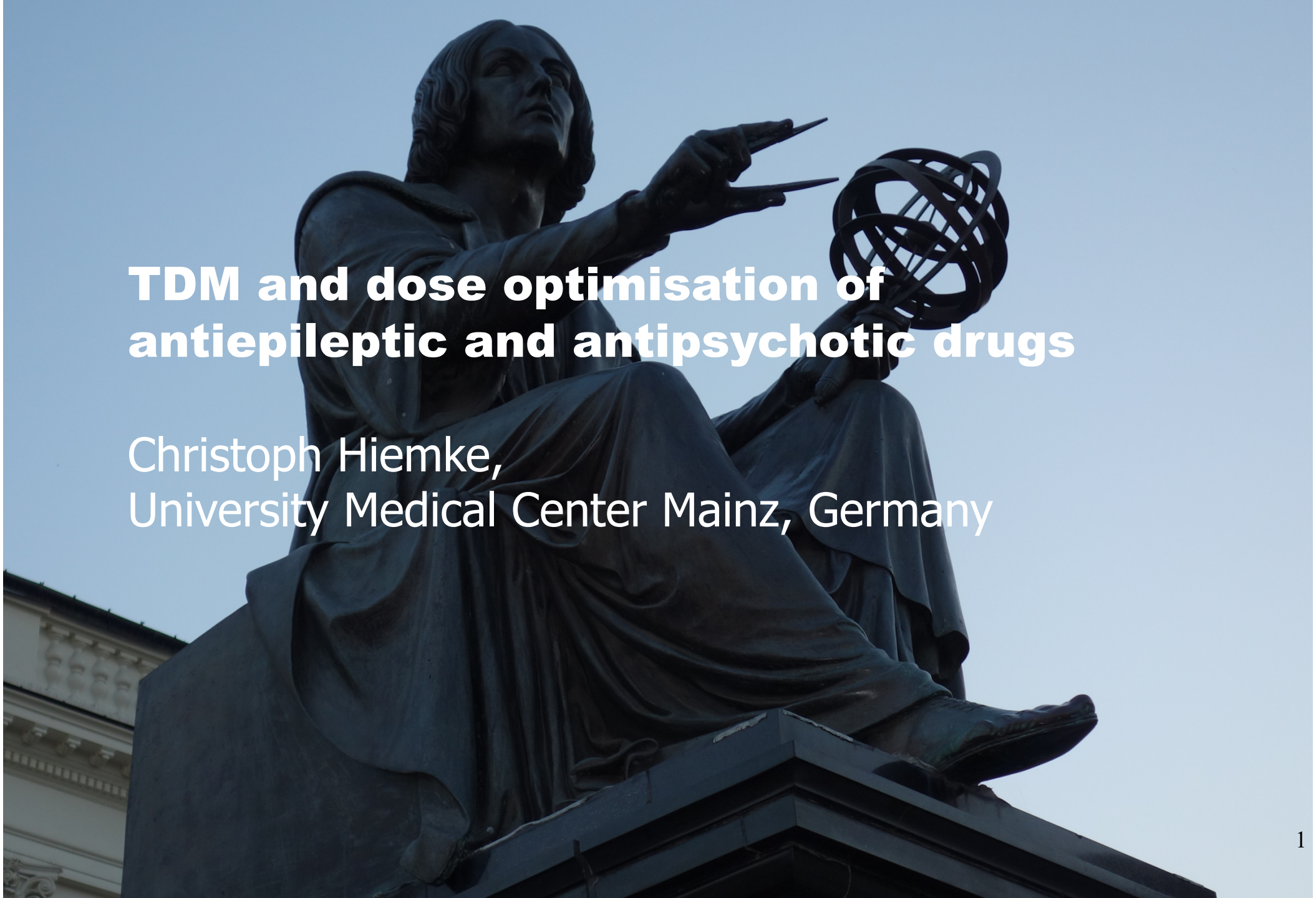


TDM and dose optimisation of antiepileptic and antipsychotic drugs

Christoph Hiemke,
University Medical Center Mainz, Germany

Christoph Hiemke

Potential conflicts of interest

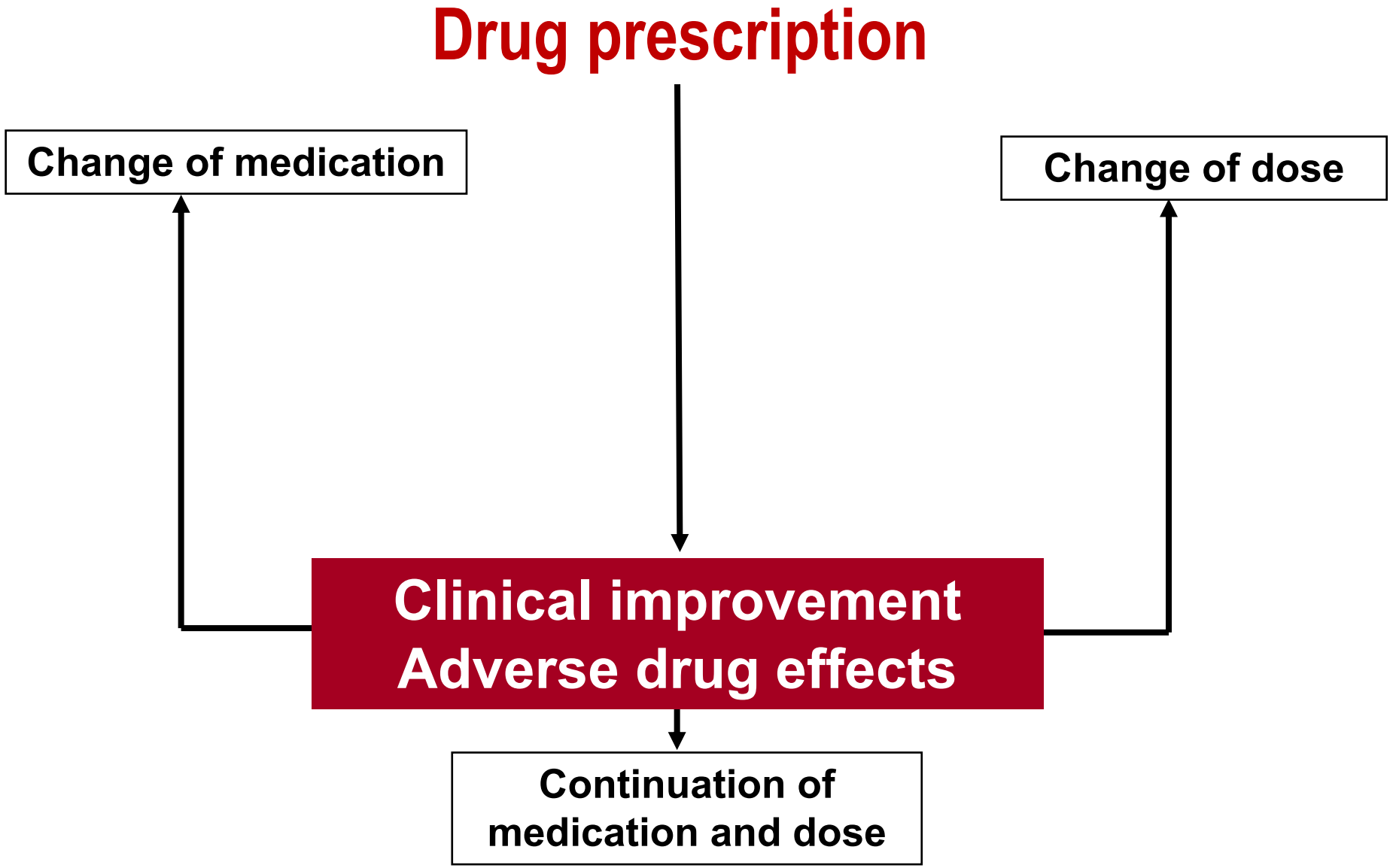
- Janssen Research and Development // Adviser
- Servier, Munich // Adviser and speaker
- STADA, Munich // Adviser and speaker
- Lohmann Transdermal Systems, Andernach // Adviser

There are no conflicts of interest to declare for this presentation

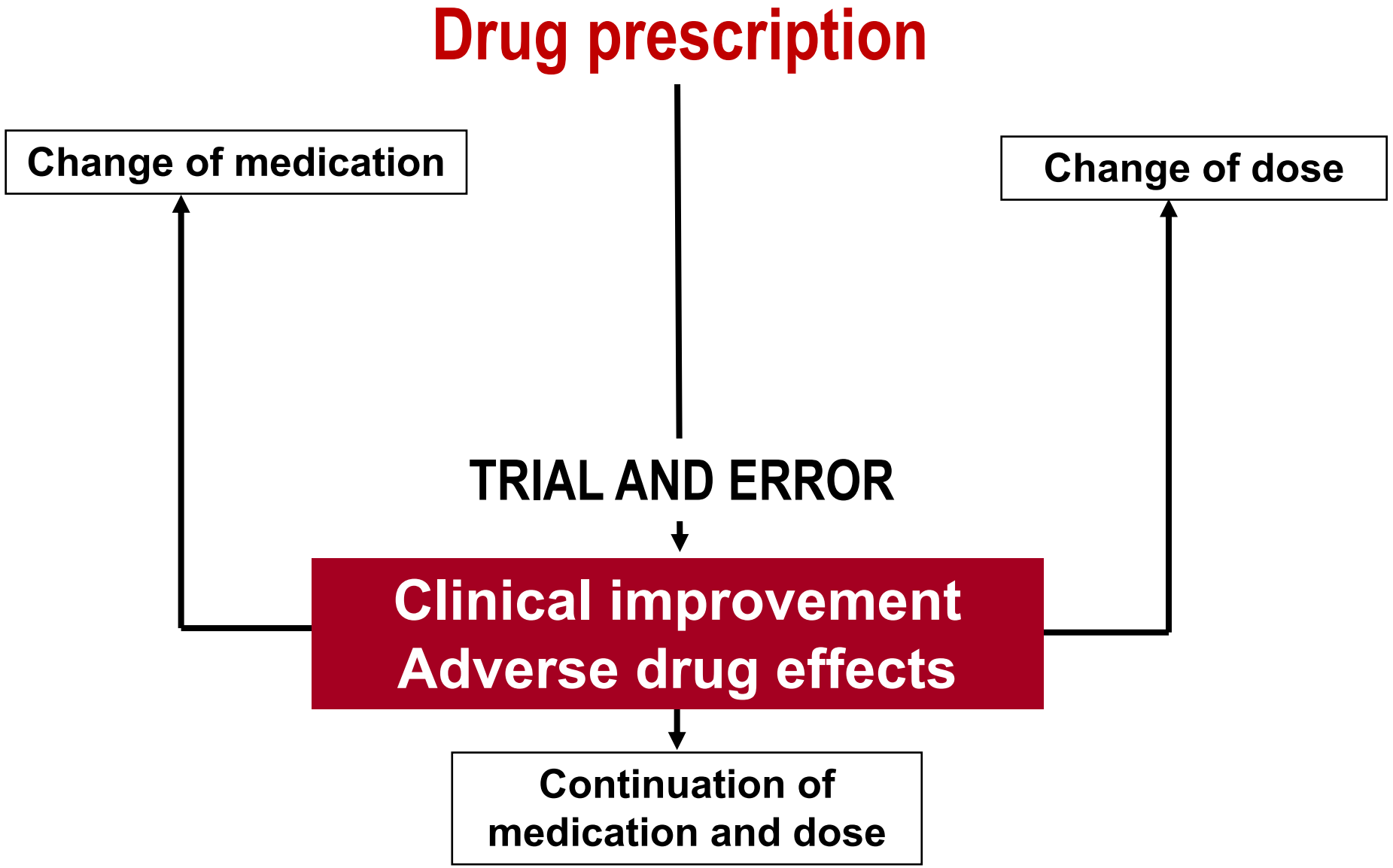
TDM and dose optimisation of antiepileptic and antipsychotic drugs

- Why TDM?
- History: TDM in psychiatry
- Limitations
  - Poor evidence base
  - Poorly defined terapeutic reference ranges
  - Inappropriate use
- How TDM ?
  - Appropriate use
  - Guidelines for TDM

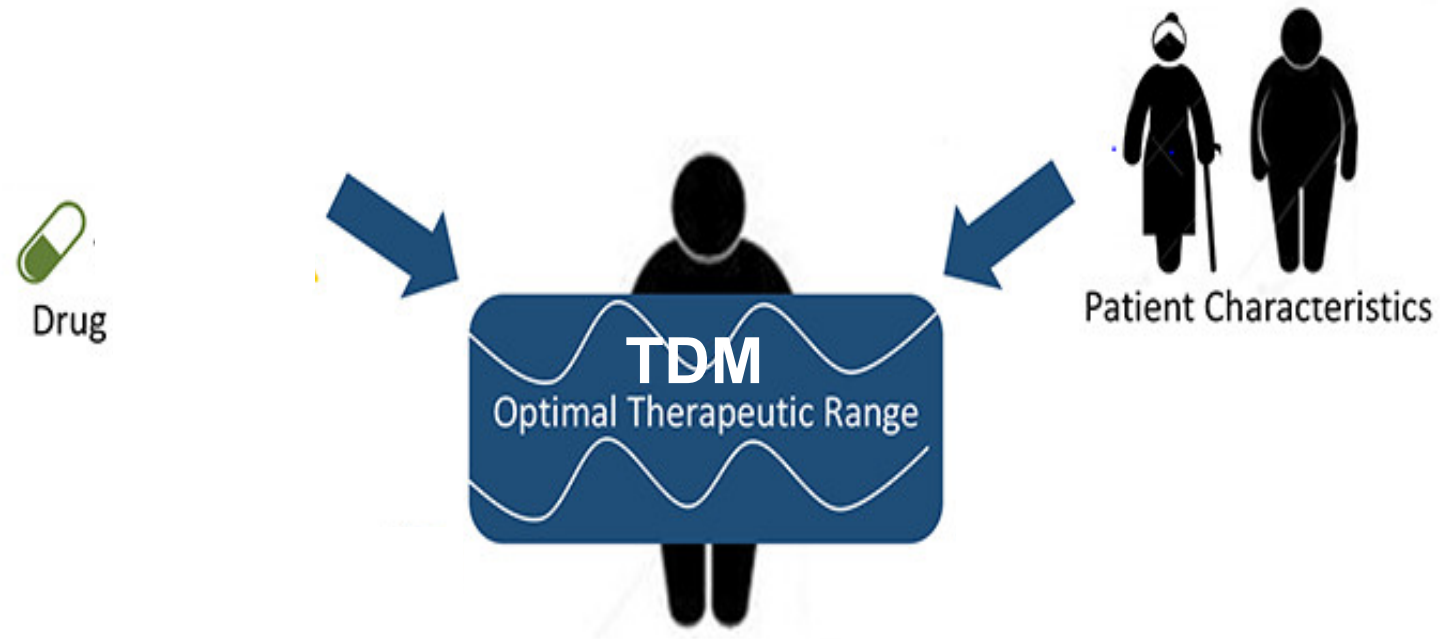
Traditional pharmacotherapy of chronic diseases without TDM



Traditional pharmacotherapy of chronic diseases without TDM

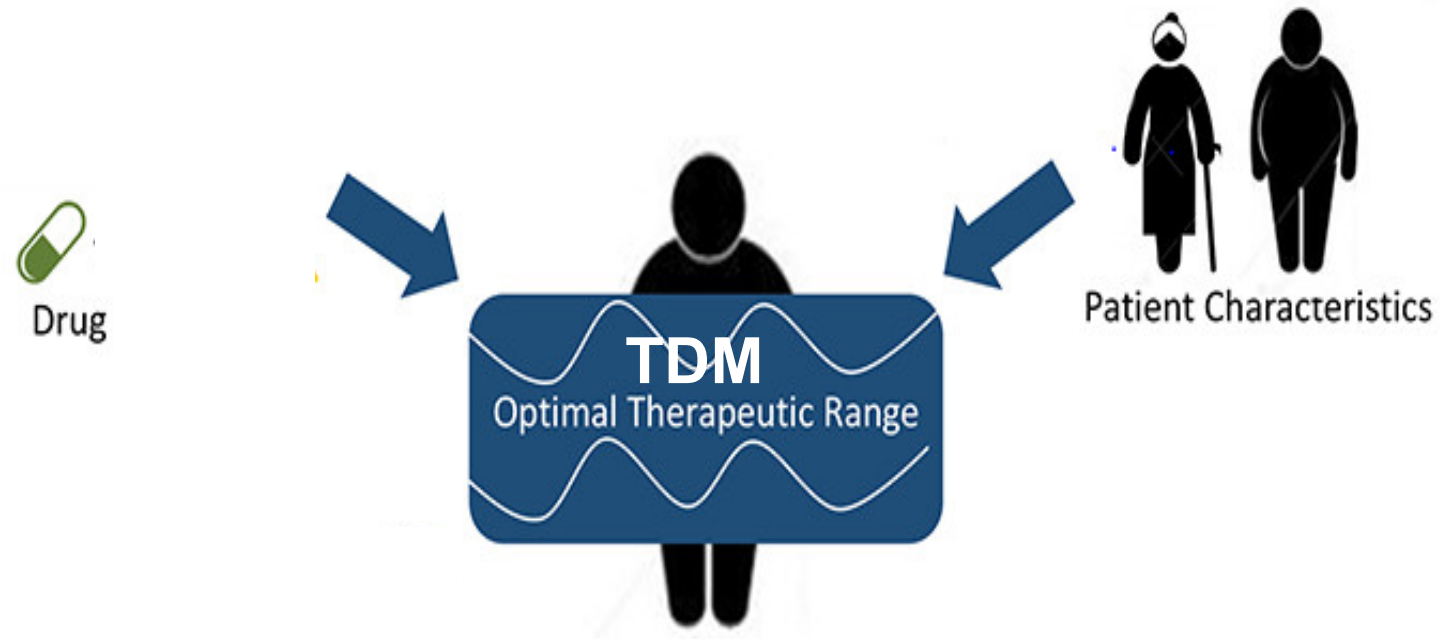


TDM guided pharmacotherapy



Clinical decision making

TDM guided pharmacotherapy



Clinical decision making

Improved efficacy,
improved safety,
shorter phases of suffering

TDM history

- 1940s Marshall: The activity of antibiotic drugs depend on concentrations in blood.
- 1960 Buchthal showed a relation between plasma concentrations of **phenytoin** in patients with epilepy and the degree of seizure control attained. 10-20 mg/L therapeutic range, toxic > 15 mg/L, severe toxicity > 30 mg/L
- 1967 Baastrup and Schou found a relationship between plasma concentrations and pharmacological effects of lithium
- 1970s Sjöqvist, Asberg, Alexanderson Nortriptyline concentrations in blood correlate with clinical improvement and side effects, and dose related plasma concentrations are influenced by genetic factors

Why TDM of antiepileptic drugs (AED)?

1. Plasma AED concentrations correlate much better than dose with the clinical effects.
2. Assessment of therapeutic response on clinical grounds alone is difficult in most cases because AED treatment is prophylactic, and seizures occur at irregular intervals. It is thus difficult to ascertain whether the prescribed dose will be sufficient to produce long-term seizure control.
3. It is not always easy to recognize signs of toxicity purely on clinical grounds.
4. AEDs are subject to substantial pharmacokinetic variability and thus, large differences in dosage are required in different patients.
5. There are no laboratory markers for clinical efficacy or toxicity of AEDs.

