The Drug Titration Paradox: Something Obvious Finally Understood

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Outline

- Reflect on the rarity of new concepts in anesthesia clinical pharmacology.
- Consider titration as the primary method of getting the dose right in anesthesia (posology!).
- Introduce the “drug titration paradox” concept.
- Explore the evidence supporting the concept in patient populations (and individuals).
- Review the research implications of the drug titration paradox.

Overall Goal

Introduce and explore the “drug titration paradox” as a new concept in anesthesia related clinical pharmacology…

The drug titration paradox: something obvious finally understood

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This editorial accompanies: Beware the drug titration paradox. Con
2022:128:e335–e337, doi: 10.1016/j.bja.2022.01.004

Concepts, figures, citations summarized here…

Summary

The *drug titration paradox* is an emerging concept in clinical pharmacology. The paradox refers to the observation that when drug is titrated to a specified level of effect in a population of patients, the expected positive correlation between dose and effect is reversed. That is, when titration rather than fixed dosing is used, greater drug exposure is associated with lesser effect, and *vice versa*. The drug titration paradox may have important implications for study design and data interpretation in anaesthesiology investigations, particularly in big data studies.

Keywords: clinical pharmacology; drug titration paradox; pharmacodynamics; pharmacokinetics pharmacology; target-controlled infusion; titration

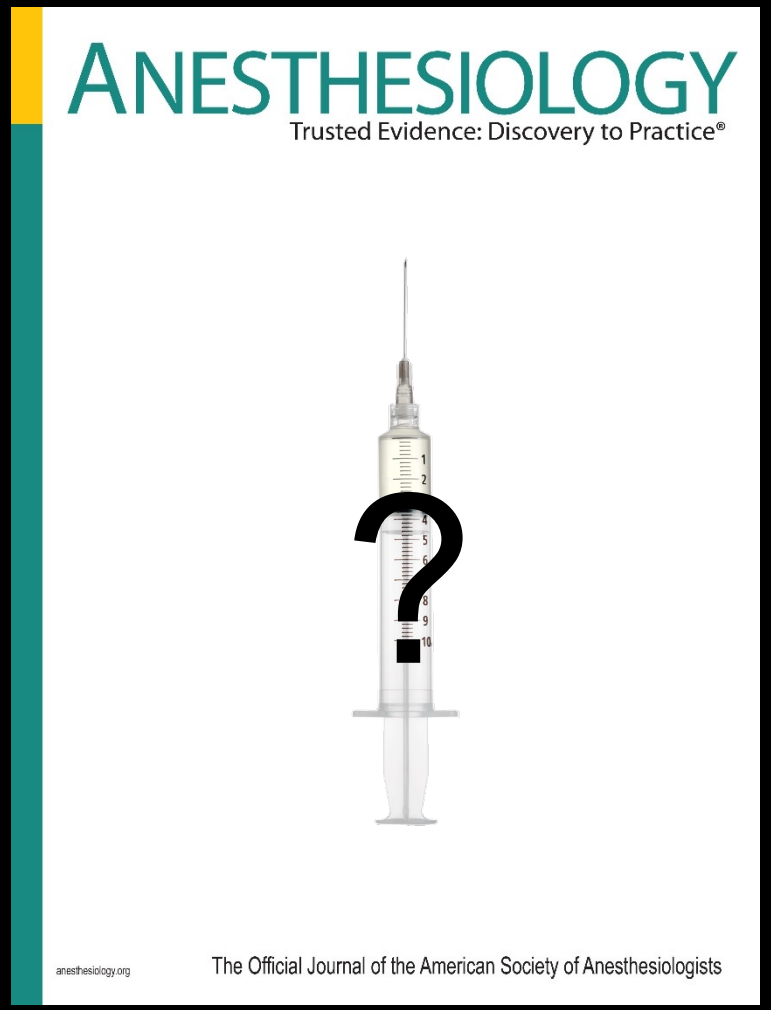
Egan (*Br J Anaesth* 2022)

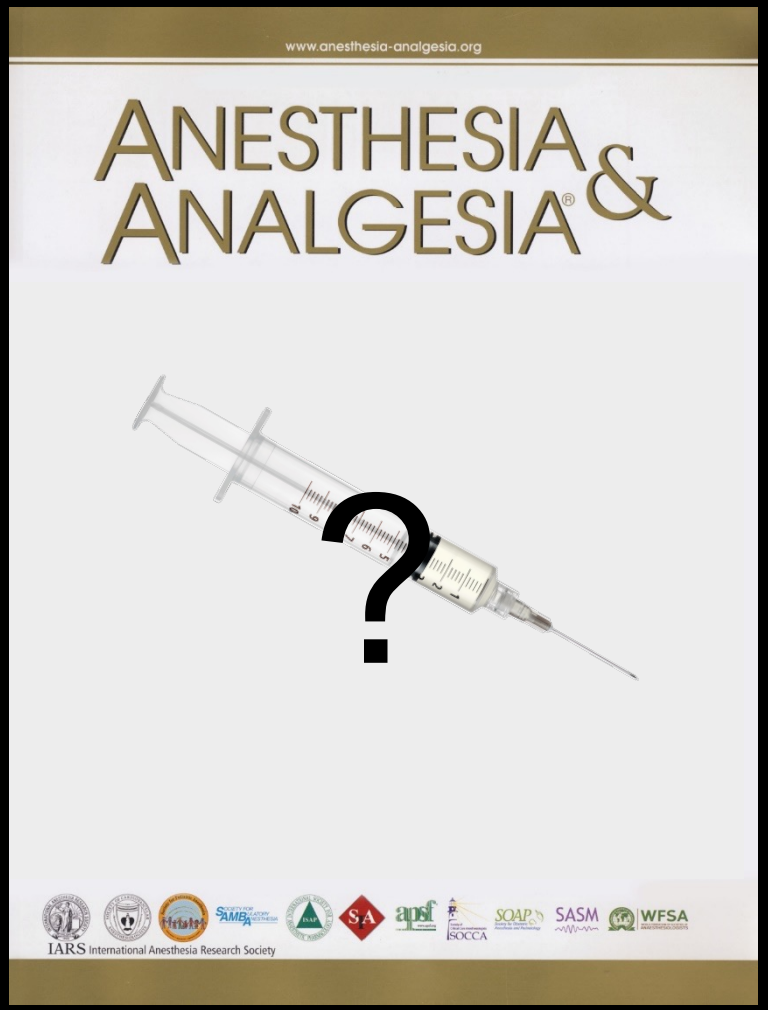
Key Point

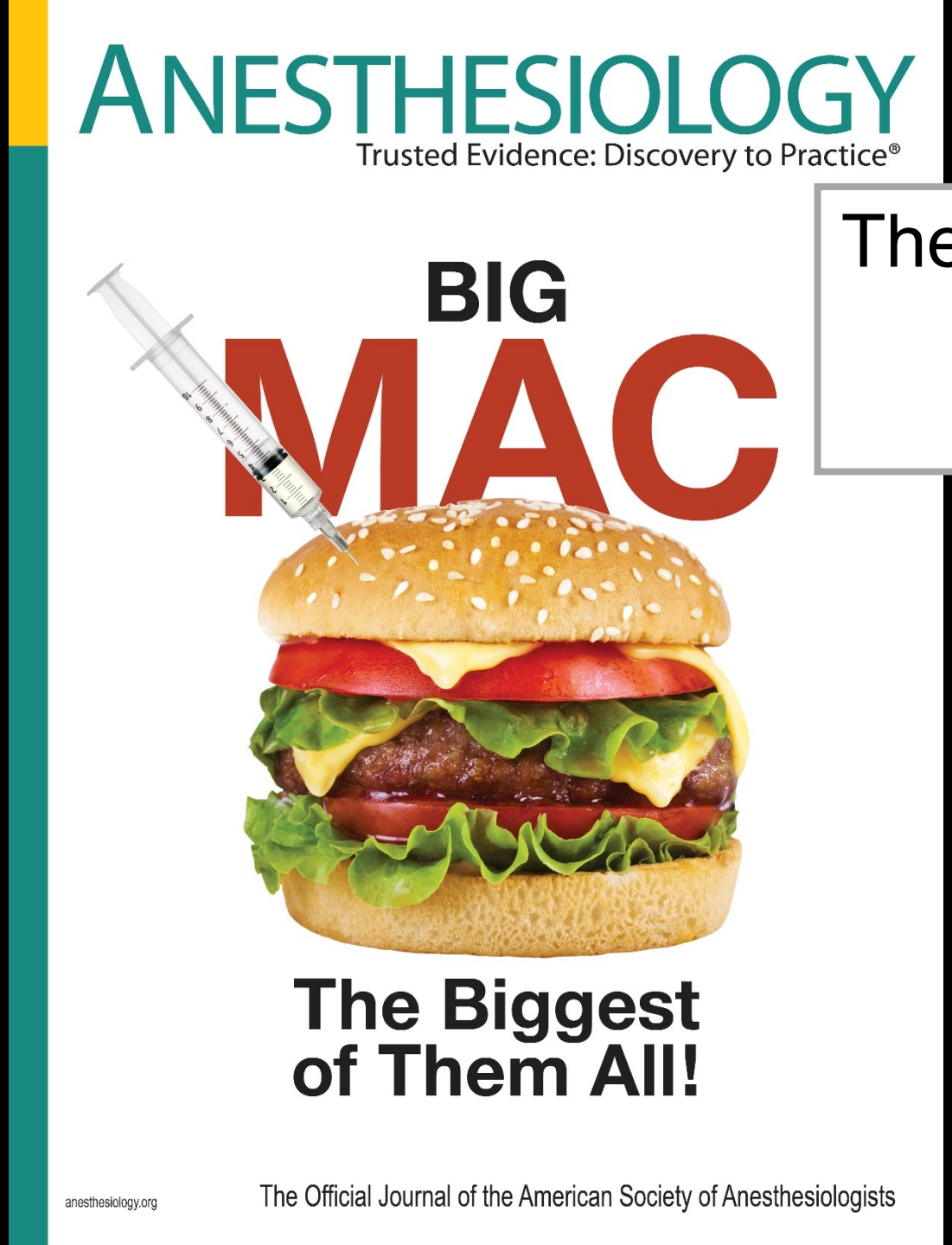
New clinical pharmacology and pharmaceutics concepts arise infrequently in anesthesiology.


MEMORY LANE
3156-3175

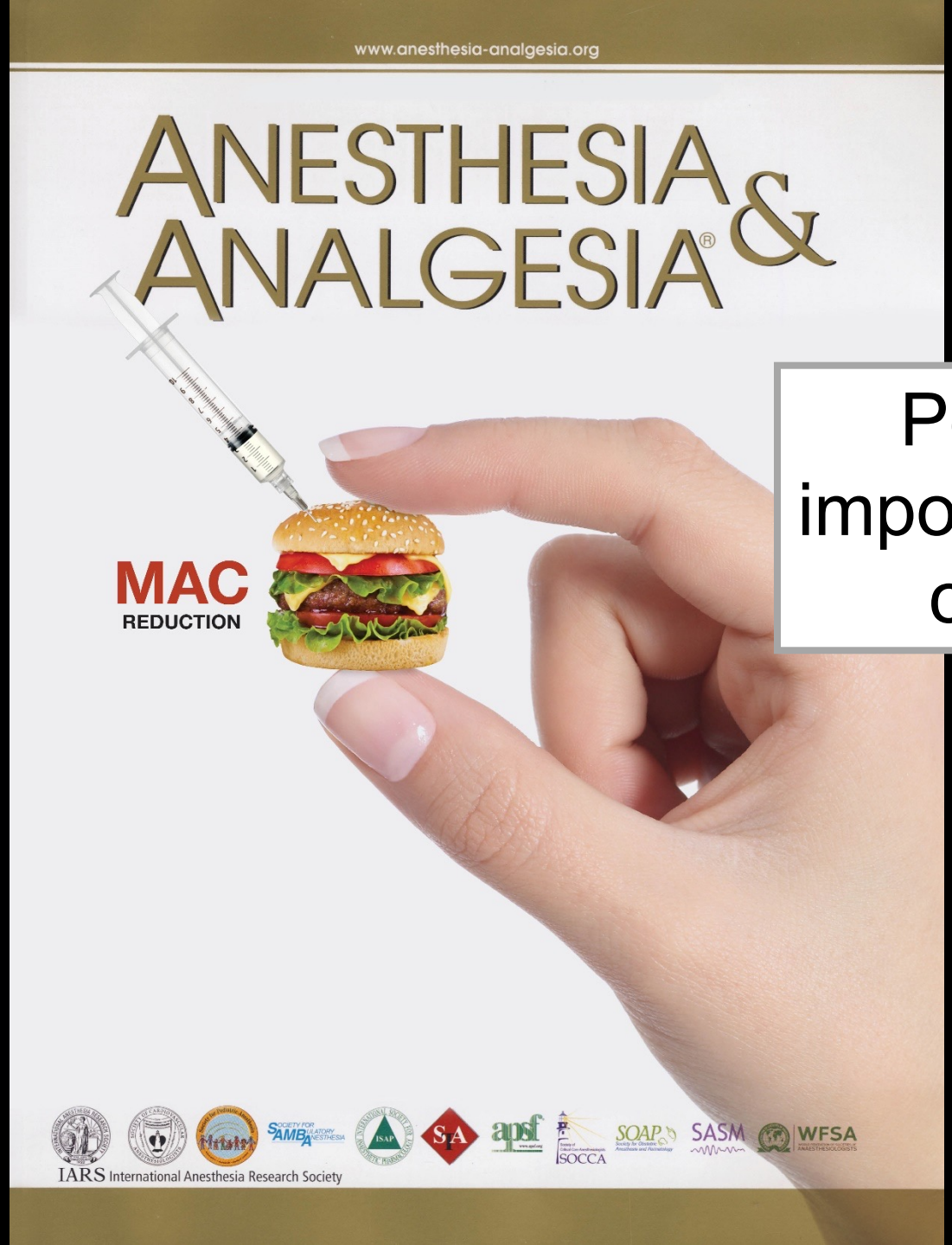
Cover Stories in Anesthesiology Clinical Pharmacology



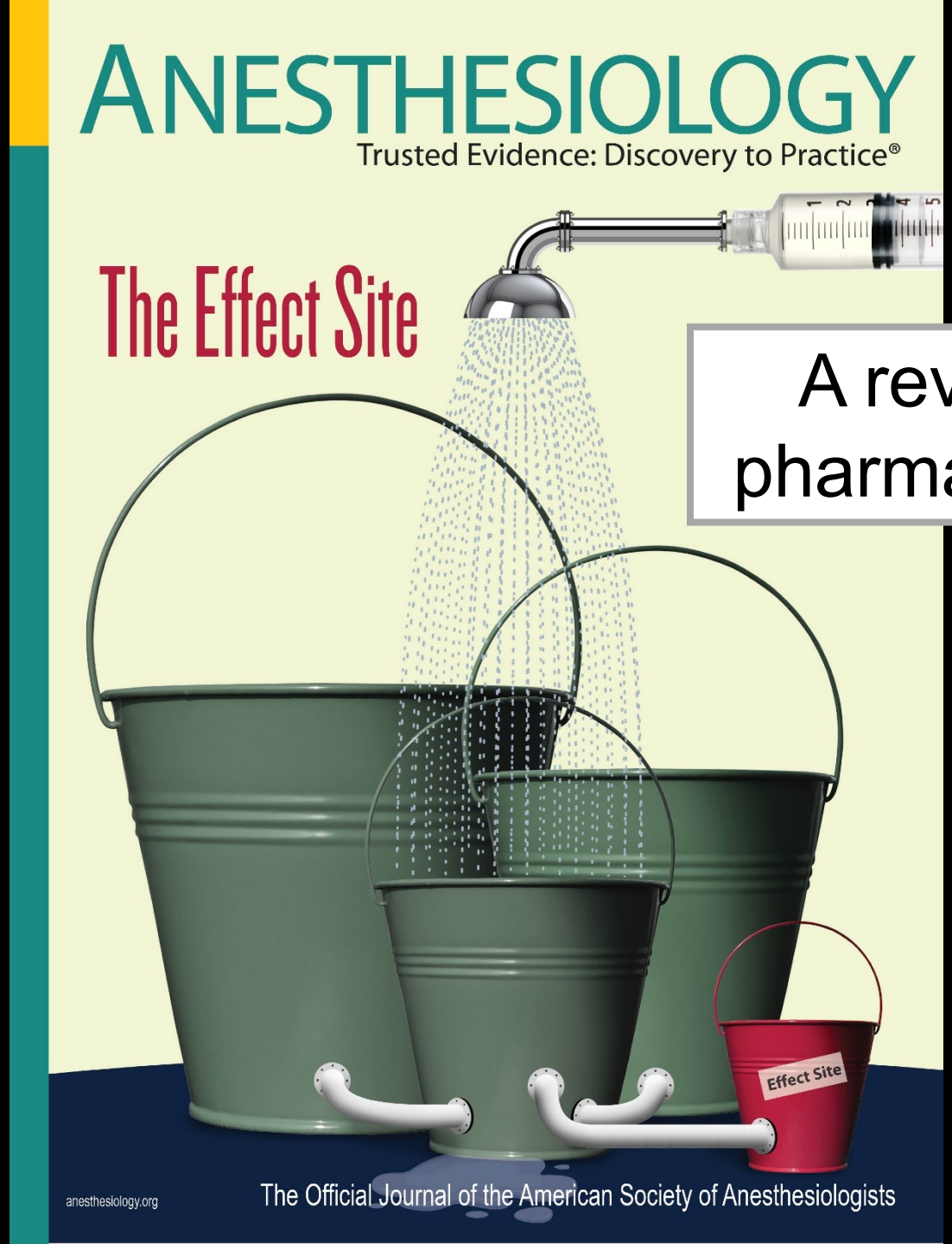




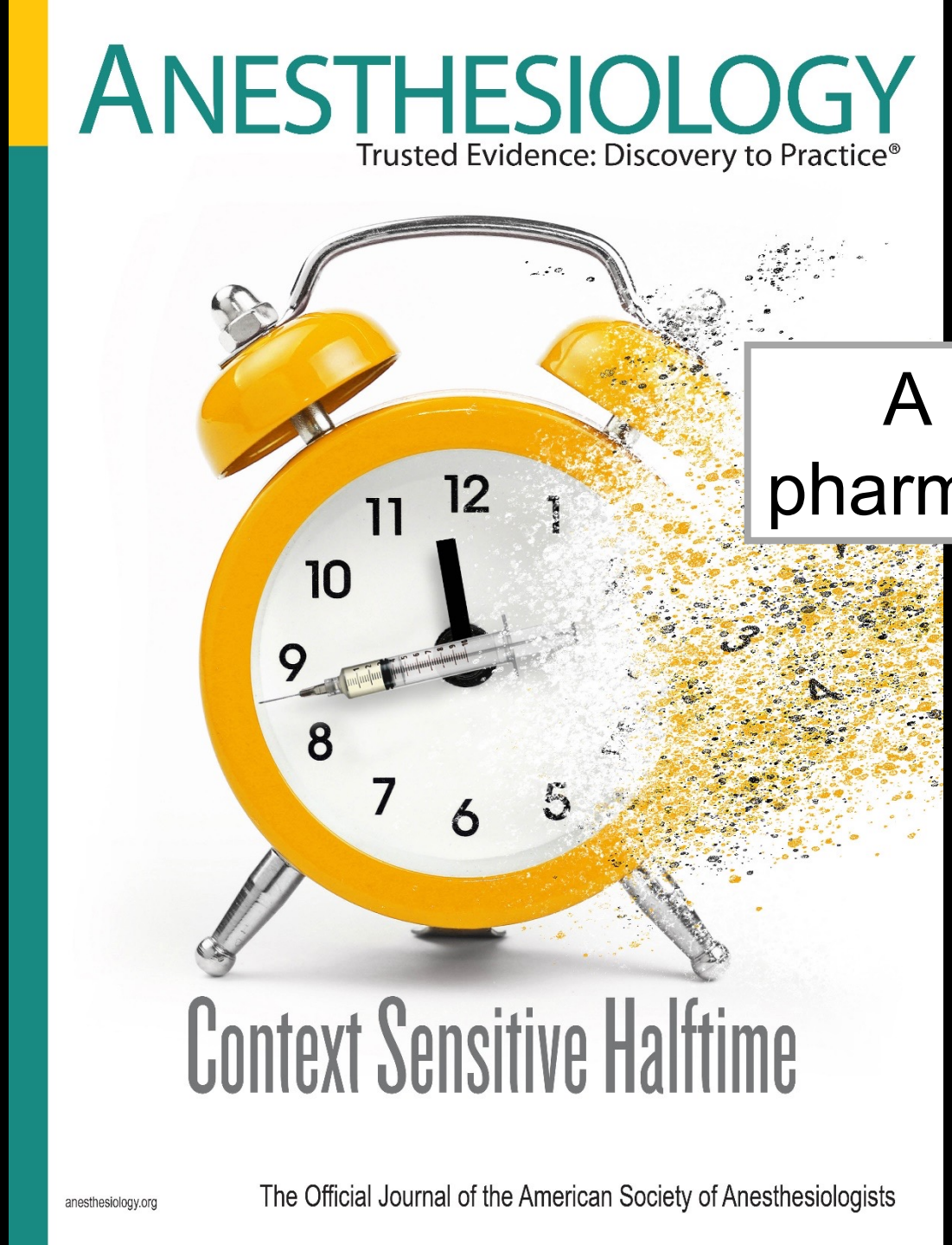
The most important concept in anesthesia clinical pharmacology…



