Altered pharmacokinetics and clinical effects of drugs in patients with obesity

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Disclosures: DJG is a scientific advisor to Emerald Lake Safety LLC, Newport Beach, CA

ACCP
American College of Clinical Pharmacology
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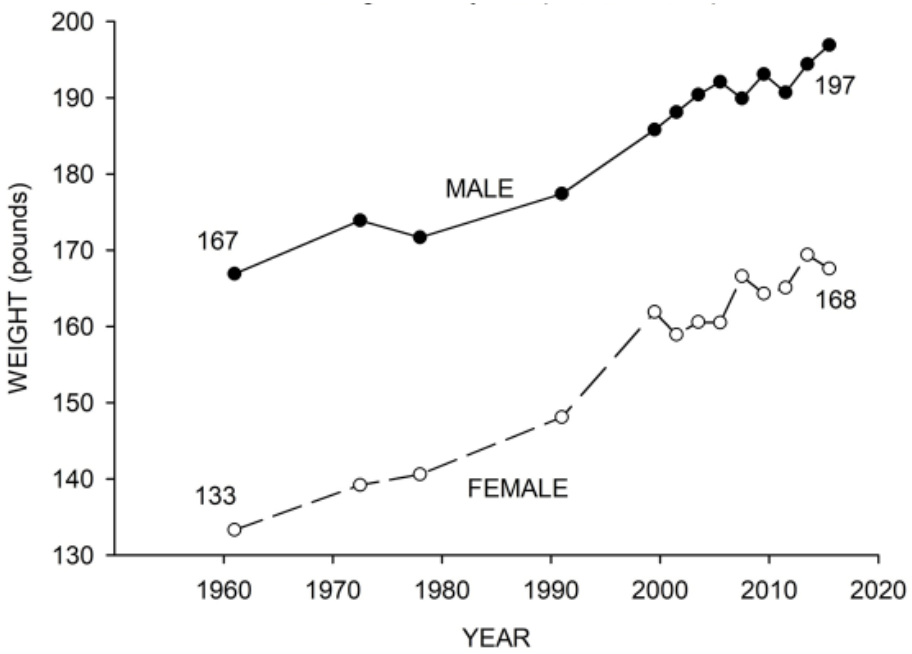
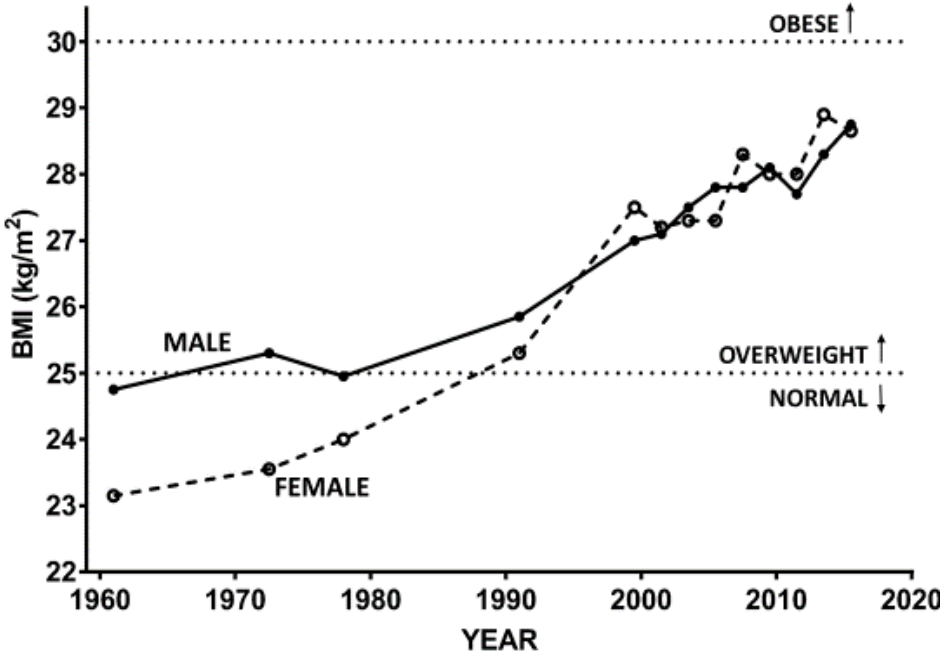
The Seventy-Kilogram Fantasy

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

NHANES data (ages 20-39)

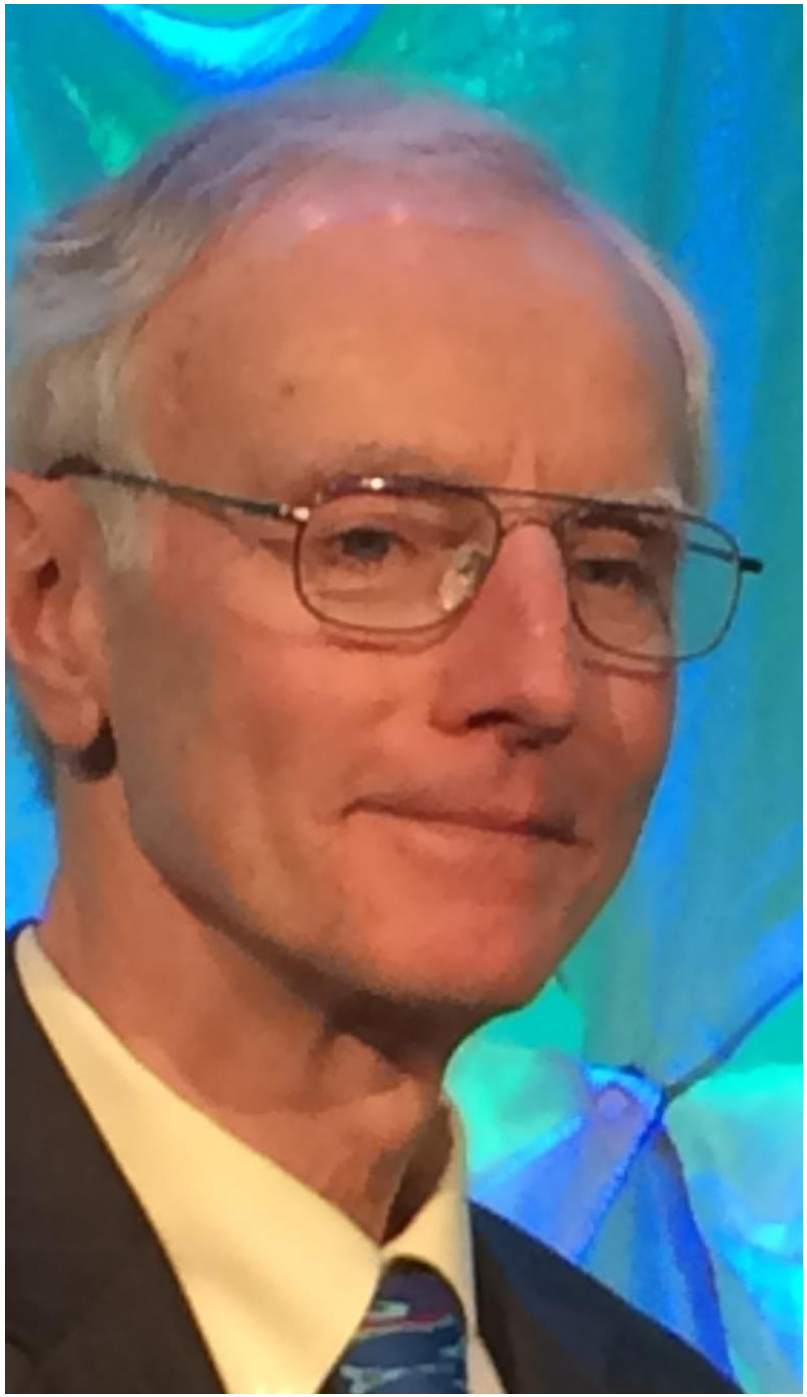




Not about pharmacologic treatment of obesity
(weight loss drugs)

