Clinical cases on dose adjustments based on TDM of antiepileptic and antipsychotic drugs

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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

Review

Thieme

Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017

Authors
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See www.agnp.de

Hiemke C et al. Consensus Guidelines for Therapeutic … Pharmacopsychiatry 2018; 51: 9–62

Pre-TDM: *Indication for TDM (Table 7)? Availability of laboratory and pharmacological advise?*

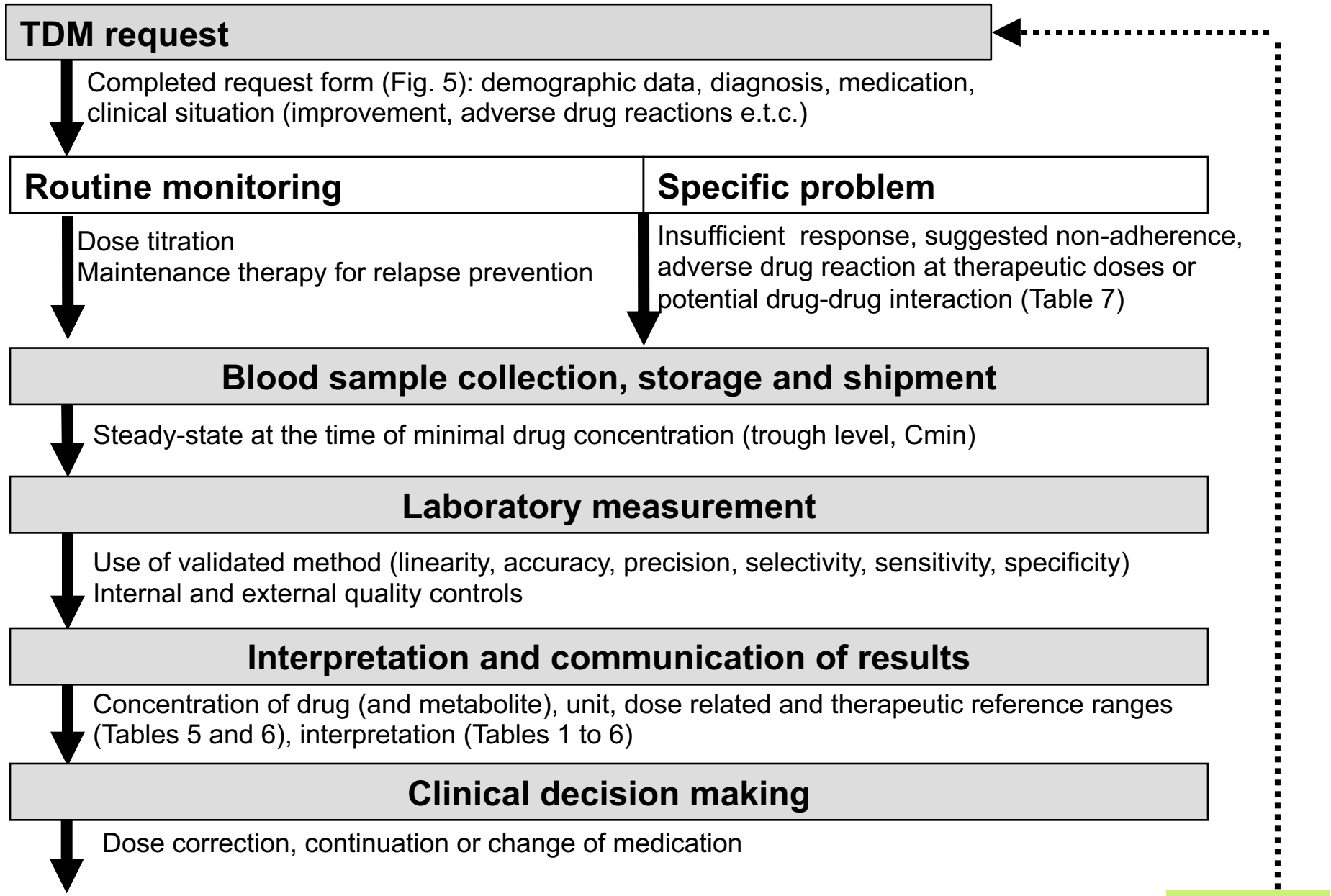

Figure 4