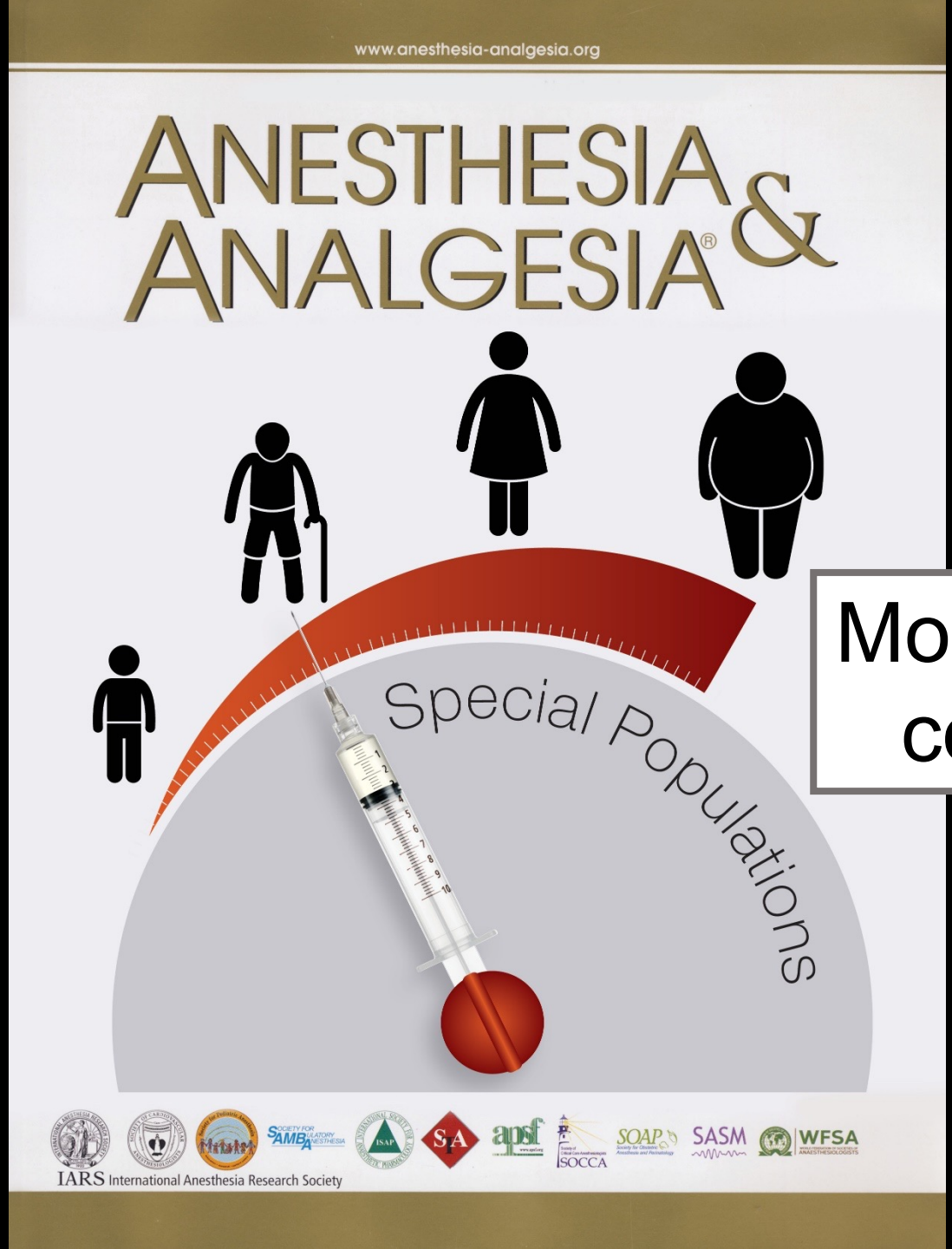
Perhaps the second most important concept in anesthesia clinical pharmacology…



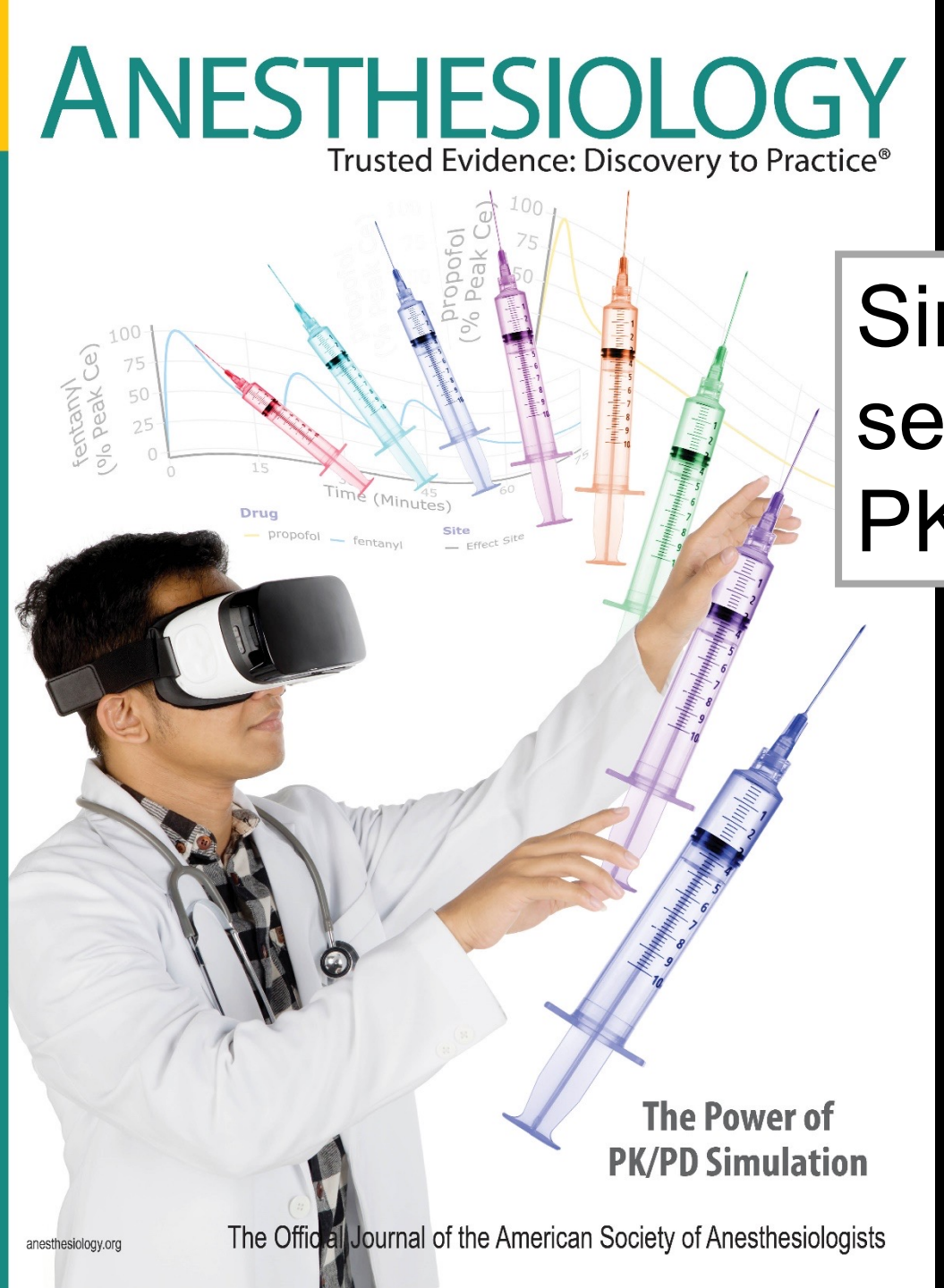
A revolutionary advance in pharmacodynamic modeling…



A revolutionary advance in pharmacokinetic understanding…



Model adjustments for covariate effects…



Simulation makes sense of the PK/PD models…

BJA

British Journal of Anaesthesia

Editor-in-Chief: Ravi P. Mahajan

BJA EDUCATION RESEARCH • DISCOVERY

Advances in propofol formulation made TIVA possible…

The Milky Way

OXFORD UNIVERSITY PRESS

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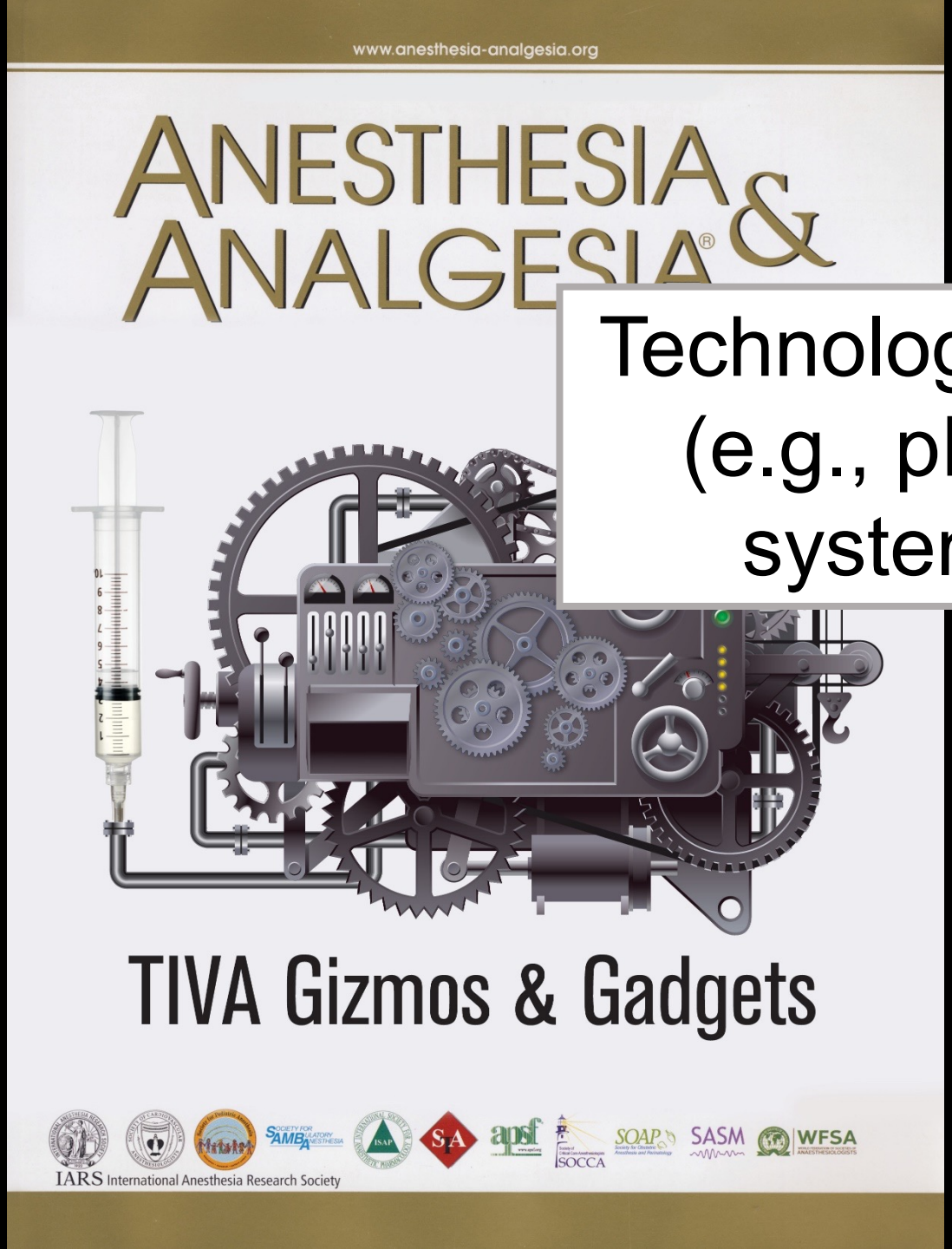
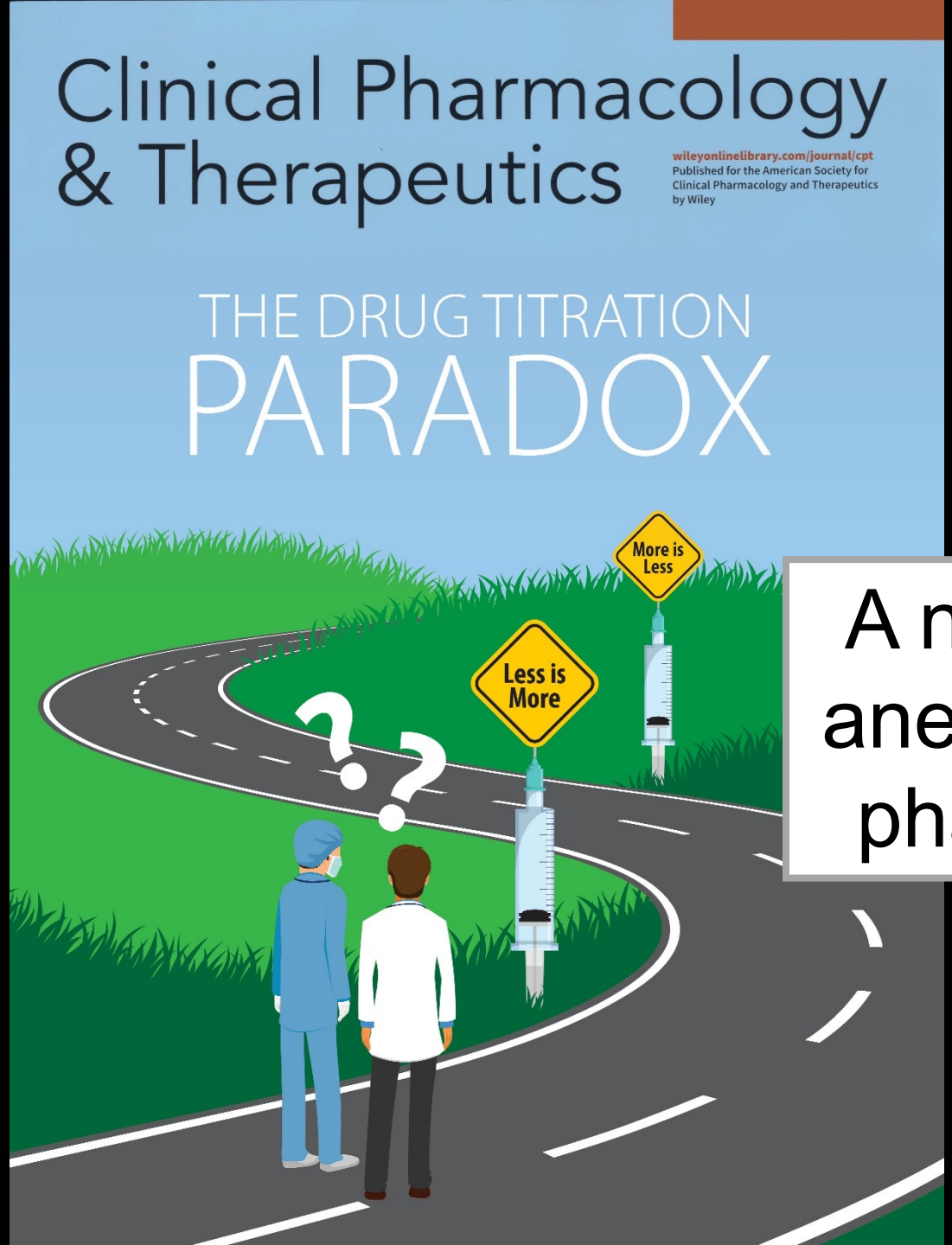
Drugs tailored for precision and efficiency…



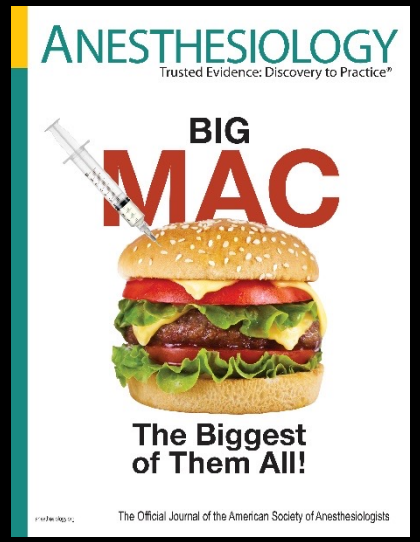
Technological innovation (e.g., pEEG, display systems, etc.….).

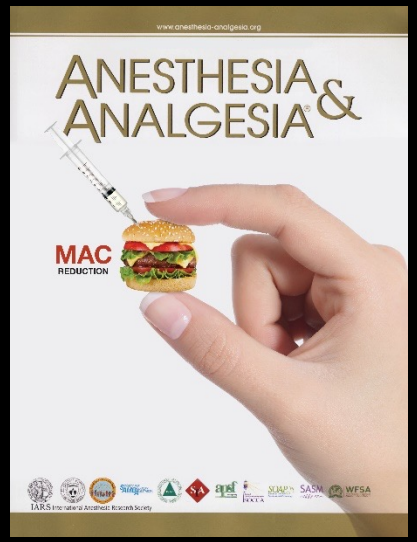
Enabling practice in the concentration domain for TIVA…

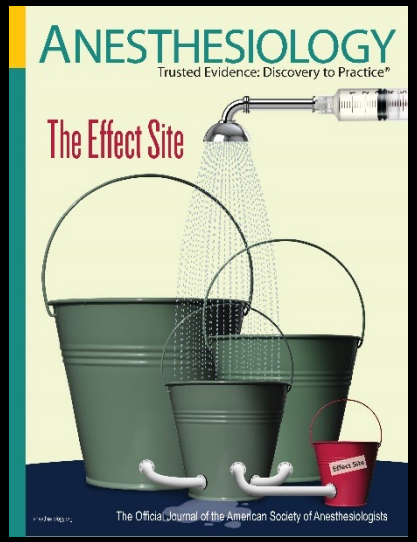


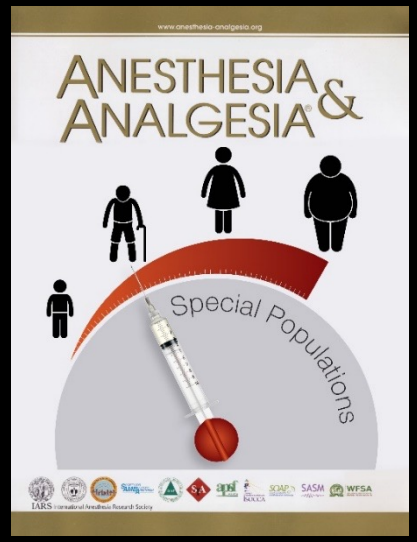
A new concept in anesthesia clinical pharmacology…

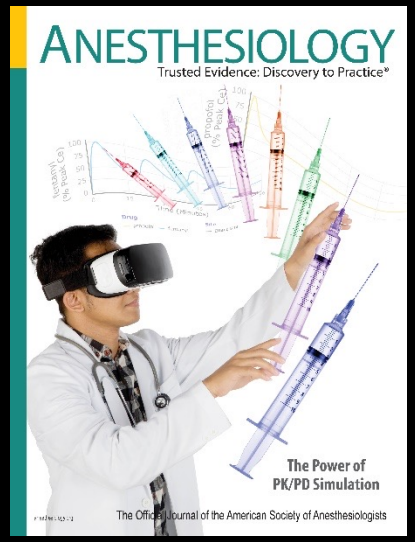
Big Ideas in Anesthesia Clinical Pharmacology