Instead – treatment of co-morbid conditions:

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



Darrell R. Abernethy
1949 - 2017

Tufts Post-Doc and Faculty
1979-1984

Dr. Abernethy's Research Problems:

- Measuring obesity
- Measuring volume of distribution
- The physiologic relation among
  volume of distribution, half-life, and clearance
- Modifications of drug distribution by obesity --
  The influence of lipid solubility
- Modifications of drug clearance by obesity
- Implications for pharmacologic treatment
  of patients with obesity

Additional complications: The influence of old age and gender

QUANTITATIVE MEASURES OF OBESITY

EASILY MEASURED

- Weight
- Weight-height combinations (BMI, etc.)
- Waist circumference, Skinfold thickness

REQUIRES INSTRUMENTATION

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

DR. ABERNETHY SETTLED ON

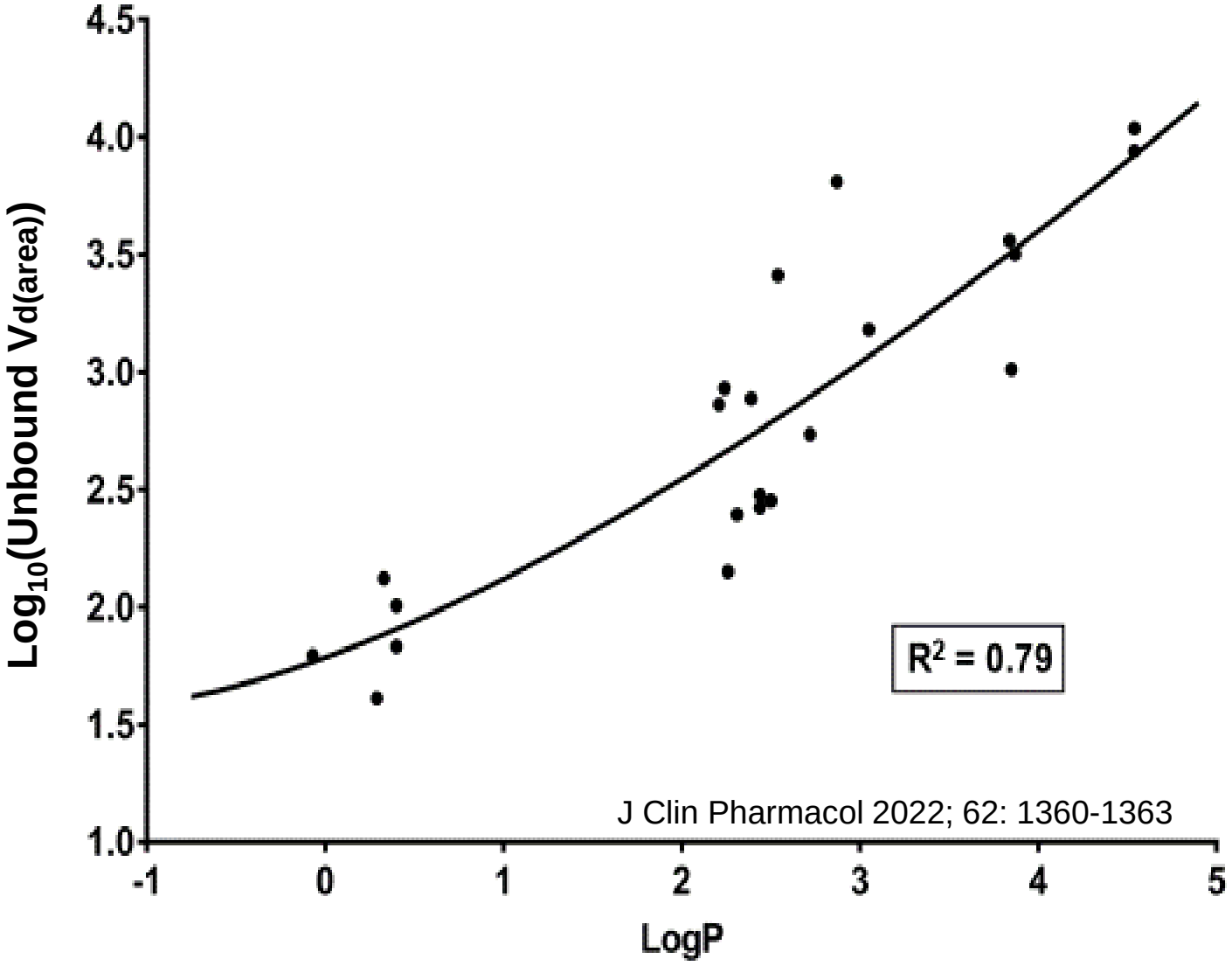
- Percent ideal body weight

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

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

Br J Clin Pharmacol. 2021; 87: 3197-3205
J Clin Pharmacol. 2023;63 (Suppl 2):s35-s47

Healthy control subjects without obesity



J Clin Pharmacol 2022; 62: 1360-1363

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

VOLUNTEER SUBJECTS (1979-1984)

Category	Weight	% IBW
Healthy controls	65 kg (142 pounds)	99%
Subjects with obesity	114 kg (251 pounds) (Max: 435 pounds)	179%