Patsalos et al. Ther Drug Monit 2018;40:526–548

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TDM of AEDs is widely established and accepted

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Why TDM of antipsychotic drugs (APD)?

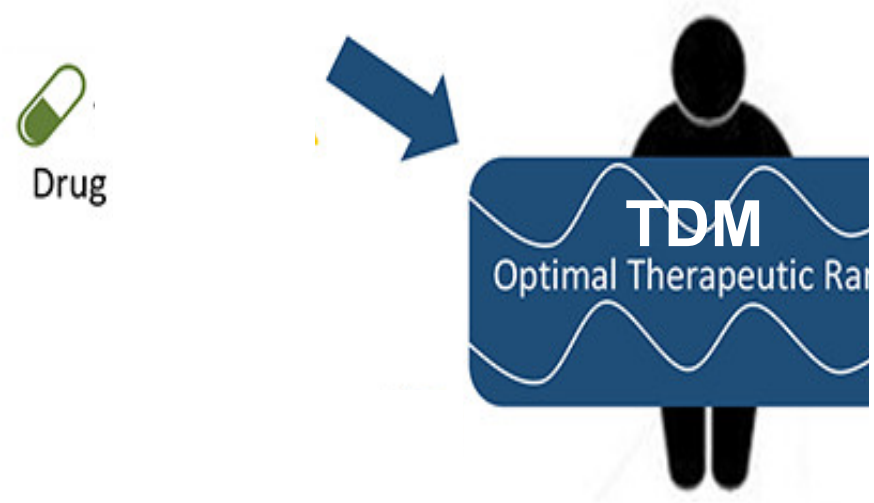
1. Plasma APD concentrations correlate much better than dose with the clinical effects?
2. Assessment of therapeutic response on clinical grounds alone is feasable (e.g. CGI or BPRS). It is difficult to ascertain whether the prescribed dose will be sufficient to produce long-term suppression of psychotic symptoms.
3. Signs of intolerance EPS can be easily recognized.
4. APDs are subject to substantial pharmacokinetic variability and thus, large differences in dosage are required in different patients.
5. There are no laboratory markers for clinical efficacy or toxicity of APDs.

Why TDM of antipsychotic drugs (APD)?

1. Plasma APD concentrations correlate much better than dose with the clinical effects?
2. Assessment of therapeutic response on clinical grounds alone is feasable (e.g. CGI or BPRS) difficult to ascertain whether the prescribed dose will be sufficient to produce long-term suppression of psychotic symptoms.
3. Signs of intolerance may be easily recognized.
4. APDs are subject to substantial pharmacokinetic variability and large differences in dosage are required in different patients.
5. There are no laboratory markers for clinical efficacy or tolerability of APDs.

TDM of APDs is a matter of debate
Exception: Clozapine

Requirements for TDM guided pharmacotherapy



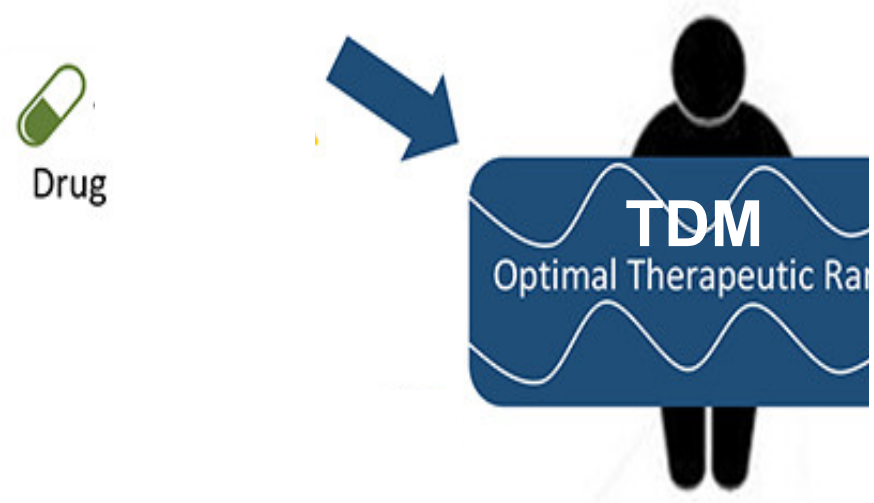
Indication for TDM request
Qualified laboratory
Validated / suitable method
Pharmacokinetic knowledge
Pharmacological knowledge

Validated reference ranges

Clinical decision ma

Requirements for TDM guided pharmacotherapy

Indication for TDM request



Clinical decision ma

TDM of antiepileptic drugs, indications

1. After initialization of AED treatment or after dose adjustment
2. On achievement of optimum desired clinical response
3. To determine the magnitude of a dose change
4. When toxicity is difficult to differentially diagnose or when toxicity is difficult to assess clinically
5. When seizures persist despite the prescribing of an adequate/typical dosage
6. When pharmacokinetic variability is expected
7. When a formulation change is to occur
8. The clinical response has unexpectedly changed
9. Poor compliance suspected

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TDM of antipsychotic drugs, indications

T
medications in blood for psychiatric or neurologic patients (adapted from the original paper: Hiemke et al. 2018).

Obligatory TDM for drugs with high levels of recommendation to use TDM

- Dosage optimization after initial prescription or after dosage change
- Drugs, for which TDM is mandatory for safety reasons (e.g., lithium or carbamazepine) **clozapine**

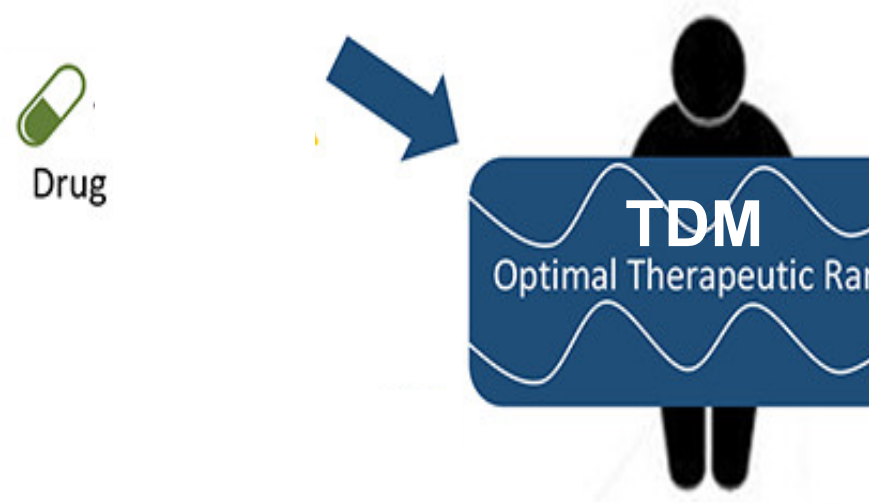
Specific indications for TDM for any drug independent of its level of recommendation to use TDM

- Uncertain adherence to medication
- Lack of clinical improvement under recommended dosage
- Relapse under maintenance treatment
- Relapse prevention because of uncertain adherence to medication
- Recurrence of symptoms under adequate dosage
- Adverse effects and clinical improvement under recommended dosage
- Combination treatment with a drug known for its interaction potential or suspected drug interaction

potential or suspected drug interaction
- Presence of a genetic peculiarity concerning drug metabolism (genetic deficiency, gene multiplication)
- Patient with differential ethnicity
- Patient with abnormally high or low body weight
- Pregnant or breast feeding patient
- Children or adolescent patient
- Elderly patient (>65 years old)
- Patients with intellectual disability
- Forensic psychiatric patient
- Court case related to neuropsychiatric medications
- Patient with pharmacokinetically relevant comorbidity (hepatic or renal insufficiency, cardiovascular disease)
- Patient with acute or chronic inflammations or infections
- Patient with restrictive gastrointestinal resection or bariatric surgery
- Problem occurring after switching from an original preparation to a generic form (and vice versa)
- Pharmacovigilance programs

TDM: therapeutic drug monitoring.

