Total Intravenous Anesthesia: Theoretical Foundation and Practical Considerations

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University of Utah School of Medicine

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October 21st, 2022

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Disclosures

In the last 2 years, Dr. Egan has the following industry relationships to disclose:

- Founder and equity partner: Medvis
- Research support: Medtronic
- Scientific Advisory Board Member: Acacia Pharma

TAKE 5 FOR TIVA

MPOG
MULTICENTER PERIOPERATIVE
OUTCOMES GROUP

THRIVE

(Brief introduction to TIVA theory and practice…)

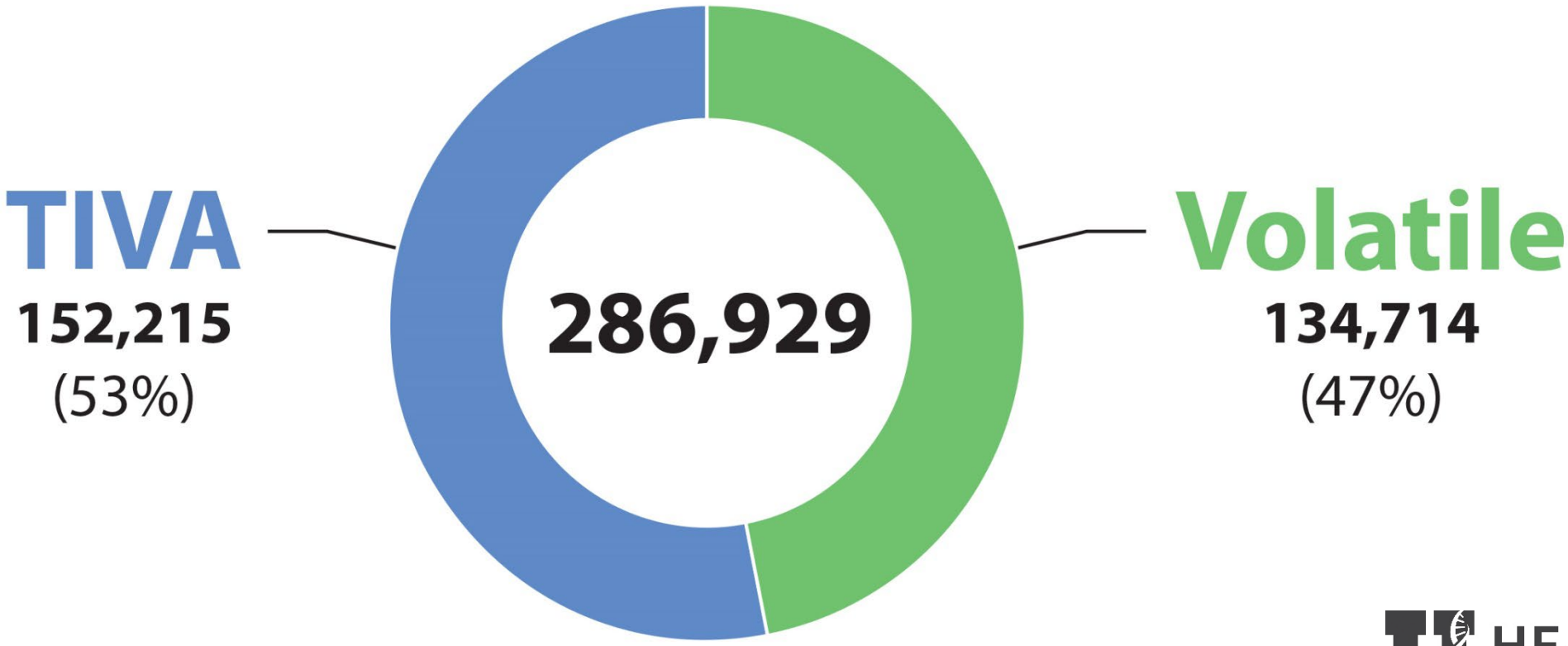
Overall Goal

Establish the scientific and practical foundation upon which to base a TIVA practice.

TAKE 5 FOR TIVA

University of Utah Department of Anesthesiology
General Anesthetic Technique

(May 2014–June 2022)



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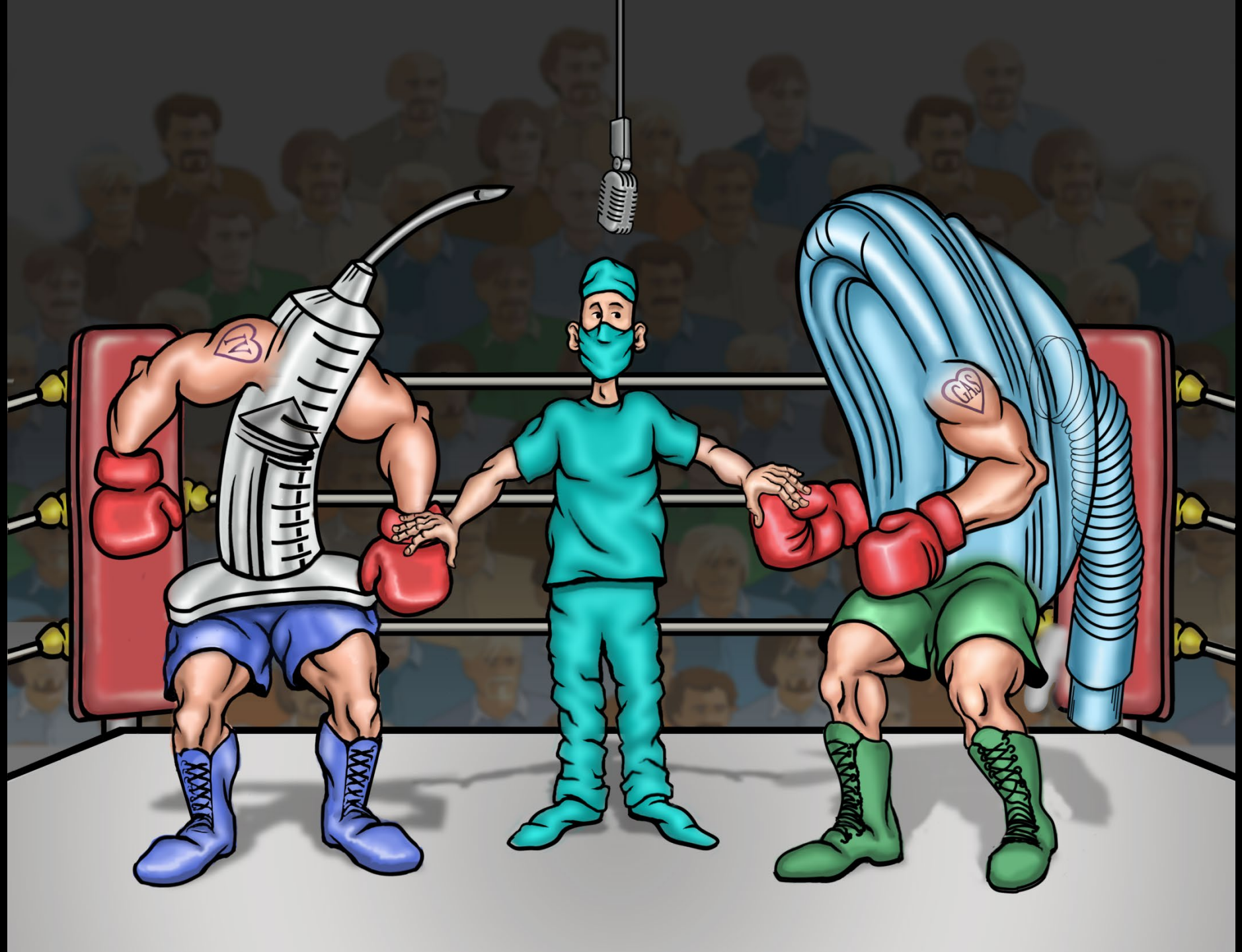

GAS

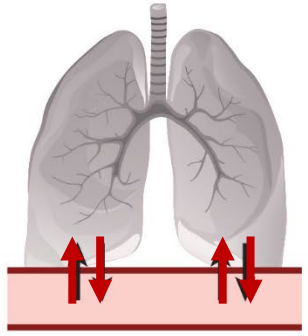
Key Point

Gaining access to the circulation via the lung affords fundamental advantages that have set a standard for innovation in TIVA practice since the mid 1990s.

TAKE 5 FOR TIVA

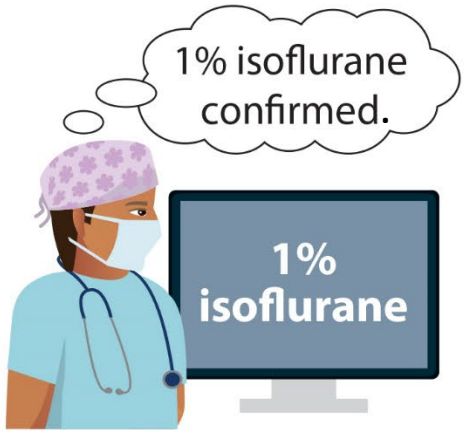
Drug Delivery: TIVA vs. Inhaled (Circa 1990s)

Access to Circulation



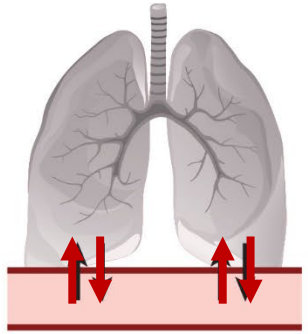
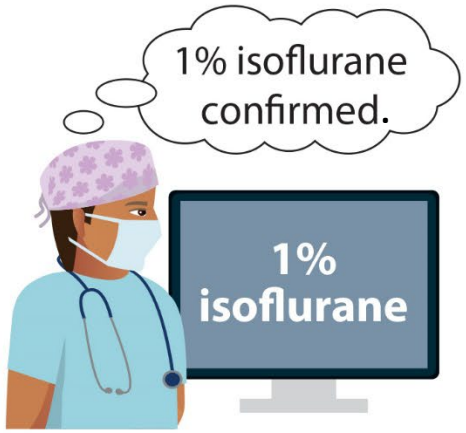
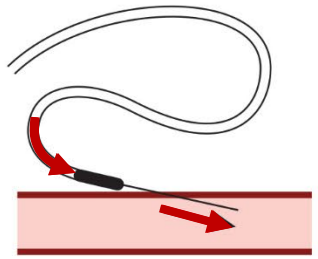
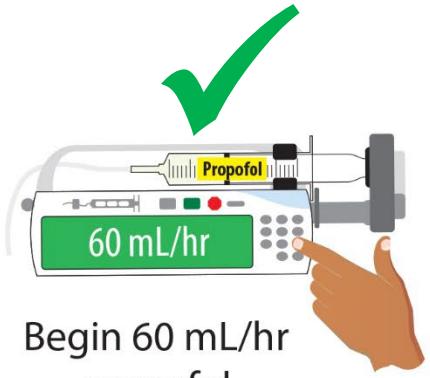
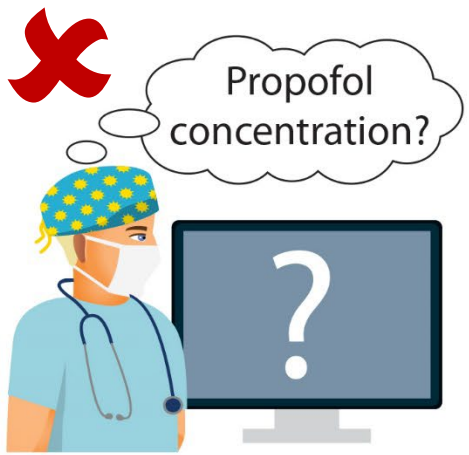
Accurate Administration

Pharmacokinetic Exactness



Pharmacodynamic Exactness

Drug Delivery: TIVA vs. Inhaled (Circa 1990s)

Access to Circulation	Accurate Administration	Pharmacokinetic Exactness	Pharmacodynamic Exactness
	Begin 1% isoflurane		
	 Begin 60 mL/hr propofol		

Egan (*J Clin Anesth* 1996)

Key Point

Anesthesia posology (the study of drug dosing) is fundamentally different than other specialties of medicine.

TAKE 5 FOR TIVA

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…."

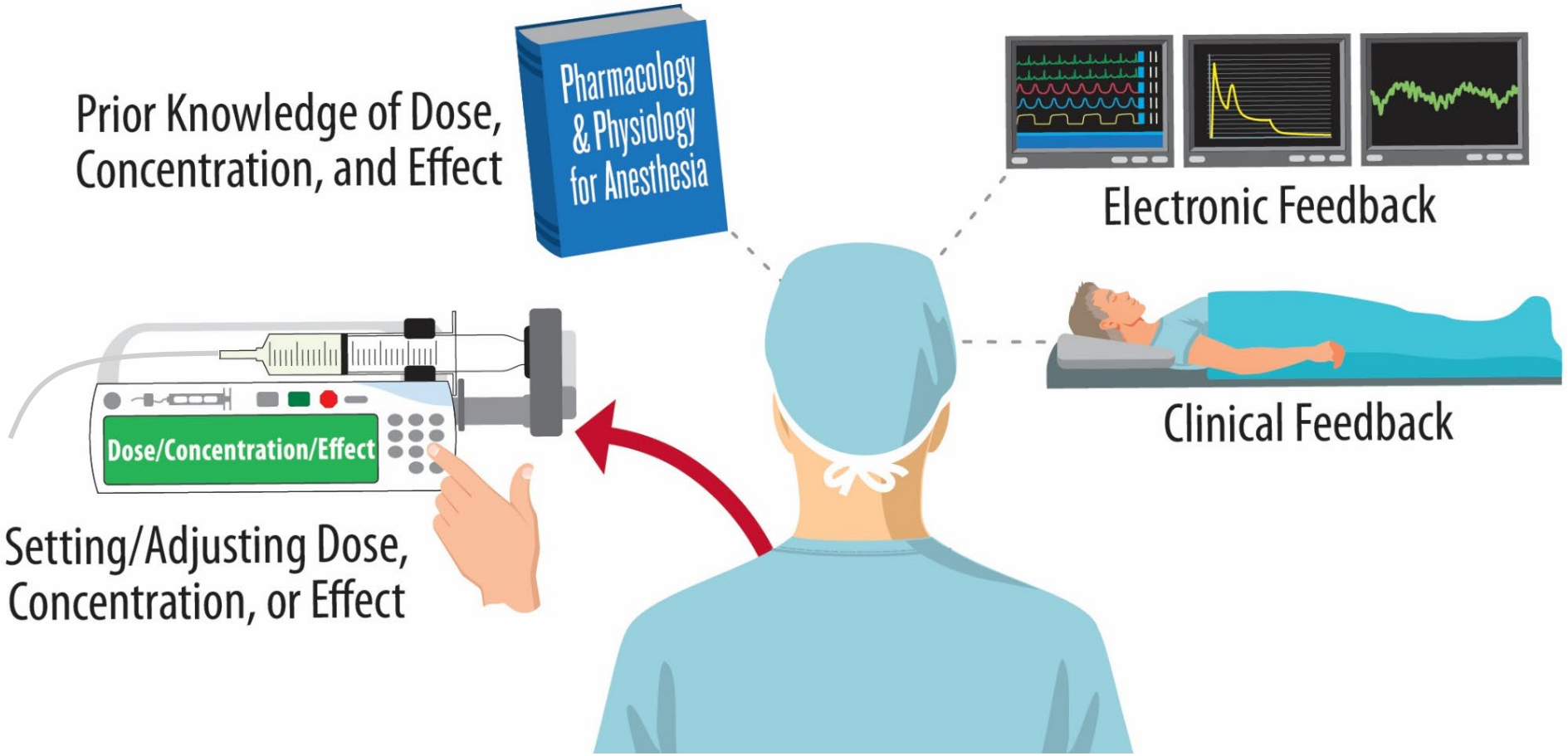
Posology, a scientific term not in common usage, is the science of drug dosage; it is thus a branch of clinical pharmacology (or perhaps a synonym of sorts). Combining the Greek word (how much) and 'logos' (science), posology more simply as 'dosology'. In the posology of an fundamental question anaesthetists 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 p 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'."

Kuck & Egan (*Br J Anaesth* 2017)

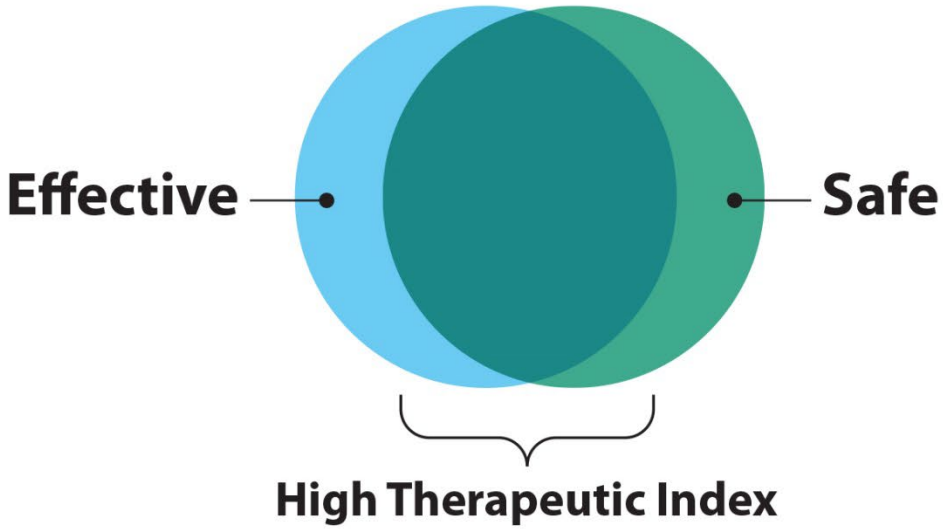
General Approach to Anesthesia Posology



Egan (*Anesth Analg* 2018)

Posology in Anesthesia: A Venn Diagram

Most Therapeutic Areas



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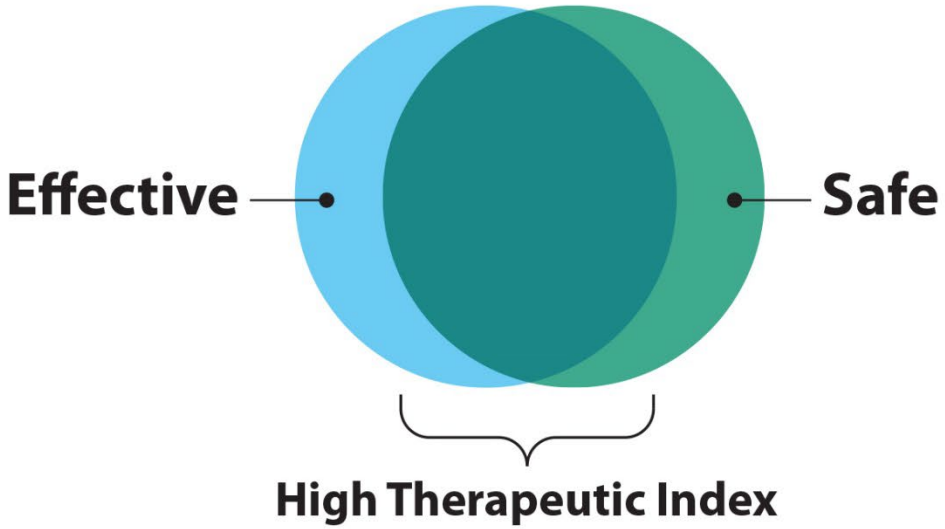
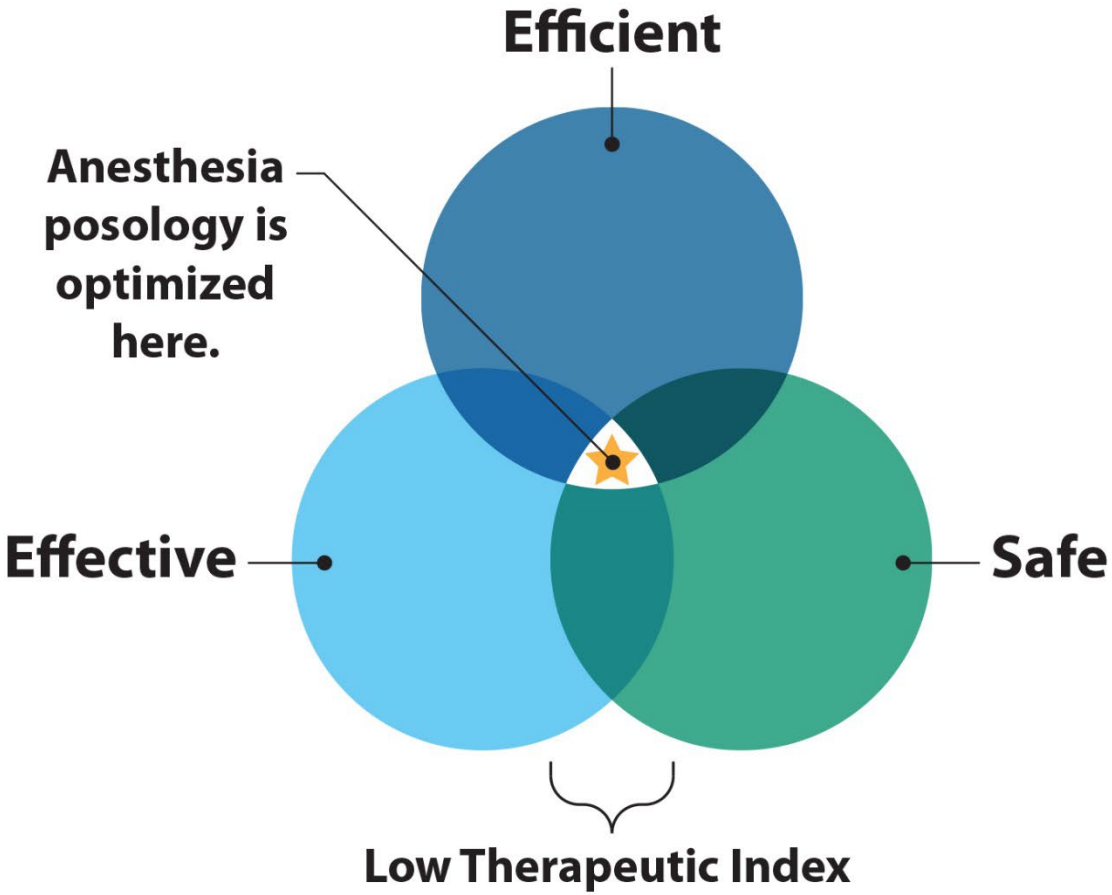


Anesthesia Therapeutics



Kuck & Egan (*Br J Anaesth* 2017)

TAKE 5 FOR TIVA

Key Point

A surfing analogy is helpful in understanding the modern approach to anesthesia posology.

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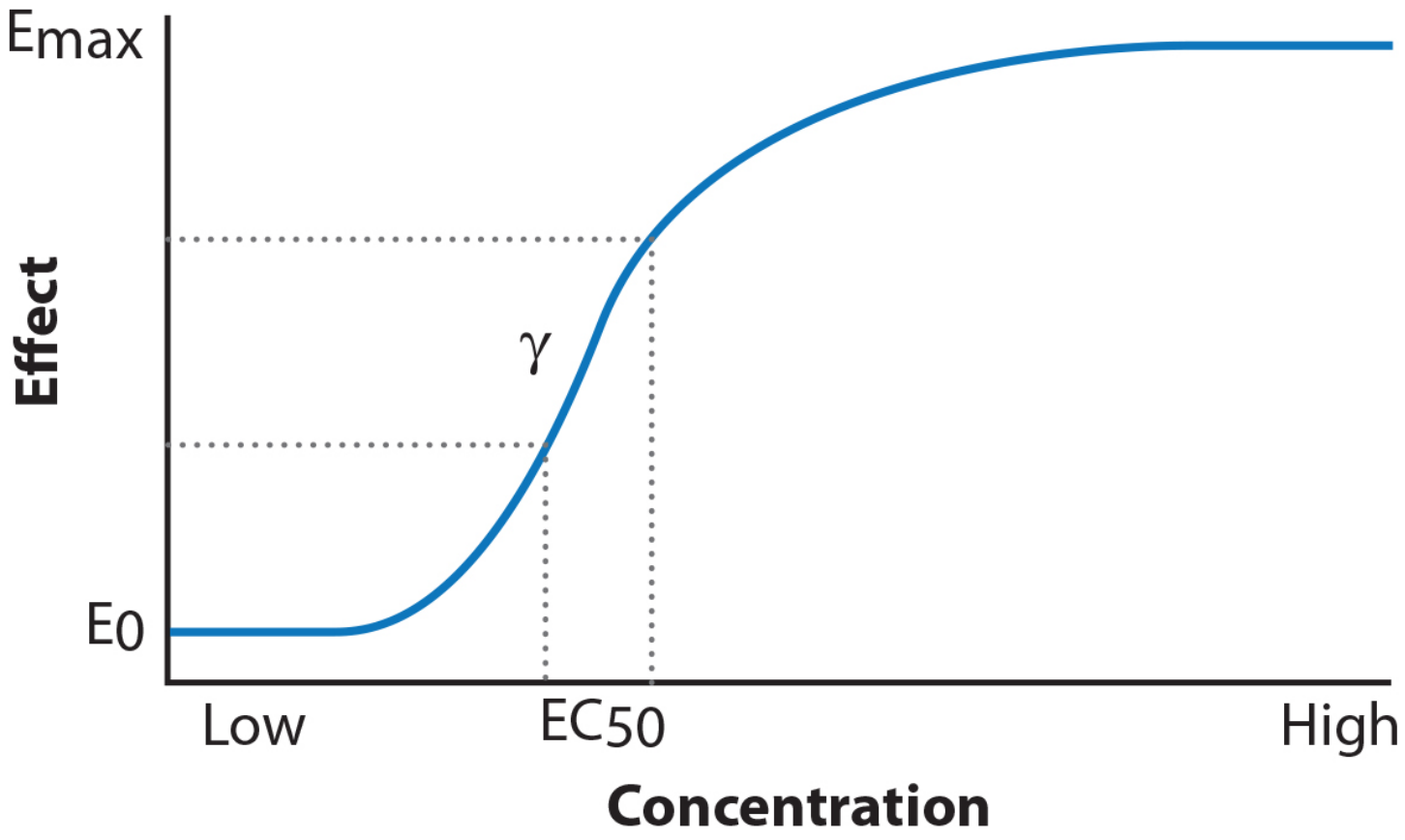
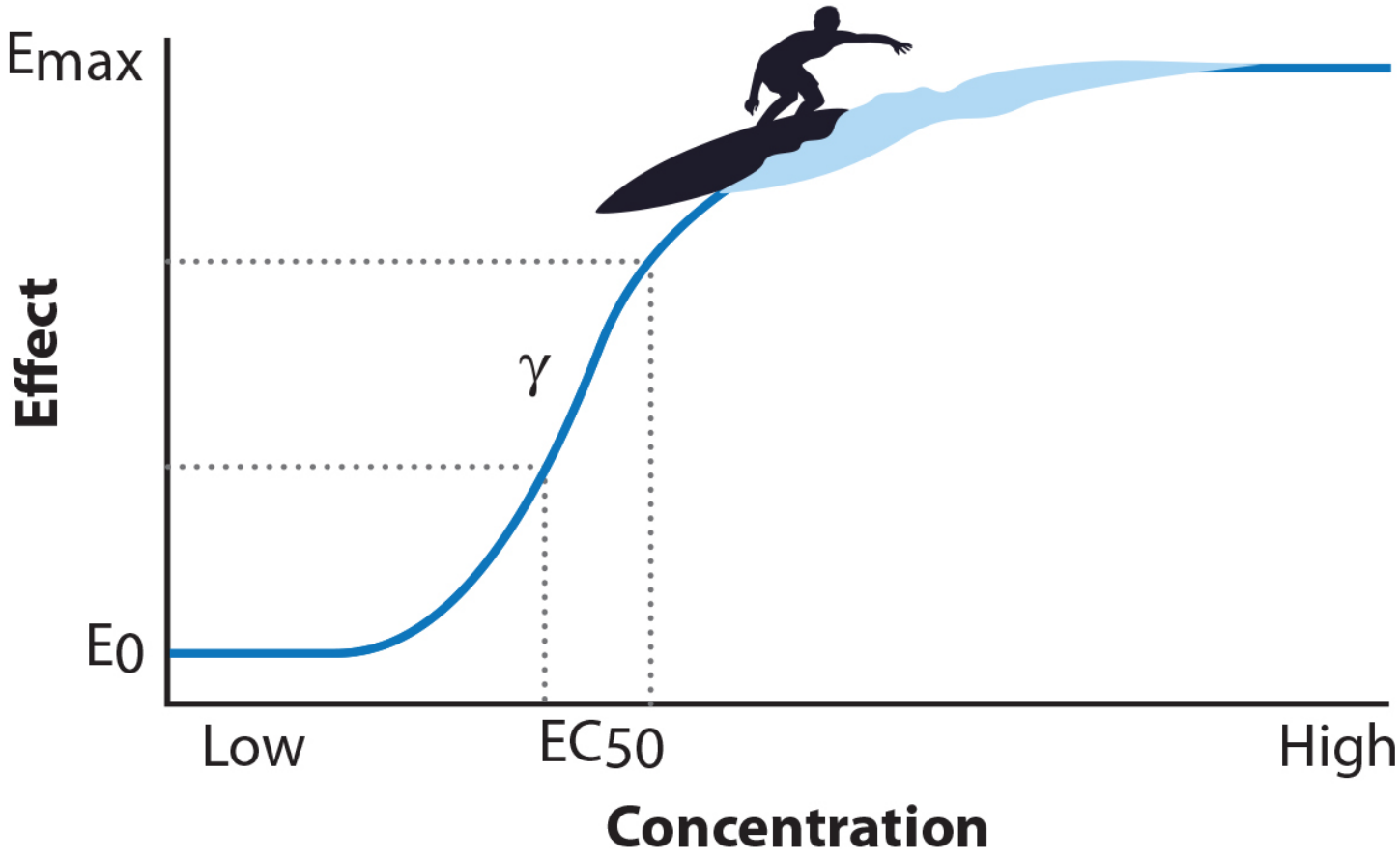
Posology in Anesthesia: A Surfing Analogy



TAKE 5 FOR TIVA

Egan & Shafer (Anesthesiology 2003)