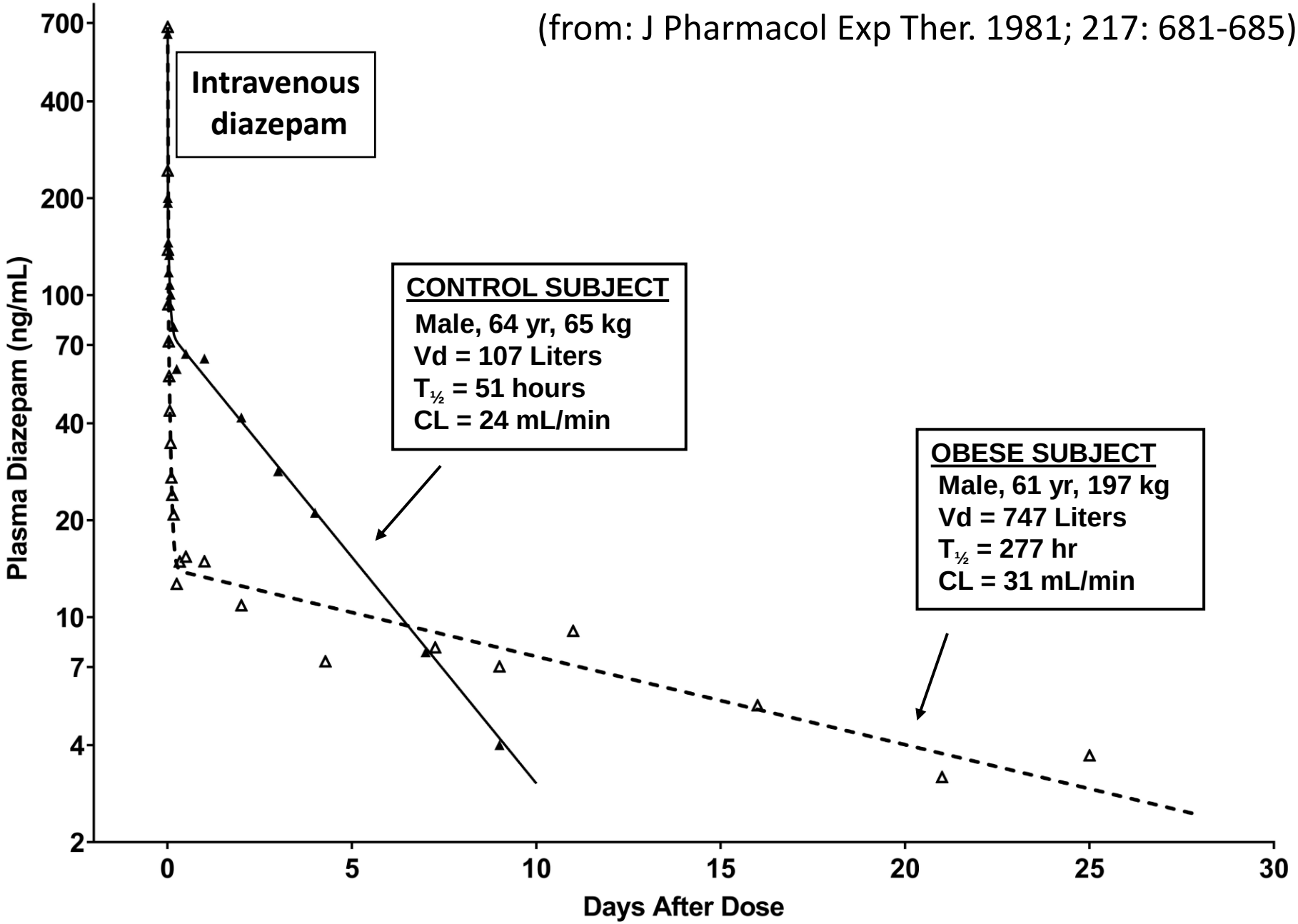
STUDY DESIGN

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

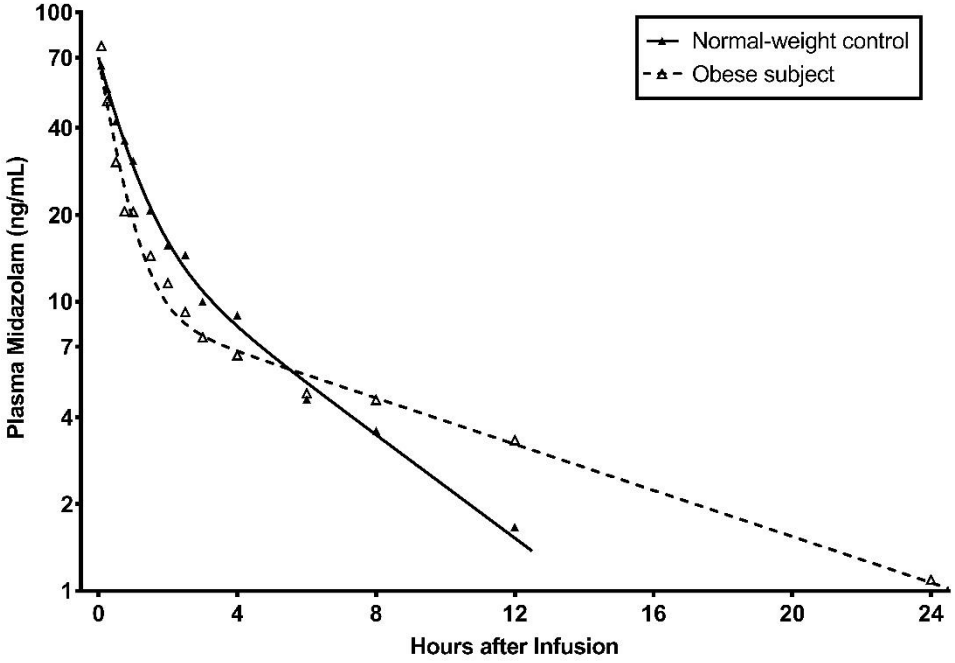
Single I. V. dose, or single oral dose (if F = 1)
Determine T½, V_d, Clearance

Pharmacokinetic analyses done by Jerold S. Harmatz

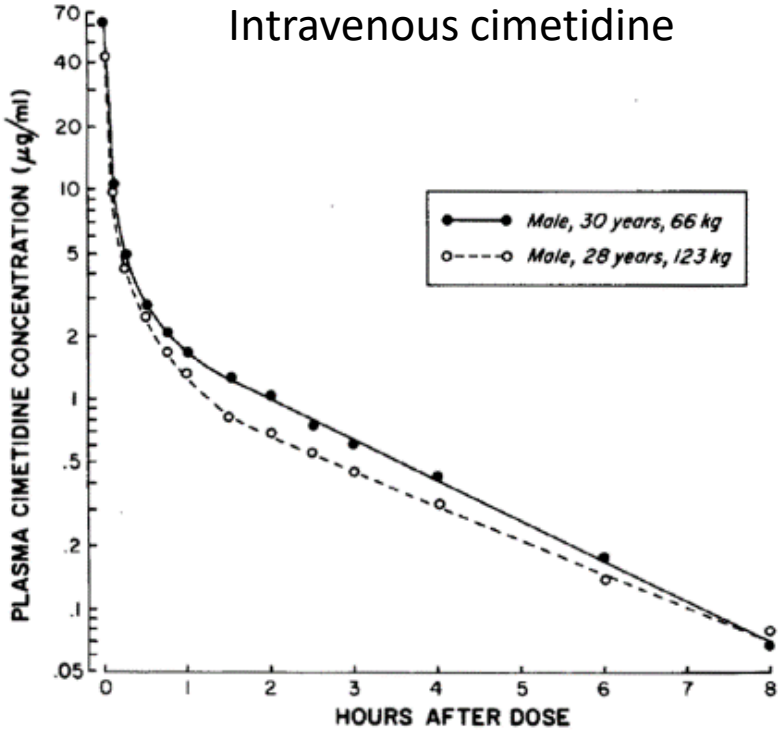
J Clin Pharmacol. 2022; 62: 1350-1363
(from: J Pharmacol Exp Ther. 1981; 217: 681-685)



