P. Baumann[1]
C. Hiemke[2]
S. Ulrich[3]
G. Eckermann[4]
I. Gaertner[5]
M. Gerlach[6]
H.-J. Kuss[7]
G. Laux[8]
B. Müller-Oerlinghausen[9]
M. L. Rao[10]
P. Riederer[11]
G. Zernig[12]

The AGNP-TDM Expert Group Consensus Guidelines: Therapeutic Drug Monitoring in Psychiatry

Therapeutic Drug Monitoring (TDM) is a valid tool to optimise pharmacotherapy. It enables the clinician to adjust the dosage of drugs according to the characteristics of the individual patient. In psychiatry, TDM is an established procedure for lithium, some antidepressants and antipsychotics. In spite of its obvious advantages, however, the use of TDM in everyday clinical practice is far from optimal. The interdisciplinary TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) has therefore worked out consensus guidelines to assist psychiatrists and laboratories involved in psychotropic drug analysis to optimise the use of TDM of psychotropic drugs. Five research-based levels of recommendation were defined with regard to routine monitoring of plasma concentrations for dose titration of 65 psychoactive drugs: (1) strongly recommended, (2) recommended, (3) useful, (4) probably useful and (5) not recommended. A second approach defined indications to use TDM, e.g. control of compliance, lack of clinical response or adverse effects at recommended doses, drug interactions, pharmacovigilance programs, presence of a genetic particularity concerning the drug metabolism, children, adolescents and elderly patients. Indications for TDM are relevant for all drugs either with or without validated therapeutic ranges. When studies on therapeutic ranges are lacking, target ranges should be plasma concentrations that are normally observed at therapeutic doses of the drug. Therapeutic ranges of plasma concentrations that are considered to be optimal for treatment are proposed for those drugs, for which the evaluation of the literature demonstrated strong evidence. Moreover, situations are defined when pharmacogenetic (phenotyping or genotyping) tests are informative in addition to TDM. Finally, practical instructions are given how to use TDM. They consider preparation of TDM, analytical procedures, reporting and interpretation of results and the use of information for patient treatment. Using the consensus guideline will help to ensure optimal clinical benefit of TDM in psychiatry.

Affiliation
[1] Department of Psychiatry, University of Lausanne, Prilly-Lausanne, Switzerland
[2] Department of Psychiatry, University of Mainz, Germany
[3] Department of Clinical Pharmacology, University of Magdeburg, Magdeburg, Germany
[4] Bezirkskrankenhaus Kaufbeuren, Kaufbeuren, Germany
[5] Department of Psychiatry, University of Tübingen, Tübingen, Germany
[6] Department of Child and Adolescent Psychiatry, University of Würzburg, Würzburg, Germany
[7] Department of Psychiatry, University of Munich, Munich, Germany
[8] Bezirksklinikum Gabersee, Wasserburg/Inn, Germany
[9] Drug Commission of the German Medical Association, Berlin and Cologne, Germany
[10] Department of Psychiatry, University of Bonn
[11] Department of Psychiatry, University of Wuerzburg, Würzburg, Germany
[12] Department of Psychiatry, University of Innsbruck, Innsbruck, Austria

Correspondence
Pierre Baumann, Ph. D. Prof. · Unité de biochimie et psychopharmacologie clinique · Département universitaire de psychiatrie adulte · Centre de neurosciences psychiatriques · CH -1008 Prilly-Lausanne/Switzerland · Phone: 0041 21 643 64 34 · Fax: 0041 21 643 64 44 · E-Mail: Pierre.Baumann@inst.hospvd.ch

Received 4.4.2004 · **Accepted** 12.5.2004

Bibliography
Pharmacopsychiatry 2004; 37: 243–265 · © Georg Thieme Verlag KG Stuttgart · New York
DOI 10.1055/s-2004-832687
ISSN 0176-3679

Submitted to Pharmacopsychiatry, April 2004. A preliminary report was presented at the IATDMCT Congress Basle, 2003: P. Baumann, C. Hiemke, S. Ulrich, I. Gaertner, M. L. Rao, G. Eckermann, M. Gerlach, H.-J. Kuss, G. Laux, B. Müller-Oerlinghausen, P. Riederer, G. Zernig, Therapeutic Monitoring of Psychotropic Drugs: An outline of the AGNP-TDM expert group consensus guideline, Ther Drug Monit 26 (2004) 167 – 170