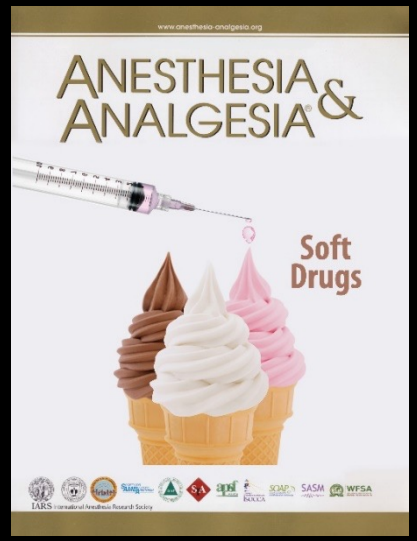


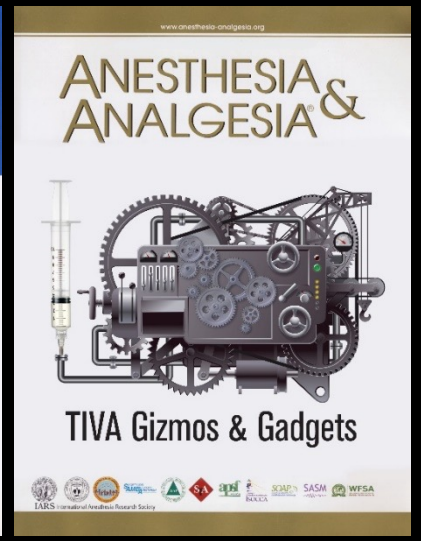


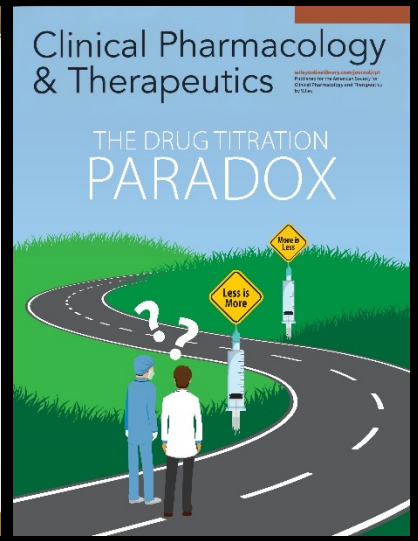


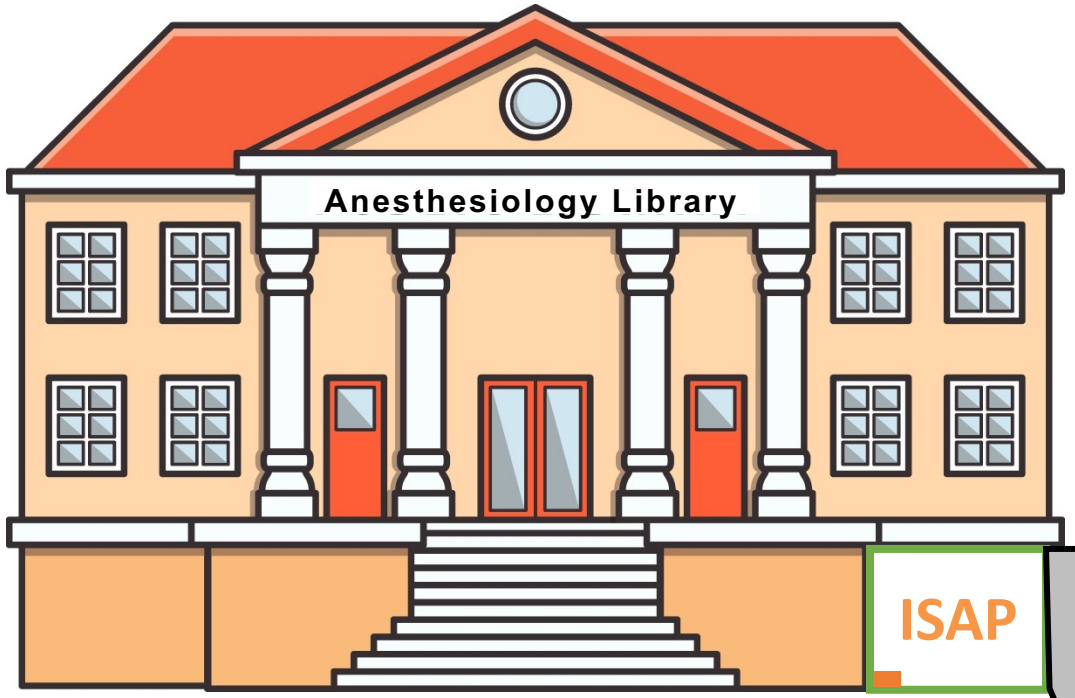












Collective Contributions of ISAP Members

The “Drug Titration Paradox” is a new brick in the foundation…

Key Point

For anesthetics, titration is the primary approach to getting the dose right (i.e., the main posological method).


“If he says POSOLOGY one more time I’m gonna kill him!”

Getting the dose right: anaesthetic drug delivery and the posological sweet spot

K. Kuck* and T. D. Egan

Department of Anesthesiology, University of Utah School of Me

*Corresponding author. E-mail: kai.kuck@hsc.utah.edu

A last try at popularizing the term "posology…."

Posology, a scientific term not in common usage, is the science of drug dosage; it is thus a branch of clinical pharmacology (or perhaps a synonym of sorts). Combining the Greek word (how much) and 'logos' (science), posology more simply as 'dosology'. In the posology of an fundamental question anaesthetists must answer ea 'What is the right anaesthetic dosing strategy for r patient?'

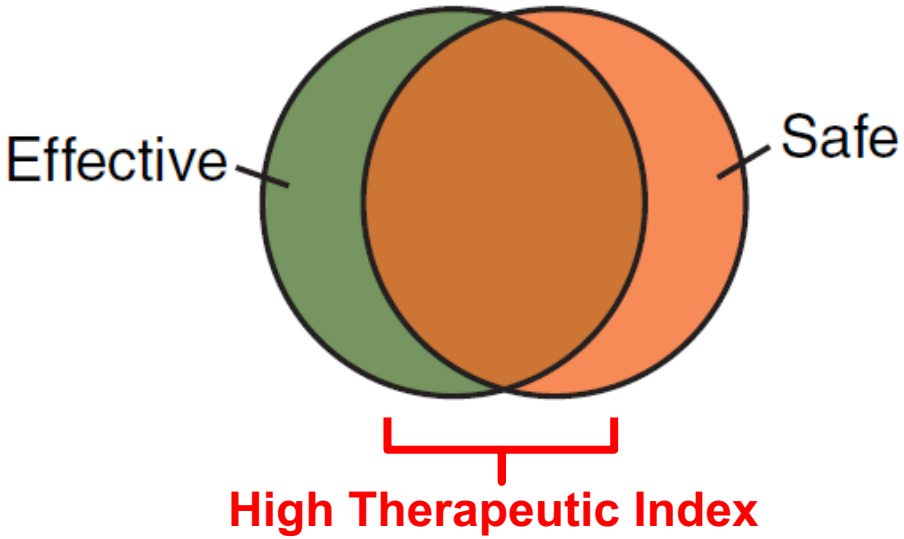
In this issue of the *British Journal of Anaesthesia*, van and colleagues[1] report a novel approach to optimizing in anaesthesia. Their study was an attempt to persona get-controlled infusion (TCI) therapy with a single observation from the patient. Taking a Bayesian approach, the authors started with pharmacokinetic (PK) parameters from a population model[2] and then adjusted them based on the difference between tion and the observation, normalized by their variability. This moves the adjusted system from the *a priori* starting point

"Combining the Greek words 'posos' (how much) and 'logos' (science), posology can be thought of more simply as 'dosology'."

Egan (*Br J Anaesth* 2017)

Anesthesia Posology: Safe, Effective & Efficient

Most Therapeutic Areas

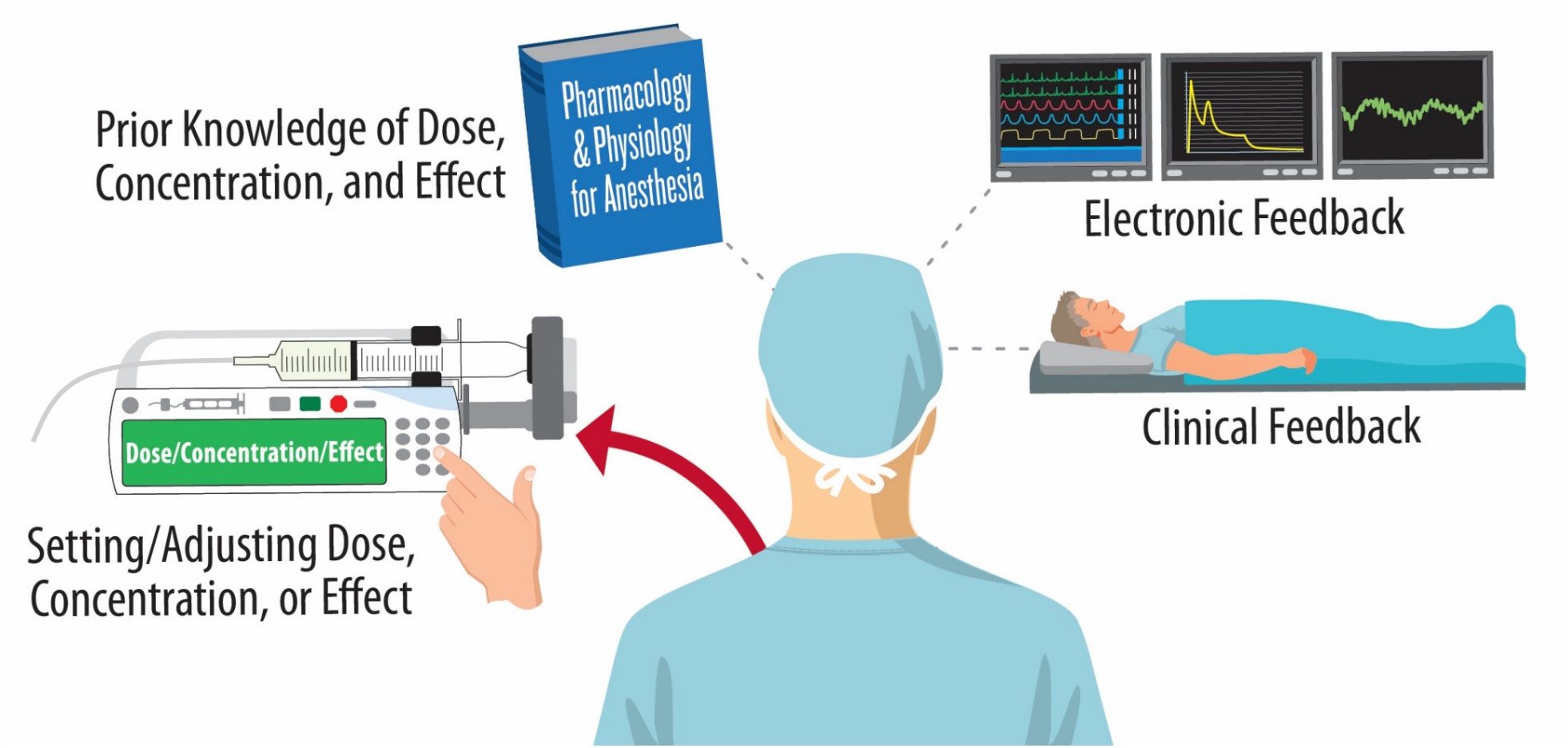


Titration is the main posological method!

Low Therapeutic Index

Kuck & Egan (*Br J Anaesth* 2017)

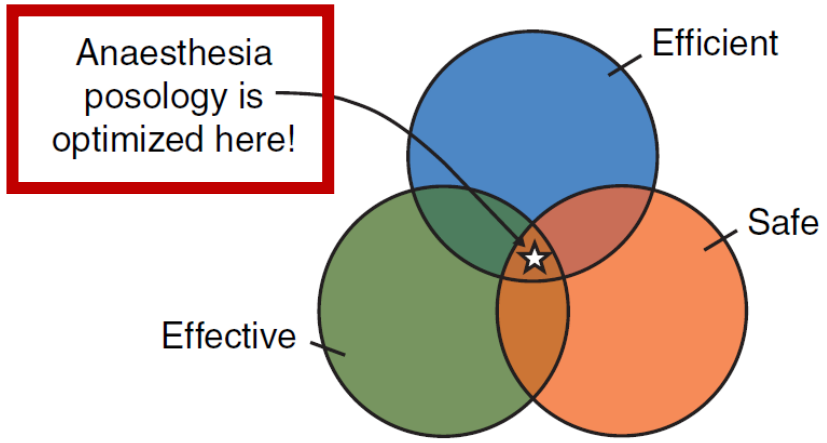
General Approach to Anesthesia Posology



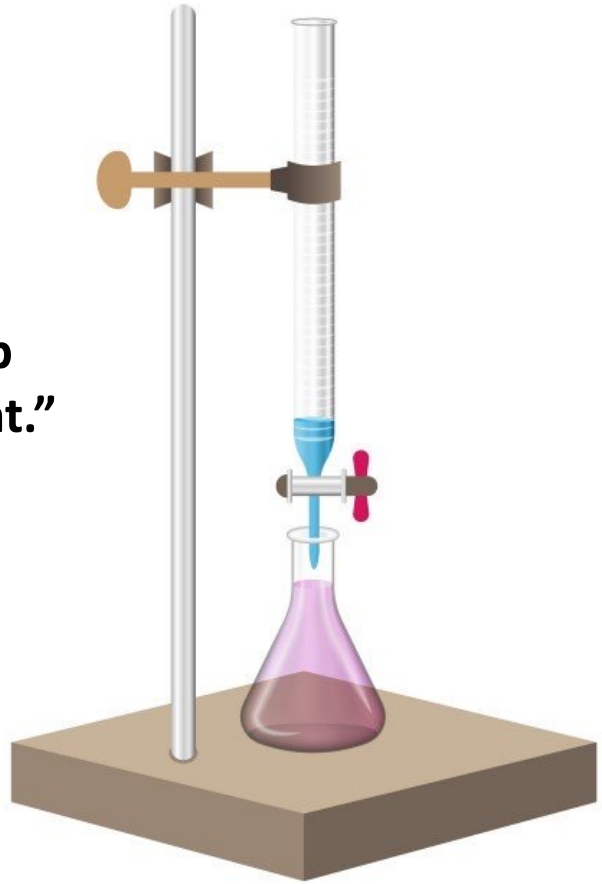
Egan (*Anesth Analg* 2018)

Titration: the Main Posological Method

How?



Drop by drop until "just right."

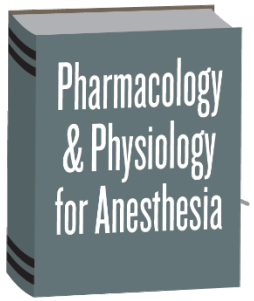


Real time, minute by minute dosage adjustment is referred to as titration…

Target Controlled Infusion and Titration

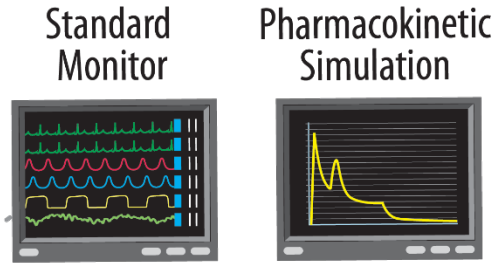
Prior knowledge:

- Pharmacologic models
- Therapeutic windows
- Covariate effects

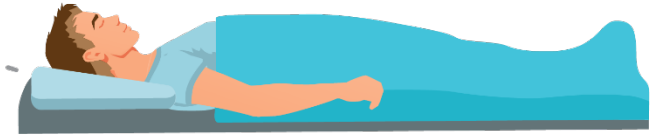


Current knowledge:

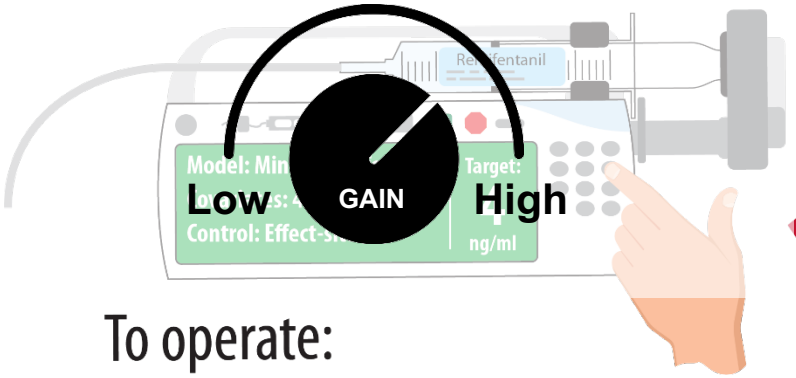
- Real-time assessment



Electronic Assessment

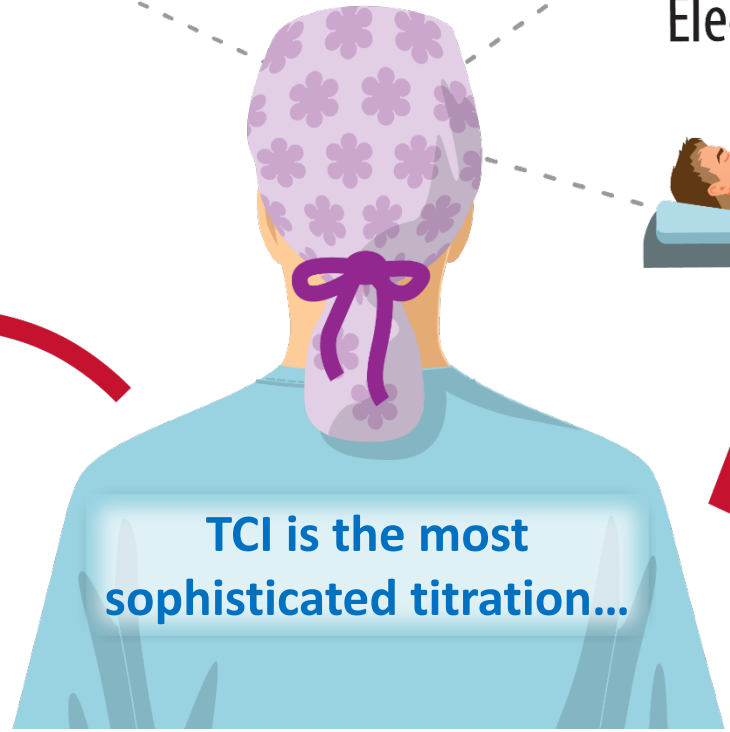


Clinical Assessment



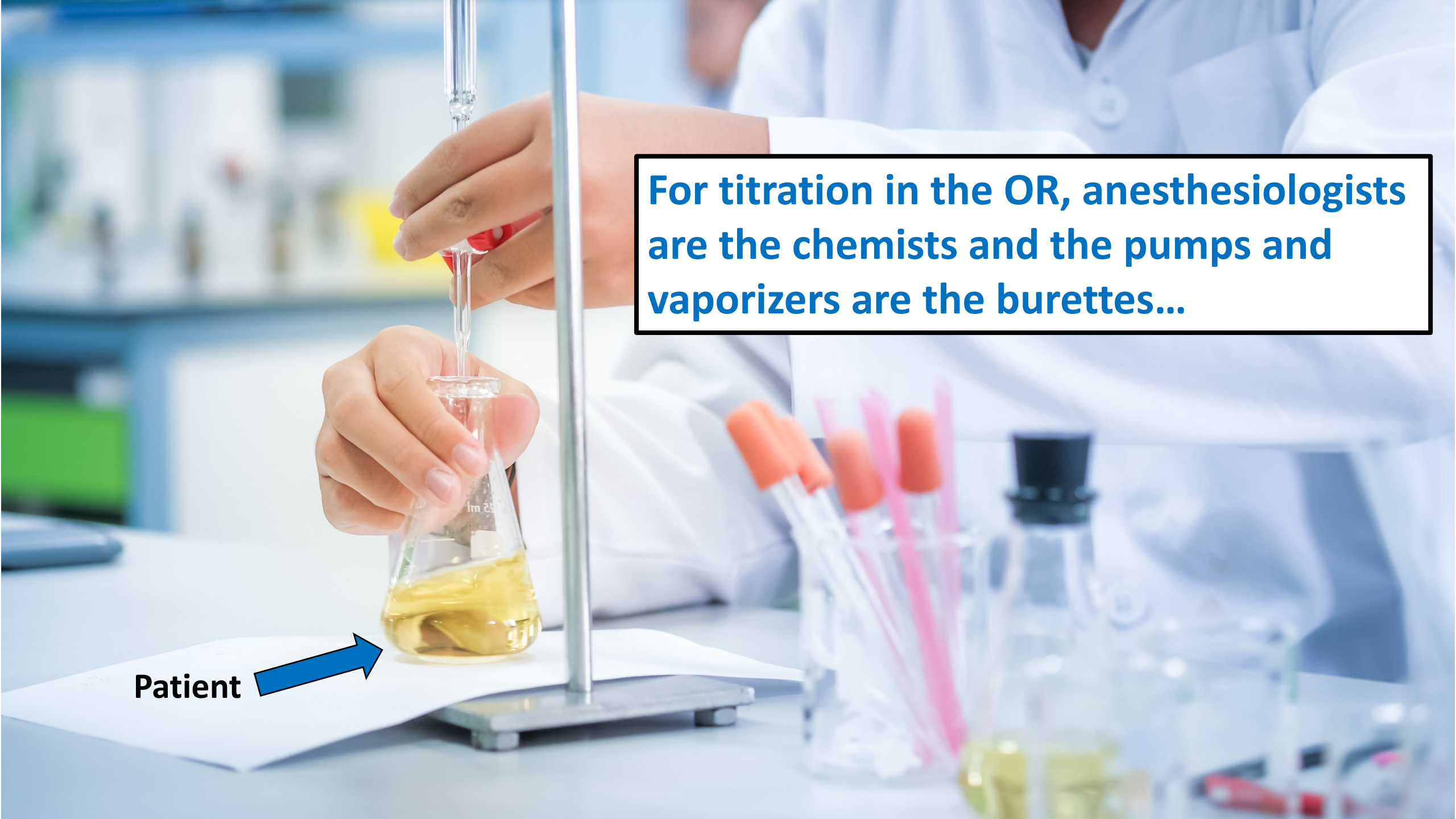
To operate:

- Select pharmacokinetic model
- Input covariates
- Choose effect-site or plasma control
- Designate/adjust target concentration



Open Loop
Control

Egan *et al* (*Br J Anaesth* 2020)


For titration in the OR, anesthesiologists are the chemists and the pumps and vaporizers are the burettes…
Patient

Key Point

The “drug titration paradox” is a new concept in anesthesia clinical pharmacology.