Intravenous midazolam

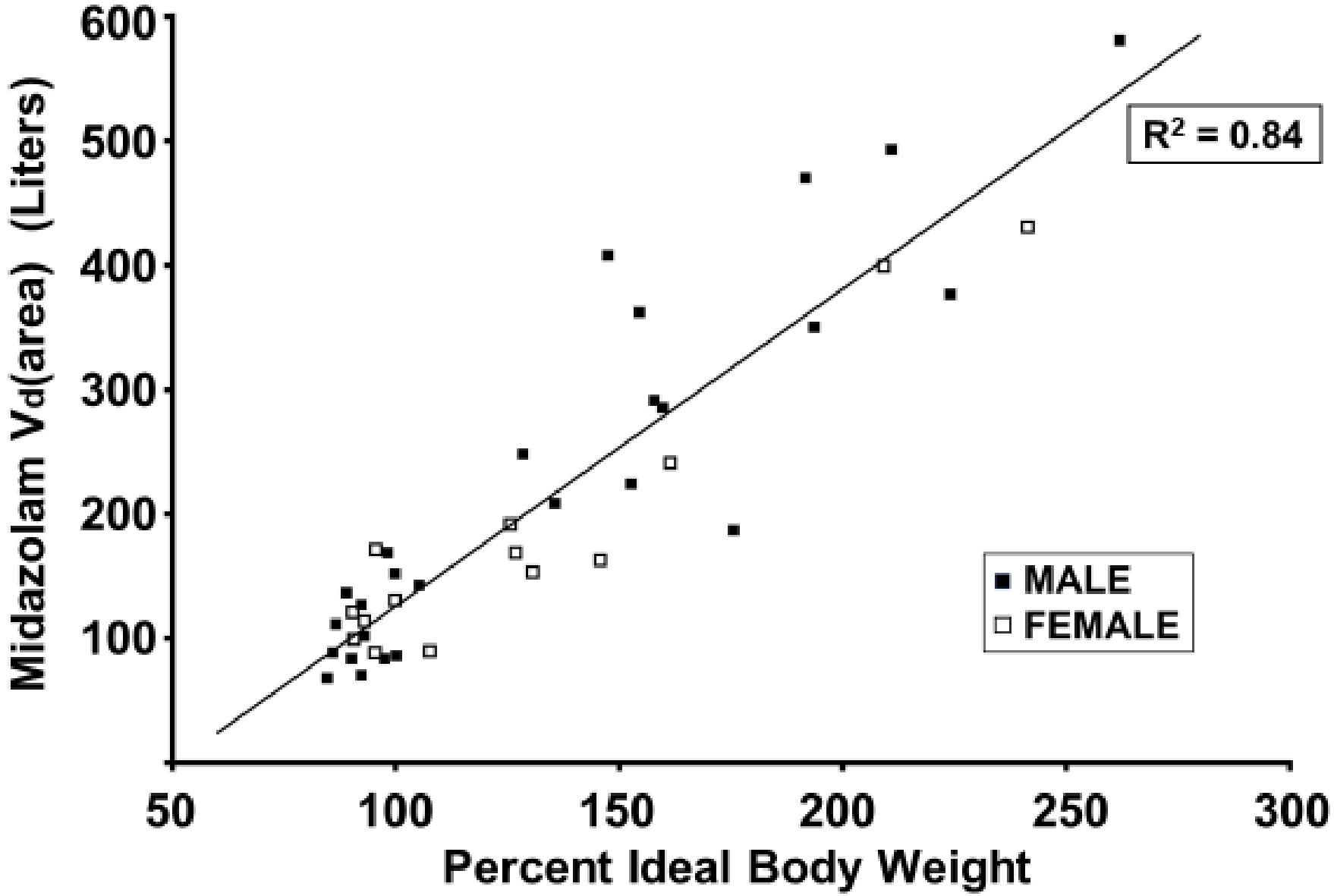


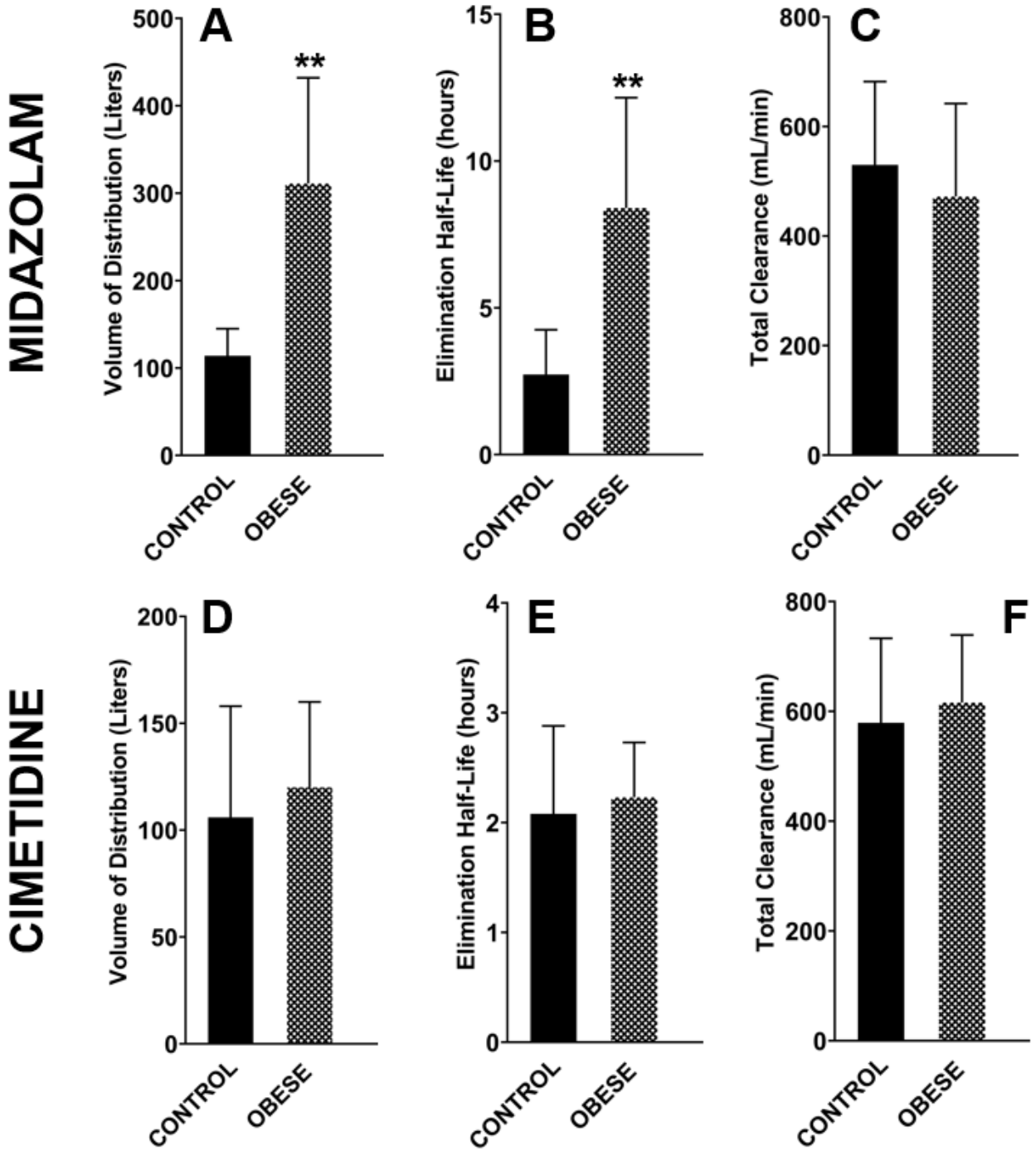
Intravenous cimetidine



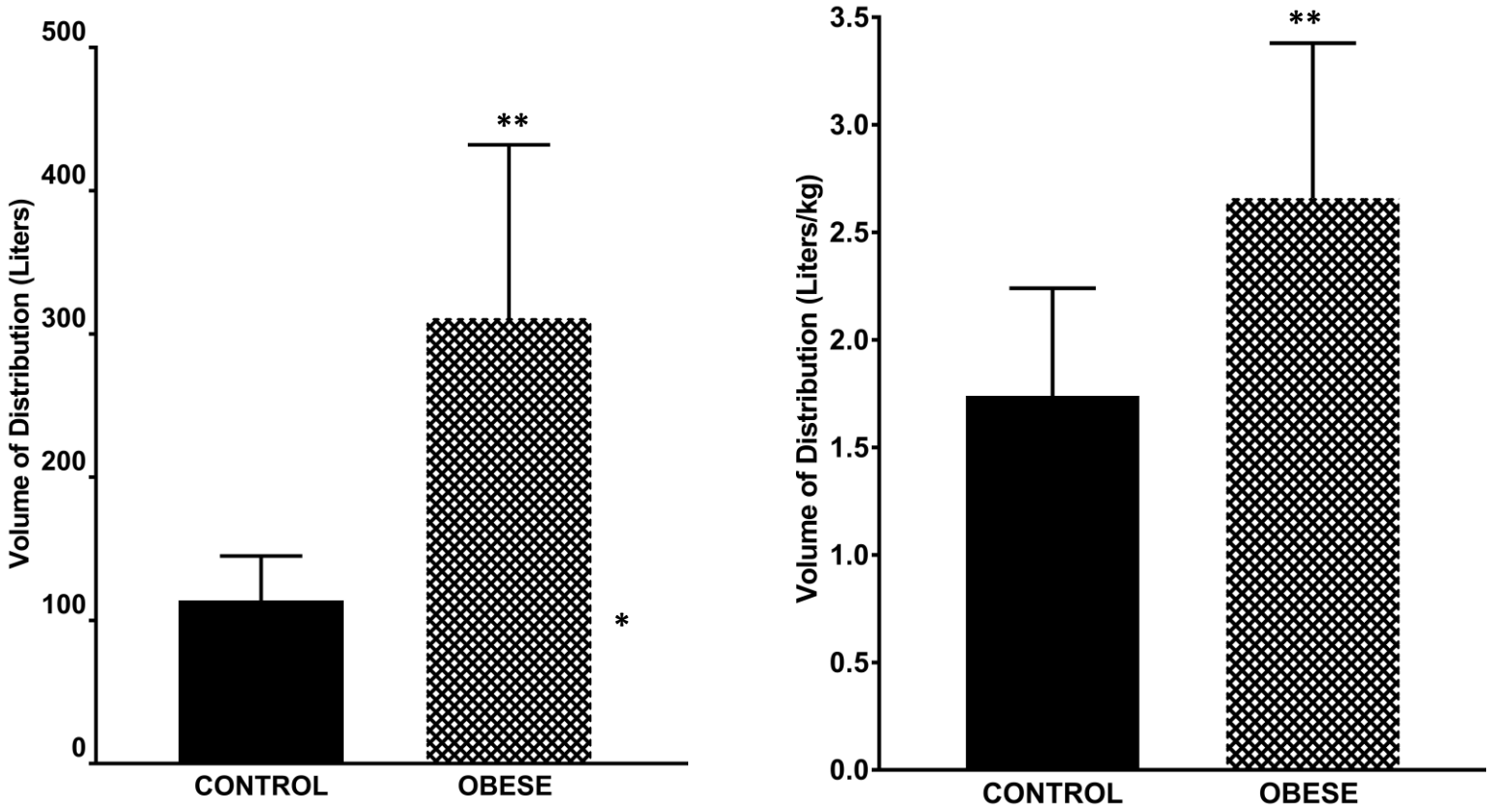
J Clin Pharmacol 2022; 62: 1360-1363
Anesthesiology 1984; 61; 27-35
Am J Gastroenterol 1984; 79: 91-94