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

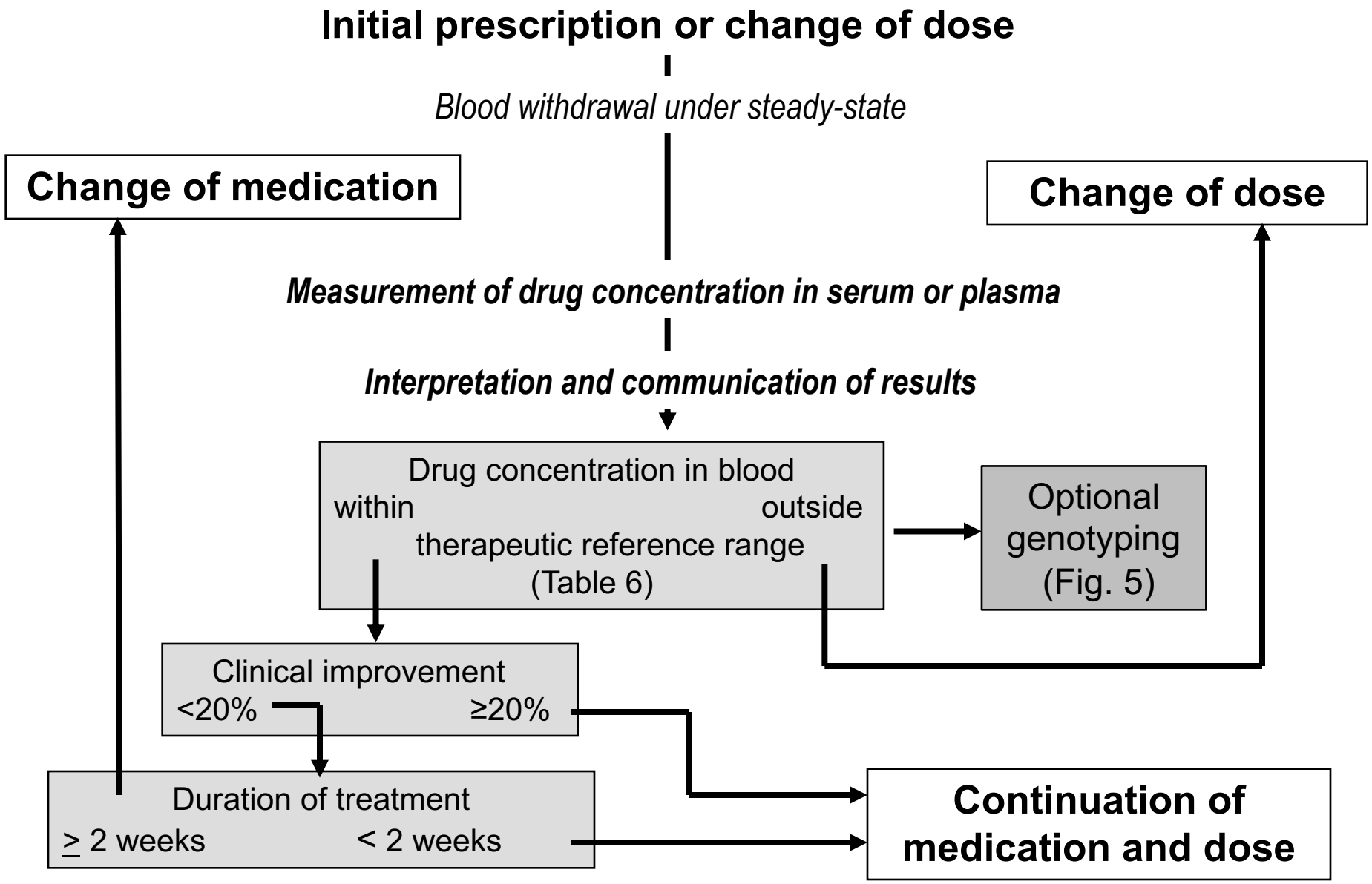
Initial prescription or change of dose
Blood withdrawal under steady-state
Change of medication
Change of dose
Measurement of drug concentration in serum or plasma
Interpretation and communication of results
Drug concentration in blood
within
outside
therapeutic reference range
(Table 6)
Optional genotyping (Fig. 5)
Clinical improvement
<20%
≥20%
Duration of treatment
≥ 2 weeks
< 2 weeks
Continuation of medication and dose

Figure 7

Pre-TDM: *Indication for TDM (Table 7)? Availability of laboratory and pharmacological advise?*