Introduction

Modern psychopharmacotherapy recently commemorated its 50th birthday, as in the early fifties of the past century, the first antipsychotic drug, chlorpromazine, was introduced into clinical practice. Within the next decade, other classes of psychotropic drugs became available, including antidepressants, mood stabilizers, and minor tranquilizers. Today, more than 100 psychoactive drugs are available, which enable the treatment of many psychiatric disorders and symptoms. In spite of the enormous progress of psychopharmacotherapy, amelioration and remission rates are far from being optimal. A significant number of patients do not respond, or the response is insufficient. Therefore, new drugs with new principles of actions are requested. However, there is also a need to optimise the efficacy of the available drugs. Psychoactive drugs differ in their pharmacological profile and with respect to their fate in the organism. The latter depends on environmental (diet, smoking habits, comorbidities, comedications) and genetic factors. The pharmacokinetic phenotype of an individual can be measured by analysis of drug concentrations in blood plasma or serum, i. e. therapeutic drug monitoring (TDM). The first method for assaying antidepressants in patient blood was introduced in the sixties [117]. The first report on plasma concentration – clinical effectiveness relationship of nortriptyline [10] has to be considered as the basis for therapeutic drug monitoring in psychiatry. Alexanderson et al. [2] observed that nortriptyline plasma concentrations were, in part, genetically determined in twins receiving this antidepressant. Bertilsson et al. [37] were the first to provide proof of the high diagnostic efficacy of combining TDM with pharmacogenetic tests with immediate consequences for the patient: A patient presented with a genetic deficiency of debrisoquine hydroxylation (CYP2D6) deficiency displayed unusually high plasma concentrations of nortriptyline and severe adverse effects.

During the past 30 years, TDM has been introduced for many drugs in psychiatry. Increasingly, TDM is combined with pharmacogenetic tests [68,139]. In spite of obvious advantages of TDM in psychiatry, its use in practice has been limited to few patients and few indications. Moreover, valid recommendations on how to use TDM adequately to improve psychopharmacotherapy are rare. With the exception of a report of the Task Force on the Use of Laboratory Tests in Psychiatry (1985) which was restricted on the TDM of tricyclic antidepressants and an update by Orsulak (1989) [196], consensus guidelines on the use of TDM in psychiatry have not been published in this field.

In the meantime, clinical and scientific organisations proposed guidelines for the treatment of psychiatric disorders, which confirmed psychopharmacotherapy as an instrument for acute and long-term treatment of mental disorders [79]. These guidelines were published by the American Psychiatric Association (2000) by the World Federation of Societies of Biological Psychiatry in their official journal "World Journal of Biological Psychiatry" (2001 – 2003) [20], by the German Society of Psychiatry and Nervous Diseases (1998), by the Drug Commission of the German Medical Association Germany (1997) and by others [170]. The introduction of algorithms in psychopharmacotherapy [95] aimed at tailoring the patient's treatment, by considering individual psychopathology, comorbidities, gender, age and other individual biological factors.

Though TDM is a valid tool to phenotype the pharmacokinetics of a drug in an individual patient, treatment guidelines do not report how to use TDM. Linder and Keck (1997) [155] have communicated aspects of TDM services for treatment with tricyclic antidepressants, and Laux and Riederer (1992) [149] published a report on the state of the art of TDM in psychiatry. The TDM group of the AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie), an interdisciplinary expert group comprising of chemists, clinical biochemists, clinical pharmacologists and psychiatrists, therefore compiled information from the literature and worked out these consensus guidelines to assist psychiatrists, laboratory practitioners and heads of laboratories involved in psychopharmacotherapy to optimise the use of TDM of psychotropic drugs. The present guidelines, with a focus on antidepressants, antipsychotics, mood stabilizers and opioid substitution drugs present the actual state of the art of TDM and propose standards on its use in practice in order to optimise psychopharmacotherapy.

Aims of the consensus document

These consensus guidelines aim to optimise the use of TDM of psychotropic drugs, including mainly antidepressants, antipsychotics, mood stabilizers and opioid substitution compounds. Moreover, some recommendations are given on the combined use of TDM and genotyping/phenotyping procedures in pharmacopsychiatry. Focus is given on the following topics related to the theory and practice of TDM of psychotropic drugs:

- definition of the indication for their TDM
- definition of levels of recommendations for their TDM
- presentation of their steady-state concentrations at clinically relevant doses
- presentation of reference plasma concentrations ranges: therapeutic windows
- definition of indications for TDM taking into account the different classes of drugs
- recommendations regarding the practice of TDM

This document will also serve as a basis for further improvements of TDM and harmonizing of its use [23].