The Drug Titration Paradox: Correlation of More Drug With Less Effect in Clinical Data

Thomas W. Schnider[1,*], Charles F. Minto[2] and Miodrag Filipovic[1]

While analyzing clinical data where an anesthetic was titrated based on an objective measure of drug effect, we observed paradoxically that greater effect was associated with lesser dose. With this study we sought to find a mathematical explanation for this negative correlation between dose and effect, to confirm its existence with additional clinical data, and to explore it further with Monte Carlo simulations. Automatically recorded dosing and effect data from [illegible] propofol and sevoflurane and the cat[illegible] processed electroencephalogram (Bispe[illegible] algorithm was developed for the simulations. [illegible] titration to the targeted effect will associate lo[illegible] tween propofol and BIS, sevoflurane and BIS, a[illegible] paradox. Monte Carlo simulations revealed two additional factors that contribute to the paradox. During stepwise titration toward a target effect, the slope of the dose–effect data for the population will be "reversed," i.e., the correlation between dose and effect *will not be positive*, but will be negative, and will be "horizontal" when the titration is "perfect." The titration paradox must be considered whenever data from clinical titration (flexible dose) studies are interpreted. Such data should not be used naively for the development of dosing guidelines.

"We observed paradoxically that greater effect was associated with lesser dose."

Schnider *et al* (*Clin Pharmacol Ther* 2021)

Really? Less drug is associated with greater effect? Could that be right?

The Titration Paradox Turns Pharmacology Upside Down

Steven L. Shafer[1] and Donald R. Stanski[1,*]

From a unique data set of two anesthetic drugs and one vaso drug in a real-world intraoperative anesthetic electronic from 9,000 patients each drug's infusion was titrated measurable targeted drug effect. The authors dose vs. effect relationship and found dec with exp exp

authors' great surprise, they found decreasing drug effect with increasing doses of each drug. It seems impossible. How could more propofol or more sevoflurane result in less anesthesia? How could more norepinephrine result in lower blood pressure? It makes no sense. In their large and meticulously gathered data set, the exposure–response relationship is turned "up-side down."

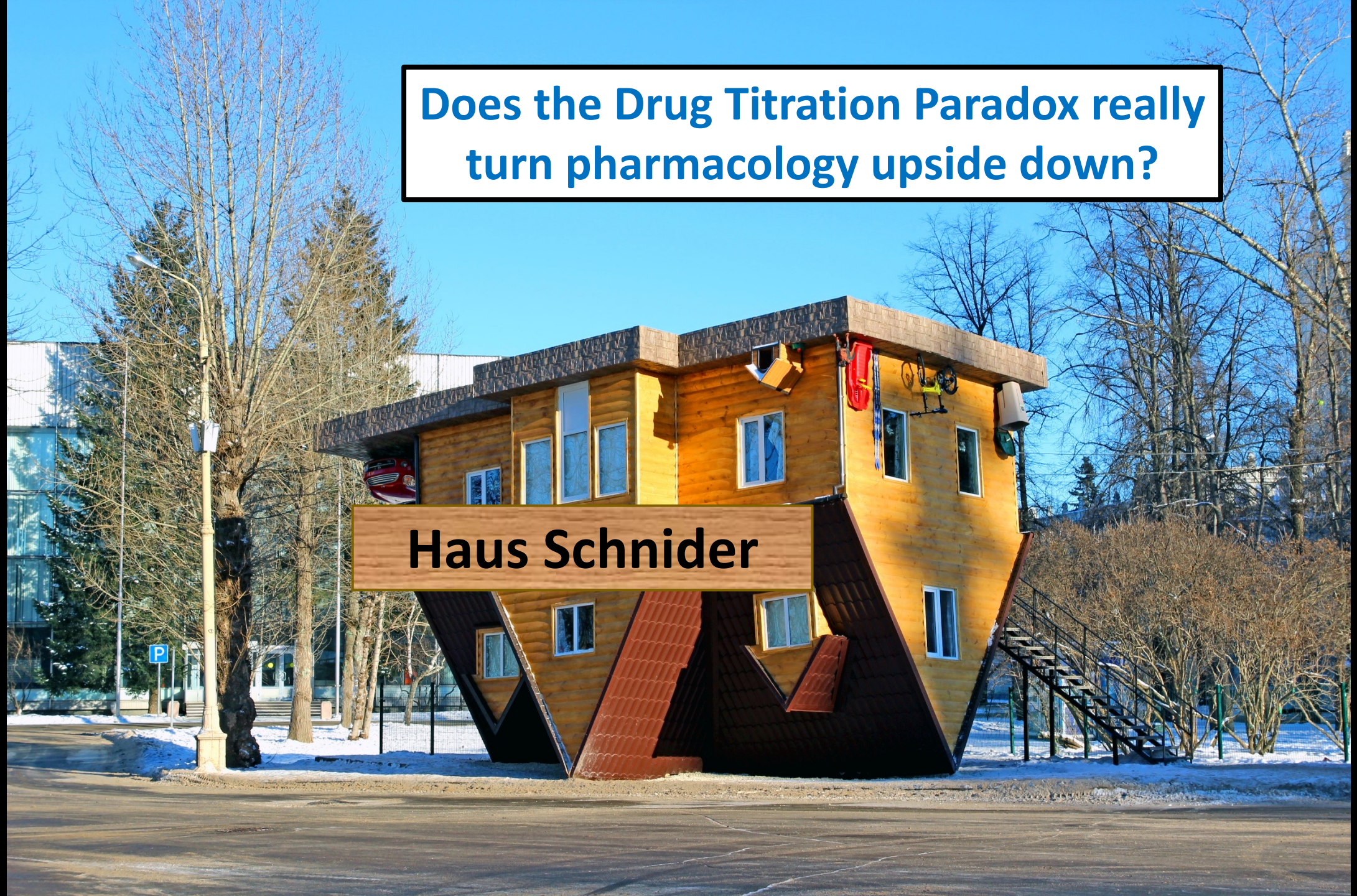
After an extensive analysis, the authors concluded that (i) this is the result of titration, (ii) this is a completely expected and (iii) approaches to understanding exposure–response relationships that consider drug titration may produce misleading results.

above can easily be explained with mple. You see two hypertensive pa-

"It seems impossible. How could more propofol or more sevoflurane result in less anesthesia? … It makes no sense. In their large … data set, the exposure–response relationship is turned "up-side down."

Shafer & Stanski (*Clin Pharmacol Ther* 2021)

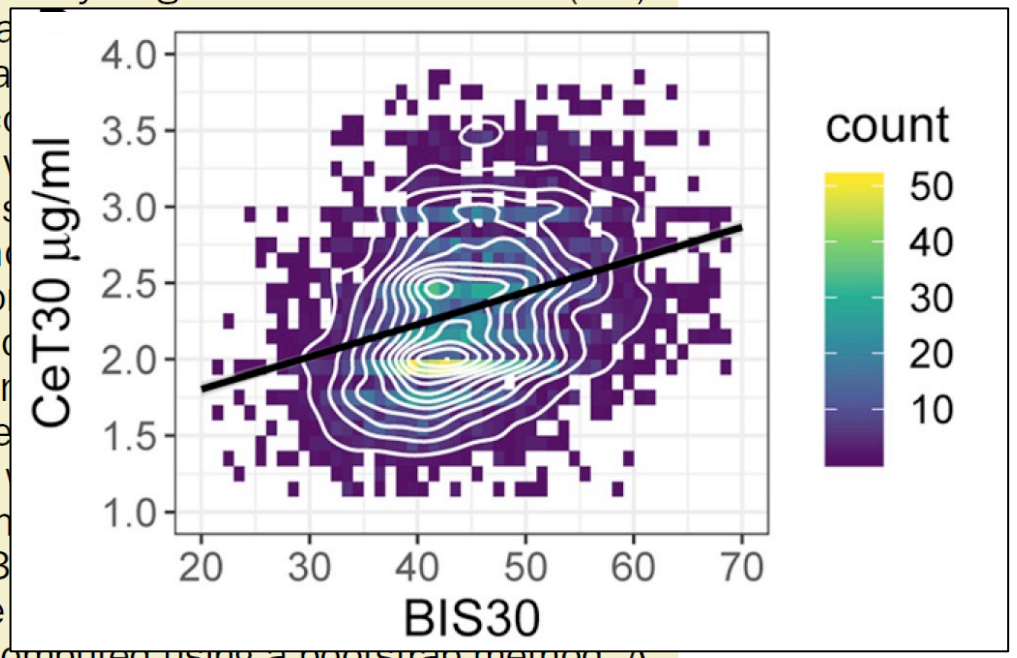
Does the Drug Titration Paradox really turn pharmacology upside down?



Relationship Between Propofol Target Concentrations, Bispectral Index, and Patient Covariates During Anesthesia

Thomas W. Schnider, Prof Dr med,* Charles F. Minto, MB, ChB, PhD,† Talmage D. Egan, MD,‡ and Miodrag Filipovic, Prof Dr med*

BACKGROUND: Internationally, propofol is commonly titrated by target-controlled infusion (TCI) to maintain a processed electroencephalographic (EEG) pa within a specified range. The overall variability in propofol ta necessary to maintain adequate anesthesia in real-world c are the patient demographic factors that contribute to this issues, hypothesizing that the variability in covariate-adju during BIS-controlled anesthesia would be substantial an patient variability in drug response would be due to rando opportunity to improve on the Schnider model with further
METHODS: With ethics committee approval and a waiver of i resolution, intraoperative database consisting of propofol targe signs from 13,239 patients anesthesia using propofol (titrated to BIS), fentanyl, remifentan 1 hour. The propofol target concentrations and BIS values 3 BIS30) were considered representative of stable intraoperative analyzed by descriptive statistics. Confidence intervals were computed using a bootstrap method. A linear model was fit to the data to test for correlation with factors of interest (eg, age and weight).

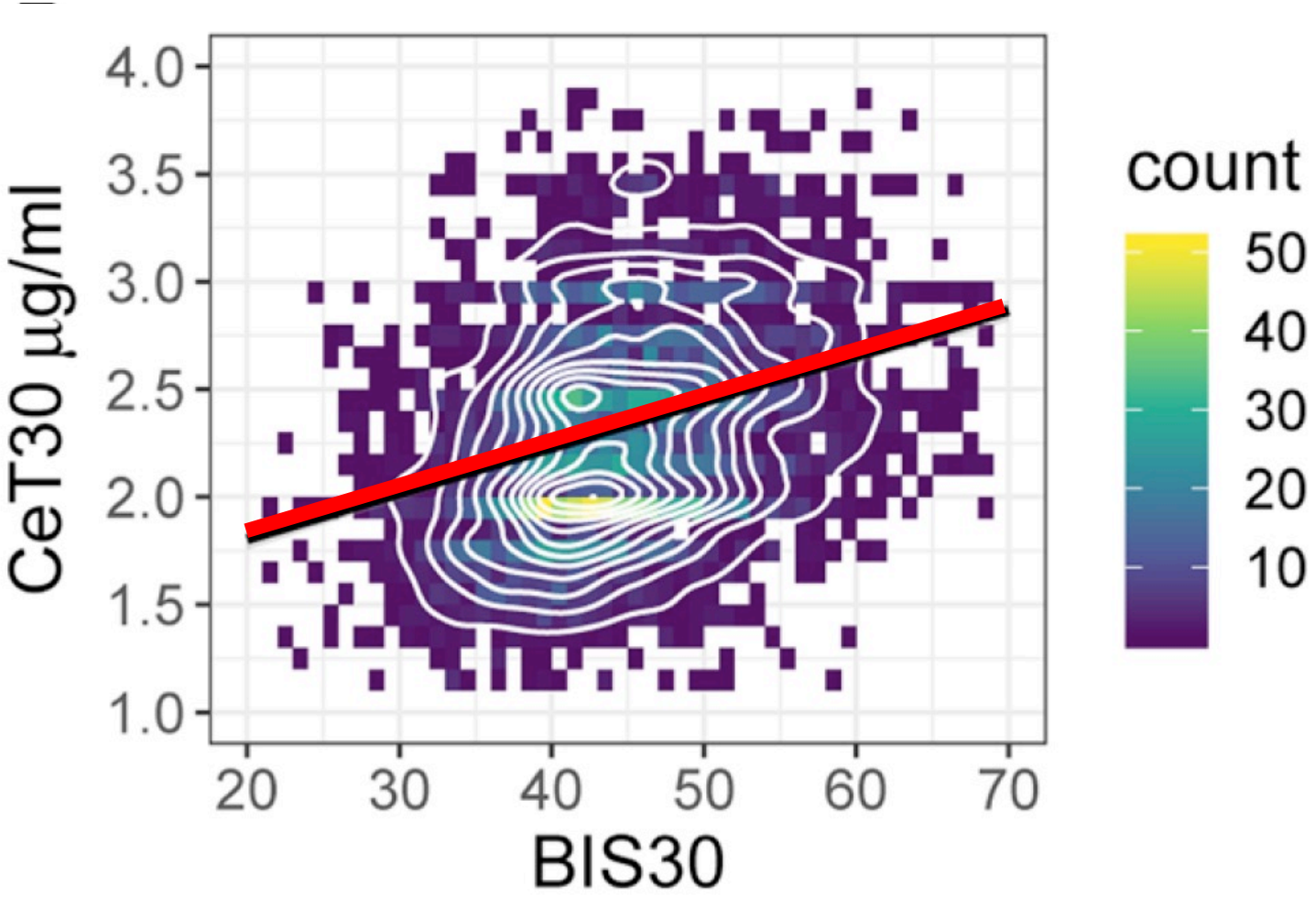


Schnider *et al* (*Anesth Analg* 2021)

Propofol Concentration vs. BIS at Steady State

- N = 4585
- GETA by TIVA
- 30 min after incision:
  - Propofol Target Ce
  - BIS Value

Unexpected Observation!

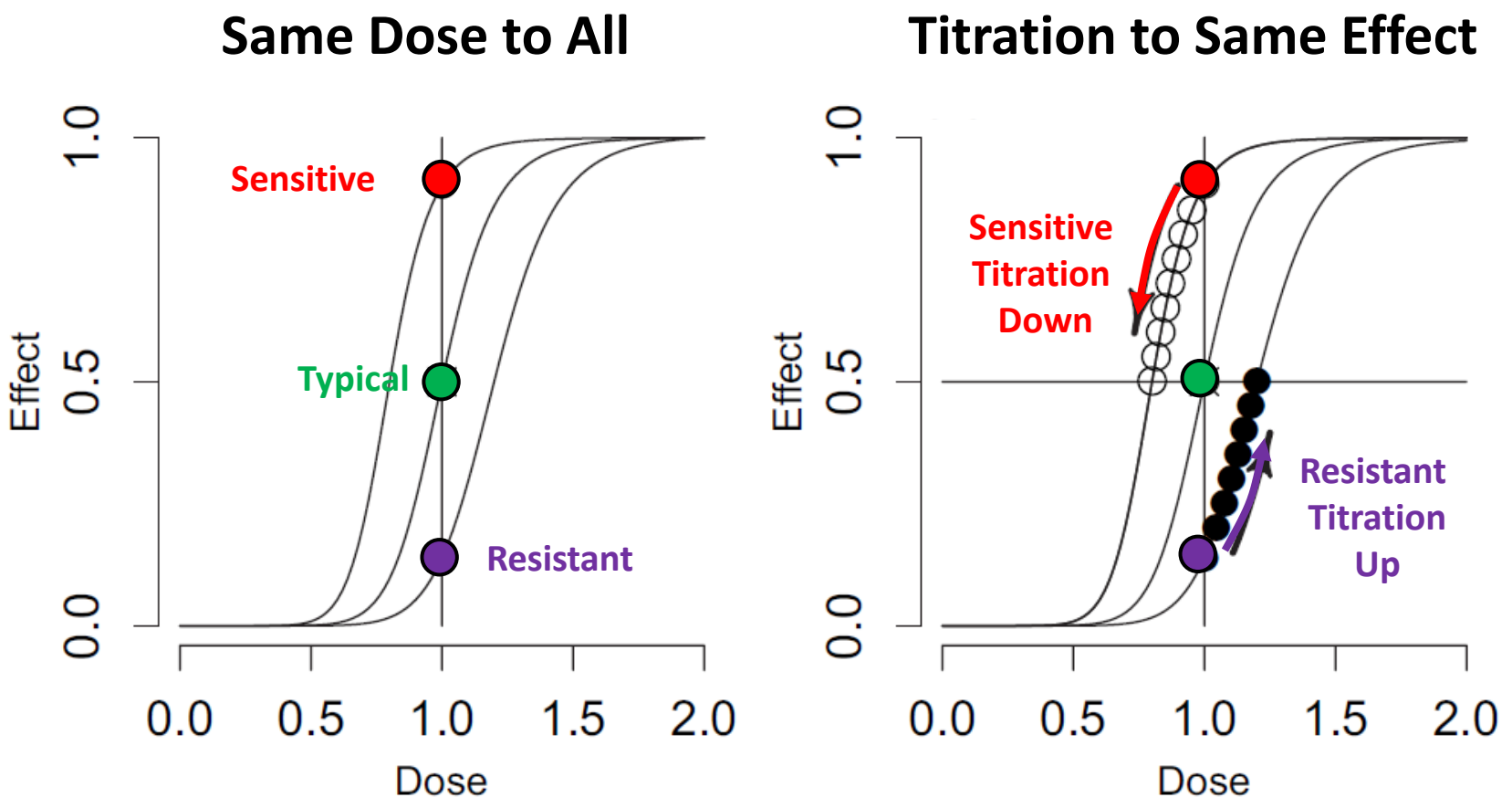


Schnider *et al* (*Anesth Analg* 2021)

Definition

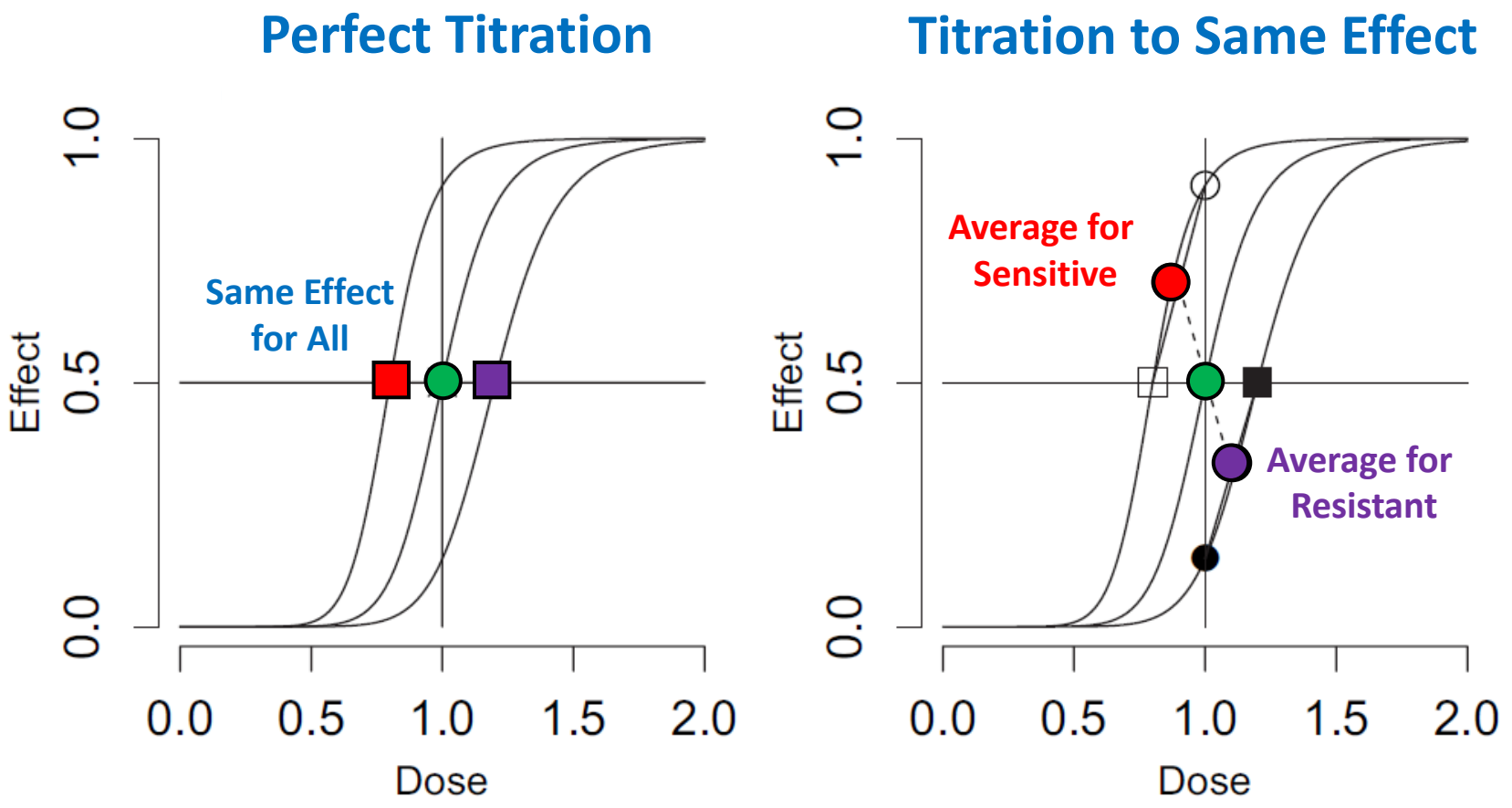
When a drug is titrated to a specified level of effect in a population of patients, the expected positive correlation between dose and effect is reversed.