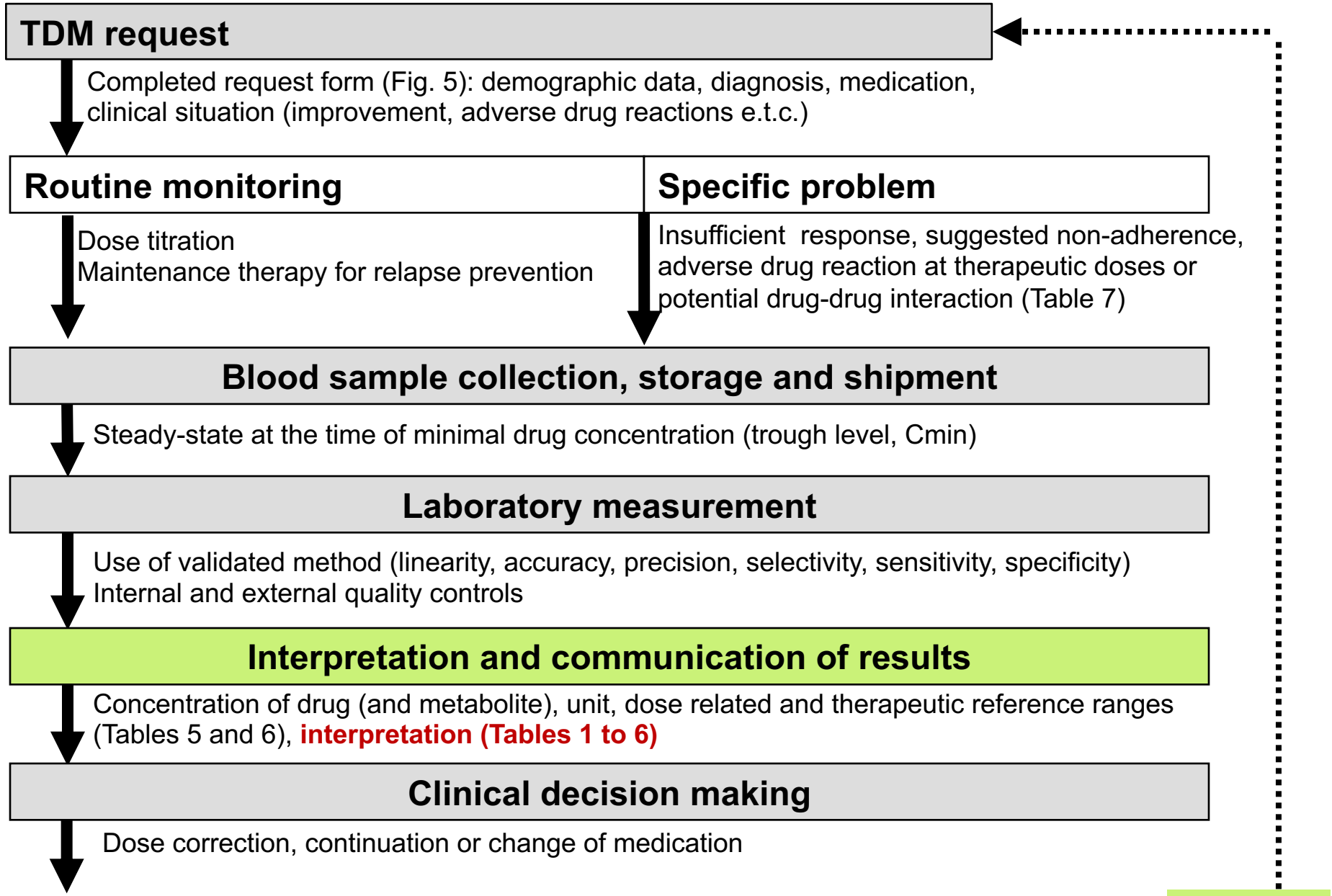

Figure 4

Clozapine

Requesting Hospital/Doctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
	Height	174 cm	ICD-10 Diagnose(s)	F 20.0
	Weight	103 kg	Blood withdrawal	08:00

Reason for request: Uncertain adherence

Drug to be assayed	Clozapine	**Concentration in blood**	
		Clozapine	225 ng/mL
		N-Desmethylclozapine	175 ng/mL

Drug(s)	**Dose morning**	**noon**	**evening**	**night**	**Last dose change**
Clozapine	100			150	2 weeks before
Simvastatine					
Sertraline	150				
ASS	100				

Clozapine

Requesting Hospital/Doctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
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Clozapine	100			150	2 weeks before
Simvastatine					
Sertraline	150				
ASS	100				

- TDM done in accordance with TDM guidelines?
- Steady state?
- Trough levels?

Clozapine

Requesting Hospital/Doctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
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	Weight	103 kg	Blood withdrawal	08:00

Reason for request: Uncertain adherence

Drug to be assayed	Clozapine	**Concentration in blood**	
		Clozapine	225 ng/mL
		N-Desmethylclozapine	175 ng/mL

- Patient is **severely ill (**6, according to nach CGI-S)
- No change since start of treatment (4, according to CGI-I)
- Patient is a **smoker,** consumes coffee (4 cups/ day)**, no alcohol**
- Adverse drug reactions**:** not reported

Clozapine

Requesting Hospital/Doctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
	Height	174 cm	ICD-10 Diagnose(s)	F 20.0
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- Patient is a **smoker,** consumes coffee (4 cups/ day)**, no alcohol**
- Adverse drug reactions**:** not reported

- TDM indicated?
- Is the concentration within the reference range?
- Are concentrations as expected for the dose of 250 mg/day?
- Possible drug-drug interactions?