Anesthesiology 1984; 61: 27-35




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

MIDAZOLAM VOLUME OF DISTRIBUTION

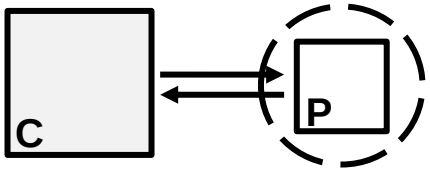


The lesson: *Disproportionate* distribution of midazolam into body weight that exceeds ideal body weight

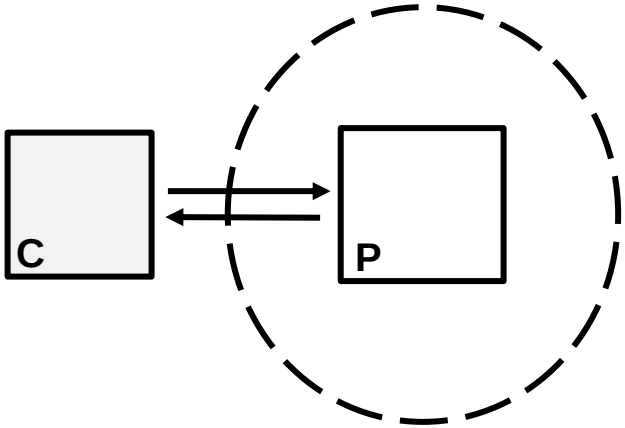
J Clin Pharmacol 2022; 62: 1360-1363

Non-Lipophilic drug

NORMAL-WEIGHT SUBJECT



SUBJECT WITH OBESITY



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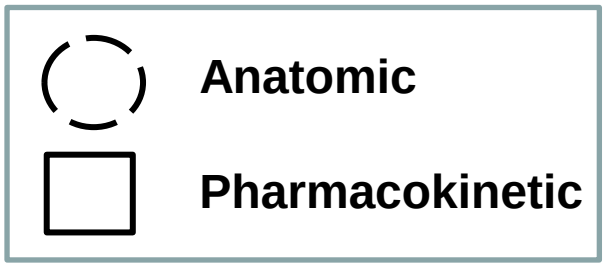
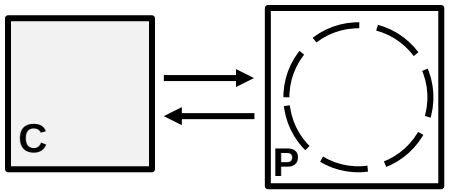


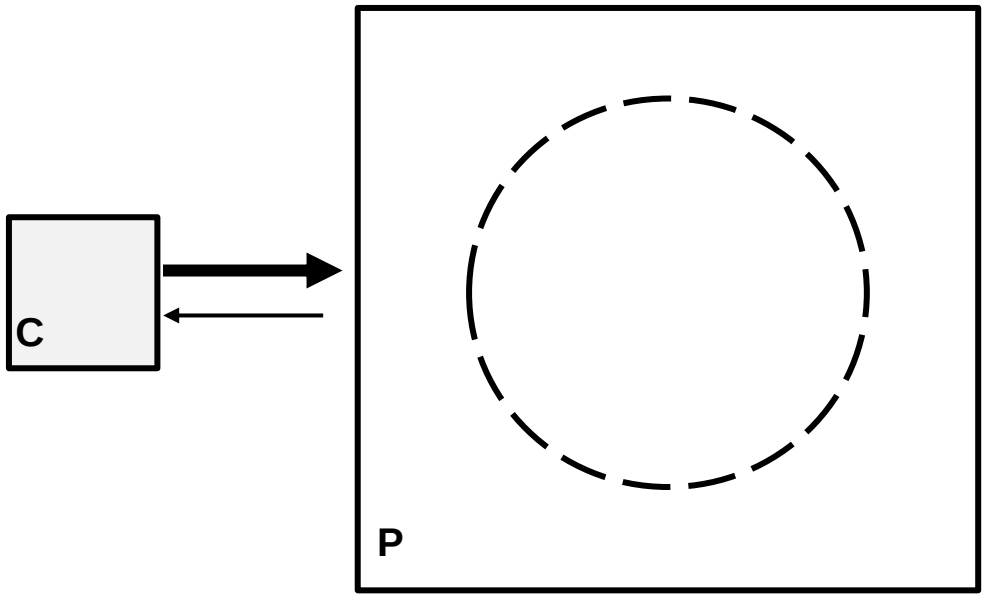
J Clin Pharmacol 2022; 62: 1360-1363
Clin Pharmacokinet 2010; 49: 71-87