Requirements for TDM guided pharmacotherapy

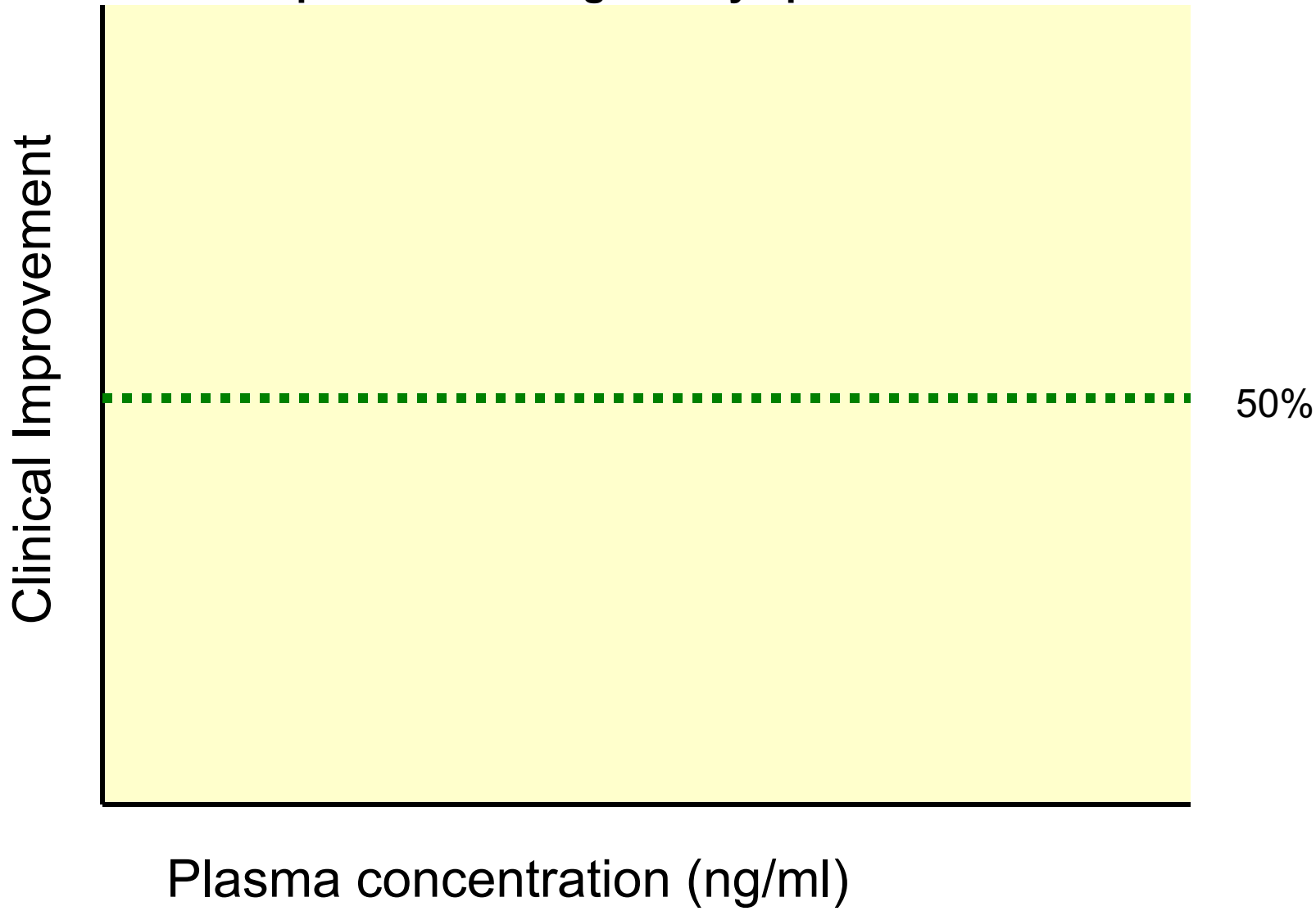


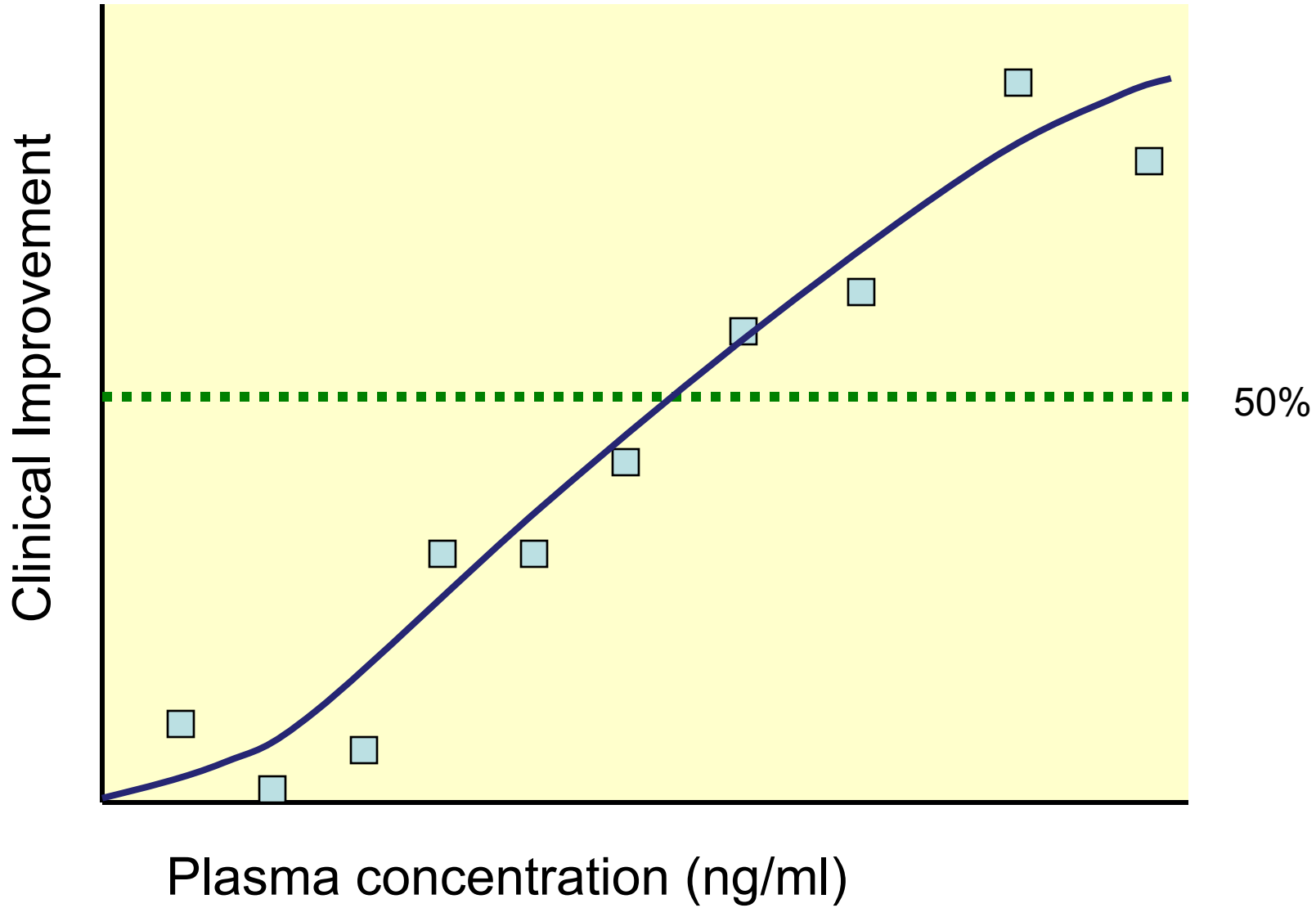
Validated reference ranges

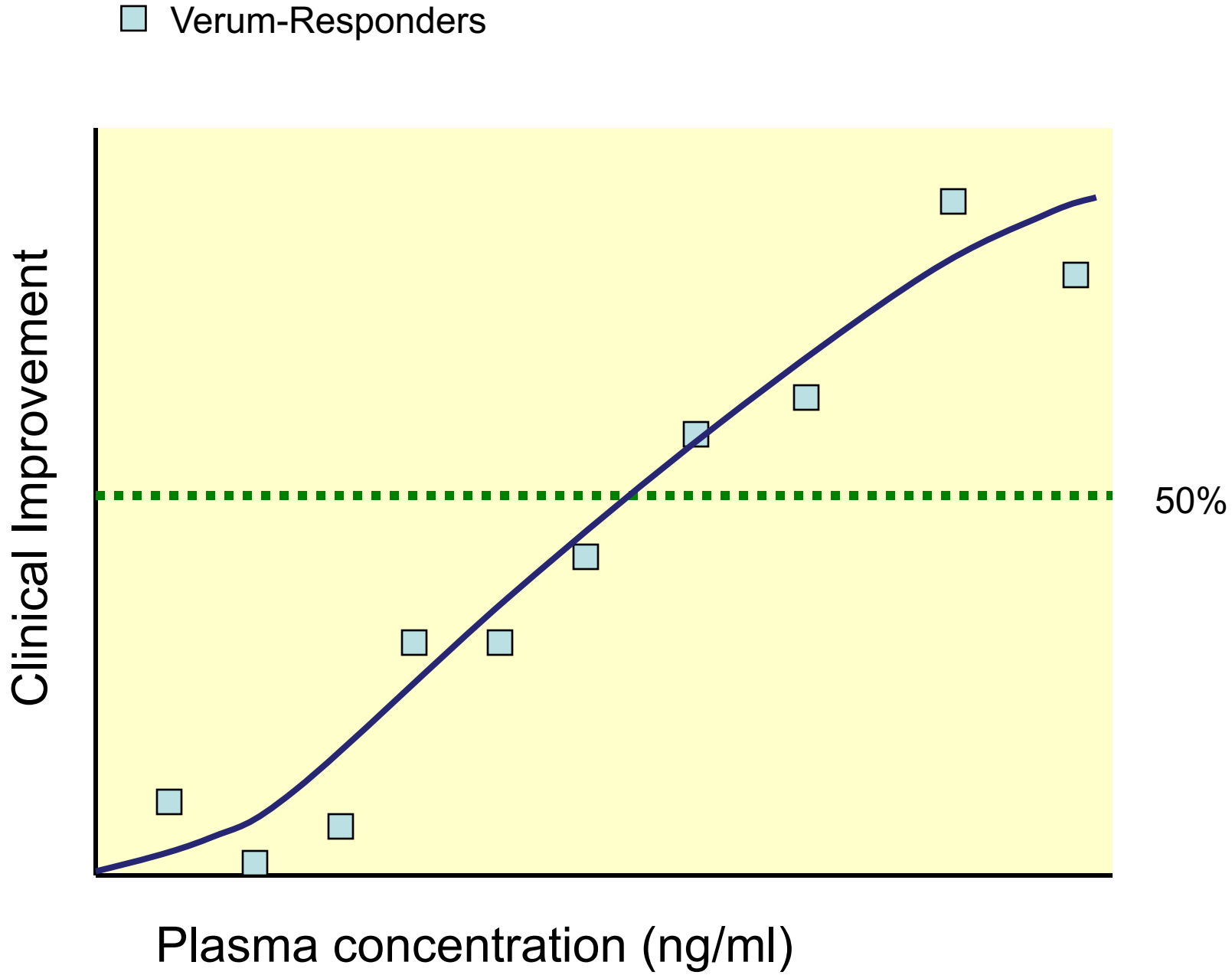
Clinical decision ma

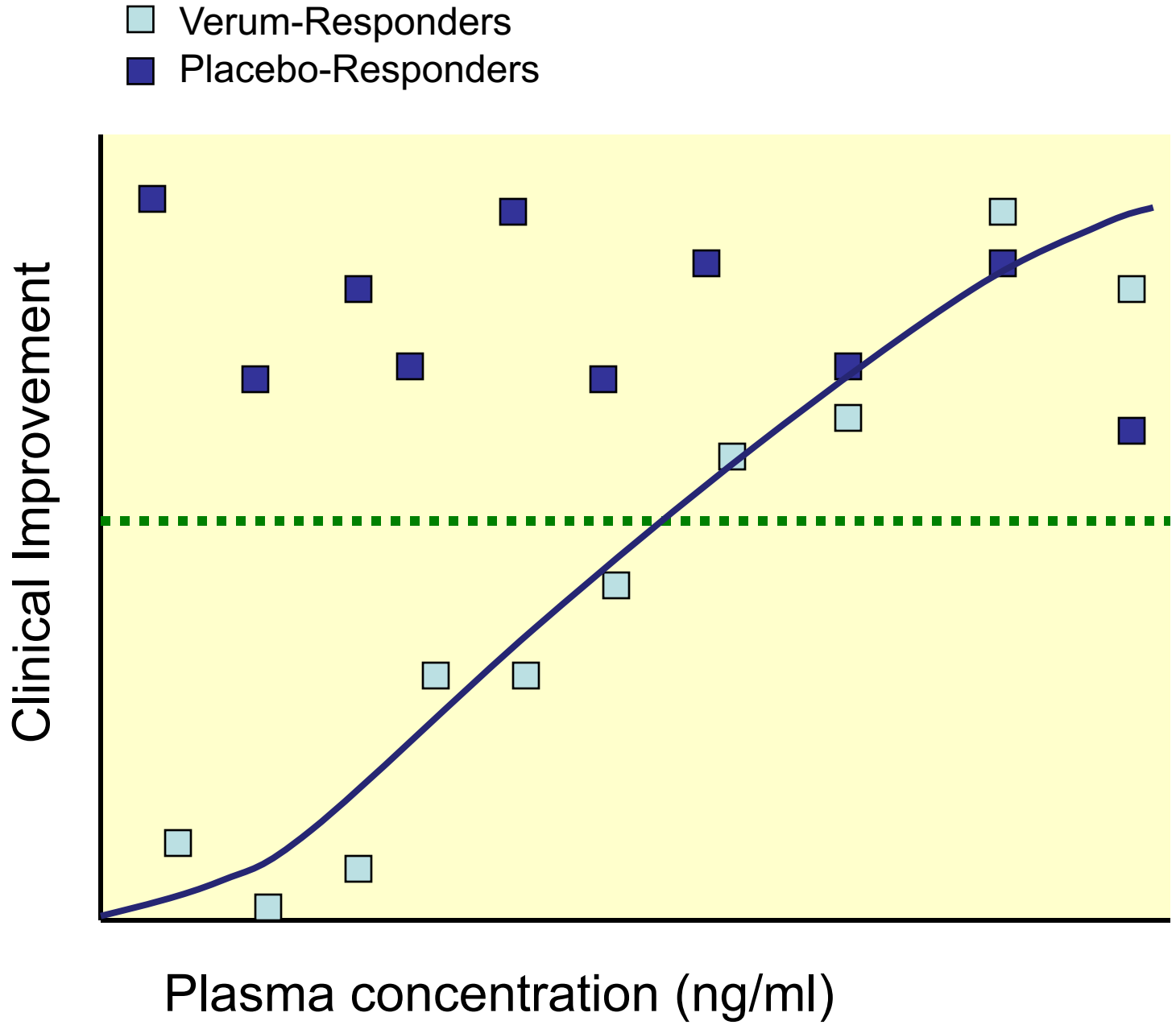
How to find (therapeutic) reference ranges?

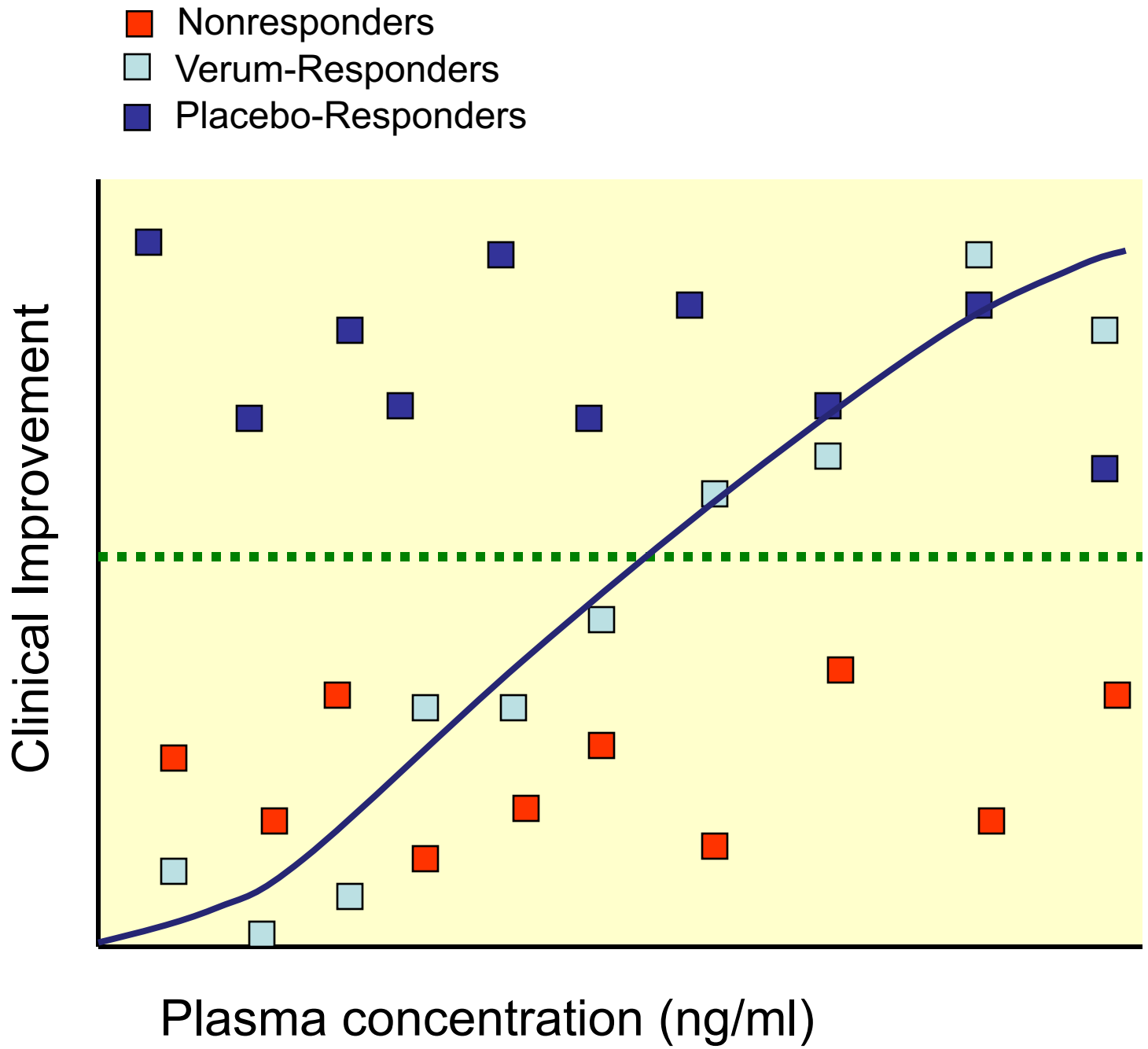
AEDs: Decreased occurrence of seizures