Clozapine

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	Height	174 cm	ICD-10 Diagnose(s)	F 20.0
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- No change since start of treatment (4, according to CGI-I)
- Patient is a **smoker,** consumes coffee (4 cups/ day)**, no alcohol**
- Adverse drug reactions**:** not reported

- TDM indicated?
- Is the concentration within the reference range?
- Are concentrations as expected for the dose of 250 mg/day?
- Possible drug-drug interactions?

Indication for TDM

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)

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

Indication for TDM

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

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

- Uncertain adherence to medication
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- 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.

Interpretation (see Table 2)

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

Clozapine and N-Desmethylclozapine

Therapeutic reference range:

t1/2:

Laboratory alert level:

CF (conversion factor):

DRC (factor for calculation of expected drug related concentration):

MPR (metabolite to parent drug ratio):

Interpretation (Table 2)

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

Clozapine and N-Desmethylclozapine

Therapeutic reference range: 350-600 ng/mL

t1/2: 12-16 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 3.06

DRC (factor for calculation of expected drug related concentration): 1.01±0.58

MPR (metabolite to parent drug ratio):

Interpretation (Table 2)

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

Clozapine and N-Desmethylclozapine

Therapeutic reference range: 225 ng/mL Cloz
175 ng/mL N-DCloz
350-600 ng/mL

t1/2: 12-16 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 225 x 3.06 = xxx nmol/L
3.06

DRC (factor for calculation of expected drug related concentration):
1.01±0.58

MPR (metabolite to parent drug ratio):

Interpretation (Table 2)

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

Clozapine and N-Desmethylclozapine

Therapeutic reference range:	225 ng/mL Cloz 175 ng/mL N-DCloz	350-600 ng/mL
t1/2:		12-16 h
Laboratory alert level:		1000 ng/mL
CF (conversion factor):	225 x 3.06 = 689 nmol/L	3.06

DRC (factor for calculation of expected drug related concentration):
1.01±0.58

MPR (metabolite to parent drug ratio):

Interpretation (Table 2)

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.

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Clozapine and N-Desmethylclozapine

Therapeutic reference range: 225 ng/mL Cloz
175 ng/mL N-DCloz
350-600 ng/mL

t1/2: 12-16 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 3.06

DRC (factor for calculation of expected drug related concentration): 1.01±0.58

MPR (metabolite to parent drug ratio):

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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

Clozapine and N-Desmethylclozapine

Therapeutic reference range: 225 ng/mL Cloz; 175 ng/mL N-DCloz — 350-600 ng/mL

t1/2: 12-16 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 3.06

DRC (factor for calculation of expected drug related concentration): 1.01±0.58

Low 250 x (1.01-0.58) = xxx ng/mL
High 250 x (1.01+0.58) = xxx ng/mL

MPR (metabolite to parent drug ratio):

Interpretation (Table 2)

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

Clozapine and N-Desmethylclozapine

Therapeutic reference range: 225 ng/mL Cloz
175 ng/mL N-DCloz
350-600 ng/mL

t1/2: 12-16 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 3.06

DRC (factor for calculation of expected drug related concentration): 1.01±0.58

MPR (meta

Low 250 x (1.01-0.58) = 108 ng/mL
High 250 x (1.01+0.58) = 398 ng/mL

108 to 398 ng/mL expected for 250 mg clozapine

Interpretation (Table 2)

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

Clozapine and N-Desmethylclozapine

Therapeutic reference range: 225 ng/mL Cloz — 350-600 ng/mL

Concentration as expected

t1/2: 12-16 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 3.06

DRC (factor for calculation of expected drug related concentration): 1.01±0.58

MPR (meta

Low 250 x (1.01-0.58) = 108 ng/mL
High 250 x (1.01+0.58) = 398 ng/mL

108 to 398 ng/mL expected for 250 mg clozapine

Drug-drug interactions

Requesting Hospital/Doctor:	Department of Psychiatry			
Patient details	Date of birth Height Weight	1967 174 cm 103 kg	Sex ICD-10 Diagnose(s) Blood withdrawal	female F 20.0 08:00
Reason for request: Uncertain adherence				
Drug to be assayed	Clozapine	**Concentration in blood**		
		Clozapine	225 ng/mL	
		N-Desmethylclozapine	175 ng/mL	

Drug	Drug-drug interactions? Perpetrator drugs (CYP-Inhibitors, CYP-Inducers), victim drugs?
Clozapine	
Simvastatin	
Sertraline	
ASS	

Drug-drug interactions (Table 1a and 1b)

Table 1(a). Inhibitors of CYP450 isoenzymes (adapted from the original paper: Hiemke et al. 2018). Inhibition of enzymes indicated in bold will significantly and markedly increase plasma concentrations of victim drugs.