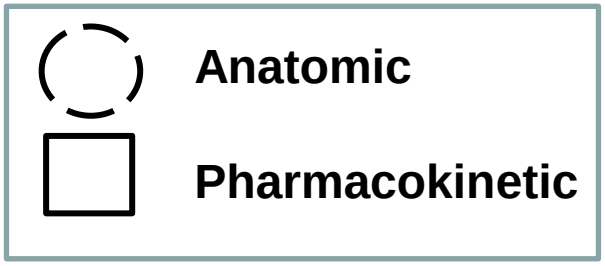
Lipophilic drug

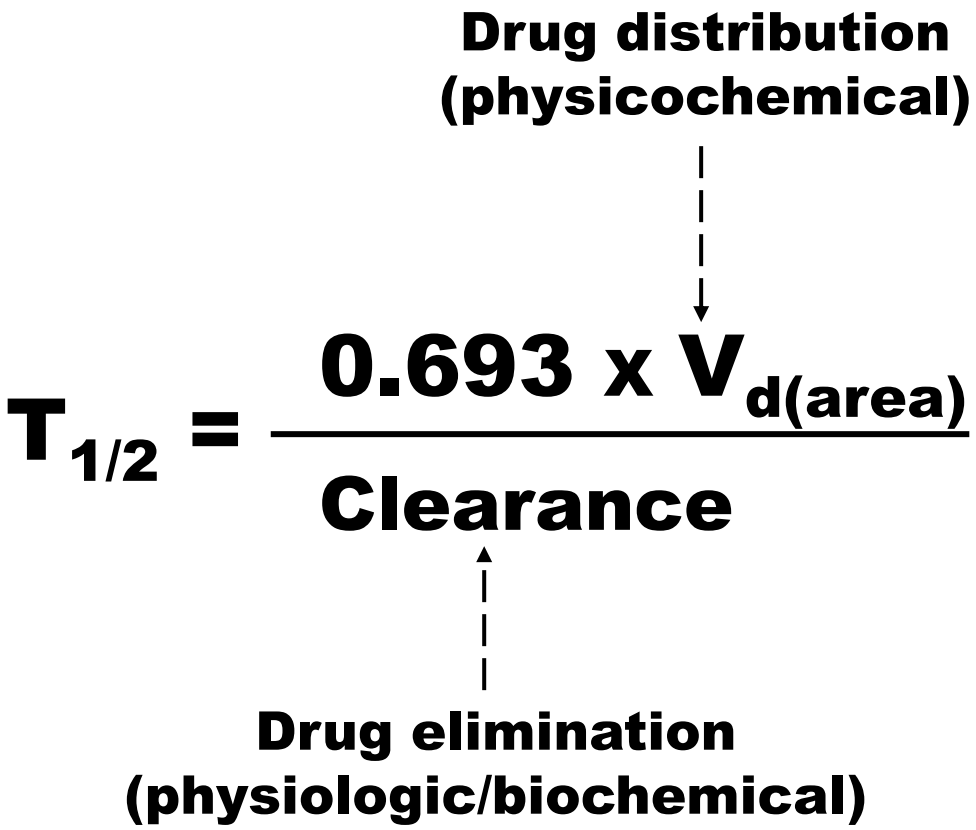
NORMAL-WEIGHT SUBJECT

SUBJECT WITH OBESITY









Clearance and volume of distribution are independent of each other.

CLEARANCE is not:

- Elimination (terminal) half-life

- Elimination rate constant

- Rate of drug disappearance

- Rate of drug elimination

CLEARANCE is:

- Volume of blood completely cleared of drug per unit time

- Independent of distribution

- Major determinant (with V_d) of T½

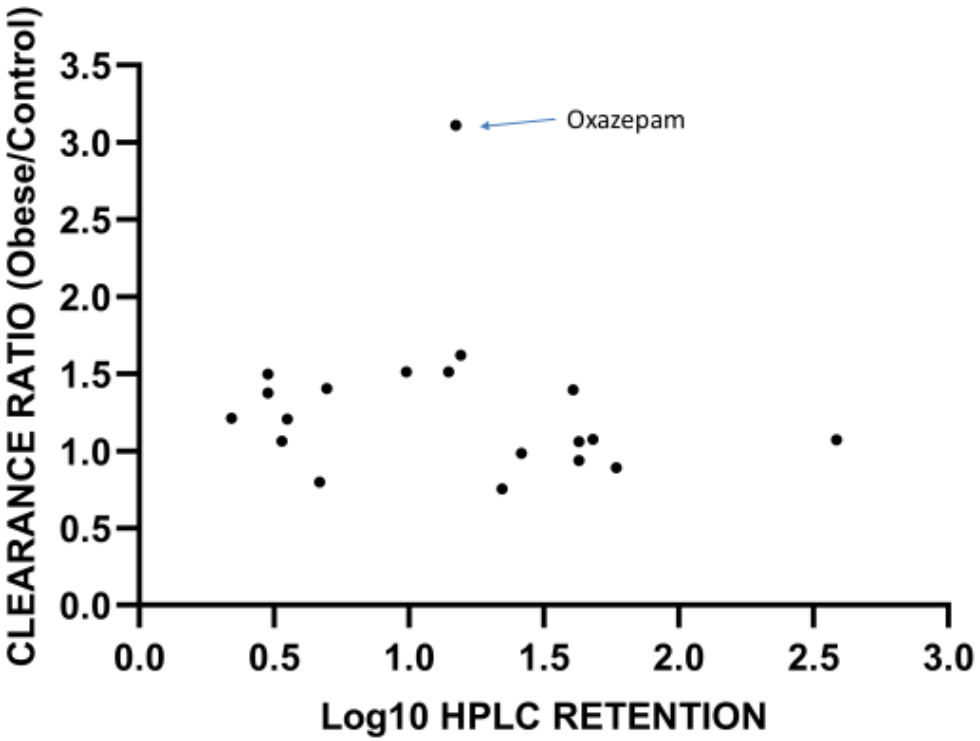
- After single IV doses, calculated as:
  (Dose) / (Total AUC)

- Major determinant of steady-state C_{ss}:
  C_{ss} = (Dosing rate) / (Clearance)

J Clin Pharmacol 2016; 56:1180-95

Drug Clearance in Subjects with 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 vs UGT



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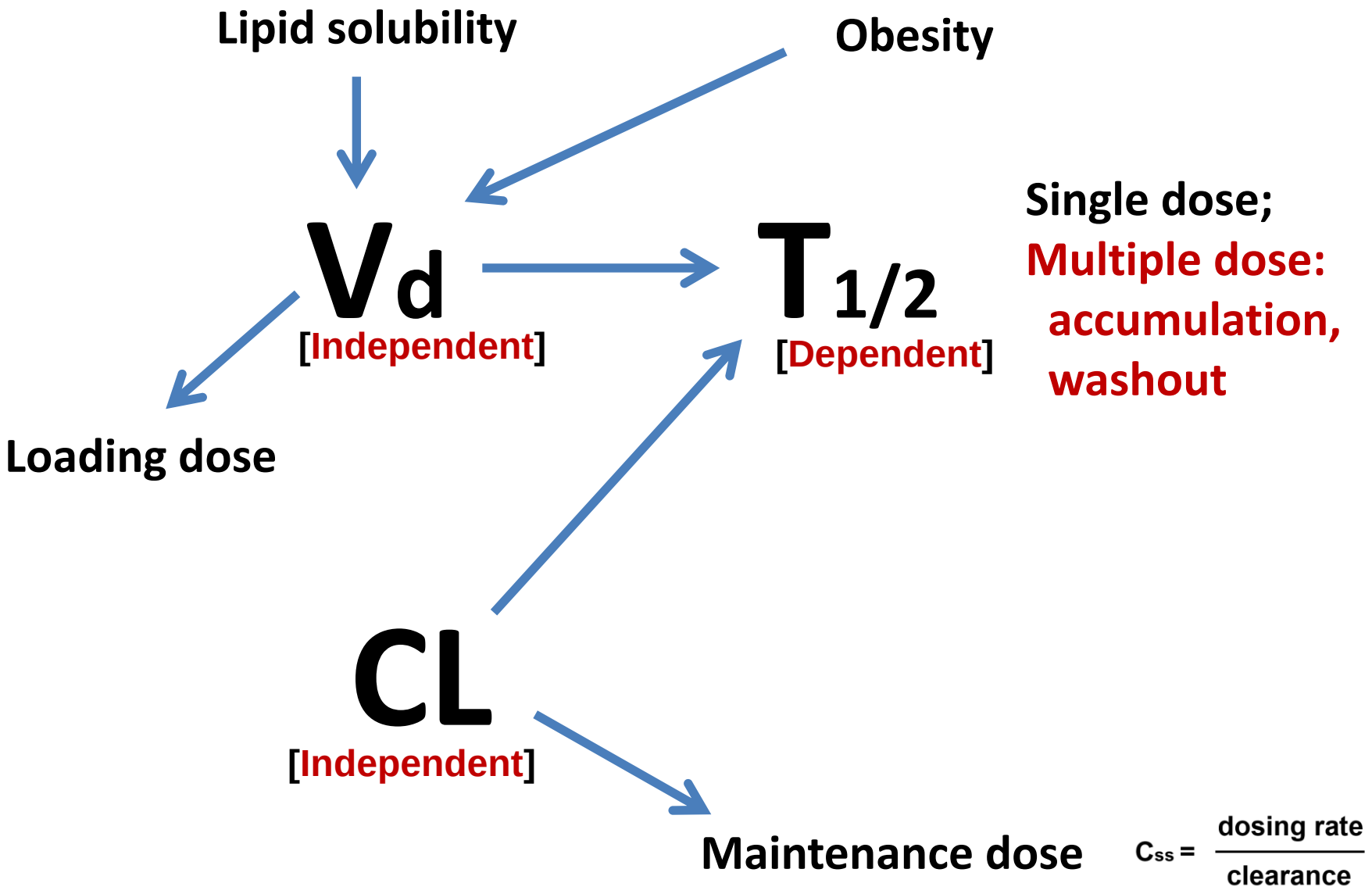