Hypothesis Illustrated Graphically



Schnider *et al* (*Clin Pharmacol Ther* 2021)

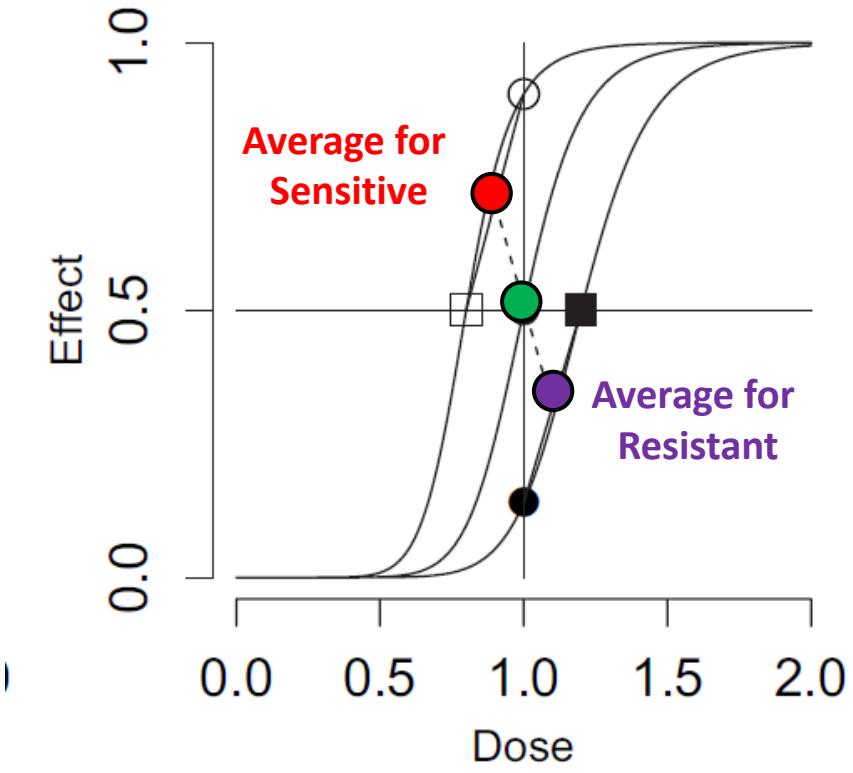
Hypothesis Illustrated Graphically



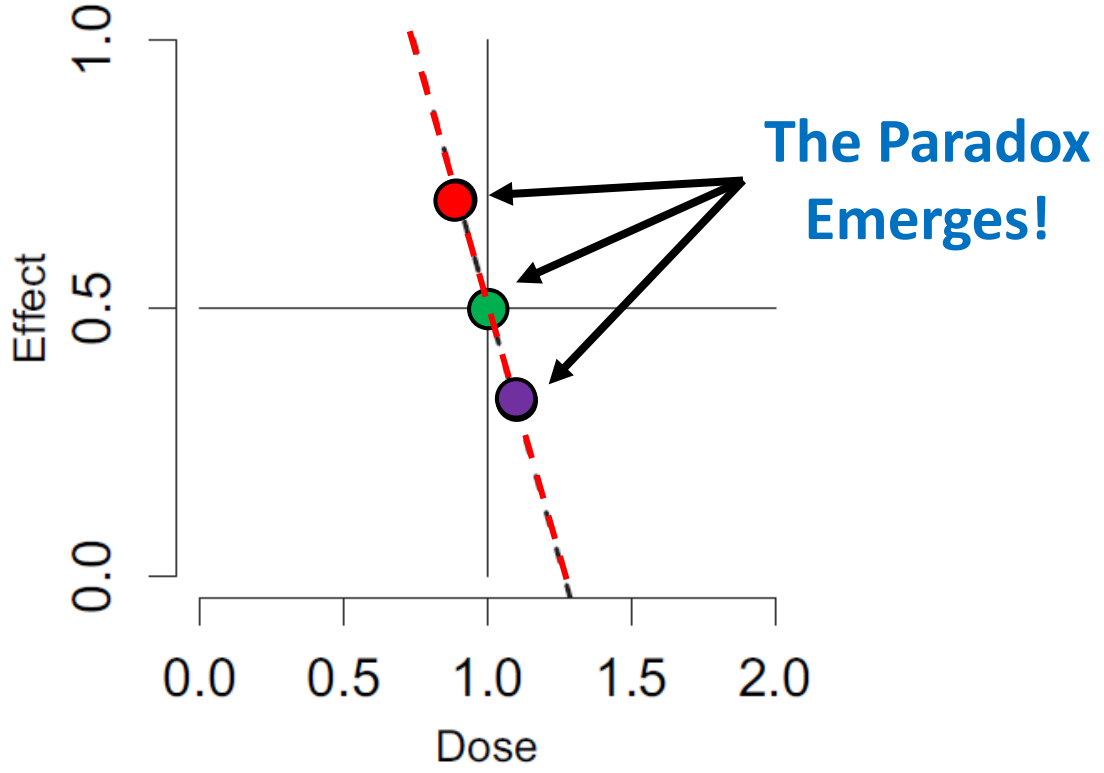
Schnider *et al* (*Clin Pharmacol Ther* 2021)

Hypothesis Illustrated Graphically

Titration to Same Effect

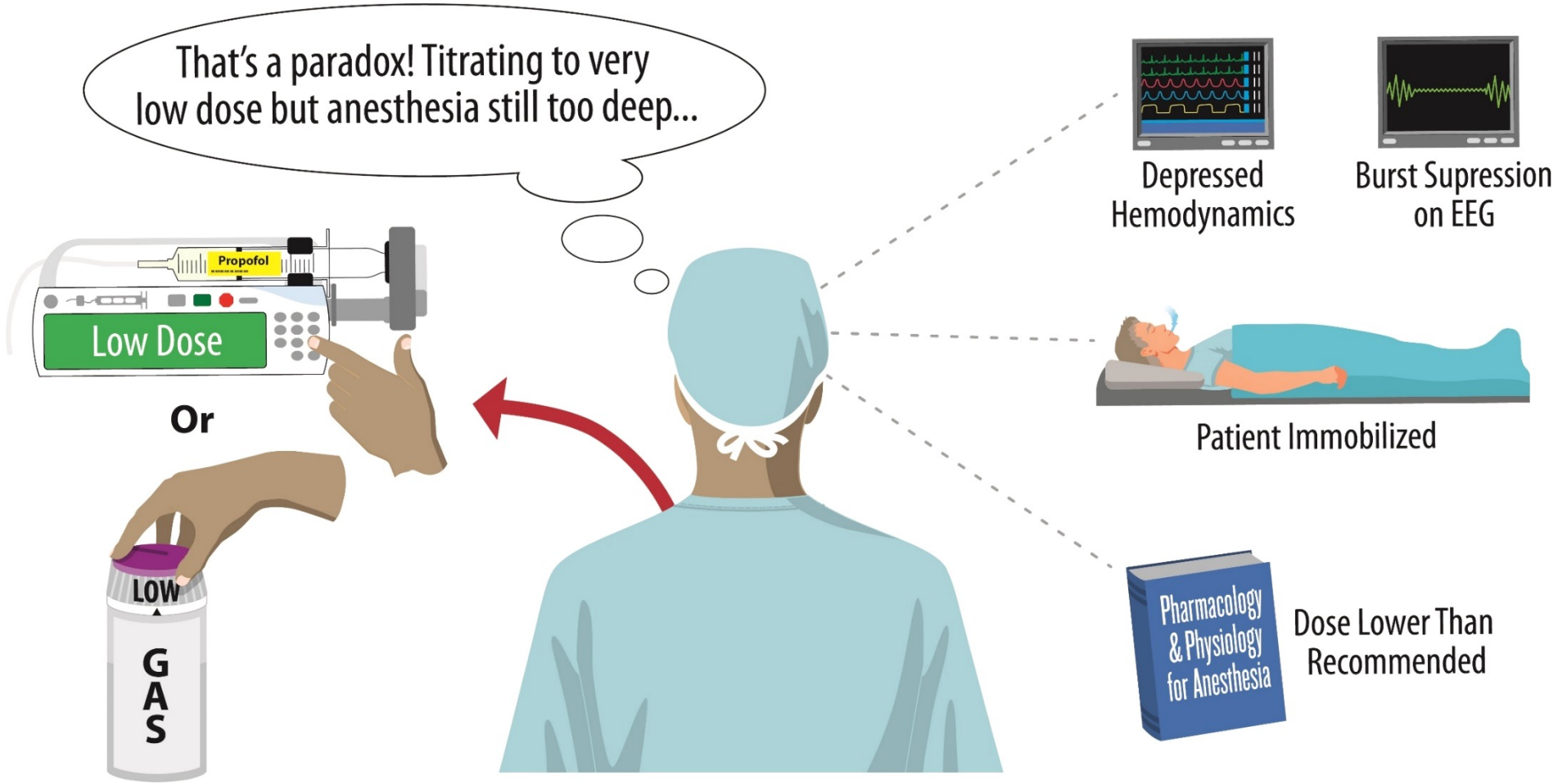


Data as Seen by Analyst



Schnider *et al* (*Clin Pharmacol Ther* 2021)

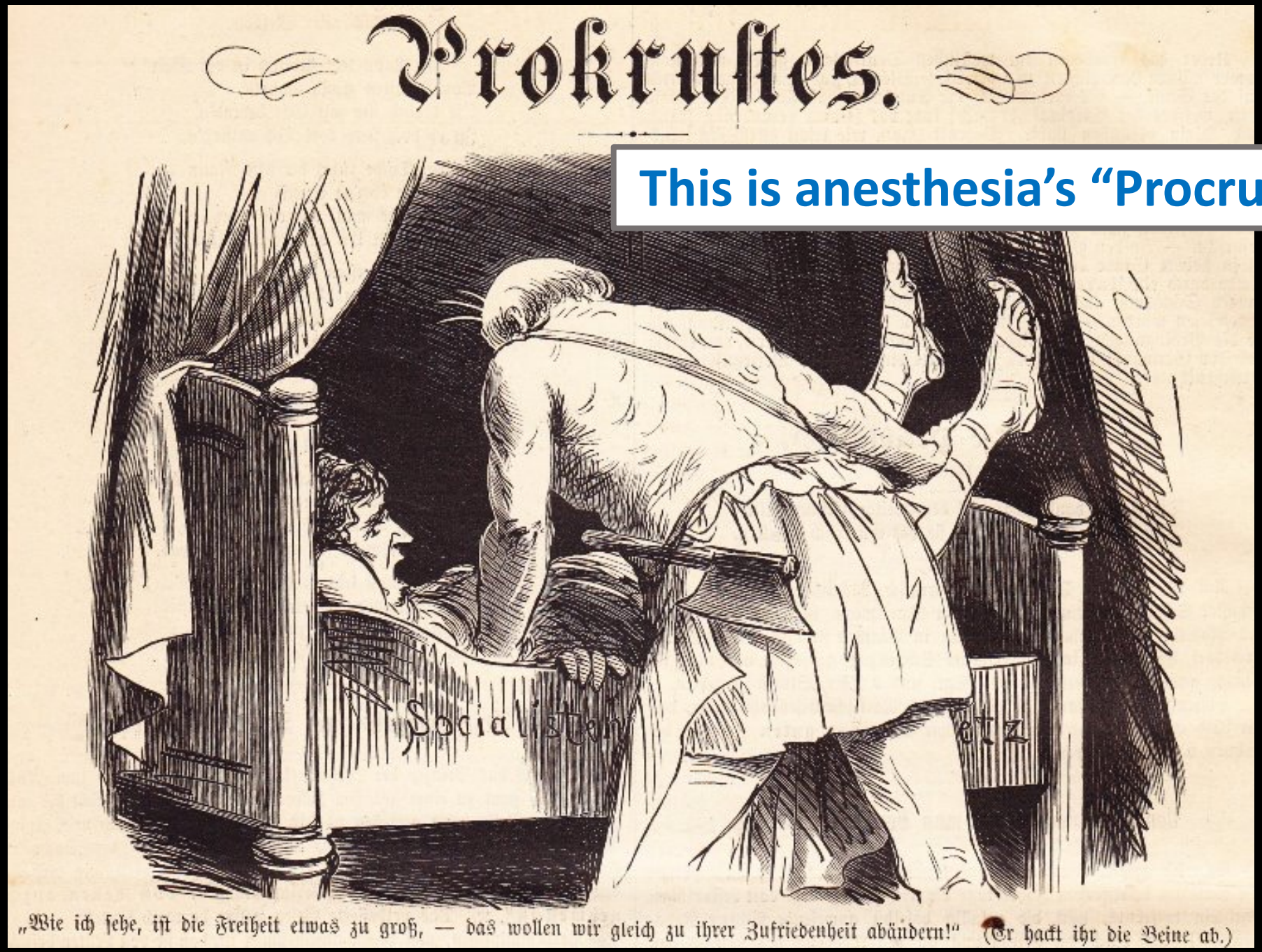
Hints of the Drug Titration Paradox in Practice



Egan (*Br J Anaesth* 2022)

Origins

The “drug titration paradox” teaches us a lot about pharmacologic variability. The phenomenon arises because “one size does not fit all.”



This is anesthesia's "Procrustean" problem…

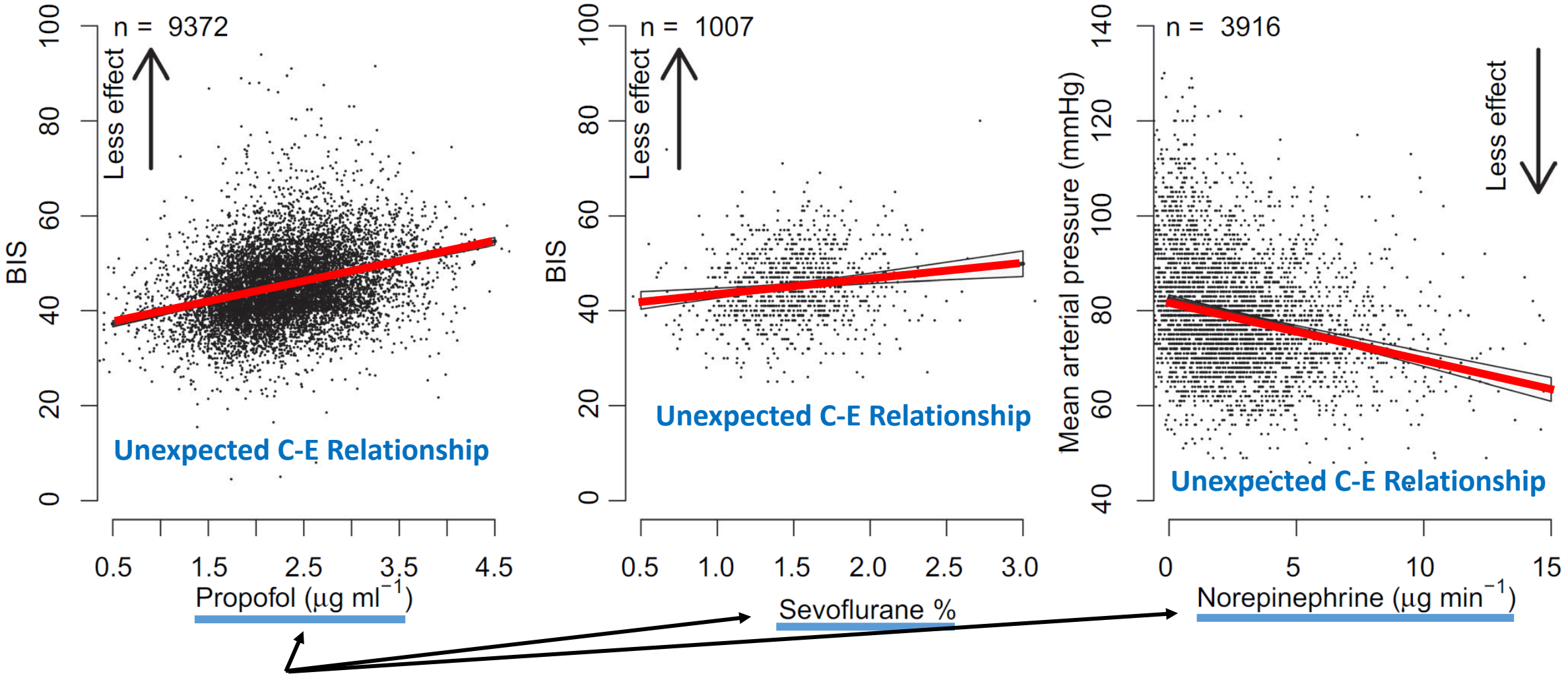
(*Berliner Wespen*, 30 August 1878)

The dose-response relationship varies widely in a population of patients; the drug titration paradox emerges from this reality…

Key Point

The “drug titration paradox” is supported by at least three lines of evidence.