Posology in Anesthesia: A Surfing Analogy



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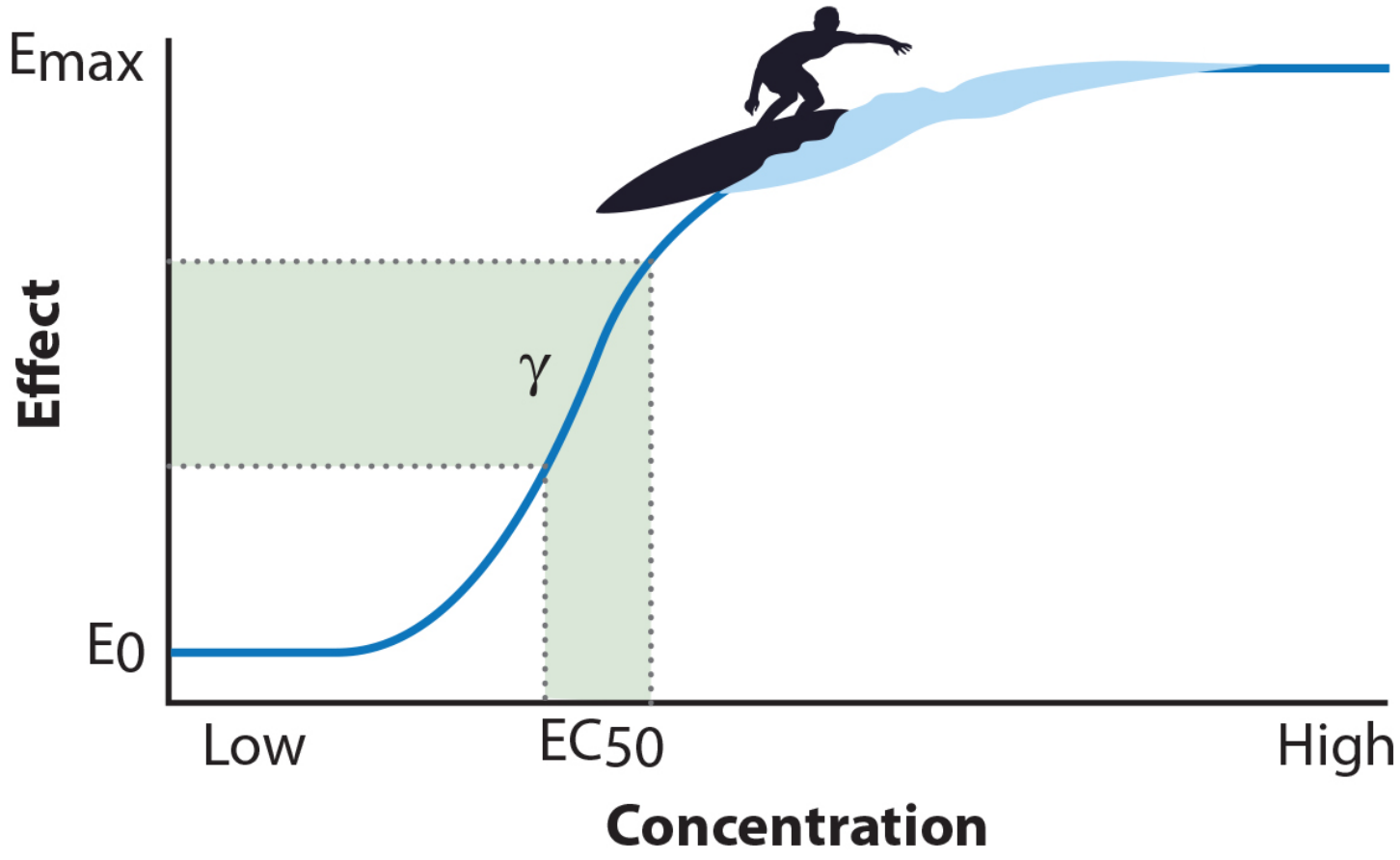

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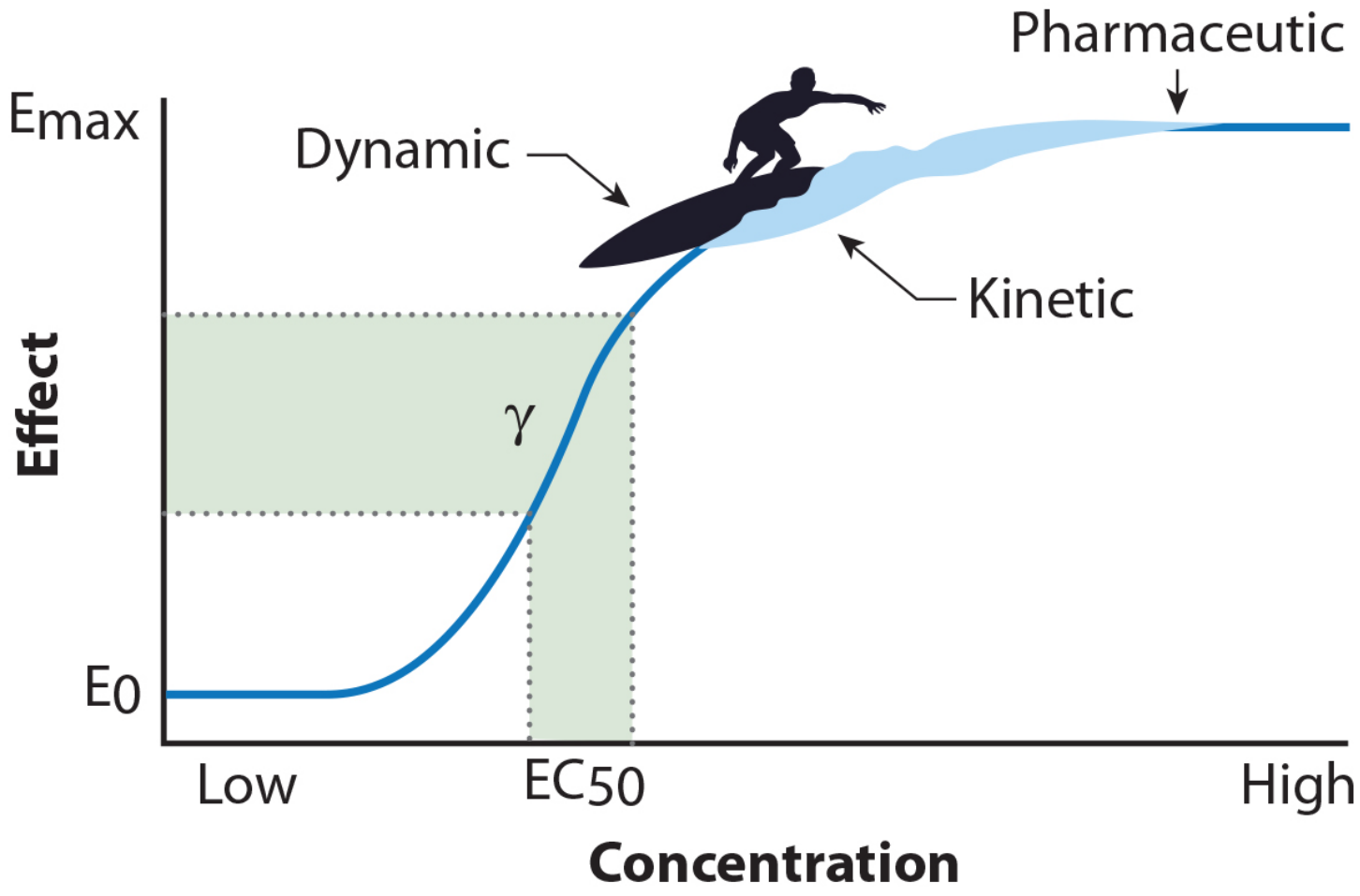

TAKE 5 FOR TIVA

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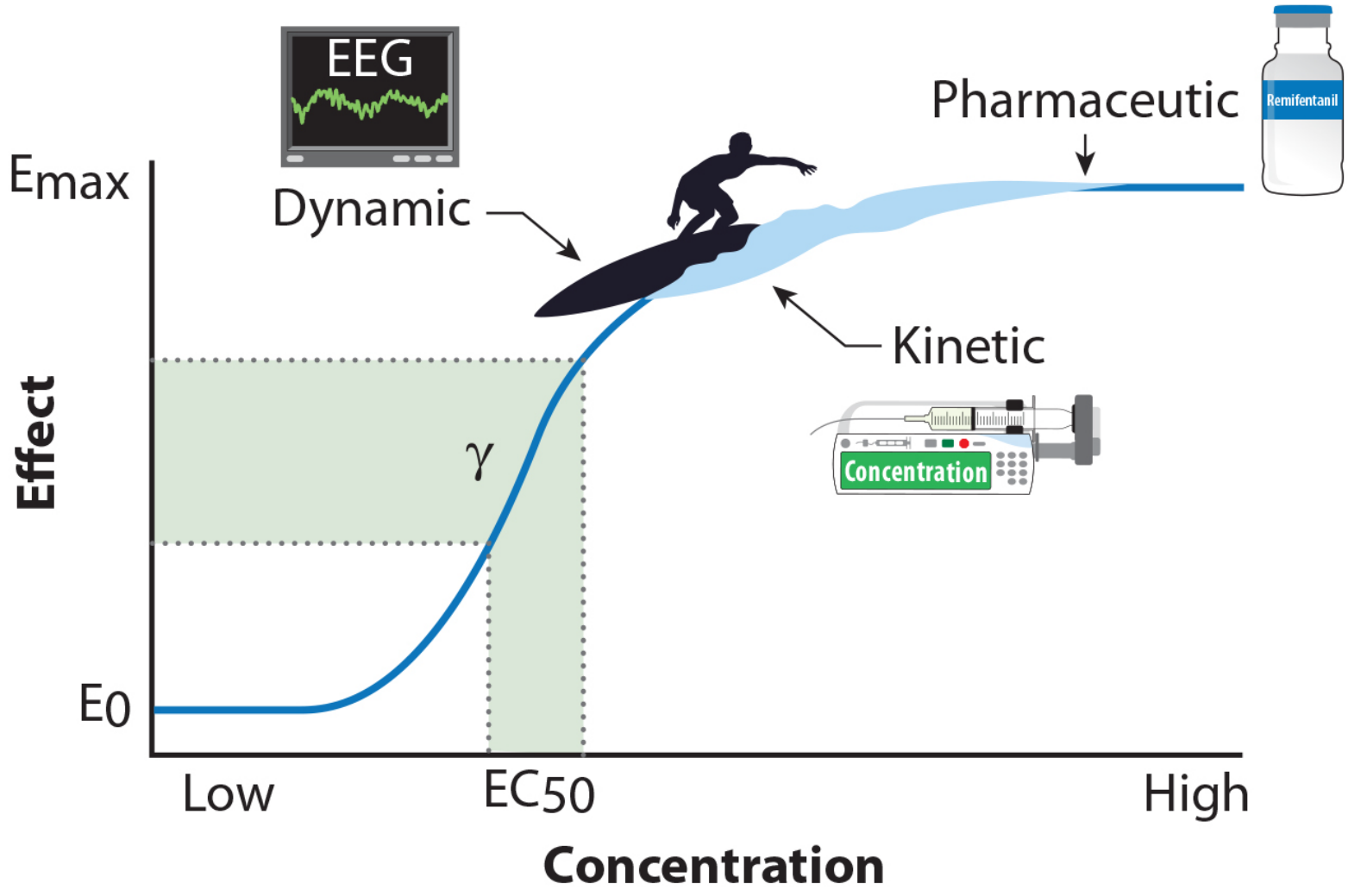
Posology in Anesthesia: A Surfing Analogy



TAKE 5 FOR TIVA

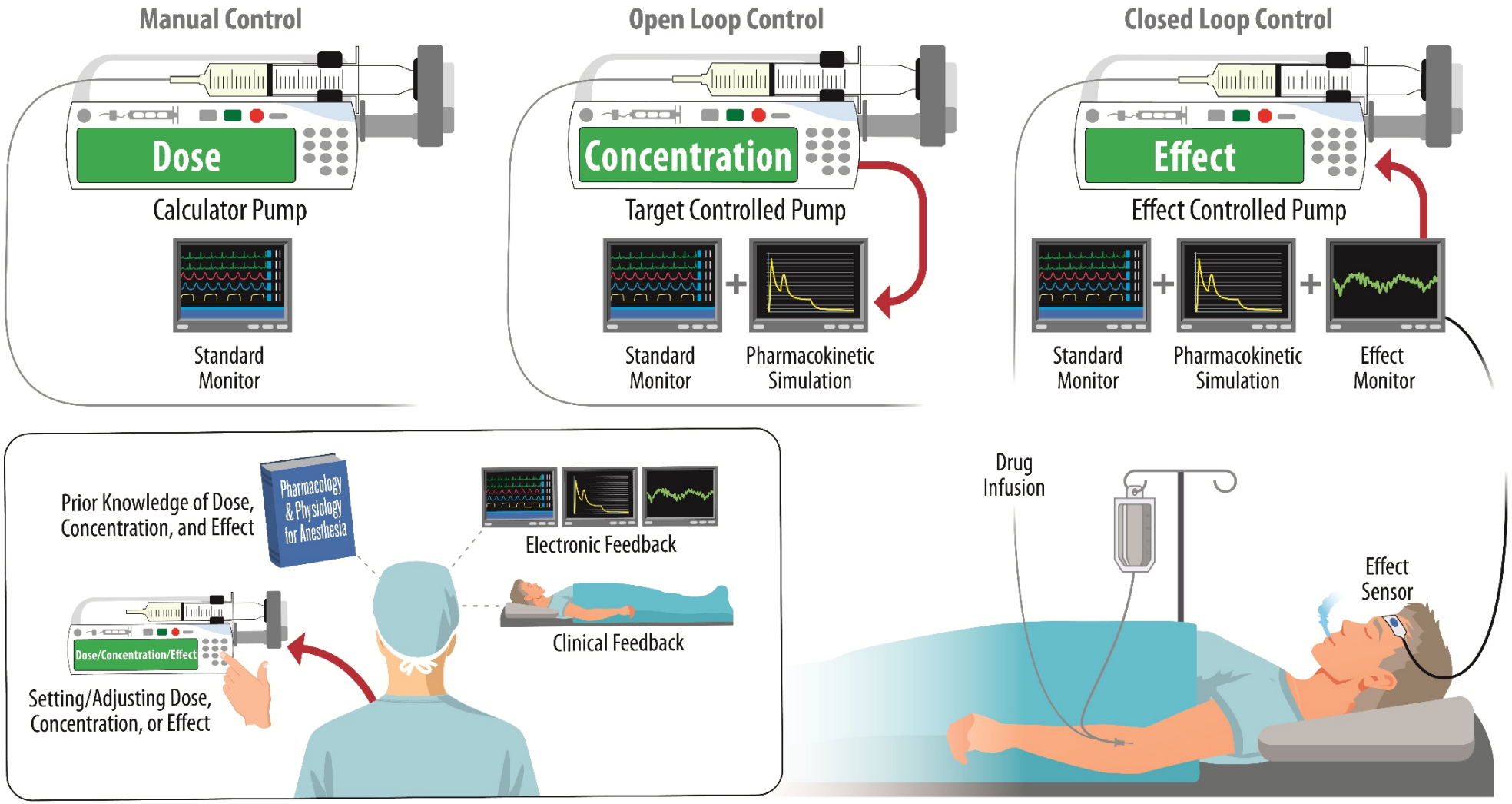
Egan & Shafer (Anesthesiology 2003)

Key Point

There are three TIVA practice domains (i.e., dose, concentration, & effect). The effect domain is optimal.

TAKE 5 FOR TIVA

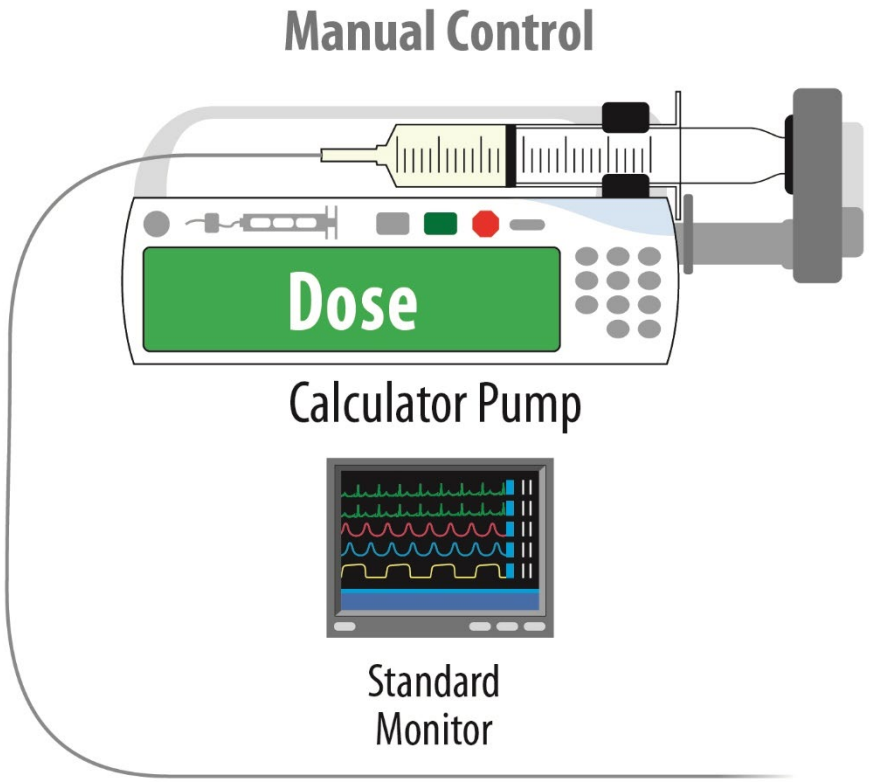
Three TIVA Practice Domains



Egan (*Anesth Analg* 2018)

The Dose Domain

- ✓ Simple to use
- ✓ Familiar to all

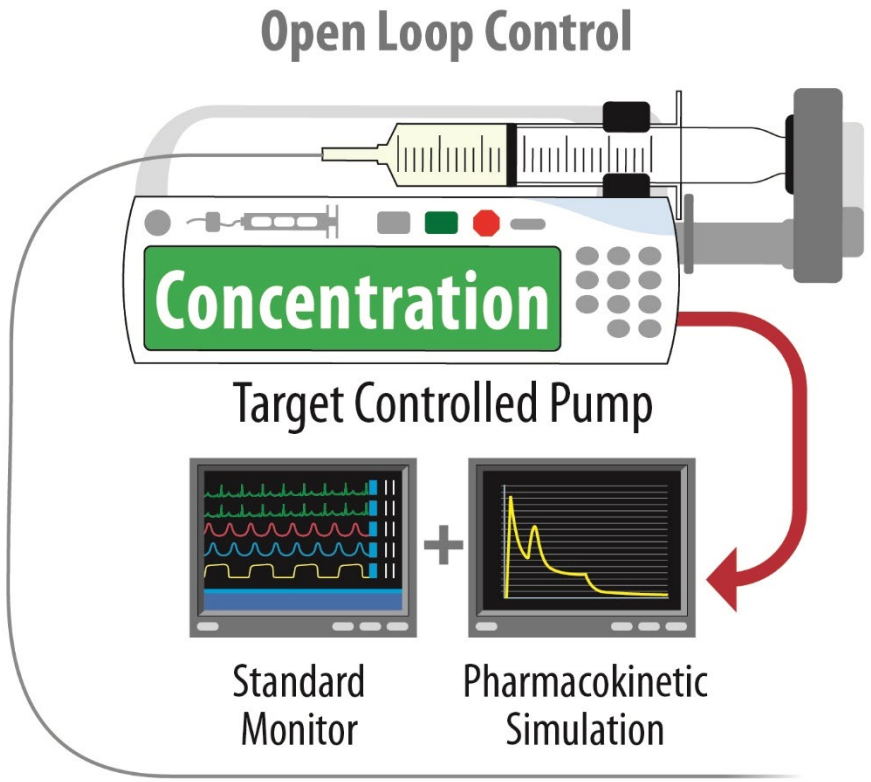


- ✓ Ignores temporal changes
- ✓ Slow to steady-state
- ✓ Ignores intersubject variability

Egan (*Anesth Analg* 2018)

The Concentration

- ✓ Automates dosage calculations
- ✓ Accounts for temporal changes
- ✓ Quick to steady-state
- ✓ Accounts for co-variate effects (PK)



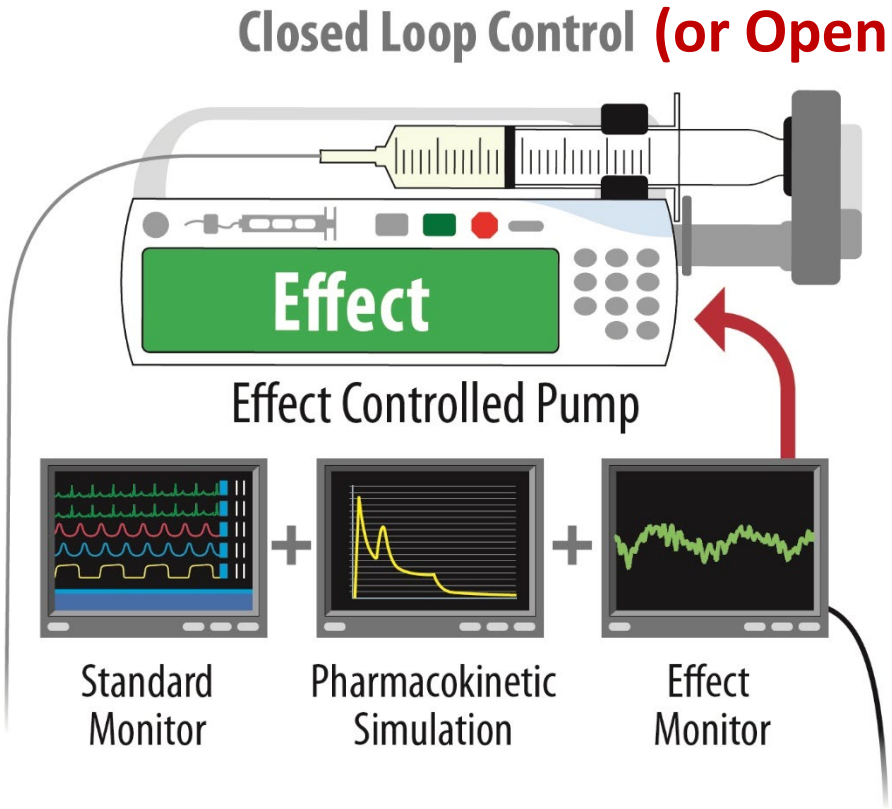
- ✓ Ignores intersubject variability
- ✓ Less familiar (USA)

Egan (*Anesth Analg* 2018)

The Effect Domain

- ✓ Automates dosage calculations
- ✓ Accounts for temporal changes
- ✓ Quick to steady-state
- ✓ Accounts for co-variate effects (PKPD)
- ✓ Accounts for intersub-ject variability

Most important!

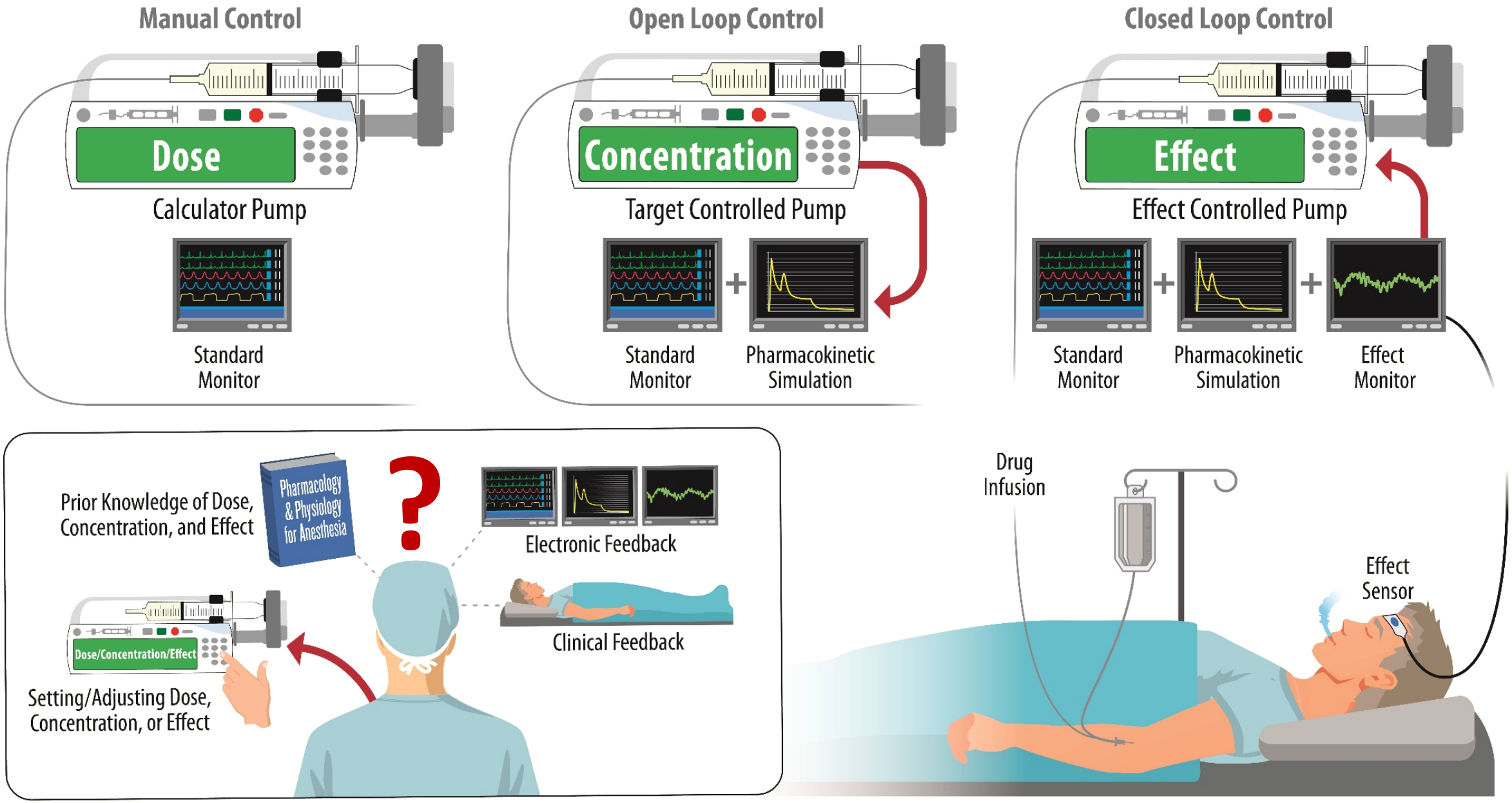


Usually Best!

- ✓ Complicated control system (automated)
- ✓ Suboptimal sensors
- ✓ Less familiar
- ✓ Unintended conse-quences?

TAKE 5 FOR TIVA

Egan (*Anesth Analg* 2018)



TAKE 5 FOR TIVA

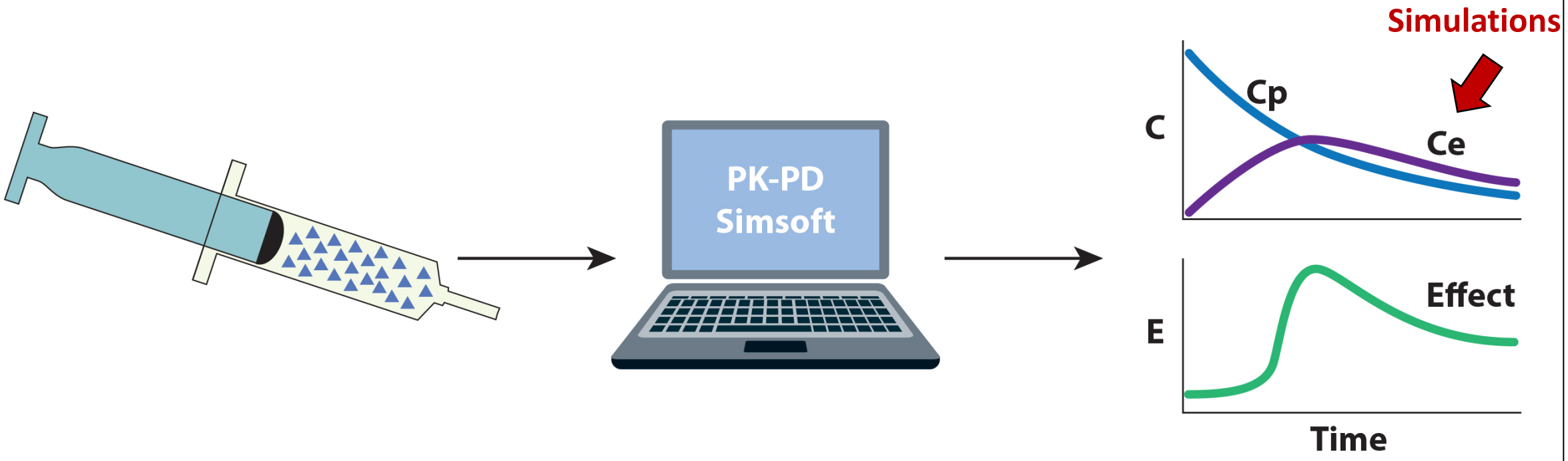
Egan (*Anesth Analg* 2018)

Key Point

Certain pharmacokinetic attributes inform TIVA posology for bolus and infusions conditions. These attributes are best understood through PK-PD simulation.