Pharmacokinetics, metabolism and pharmacogenetics of psychoactive drugs

Pharmacokinetics

The chemical structure of psychoactive drugs differs markedly as do their pharmacokinetics and metabolic fate. Nevertheless, most psychotropic drugs are similar in chemical properties such

as high lipophilicity, relative molecular weight between 200 and 500 and basicity. *Hypericum* constituents and some antipsychotics differ in these aspects. As a consequence, most psychotropic drugs share a number of pharmacokinetic characteristics [14,46,91,114,190]:

- good absorption from the gastrointestinal tract within a short time to yield maximum plasma concentration (t_{max} of about 0.5 to 4 hours)
- high first-pass metabolism (systemic availability 10 to 70%)
- fast distribution from plasma to the central nervous system with 10- to 40-fold higher levels in brain than in blood
- high plasma protein binding (> 90%)
- high apparent volume of distribution (about 10 to 50 L/kg)
- low plasma concentrations (trough levels) in the steady-state (about 0.5 to 500 ng/ml)
- metabolism is a pre-requisite for excretion
- slow elimination from plasma (half-life 12 to 36 h) mainly by hepatic metabolism
- linear pharmacokinetics at therapeutic doses
- low renal excretion with small effect of renal insufficiency on the plasma concentrations of parent drug and active metabolites
- cytochrome P450 and UDP-glucuronosyltranferases as major metabolic enzyme systems

There are numerous exceptions, e.g. citalopram which is known for its high bioavailability (about 90%); venlafaxine, nefazodone, trazodone, tranylcypromine, moclobemide, quetiapine and ziprasidone which display a short (about 2 – 10 h) and fluoxetine with a long $t_{1/2,ß}$ (3 – 15 d, taking into account its active metabolite). Sulpiride and amisulpride are poorly metabolised and mainly excreted renally.

Depot formulations of some antipsychotic drugs such as haloperidol decanoate, are characterised by an extremely slow absorption after intramuscular application. The maximum plasma concentration is reached after about 1 week and the apparent half-life $t_{1/2,ß}$ is in the range of 2 to 3 weeks.

Many psychotropic drugs are used as racemic compounds, and their enantiomers differ markedly in their pharmacology, metabolism and pharmacokinetics [22]. However, methadone is probably at present the only racemic psychotropic compound for which routine TDM of the enantiomers has been introduced.

Metabolism

The metabolic fate of psychotropic and other drugs share many features (Testa and Soine, 2003; www.mrw.interscience.wiley.com/bmcdd/). Briefly, the main steps are: phase-I metabolism by oxidative, reductive or hydrolytic reactions such as aromatic ring and aliphatic hydroxylation, N- and O-dealkylation, N-oxidation to N-oxides, carbonyl reduction to secondary alcohols and S-oxidation to sulfoxides or sulfones. As a result of phase-I metabolism, polarity is increased by introduction of a functional group, which may enable a phase-II metabolization reaction, i.e., conjugation with highly polar molecules such as glucuronic acid (glucuronidation) [55,156] or sulphuric acid (sulphatation). For psychotropic drugs possessing functional groups in the parent compound, glucuronidation of a hydroxyl group (for example oxazepam and lorazepam) [113] or of an N-H group (for example olanzapine) [59] may represent the essential metabolic pathway. In addition, tertiary amine groups can be conjugated with the formation of quaternary ammonium glucuronides.

Other enzymatic systems may also be involved, such as aldehyde oxidase, which has been shown to reduce ziprasidone to its dihydro-derivative [31], or MAO-A and MAO-B, which deaminate citalopram stereoselectively to an apparently inactive acidic metabolite [224].

Drugs are metabolised mainly in the liver and to a minor degree in extrahepatic tissues such as the intestinal mucosa or the brain. Inter- and intra-individual differences in plasma concentrations of psychotropic drugs (the pharmacokinetic variability) are caused by different activities of drug-metabolising enzymes. Therefore, patient- and treatment-related variables are relevant, i.e. the enzyme activity may decrease with age, and may be modified by renal and hepatic diseases. Gender differences have been reported for psychotropic drugs, but the findings are inconsistent and the clinical relevance is not clear [173,250]. The enzymatic activity may be enhanced by concurrent psychotropic or non-psychotropic drugs and smoking (induction). Other comedications and food (inhibition) may decrease it.

Since metabolites may be of importance in the overall effect of psychotropic drugs [58,81,228], TDM must include the assay of active metabolites, for example in case of clomipramine (norclomipramine), fluoxetine (norfluoxetine) or risperidone (9-hydroxyrisperidone). For drugs like sertraline (norsertraline) or clozapine (norclozapine), the clinical relevance of the measurement of pharmacologically active metabolites is less convincing though the analysis of the metabolites may give useful information on the metabolic state of the patient, or on his compliance. Clearly, the assay of metabolites is not mandatory during treatment with drugs like amisulpride or methadone.

