD et al. Br J Clin Pharmacol. 2021; 87: 3197-3205





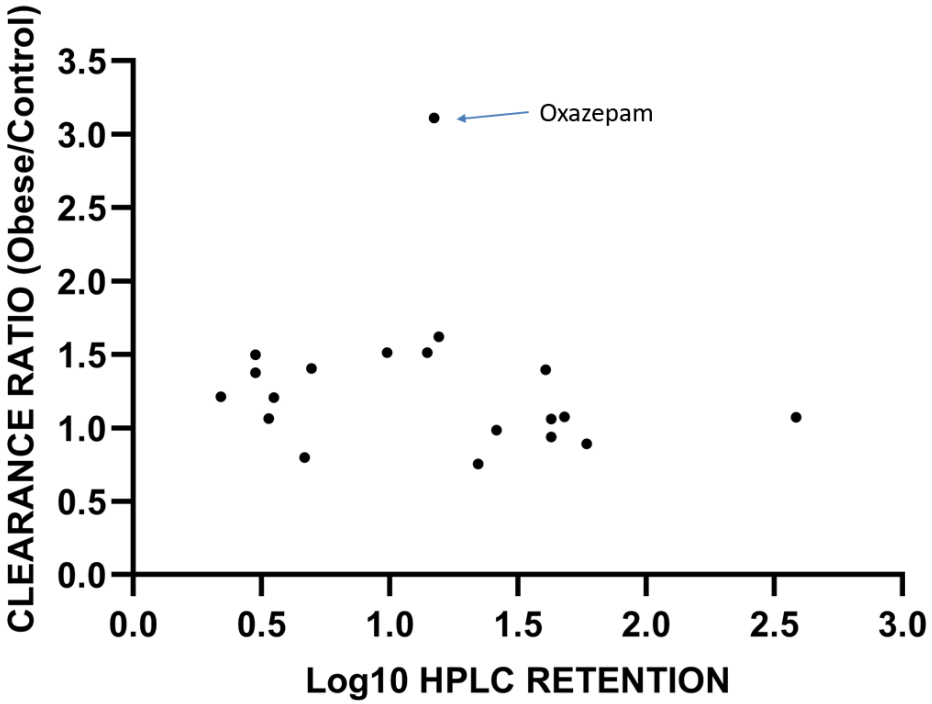
HPLC RETENTION CATEGORY

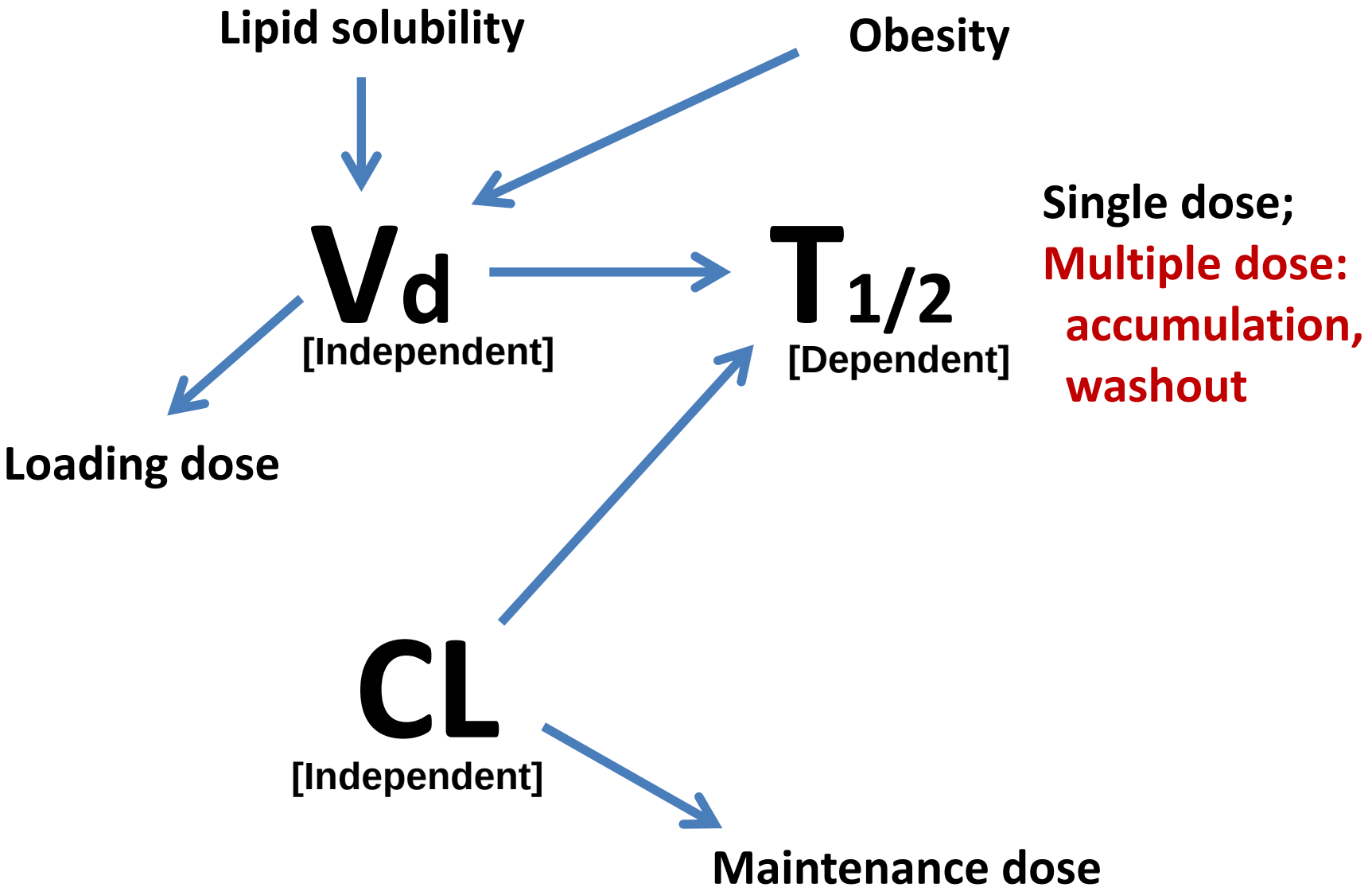
Clearance in Obesity

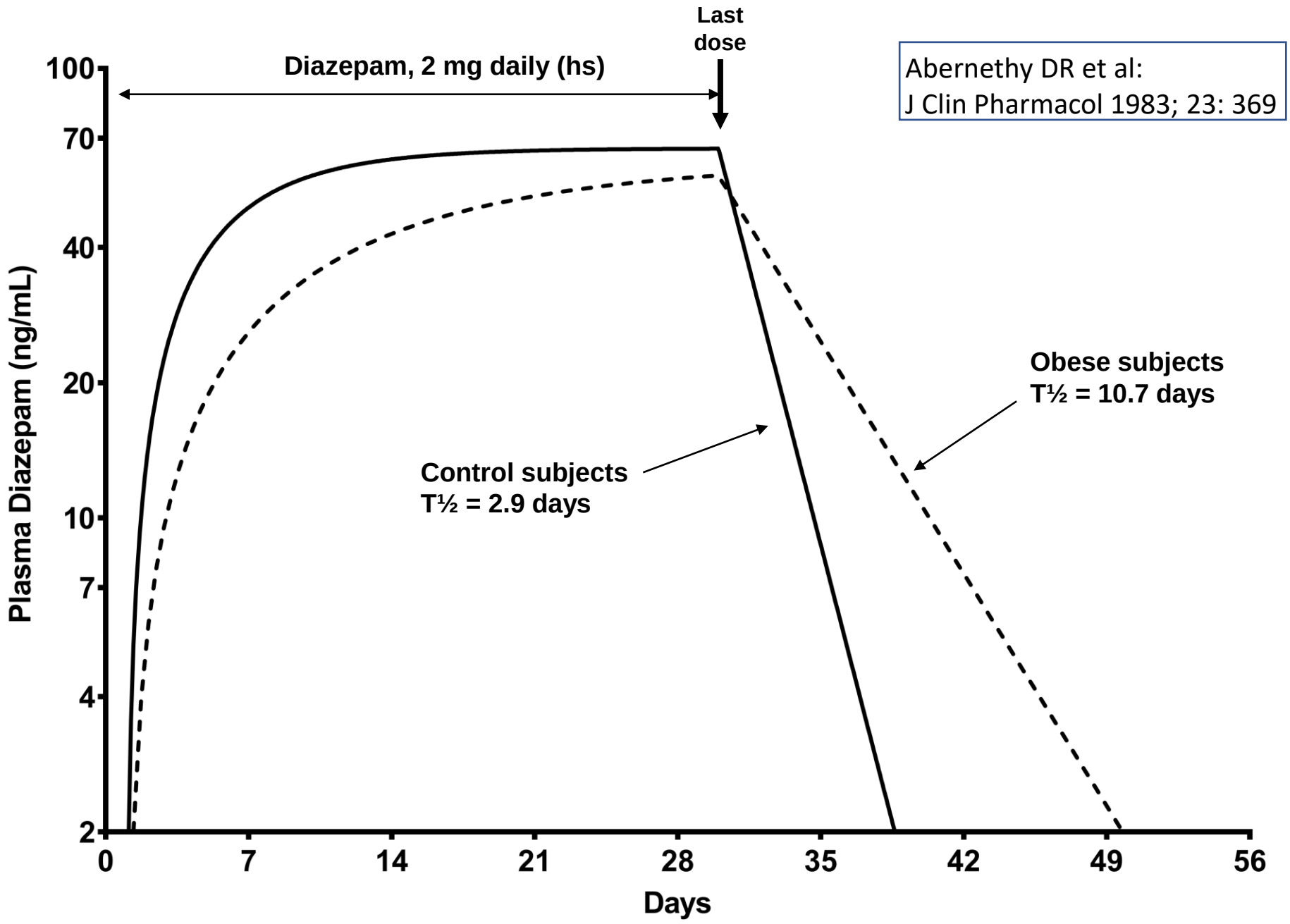
- No evident relation to V_d or lipid solubility

- No consistent relation to degree of obesity

- Obesity effect may be related to clearance pathway:
  - Renal
  - Hepatic -- CYP
  - Hepatic -- UGT




Lipid solubility
Obesity
Vd
[Independent]
T1/2
[Dependent]
Single dose;
Multiple dose:
accumulation,
washout
Loading dose
CL
[Independent]
Maintenance dose


Last dose
Diazepam, 2 mg daily (hs)
Abernethy DR et al:
J Clin Pharmacol 1983; 23: 369
Obese subjects
T½ = 10.7 days
Control subjects
T½ = 2.9 days
Plasma Diazepam (ng/mL)
100
70
40
20
10
7
4
2
0
7
14
21
28
35
42
49
56
Days

Emerald Lake Safety LLC

- Sundar Srinavasan
- Christina R. Chow, Ph. D.
- Christopher D. Bruno

Patient efficacy/safety consequences of:

- Delayed washout of lipophilic drugs after chronic therapy in obese patients (sustained serotonergic effects,[1] sustained/prolonged DDIs involving inhibitors[2,3])

- Delayed attainment of steady-state with lipophilic drugs in obese patients[4]