APDs: Decrease of positive and negative symptoms

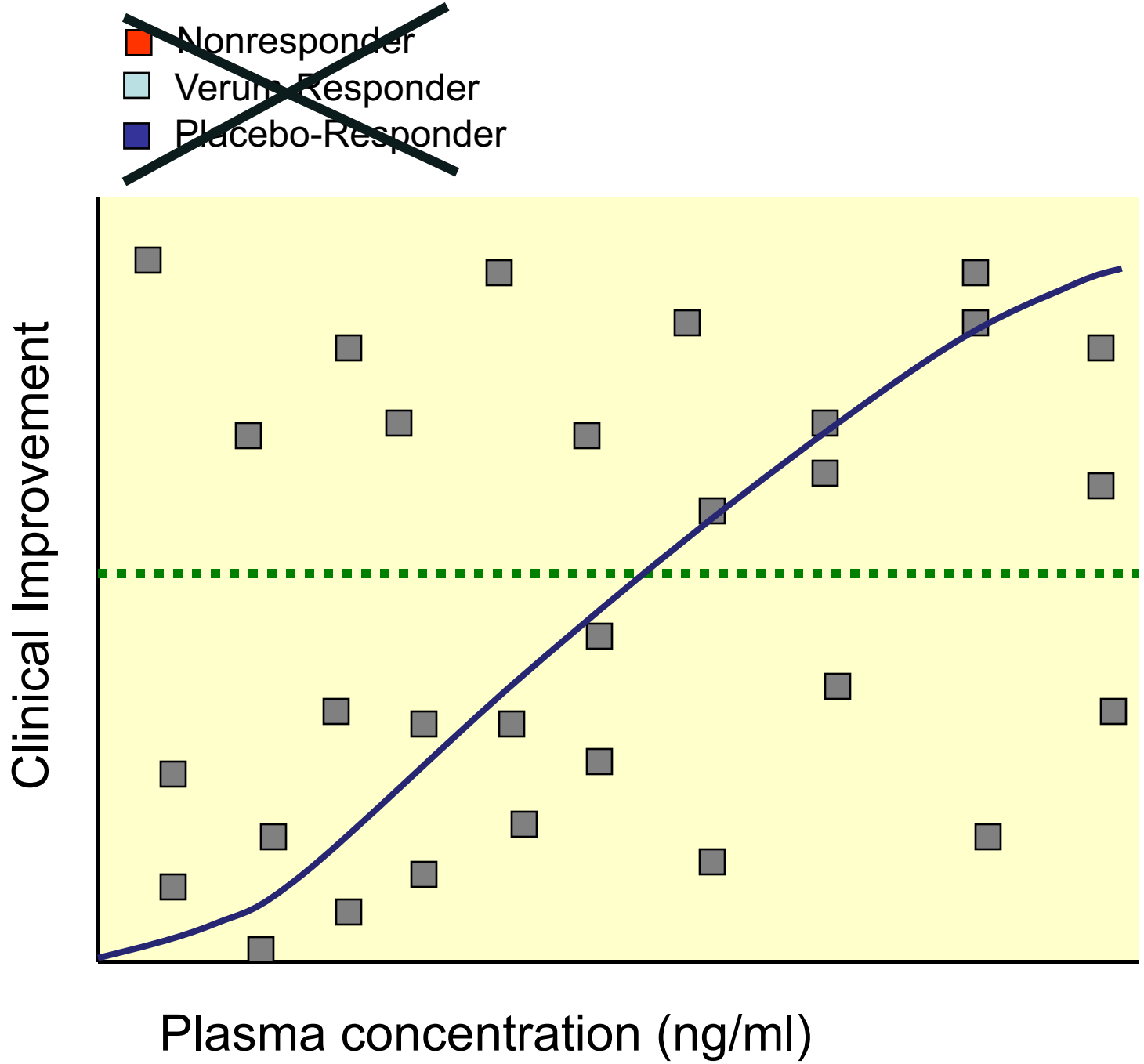



Clinical Improvement
50%
Plasma concentration (ng/ml)

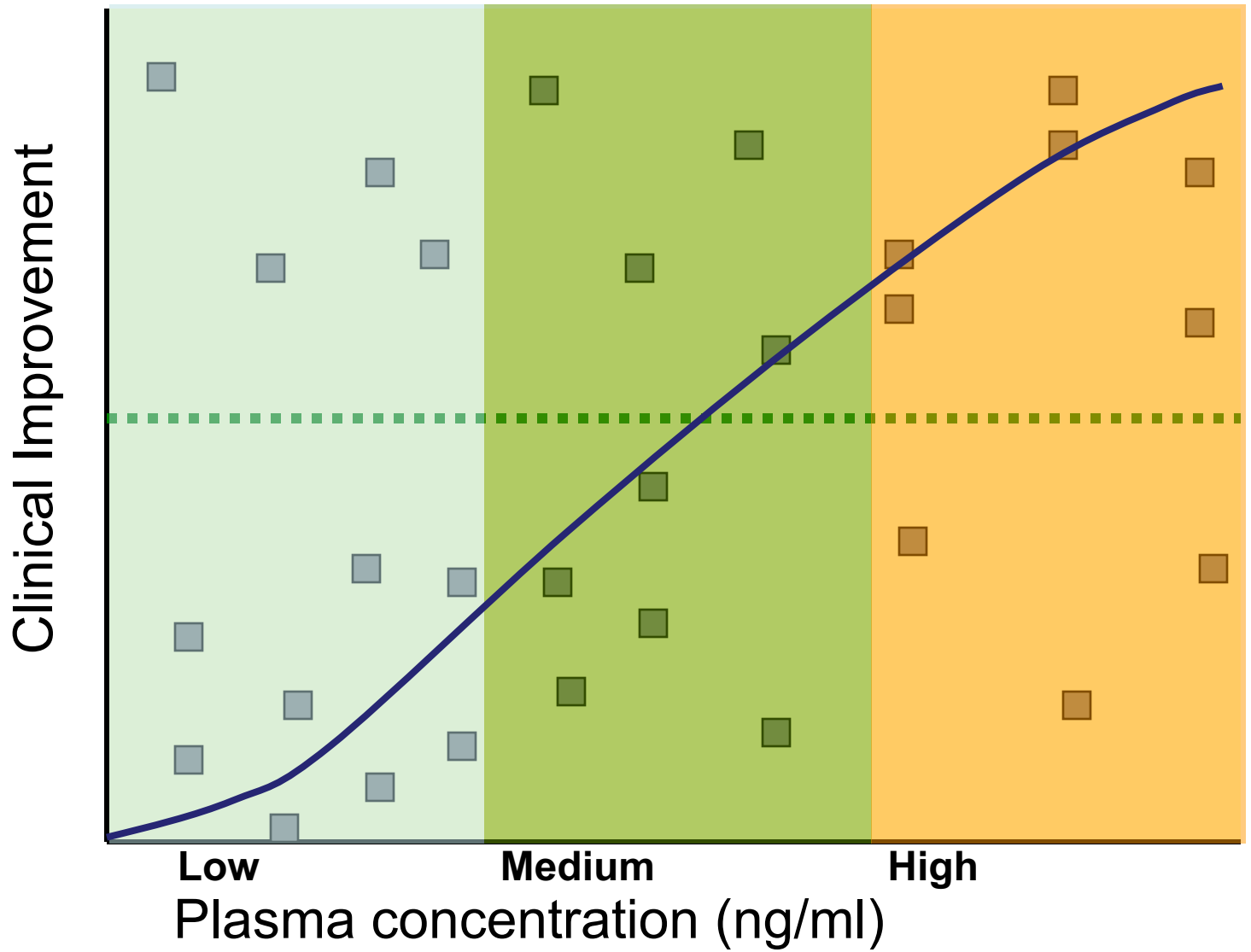

Verum-Responders
Clinical Improvement
50%
Plasma concentration (ng/ml)

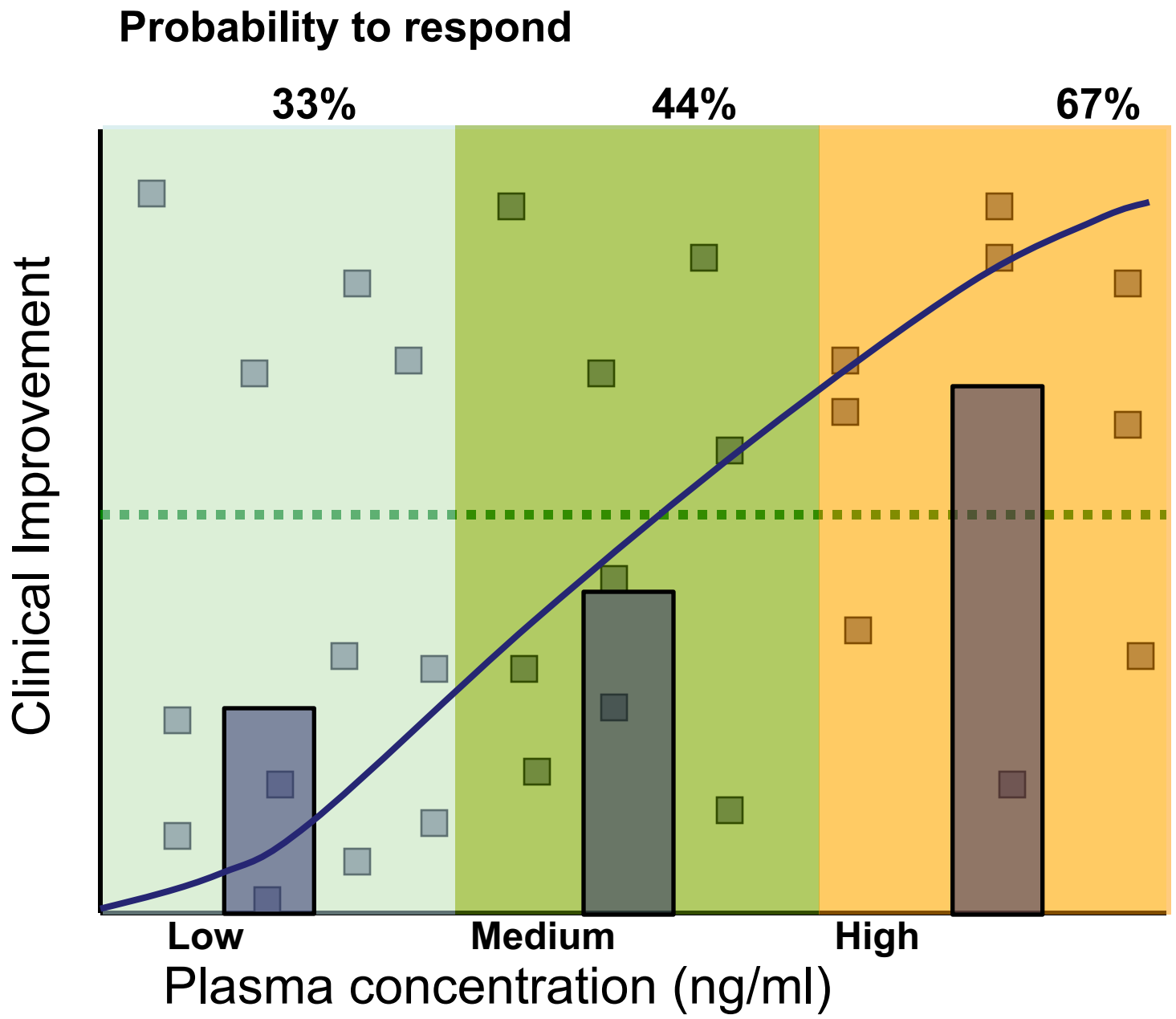

Verum-Responders
Placebo-Responders
Clinical Improvement
Plasma concentration (ng/ml)