Pharmacogenetic aspects

Individual genetic disposition fundamentally determines the activity of a drug-metabolising enzyme. The number of active alleles in a gene determines how much of the enzyme is expressed (phenotype). Patients with low activity of a certain enzyme are "poor metabolizers" (PM), patients with normal activity are characterised as "extensive metabolizers" (EM) and patients with high activity are "ultra rapid metabolizers" (UM). If the frequency of a deviation in the alleles is at least 1% of the population, it is considered as a genetic polymorphism. Genetic polymorphism of drug-metabolising enzymes is clinically important because unexpected adverse reactions and toxicity may occur in PM due to increased plasma concentrations and non-response may occur in UM due to subtherapeutic plasma concentrations [52,69,76,197,245].

The cytochrome P450 (CYP) isoenzyme system, comprises more than 200 enzymes in about a dozen enzyme families and is primarily involved in phase I reactions of psychoactive drugs [66,188]. CYP1A2, CYP2D6, CYP2C19 and CYP3A4/5 are the most important isoenzymes for psychotropic drugs with high catalytic specificity for distinct metabolic reactions. On the other hand, they exert broad substrate specificity in spite of enantioselectivity in case of racemic drugs such as citalopram and fluoxetine

[29]. Specificity may be concentration-dependent (overlapping substrate specificity) as in the case of haloperidol, which is metabolized mainly by CYP2D6 at low plasma concentrations and mainly by CYP3A4 at high plasma concentrations [227]. The genetic polymorphism of CYP2D6 which catalyses the hydroxylation of tricyclic antidepressants and many other psychotropic drugs, brings about 5 to 8% PM and about 1–7% UM in Caucasians [33,116,236]. CYP3A4 shows considerable interindividual differences in its expression and CYP3A5 is expressed in only one third of the Caucasian population [146].

Besides, environmental and genetic factors always interact with synergistic or antagonistic effects; e.g. the inducibility (e.g. by tobacco smoke) of CYP1A2, is genetically polymorphic [189,229]. The consequence of this CYP1A2 polymorphism has been examined in clinical studies with clozapine [200,264].

Depending on the particular CYP, phenotyping and/or genotyping methods are now available. Phenotyping and genotyping differ in their clinical significance. While phenotyping generally represents a "state marker", which is influenced by environmental factors such as smoking or comedications, it may be considered as a "trait marker" in well-defined conditions. Phenotyping carries the advantage of indicating the metabolic situation of the patient at the moment of the test, and allows to follow its evolution. Among the disadvantages, phenotyping represents an invasive procedure and many phenotyping probes lack specificity [90]. The clear advantage of genotyping is that it represents a "trait marker" and that its result is not influenced by environmental factors. It can be carried out in any situation and its result has a lifetime value. On the other hand, the functional significance of many genotypes remains to be established [68,90].

Other enzyme systems such as UDP-glucuronosyltransferases also display genetic polymorphism, but the literature is relatively scarce with regard to its clinical relevance in pharmacopsychiatry [73,156].

Recent investigations indicate that drug transporters such as P-glycoprotein in the intestinal mucosa and in the blood brain barrier are also relevant for the pharmacokinetic variability of psychotropic drugs [154,223,259]. Food constituents, drugs, smoking, age and gender influence the expression of drug transporters. Moreover, reported genetic polymorphisms of drug transporters indicate that they play a role similar to drug-metabolizing enzymes [58,78,243]. With regard to the occurrence of wanted or unwanted clinical effects of psychoactive drugs, however, the contribution of drug transporters has so far not been documented.

As illustrated by the example of clozapine [165], SSRIs [166] and other drugs [151], applying pharmacogenetic tests for both pharmacodynamic (receptor proteins, transporter proteins for antidepressants, etc) and pharmacokinetic (cytochrome P-450, drug transporters) variables will become increasingly important. However, pharmacogenetic tests for pharmacodynamic parameters have not yet been validated in clinical practice, and therefore, this issue will not be further considered in the present guidelines.

In conclusion, there are situations in which the combination of pharmacogenetic tests with TDM of psychotropic drugs may be clinically advantageous in order to determine the metabolic capacity of patients treated with antidepressants [139], antipsychotics [68] or methadone [85].

Relationships between drug doses, its plasma concentrations and clinical variables

Dose dependant steady-state plasma concentrations

The preceding chapters described the influence of both, environmental and genetic factors on plasma concentrations of psychoactive drugs and their metabolites. Their steady-state concentrations are available from studies in which they were measured in plasma of healthy volunteers or patients treated with fixed drug doses. Very often these studies lack the measurement of clinical variables such as therapeutic or adverse effects. However, TDM data from a particular patient may inform the physician on their plausibility in the context of the treatment.