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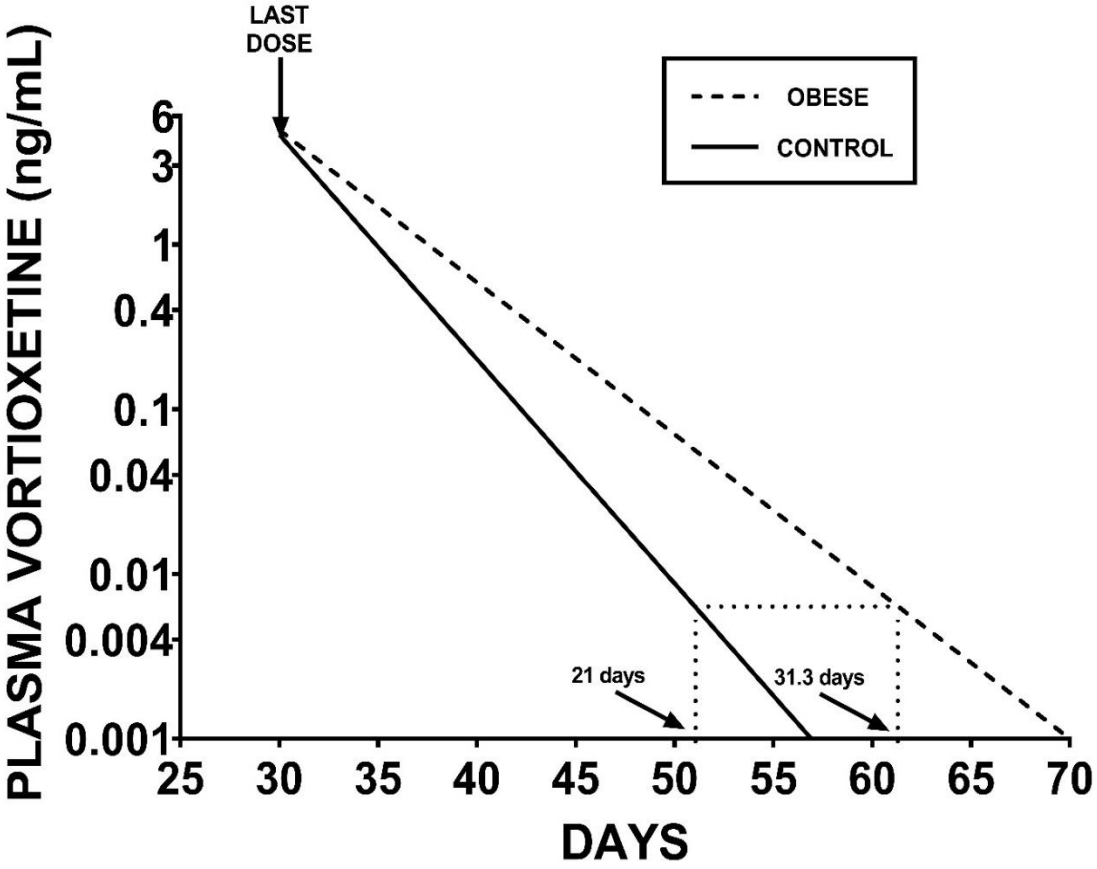
1. J Clin Psychopharmacol 2018; 2018; 38: 172-179
2. J Clin Psychopharmacol 2018; 2018; 38: 289-295
3. J Clin Pharmacol 2018; 58: 1436-1442
4. J Clin Pharmacol 2022; 62: 55-65

Vortioxetine-MAOI Serotonin Syndrome Risk



- 21-day prohibition against starting on a MAO inhibitor (risk of serotonin syndrome)