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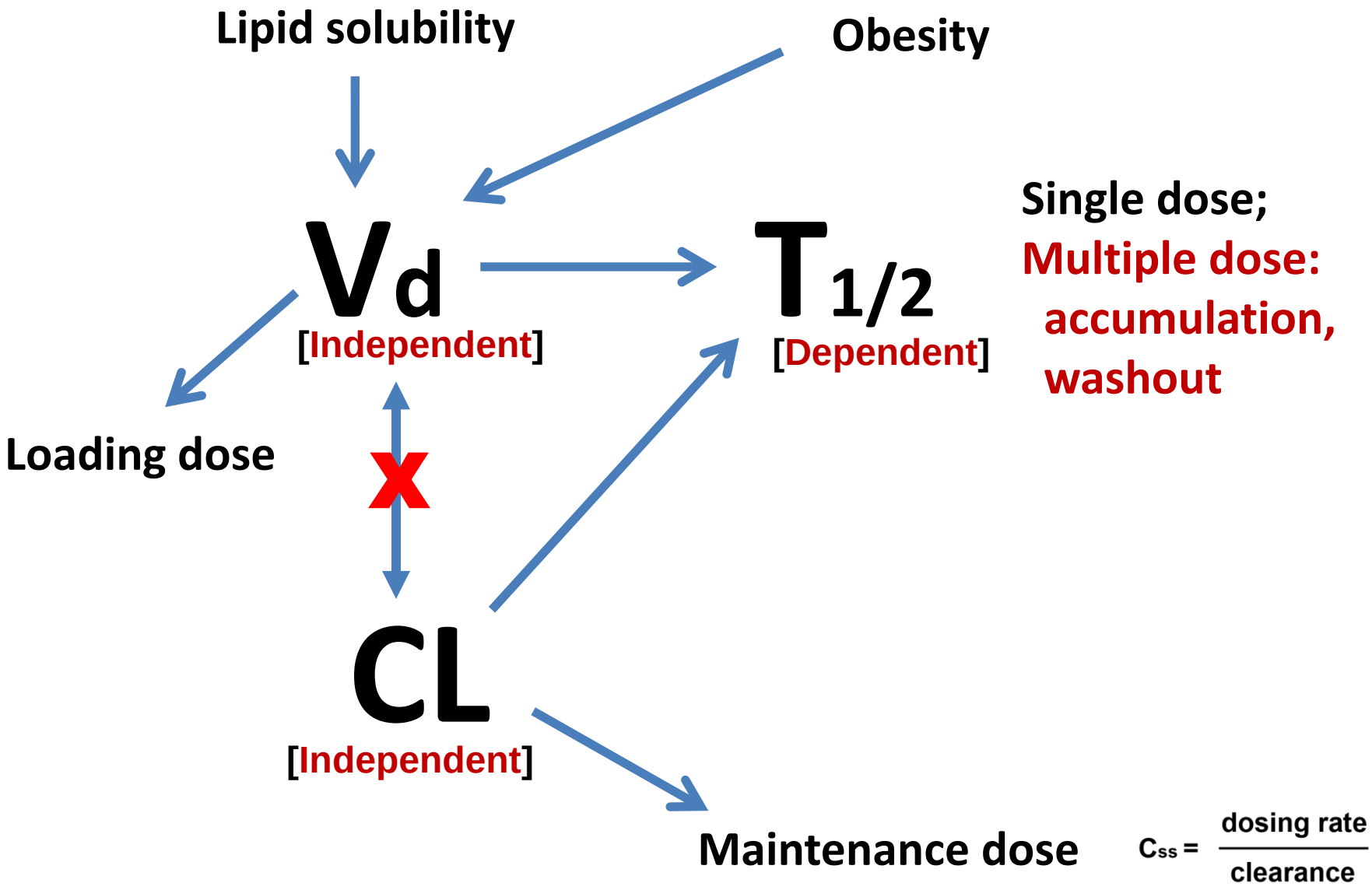
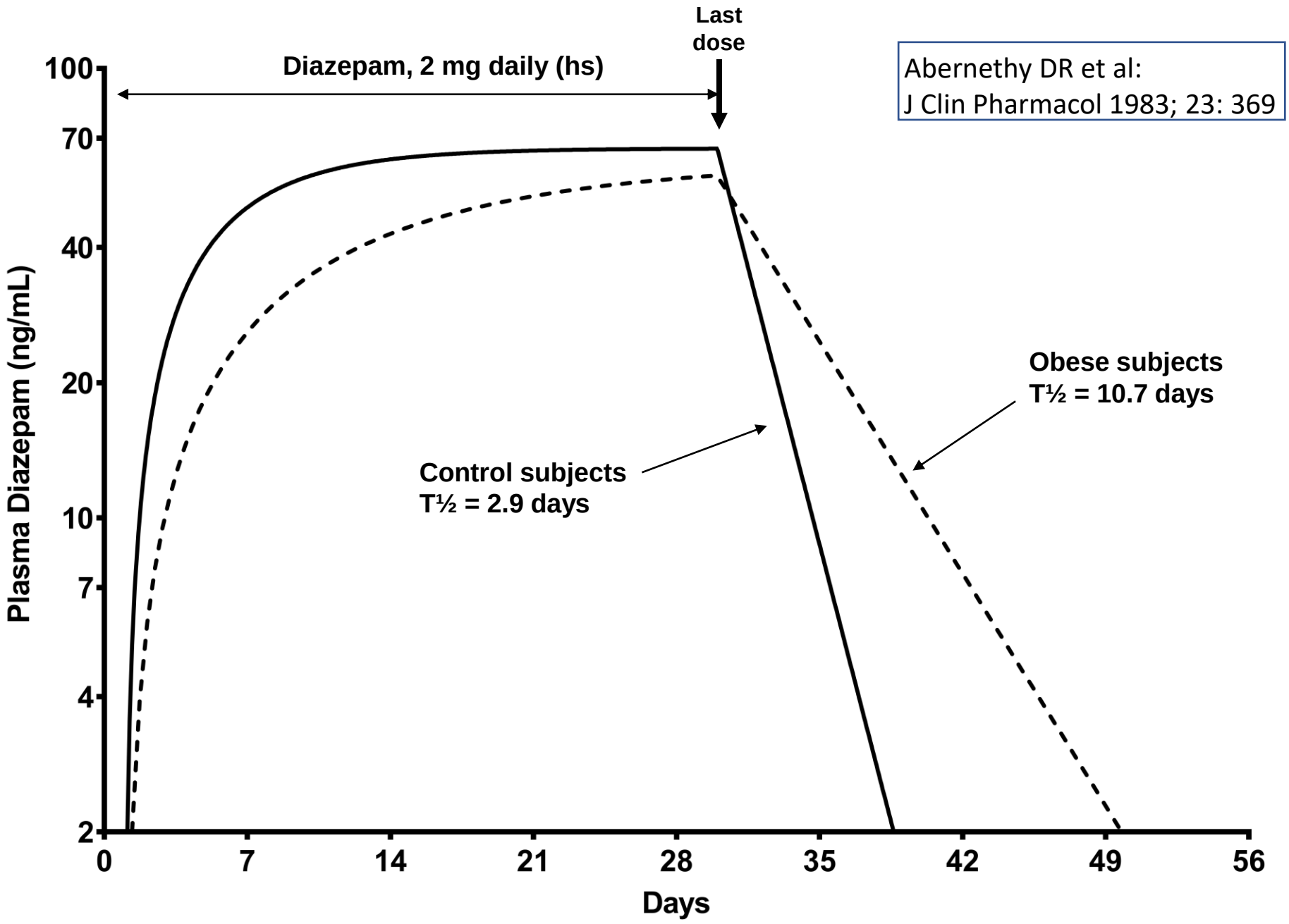