Inhibitors	Inhibited enzymes
Amiodarone	**CYP2C9**, CYP2D6, CYP3A4
Amprenavir	**CYP3A4**
Aprepitant	**CYP3A4**
Atazanavir	**CYP3A4**
Boceprevir	**CYP3A4**
Bupropion	**CYP2D6**
Cimetidin	CYP1A2, CYP2D6, CYP3A4
Ciprofloxacin	**CYP1A2, CYP3A4**
Clarithromycin	**CYP3A4**
Clomethiazole	**CYP2E1**
Clopidogrel	CYP2B6
Crizotinib	**CYP3A4**
Diltiazem	**CYP3A4**
Disulfiram	**CYP2E1**
Duloxetine	**CYP2D6**
Enoxacin	**CYP1A2**
Erythromycin	**CYP3A4**
Esomeprazole	**CYP2C19**
Felbamate	CYP2C19

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.

Drug-drug interactions (Table 1a and 1b)

▶ **Table 1** Enzymes and efflux transporters involved in the metabolism and distribution of neuropsychopharmacological compounds.

Drugs	Enzymes and transporters	References
Acamprosate	Not metabolized	[1033]
Agomelatine	**CYP1A2**, CYP2C19, CYP3A4	[126, 721]
Alprazolam	**CYP3A4/5**	[24, 905]
Amantadine	90 % is excreted unchanged via the kidney	[38]
Amisulpride	More than 90 % is excreted unchanged via the kidney	[1018]
Amitriptyline	CYP1A2, CYP2C9, **CYP2C19, CYP2D6**, CYP3A4, UGT1A3, UGT1A4, UGT2B10, P-gp (ABCB1)	[84, 150, 516, 878, 1187, 1215, 1216, 1293]
Amitriptyline oxide	FMO, **CYP2C19, CYP2D6**	[150, 276]
Amfetamine (dexamfetamine, lisdexamfetamine)	CYP2D6	[55]
Aripiprazole	**CYP2D6, CYP3A4**, P-gp (ABCB1)	[509, 639, 832, 1273]
Asenapine	**CYP1A2**, UGT1A4	[222, 1285]
Atomoxetine	**CYP2C19, CYP2D6**, P-gp (ABCB1)	[217, 805, 1354]
Benperidol	Unknown	[1068]
Benserazide	Hydroxylation, COMT	[504]
Biperiden	Unknown	
Brexpiprazole	**CYP3A4, CYP2D6**	[443]
Brivaracetam	CYP2C8, **renal elimination**	[1042]

Hiemke et al. 2018

Drug-drug interactions

Requesting Hospital/Doctor:	Department of Psychiatry			
Patient details	Date of birth Height Weight	1967 174 cm 103 kg	Sex ICD-10 Diagnose(s) Blood withdrawal	female F 20.0 08:00
Reason for request: Uncertain adherence				
Drug to be assayed	Clozapine	**Concentration in blood**		
		Clozapine	225 ng/mL	
		N-Desmethylclozapine	175 ng/mL	

Drug	Substrate (see Table 1, Hiemke et al. 2018)
Clozapine	CYP1A2, CYP2C19, FMO
Simvastatin	CYP3A4
Sertraline	CYP2B6, CYP2C19
ASS	

Drug-drug interactions (Table 1a and 1b)

Table 1(a). Inhibitors of CYP450 isoenzymes (adapted from the original paper: Hiemke et al. 2018). Inhibition of enzymes indicated in bold will significantly and markedly increase plasma concentrations of victim drugs.

Inhibitors	Inhibited enzymes
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Bupropion	**CYP2D6**
Cimetidin	CYP1A2, CYP2D6, CYP3A4
Ciprofloxacin	**CYP1A2, CYP3A4**
Clarithromycin	**CYP3A4**
Clomethiazole	**CYP2E1**
Clopidogrel	CYP2B6
Crizotinib	**CYP3A4**
Diltiazem	**CYP3A4**
Disulfiram	**CYP2E1**
Duloxetine	**CYP2D6**
Enoxacin	**CYP1A2**
Erythromycin	**CYP3A4**
Esomeprazole	**CYP2C19**
Felbamate	CYP2C19

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.

Drug-drug interactions

Requesting Hospital/Doctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
	Height	174 cm	ICD-10 Diagnose(s)	F 20.0
	Weight	103 kg	Blood withdrawal	08:00

Reason for request: Uncertain adherence

Drug to be assayed	Clozapine	**Concentration in blood**	
		Clozapine	225 ng/mL
		N-Desmethylclozapine	175 ng/mL

- Patient is **severely ill (**6, according to nach CGI-S)
- No change since start of treatment (4, according to CGI-I)
- Patient is a **smoker,** consumes coffee (4 cups/ day)**, no alcohol**
- Adverse drug reactions**:** not reported

Drug-drug interactions

Requesting Hospital/Doctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
	Height	174 cm	ICD-10 Diagnose(s)	F 20.0
	Weight	103 kg	Blood withdrawal	08:00

Reason for request: Uncertain adherence

Drug to be assayed	Clozapine	**Concentration in blood**	
		Clozapine	225 ng/mL
		N-Desmethylclozapine	175 ng/mL