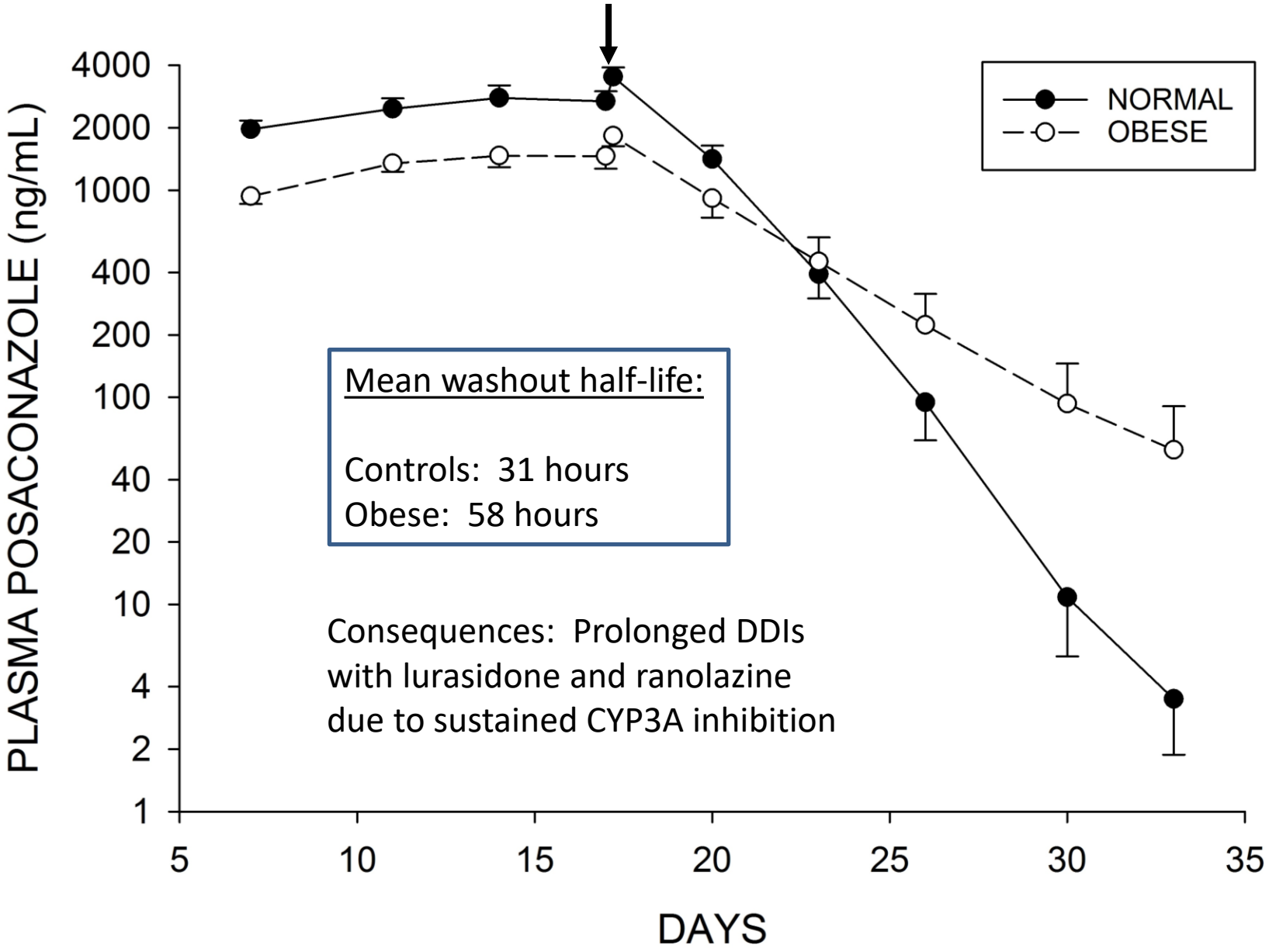
- NDA PK studies excluded BMI ≥ 35 kg/m^2