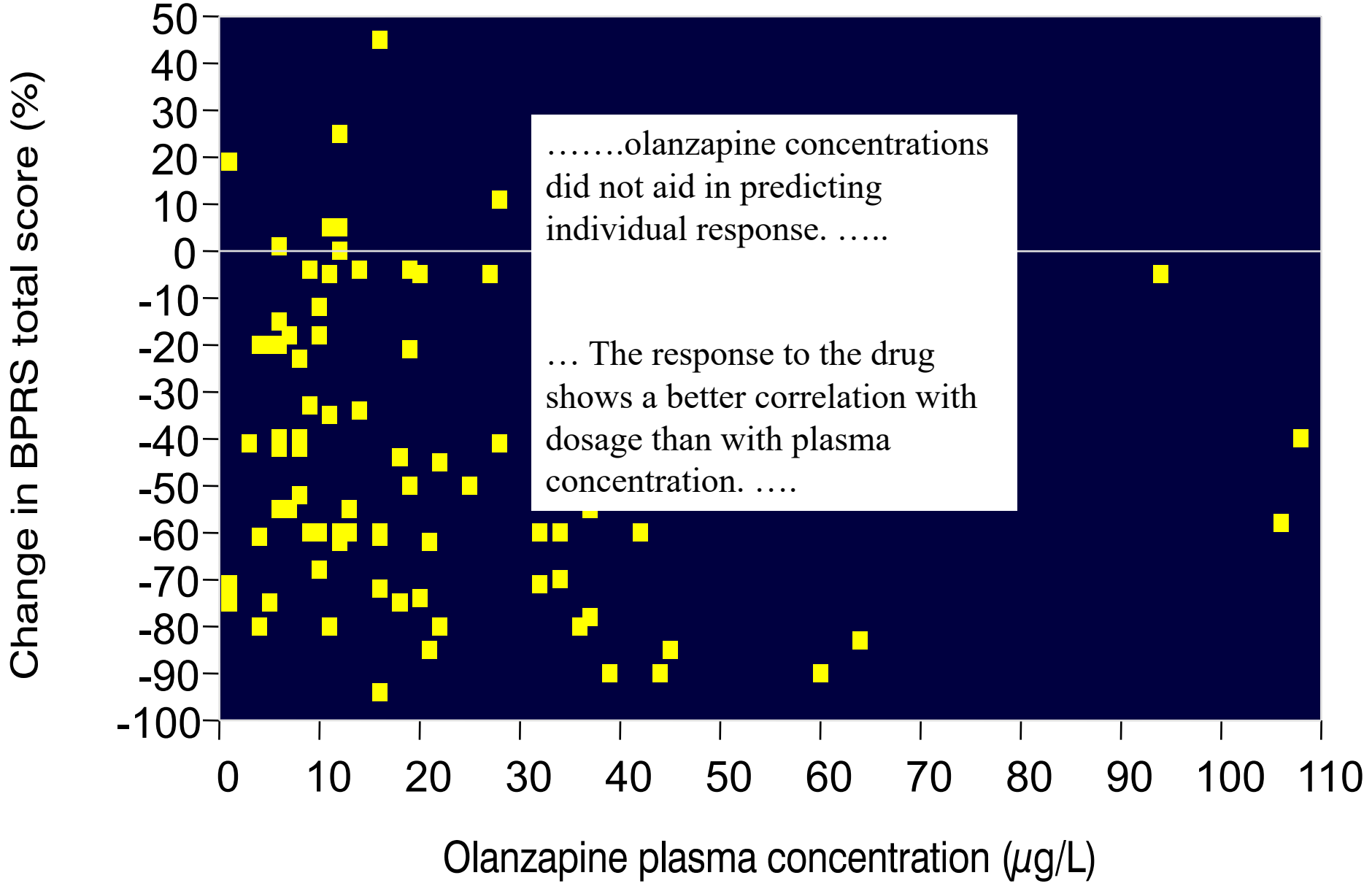

Nonresponders
Verum-Responders
Placebo-Responders
Clinical Improvement
Plasma concentration (ng/ml)


Nonresponder
Verum-Responder
Placebo-Responder
Clinical Improvement
Plasma concentration (ng/ml)

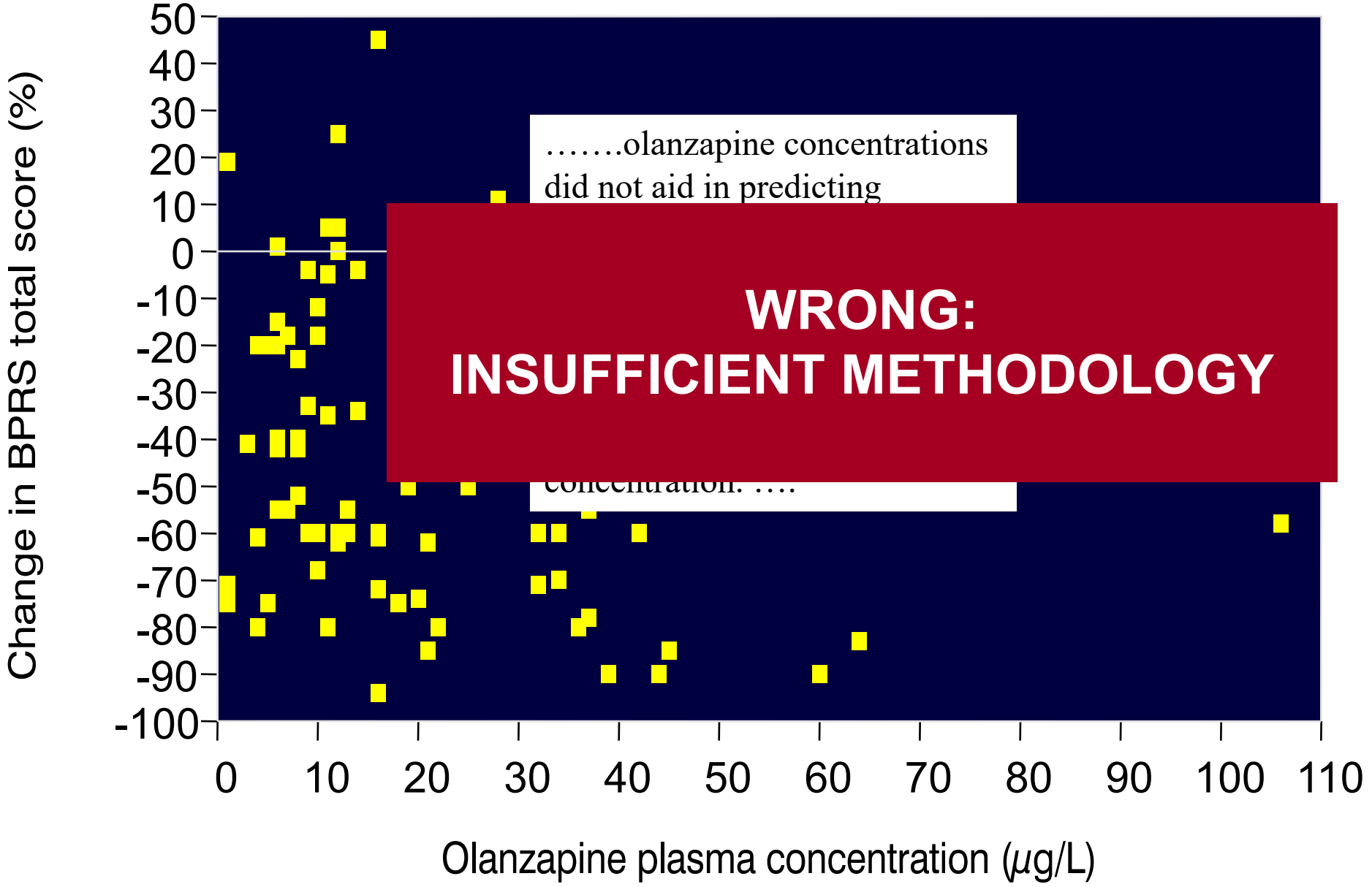
Probability to respond




Probability to respond
33%
44%
67%
Clinical Improvement
Low
Medium
High
Plasma concentration (ng/ml)



Callaghan et al., 1999: Olanzapine. Pharmacokinetic and Pharmacodynamic Profile



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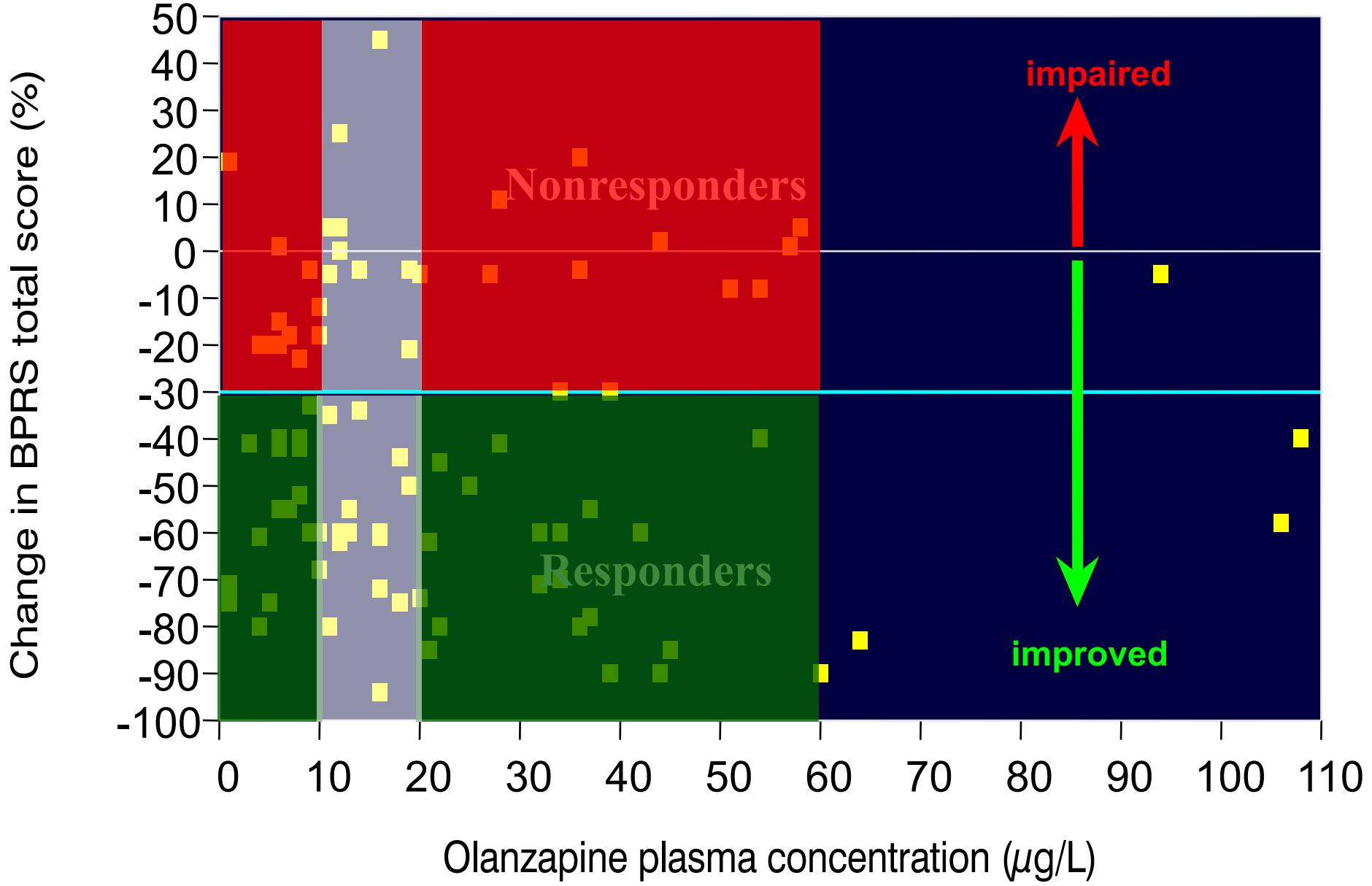

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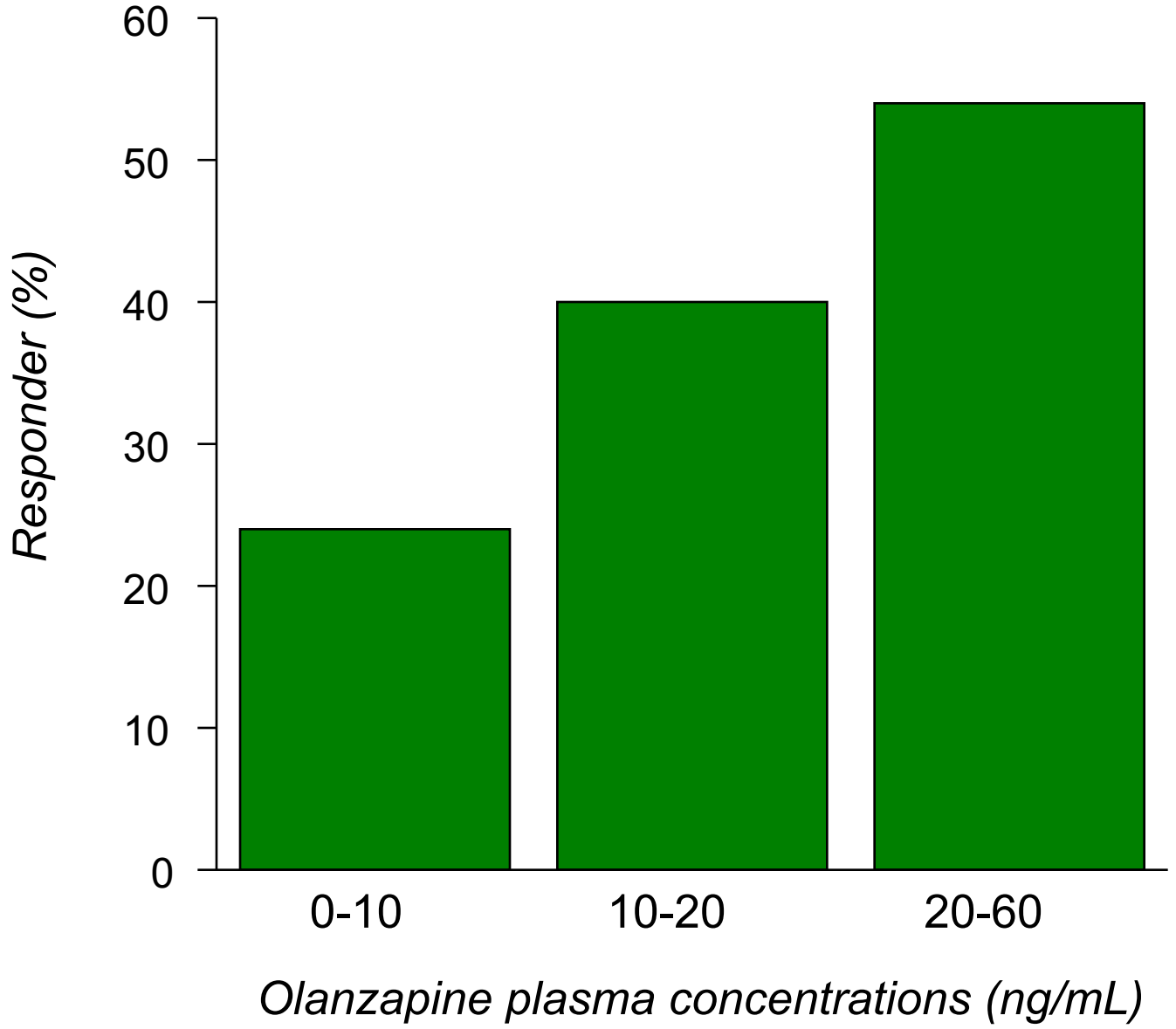
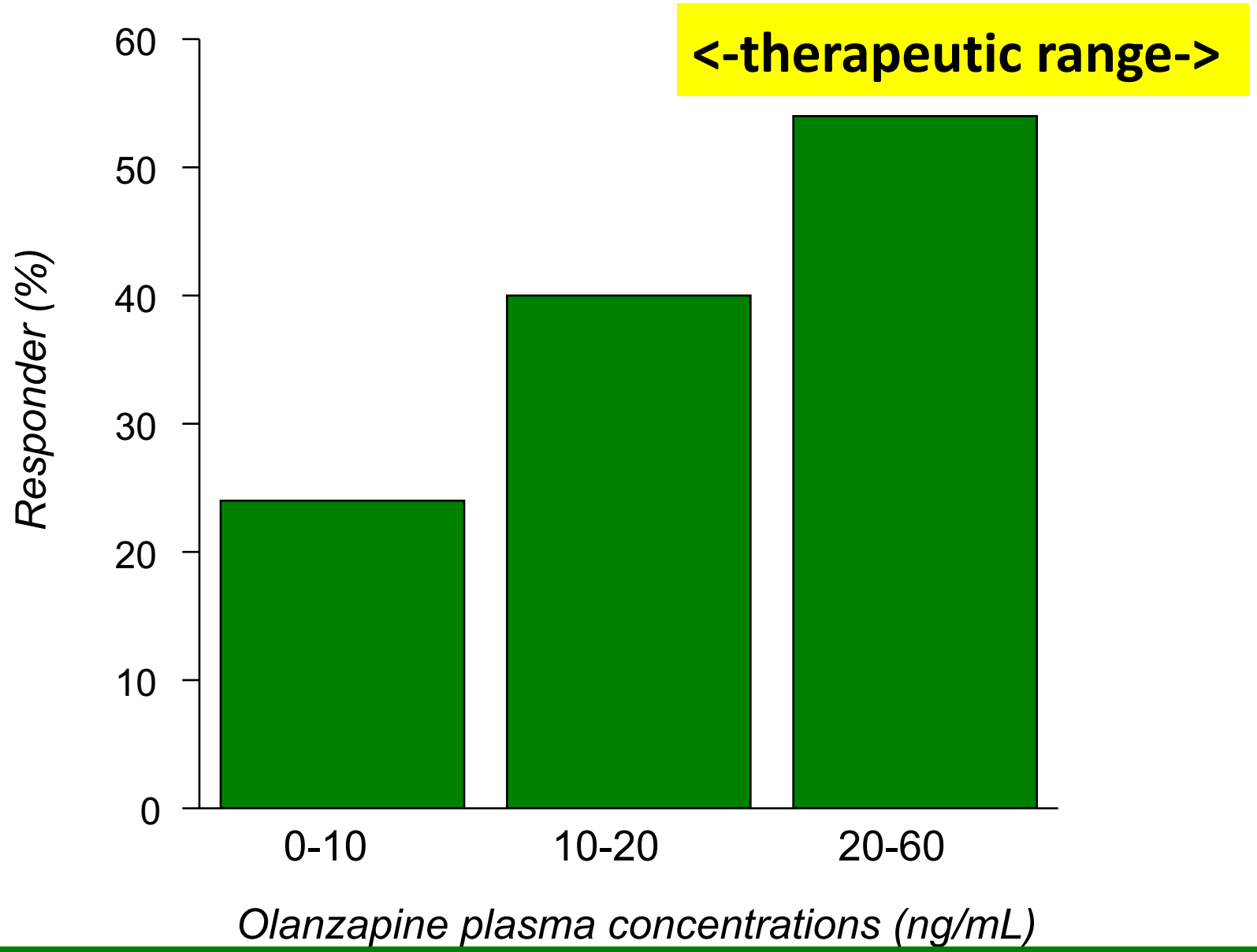
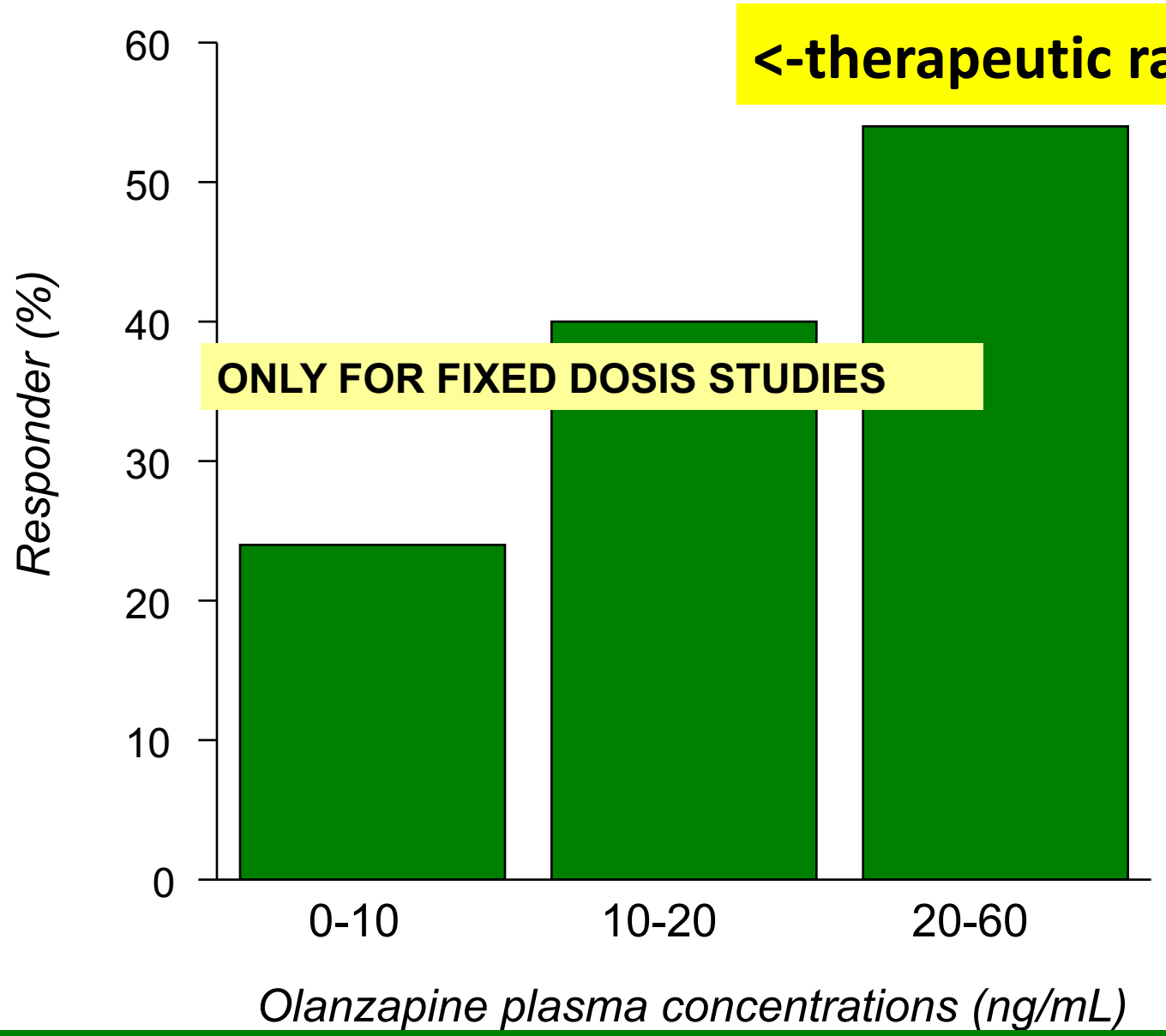