- Patient is **severely ill (**6, according to nach CGI-S)
- No change since start of treatment (4, according to CGI-I)
- Patient is a **smoker,** consumes coffee (4 cups/ day)**, no alcohol**
- Adverse drug reactions**:** not reported

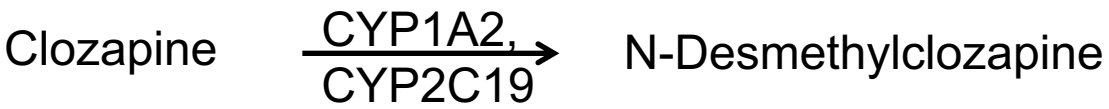
Smoke induces CYP1A2

Drug-drug interactions

Requesting Hospital/Doctor:	Department of Psychiatry			
Patient details	Date of birth Height Weight	1967 174 cm 103 kg	Sex ICD-10 Diagnose(s) Blood withdrawal	female F 20.0 08:00
Reason for request: Uncertain adherence				
Drug to be assayed	Clozapine	**Concentration in blood**		
		Clozapine	225 ng/mL	
		N-Desmethylclozapine	175 ng/mL	

Drug	Substrate (see Table 1, Hiemke et al. 2018)
Clozapine	CYP1A2, CYP2C19, FMO
Simvastatin	CYP3A4
Sertraline	CYP2B6, CYP2C19
ASS	

Metabolite to parent compound ratio (MPR)

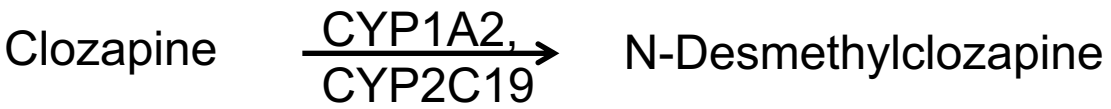


$$\frac{[\text{N-Desmethylclozapine}]}{[\text{Clozapine}]} = \text{MPR clozapine}$$

MPR Measured / calculated: ……

MPR Expected: ……

Metabolite to parent compound ratio (MPR)



$$\frac{[\text{N-Desmethylclozapine}]}{[\text{Clozapine}]} = \text{MPR clozapine}$$

MPR Measured / calculated: 175/225 = 0.78
MPR Expected: 0.5-0.6

Interpretation (Table 2)

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

Clozapine and N-Desmethylclozapine

Therapeutic reference range: 225 ng/mL Cloz
175 ng/mL N-DCloz — 350-600 ng/mL

t1/2: 12-16 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 3.06

DRC (factor for calculation of expected drug related concentration): 1.01±0.58

108 to 398 ng/mL expected for 250 mg clozapine

MPR (metabolite to parent drug ratio): 0.5-0.6

0.78 higher than usual enhanced degradation of clozapine

Clozapine Interpretation / Recommendation?

Requesting Hospital/Doctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
	Height	174 cm	ICD-10 Diagnose(s)	F 20.0
	Weight	103 kg	Blood withdrawal	08:00

Reason for request: Uncertain adherence

Drug to be assayed	Clozapine	**Concentration in blood**	
		Clozapine	225 ng/mL
		N-Desmethylclozapine	175 ng/mL

- Patient is **severely ill (**6, according to nach CGI-S)
- No change since start of treatment (4, according to CGI-I)
- Patient is a **smoker,** consumes coffee (4 cups/ day)**, no alcohol**
- Adverse drug reactions**:** not reported

Clozapine Interpretation / Recommendation

Requesting Hospital/Dcctor: Department of Psychiatry

Patient details	Date of birth	1967	Sex	female
	Height	174 cm	ICD-10 Diagnose(s)	F 20.0
	Weight	103 kg	Blood withdrawal	08:00

Reason for request: Uncertain adherence

Drug to be assayed	Clozapine	**Concentration in blood**	
		Clozapine	225 ng/mL
		N-Desmethylclozapine	175 ng/mL

- Patient is **severely ill (**6, according to nach CGI-S)
- No change since start of treatment (4, according to CGI-I)
- Patient is a **smoker,** consumes coffee (4 cups/ day)**, no alcohol**
- Adverse drug reactions**:** not reported

- TDM indicated because of suggested uncertain adherence and lack of improvement under therapeutic dose. The concentrations below the thereapeutically recommended reference range. The concentrations of clozapine and N-desmethylclozapine were as expected a dose of 250 mg/day. Low drug concentration due to smoking which induces CYP1A2. It is recommended to increase the dose to 350 mg/ day

TDM of antiepileptic and antipsychotic drugs

Use TDM guidelines to optimize pharmacotherapies of individual patients

Case

Quetiapine

Requesting Hospital/Doctor: Psychiatric Hospital

Patient details	Age Height Weight	63 y	Sex ICD-10 Diagnose(s) Blood withdrawal	female Bipolar, Hypertonia, Diabetes, etc. 08:00

Reason for request: Why did quetiapine concentrations increase?