TAKE 5 FOR TIVA

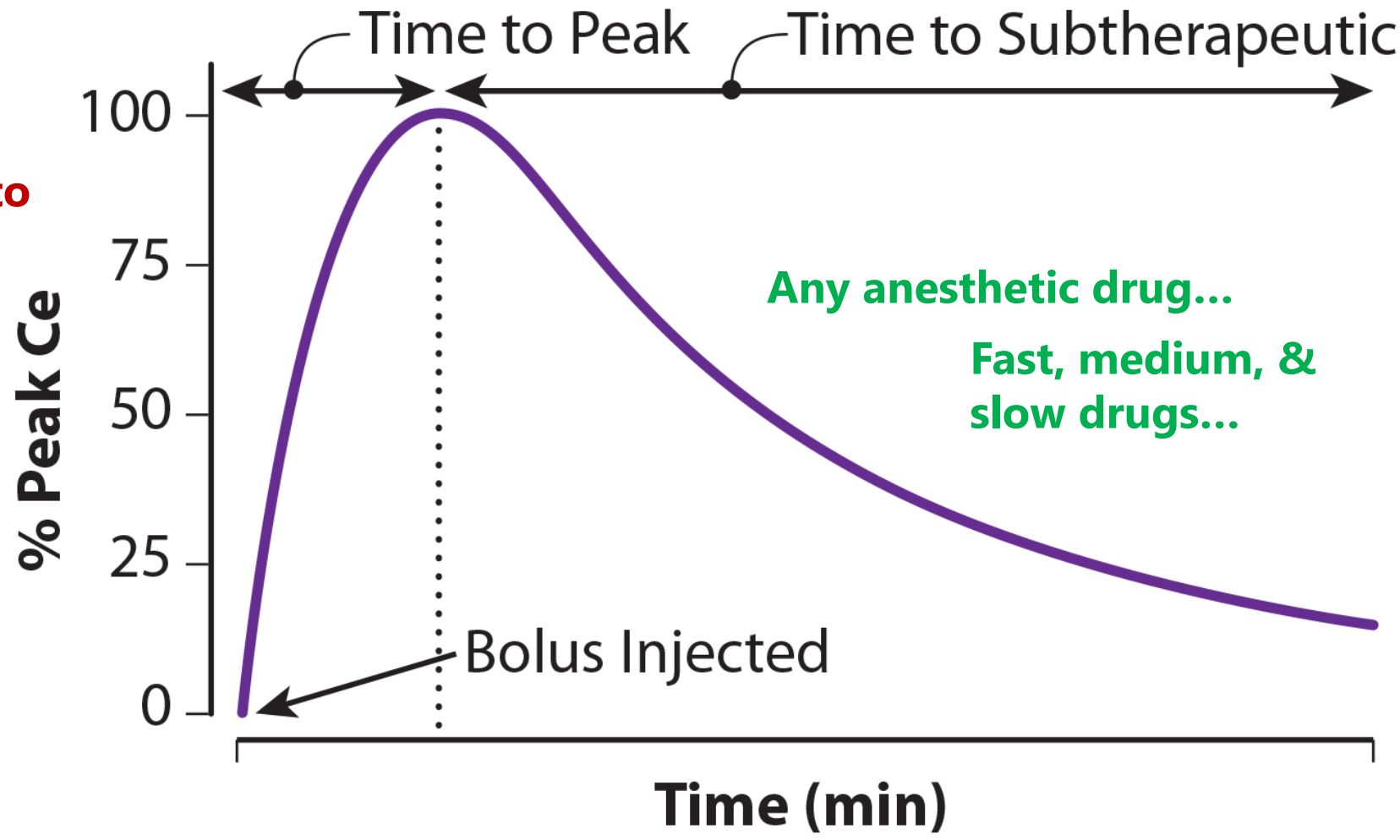
Clinical Inference via PK/PD Simulation



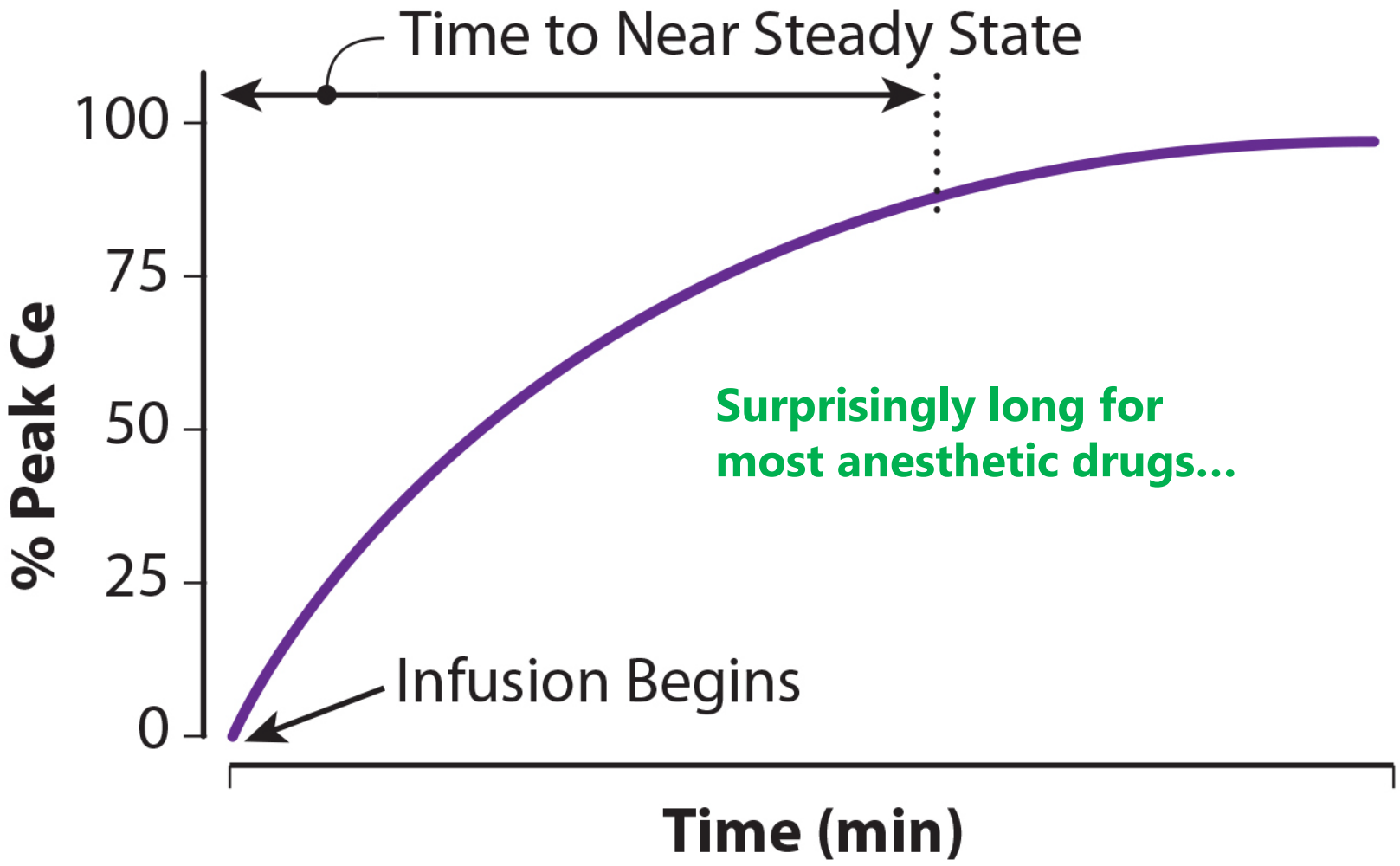
Obara & Egan
(in Hemmings & Egan, Elsevier 2019)

Bolus Front-End & Back-End

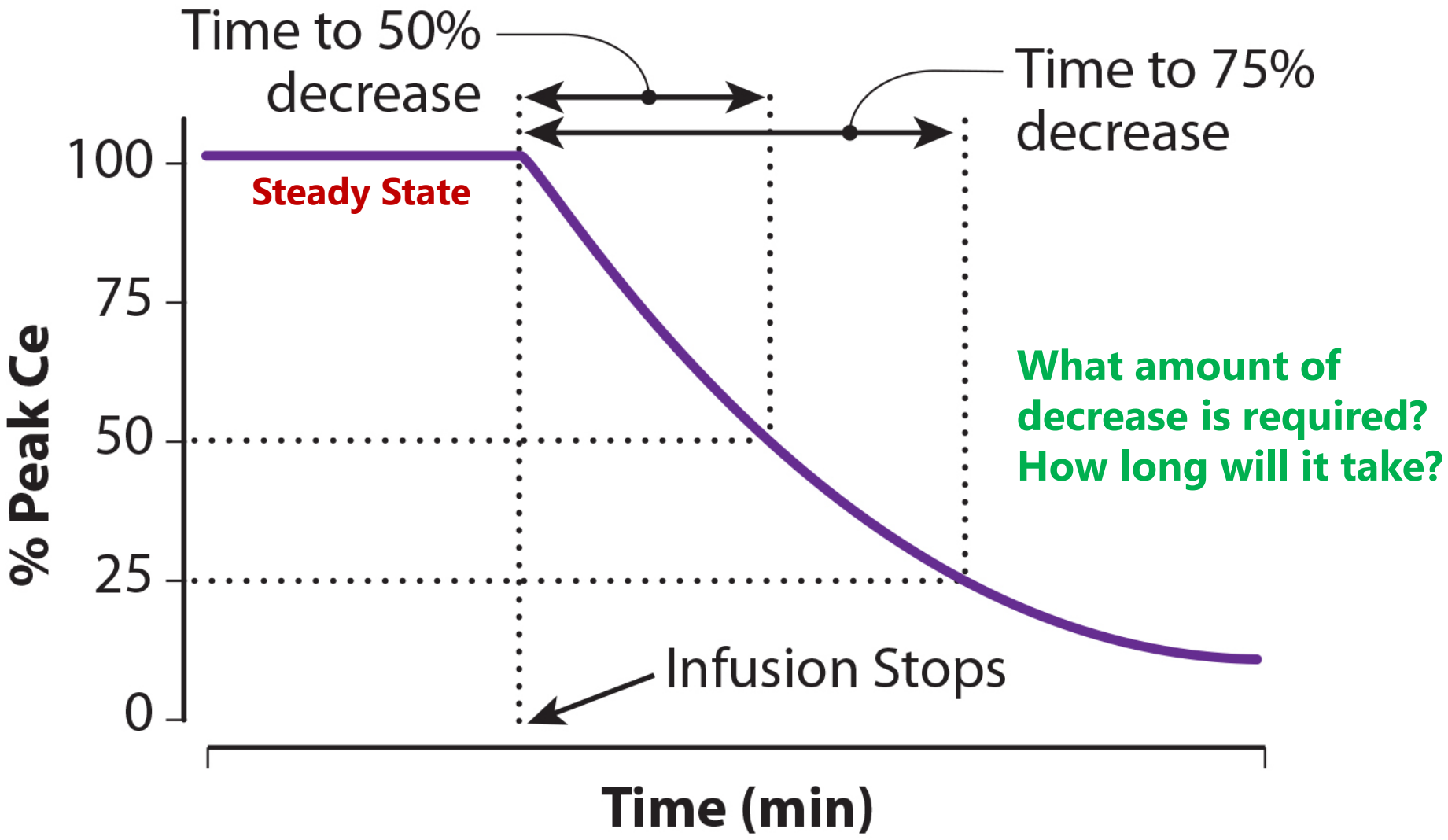
Normalized to peak Ce!



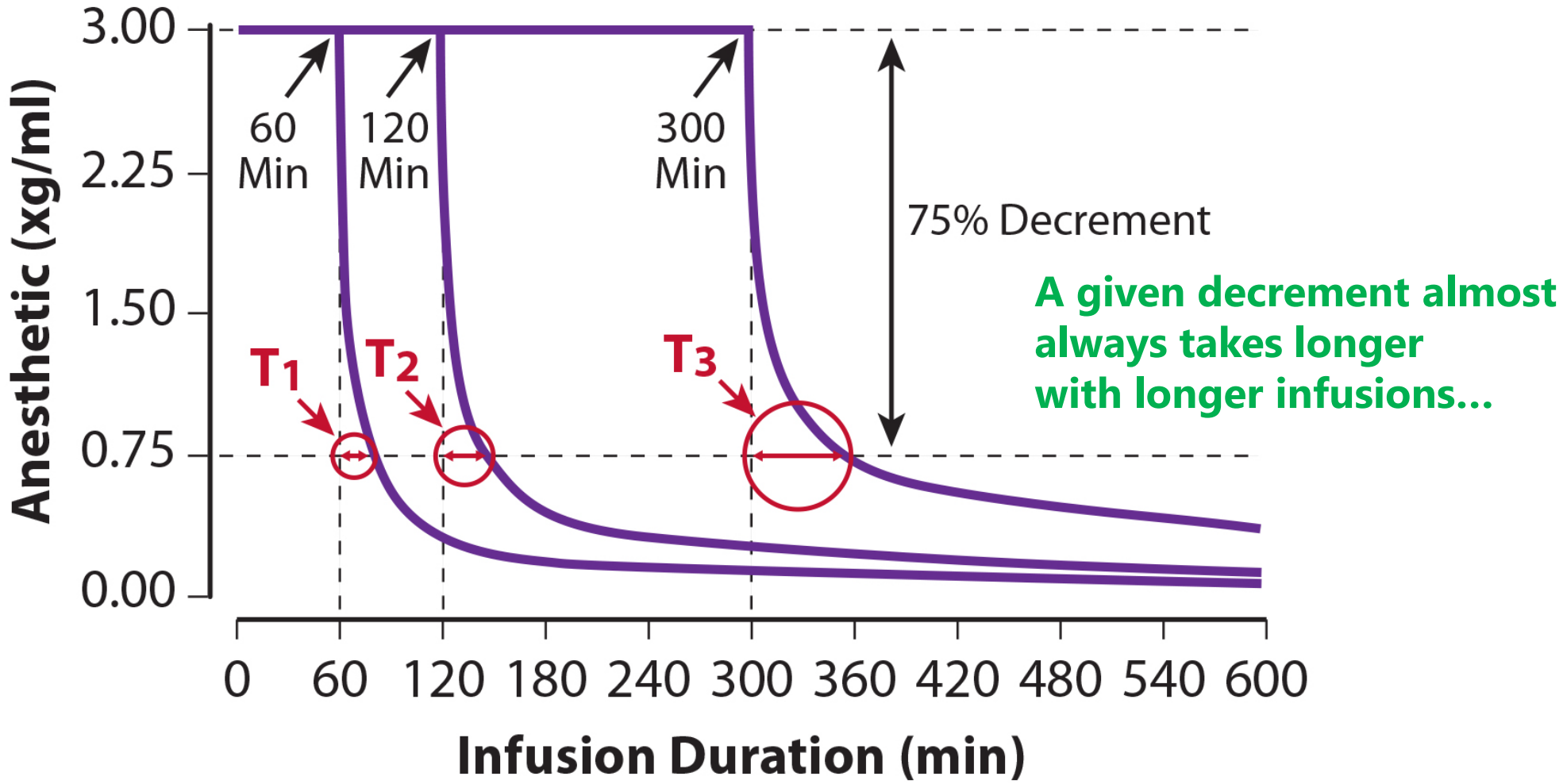
Infusion Front-End



Infusion Back-End

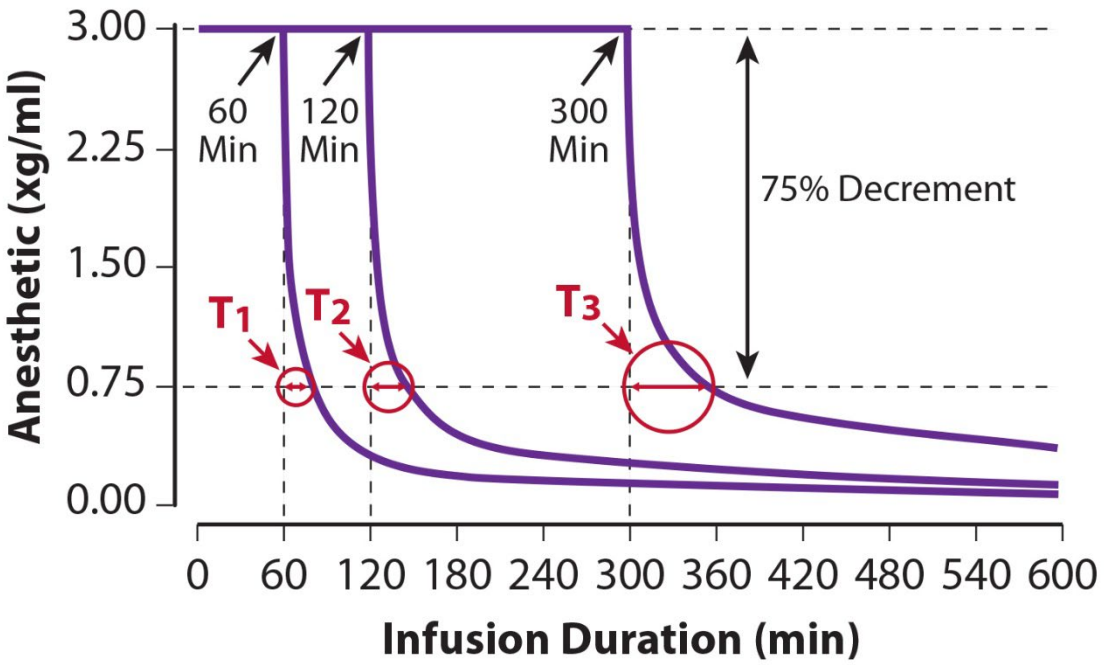


Impact of Infusion Duration

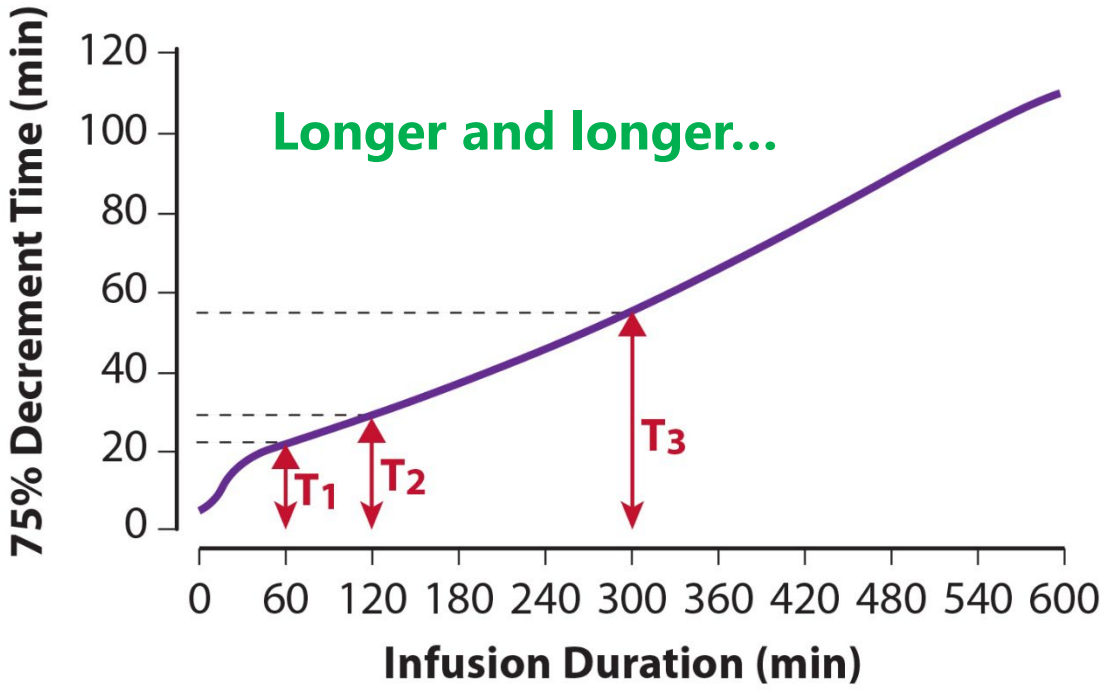


A given decrement almost always takes longer with longer infusions…

Impact of Infusion Duration



75% Decrement Times

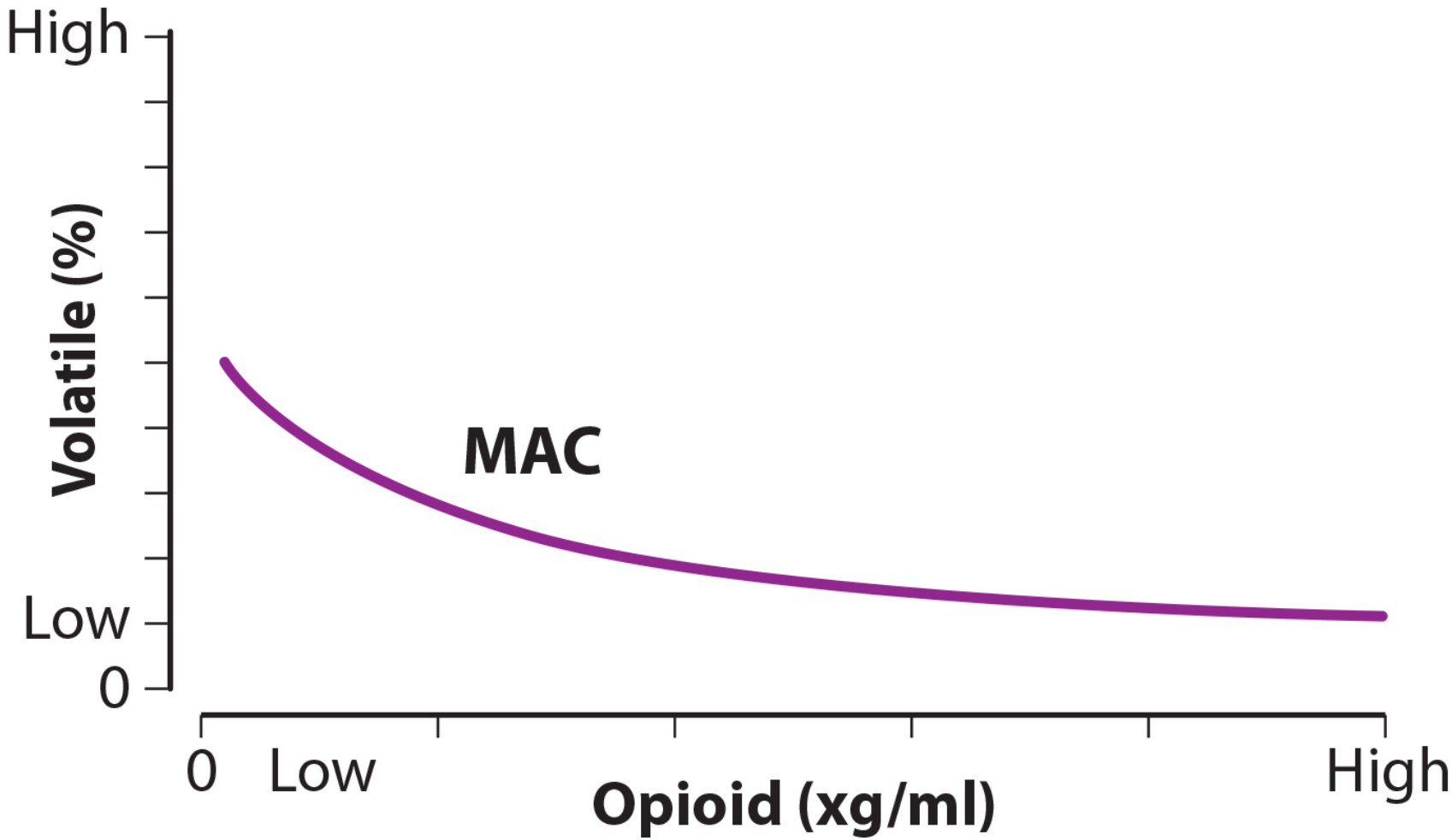


Key Point

Certain pharmacodynamic concepts inform TIVA posology. Chief among these are propofol-opioid pharmacodynamic interactions.

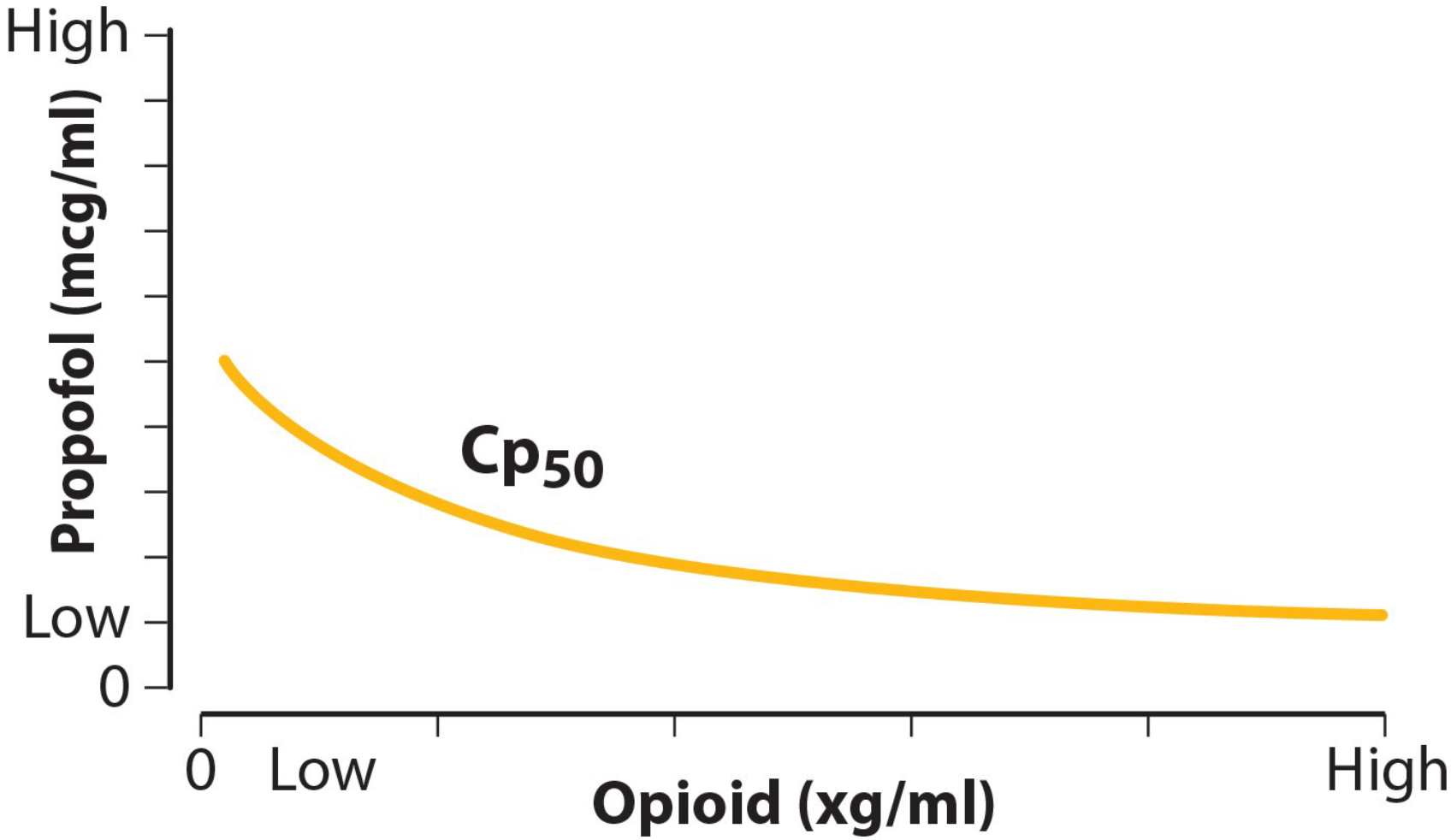
TAKE 5 FOR TIVA

MAC Reduction by Opioids



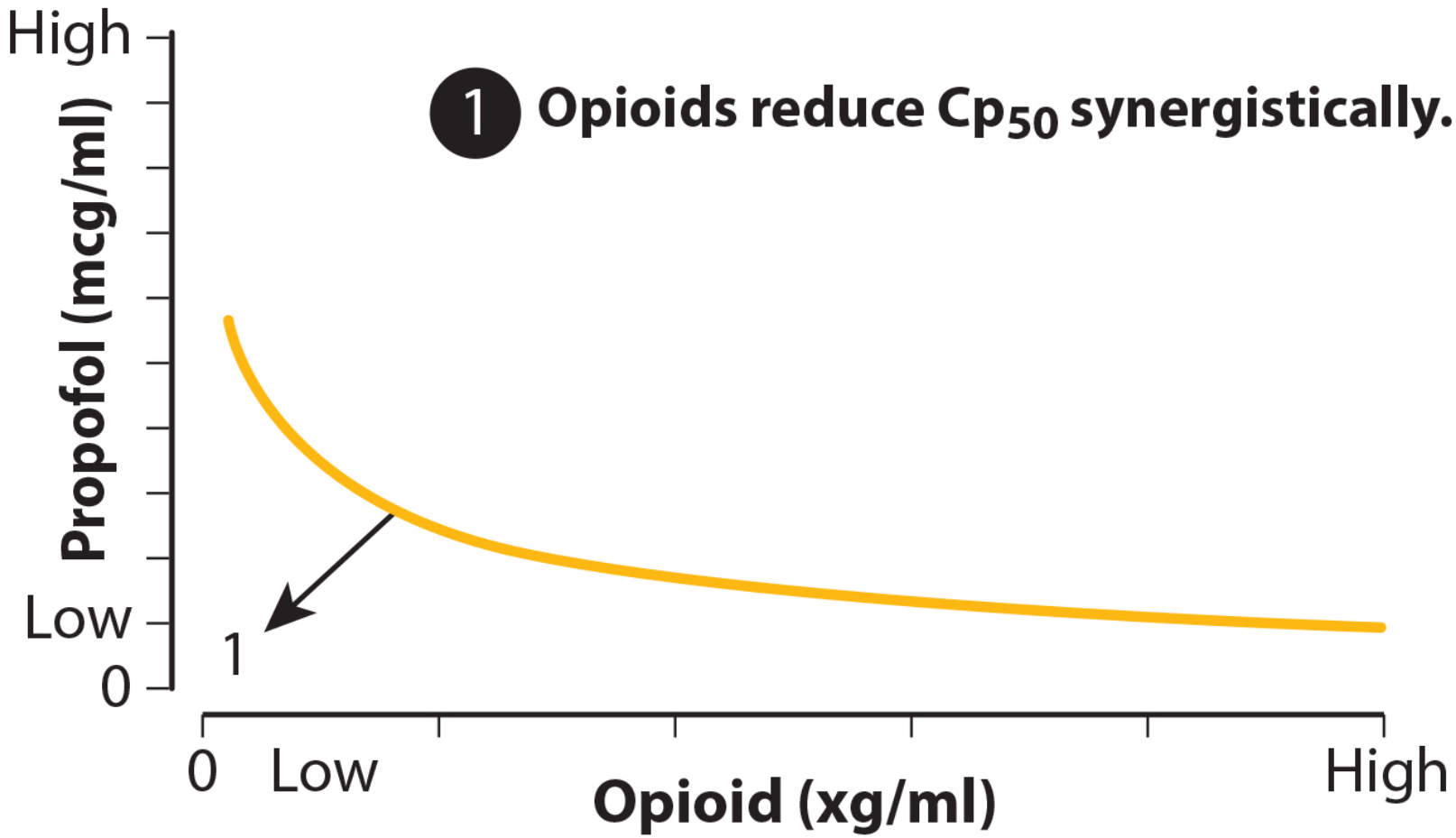
Ogura & Egan (in Hemmings & Egan, Elsevier 2019)