Drug plasma concentrations – clinical effectiveness relationship: the "therapeutic window"

TDM is based on the assumption that there is a definable relationship between plasma concentration and clinical effects (therapeutic effect, adverse effects and toxicity). These relationships have been investigated mainly for lithium, tricyclic antidepressants and classical antipsychotic drugs with inconsistent results (for review see [16,88,203,207,260,263]). For antipsychotic drugs, Baldessarini and co-workers (1988) [17] stated that, "the contradictory findings of past studies are not strong evidence that a relationship between blood levels and clinical effect of neuroleptics cannot be demonstrated". Methodological shortcomings of numerous studies are most likely responsible for the lack of an evident relationship between concentration and therapeutic or side effects [11,74,111,210,265]. Systematic reviews and meta-analyses [108,207] that were based on adequately designed studies led to convincing evidence of a relationship between clinical variables and plasma concentration for nortriptyline, imipramine and desipramine, the size of the effect being proportional to the plasma level of the drug for low to intermediate plasma levels, and no further increase – or even a decrease – in effectiveness for high to very high plasma levels.

Recently Ulrich and associates [260,263] proposed the following criteria to be considered for quality assessment of TDM studies dealing with the therapeutic window of different drugs in clinical treatment settings:

- valid chemical-analytical method
- adequate psychopathology rating scale and sufficient severity of the disorder at treatment onset, appropriate registration of change and exclusion of known non-responders
- reporting of patient selection criteria
- reporting of exclusion criteria
- concentration design, i.e. representative plasma used in the data analysis and adequate range of plasma concentrations investigated
- dose regimen, i.e., consideration of causality (false evidence of a relationship by flexible dose design)
- reporting of pre-medication, adequate washout period before randomisation

– reporting of co-medication
– adequate sample size

Using these criteria, the authors could point out in a well-designed meta-analysis the following characteristics for TDM in psychotropic drugs
– biphasic curvilinear relationships between plasma concentration
– therapeutic effect existing for the important model compounds haloperidol (typical antipsychotic in schizophrenia and schizoaffective disorder) and amitriptyline (tricyclic antidepressant in major depression)
– the therapeutic index is relatively low for the treatment of acutely and severely ill patients
– plasma concentrations may explain about 25 to 35% of the variability of therapeutic effects
– studies with adequate designs revealed significant relationships
– studies with inadequate design did not find significant relationships
– since the power of most individual studies was < 80%, the chance to find a relationship was low
– the few studies with sufficient power (> 80%) demonstrated a relationship.

For amitriptyline as a model compound, a meta-analysis of 45 studies has shown that various statistical approaches (continuous or dichotomised data) provided almost identical results, i.e. regression analysis, comparison of means of therapeutic effect in ranges of plasma concentrations, analysis of distribution of plasma concentrations in responders and non-responders, sensitivity of receiver operating characteristic curves with analysis of the frequency of responders and non-responders in ranges of plasma concentrations and logistic regression [260].

Analytical procedures

Generally, TDM is carried out using plasma or serum samples, while the analysis of whole blood for TDM purposes has been abandoned. There is no consensus about the use of plasma or serum, as generally, definite experimental data are lacking which clearly demonstrate differences in the drug concentrations using either tissue (exceptions possibly exist, and they should be clearly indicated by the laboratories). However, in future, this point should increasingly be considered as most laboratories probably validate their method for either plasma or serum but rarely for both preparations [119]. Analysis of psychotropic drugs in other materials such as whole blood, urine, CSF, tears, hairs and maternal milk has, generally, not been introduced for TDM purposes, and no validated data are available which deal with therapeutic concentrations.

In comparison to many somatic drugs, plasma concentrations of psychotropic drugs are low. Therefore, analytical methods must be developed which are highly sensitive, selective and appropriate for accurate and precise quantification [53, 60, 112, 239].

Three groups of analytical procedures can be distinguished: (i) measurement of physicochemical properties of the drug after extraction from plasma (ultraviolet light absorption, fluorescence, scintillation or electrochemical detection); (ii) immunological, i.e. sterical recognition of the drug molecule as an antigen with a suitable antibody and detection by ultraviolet light absorption, fluorescence polarization or scintillation and (iii) chromatographic separation of the drug from the matrix and detection by, for example, ultraviolet light absorption, fluorescence, energy of oxidation, electrochemical methods or (tandem) mass spectrometry.

Group (i) methods are obsolete because of low selectivity. Immunological methods (ii) are high throughput assays. With few exceptions, they do not require separation of the drug from the matrix in a sample preparation step. They are therefore rapid and easy, but they do not well discriminate active drug from similar molecules such as metabolites or comedication. Cross-reactivity is therefore a common problem of immunoassays used for the TDM of psychoactive drugs [216]. Moreover, antibodies are available only for a limited number of psychotropic drugs. Clinical pharmacologists and psychiatrists often demand additive and valuable information on the concentrations of the parent compound and an active metabolite, separately. In case of risperidone, the concentration of the "active moiety" (sum of the concentrations of risperidone and 9-hydroxyrisperidone, as determined by an immunological method) was frequently reported in clinico-pharmacological studies. However, giving data for risperidone and its metabolite individually provides additional, useful information on the pharmacogenetic status of the patients or on a pharmacokinetic interaction [41, 43]. For antipsychotic drugs, the radio receptor assay [67, 215] is another method based on sterical recognition. Measuring the displacement of a radioligand from a dopamine D2-like receptor preparation, a surrogate of the pharmacological activity is given instead of the plasma concentration.