Drug to be assayed :	**Concentration in blood**
quetiapine	178 ng/mL 247 ng/mL after switch from oxybutynin to solifenacin to treat urinary incontinence

Drug(s)	**Dose morning**	**noon**	**evening**	**night**	**Last dose change**
Quetiapine	200		40		> 3 months
Other drugs lithium, metformin, L-thyroxin, ASS, magnesium, furosemide, spironolactone, oxybutynin to solifenacin					

Much improved according to CGI, side effects especially marked sedation

Quetiapine

Requesting Hospital/Doctor: Psychiatric Hospital

Patient details	Age Height Weight	63 y	Sex ICD-10 Diagnose(s) Blood withdrawal	female Bipolar, Hypertonia, Diabetes, etc. 08:00

Reason for request: Why did quetiapine concentrations increase?

Drug to be assayed :	**Concentration in blood**
quetiapine	178 ng/mL 247 ng/mL after switch from oxybutynin to solifenacin to treat urinary incontinence

- TDM in accordance with the guidelines?
- TDM indicated?
- Is the concentration within the reference range?
- Are concentrations as expected for the dose of mg/day?
- Possible drug-drug interactions?

Interpretation (see Table 2)

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

Quetiapine

Therapeutic reference range:

t1/2:

Laboratory alert level:

CF (conversion factor):

DRC (factor for calculation of expected drug related concentration):

Interpretation (see Table 2)

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

Quetiapine

Therapeutic reference range: 100-500 ng/mL

t1/2: 6-12 h

Laboratory alert level: 1000 ng/mL

CF (conversion factor): 2.61

DRC (factor for calculation of expected drug related concentration):
0.52+/-0.22 0.30 (low) 0.78 (high)
72-177 ng/mL

Quetiapine Interpretation / Recommendations

Requesting Hospital/Doctor: Psychiatric Hospital

Patient details	Age Height Weight	63 y	Sex ICD-10 Diagnose(s) Blood withdrawal	female Bipolar, Hypertonia, Diabetes, etc. 08:00

Reason for request: Why did quetiapine concentrations increase?

Drug to be assayed :	**Concentration in blood**
quetiapine	178 ng/mL 247 ng/mL after switch from oxybutynin to solifenacin to treat urinary incontinence

- TDM in accordance with the guidelines? Request form incomplete
- TDM indicated? Several indications. Distinct problem, drug-drug interactions, multimobidity, old age
- Is the concentration within the therapeutic reference range? Yes (100-500 ng/mL)
- Are concentrations as expected for the dose of mg/day? Yes and no
- Possible drug-drug interactions? Yes, induction of CYP3A4 by oxybutynin and de-induction after switch to solifenacin, reason for the increase of plasma concentration

Case

Olanzapine

Requesting Hospital/Doctor: Psychiatric Hospital Outpatient Unit

Patient details	Age Height Weight	22 y	Sex ICD-10 Diagnose(s) Blood withdrawal	Male F70.1, F07.8 15:30

Reason for request: Change of medication (olanzapine), uncertain compliance

Drug to be assayed :	**Concentration in blood**
olanzapine	19 ng/mL
brivaracetam	500 ng/mL

Drug(s)	**Dose morning**	**noon**	**evening**	**night**	**Last dose change**
Olanzapine	5		10		2 weeks
Brivaracetam	50		50		> 8 weeks
Other drugs oxcarbazepine, clobazam, melatonin, folic acid					

Markedly ill according to CGI, slightly improved during the last days, 20 cig. per day, 1 cup of coffee per day, moderate alcohol comsumption

Olanzapine

Requesting Hospital/Doctor: Psychiatric Hospital Outpatient Unit

Patient details	Age Height Weight	22 y	Sex ICD-10 Diagnose(s) Blood withdrawal	Male F70.1, F07.8 15:30

Reason for request: Change of medication (olanzapine), uncertain compliance

Drug to be assayed :	**Concentration in blood**
olanzapine	19 ng/mL
brivaracetam	500 ng/mL

Drug(s)	**Dose morning**	**Noon**	**evening**	**night**	**Last dose change**
Olanzapine	5		10		2 weeks
Brivaracetam	50		50		> 8 weeks
Other drugs oxcarbazepine, clobazam, melatonin, folic acid					

- TDM in accordance with the guidelines?
- TDM indicated?
- Is the concentration within the reference range?
- Are concentrations as expected for the dose of mg/day?
- Possible drug-drug interactions?