Propofol Cp_{50} Reduction by Opioids



Ogura & Egan (in Hemmings & Egan, Elsevier 2019)

Propofol-Opioid PD Interaction



TAKE 5 FOR TIVA

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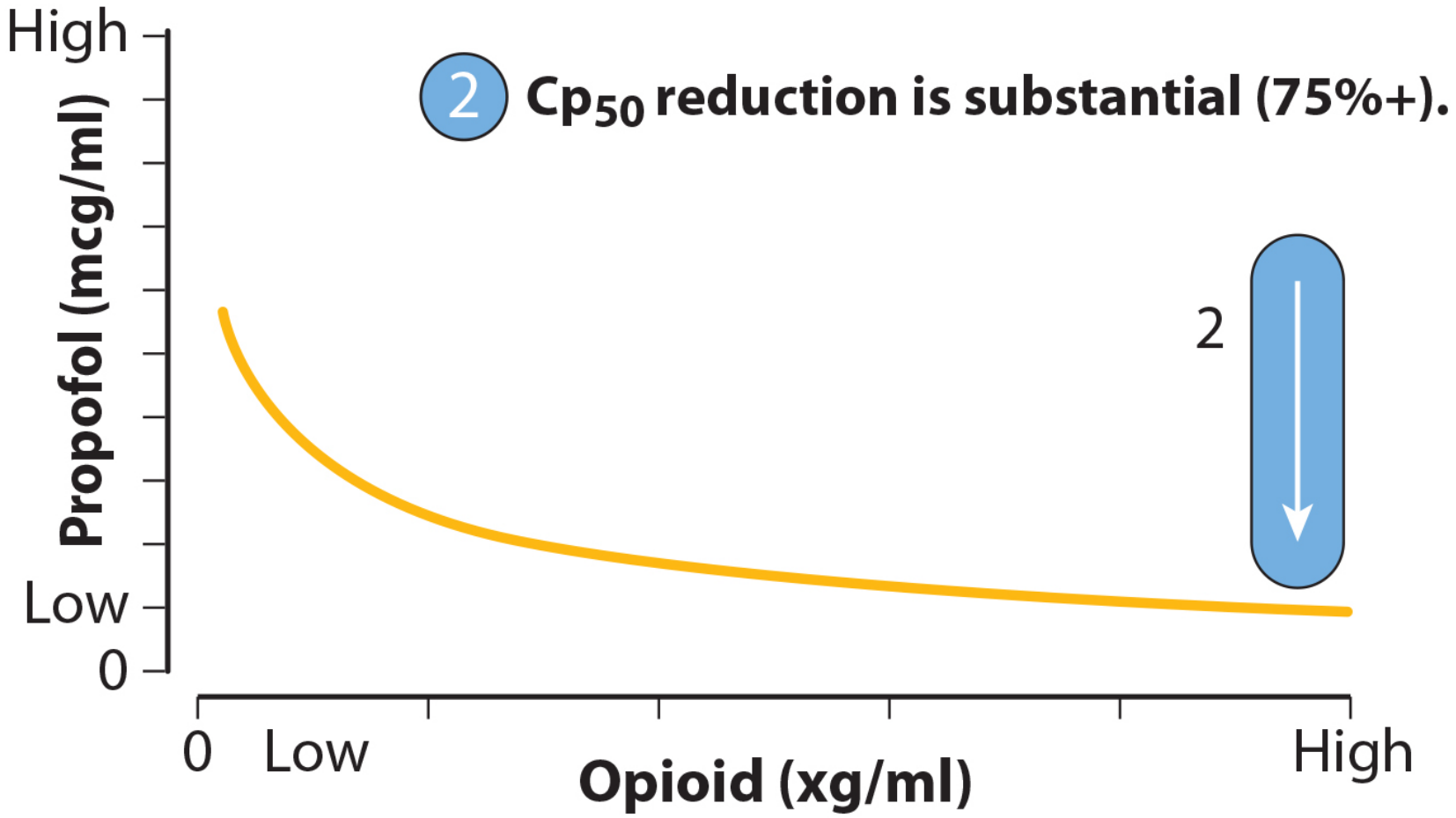

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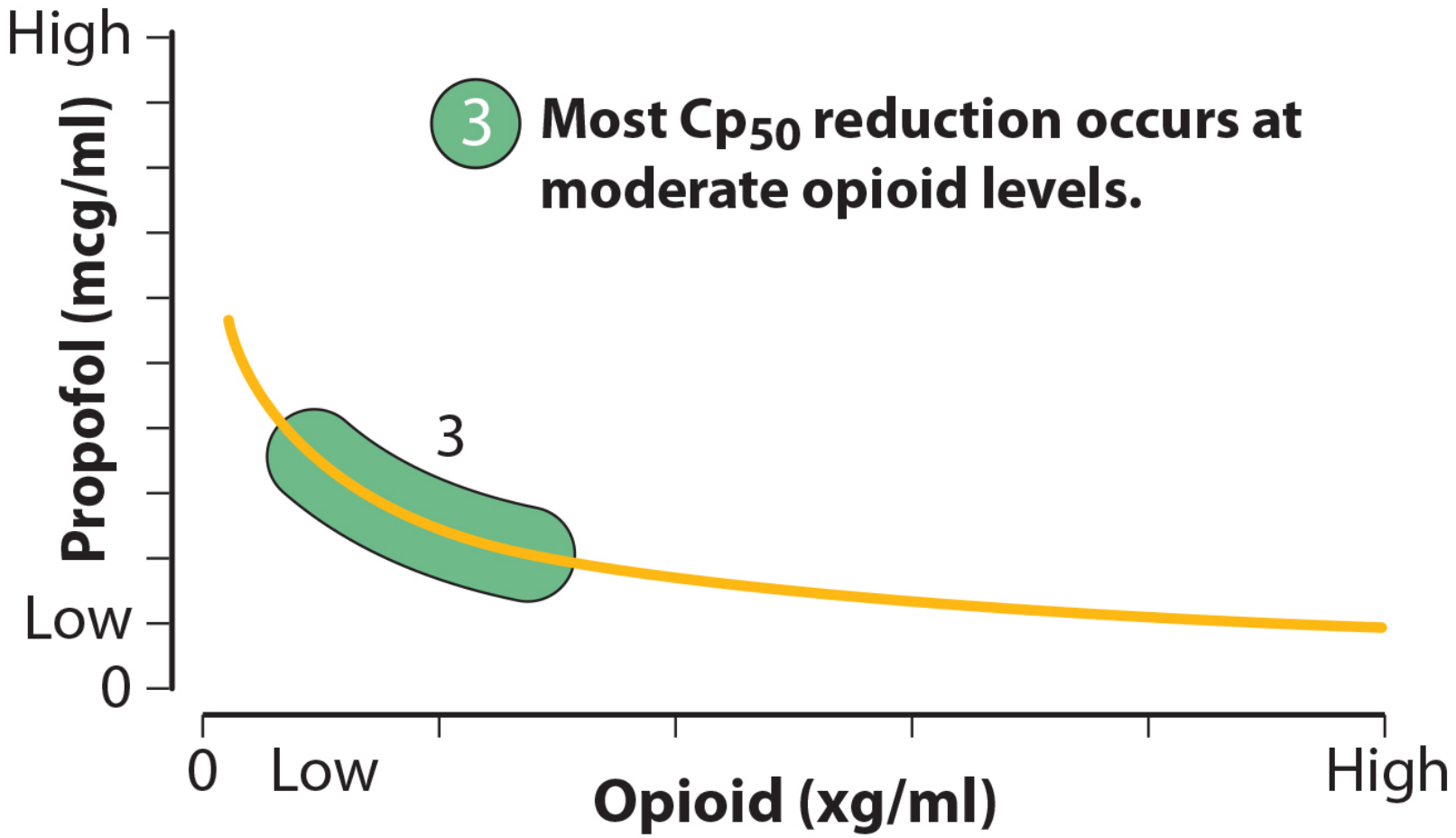

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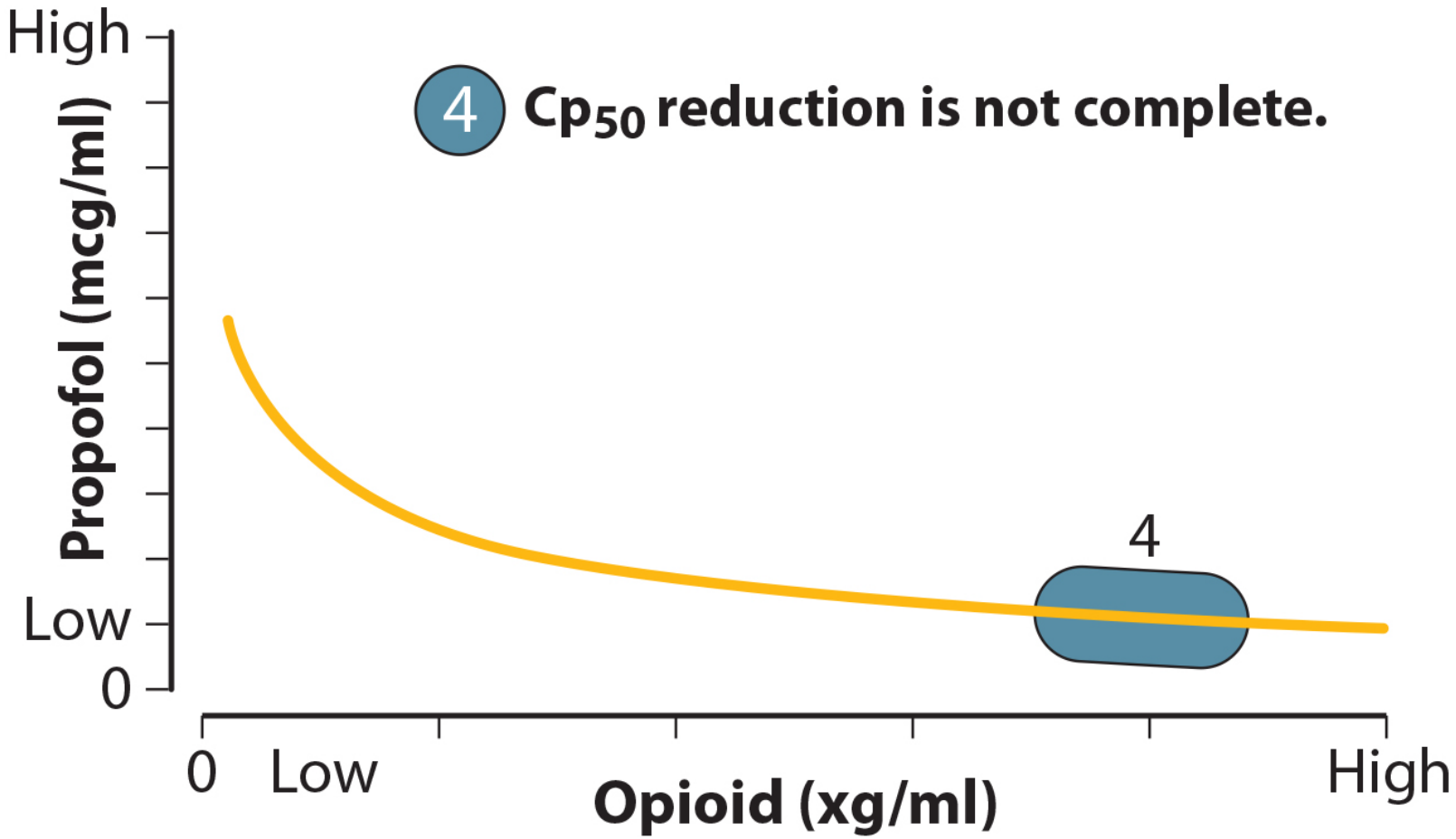

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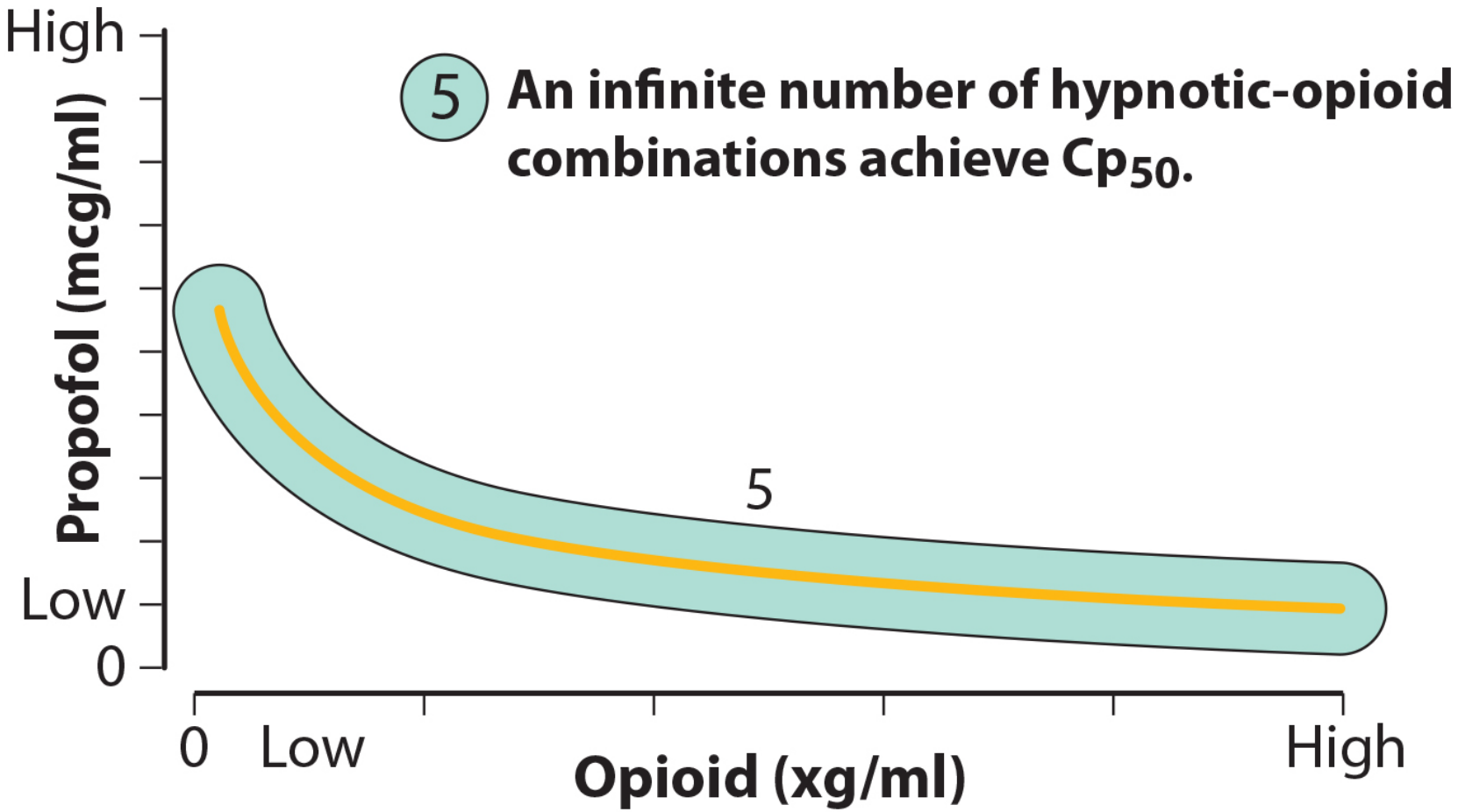
Propofol-Opioid PD Interaction



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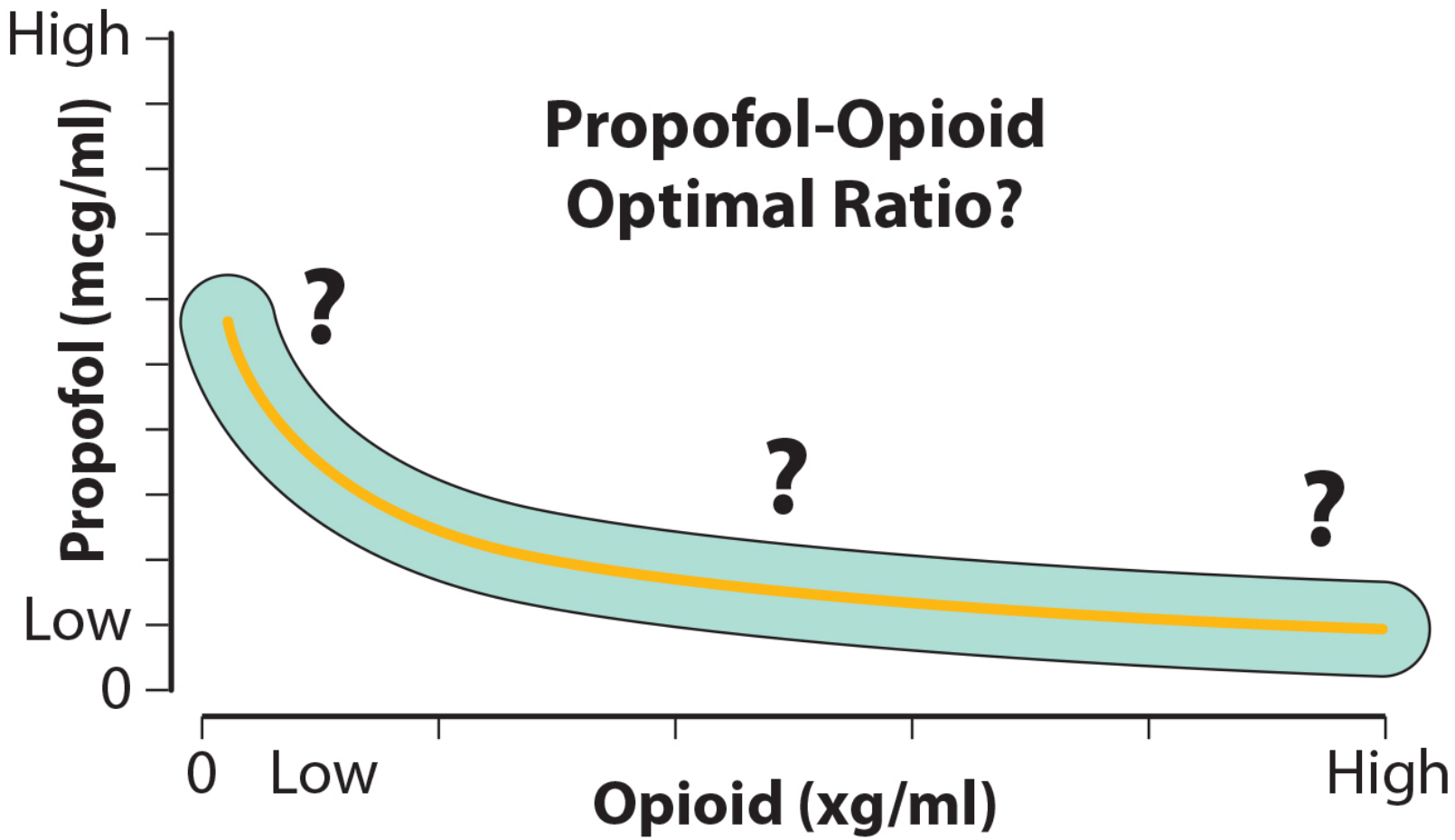
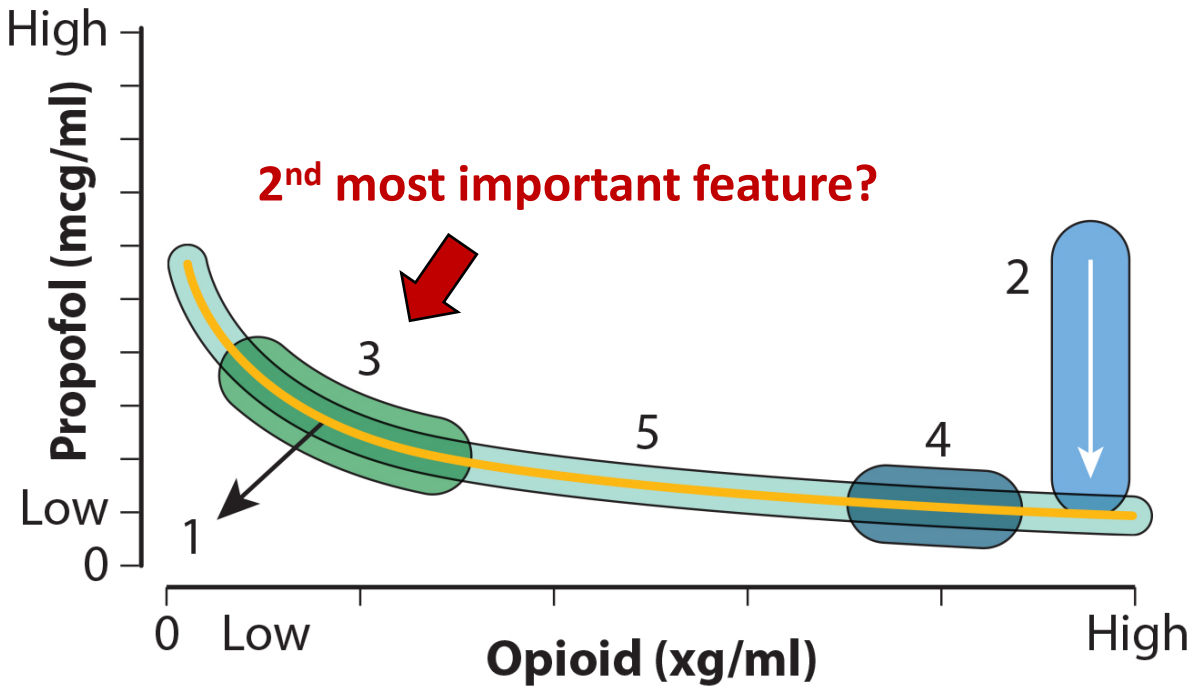
Propofol-Opioid PD Interaction



Propofol-Opioid PD Interaction



1. Opioids reduce Cp_{50} synergistically.
2. Cp_{50} reduction is substantial (75%+).
3. Most Cp_{50} reduction occurs at moderate opioid levels.
4. Cp_{50} reduction is not complete.
5. An infinite number of hypnotic-opioid combinations achieve Cp_{50}.

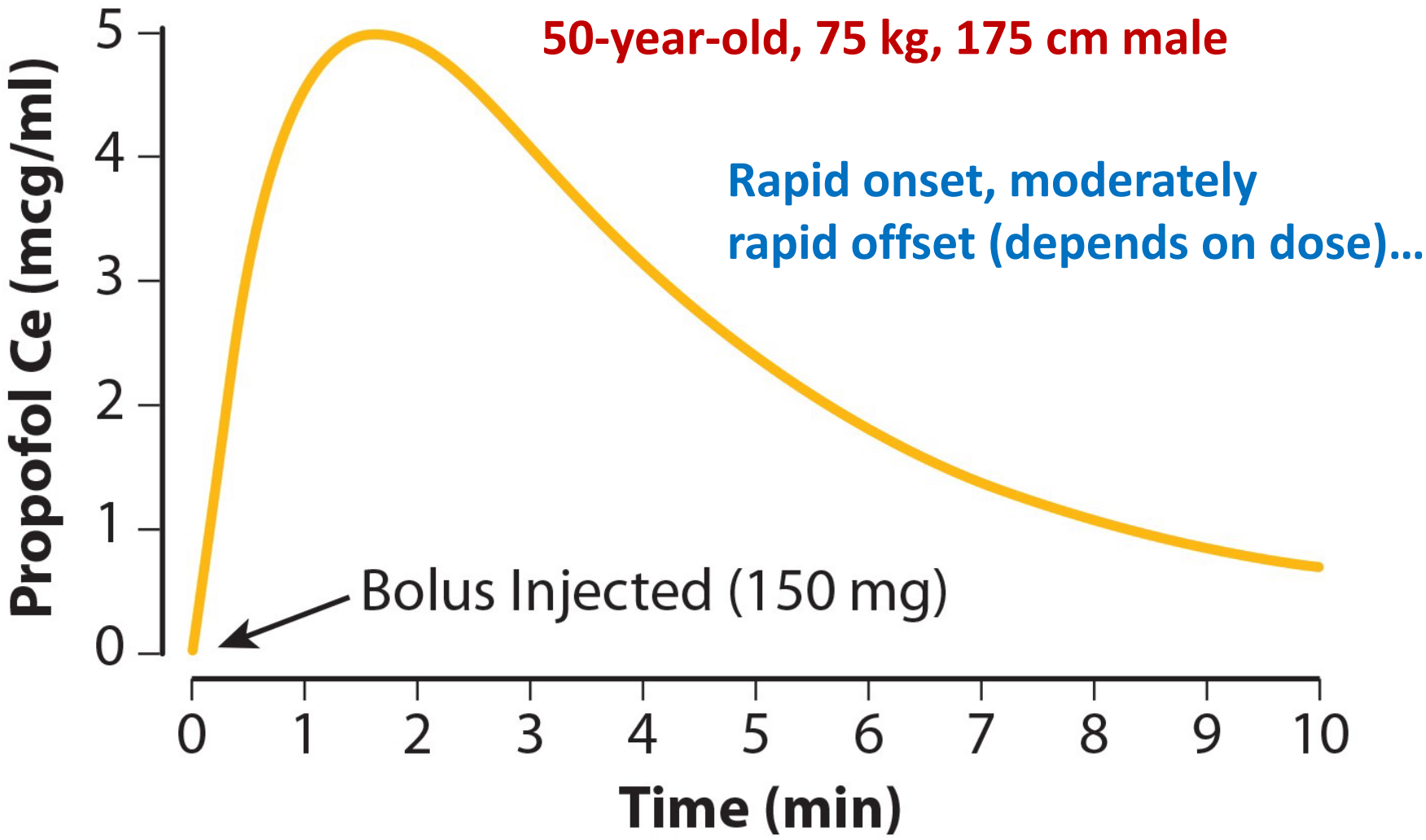
Ogura & Egan (in Hemmings & Egan, Elsevier 2019)

Key Point

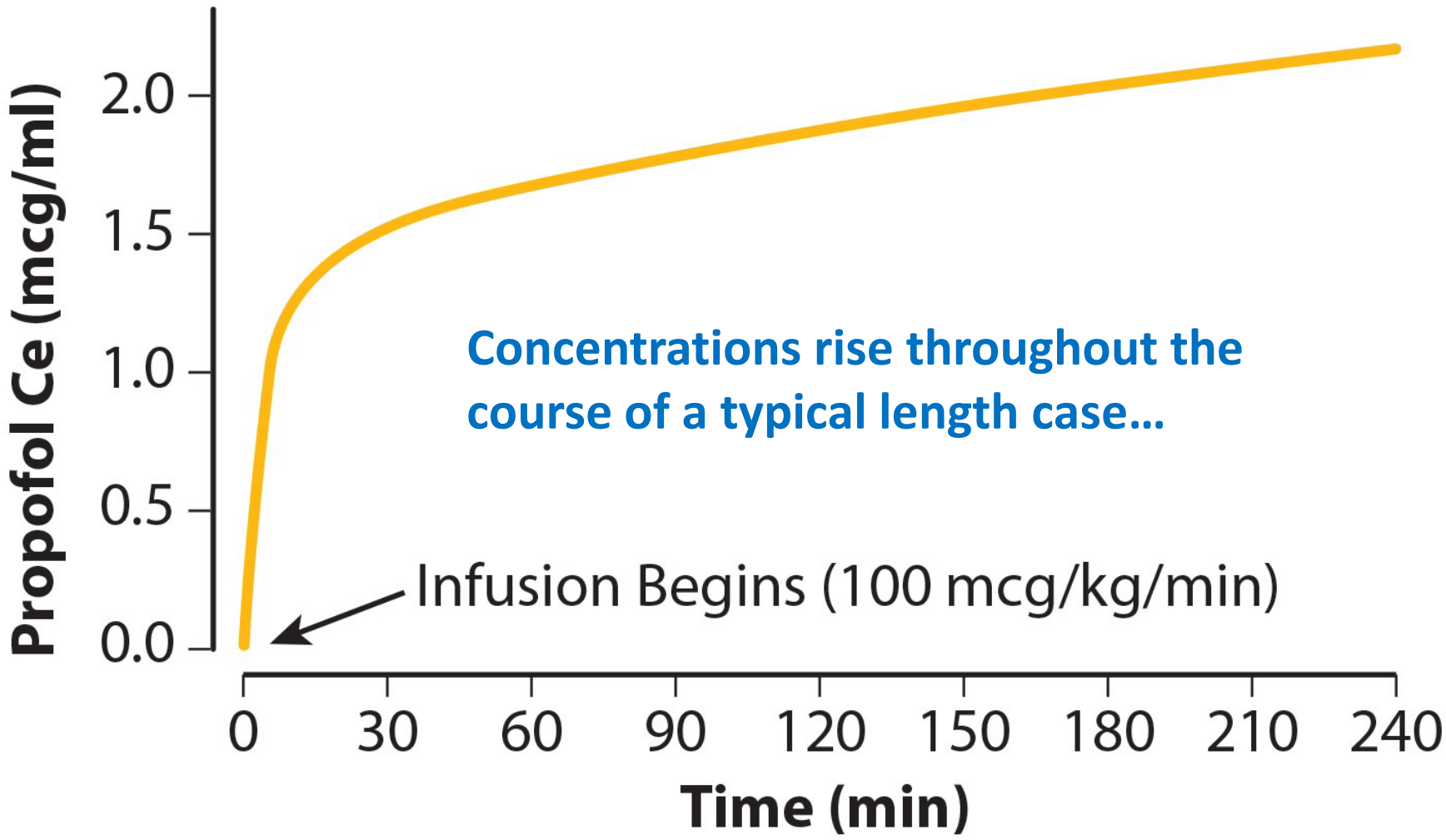
Simulation of propofol's pharmacokinetic behavior helps inform posological decisions in TIVA.