Chromatographic techniques (iii) (gas chromatography (GC), and high-performance liquid chromatography (HPLC)), in combination with suitable detection methods, are most selective and sensitive. They are highly versatile and can be adapted to the analysis of a huge number of drugs. A disadvantage is the need for sample preparation before chromatographic separation and hence a limited sample throughput of classical chromatographic methods. It can be enhanced by automated sample preparation prior to GC or HPLC [72]. Some laboratories have introduced HPLC with column switching which allows direct injection of plasma or serum into the HPLC system. Such procedures are available for a number of antidepressants [18, 141, 272] and antipsychotics [184]. Another high-throughput chromatographic method is liquid chromatography coupled with mass spectroscopy (LC/MS). LC/MS methods can be applied to almost any psychotropic drug including metabolites. They are most sensitive and selective and can be used without time-consuming sample preparation, and many compounds can be analysed simultaneously [145]. GC/MS is another selective and sensitive procedure, which is applicable only for volatile compounds. Non-volatile compounds have to be derivatised, which is not always possible. The disadvantages of MS procedures are high costs and the need for highly qualified staff to run the system. The cost-effectiveness of LC/MS methods for TDM of psychoactive drugs still needs to be demonstrated.

The assay of enantiomers of chiral compounds requires either stereoselective derivatisation of the drugs prior to their quantification, or their separation by chiral chromatographic GC or HPLC columns. LC/MS may be the method of choice. As an example, the TDM of the enantiomers of methadone using a classical detection method such as fluorescence or ultraviolet light absorption is often handicapped by co-medication or drugs of abuse. These problems may be circumvented by use of a mass detector.

Increasingly, the powerful but still expensive LC/MS/MS procedures will gain interest from an economic point of view. They will probably replace many other methods, due to their high selectivity and the speed of analysis, as they allow simplification of the prepurification of the samples.

Economic aspects of TDM in psychiatry

Cost-effectiveness calculations of TDM are rare. The assay of a single psychoactive drug costs between 20 and 80 € which includes costs for staff, instrumentation, chemicals and other materials. Expenses for drug assays vary between laboratories depending on the analytical system that is used and the number of samples that are analysed daily.

For psychoactive drugs, proof of cost-effectiveness has been provided for nortriptyline [240] in a setting that used prospective pharmacokinetic dosing prediction. The benefit of TDM was demonstrated, in that patients who underwent TDM were earlier discharged from the hospital and returned to work earlier than empirically dosed patients. Preskorn and Fast (1991) [211] calculated significant savings when using TDM for tricyclic antidepressants primarily by avoiding adverse events. With regard to new antidepressants, a Swedish group [159] proved TDM to be cost effective in elderly patients. Including TDM, the direct expenditures were reduced by 10%. TDM led to dose reduction with sustained clinical efficacy, which resulted in a 38% net drug cost reduction.

Regarding the cost-effectiveness of TDM of antipsychotic or other psychoactive drugs, data on the economic impact of TDM are still lacking.

As for many other diagnostic tests, cost-effectiveness studies are required for TDM. TDM of psychoactive drugs is a complex process (Fig. **1**). It starts with the physician's decision to request plasma concentration analysis and ends with a change or no change of the pharmacotherapy. A recent prospective investigation, which was conducted under naturalistic conditions, failed to find a clinically significant impact of the TDM of tricyclic antidepressants [183], but the study revealed that in many cases dose adjustment was inappropriate and did not take the results of the laboratory assays into consideration. Future cost-effectiveness studies on TDM must therefore consider possible pitfalls with respect to physician's non-compliance. A test providing clear-cut results and nevertheless not resulting in therapeutic consequences is expensive and useless.