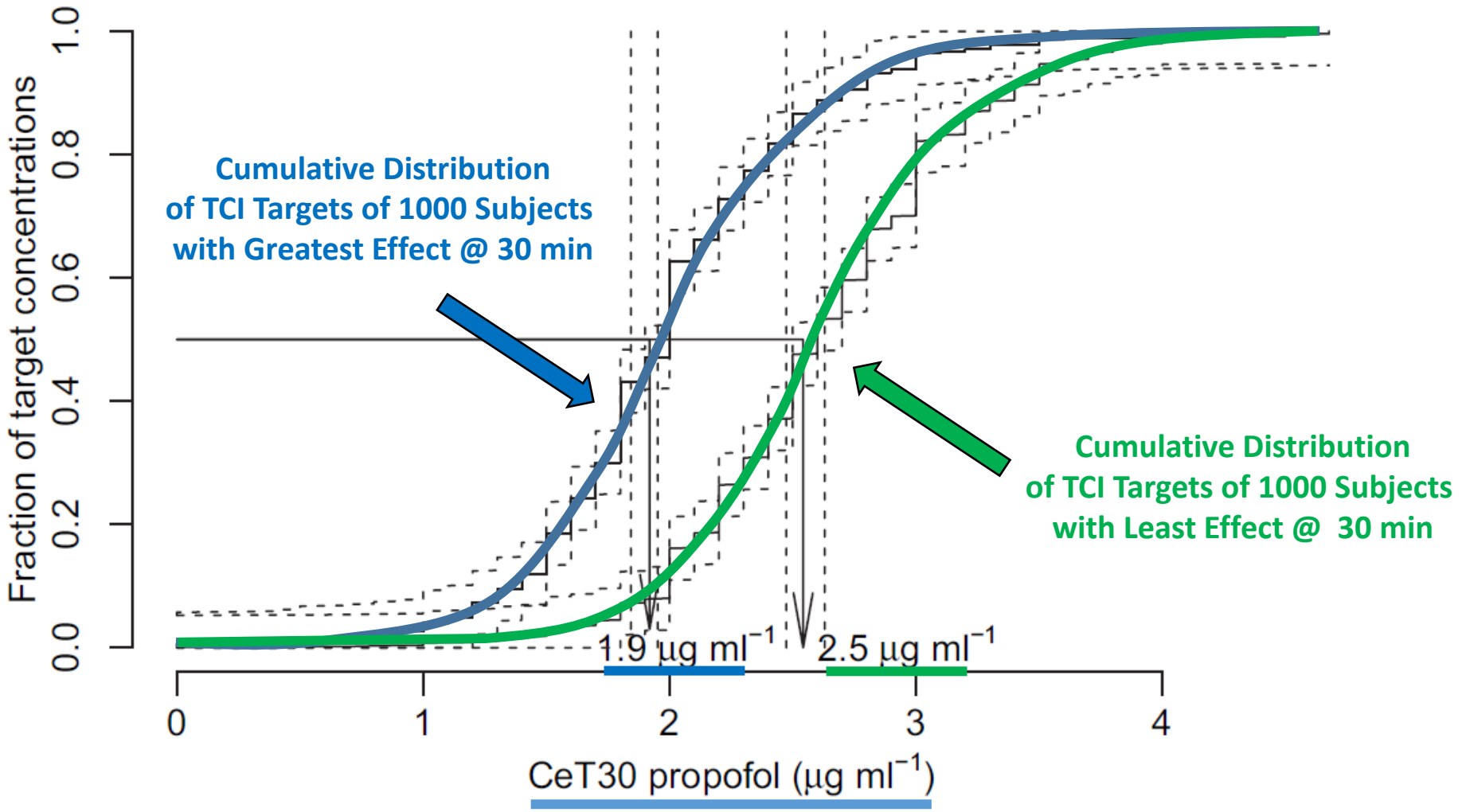
Paradox in the Raw Data



@ 30 minutes after incision…

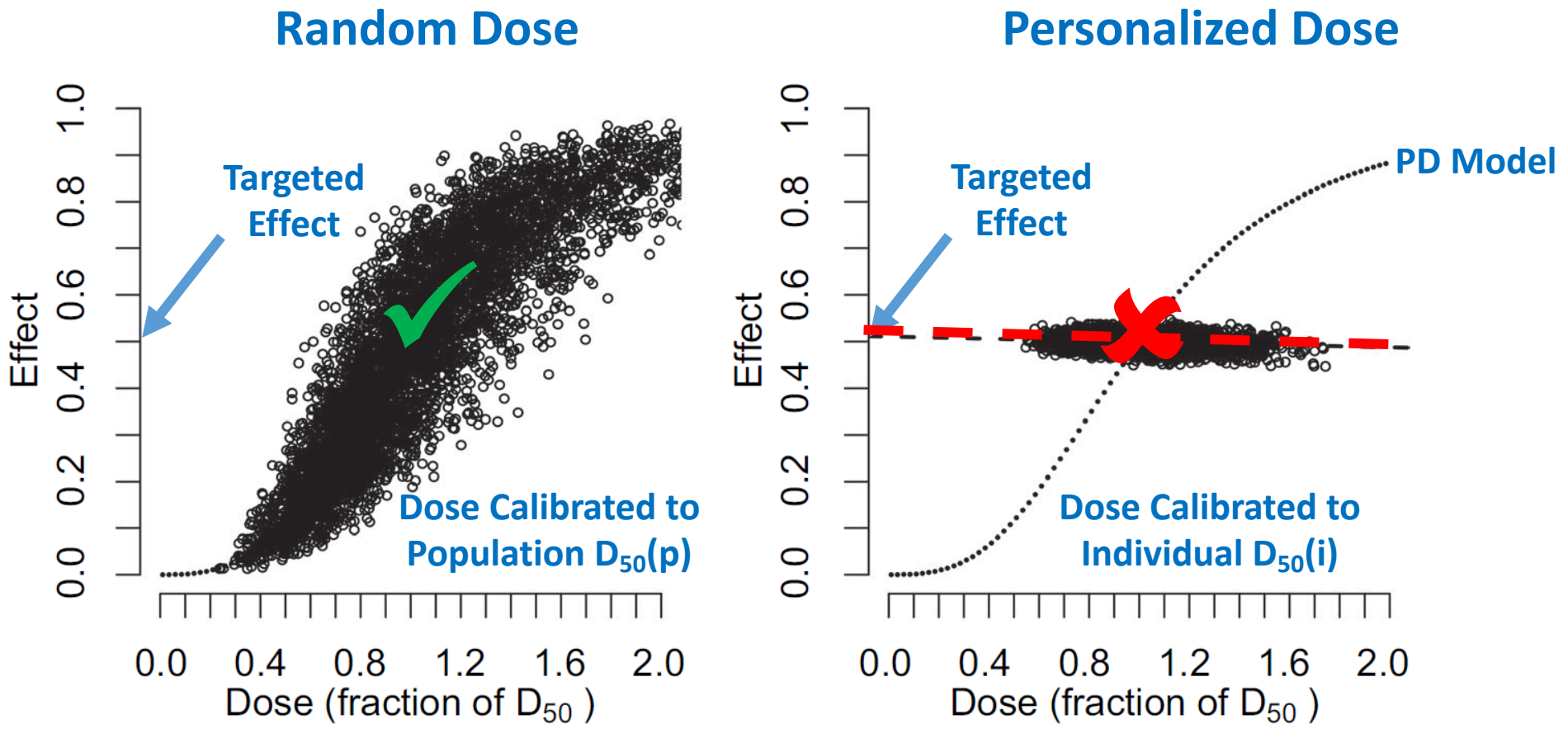
Schnider *et al* (*Clin Pharmacol Ther* 2021)

Paradox in the Raw Data (cont.)



Schnider *et al* (*Clin Pharmacol Ther* 2021)

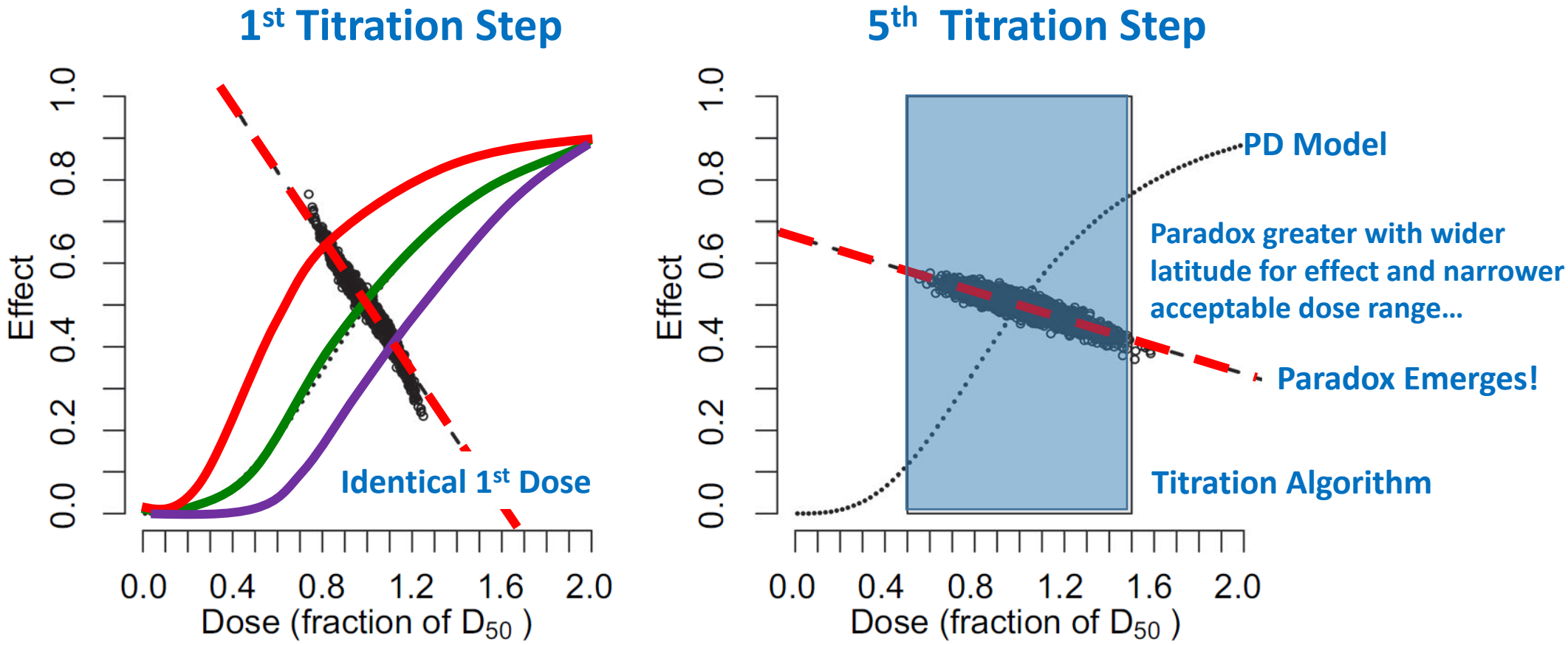
Paradox in Monte Carlo Simulations



N=5000 for each

Schnider *et al* (*Clin Pharmacol Ther* 2021)

Paradox in Monte Carlo Simulations



N=5000 for each

Schnider *et al* (*Clin Pharmacol Ther* 2021)

Paradox in a Mathematical Proof

Mathematical proof

By deduction we prove that the average dose–effect relationship during titration to the targeted effect will associate lower doses with greater effects:

Given:

$$E = E_0 + \left(E_{max} - E_0\right)\left(\frac{\left(\frac{D}{D_{50}}\right)^{\gamma}}{1+\left(\frac{D}{D_{50}}\right)^{\gamma}}\right) = f_1\left(D_{50}, D\right).$$

Solved for D:

$$D = \sqrt[\gamma]{\frac{\left(E - E_0\right)D_{50}^{\gamma}}{\left(E_{max} - E\right)}} = f_2\left(D_{50}, E\right).$$

Where:

E = Effect.
E_0 = Baseline effect.
E_{max} = Maximum effect.
γ = Steepness parameter.
D = Dose.
D_{50} = Dose associated with 50% Effect.

f_1 and f_2 are abbreviations of the Hill function and inverse Hill function, respectively, and read as "is function of," e.g., D_{50} and D and E, respectively.

Etc., etc., etc…

"By deduction we prove that the average dose–effect relationship during titration to the targeted effect will associate lower doses with greater effects."

Schnider *et al* (*Clin Pharmacol Ther* 2021)

FOR (N IN 1:1000)

{

C_{50} = $C_{50\,TG}$ + RANDOM ( )

TARGET = 1

FOR (I IN 1:6)

{

EFFECT [N.6 + I] = $\frac{TARGET^4}{C_{50}^4 + TARGET^4}$

TARGET [N.6 + I] = TARGET

TARGET = TARGET (SIGN (EFFECT - 0.5) + 0.1)

}

}

SIGN (X)

IF X < 0 -1

IF X = 0 0

IF X > 0 1

1.

CLINICAL INVESTIGATION

The drug titration paradox: more drug does not correlate with more effect in individual clinical data

Thomas W. Schnider[1,*], Charles F. Minto[2], Martin Luginbühl[3] and Talmage D. Egan[4]

[1]Department of Anesthesia, Intensive Care, Emergency and Pain Medicine, Kantonsspital, St. Gallen, Switzerland [2] [3]partment of Anesthesiol itzerland and [4]Departmen

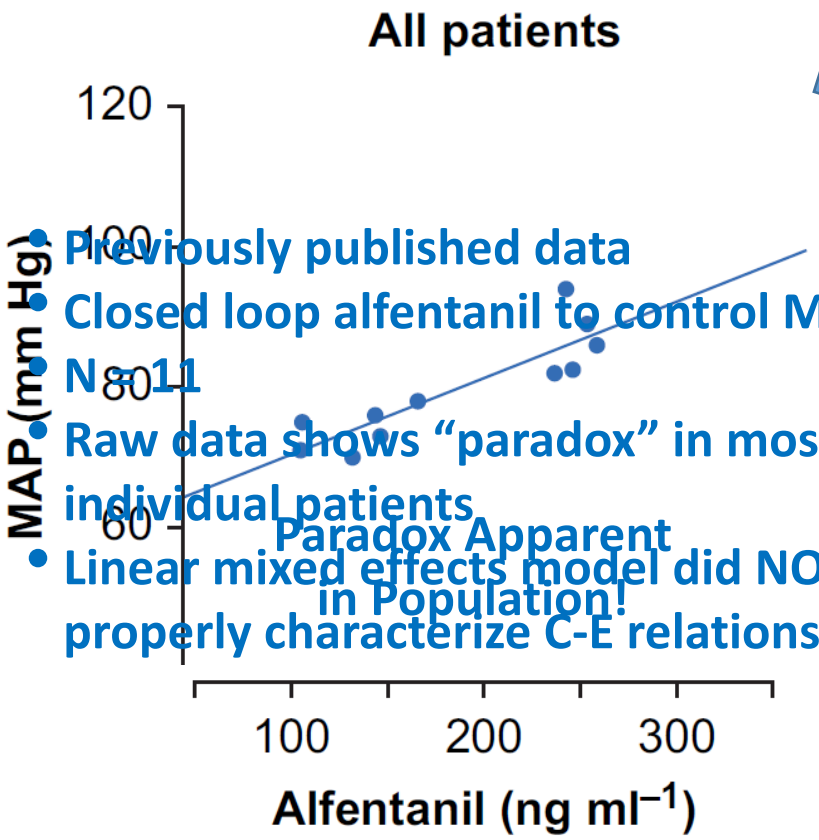
*Correspondin

"...identified the titration paradox in the individual data and suggest that changing levels of surgical stimulus is the most likely confounding factor that accounts for this paradoxical result."

Abstract

Background: A fundamental concept in pharmacology is that increasing dose incre ffect. This is the basis of anaesthetic titration: the dose is increased when increased drug effect is desired and decrease duced drug effect is desired. In the setting of titration, the correlation of doses and observed drug effects can be negati example increasing dose reduces drug effect. We have termed this the drug titration paradox. We hypothesised that this uld be explained, at least in part, by intrasubject variability. If the drug titration paradox is simply an artifact of pooling pop ulation data, then a mixed-effects analysis that accounts for interindividual variability in drug sensitivity should 'flip' the observed correlation, such that increasing dose increases drug effect.

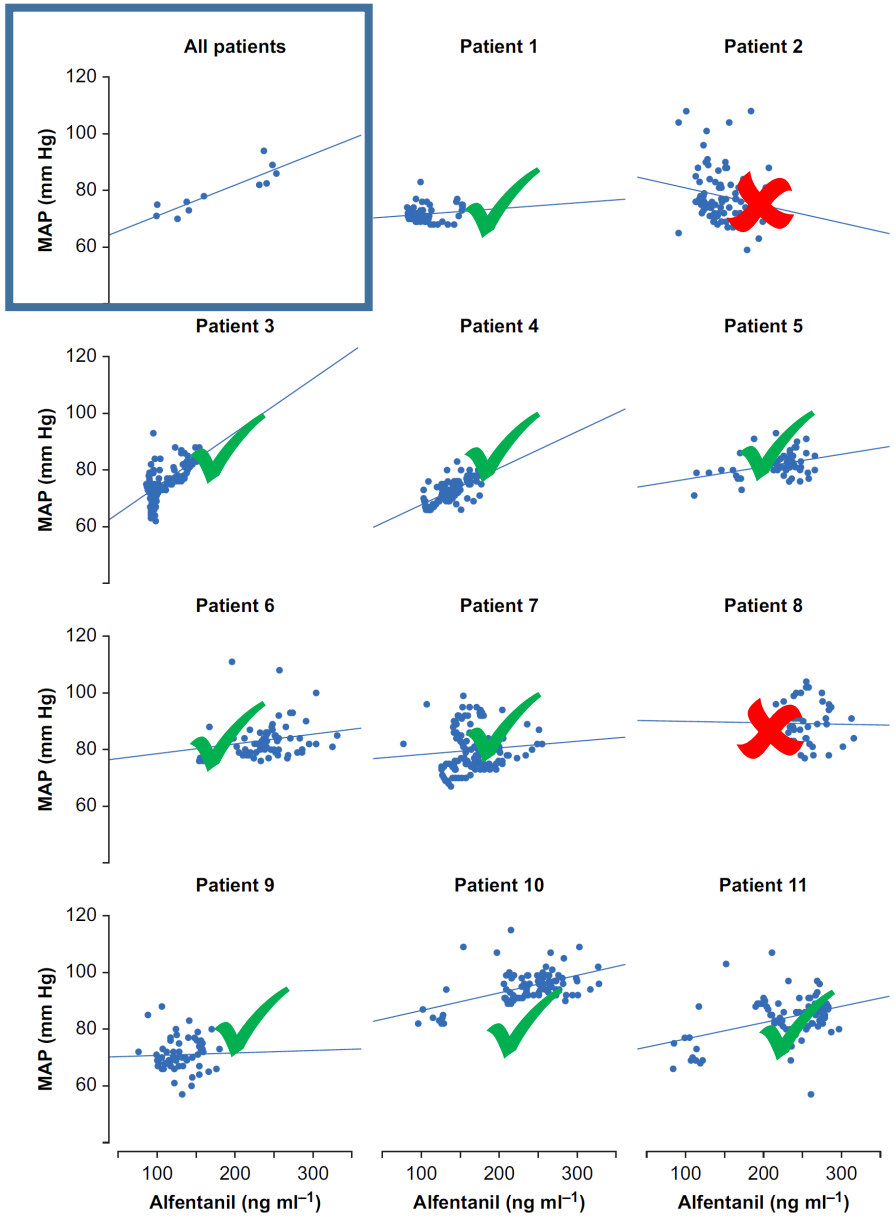
Schnider *et al* (*Br J Anaesth* 2021)



- Previously published data
- Closed loop alfentanil to control MAP
- N=11
- Raw data shows "paradox" in most individual patients
- Linear mixed effects model did NOT properly characterize C-E relationship!

Paradox Apparent in Population!

Also Apparent in Most Individuals! (result of varying stimulus?)



Schnider *et al* (*Br J Anaesth* 2021)

CLINICAL INVESTIGATION

The drug titration paradox: more drug does not correlate with more effect in individual clinical data

Thomas W. Schnider[1,*], Charles F. Minto[2], Martin Luginbühl[3] and Talmage D. Egan[4]

[1]Department of Anesthesia, Intensive Care, Emergency and Pain Medicine, Kantonsspital, St. Gallen,
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[4]De

*Cor

"In routine care, where the effect is profoundly influenced by varying clinical conditions and drugs are titrated to achieve the desired effect, it is nearly impossible to draw meaningful conclusions about the relationship between dose and effect."

Abstract

Background: A fundamental concept in pharmacology is that increasing dose increase This is the basis of anaesthetic titration: the dose is increased when increased drug effect is desired and decreased d drug effect is desired. In the setting of titration, the correlation of doses and observed drug effects can be negati mple increasing dose reduces drug effect. We have termed this the drug titration paradox. We hypothesised that thi d be explained, at least in part, by intrasubject variability. If the drug titration paradox is simply an artifact of pooling pop ulation data, then a mixed-effects analysis that accounts for interindividual variability in drug sensitivity should 'flip' the observed correlation, such that increasing dose increases drug effect.

Schnider *et al* (*Br J Anaesth* 2021)

Key Point

The “drug titration paradox” is a form of Simpson’s Paradox.


it of a paradox...

LETTER TO THE EDITOR

The Drug Titration Paradox is Simpson's Paradox

Gabriel Schamberg[1,2,*] and Emery N. Brown[1,2,3]

In their recent
troduce the "dr
phenomenon is
ant implications
data collected i
paper provides
of the titration paradox, but omits an important observation—*the titration paradox is Simpson's Paradox*. The goal of this letter is not to undermine the value of Schnider

shown in **Figure 1b** of Schnider et al.[1]), but negatively correlated without conditioning (as shown in **Figure 1e** of Schnider et al.[1]).

Simpson's Paradox is most clearly illuminated through the lens of causality.[3] The paradoxical nature of the phenomenon identified by Schnider *et al*. arises from
disconnect between our caus
anced relationship between causation and correlation of observed variables is the graphical causal model.[3] **Figure 1** depicts models associated with three dif-

removed by stratifying the data according to sensitivity (as in Schnider *et al*. fig 3, for example).

In this letter we seek to provide additional context f
ionship to Simpson's Paradox and
. As addressing the titration paradox
trivial, we believe that it is important
ble knowledge from the
erature.

ported by the Picower
hip (to G.S.) and the
Health P01 GM118629
(to E.N.B.)

CONFLICT OF INTEREST
All authors declared no competing interests for this work.

"...we seek to provide additional context for the titration paradox by elucidating its relationship to Simpson's Paradox..."