TAKE 5 FOR TIVA

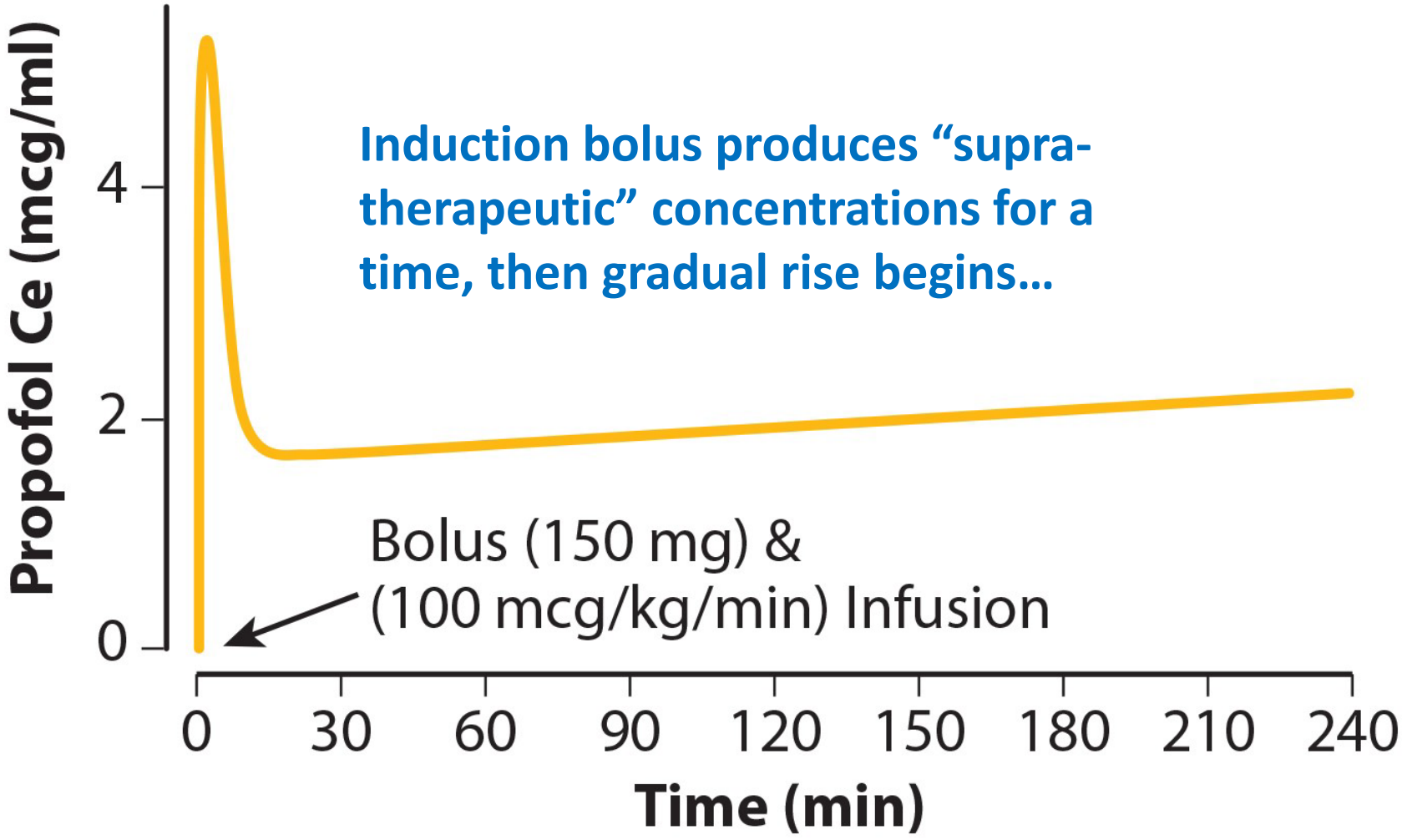
Bolus Front-End & Back-End



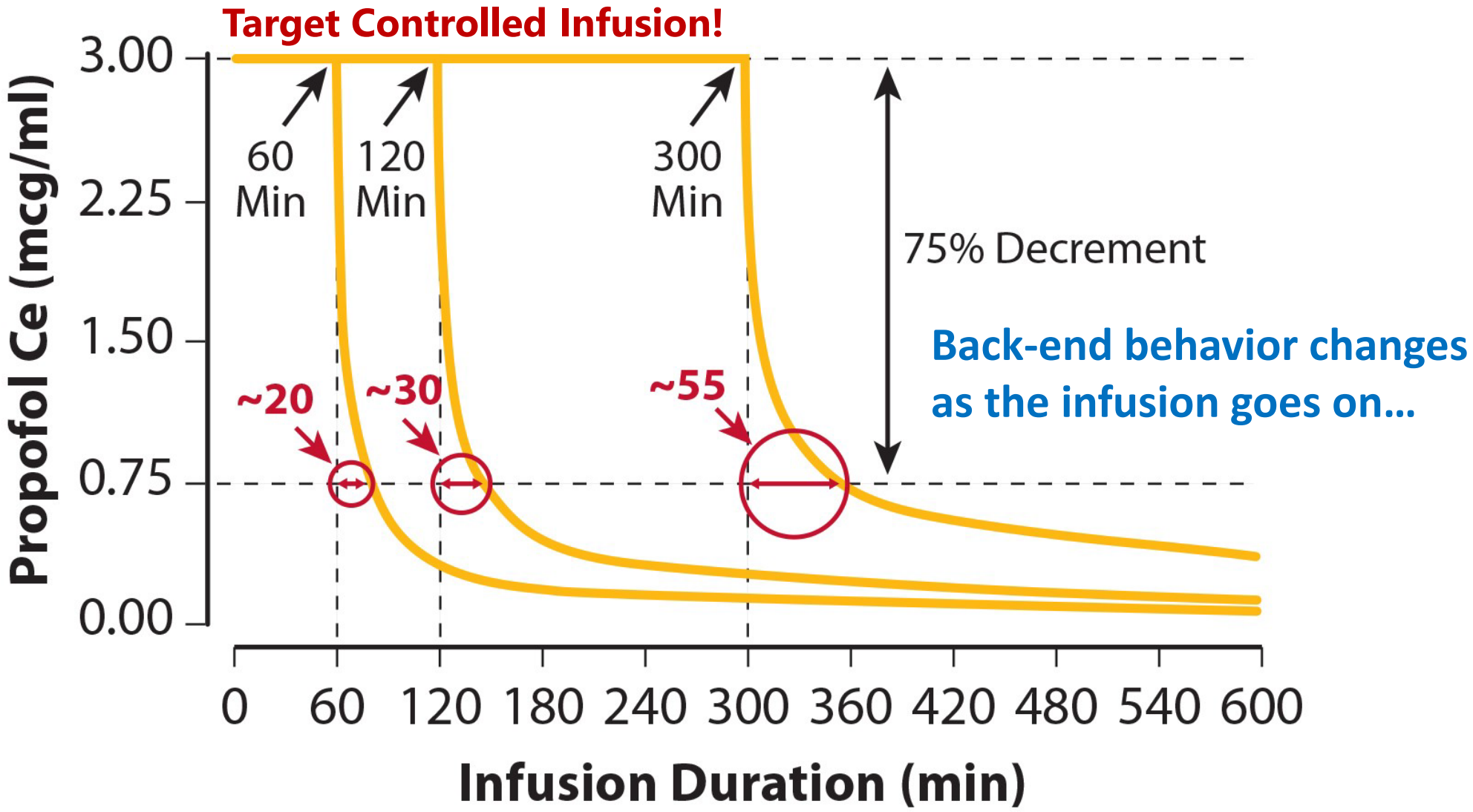
Infusion Front-End



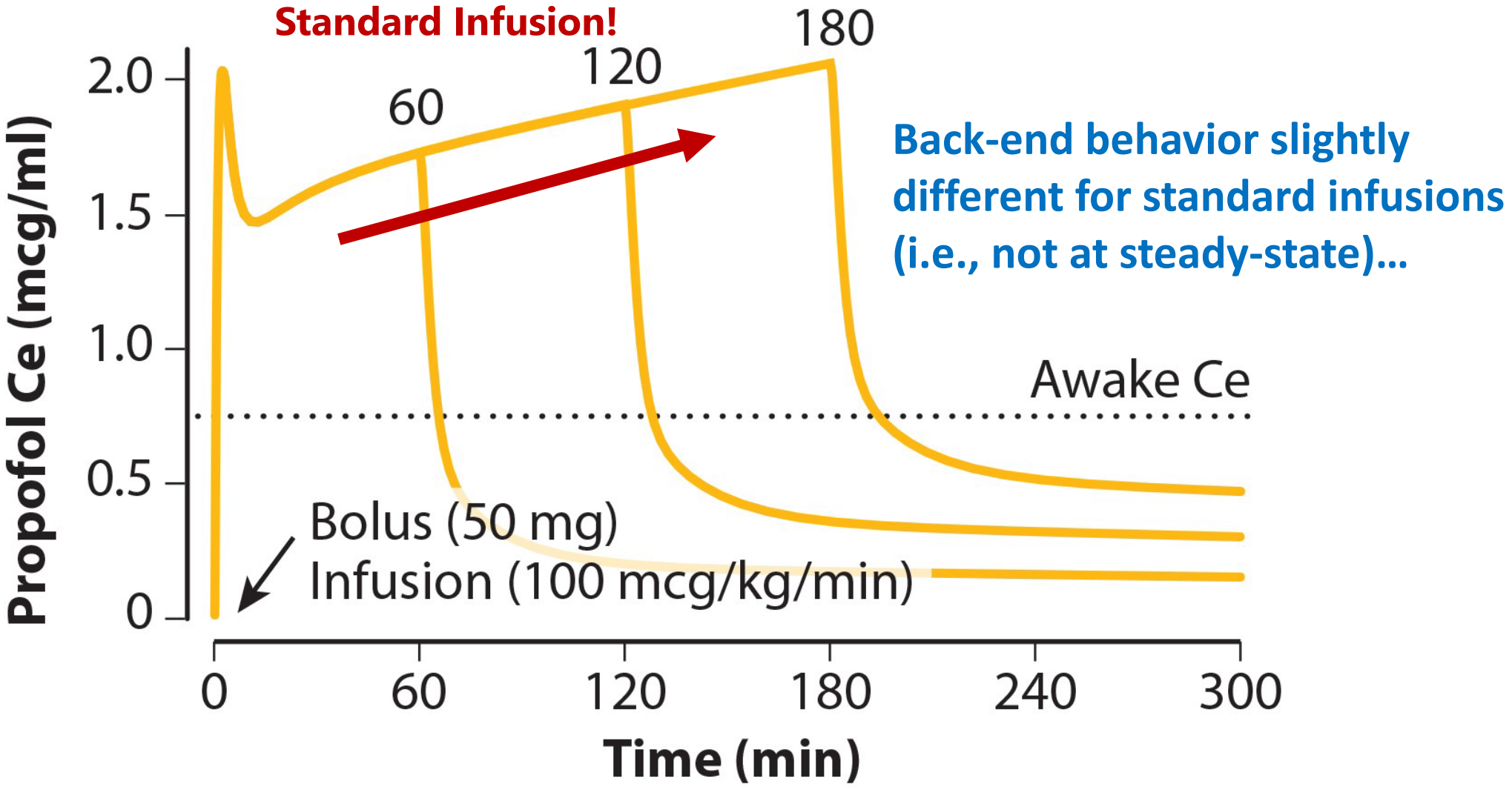
Impact of Loading Dose



Infusion Back-End

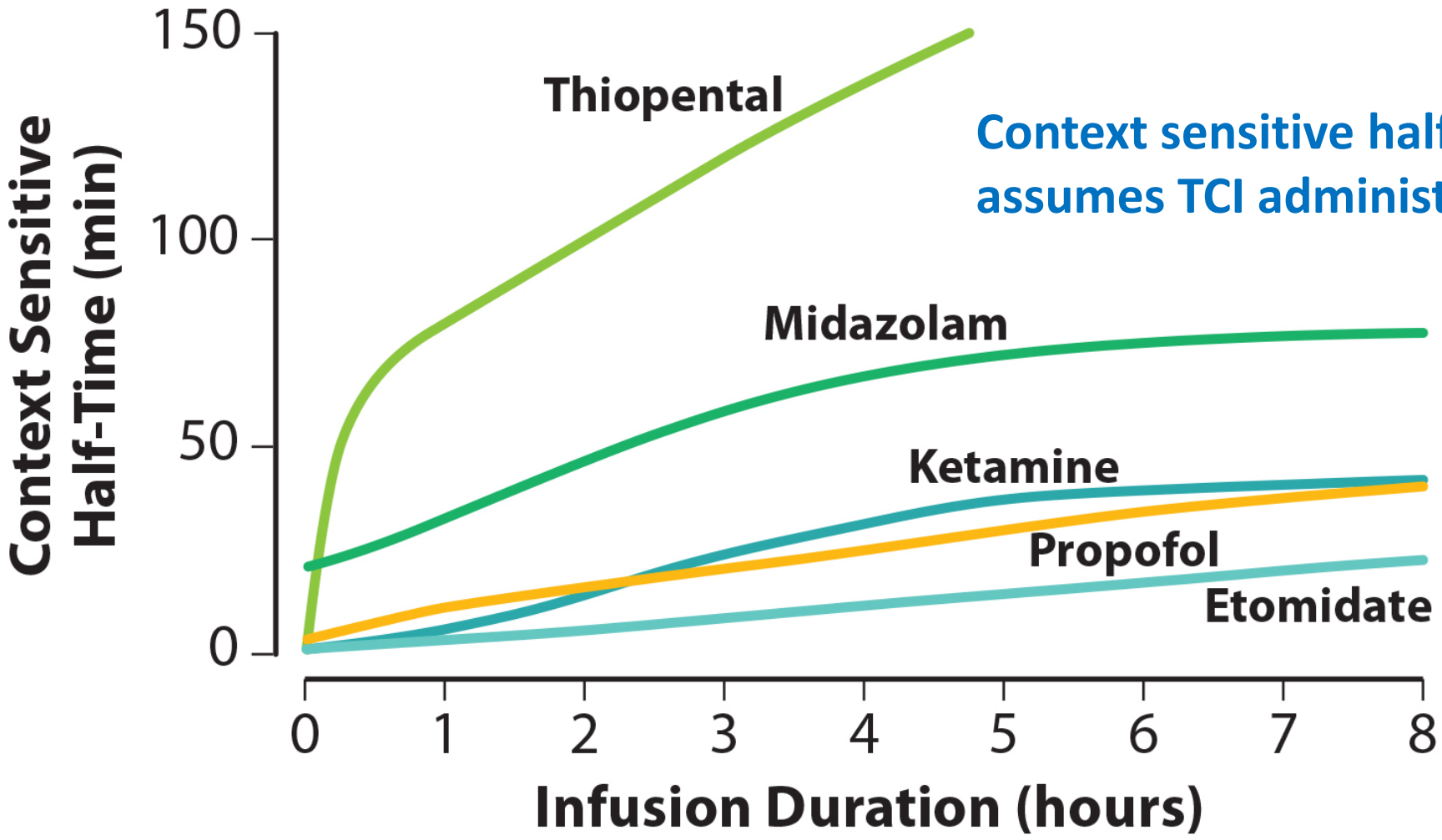


Impact of Infusion Duration



Back-end behavior slightly different for standard infusions (i.e., not at steady-state)…

Context Sensitive Half-Time



Context sensitive half-time assumes TCI administration…

TAKE 5 FOR TIVA

Obara & Egan (in Hemmings & Egan, Elsevier 2019)

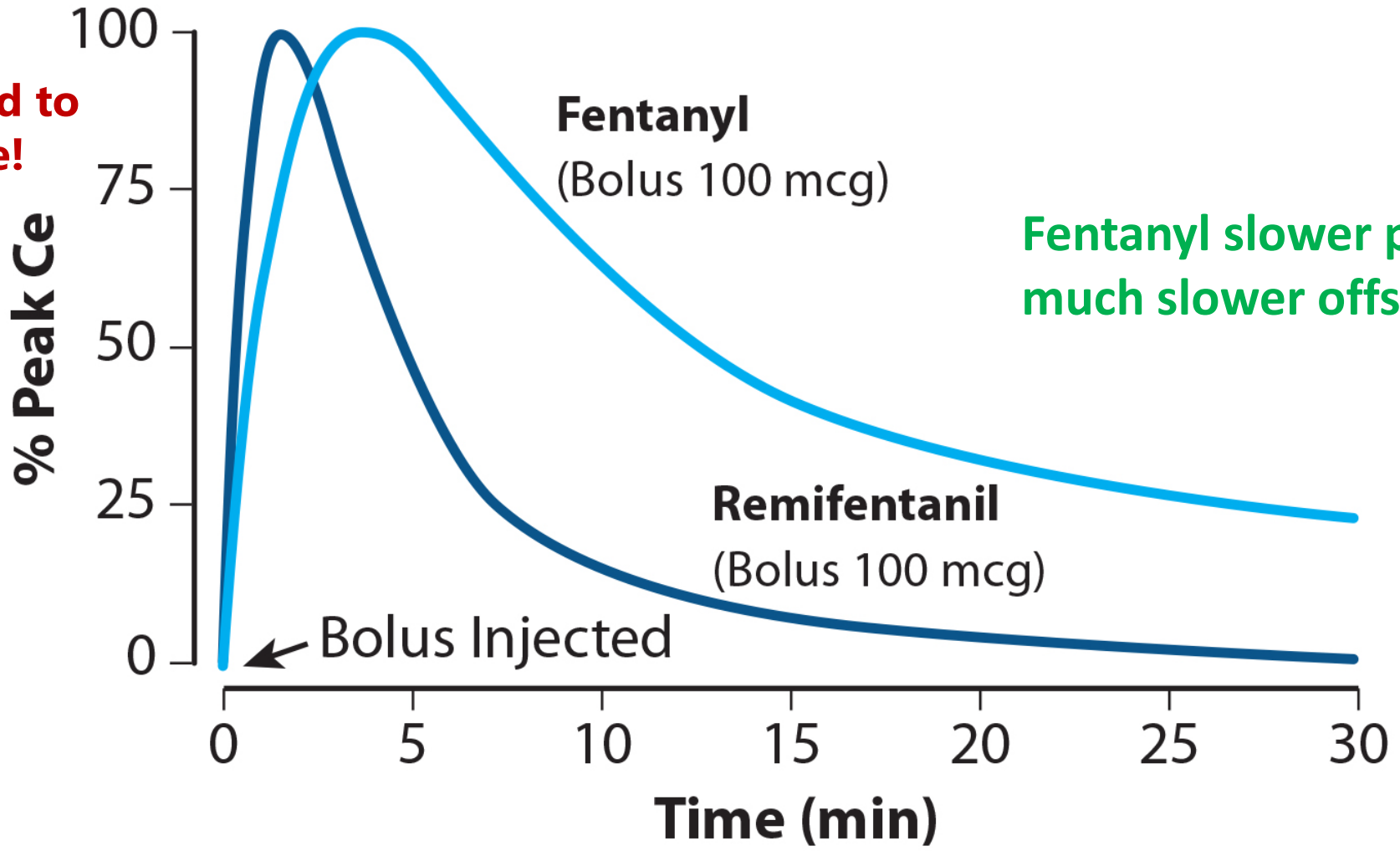
Key Point

Simulation of remifentanil and fentanyl pharmacokinetic behavior helps inform posological decisions in TIVA.

TAKE 5 FOR TIVA

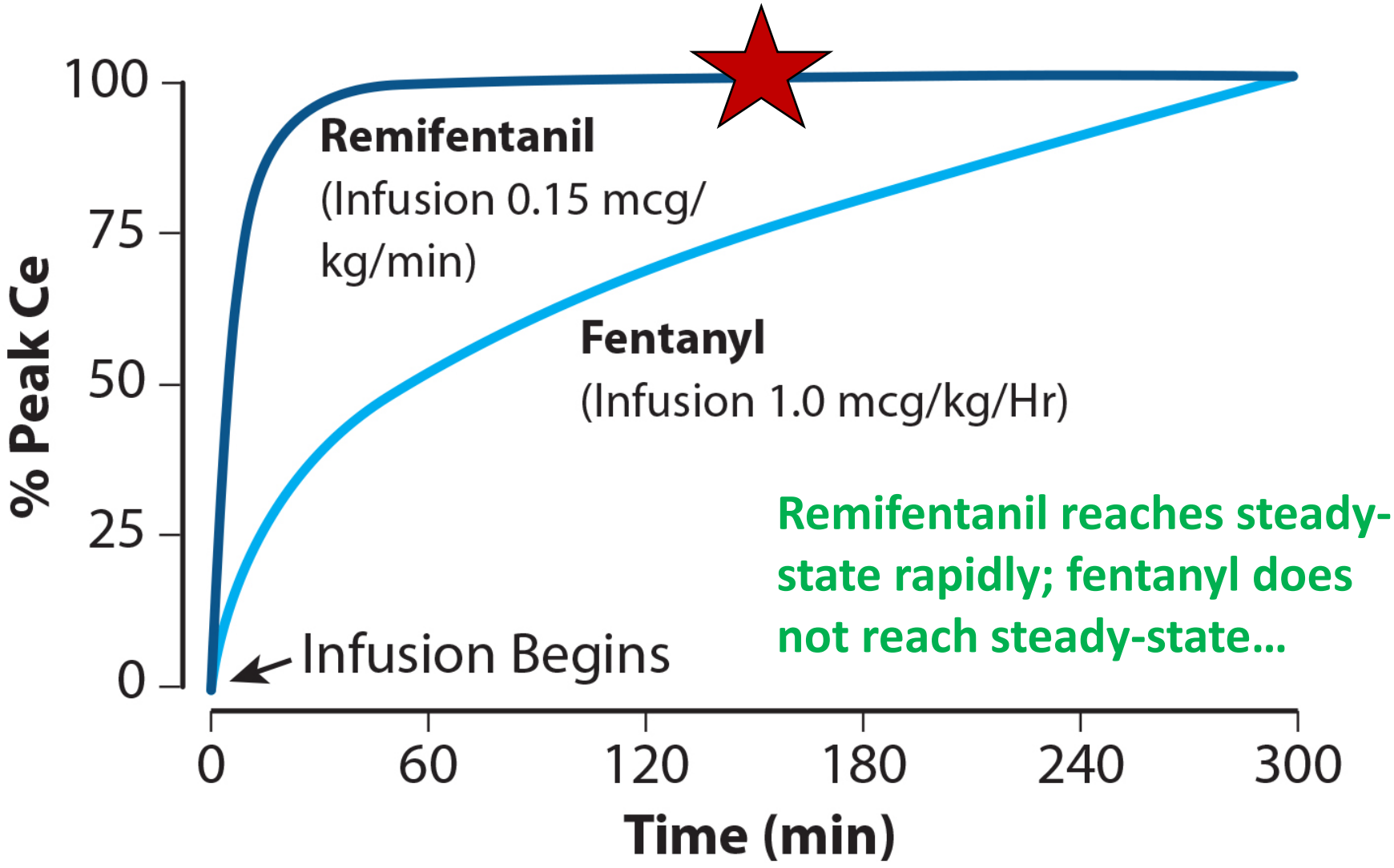
Bolus Front-End & Back-End

Normalized to peak Ce!



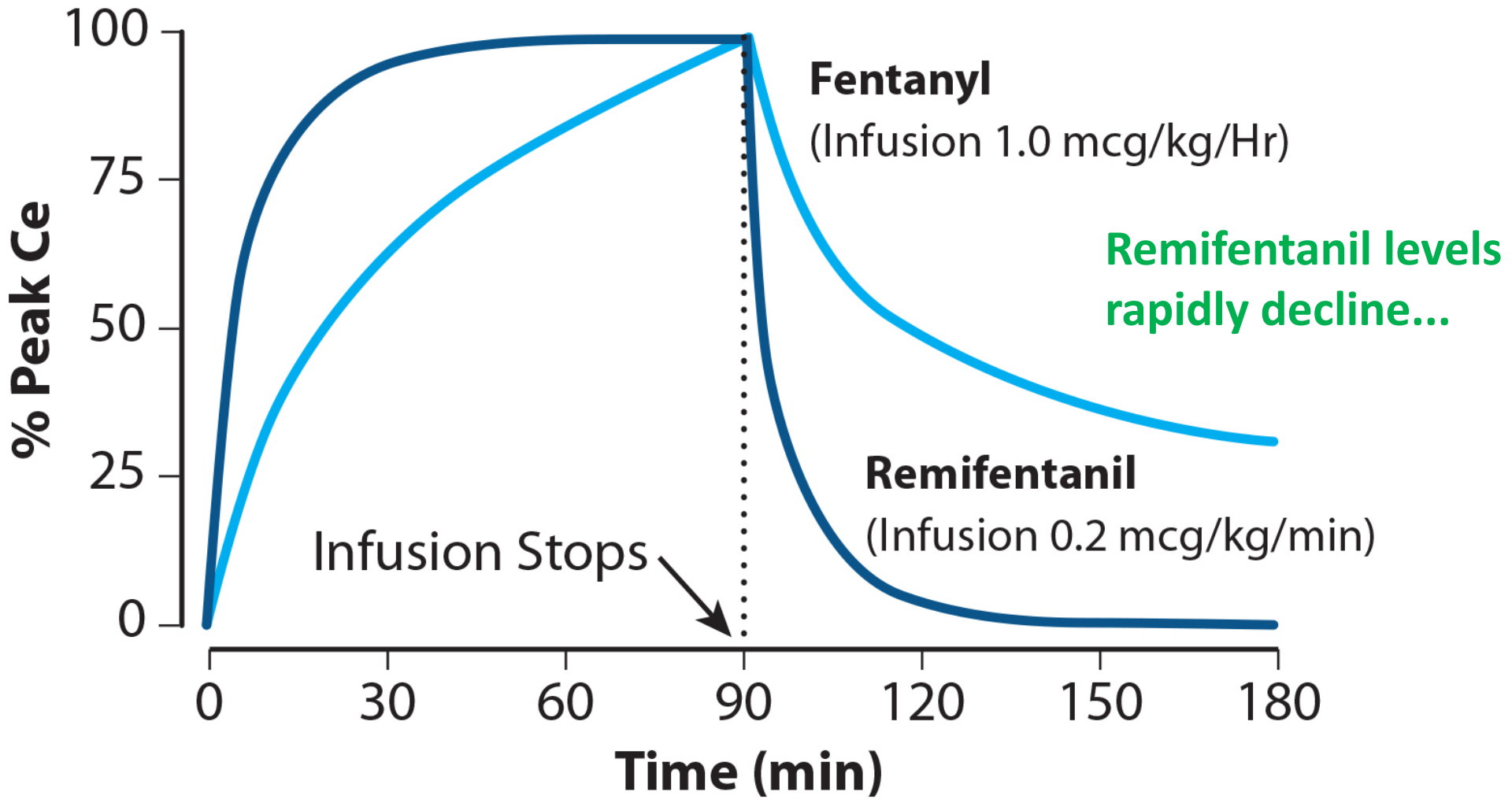
Fentanyl slower peak, much slower offset…