Phenotyping and genotyping are expensive procedures [62], but it should be emphasized that many psychotropic drugs are substrates of the most frequently phenotyped or genotyped isoform of cytochrome P450, CYP2D6, and that adverse effects occur readily in patients presenting a genetic peculiarity of metabolism. Preliminary data suggest that the costs of treating patients who are either UMs or PMs (CYP2D6) are 4,000 – 6,000 $ per year higher than those for EMs [63]. However, as is the case for con-

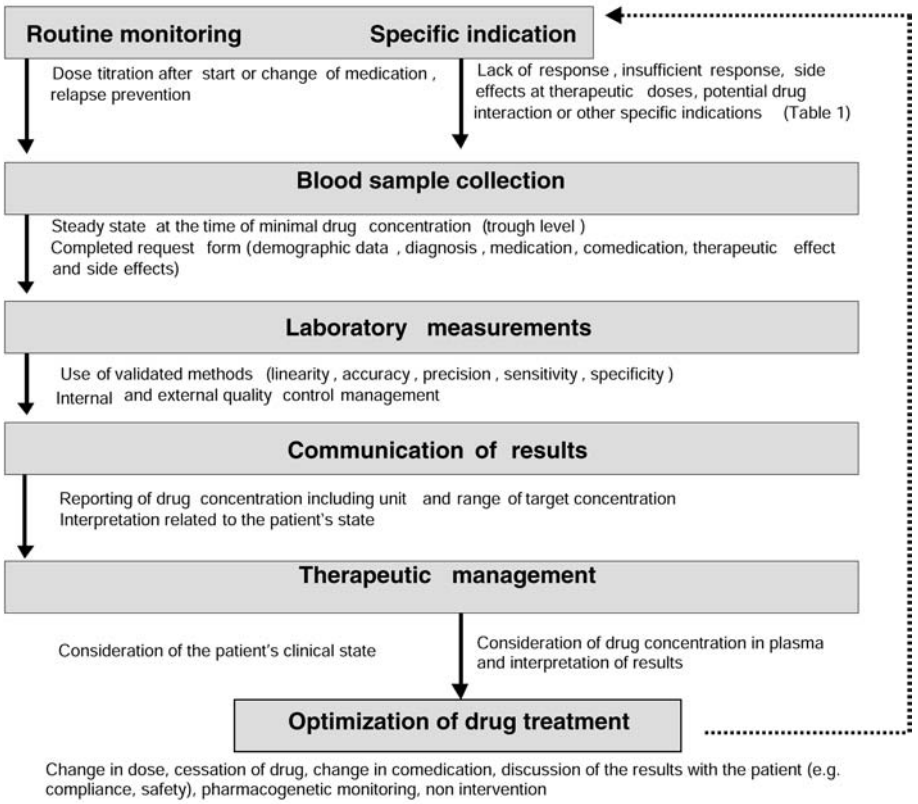

Fig. **1** Summary of the TDM process for optimization of the pharmacotherapy of psychiatric patients. Routine monitoring should be restricted to psychoactive drugs with established therapeutic ranges and whose levels of recommendation to use TDM are at least 2 (see Table **4**). Specific requests may be useful for any psychoactive drug and many indications (Table **1**) even without well established therapeutic ranges.

ventional TDM, the tools to assess the cost-effectiveness of phenotyping and genotyping still need to be fully developed [270].

Consensus

Levels of recommendations and indications for the TDM of psychoactive drugs

The usefulness of TDM varies with the clinical situation and the particular drug involved. Table **1** presents a list of indications for TDM of psychotropic drugs in plasma or serum of patients. Some indications such as suspected non-compliance, intoxication or TDM in pharmacovigilance programs may be considered as valid for all drugs and groups of patients, but the validity of other indications has to be examined on an individual basis, dependent on each case. Similar to diagnostic tests, TDM should only be requested when there is evidence that the result will provide an answer to a distinct question. TDM will improve the therapeutic strategy when the criteria presented above (cf "therapeutic window") apply.

These criteria are fulfilled for lithium, several antidepressants, antipsychotics and anticonvulsants, and methadone. There is sufficient evidence that TDM can be useful for patients treated with these drugs. For many psychoactive drugs, however, studies on the therapeutic benefit of TDM are lacking, incomplete or inconsistent. Therefore the available literature was screened and reports were selected according to the following decreasing priority: 1) Guidelines (e.g. lithium), 2) meta-analyses (e.g. haloperidol, amitriptyline), 3) prospective studies on the clinical effectiveness of drugs in which drug plasma concentrations were reported, and 4) pharmacokinetic studies. The absence of clinical data puts the definition of a therapeutic plasma concentration range into question.