Interpretation (see Table 2)

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

Olanzapine

Therapeutic reference range:

t1/2:

Laboratory alert level:

CF (conversion factor):

DRC (factor for calculation of expected drug related concentration):

Interpretation (see Table 2)

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

Olanzapine

Therapeutic reference range: 20-80 ng/mL

t1/2: 30 to 60 h

Laboratory alert level: 100 ng/mL

CF (conversion factor): 3.2

DRC (factor for calculation of expected drug related concentration): 1.85+/-0.74

Interpretation (see Table 2)

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

Brivaracetam

Therapeutic reference range:

t1/2:

Laboratory alert level:

CF (conversion factor):

DRC (factor for calculation of expected drug related concentration):

Interpretation (see Table 2)

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

Brivaracetam

Therapeutic reference range: not in Hiemke et al, but in Patsalos et al. 0.2-2.0 mg/L

t1/2: 7-8 h

Laboratory alert level: not defined (suggestion 4 mg/L

CF (conversion factor): must still be calculated

DRC (factor for calculation of expected drug related concentration):
not yet reported
new calculation (CH)
13.09+/-3.23
expected 1.0 to 1.6 mg/L

Ct : 0.5 mg/L Cmin 0.33 mgL

Olanzapine Interpretation / Recommendations

Requesting Hospital/Doctor: Psychiatric Hospital Outpatient Unit

Patient details	Age Height Weight	22 y	Sex ICD-10 Diagnose(s) Blood withdrawal	Male F70.1, F07.8 15:30

Reason for request: Change of medication (olanzapine), uncertain compliance

Drug to be assayed :	**Concentration in blood**
olanzapine	19 ng/mL
brivaracetam	500 ng/mL

Drug(s)	**Dose morning**	**Noon**	**evening**	**night**	**Last dose change**
Olanzapine	5		10		2 weeks
Brivaracetam	50		50		> 8 weeks
Other drugs oxcarbazepine, clobazam, melatonin, folic acid					

- TDM in accordance with the guidelines? Time of blood withdrawal, no trough, uncertain therapeutic range of brivaracetam
- TDM indicated? Intellectual disability, polypharmacy
- Is the concentration within the reference range? Too low
- Are concentrations as expected for the dose of mg/day? Too low

Case

Carbamazepine

Requesting Hospital/Doctor: Department of Neurology

Patient details	Age Height Weight	51 y	Sex ICD-10 Diagnose(s) Blood withdrawal	Male 13:00

Reason for request: Routine control

Drug to be assayed :	**Concentration in blood**
carbamazepine	2.7 mg/L

Drug(s)	**Dose morning**	**noon**	**evening**	**night**	**Last dose change**
Carbamazepine	300	300	300		> 6 months
Other drugs gabapentin, primidone, lorazepam					

Markedly ill according to CGI, impaired during the last days

Carbamazepine

Requesting Hospital/Doctor: Department of Neurology

Patient details	Age Height Weight	51 y	Sex ICD-10 Diagnose(s) Blood withdrawal	Male 13:00

Reason for request: Routine control

Drug to be assayed :	**Concentration in blood**
carbamazepine	2.7 mg/L

Drug(s)	**Dose morning**	**noon**	**evening**	**night**	**Last dose change**
Carbamazepine	300	300	300		> 6 months
Other drugs gabapentin, primidone, lorazepam					

Markedly ill according to CGI, impaired during the last days

- TDM in accordance with the guidelines?
- TDM indicated?
- Is the concentration within the reference range?
- Are concentrations as expected for the dose of mg/day?
- Possible drug-drug interactions?

Interpretation (see Table 2)

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

Carbamazepine

Therapeutic reference range:

t1/2:

Laboratory alert level:

CF (conversion factor):

DRC (factor for calculation of expected drug related concentration):

Interpretation (see Table 2)

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

Carbamazepine

Therapeutic reference range: 4-12 mg/L

t1/2: 10-20 h

Laboratory alert level: 20 mg/L

CF (conversion factor): 4.23

DRC (factor for calculation of expected drug related concentration):
11.3+/-5.0
expected 8.5 to 10.9 at trough
higher at tmax, around 10 to 13 mg/L

Carbamazepine Interpretation / Recommendations

Requesting Hospital/Doctor: Department of Neurology

Patient details	Age Height Weight	51 y	Sex ICD-10 Diagnose(s) Blood withdrawal	Male 13:00

Reason for request: Routine control

Drug to be assayed :	**Concentration in blood**
carbamazepine	2.7 mg/L

Drug(s)	**Dose morning**	**noon**	**evening**	**night**	**Last dose change**
Carbamazepine	300	300	300		> 6 months
Other drugs gabapentin, primidone, lorazepam					

Markedly ill according to CGI, impaired during the last days

- TDM in accordance with the guidelines? Not trough, blood withdrawal at Tmax
- TDM indicated? Drug-drug interactions, impaired, reduced adherence
- Is the concentration within the reference range? Too low, Cmin 1,0 mg/L
- Are concentrations as expected for the dose of mg/day?
- Possible drug-drug interactions? Induction of CYP3A4 by phenobarbital, poor adherence

TDM of antiepileptic and antipsychotic drugs

Use TDM guidelines to optimize pharmacotherapies of individual patients