Infusion Front-End

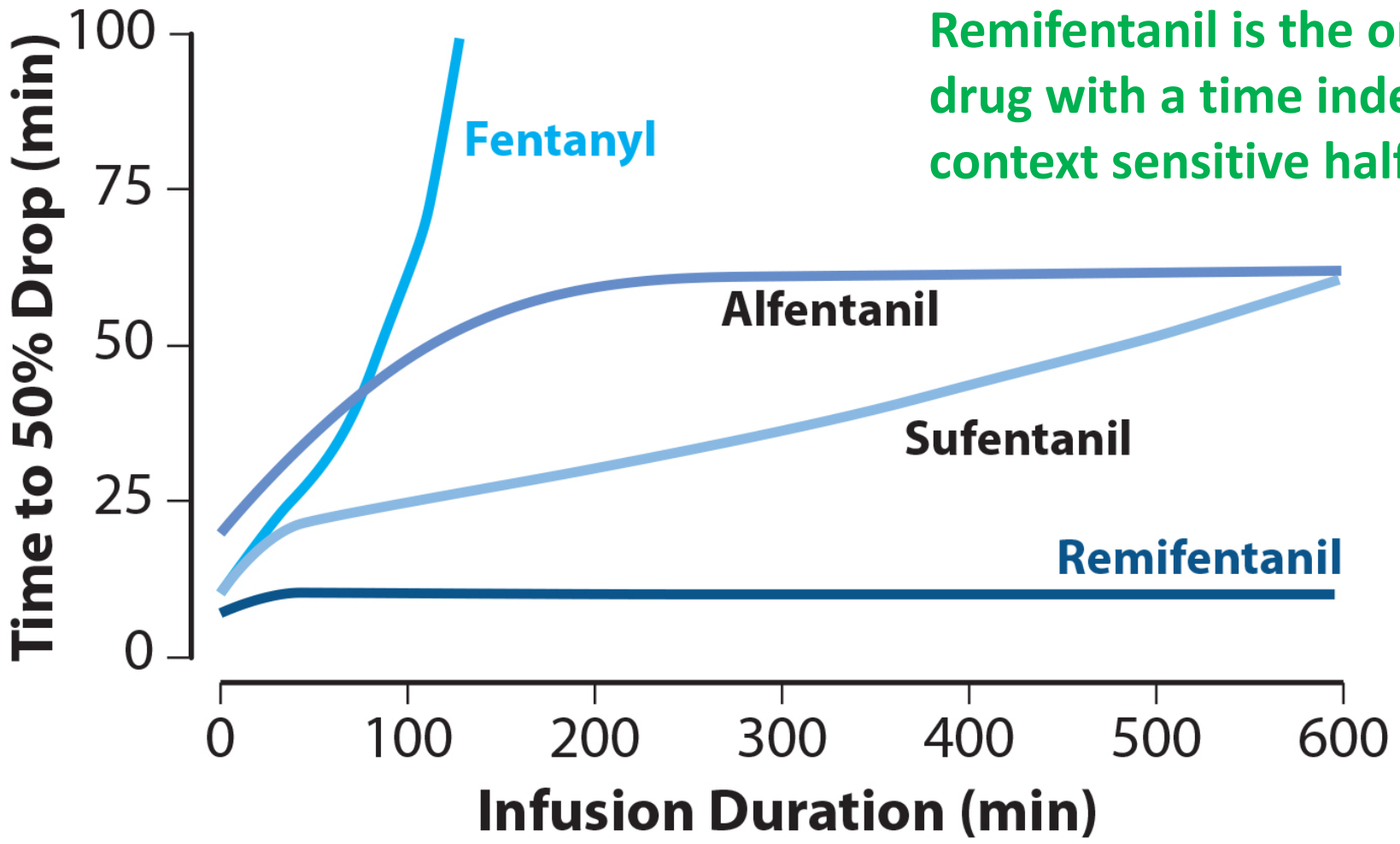


Remifentanil reaches steady-state rapidly; fentanyl does not reach steady-state…

Infusion Back-End



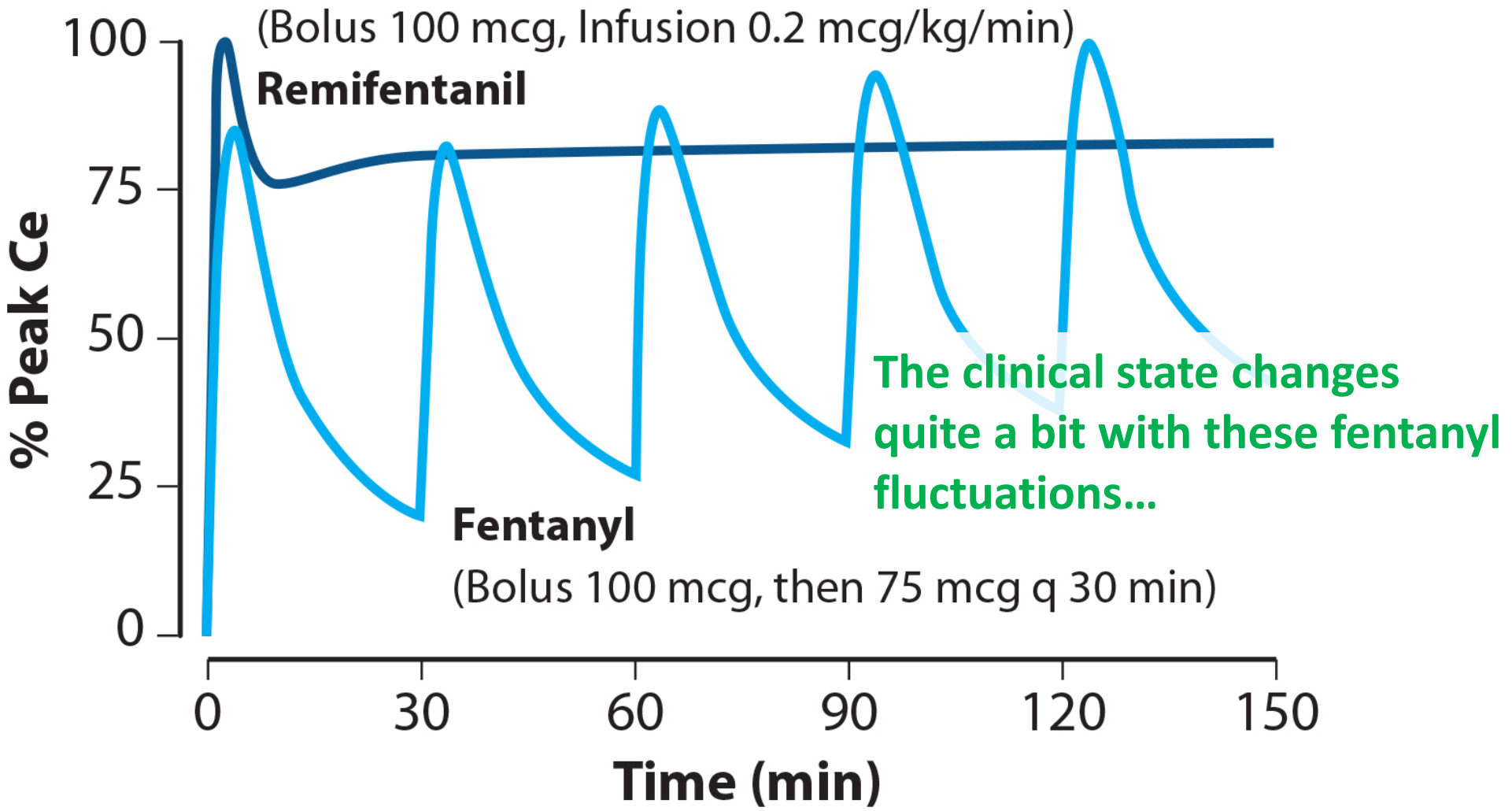
Context Sensitive Half-Time



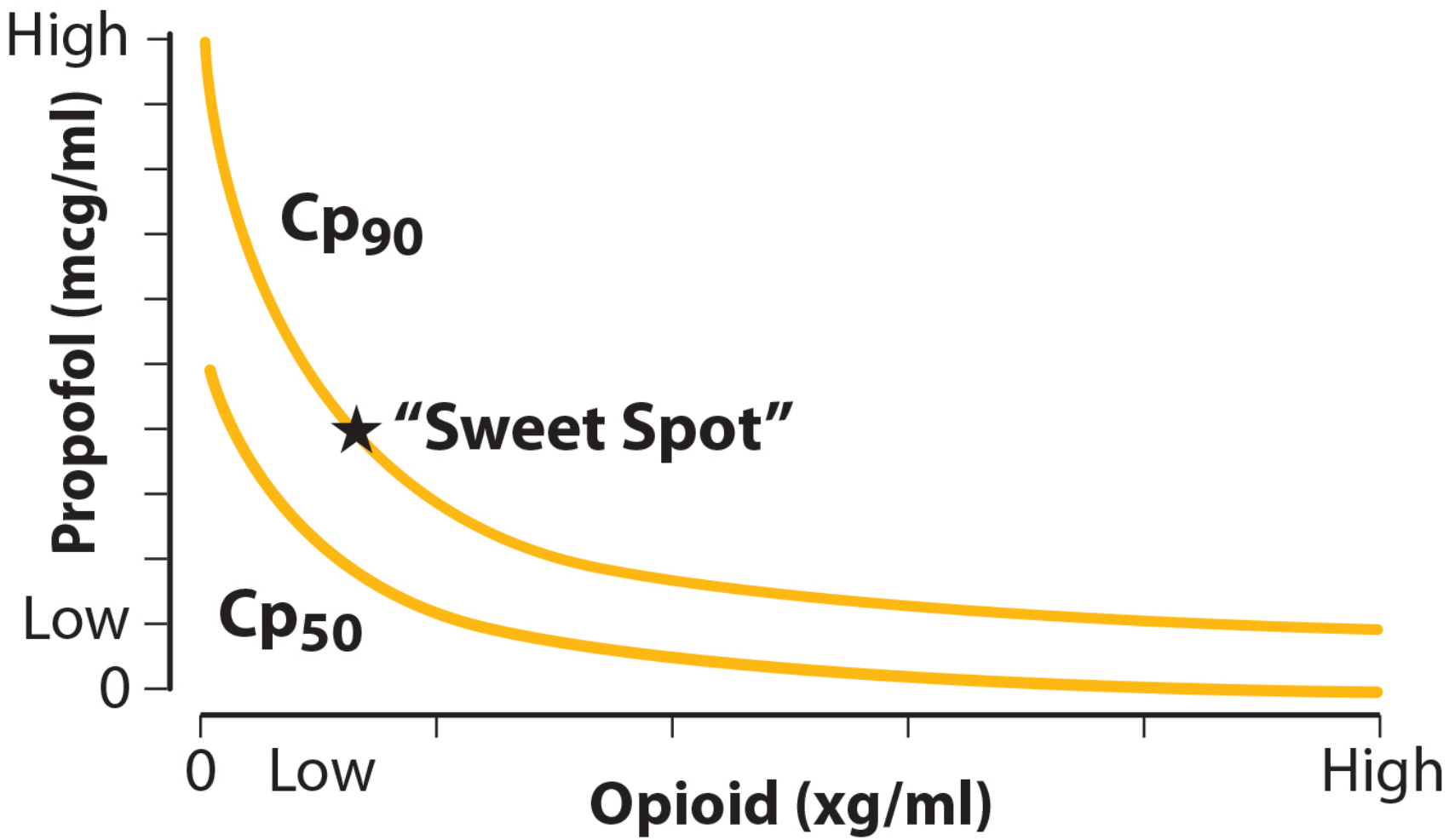
Remifentanil is the only TIVA drug with a time independent context sensitive half-time…

Egan *et al* (*Anesthesiology* 1993)

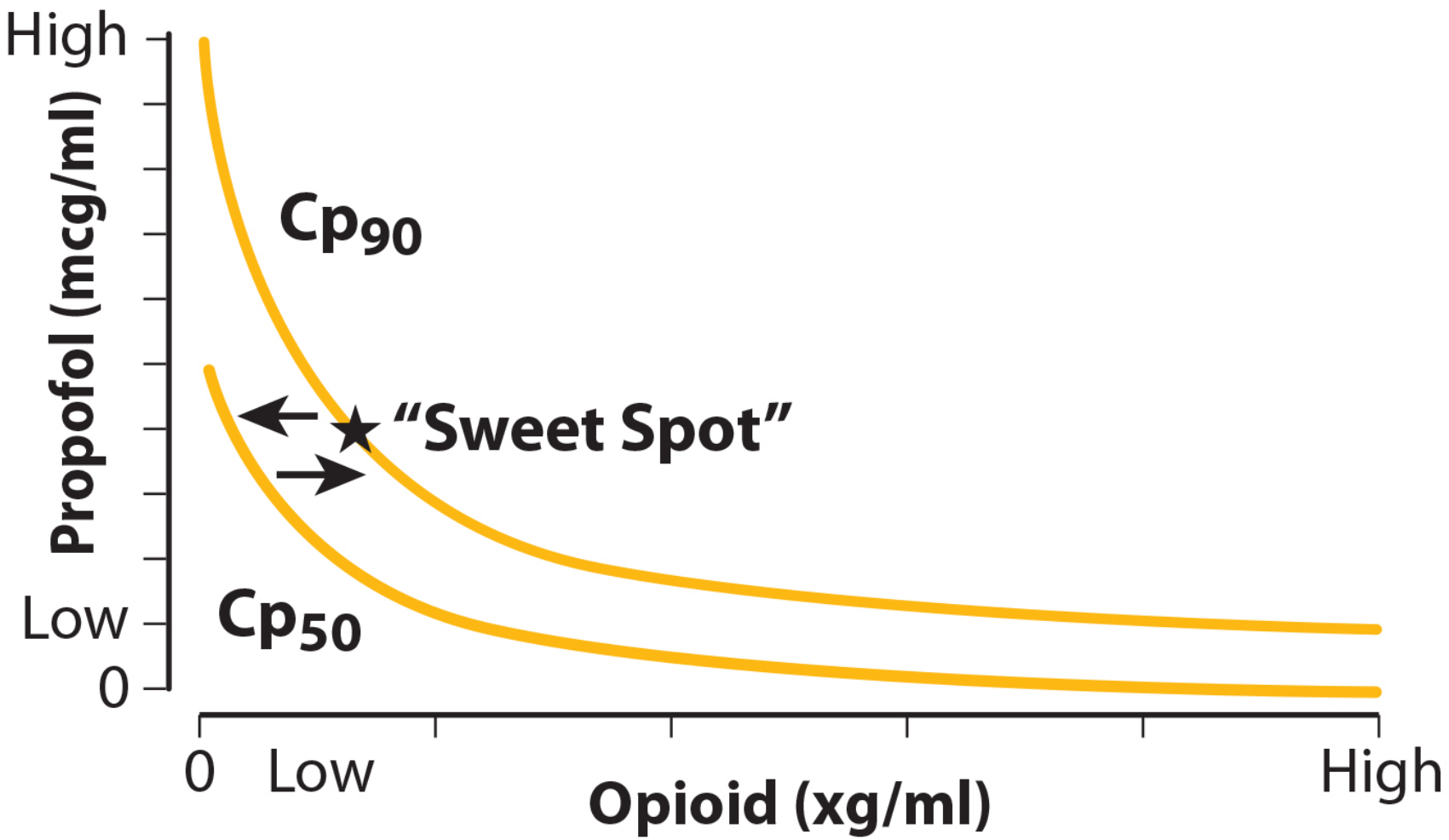
Impact of Infusion vs. Bolus



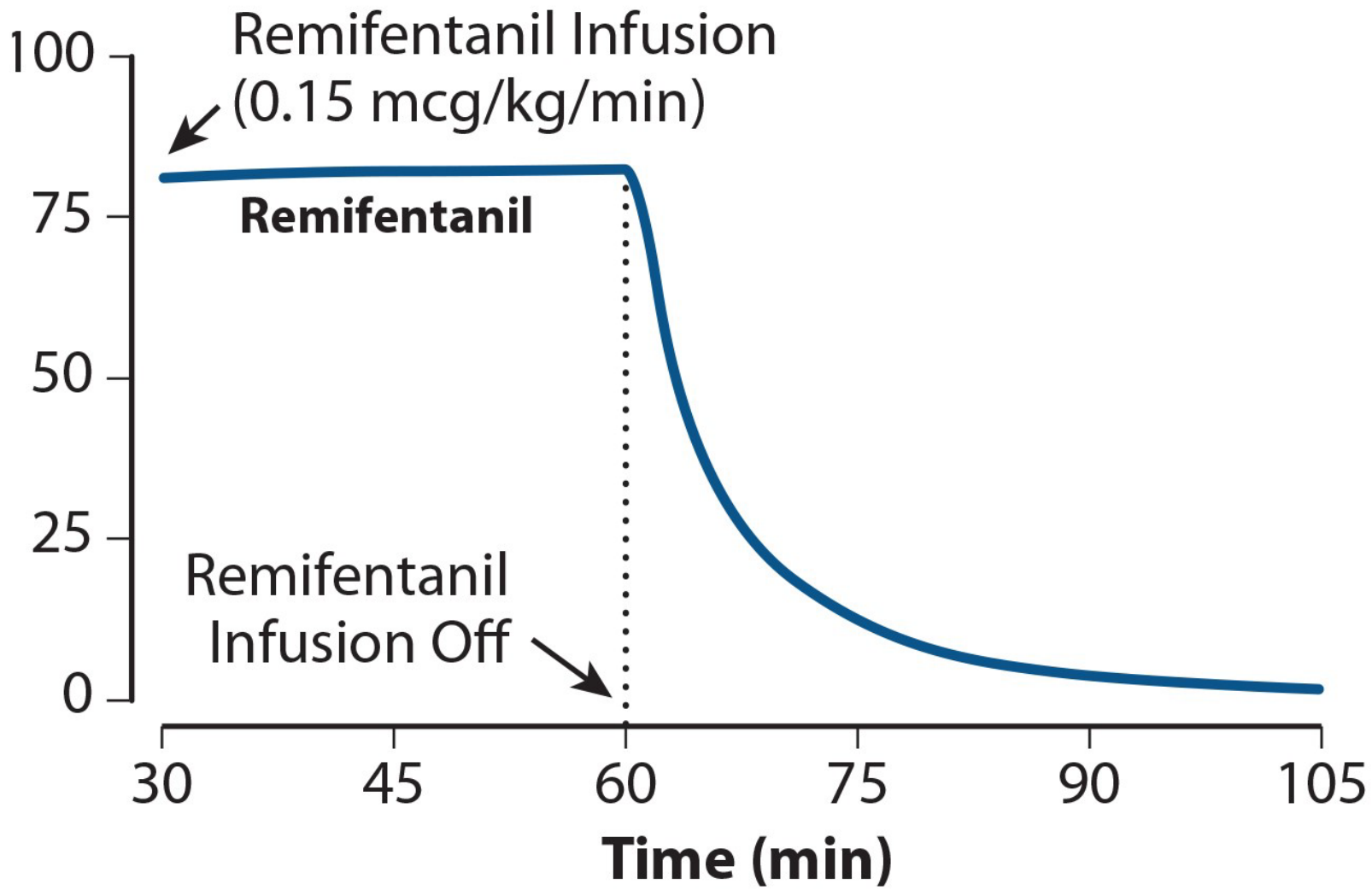
Disruptive Impact of Boluses



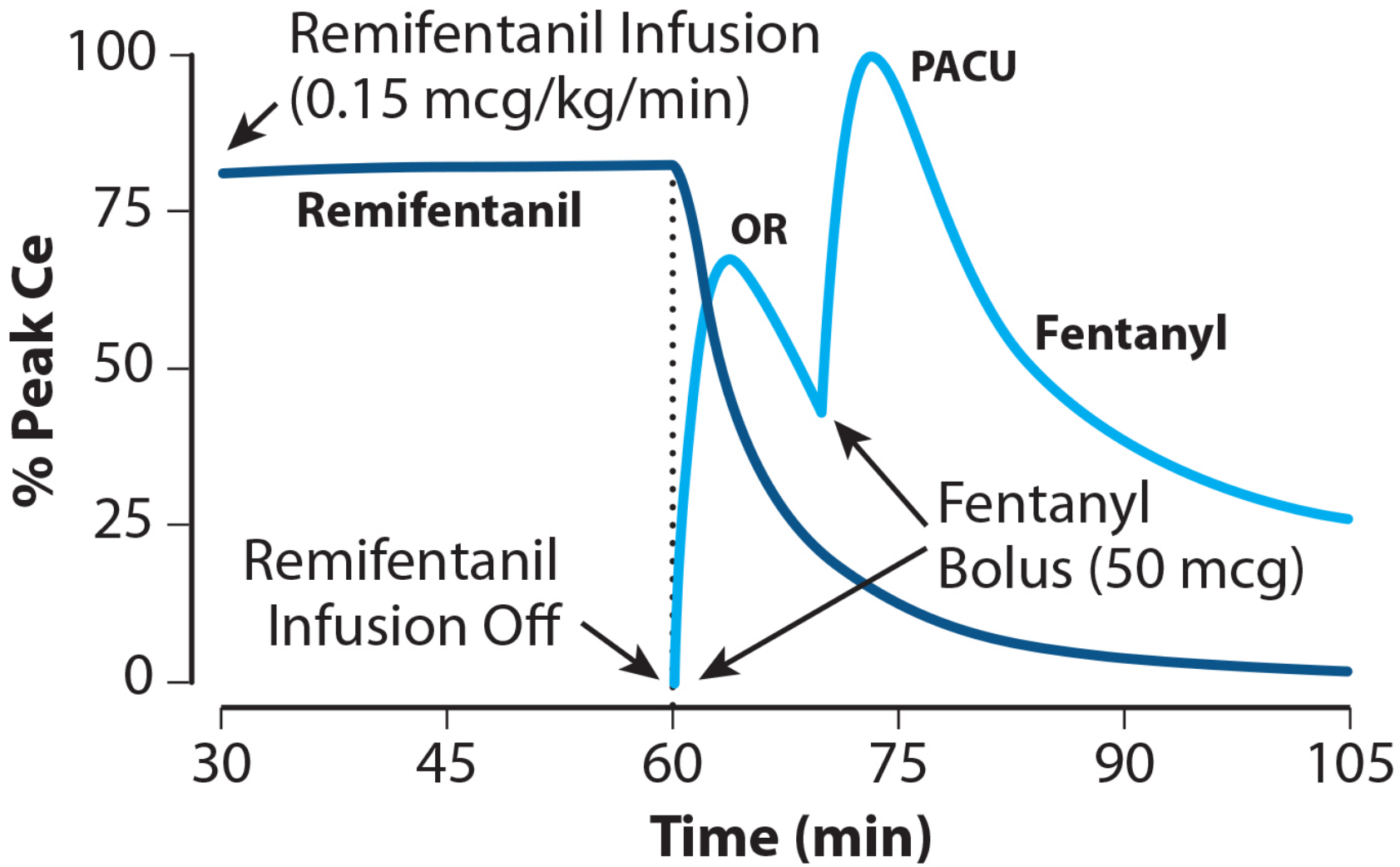
Disruptive Impact of Boluses



Transition Opioid



Transition Opioid

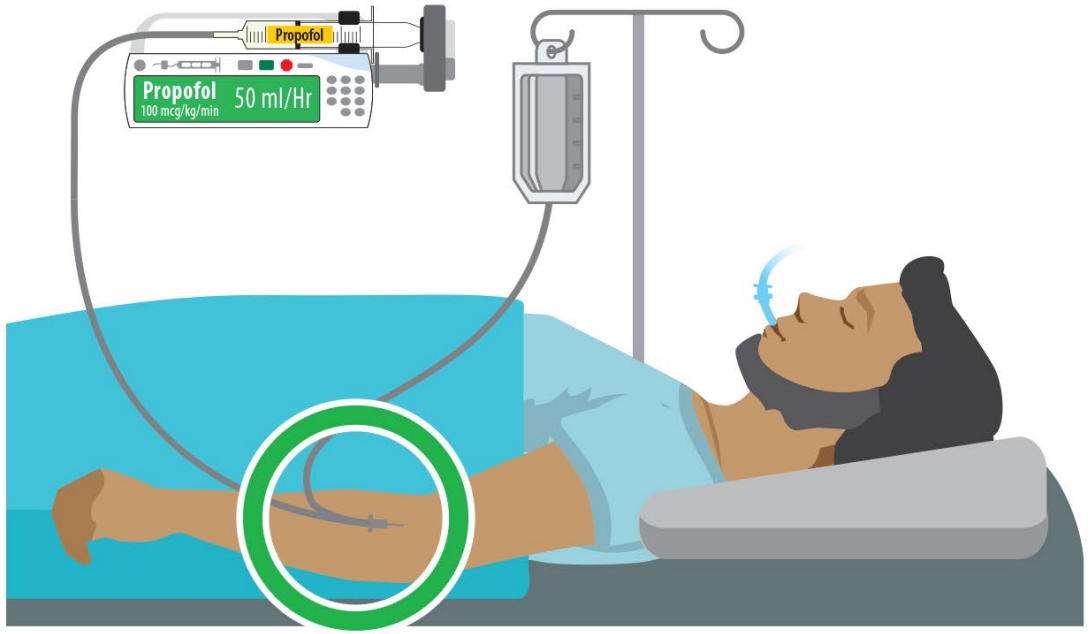


Key Point

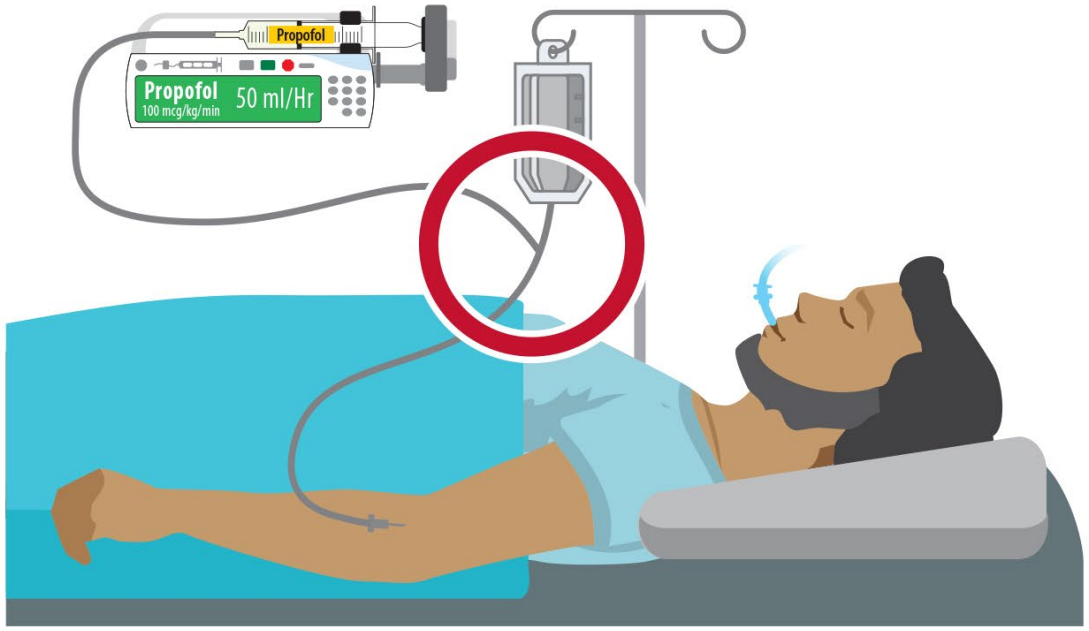
Certain practical tips are helpful for successful TIVA practice.