Lipid solubility
Obesity
Vd
[Independent]
T1/2
[Dependent]
Single dose;
Multiple dose:
accumulation,
washout
Loading dose
X
CL
[Independent]
Maintenance dose
Css = dosing rate / clearance


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

TO THE LATE 2010s:

Patient safety consequences of:

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

- **Delayed attainment of steady-state with lipophilic drugs in patients with obesity[4,5]**

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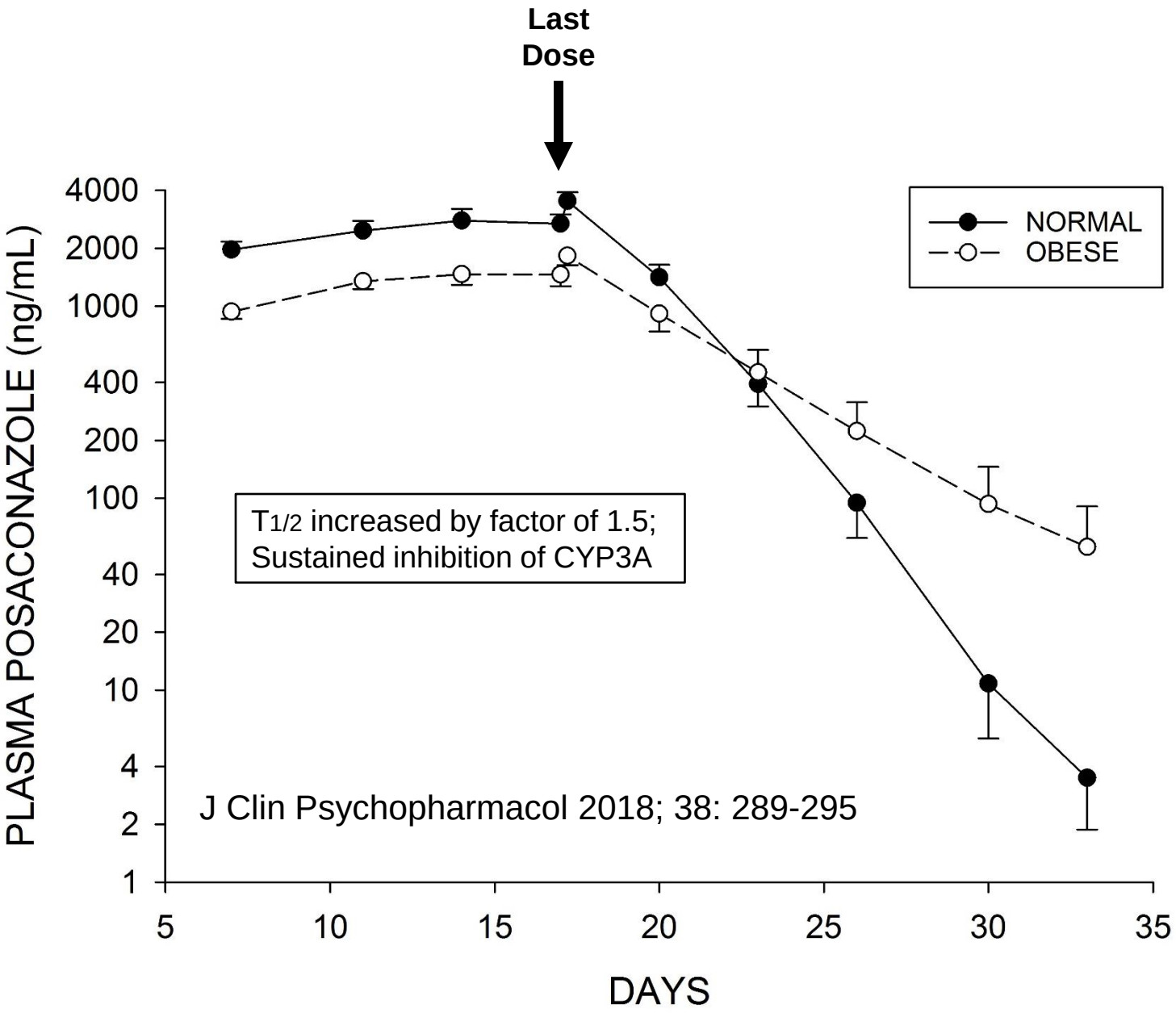
1. J Clin Psychopharmacol 2018; 2018; 38: 172-179
2. J Clin Psychopharmacol 2018; 2018; 38: 289-295
3. J Clin Pharmacol 2018; 58: 1436-1442
4. J Clin Pharmacol 2022; 62: 55-65
5. J Clin Pharmacol 2023; 63: s25-s34

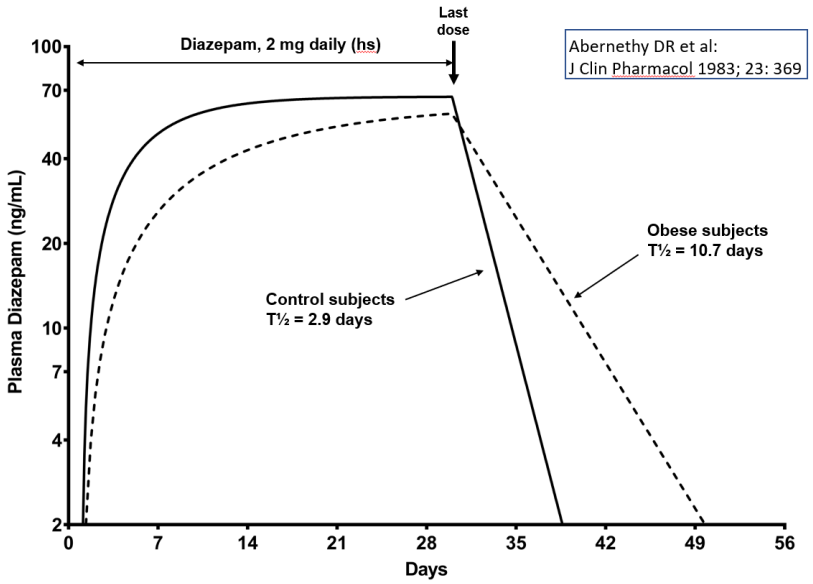

Last
Dose
PLASMA POSACONAZOLE (ng/mL)
4000
2000
1000
400
200
100
40
20
10
4
2
1
5
10
15
20
25
30
35
DAYS
NORMAL
OBESE
T1/2 increased by factor of 1.5;
Sustained inhibition of CYP3A
J Clin Psychopharmacol 2018; 38: 289-295

IMPLICATIONS FOR EXTENDED DOSING, AND POST-DOSAGE WASHOUT

- **"Loading" regimen might be needed at the start**

- **If clearance is not altered in patients with obesity, maintenance dose adjusted based on ideal rather than actual weight**

- **Drug washout and clinical effects delayed after discontinuation (DDIs, etc.)**



WHAT IS THE DESTINATION?

Patients with obesity to be studied as a "special population" as a customary component of the drug development process

Altered drug disposition and clinical effects in patients with obesity to become a customary component of training and education for health care professionals

COLLEAGUES ALONG THE WAY

Milton Greenblatt (1914-1994)
Jan Koch-Weser (1927-2018)
Richard I. Shader
Jerold S. Harmatz (1939-2023)
Hershel Jick

Hermann R. Ochs (1943-2013)
Edward M. Sellers
Lisa L. von Moltke
H. Karl Greenblatt
Sundar Srinavasan
Christina R. Chow
Christopher D. Bruno
Qingchen Zhang