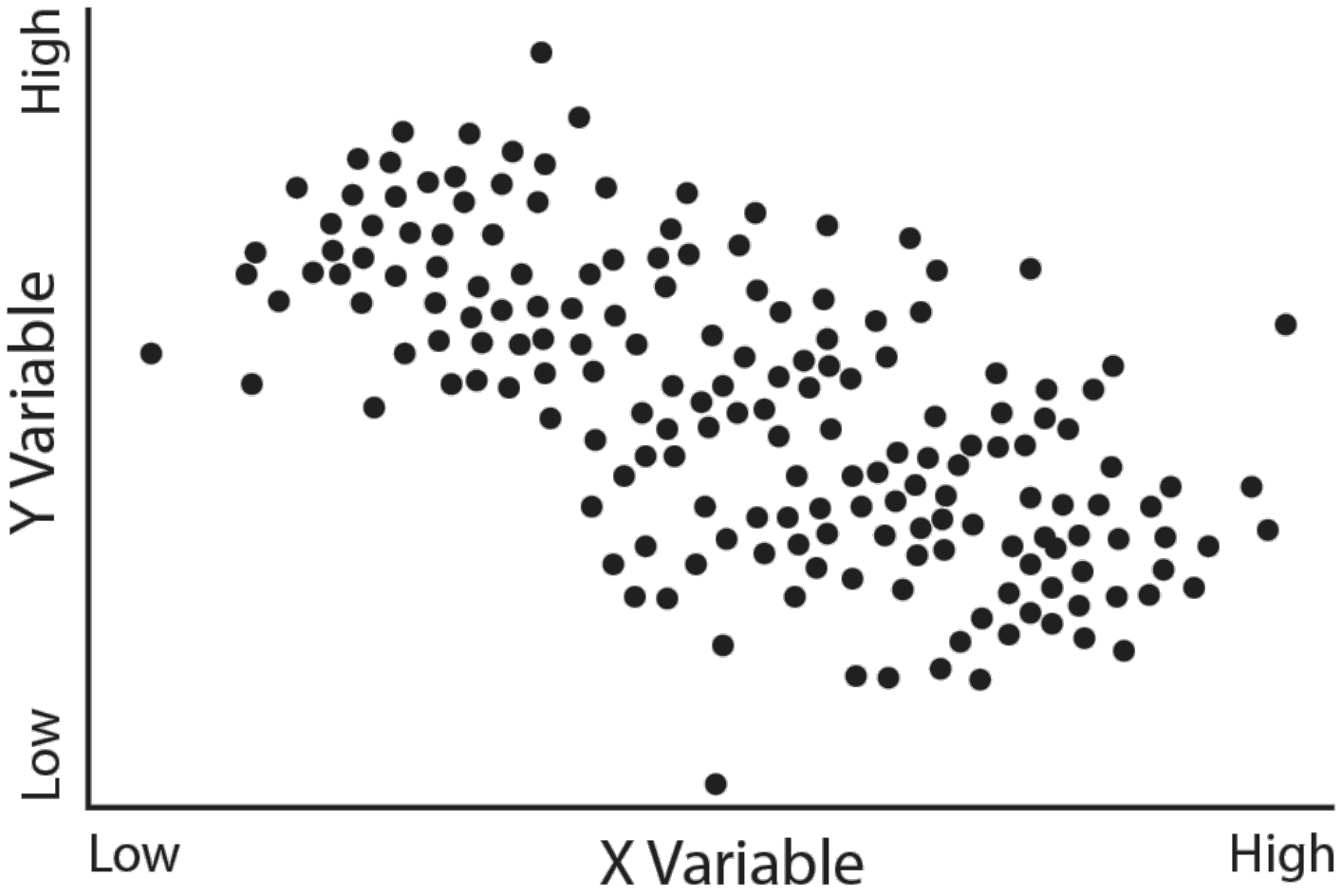
Schamberg & Brown (*Clin Pharmacol Ther* 2021)

Definition

A trend or result that is present when data are aggregated that reverses when the data are considered as sub-groups.

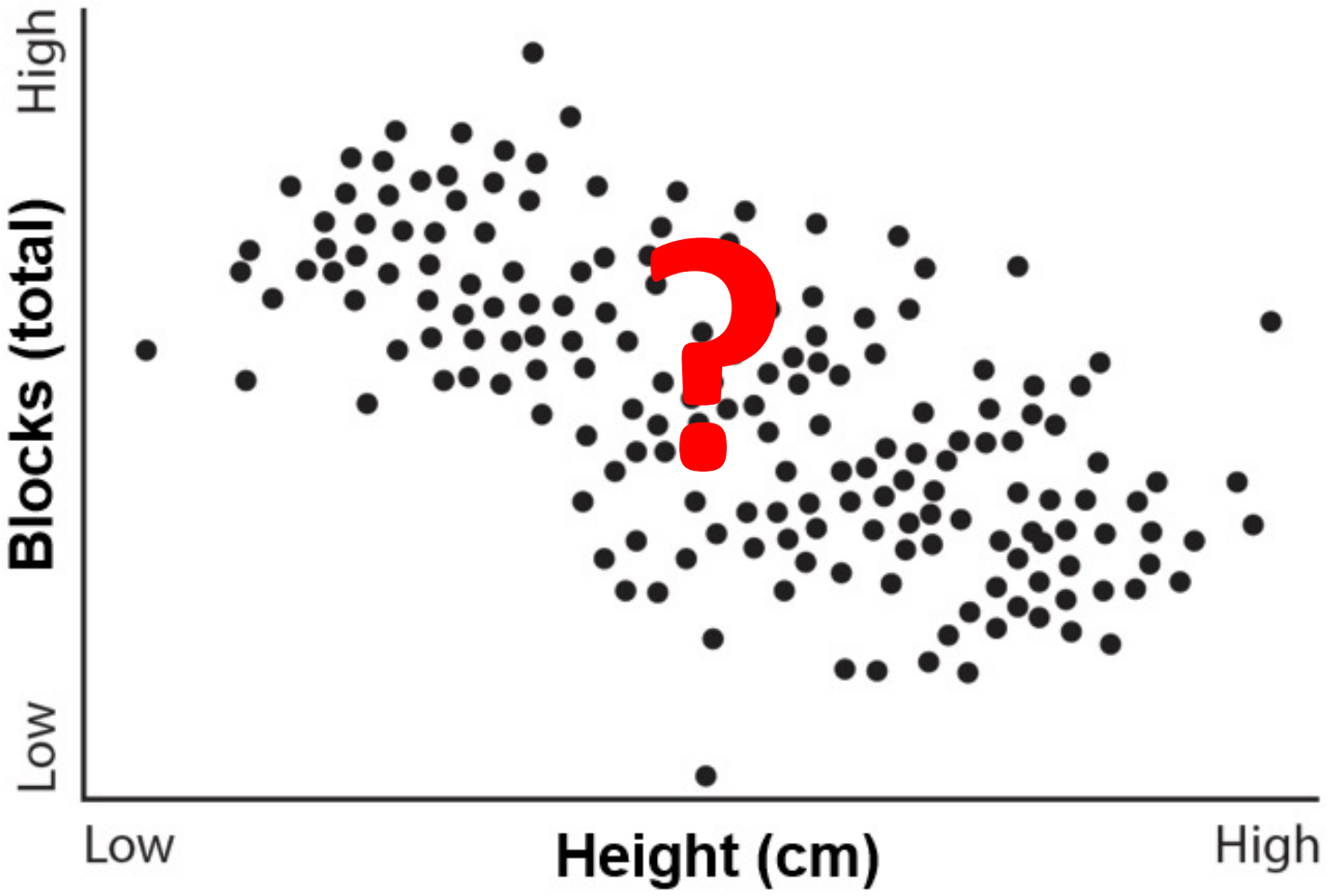
- Often counter-intuitive
- Conditional probability issue
- Understanding requires context
- Explained by “confounding” influence

Simpson's Paradox: a Graphical Demonstration



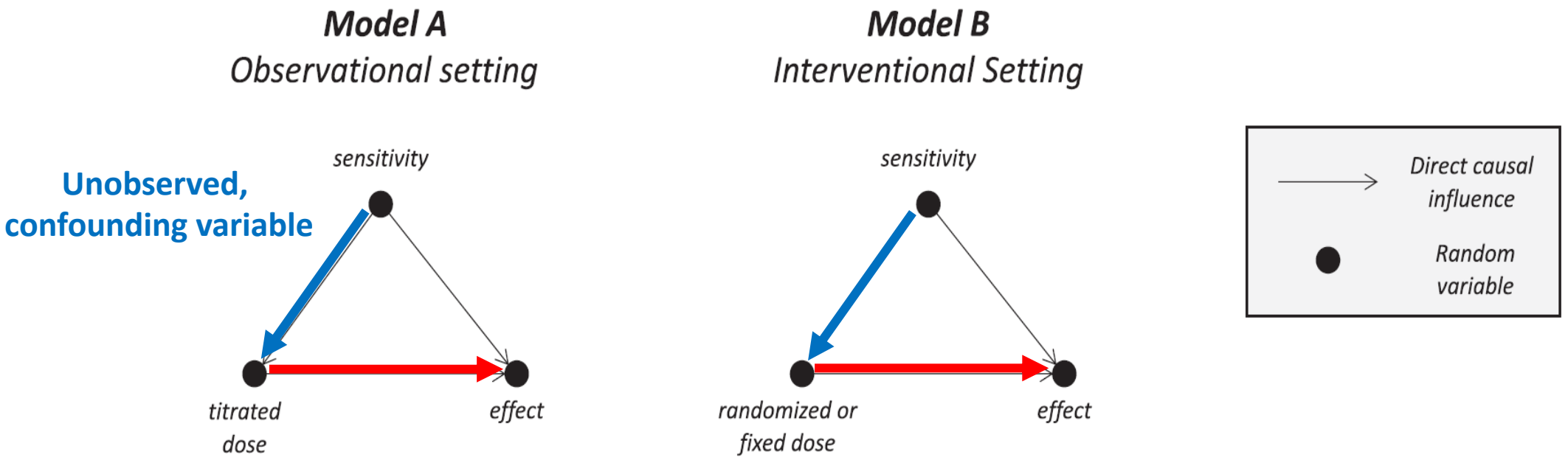
Simpson's Paradox: a Simple Example

Taller players block fewer shots?



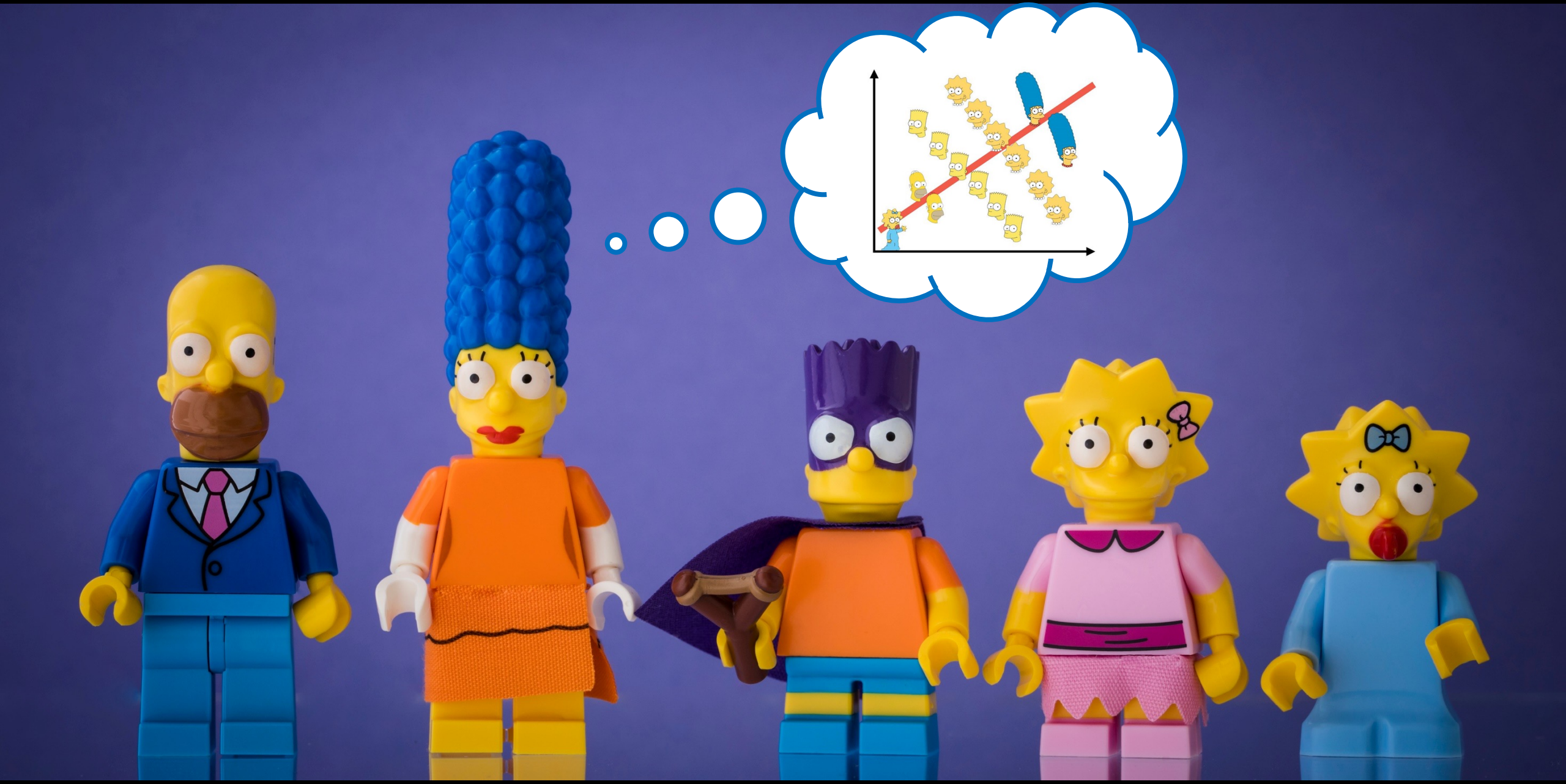
Blocked Shots in Basketball

Causal Models Associated with Various Dose/Effect Scenarios



A common goal of a clinical pharmacology study is to establish a dose-response relationship.

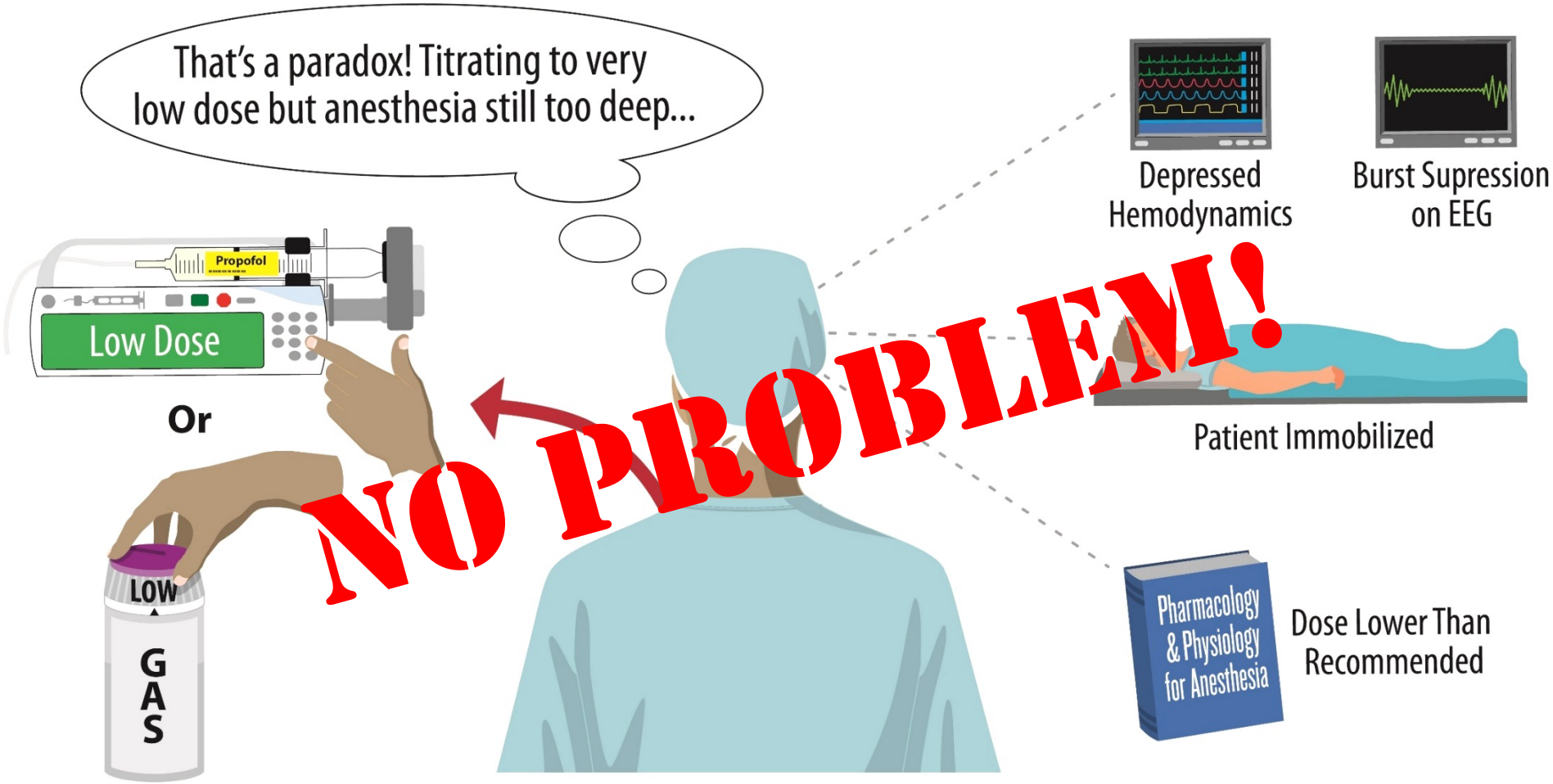
Schamberg & Brown (*Clin Pharmacol Ther* 2021)



Key Point

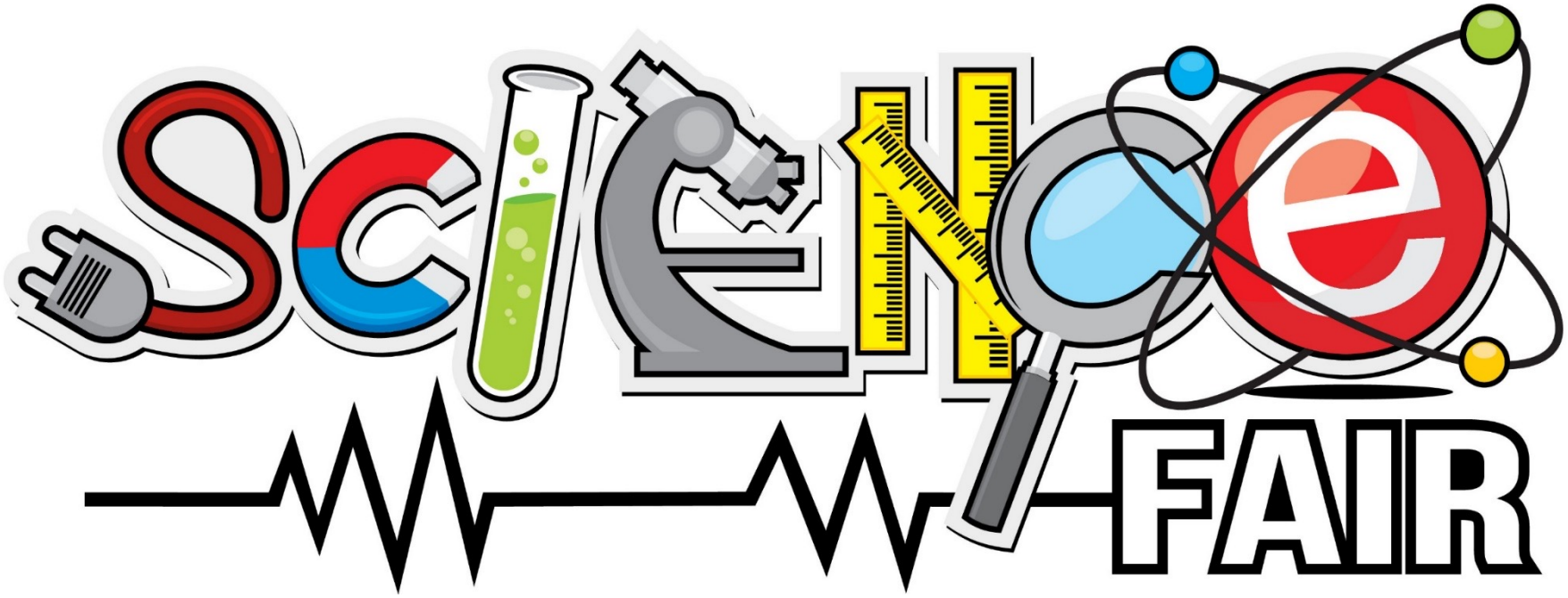
The “drug titration paradox” has important implications for anesthesiology research.