TAKE 5 FOR TIVA

Infuse Close and Secure



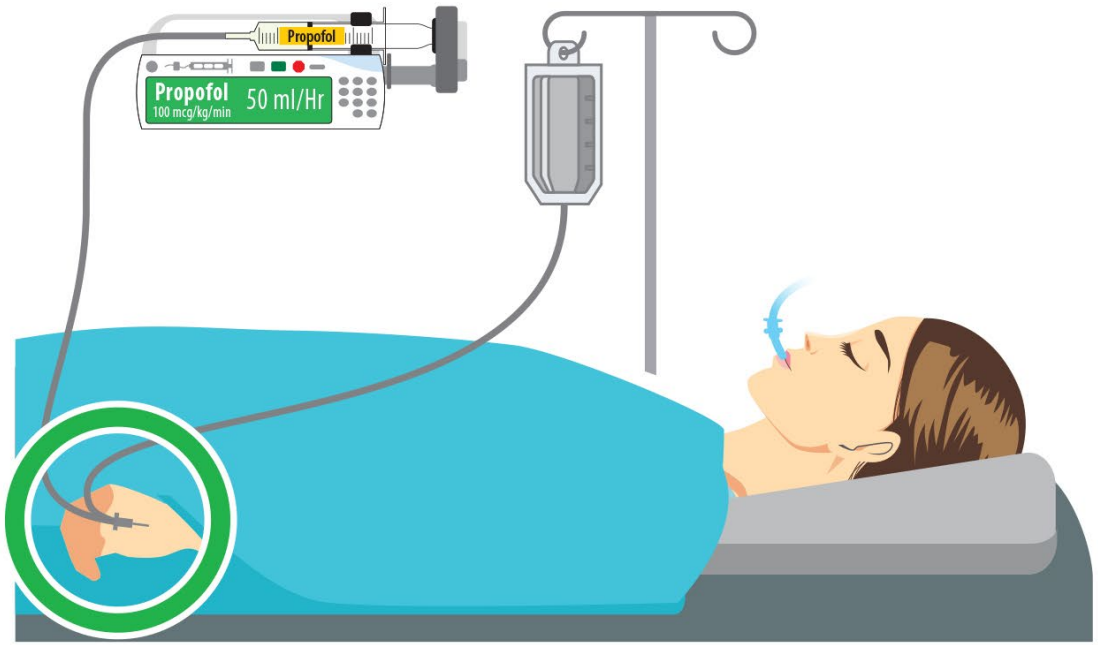
Infuse Close to IV



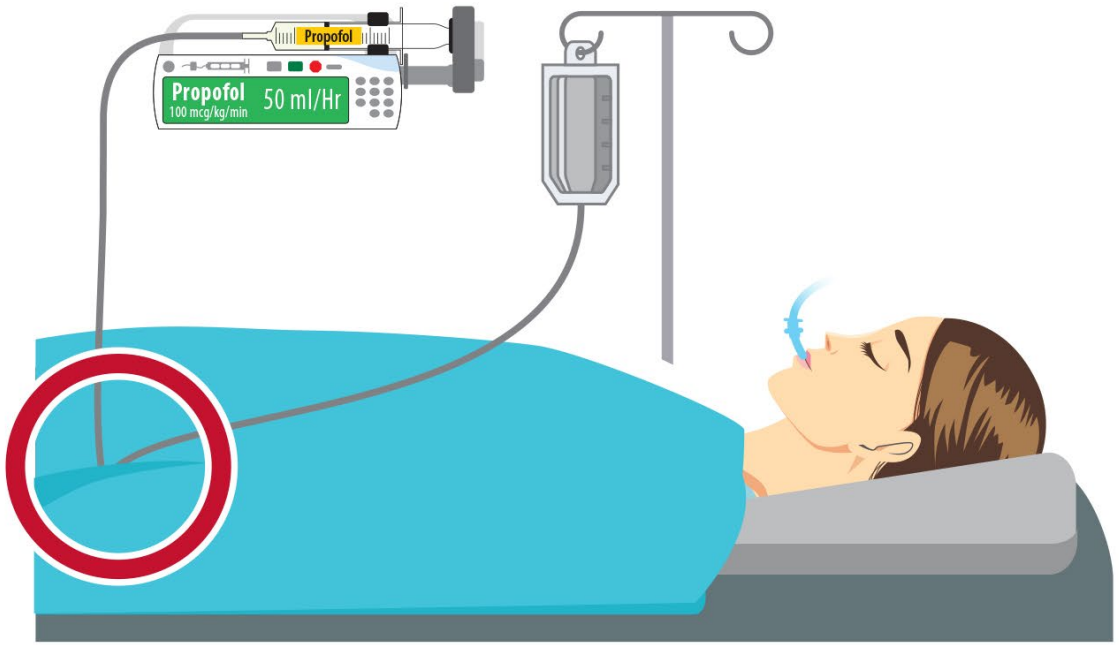
Do Not Infuse Far from IV

TAKE 5 FOR TIVA

Keep IV Visible



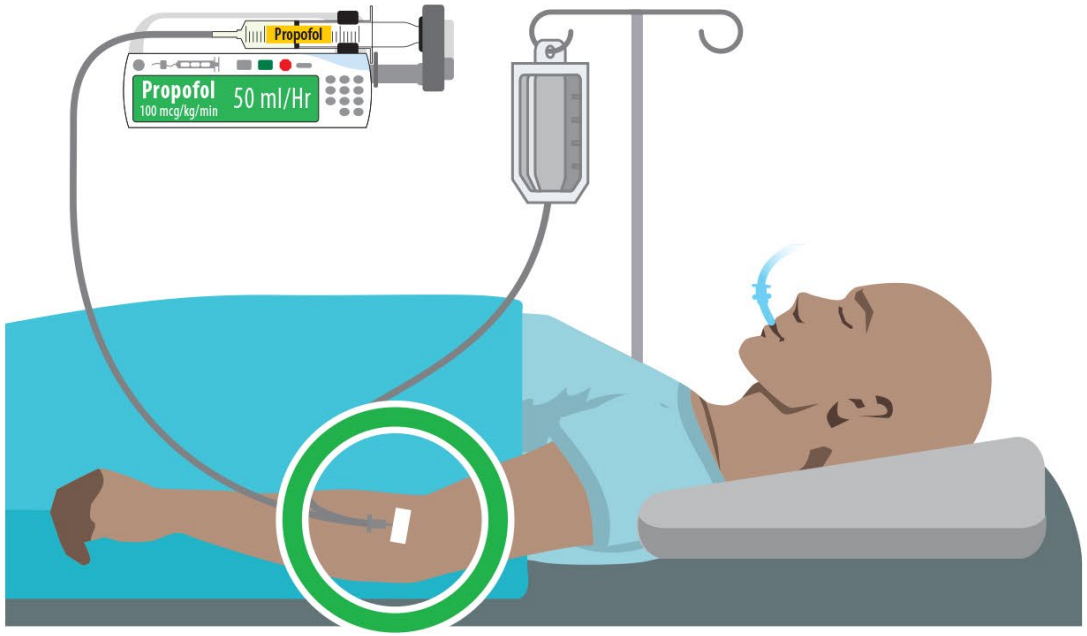
IV Visible: Optimal



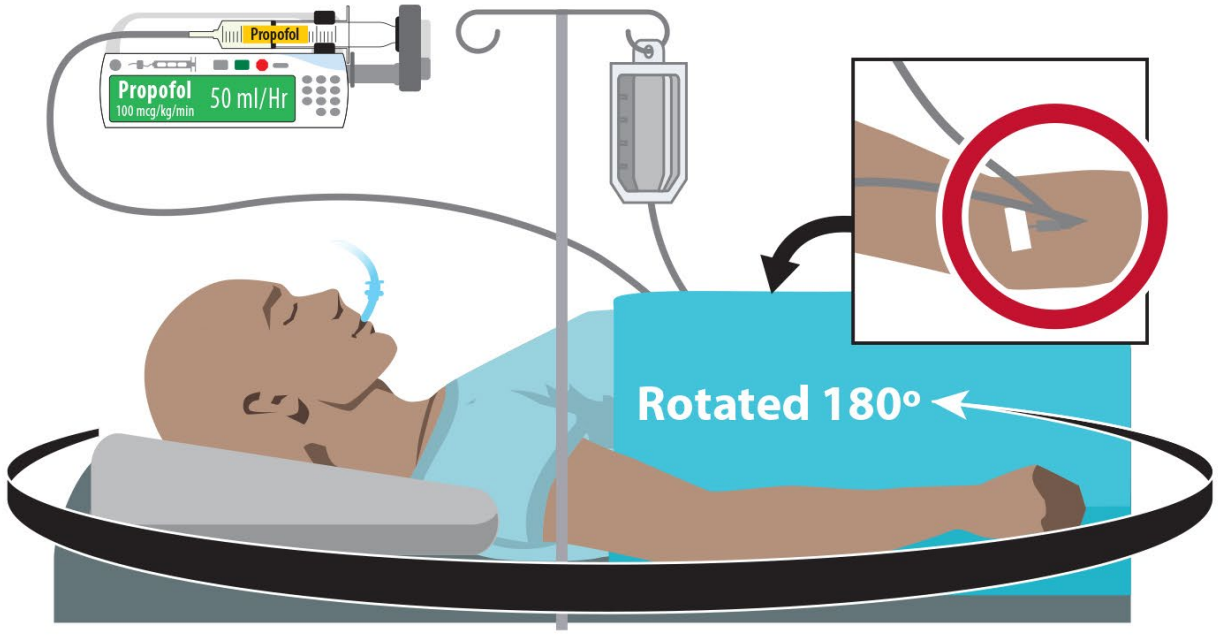
IV Not Visible: Suboptimal

TAKE 5 FOR TIVA

Be Alert for Infusion Disruption



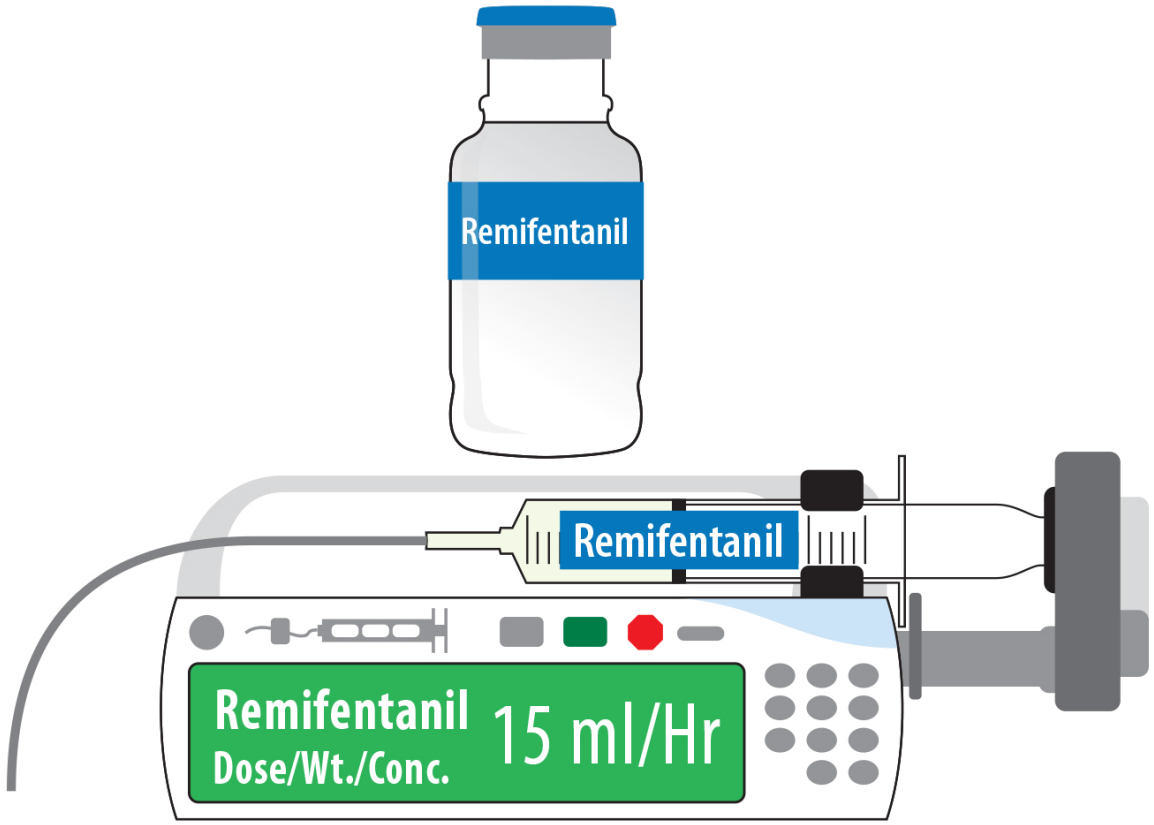
IV Flowing



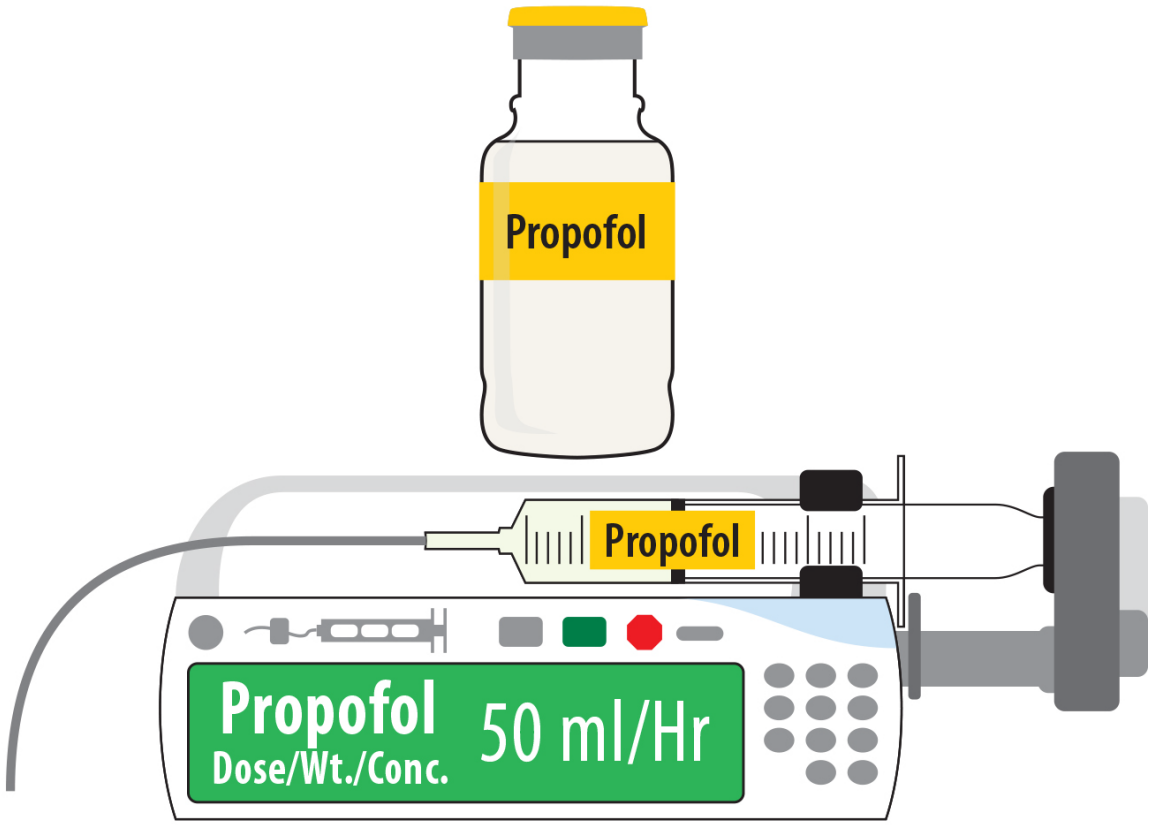
IV Kinked, **Not** Flowing

TAKE 5 FOR TIVA

Check for Pump Programming Error

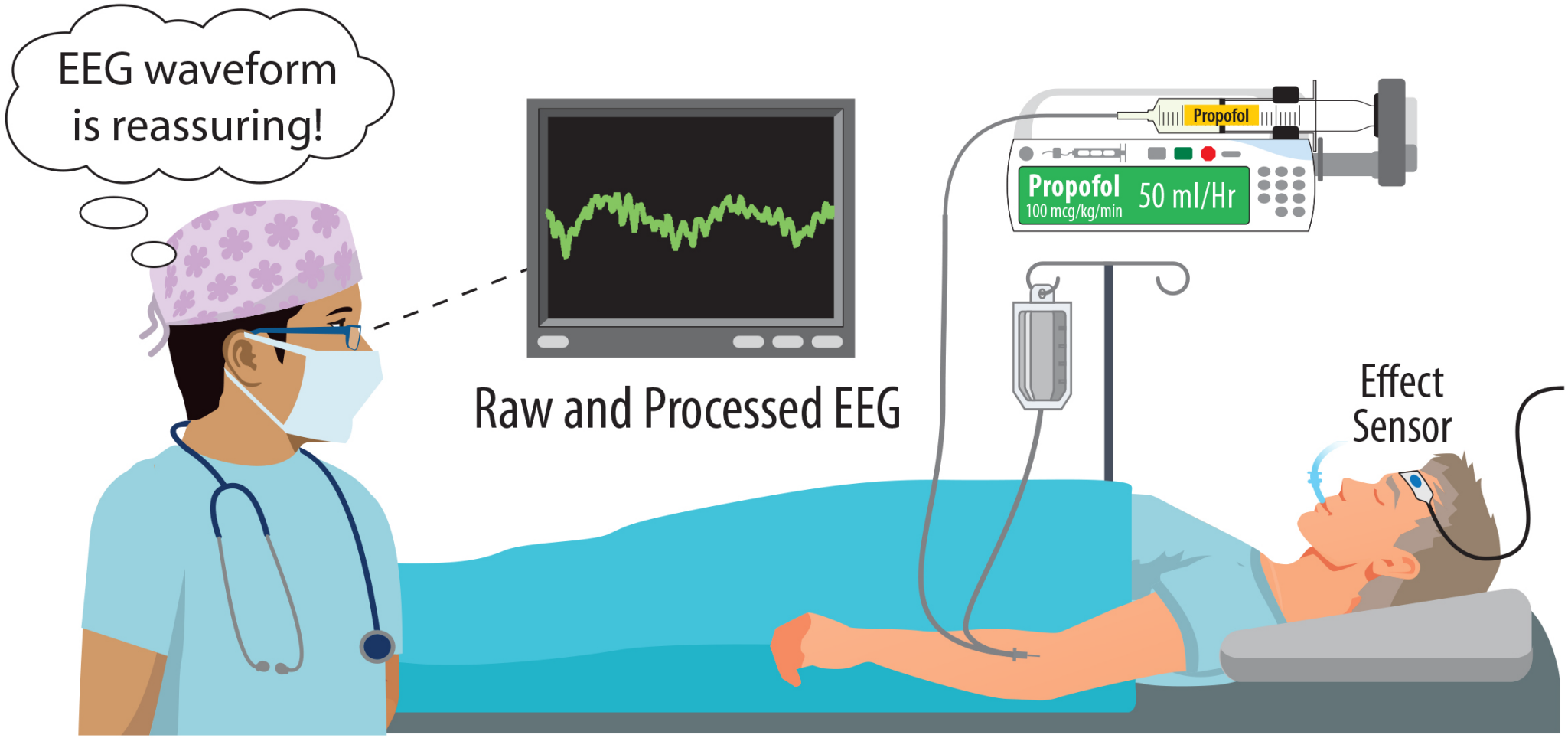


Typical Rate = 10-20 ml/Hr



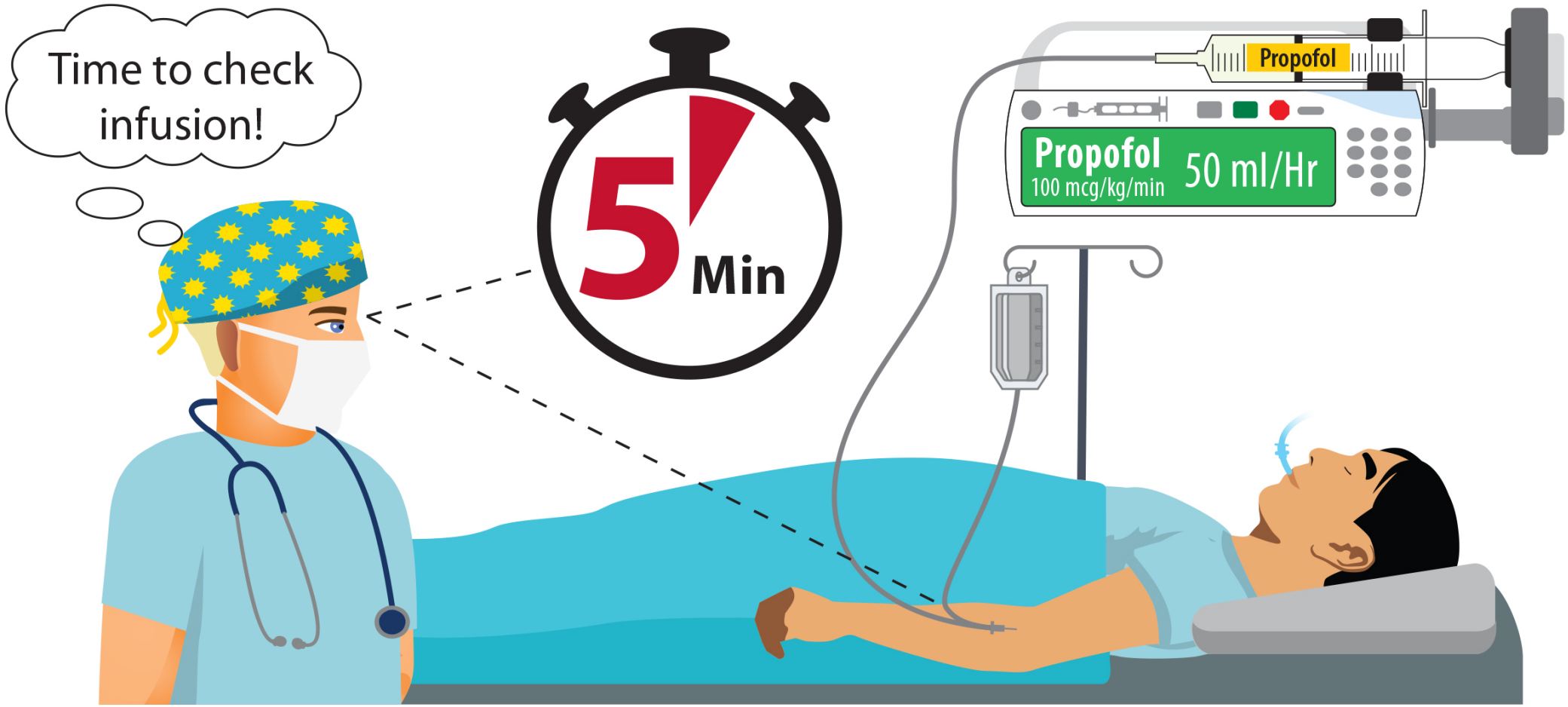
Typical Rate = 40-60 ml/Hr

Consider Using EEG



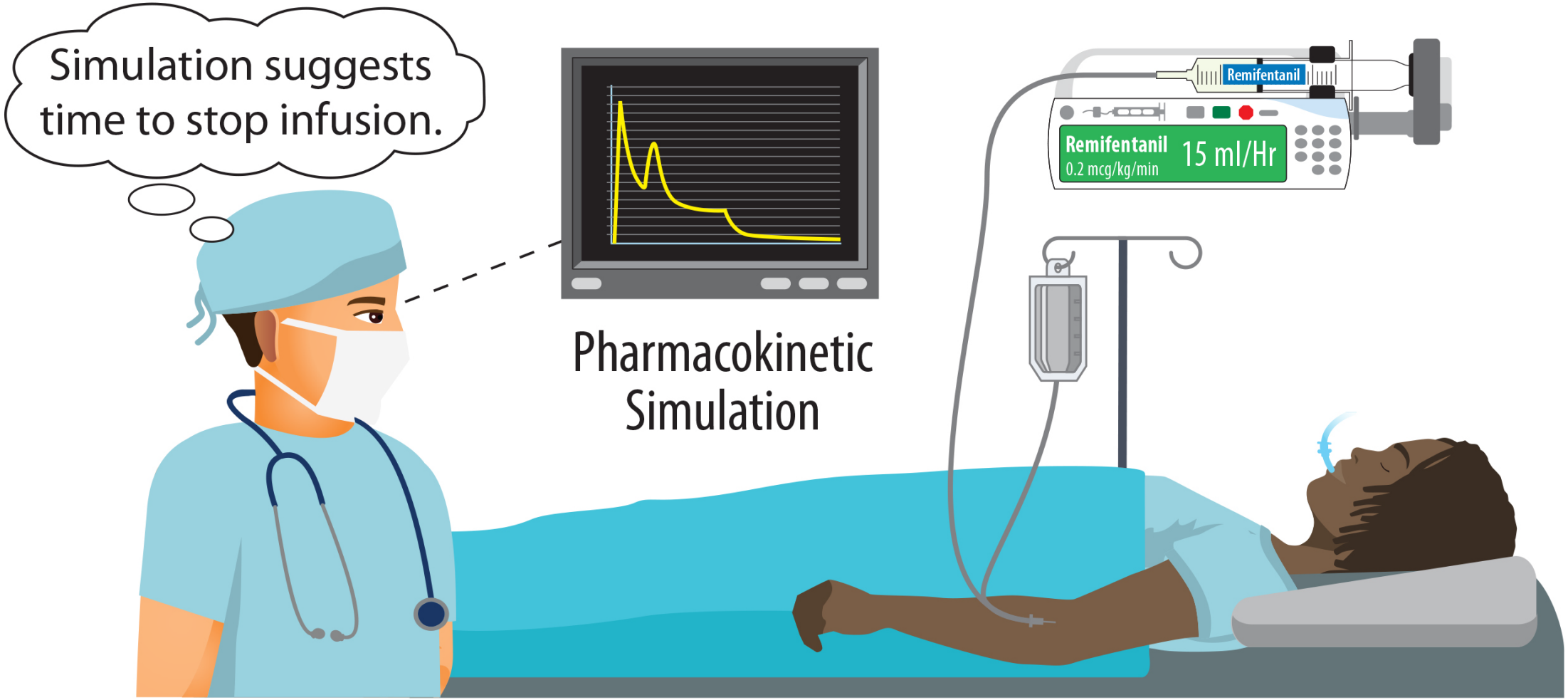
TAKE 5 FOR TIVA

Check Infusions Frequently



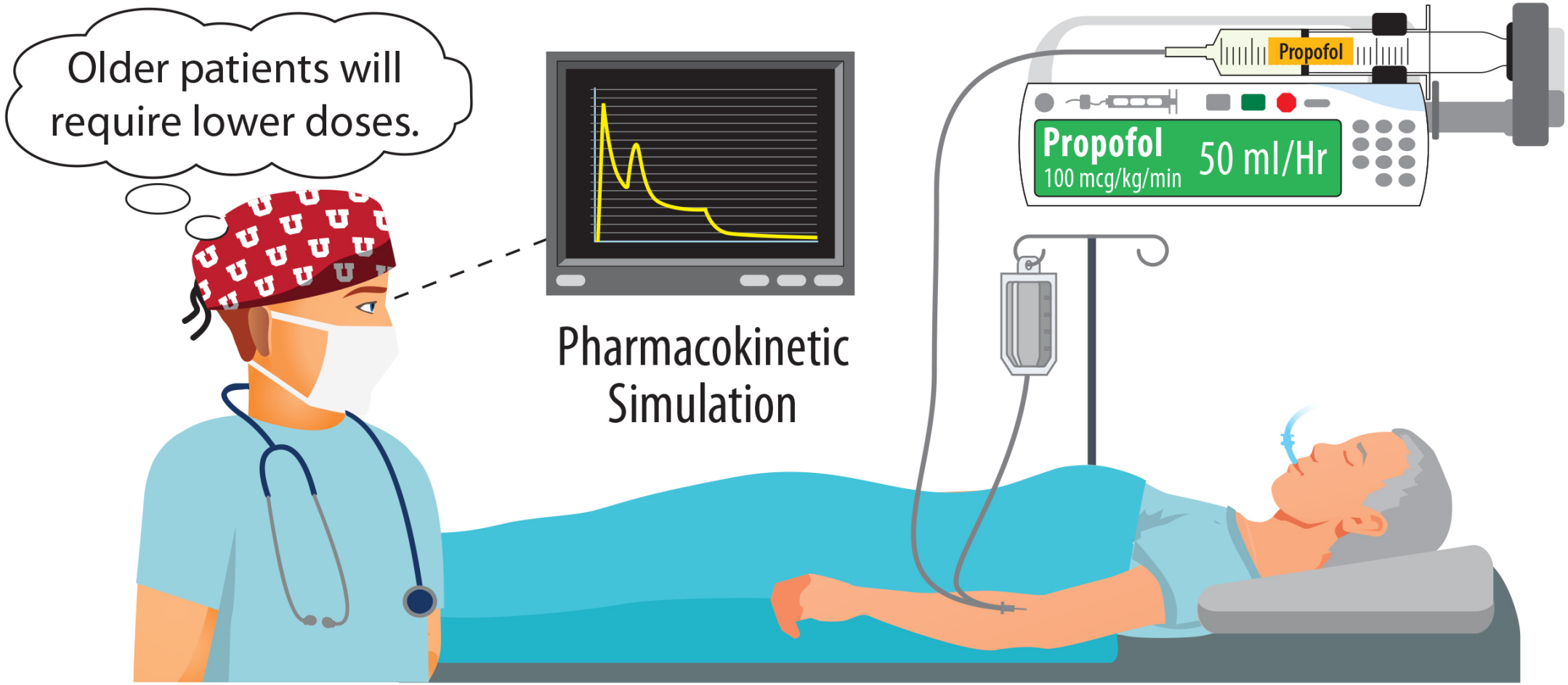
TAKE 5 FOR TIVA

Consider Real Time PK/PD Simulation

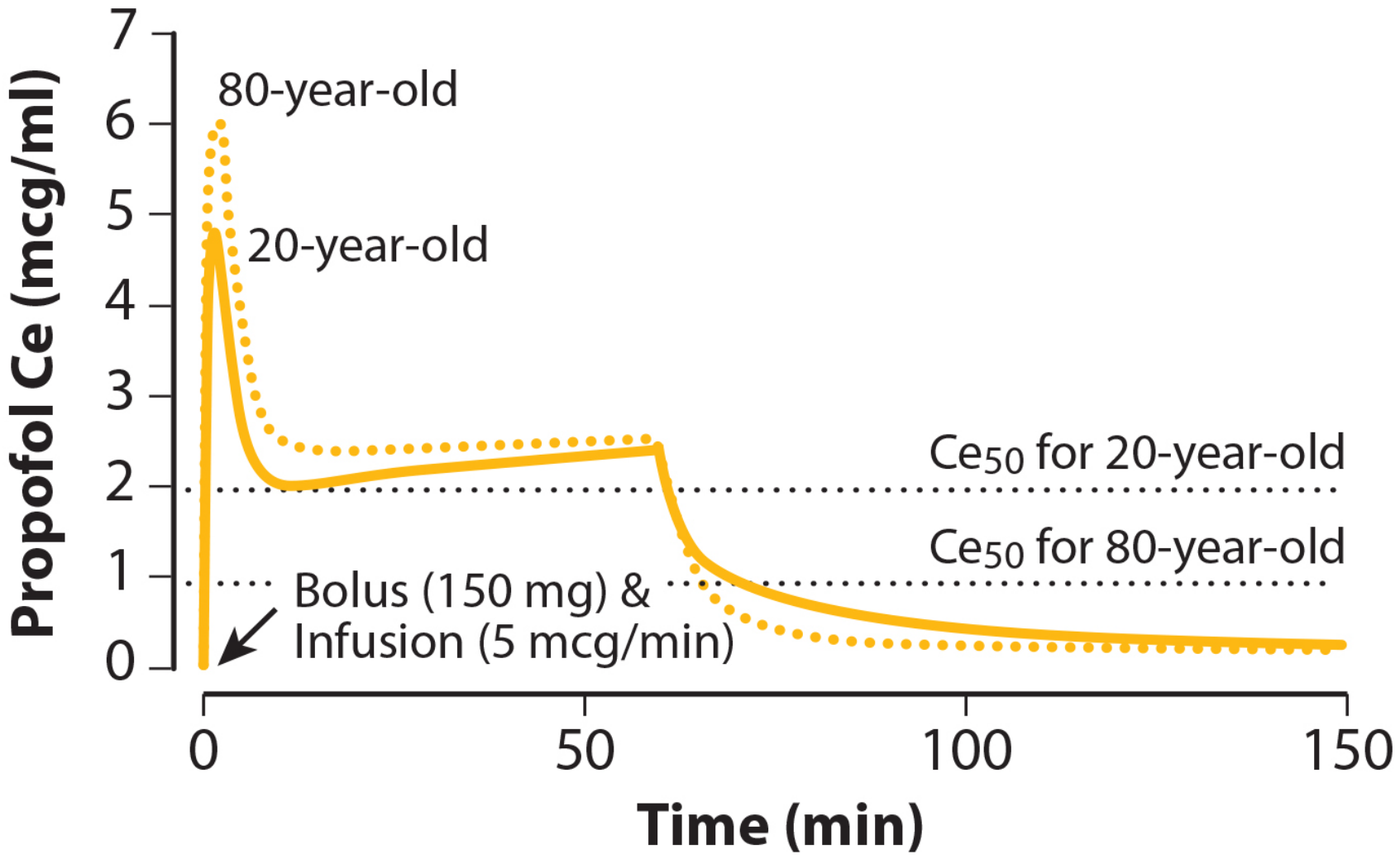


TAKE 5 FOR TIVA

Adjust Dose for Senior Patients

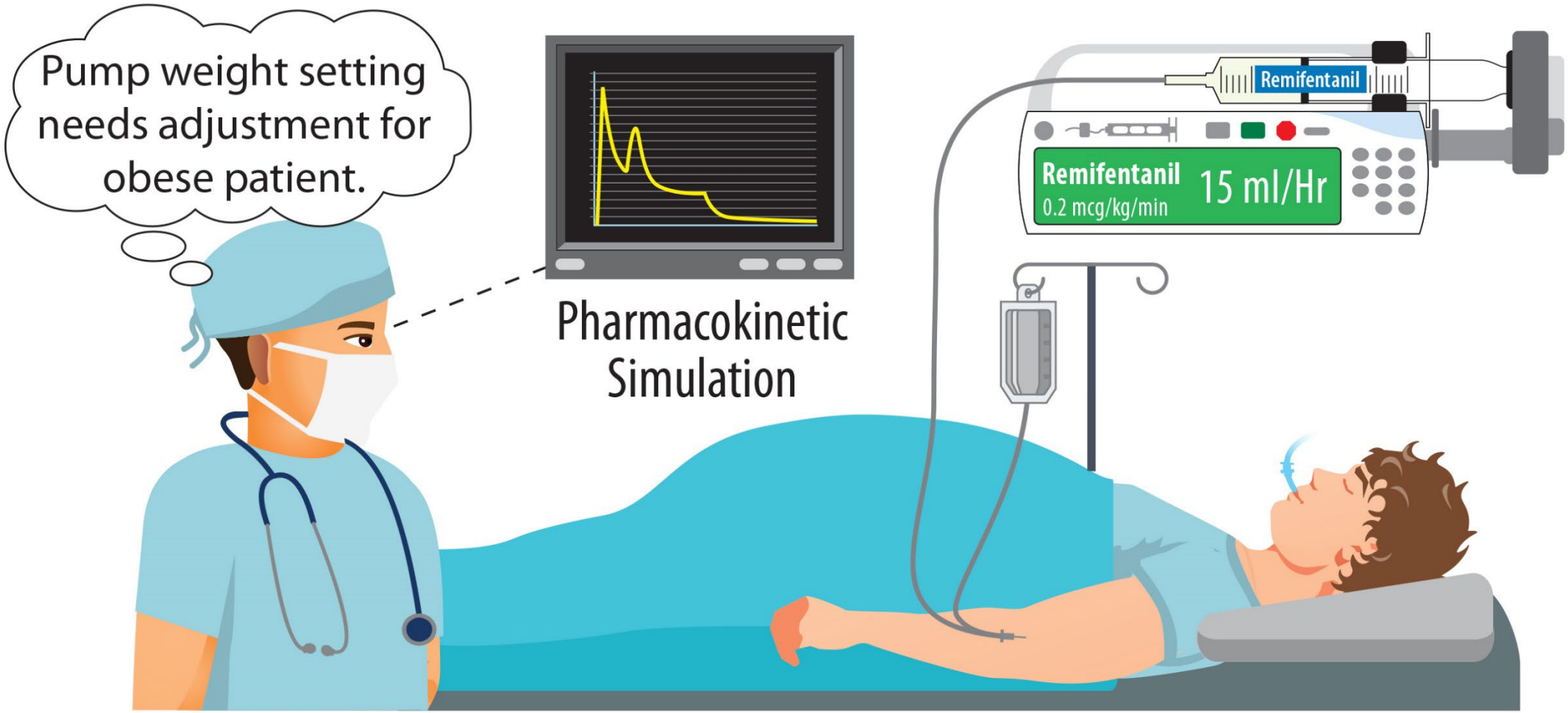


Impact of Age



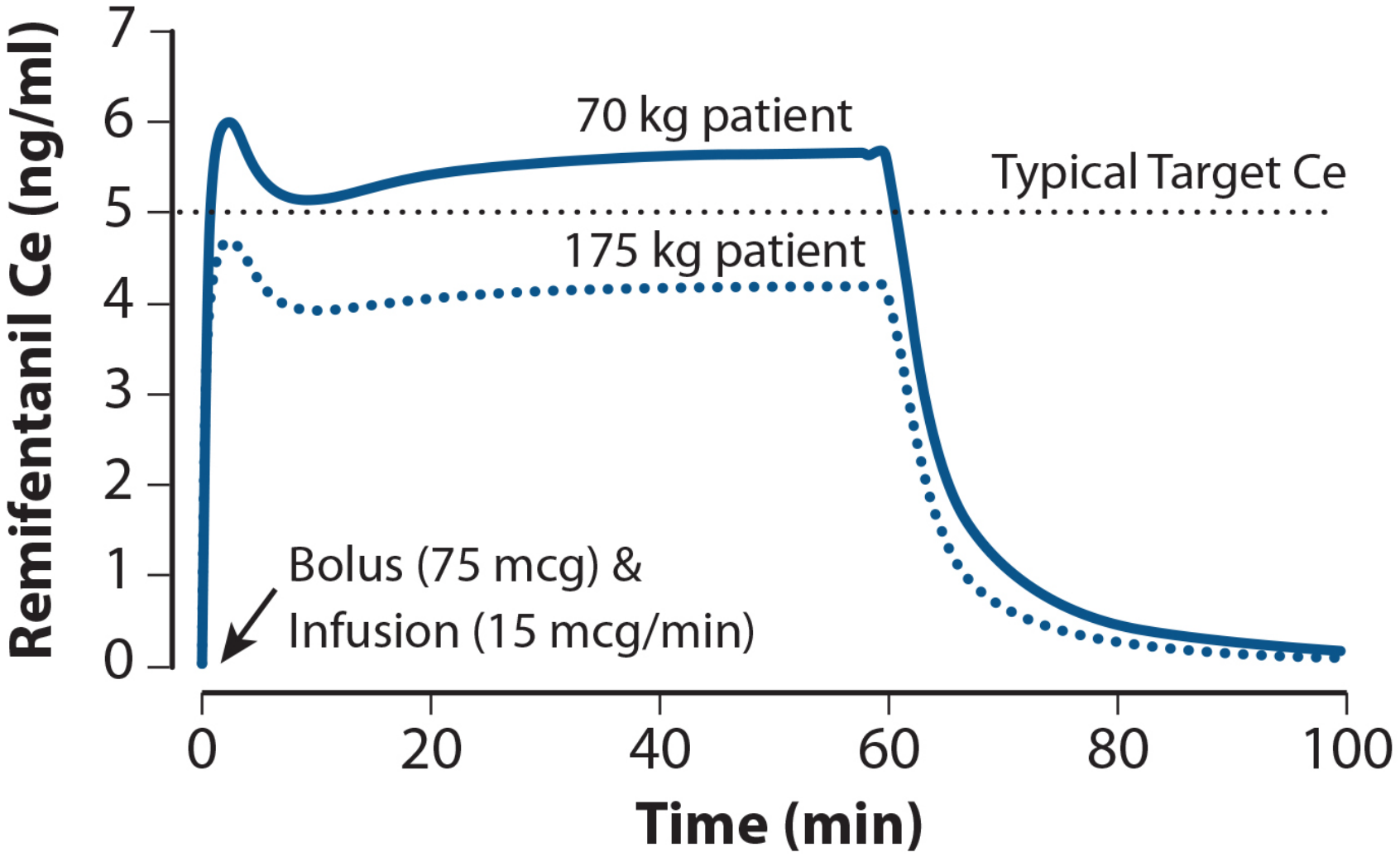
Obara & Egan (in Hemmings & Egan, Elsevier 2019)