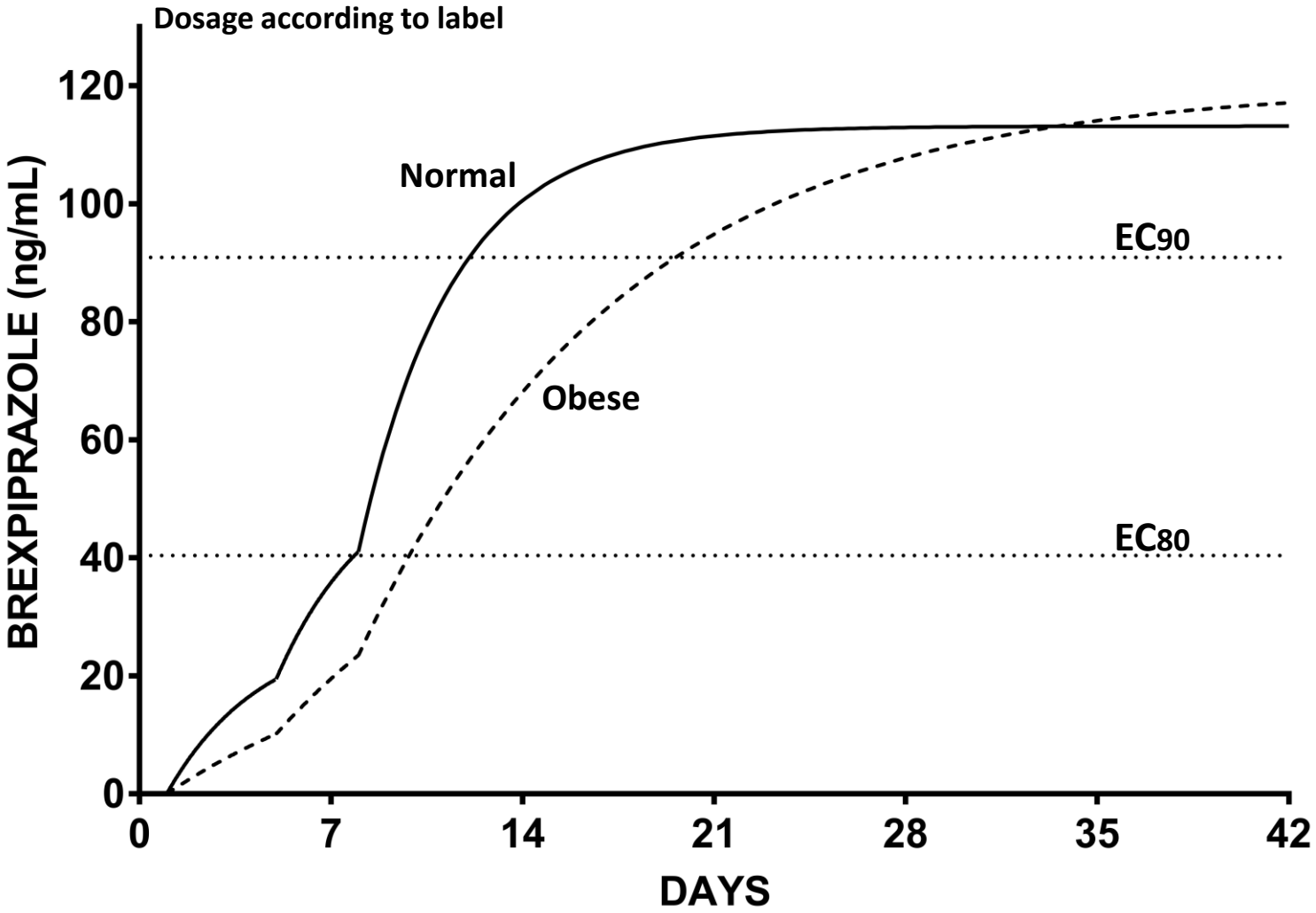
- 'Safe' concentration in normals not reached until 31 days in obese patients

- Product label should provide this information

Data from J Clin Psychopharmacol 2018; 38: 172-179

J Clin Psychopharmacol 2018; 38: 289-295, and J Clin Pharmacol 2018; 58: 1436-1442





J Clin Pharmacol 2022; 62: 55-65

WHAT IS THE DESTINATION?

- Mandated study of obesity for all new drug development

- Current labels MUST be updated to incorporate consequences of prolonged half-life of lipophilic drugs in obesity

- Understand the unexplained variance

- Can DXA be bypassed?