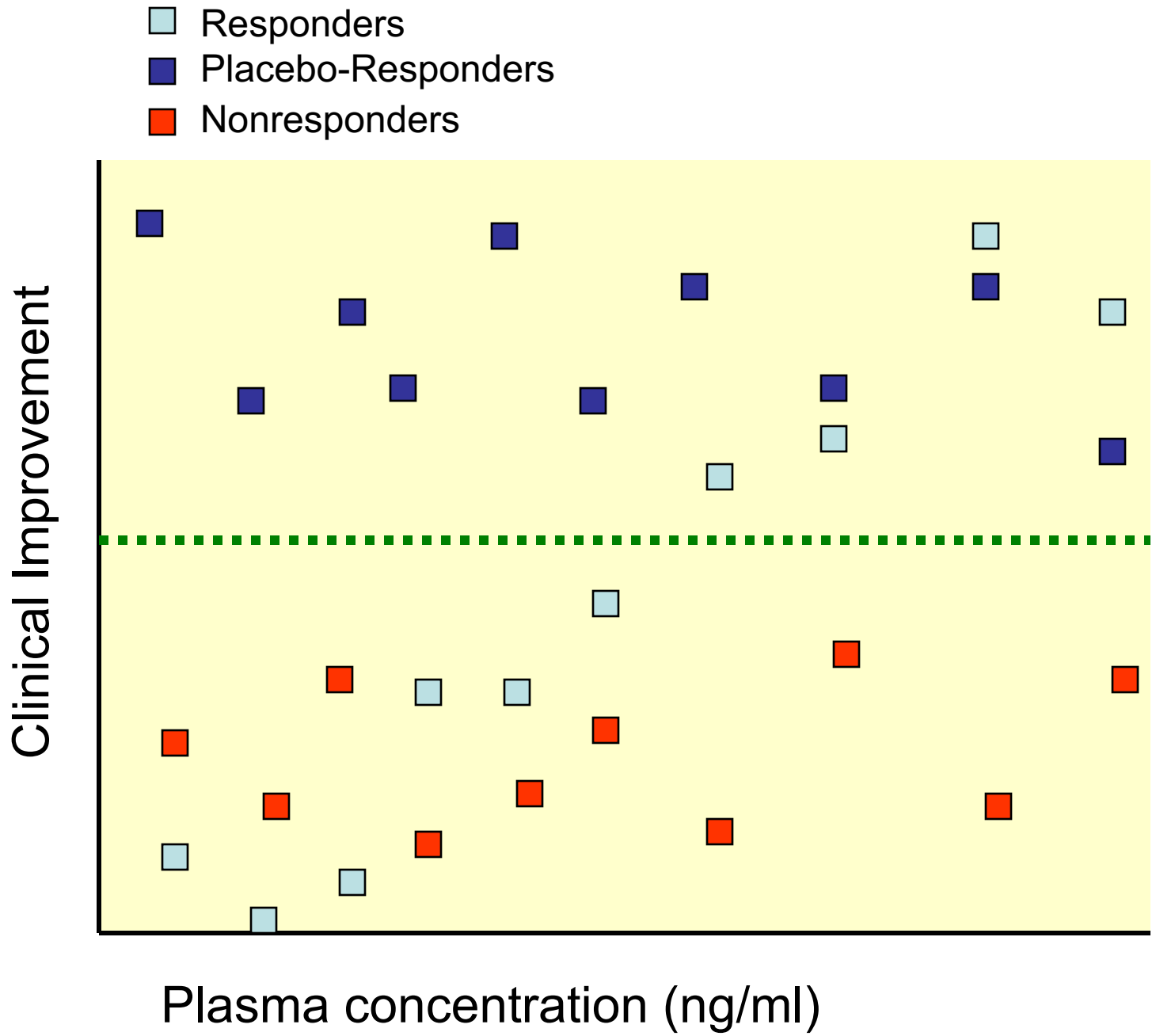
Data taken from Callaghan et al., 1999

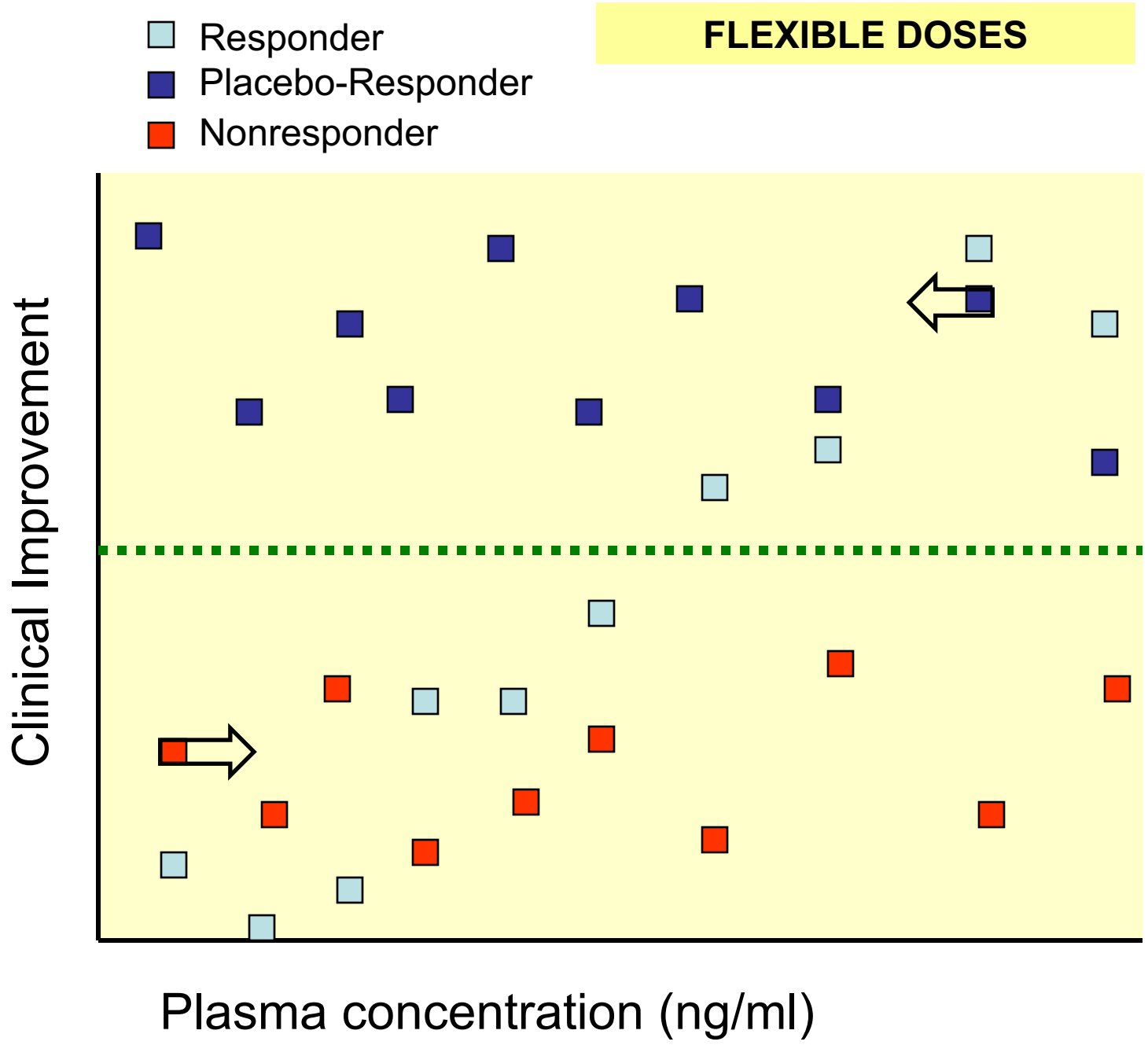


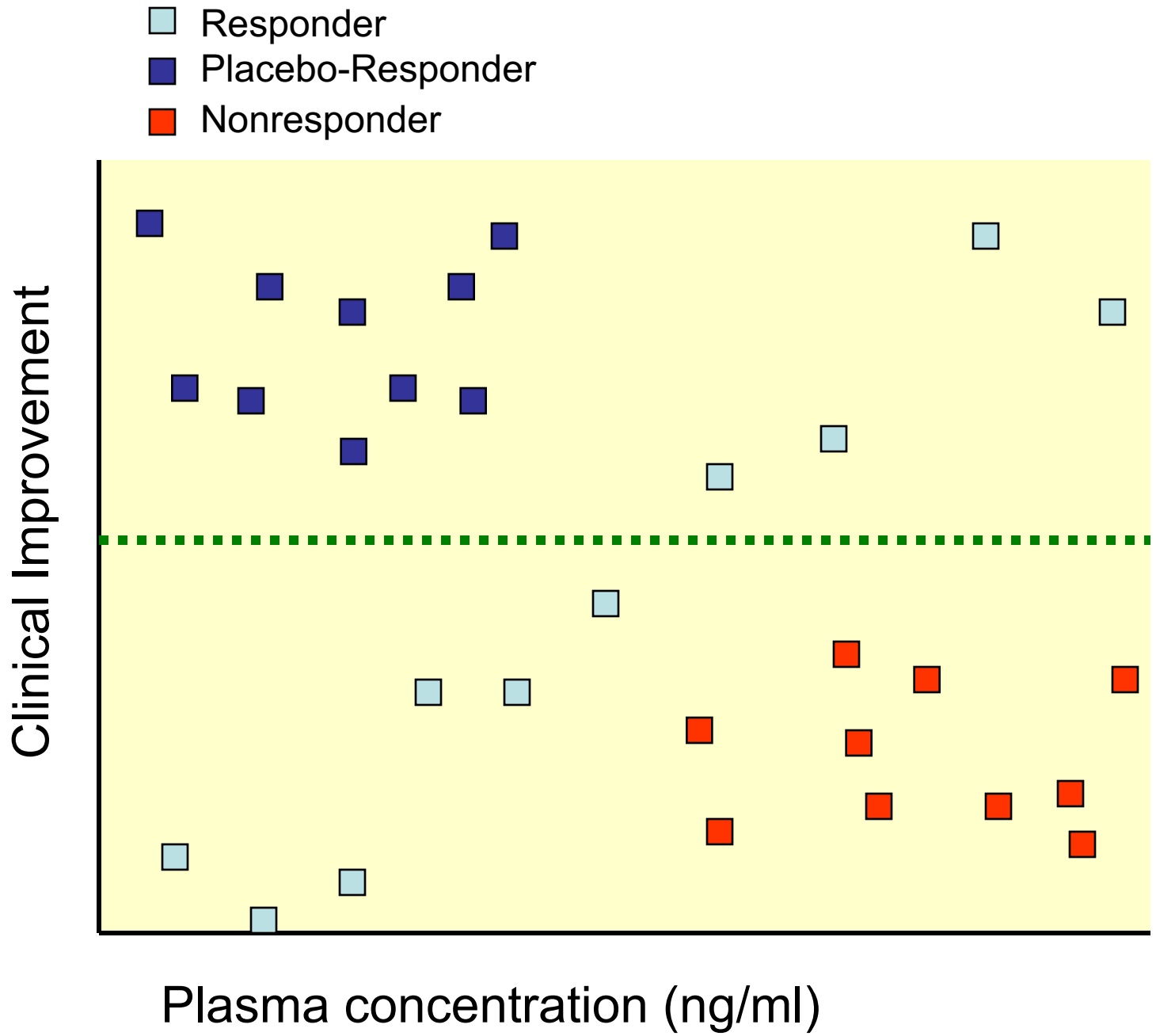
CLINICAL RESPONSE CORRELATES WITH DRUG CONCENTRATIONS IN BLOOD

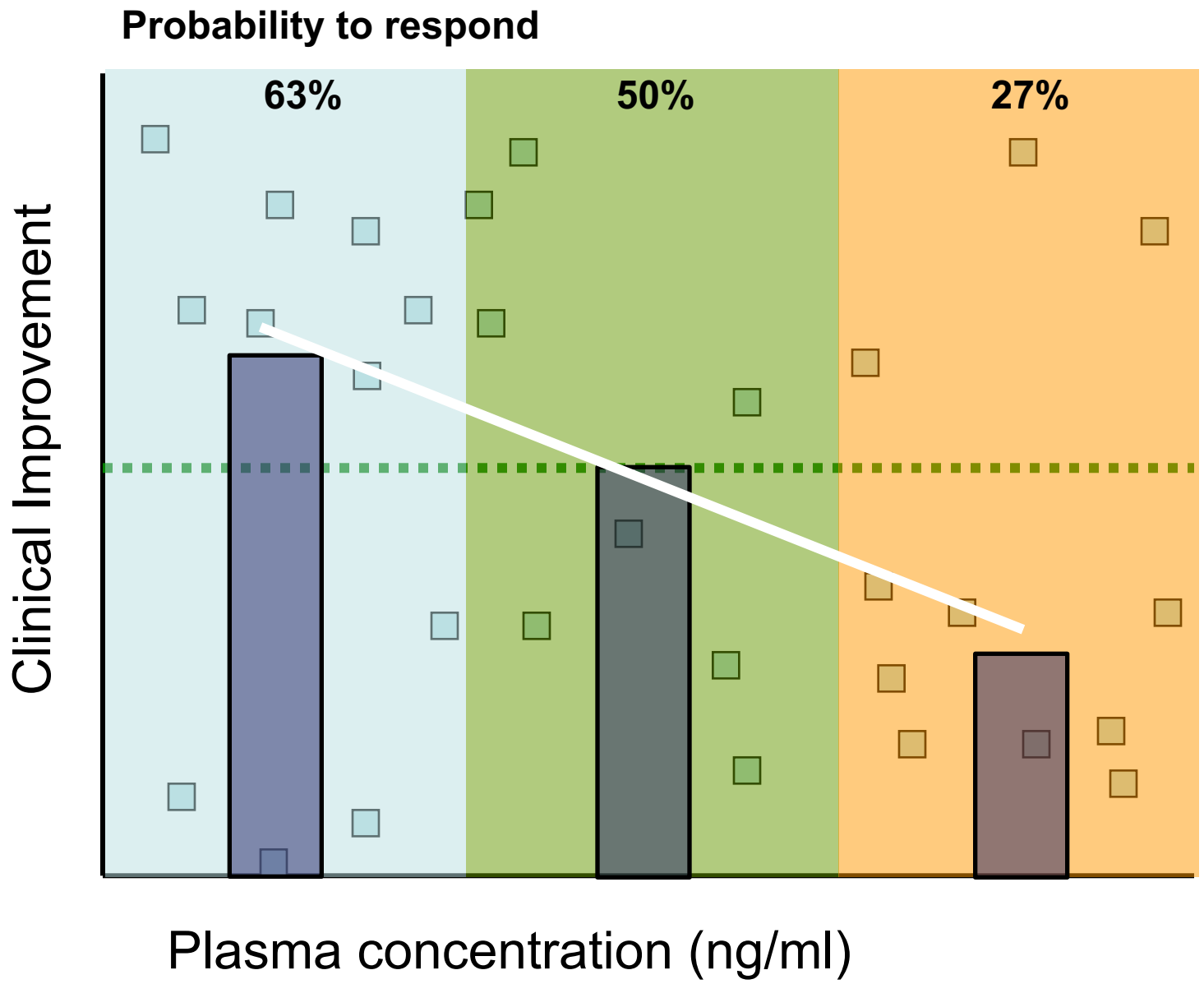


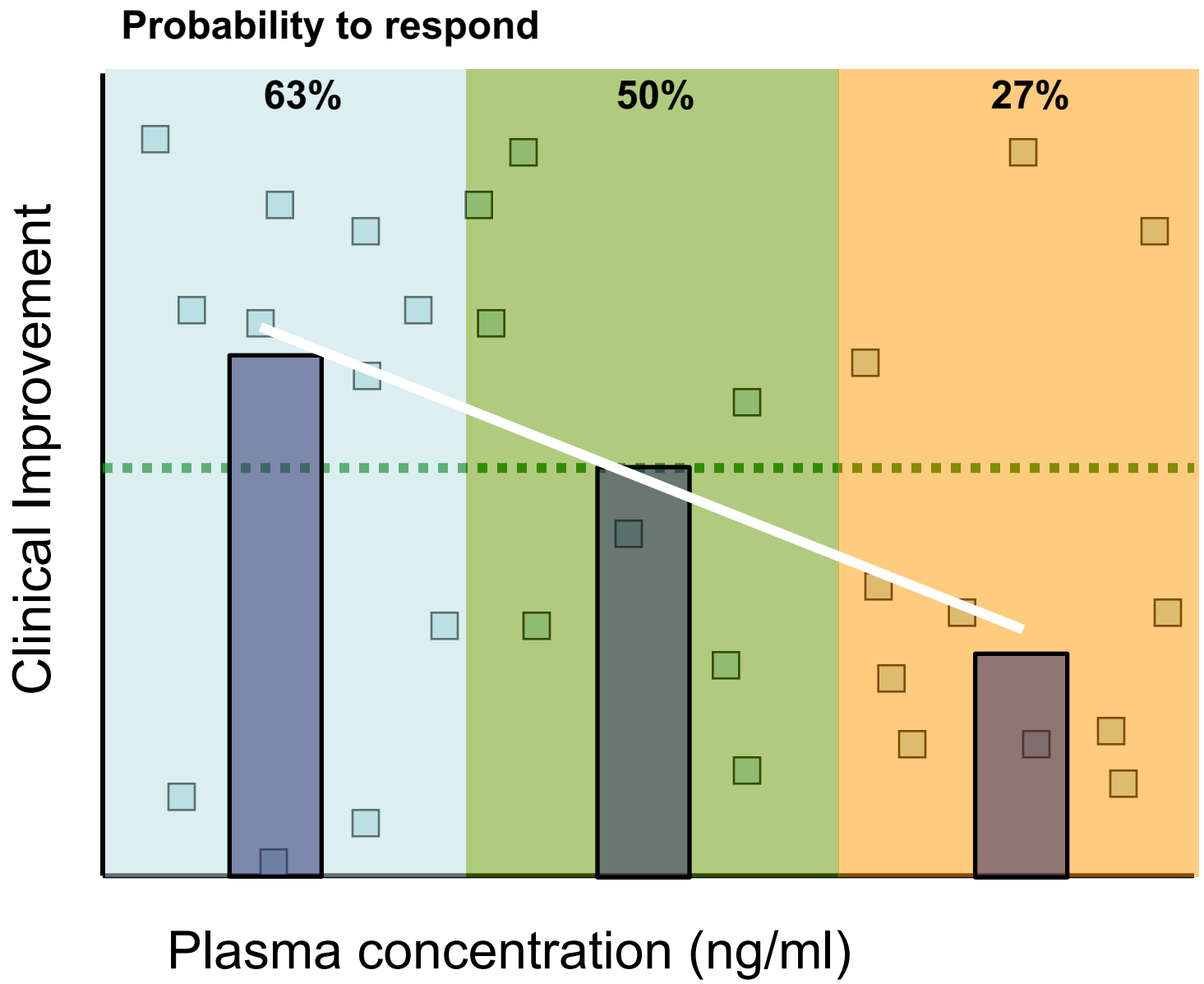
CLINICAL RESPONSE CORRELATES WITH DRUG CONCENTRATIONS IN BLOOD

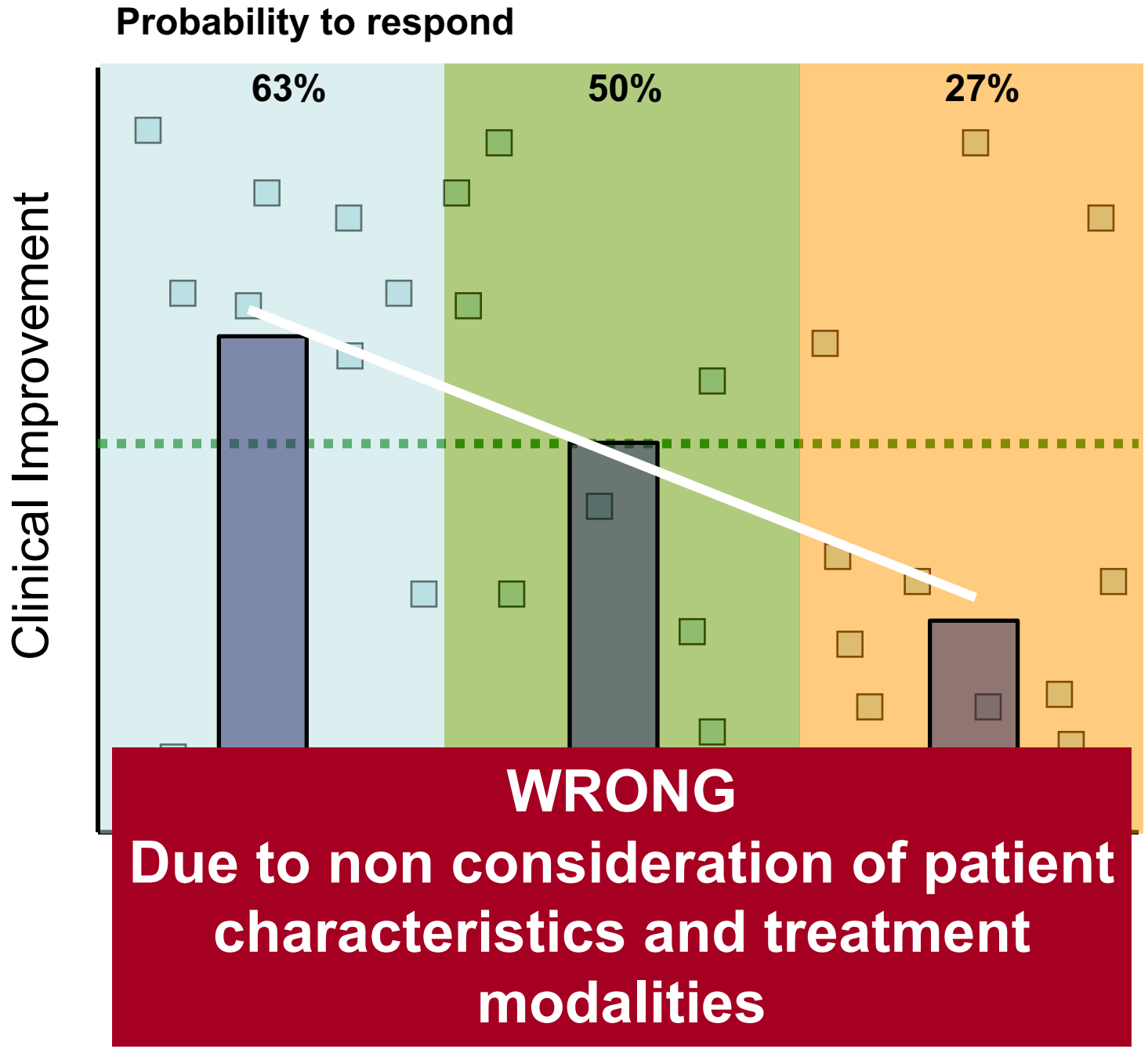

Responders
Placebo-Responders
Nonresponders
Clinical Improvement
Plasma concentration (ng/ml)


Responder
Placebo-Responder
Nonresponder
FLEXIBLE DOSES
Clinical Improvement
Plasma concentration (ng/ml)


Responder
Placebo-Responder
Nonresponder
Clinical Improvement
Plasma concentration (ng/ml)


Probability to respond
63%
50%
27%
Clinical Improvement
Plasma concentration (ng/ml)


Probability to respond
63%
50%
27%
Clinical Improvement
Plasma concentration (ng/ml)


Probability to respond
63%
50%
27%
Clinical Improvement
WRONG
Due to non consideration of patient characteristics and treatment modalities

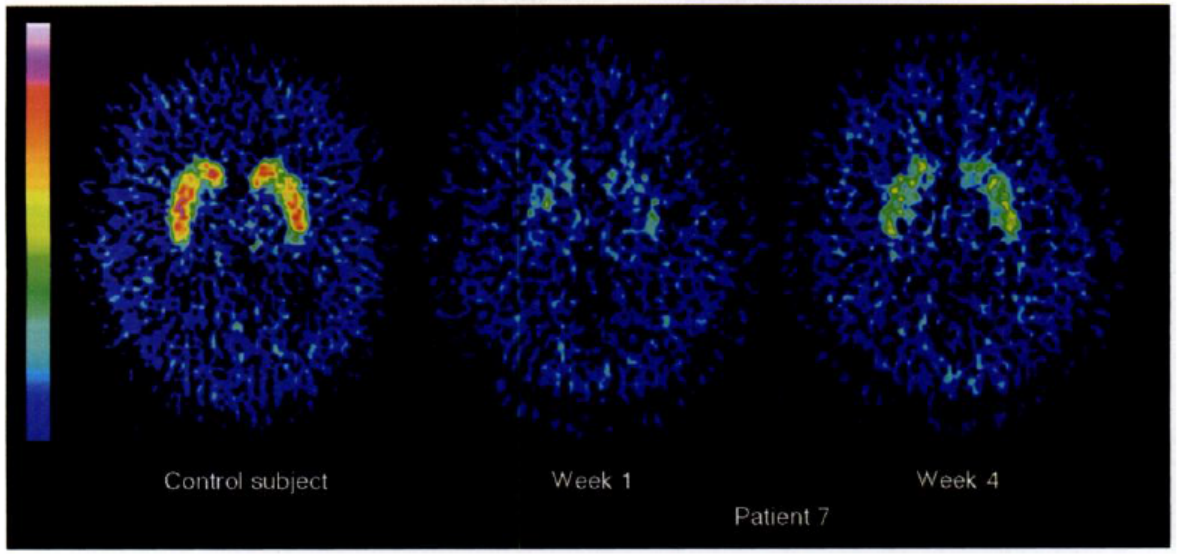
How to find (therapeutic) reference ranges?

PET-Imaging

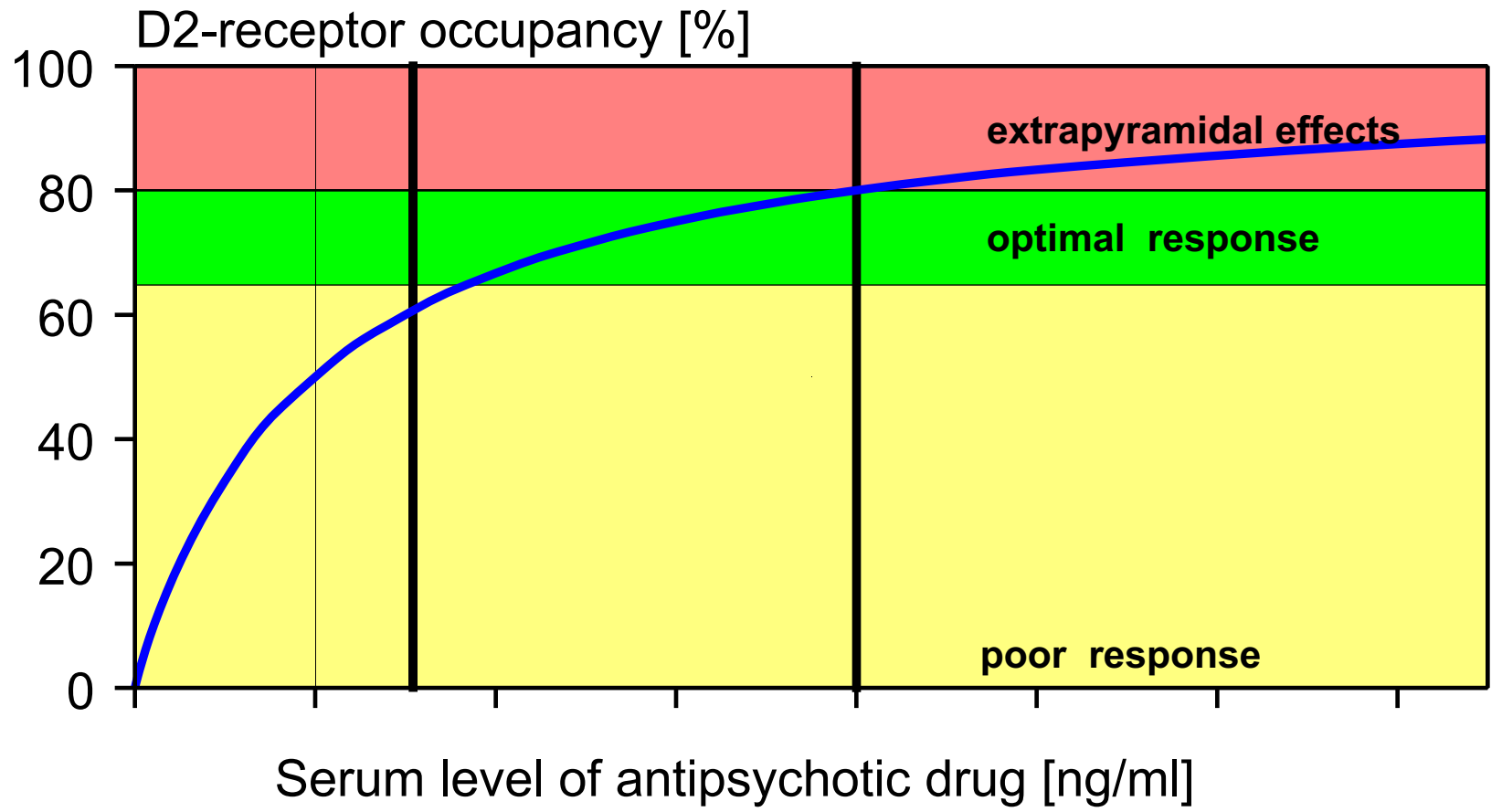
D_2 Dopamine Receptor Occupancy During Low-Dose Treatment With Haloperidol Decanoate

Svante Nyberg, M.D., Lars Farde, M.D., Ph.D., Christer Halldin, Ph.D., Marja-Liisa Dahl, M.D., Ph.D., and Leif Bertilsson, Ph.D.

FIGURE 2. Reconstructed PET Images Representing a Transverse Section of the Brain at the Level of the Basal Ganglia in a Healthy Subject (Left) and in a Schizophrenic Patient (Study Patient 7) 1 Week After Injection (Middle) and 4 Weeks After Injection (Right) of 50 mg of Haloperidol Decanoate