The Paradox in the Individual Clinical Patient



Egan (*Br J Anaesth* 2022)

Epinephrine and Blood Pressure science fair project…

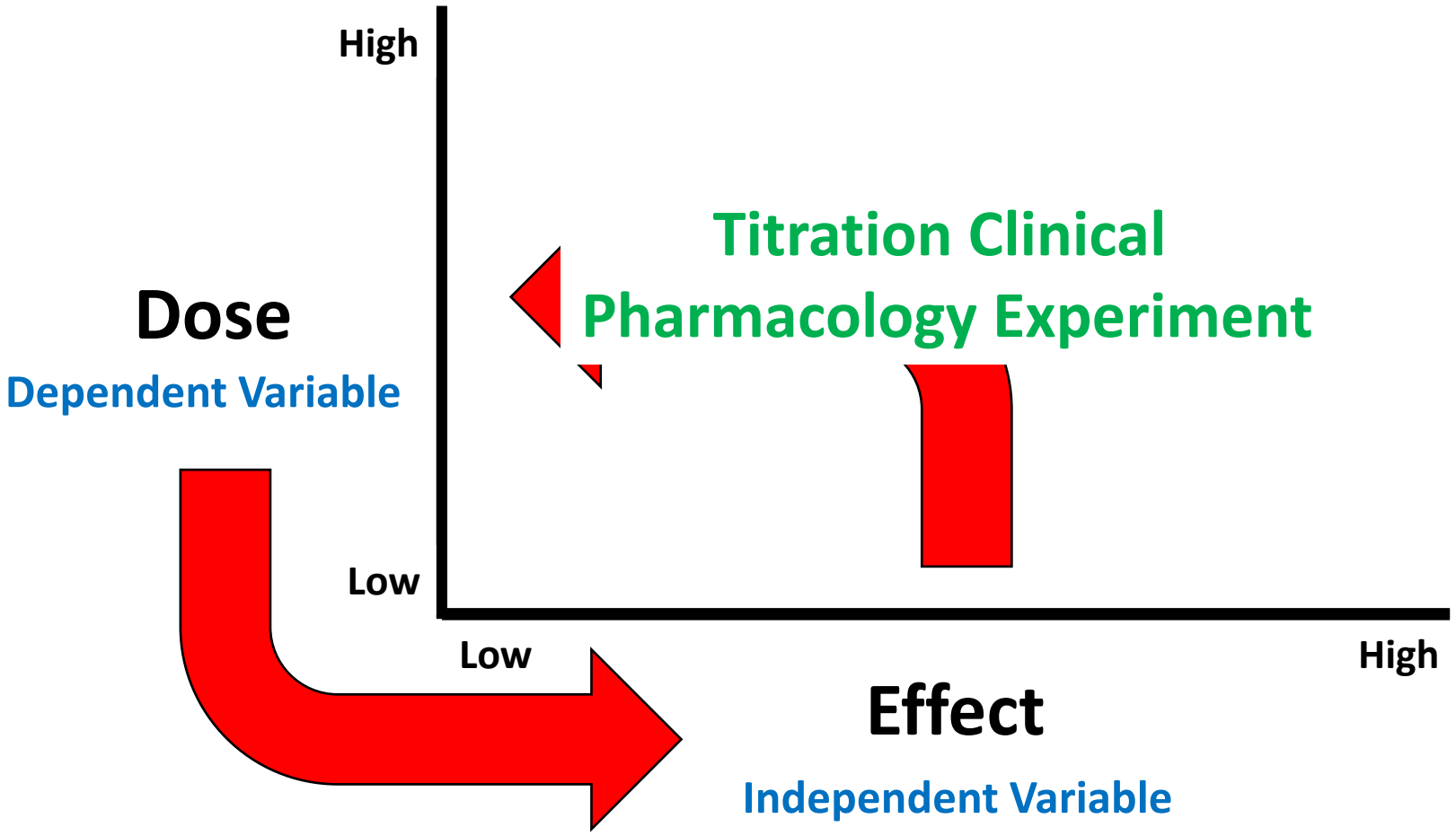


What would a student conclude?

Main Research Implication of the Paradox

In the conventional clinical pharmacology experiment, drug exposure is the independent variable responsible for drug effect. But **when drugs are titrated, the drug effect becomes the independent variable!**

Main Research Implication of the Paradox



A Tale of Two Trials…

JAMA | Original Investigation

Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery

The ENGAGES Randomized Clinical Trial

Troy S. Wildes, MD; Angela M. Mickle, MS; Arbi Ben Abdallah, PhD; Hannah R. Maybrier, BS; Jordan Oberhaus, BS; Thaddeus P. Budelier, MD, MSF; Alex Kronzer, BA; Sherry L. McKinney, BS; [illegible]; Daniel A. Emmert, MD, PhD; Ben J. Palanca, MD, PhD; [illegible]; Matthew A. Fritz, MD; Tracey W. Stevens, MD; Eric Jacobsohn, MBChB, MPHE, FRCPC; [illegible]; Sharon K. Inouye, MD, MPH; Susan Stark, PhD; Eric J. Lenze, MD; Michael S. Avidan, MBBCh; for the ENGAGES Research Group

Engages Trial

IMPORTANCE Intraoperative electroencephalogram (EEG) waveform suppression, often suggesting excessive general anesthesia, has been associated with postoperative delirium.

OBJECTIVE To assess whether EEG-guided anesthetic administration reduces the incidence of postoperative delirium.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial of 1232 adults aged 60 years and older undergoing major surgery and receiving general anesthesia at Barnes-Jewish Hospital in St Louis. Recruitment was from January 2015 to May 2018, with follow-up until July 2018.

INTERVENTIONS Patients were randomized 1:1 (stratified by cardiac vs noncardiac surgery and positive vs negative recent fall history) to receive EEG-guided anesthetic administration (n = 614) or usual anesthetic care (n = 618).

MAIN OUTCOMES AND MEASURES The primary outcome was incident delirium during postoperative days 1 through 5. Intraoperative variables included anesthetic concentration, EEG suppression, and hypotension. Adverse events included undesirable intraoperative movement, intraoperative awareness with recall, postoperative nausea and vomiting, medical complications, and death.

RESULTS Of the 1232 randomized patients (median age, 69 years [range, 60 to 95]; 563 women [45.7%]), 1213 (98.5%) were assessed for the primary outcome. Delirium during postoperative days 1 to 5 occurred in 157 of 604 patients (26.0%) in the guided group and 140 of 609 patients (23.0%) in the usual care group (difference, 3.0% [95% CI, −2.0% to 8.0%]; $P = .22$). Median end-tidal volatile anesthetic concentration was significantly lower in the guided group than the usual care group (0.69 vs 0.80 minimum alveolar concentration; difference, −0.11 [95% CI, −0.13 to −0.10), and median cumulative time with EEG suppression was significantly less (7 vs 13 minutes; difference, −6.0 [95% CI, −9.9 to −2.1]). There was no significant difference between groups in the median cumulative time with mean arterial pressure below 60 mm Hg (7 vs 7 minutes; difference, 0.0 [95% CI, −1.7 to 1.7]). Undesirable movement occurred in 137 patients (22.3%) in the guided and 95 (15.4%) in the usual care group. No patients reported intraoperative

Visual Abstract

Editorial page 459

Supplemental Content

Does pEEG guided practice reduce delirium?

BJA

British Journal of Anaesthesia, 127 (5): 704–712 (2021)

doi: 10.1016/j.bja.2021.07.021

Advance Access Publication Date: 28 August 2021

Neuroscience and Neuroanaesthesia

NEUROSCIENCE AND NEUROANAESTHESIA

Anaesthetic depth and delirium after major surgery: a randomised clinical trial

“Balanced” Trial

Lisbeth A. Evered[1,2,3,*,†], Matthew T. V. Chan[4], Ruquan Han[5], Mandy H. M. Chu[4], Benny P. Cheng[4], David A. Scott[6], [illegible][1], Daniel I. Sessler[7], Radmila Veselis[1], Christopher Frampton[8], Matthew Sumner[9], [illegible], Douglas Campbell[11], Kate Leslie[12,13] and Timothy G. Short[9,11]

[1]Department of Anesthesiology, Weill Cornell Medicine, New York, NY, USA, [2]Department of Anaesthesia and Acute Pain Medicine, St Vincent's Hospital, Melbourne, VIC, Australia, [3]Department of Critical Care Medicine, University of Melbourne, Melbourne, VIC, Australia, [4]Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China, [5]Department of Anesthesiology, Chinese PLA General Hospital and Capital Medical University, Beijing, China, [6]Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA, [7]Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [8]Department of Medicine, University of Otago, Christchurch, New Zealand, [9]Department of Anaesthesiology, Auckland City Hospital, Auckland, New Zealand, [10]Department of Anaesthesia and Perioperative Medicine, Alfred Hospital and Monash University, Melbourne, VIC, Australia, [11]Department of Anaesthesiology, University of Auckland, Auckland, New Zealand, [12]Department of Anaesthesia and Pain Medicine, Royal Melbourne Hospital, Melbourne, VIC, Australia and [13]Monash University, Melbourne, VIC, Australia

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[†]Chief investigator.

This article is accompanied by the following editorials:
The quagmire of postoperative delirium: does dose matter? by Gaskell [illegible]gh, *Br J Anaesth* 2021:127:664–666, doi: 10.1016/j.bja.2021.08.008
Anaesthetic depth and delirium: a challenging balancing act by W[illegible] et al., *Br J Anaesth* 2021:127:667–671, doi: 10.1016/j.bja.2021.08.003

Abstract

Background: Postoperative delirium is a serious complication of surgery associated with prolonged hospitalisation, long-term cognitive decline, and mortality. This study aimed to determine whether targeting bispectral index (BIS) readings of 50 (light anaesthesia) was associated with a lower incidence of POD than targeting BIS readings of 35 (deep anaesthesia).
Methods: This multicentre randomised clinical trial of 655 at-risk patients undergoing major surgery from eight centres in three countries assessed delirium for 5 days postoperatively using the 3 min confusion assessment method (3D-CAM) or CAM-ICU, and cognitive screening using the Mini-Mental State Examination at baseline and discharge and the Abbreviated Mental Test score (AMTS) at 30 days and 1 yr. Patients were assigned to light or deep anaesthesia. The primary outcome was the presence of postoperative delirium on any of the first 5 postoperative days. Secondary outcomes included mortality at 1 yr, cognitive decline at discharge, cognitive impairment at 30 days and 1 yr, unplanned ICU admission, length of stay, and time in electroencephalographic burst suppression.
Results: The incidence of postoperative delirium in the BIS 50 group was 19% and in the BIS 35 group was 28% (odds ratio 0.58 [95% confidence interval: 0.38–0.88]; P=0.010). At 1 yr, those in the BIS 50 group demonstrated significantly better cognitive function than those in the BIS 35 group (9% with AMTS ≤6 *vs* 20%; P<0.001).

Anaesthetic depth and delirium: a challenging balancing act

Elizabeth L. Whitlock[1], Eric R. Gross[2], C. Ryan King[3] and Michael S. Avidan[3,*]

[1]Department of Anesthesia & Perioperative Care, University of California, School of Medicine, San Francisco, CA, USA, [2]Department of Anesthesiology, Perioperative and Pain Medicine, School of Medicine, Stanford University, Stanford, CA, USA and [3]Department of Anesthesiology, Washington University in St. Louis School of Medicine, St. Louis, MO, USA

*Corresponding author.

This editorial ac J Anaesth 2021:127:704–71

"We posit that subpopulation-based differences within this multicentre substudy could have affected delirium occurrence, since the findings appeared to rest on outcomes in patients from East Asia."

Summary

This editorial highli ne 6644 patient Balanced Anaesthesia trial, which found that targeting deep anaes dergoing major noncardiac surgery was not associated with significantly increased postoperative death . The substudy found that using bispectral index (BIS) guidance with the intention of deliberately achieving gent-based anaesthesia (target BIS reading 35 *vs* 50) significantly increased delirium incidence (28% *vs* 19 h not subsyndromal delirium incidence (45% *vs* 49%). We discuss the implications of these findings for an tic practice, and address whether the BIS should be used as a guide to deliver precision anaesthesia for delirium prevent We posit that subpopulation-based differences within this multicentre substudy could have affected delirium occurrence, since the findings appeared to rest on outcomes in patients from East Asia. We conclude that questions of whether and for whom deep anaesthesia is deliriogenic remain unanswered.

Whitlock *et al* (*Br J Anaesth* 2021)

The quagmire of postoperative delirium: does dose matter?

Amy Gaskell* and Jamie Sleigh

Department of Anaesthesia, Waikato Clinical Campus, University of Auckland, Hamilton, New Zealand

*Corresponding author. E-mail: amy.gaskell@waikatodhb.health.nz

This editorial accompanies: Anaesthetic depth and delirium after major surgery: a randomised clinical trial by Evered et al., *Br J Anaesth* 2021:127:704–712

"A strong argument could be made for randomisation to anaesthetic dose (MAC) rather than EEG targets in future studies to better determine dose-outcome effects."

Keywords: anaesthe

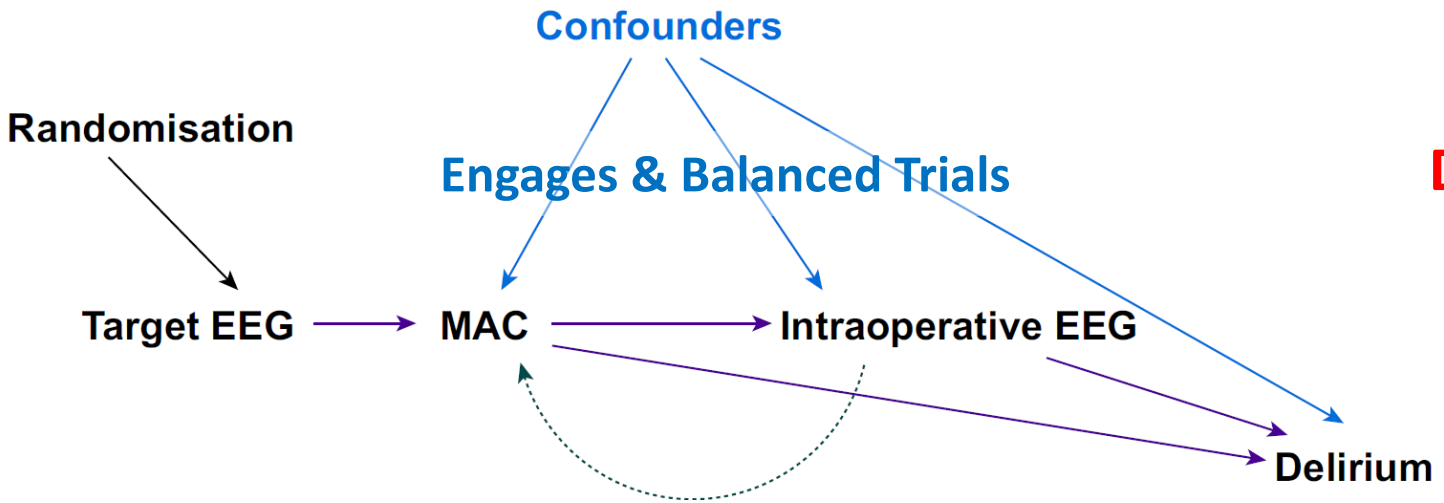
In this issue of the *British Journal of Anaesthesia*, Evered and colleagues[1] report on the results from a delirium sub-study of the larger The BALANCED Anaesthesia Study: A Prospective, Randomised Clinical Trial of Two Levels of Anaesthetic Depth on Patient Outcome After Major Surgery (BALANCED) trial.[2] This sub-study attempted to determine the role of depth of anaesthesia in the development of postoperative delirium and cognitive decline. The authors demonstrated 34% relative reduction in postoperative delirium with 'lighter' anaesthesia compared with 'deeper' anaesthesia defined by bispectral in-

by EEG features as ed anaesthetic dose, contributes to the range o in syndromes we collectively label 'delirium'.

In medical research, there exists a t ith in the ability of the RCT design to give us the truth abou fficacy of an intervention or causation. However, failure of repli tion of RCT findings in perioperative research is common and worrisome. Inevitably, the cry goes up that all these epistemological problems can be solved by doing ever-larger studies. This assumes that the 'noise' in any study is random. We

Gaskell & Sleigh (*Br J Anaesth* 2021)

Applicable Casual Diagrams



Drug exposure confounded with the outcome?

Gaskell & Sleigh (*Br J Anaesth* 2021)

Beware the drug titration paradox. Comment on *Br J Anaesth* 2021; 127: 704–12

Thomas W. Schnider[1,*] and Charles F. Minto[2]

[1]Department of Anaesthesia
[2]Department of Anaesthesia

*Corresponding author. E-mail: tho

"Whitlock and colleagues base some of their arguments on the assumption that lower BIS is related to higher dose (MAC fraction), which ignores the titration paradox."

This article is accompanied
2022:128:900–902, doi: 10.1016/j.bja.2022.03.007

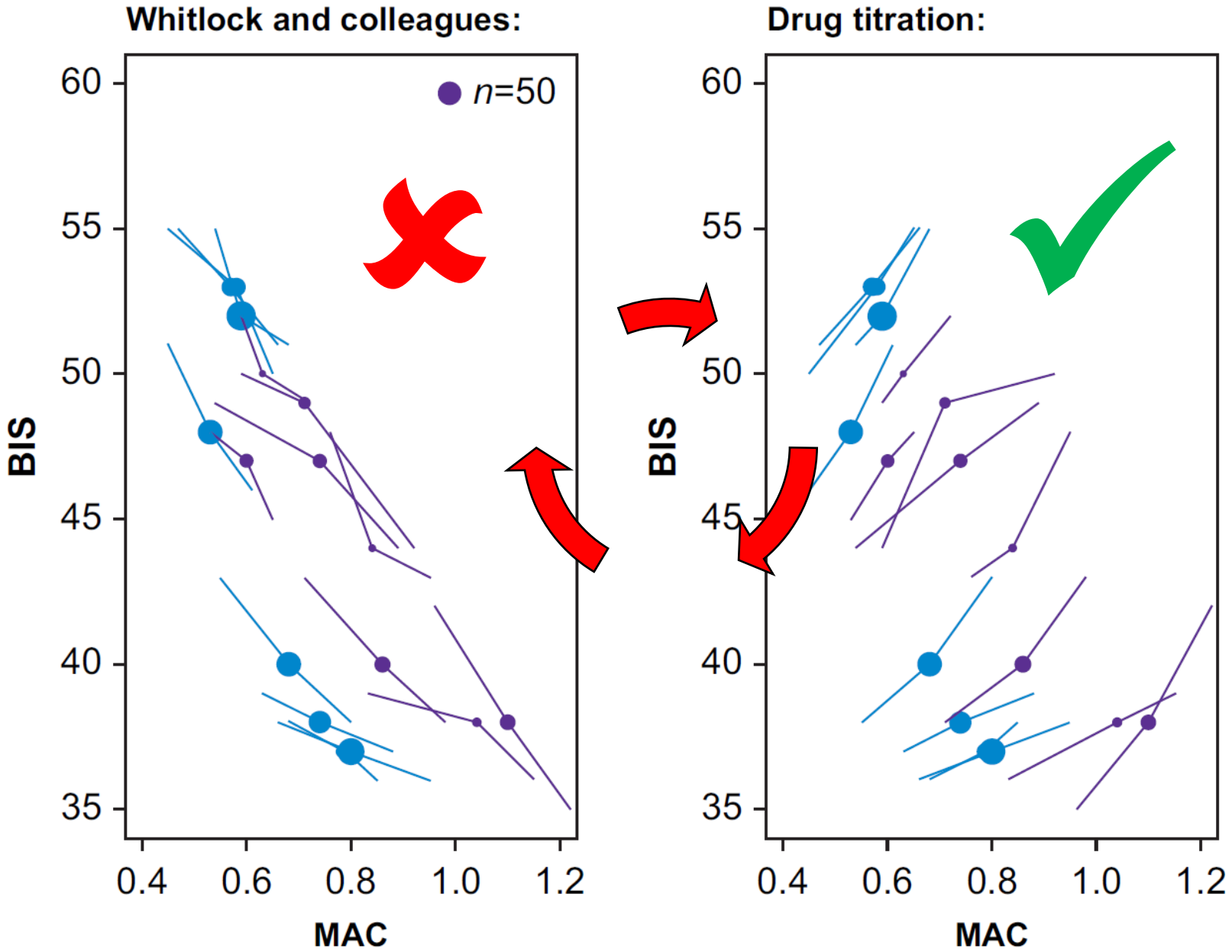
Keywords: anaesthesia; BIS; delirium; drug titration paradox; electroencephalography; ysfunction; pharmacodynamics; titration

Editor—We read with interest the article by Evered and col-
le
de
concluded that patients receiving bispectral index (BIS)-guided 'lighter anaesthesia' had a reduced risk of POD and

appears in several groups of data but can disappear or reverse
d
al
data can be perilous. In the relationship between dose and effect, it is critical whether dose is the independent variable

Alternative Explanation: The drug dose was a dependent variable!

Schnider & Minto (*Br J Anaesth* 2022)



Schnider & Minto (*Br J Anaesth* 2022)

The drug titration paradox: something obvious finally understood

Talmage D. Egan

Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, UT, USA

E-mail: Talm

An editorial about a letter, about an editorial, about a RCT!

This Br J Anaesth 2022:128:e335–e337, doi: 10.1016/j.bja.2022.01.004

Summary

The *drug titration* bservation that when drug is titra relation between dose and effect is ure is associated with lesser effect, design and data interpretation in

"This paradox has potentially important implications in anaesthesiology, especially when applied to clinical studies that seek to establish a relationship between drug exposure and a specified clinical effect or outcome."

Keywords: clinical pharmacology; drug titration paradox; pharmacodynamics; tics pharmacology; target-controlled infusion; titration

Egan (*Br J Anaesth* 2022)

Take Home Points for Research Trials

For trials seeking to establish an association between drug exposure and outcome:

- ✓ Recognize that establishing a exposure-outcome relationship is very difficult when titration employed!
- ✓ Include dose-effect plot to confirm titration properly performed (if titration part of design…).
- ✓ Consider randomization of dose (rather than titration).
- ✓ Consider casual diagrams to assist in design.
- ✓ Beware drug titration paradox problem in retrospective “big data” studies.
- ✓ Consider re-examination of some existing trials because of “drug titration paradox” problems.


ISAP
ISAP