Adjust Pump Weight Setting for Obese Patients



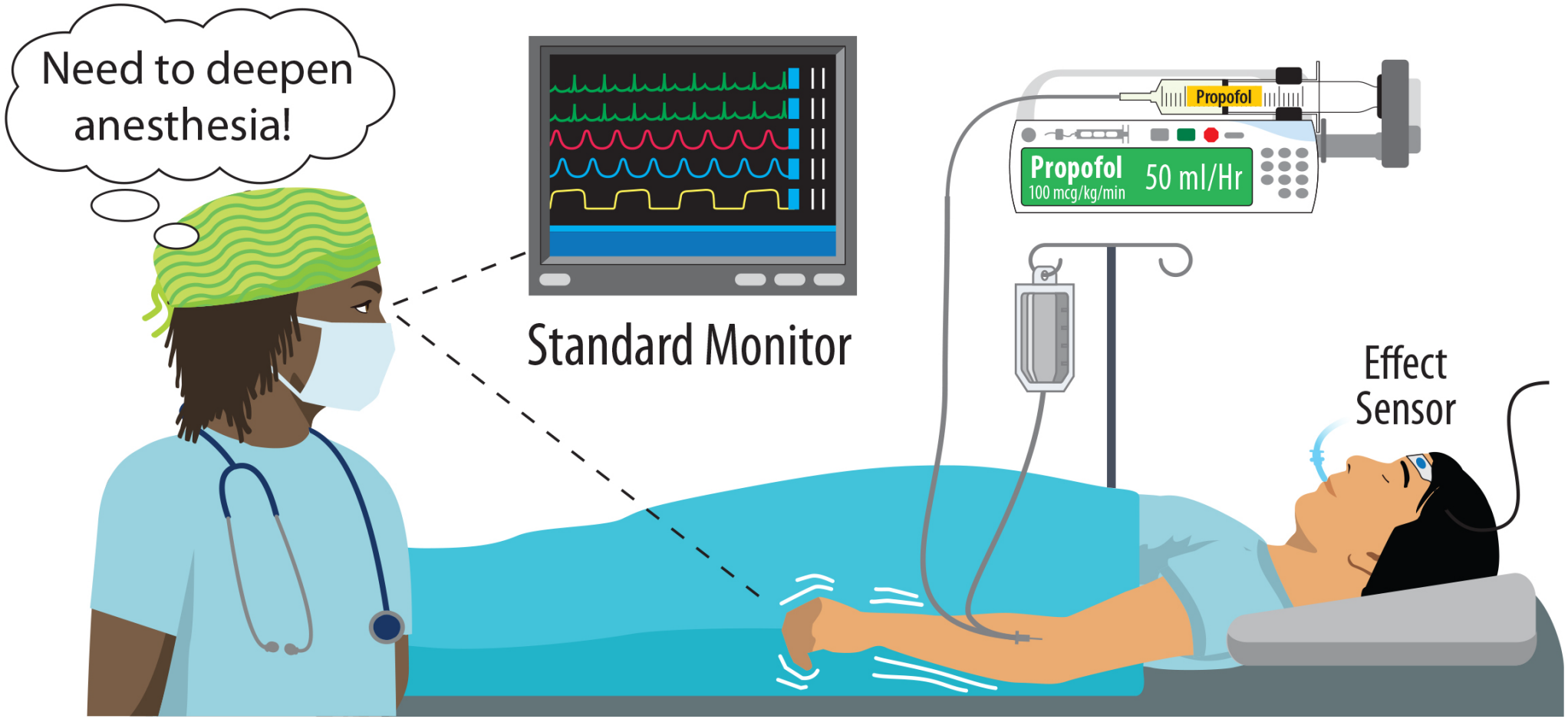
TAKE 5 FOR TIVA

Impact of Body Weight



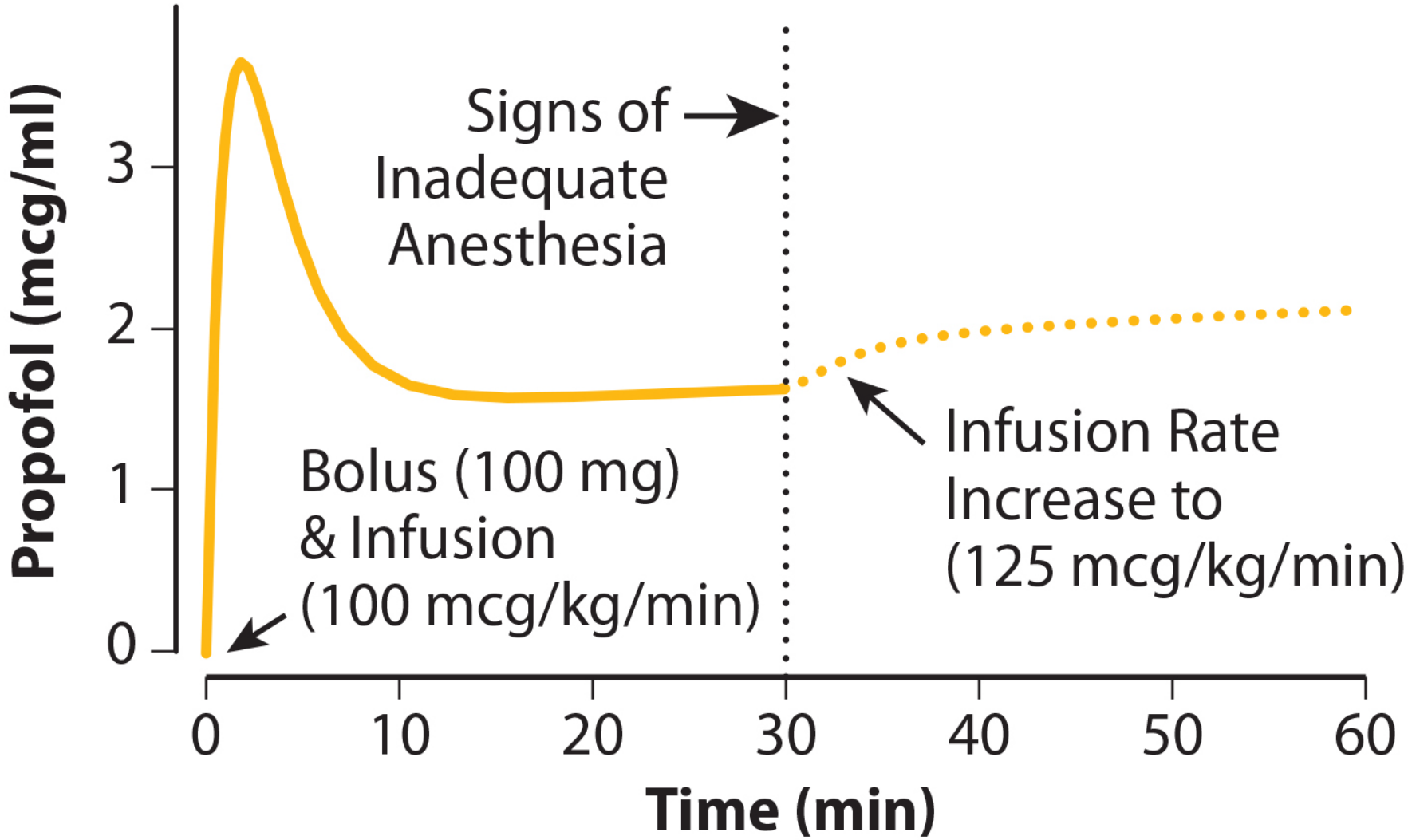
Obara & Egan (in Hemmings & Egan, Elsevier 2019)

Deepen Anesthesia with Small Bolus and Infusion Rate Increase

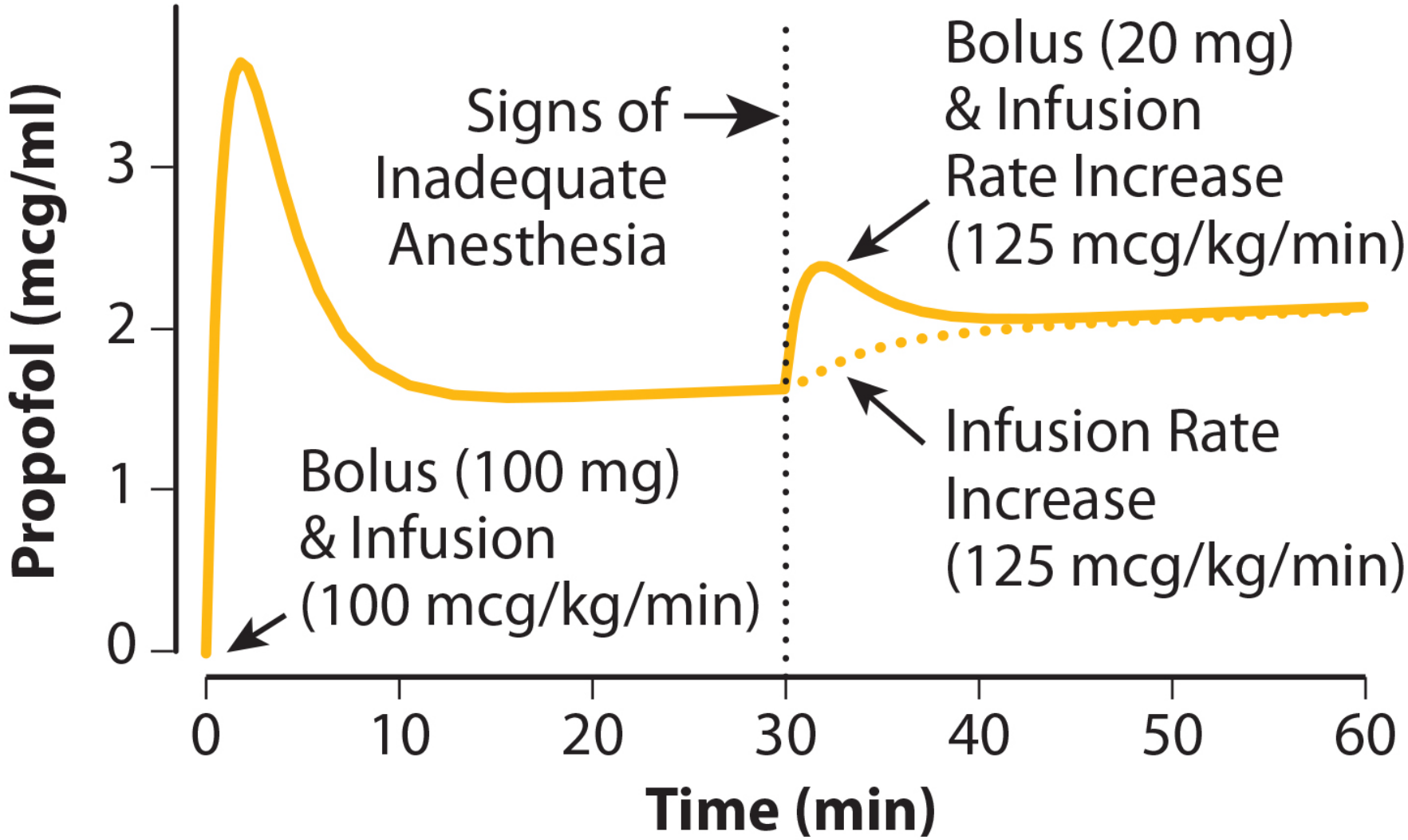


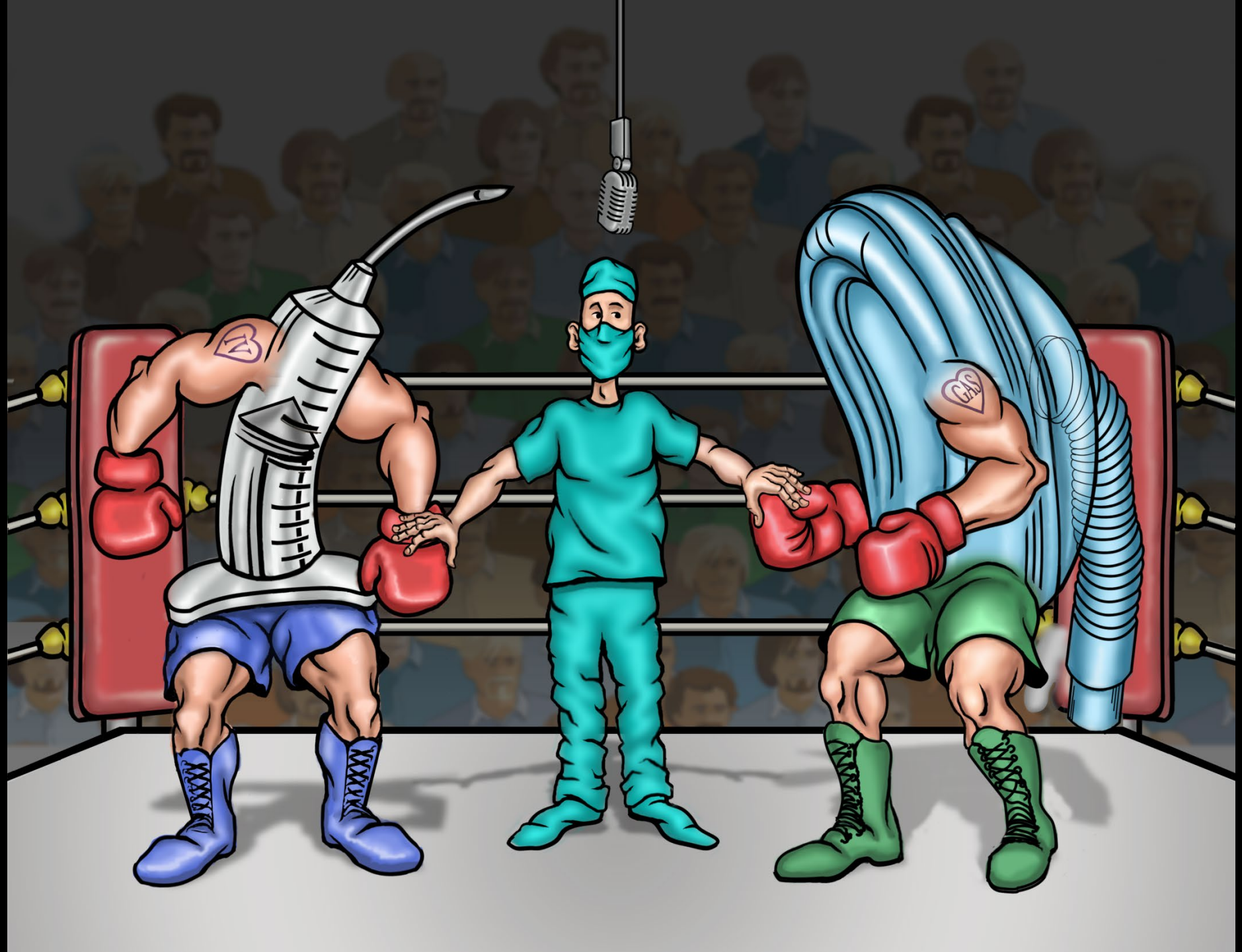
TAKE 5 FOR TIVA

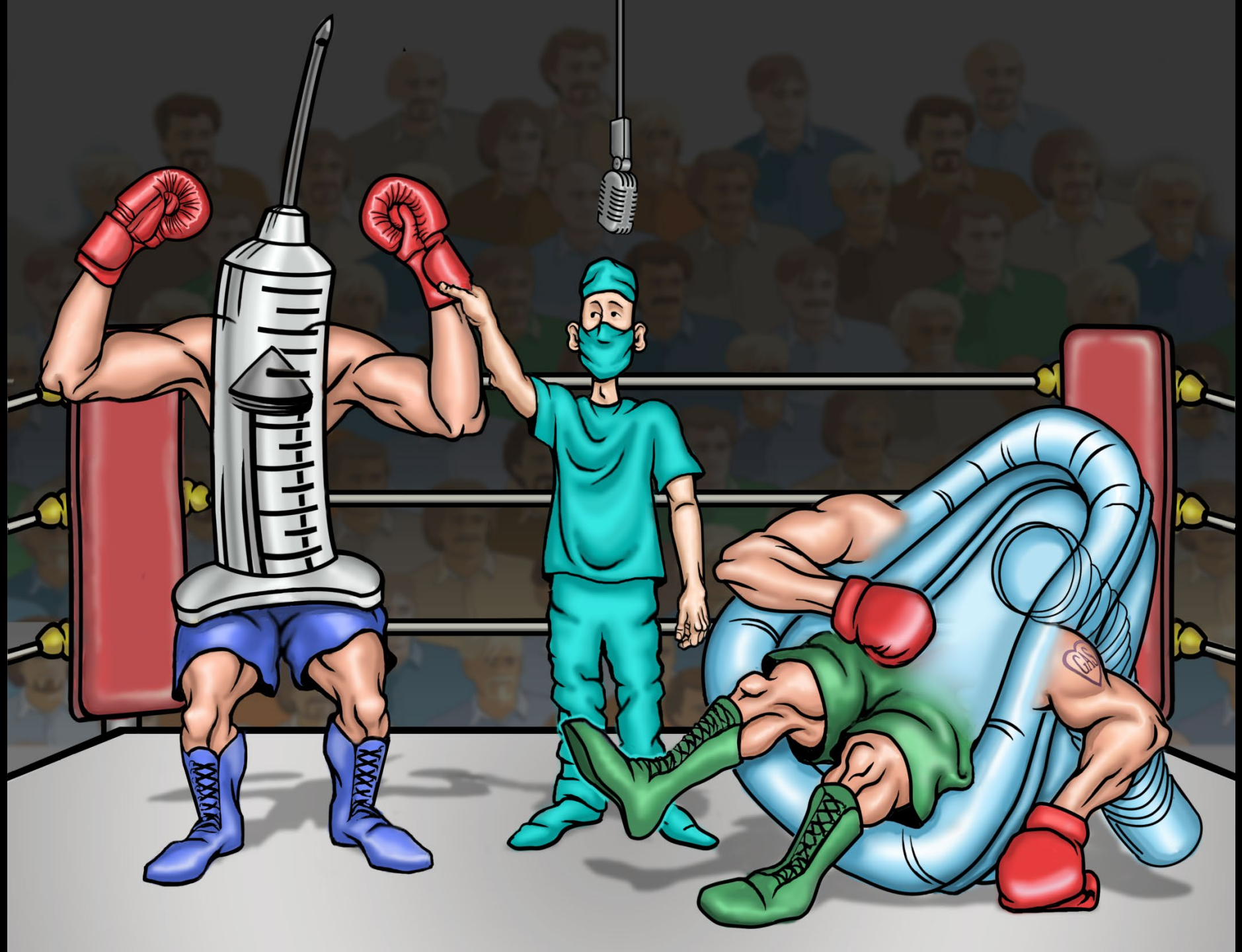
Impact of Bolus & Infusion



Impact of Bolus & Infusion




GAS

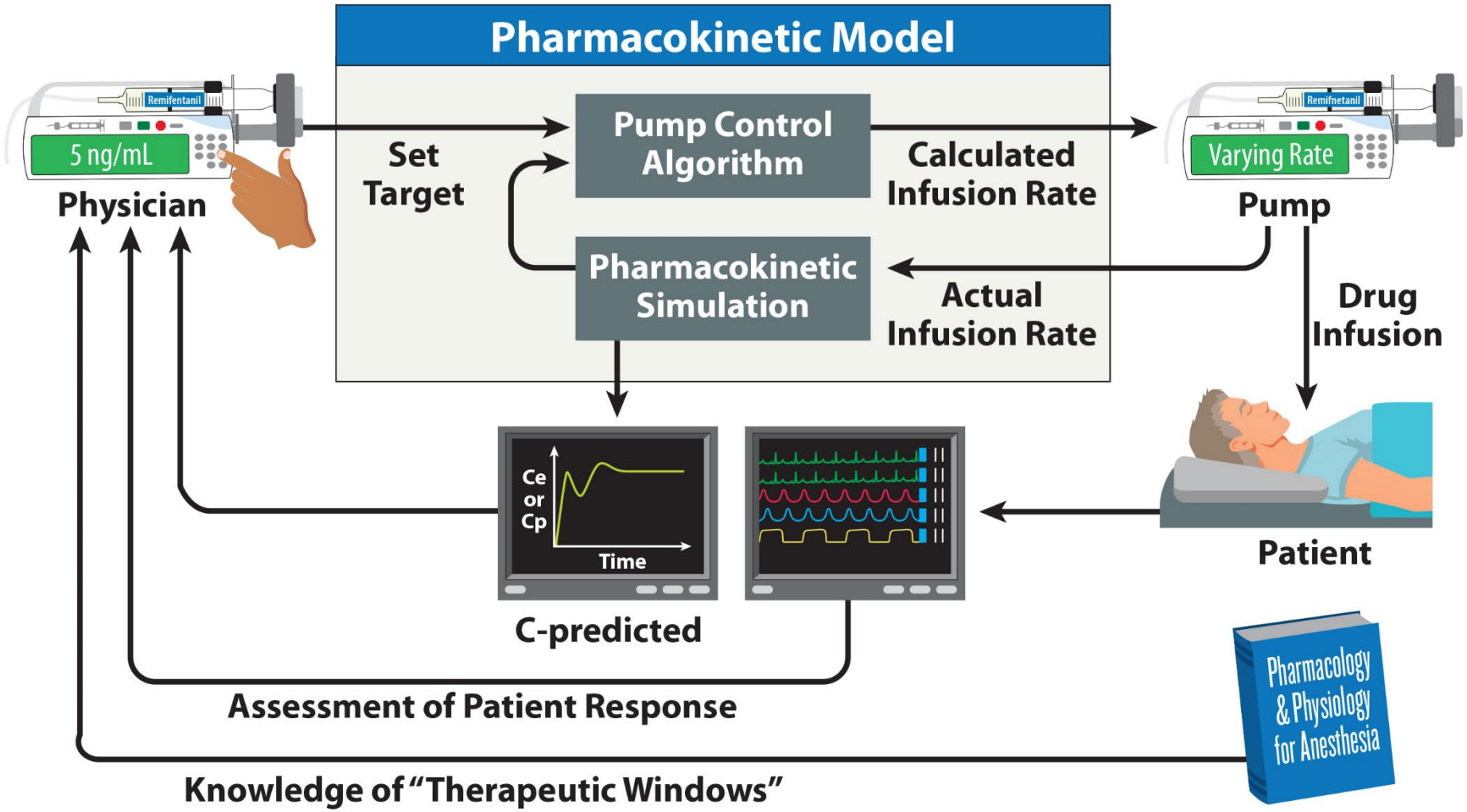


MPOG
MULTICENTER PERIOPERATIVE
OUTCOMES GROUP

THRIVE

Supplementary Material

Target Controlled Infusion System

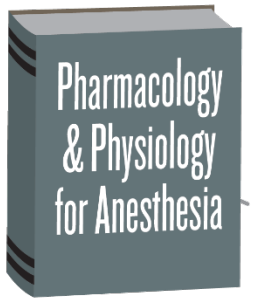


Egan (*Anesthesiology* 2003)

Target Controlled Infusion Practice

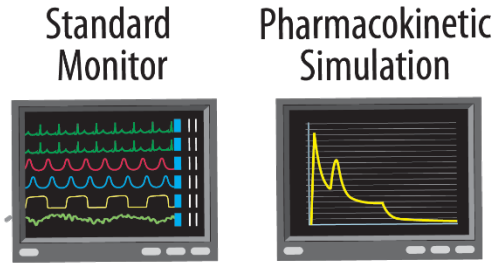
Prior knowledge:

- Pharmacologic models
- Therapeutic windows
- Covariate effects

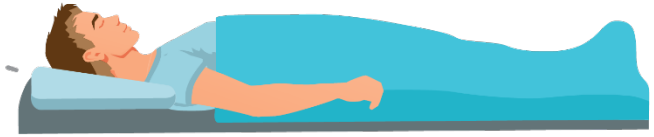


Current knowledge:

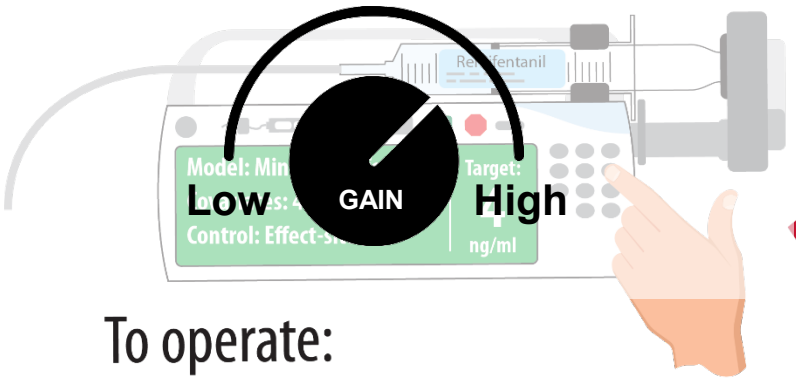
- Real-time assessment



Electronic Assessment

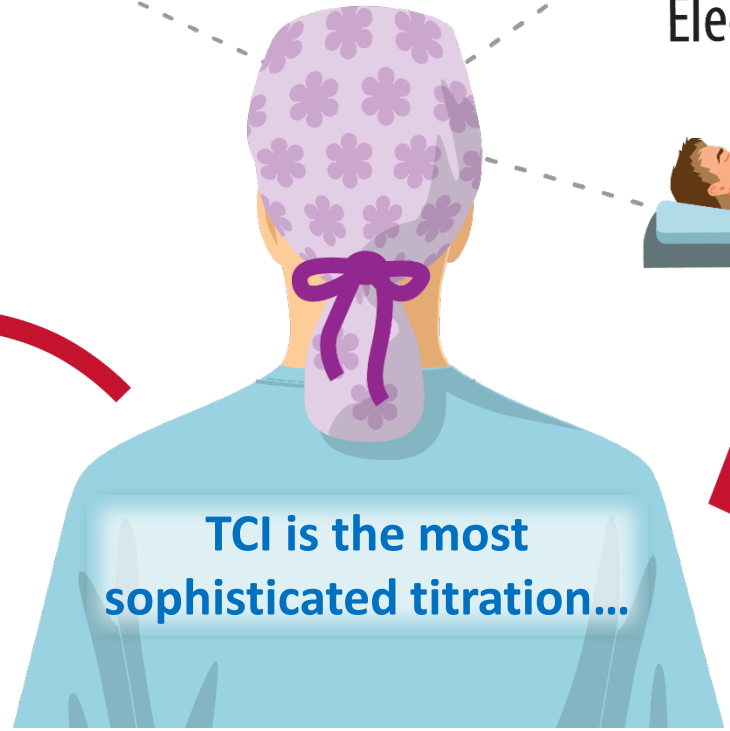


Clinical Assessment



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)