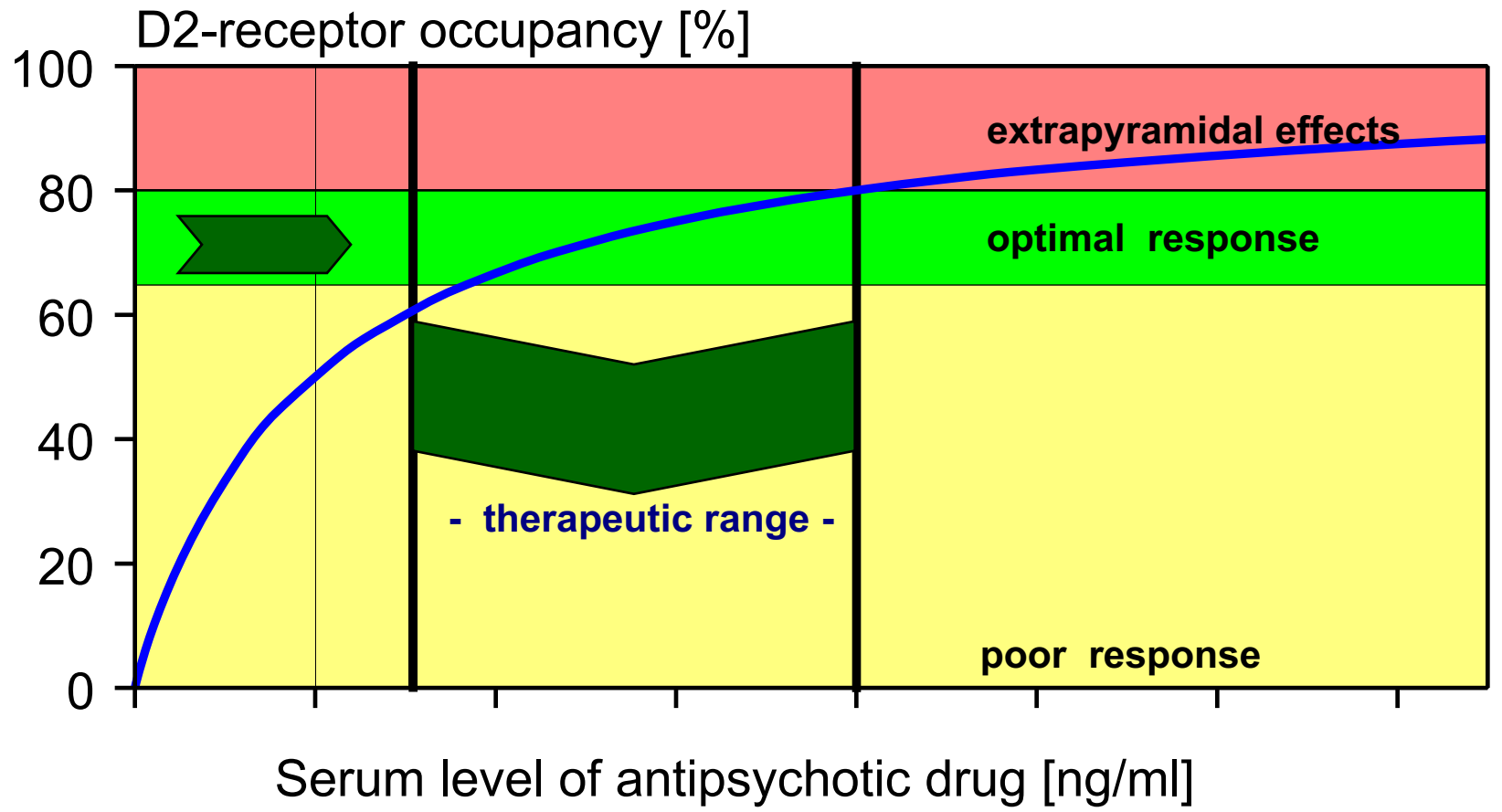


PET-Imaging
Antipsychotic Drugs



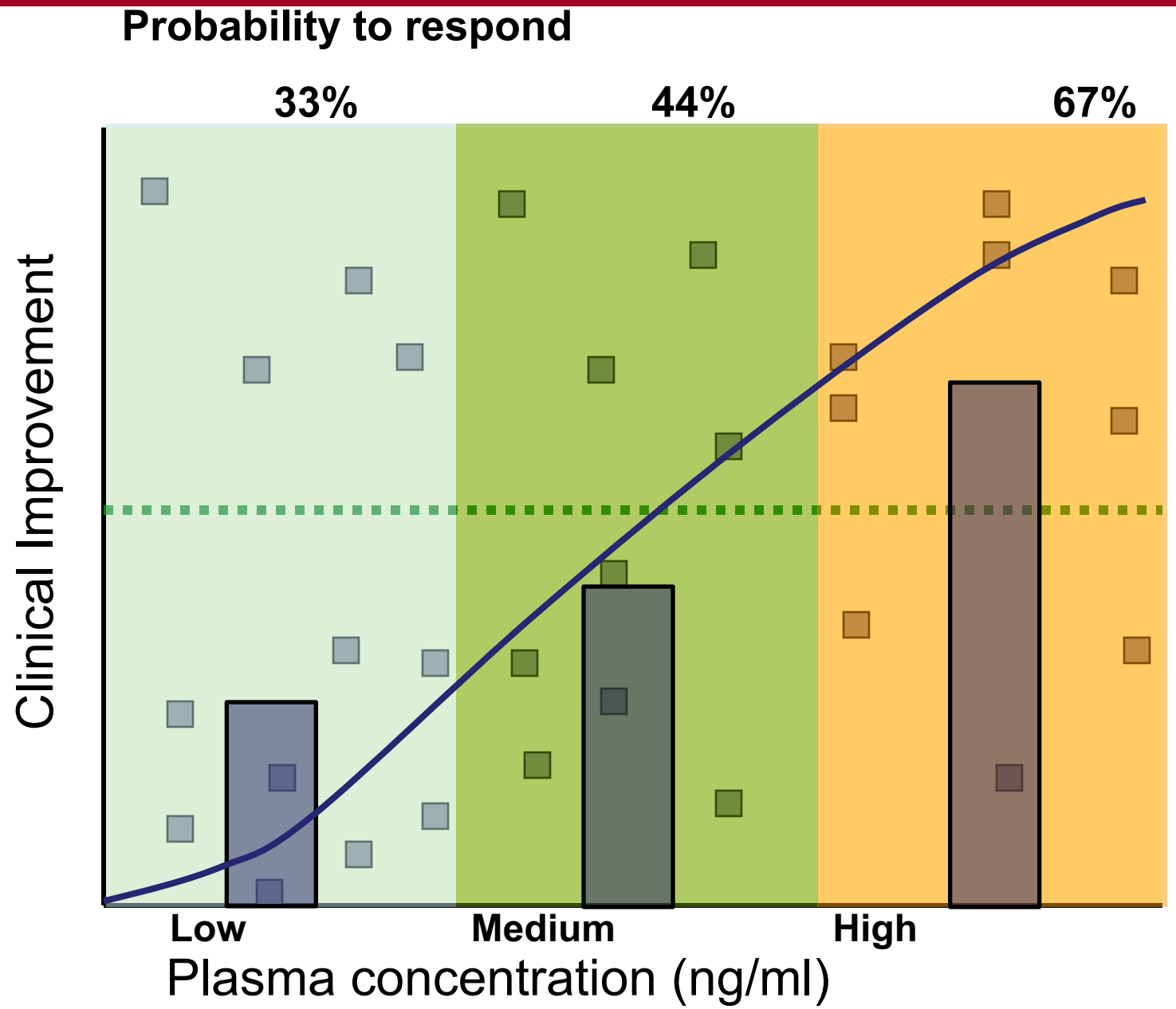
Sedvall, Farde 1996, modified

PET-Imaging
Antipsychotic Drugs

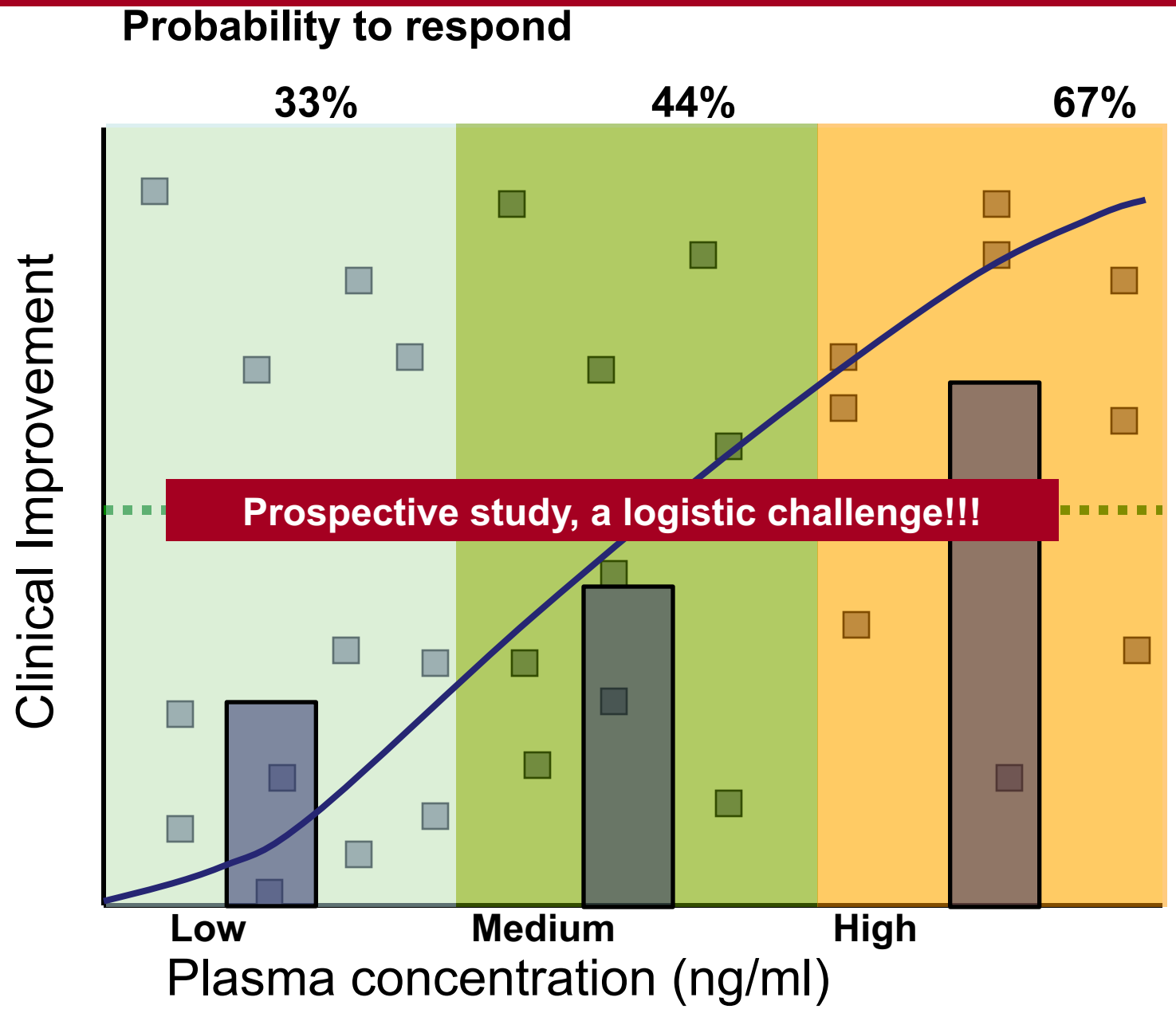


Sedvall, Farde 1996, modified

How to find (therapeutic) reference ranges?



How to find (therapeutic) reference ranges?



Effects of first-generation antipsychotics versus second-generation antipsychotics on quality of life in schizophrenia: a double-blind, randomised study

Gerhard Gründer, Martin Heinze*, Joachim Cordes, Bernd Mühlbauer, Georg Juckel, Constanze Schulz, Eckart Rüther, Jürgen Timm, for the NeSSy Study Group†*

Drugs and active metabolites	Therapeutic reference range/recommended drug concentration
Antipsychotic drugs	

Change of reference range during clinical trial

Haloperidol	**5-17 ng/mL**	**Baumann et al. 2004**
Haloperidol	**1-10 ng/mL**	**Hiemke et al. 2011**

Lancet Psychiatry. 2016 Aug;3(8):717-29.

Effects of first-generation antipsychotics versus second-generation antipsychotics on quality of life in schizophrenia: a double-blind, randomised study

Gerhard Gründer, Martin Heinze*, Joachim Cordes, Bernd Mühlbauer, Georg Juckel, Constanze Schulz, Eckart Rüther, Jürgen Timm, for the NeSSy Study Group†*

Were concentrations of haloperidol in blood of patients who had been treated under well controlled clinical supervision who had responded well within

- the reference range 2004: 5-17

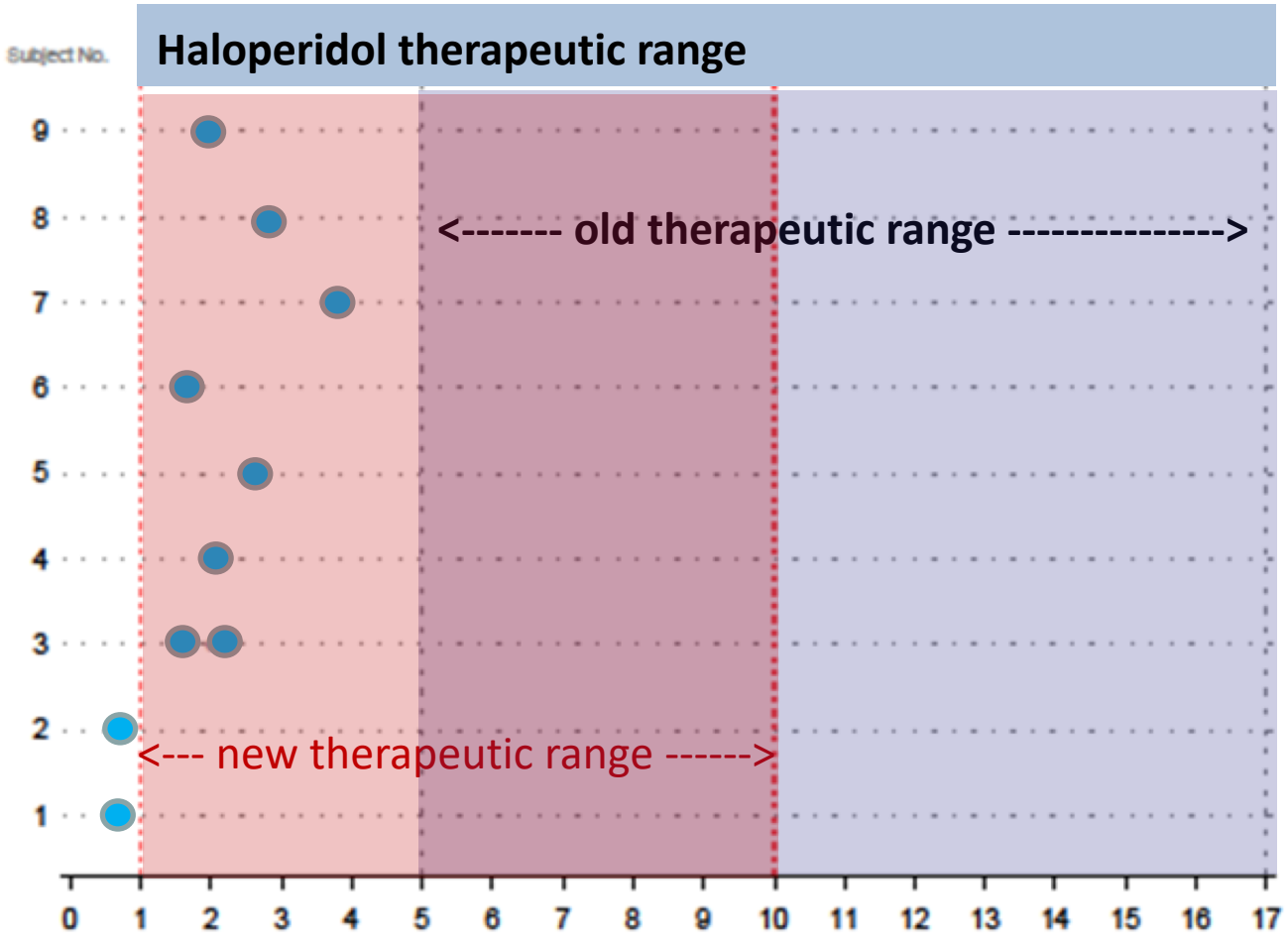
or

- the reference range 2011: 1-10 ng/mL

Lancet Psychiatry. 2016 Aug;3(8):717-29.

Effects of first-generation antipsychotics versus second-generation antipsychotics on quality of life in schizophrenia: a double-blind, randomised study

Gerhard Grü ... *for the NeSS* ... *mm,*



The NESSY group

Hypothesis

The concentration range of drugs in blood of patients who have responded to the drug reflects the therapeutic reference range.

Methods

Selection of concentrations from TDM data bases for psychoactive drugs in blood of patients who had improved under treatment (measured by CGI) at least „much improved“

Results

Concentrations of drugs in blood of patients who had at least „much improved“ according to CGI.

Antipsychotic drugs

Drug	Consensus* range (ng/ml)	Observed** Q1-Q3 range (ng/ml)
Amisulpride	100-320	93-281
Aripiprazole	150-500	146-300
Quetiapine	100-500	66-227
Olanzapine	20-80	23-56
Risperidone	20-60	20-44
Ziprasidone	50-120	39-97

Gründer and Hiemke

*** Consensus Guidelines 2018** **** TDM data**

Conclusion

The interquartile concentration range of drugs in blood of patients who have responded to the drug can be used as preliminary therapeutic reference range as long as clinical trials with appropriate methodology are lacking.

How to do TDM of AEDs or APDs?

Handbooks, guidelines?

TDM of antiepileptic drugs

SPECIAL REPORT

Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies

*Philip N. Patsalos, †David J. Berry, ‡Blaise F. D. Bourgeois, §James C. Cloyd, ¶Tracy A. Glauser, #Svein I. Johannessen, $Ilo E. Leppik, **Torbjörn Tomson, and ††Emilio Perucca

Patsalos et al. *Epilepsia*, 49(7):1239–1276, 2008

TDM of antiepileptic drugs

Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy: A 2018 Update

Philip N. Patsalos, FRCPath, PhD,† Edgar P. Spencer, CChem, FRSC, PhD,* and Dave J. Berry, FRCPath, PhD**

Background: Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment. Since 1989, 18 new AEDs have been licensed for clinical use and there are now 27 licensed AEDs in total for the treatment of patients with epilepsy. Furthermore, several AEDs are also used for the management of other medical conditions, for example, pain and bipolar disorder.

ampanel, piracetam, pregabalin, rufinamide, stiripentol, sulthiame, tiagabine, topiramate, vigabatrin, and zonisamide).

Key Words: AEDs, TDM, pharmacokinetics, drug–drug interactions, plasma, serum, saliva

(*Ther Drug Monit* 2018;40:526–548)

Patsalos et al. Ther Drug Monit 2018;40:526–548

TDM of antiepileptic drugs

TABLE 3. Pharmacokinetic Parameters and Serum Reference Ranges for the Various AEDs Prescribed as Monotherapy to Adults

	Time to Steady State (d)	Plasma Protein Binding (%)¶¶	Half-Life (h)	Pharmacologically Active Metabolites That Also Need Monitoring	Plasma Reference Range*		Monitoring Useful of:	
					mg/L	μmol/L	Saliva	Plasma Free Fraction
Brivaracetam (Briviact)	1–2	35	7–8		0.2–2	1–10	Yes	No
Carbamazepine (Tegretol)	2–4†	75	8–20†	Carbamazepine-epoxide§§	4–12	17–51	Yes	Yes
Clobazam (Frisium)	7–10‡	90	10–30	N-Desmethylclobazam	0.03–0.3 0.3–3.0§	0.1–1.0 1.0–10.5§	Yes	No
Clonazepam (Rivotril)	3–10	90	17–56		0.02–0.07	0.06–0.22	No	No
Eslicarbazepine acetate (Zebinix)¶	3–4	44	13–20	Eslicarbazepine	3–35‖	12–139‖	Yes	No
Ethosuximide (Emeside)	8–12	22	40–60		40–100	283–708	Yes	No
Felbamate (Felbatol)	3–5	48	16–22		30–60	126–252	Yes	No
Gabapentin (Neurontin)	1–2	0	5–9		2–20	12–117	Yes	No
Lacosamide (Vimpat)	2–3	14	12–14		10–20	40–80	Yes	No

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TDM of antiepileptic drugs

Carbamazepine

Indications

Carbamazepine is a first-line drug for the treatment of partial and secondarily generalized tonic–clonic seizures as well as primary generalized tonic–clonic seizures. It is also used to treat trigeminal neuralgia and bipolar disorder unresponsive to lithium.

Pharmacokinetics

The pharmacokinetics of carbamazepine are nonlinear because of autoinduction that completes within 3 weeks and can result in a 3-fold increase in elimination.[67,68] After oral ingestion, the absorption of carbamazepine is erratic and variable with T_{max} being formulation-dependent (range 0.5–9.0 hours),[69] bioavailability being 75%–85%, and V_d being 0.8–2.0 L/kg. Carbamazepine is 75% bound to plasma proteins and its pharmacologically active metabolite, carbamazepine-epoxide, is 50% protein-bound.[61] Carbamazepine is extensively metabolized in the liver, primarily by CYP3A4, to carbamazepine-epoxide, which accumulates in plasma and is pharmacologically equipotent to carbamazepine. Carbamazepine-epoxide is further metabolized, by epoxide hydrolase, to the pharmacologically inactive 10, 11-diol, which is eliminated in urine partly unchanged and partly as a glucuronide conjugate. The $t_{1/2}$ of carbamazepine in adults is 8–20 hours, whereas in children and the elderly, it is 10–13 hours and 30–50 hours, respectively. The $t_{1/2}$ of carbamazepine-epoxide is ~34 hours.

that inhibit the metabolism of carbamazepine and thus increase carbamazepine blood concentrations include clobazam and stiripentol. By contrast, felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide induce carbamazepine metabolism and decrease carbamazepine concentrations.[70]

Carbamazepine metabolism can also be affected by many nonepilepsy drugs. The drugs that inhibit carbamazepine metabolism and increase blood concentrations include: clarithromycin, cimetidine, ciprofloxacin, danazol, diltiazem, erythromycin, fluconazole, fluoxetine, flurithromycin, grapefruit juice, haloperidol, isoniazid, isotretinoin, josamycin, ketoconazole, metronidazole, miconazole, nefazodone, nelfinavir, nicotinamide, ponsinomycin, propoxyphene, ritonavir, ticlopidine, trazodone, troleandomycin, verapamil, and viloxazine. Nonepilepsy drugs that induce carbamazepine metabolism and decrease blood concentrations include efavirenz, probenecid, rifampicin, risperidone, St John's Wort, and theophylline. Some drugs do not alter carbamazepine concentrations per se, but can increase carbamazepine-epoxide concentrations, through the inhibition of epoxide hydrolase, and may cause typical carbamazepine toxicity. These drugs include brivaracetam, valproic acid, zonisamide, amoxapine, loxapine, and quetiapine.[70,71]

Carbamazepine TDM

Because the pharmacokinetics of carbamazepine are nonlinear (due to autoinduction), that its efficacy and adverse

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TDM of antipsychotic drugs

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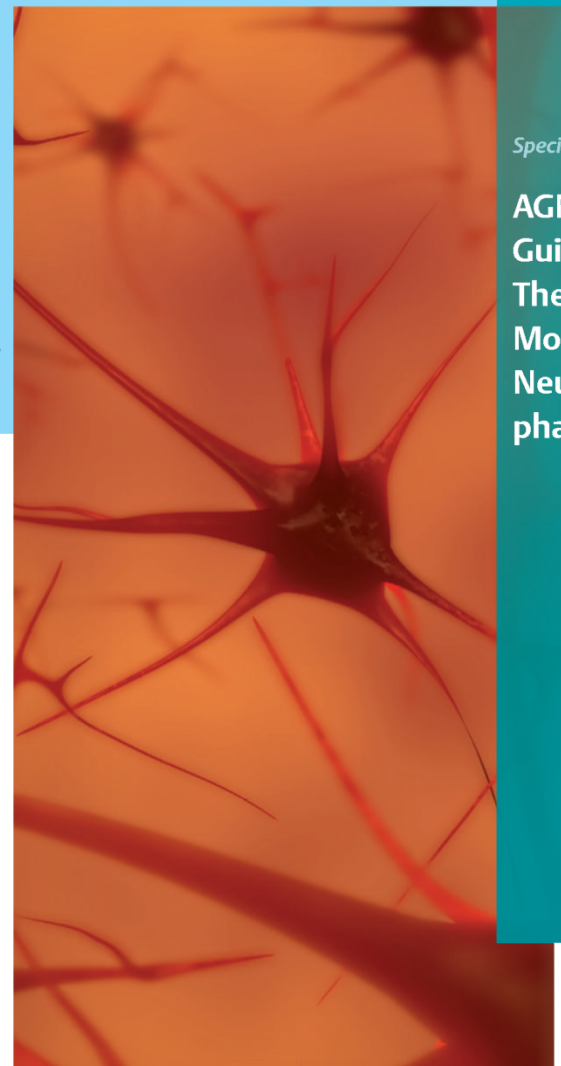

Special Issue

AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsycho-pharmacology

This journal is indexed in Current Contents (LS), Science Citation Index, MEDLINE, EMBASE and SCOPUS.

Official Organ of the Arbeitsgemeinschaft für Neuropsycho-pharmakologie und Pharmakopsychiatrie (AGNP)

Thieme

Review

Thieme

Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017

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TDM in psychiatry and neurology: A comprehensive summary of the consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology, update 2017; a tool for clinicians

Georgios Schoretsanitis, Michael Paulzen, Stefan Unterecker, Markus Schwarz, Andreas Conca, Gerald Zernig, Gerhard Gründer, Ekkerhard Haen, Pierre Baumann, Niels Bergemann, Hans Willi Clement, Katharina Domschke, Gabriel Eckermann, Karin Egberts, Manfred Gerlach, Christine Greiner, Ursula Havemann-Reinecke, Gudrun Hefner, Renate Helmer, Ger Janssen, Eveline Jaquenoud-Sirot, Gerd Laux, Thomas Messer, Rainald Mössner, Matthias J. Müller, Bruno Pfuhlmann, Peter Riederer, Alois Saria, Bernd Schoppek, Margarete Silva Gracia, Benedikt Stegmann, Werner Steimer, Julia C. Stingl, Manfred Uhr, Sven Ulrich, Roland Waschgler, Gabriela Zurek & Christoph Hiemke

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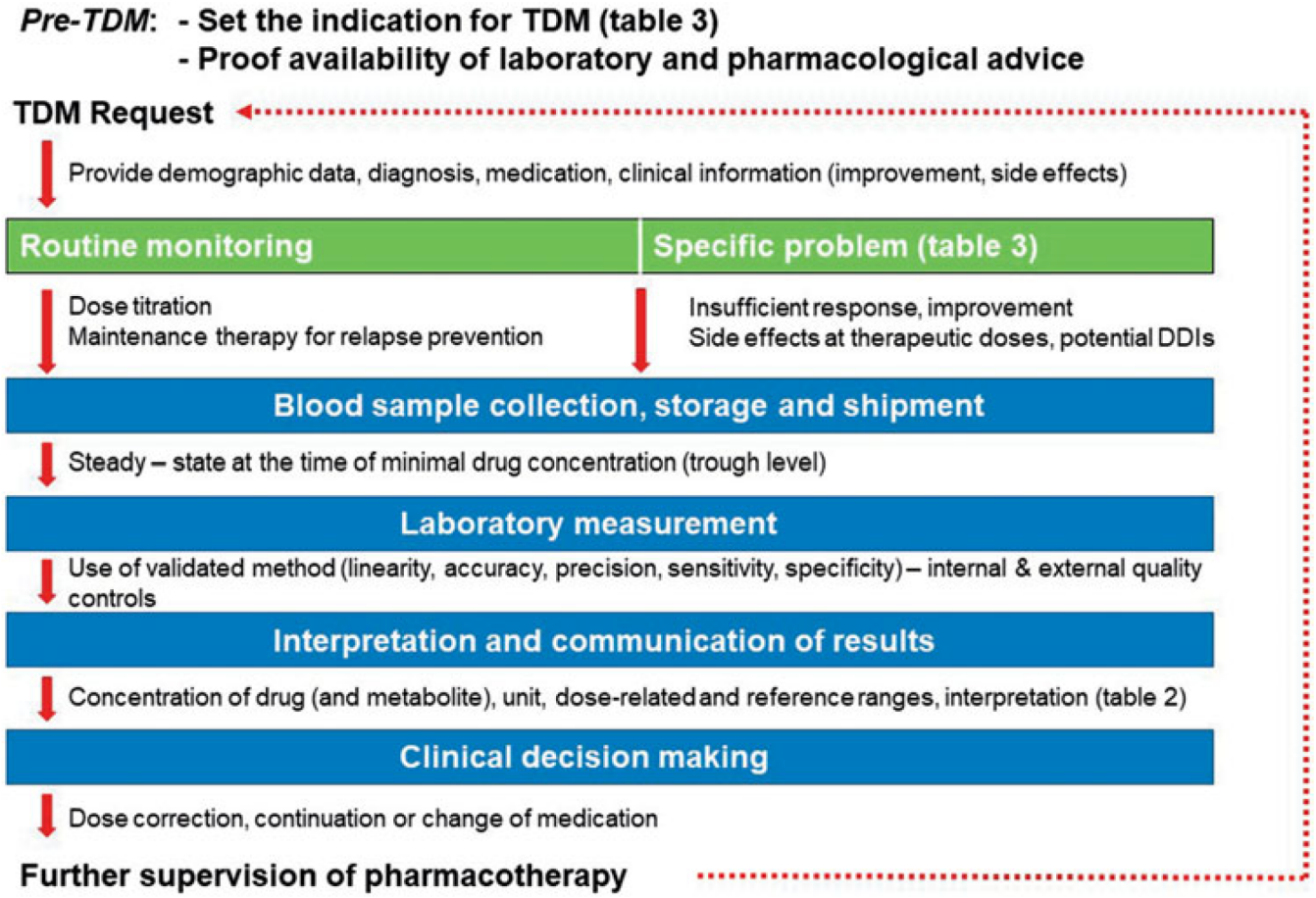

Figure 1. Schematic overview of the therapeutic drug monitoring (TDM) process as a guide for psychopharmacotherapy in everyday clinical practice (adapted from the original article (Hiemke et al. 2018)).

LABORATORY
Address
Phone
Fax

REQUESTING HOSPITAL / DOCTOR
Address
Phone in case of alert
Fax

PATIENT DETAILS	Name or Code	☐ Inpatient ☐ Outpatient	Date and time of blood withdrawal
Date of birth	Sex	Diagnosis / Symptom(s)	
☐ HIV-patient	Weight (kg)	Smoker ☐ No ☐ Moderate (<10 cig/day) ☐ Heavy (≥10cig/day) Genotype/phenotype to be considered (e.g. CYP2D6, 2C19, 1A2):	

REASON FOR REQUEST
(tick more than one if applicable)
☐ Control of adherence
☐ Dose adaptation
☐ Insufficient improvement
☐ Adverse effects (specify below)
☐ Drug-drug interaction
☐ Control under maintenance therapy
☐ Other reason (to be specified)

SEVERITY OF ILLNESS *(CGI-S)*
How mentally ill is the patient at this time?
☐ Not at all ill (1)
☐ Borderline mentally ill (2)
☐ Mildly ill (3)
☐ Moderately ill (4)
☐ Markedly ill (5)
☐ Severely ill (6)
☐ Extremely ill (7)

IMPROVEMENT *(CGI-I)*
Change compared to condition at admission?
☐ Very much improved (1)
☐ Much improved (2)
☐ Minimally improved (3)
☐ No change (4)
☐ Minimally worse (5)
☐ Much worse (6)
☐ Very much worse (7)

ADVERSE DRUG REACTION *(UKU)*
☐ not at all (0) ☐ a little (1) ☐ moderate (2) ☐ severe (3)

☐☐ Concentration difficulties ☐☐ Asthenia ☐ Sleepiness/Sedation
☐☐ Tension/inner unrest ☐☐ Sleep disturbances ☐☐ Emotional indifference
☐☐ Dystonia ☐☐ Rigidity ☐☐ Hypokinesia/Akinesia ☐☐ Hyperkinesia ☐ Tremor
☐☐ Akathisia ☐☐ Epileptic seizures ☐ Paresthesias ☐☐ Headache
☐☐ Accomodation disturbance ☐☐ Increased salivation ☐☐ Dry mouth
☐☐ Nausea/Vomiting ☐☐ Diarrhoea ☐☐ Constipation ☐☐ Micturation disturbance
☐☐ Polyuria/Polydypsia ☐☐ Increased sweeting ☐☐ Galactorrhoea ☐☐ Weight gain
☐☐ Sexual dysfunction ☐☐ Other (to be specified)
Causal relationship: ☐☐ improbable ☐☐ possible ☐☐ probable

Drug(s) to be assayed	**Formulation**	**Daily dose / dosing schedule**	**Date started**	**Time of last dose**

Other medications (include herbals, over-the-counter drugs etc)

TDM request: *Blood should be withdrawn under steady-state conditions, preferably in the morning BEFORE taking the morning dose.*
Return the completed form, together with a minimum of 1 ml serum or plasma.

Date of sample receipt:

Signature :

Figure 5

Tables

1. CYP Substrates
2. CYP Inhibitors
3. CYP Inducers
4: Therapeutic reference range
5: Dose related reference range
6: Metabolite to parent compund ratios
7: Indications for TDM

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TDM – Case

Olanzapine

Schizophrenia, F 20.0
62 years / male / outpatient

- **Smoker, but stop of smoking because of severe cough**
- **Olanzapine**
- **Dose increased from 10 to 20 mg/d**
- **Last change of dose: 1 week before**
- **Last drug intake: 50 hours before olanzapine discontinued because of bike acccident (broken shoulder)**
- **Clinical improvement: Moderate**
- **Side effects: Not reported**

Laboratory result:

Olanzapine:

115 ng/mL

Questions that can be answered using the TDM guidelines of the AGNP:

1. Indication for TDM?
2. Enzymes involved in the degradation of olanzapine?
3. Concentration of olanzapine in accordance with the dose?
4. Does smoking have an impact on drug concentration?
5. Other factors?
6. Interpretation and recommendations?

TDM – Case

Olanzapine

Schizophrenia, F 20.0
62 years / male / outpatient

- **Smoker, but stop of smoking because of severe cough**
- **Olanzapine**
- **Dose increased from 10 to 20 mg/d**
- **Last change of dose: 1 week before**
- **Last drug intake: 50 hours before olanzapine discontinued because of bike acccident (broken shoulder)**
- **Clinical improvement: Moderate**
- **Side effects: Not reported**

Laboratory result:

Olanzapine:

115 ng/mL

Questions that can be answered using the TDM guidelines of the AGNP:

1. Indication for TDM? **Yes**
2. Enzymes involved in the degradation of olanzapine? **CYP1A2**
3. Concentration of olanzapine in accordance with the dose? **No, higher**
4. Does smoking have an impact on drug concentration? **Yes**
5. Other factors? **Infection**
6. Interpretation and recommendations?

Table 3. Typical indications for measuring concentrations of medications in blood for psychiatric or neurologic patients (adapted from the original paper: Hiemke et al. 2018).

Obligatory TDM for drugs with high levels of recommendation to use TDM

- Dosage optimization after initial prescription or after dosage change
- Drugs, for which TDM is mandatory for safety reasons (e.g., lithium or carbamazepine)

Specific indications for TDM for any drug independent of its level of recommendation to use TDM

- Uncertain adherence to medication
- Lack of clinical improvement under recommended dosage
- Relapse under maintenance treatment
- Relapse prevention because of uncertain adherence to medication
- Recurrence of symptoms under adequate dosage
- Adverse effects and clinical improvement under recommended dosage
- Combination treatment with a drug known for its interaction potential or suspected drug interaction

► **Table 1** Continued.

Drugs	Enzymes and transporters
Olanzapine	**UGT1A4**, UGT2B10, FMO, **CYP1A2**, CYP2D6, P-gp (ABCB1)

Table 2. Recommended therapeutic reference ranges, elimination half-lives ($t_{1/2}$), laboratory alert levels, levels of recommendation to use therapeutic drug monitoring (TDM) for dose optimization without specific indications, conversion factors (CFs) and factors for calculation of dose-related drug concentrations (DRCs) and metabolite-to-parent ratios (MPRs) (adapted from the original paper: Hiemke et al. 2018). Unless otherwise indicated, reference ranges and alert levels refer to trough concentrations.

Drugs and active metabolites	Therapeutic reference ranges in blood	$t_{1/2}$	Laboratory alert levels	Recommendation levels	CF	DRC	MPR
Lurasidone	15–40 ng/ml	20–40 h	120 ng/ml	3	2.03	0.11 ± 0.02	
Melperone	30–100 ng/ml	4–6 h	200 ng/ml	3	3.80	0.18 ± 0.03	
Olanzapine	20–80 ng/ml	30–60 h[3]	100 ng/ml	1	3.20	1.85 ± 0.74	0.1–0.3
Paliperidone	20–60 ng/ml	17–23 h[4]	120 ng/ml	2	2.35	3.97 ± 1.92	

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Table 1(b). Inhibitors of CYP450 isoenzymes (adapted from the original paper: Hiemke et al. 2018). Induction of enzymes indicated in bold will decrease plasma concentrations of victim drugs by more than 50%.

Inductors	Induced enzymes or ABC transporters
Bosentan	**CYP3A4**
Carbamazepine	CYP1A2, **CYP2B6**, CYP2C9, **CYP3A4, P-gp, UGT**
Efavirenz	**CYP2B6, CYP3A4**
Ethanol	**CYP2E1**
Isoniazide	**CYP2E1**
Lamotrigine	**UGT**
Modafinil	CYP1A2, CYP2B6, CYP3A4
Oxybutynin	**CYP3A4**
Phenobarbital	CYP1A2, **CYP2B6**, CYP2C9, CYP2C19, **CYP3A4, UGT1A1**
Phenytoin	CYP1A2, **CYP2B6**, CYP2C9, CYP2C19, **CYP3A4, UGT**
Primidon	CYP2C9, CYP2C19, **CYP3A4**
Rifabutin	**CYP3A4**
Rifampicin	**CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4**
Ritonavir	**CYP2C9**, CYP3A4 (high dose), UGT
Smoking	**CYP1A2**
St. John's wort	**CYP3A4**, CYP2C9, **P-gp**

ABC: ATP-binding cassette transporter; CYP: cytochrome P450; P-gp: P-glycoprotein; UGT: UDP-glucuronosyltransferase

potential or suspected drug interaction
- Presence of a genetic peculiarity concerning drug metabolism (genetic deficiency, gene multiplication)
- Patient with differential ethnicity
- Patient with abnormally high or low body weight
- Pregnant or breast feeding patient
- Children or adolescent patient
- Elderly patient (>65 years old)
- Patients with intellectual disability
- Forensic psychiatric patient
- Court case related to neuropsychiatric medications
- Patient with pharmacokinetically relevant comorbidity (hepatic or renal insufficiency, cardiovascular disease)
- Patient with acute or chronic inflammations or infections
- Patient with restrictive gastrointestinal resection or bariatric surgery
- Problem occurring after switching from an original preparation to a generic form (and vice versa)
- Pharmacovigilance programs

TDM: therapeutic drug monitoring.

Therapeutic reference range

▶ **Table 4** Recommended therapeutic reference ranges (consensus), elimination half-life (t1/2) ranges and laboratory alert levels for neuropsychopharmacological drugs and levels of recommendation to use TDM as clinical routine for dose optimization without specific indications (see ▶ **Table 7**).

Drugs and active metabolites	Therapeutic reference range	t1/2 (h)	Laboratory alert level	Level of recommendation to use TDM	Conversion factor, CF	Comments	References
Antidepressant drugs							
Agomelatine	7–300 ng/mL (1–2 h after 50 mg)	1–2 h	600 ng/mL	4	4.11	Because of rapid elimination, trough drug concentrations are not measurable under chronic treatment; determinations, preferentially of Cmax, should be restricted to specific indications.	[126]
Amitriptyline plus nortriptyline	80–200 ng/mL	10–28 h 18–44 h	300 ng/mL	1	3.60 3.80	Increased toxicity in children and PM of CYP2D6, concentration-related impairment of driving performance	[451,465,557,924, 1101,1222]
Amitriptyline oxide amitriptyline plus nortriptyline	80–200 ng/mL	1.1–2.5 h 5–17 h 18–44 h	300 ng/mL	1	3.41 3.60 3.80	Prodrug, active moiety is the sum of amitriptyline and nortriptyline	[357]
Bupropion hydroxybupropion	10–100 ng/mL 850–1 500 ng/mL	1–15 h 17–47 h	2 000 ng/mL	2	4.17 3.91	Bupropion is unstable, hydroxybupropion is the major active compound exhibiting about 50 % of bupropion's activity, other metabolites exhibit 20 % of the activity of bupropion at best, the therapeutic reference range refers to hydroxybupropion only.	[259,260,570,678, 963,1160]
Citalopram	50–110 ng/mL	38–48 h	220 ng/mL	1	3.08	The N-demethylated metabolite might weakly contribute to pharmacological actions.	[71,117,180,413,581, 688,800,852,895,896, 988,990,1036,1087,1228]
Clomipramine plus N-desmethyl-clomipramine	230–450 ng/mL	16–60 h 37–43 h	450 ng/mL	1	3.18 3.32	Differential pharmacological profile of parent drug (preferential serotonin reuptake inhibition) and metabolite (preferential noradrenaline uptake inhibition)	[403]

Olanzapine	20–80 ng/mL	30–60 h	100 ng/mL

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TDM – Case

Olanzapine

Schizophrenia, F 20.0
62 years / male / outpatient

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- **Clinical improvement: Moderate**
- **Side effects: Not reported**

Laboratory result:

Olanzapine:

115 ng/mL

Questions that can be answered using the TDM guidelines of the AGNP:

Intoxication, infection and cessation of smoking were indications for TDM.
Enzymes involved in the degradation of olanzapine: CYP1A2

Concentration of olanzapine was much higher than expected.

Dose increase, cessation of smoking and infection all increased the concentration of olanzapine leading to an intoxication. Suicidality seemed unlikely. Thde patient can be re-expose to olanzapine under TDM control.

TDM guided pharmacotherapy

Indication for TDM

Blood withdrawal under Steady-State

Change of medication

Dose adaptation

Determination of drug concentrations in blood

Pharmacokinetics **Pharmacodynamics**

Continuation of medication and dose

TDM of antiepileptic and antipsychotic drugs