Using this strategy and based on empirical evidence, 5 levels of recommendation for TDM were defined, which range from "strongly recommended" to "not recommended". In a second step, a recommendation tailored to the individual drug was defined. In patients suspected to be non-compliant, TDM is recommended for all drugs. We propose the following five research-based levels of certainty for our recommendation:

1 = Strongly recommended

Established therapeutic range

Level of evidence: Controlled clinical trials have shown benefit of TDM, reports on toxic effects at "supratherapeutic" plasma concentrations

Clinical consequences: at therapeutic plasma concentrations highest probability of response, at "subtherapeutic" plasma concentrations response rate similar to placebo, at plasma concentrations higher than therapeutic concentrations increasing risk of adverse effects

2 = Recommended

Suggested therapeutic ranges obtained from plasma concentrations at therapeutically effective doses (fixed dose studies)

Level of evidence: At least one well designed prospective study with well-defined outcome criteria, reports on intoxications at "supratherapeutic" plasma concentrations

Clinical consequences: TDM most probably will optimise response in non-responders: at "subtherapeutic" plasma concentrations, risk of poor response; at "supratherapeutic" plasma concentrations, risk of adverse effects and/or decreased response

3 = Useful

Suggested therapeutic ranges are plasma concentrations at effective doses obtained from steady-state pharmacokinetic studies

Level of evidence: Clinical data from retrospective analysis of TDM data, single case reports or non-systematic clinical experience

Clinical consequences: TDM useful to control whether plasma concentrations are plausible for a given dose; optimising of clinical response in non-responders who display low concentrations is possible

Table **1** Indications for therapeutic drug monitoring of psychotropic drugs such as antidepressants, antipsychotics, mood stabilizers and opioid substituents

Suspected non-compliance
Drugs, for which TDM is mandatory for safety reasons (e.g. lithium)
Lack of clinical response, or insufficient response even if doses considered as adequate
Adverse effects despite the use of generally recommended doses are used
Suspected drug interactions
TDM in pharmacovigilance programs
Combination treatment with a drug known for its interaction potential, in situations of comorbidities, "augmentation", etc.
Relapse prevention in long term treatments, prophylactic treatments
Recurrence despite good compliance and adequate doses
Presence of a genetic particularity concerning the drug metabolism (genetic deficiency, gene multiplication)
Children and adolescents
Elderly patients (> 65 y)
Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
Forensic psychiatry
Problems occurring after switching from an original preparation to a generic form (and vice versa)

4 = Probably useful
Suggested therapeutic ranges from steady-state pharmacokinetic studies at therapeutically effective doses
Level of evidence: valid clinical data so far lacking or inconsistent results
Clinical consequences: TDM useful to control whether plasma concentrations are plausible for a given dose

5 = Not recommended
Unique pharmacology of the drug, e.g. irreversible blockade of an enzyme or flexible dosing according to clinical symptoms
Level of evidence: Textbook knowledge, basic pharmacology
Clinical consequences: TDM should not be used

Drug-specific TDM recommendations
Some indications for TDM listed in Table **1** do not necessarily require the existence of clearly demonstrated "therapeutic windows", but the knowledge of experimentally well established plasma concentrations ranges may efficiently help the clinician, when he suspects non-compliance, drug interactions, problems occurring after switching from an original preparation to a generic form (and vice versa), presence of a pharmacogenetic problem, and other situations. Table **2** and **3** summarize present knowledge on dose related steady-state concentrations of different categories of psychotropic drugs and their active metabolites as observed in studies with healthy volunteers or patients treated with these drugs. These drug concentration ranges are also especially helpful in situations where the levels of recommendation 3 and 4 apply (TDM useful or probably useful). However, Tables **2** and **3** also show that, especially for recently introduced drugs, no, or almost no studies, were published on steady-state drug concentrations.

Especially when levels of recommendations 1 or 2 apply, only studies on the plasma concentrations – clinical effectiveness, which yielded "therapeutic windows", can be used as reference for TDM. We have therefore reviewed and evaluated the literature for 65 psychoactive drugs, defined their individual level of recommendation for their monitoring and, by a consensus, listed their therapeutic range. Recently, a comprehensive list of therapeutic and toxic plasma concentrations of most common drugs available including psychotropic agents was published, but unfortunately, the authors did not explain how they selected these ranges from the literature [218].

Table **4** presents recommended therapeutic ranges for antidepressants, antipsychotics, mood stabilizers, anxiolytic and hypnotic drugs, antidementia drugs, and drugs used for the treatment of addiction.

Many drugs are not only recommended for a single indication. For example, antidepressants are also introduced for the treatment of anxiety states, and antipsychotics for mania, but little information is available on optimal plasma concentrations in these situations. Therefore, the therapeutic ranges listed in Table **4** are generally those for the "main" indication.

TDM of antidepressants
Antidepressants are heterogeneous with respect to their chemical structure and their mechanism of action. Most of them enhance the tone of serotonergic and/or noradrenergic neurotransmission by blockade of uptake or enzymatic degradation of transmitter amines. TDM is established for tricyclic antidepressants, as for many of them a plasma concentration – clinical effectiveness relationship was shown, and TDM is recommended to avoid intoxications (Table **4**).

Since toxicity of new antidepressants is, in general, not relevant, it was widely accepted that TDM is of little clinical importance for this type of drugs [172]. Evidence for a significant relationship between drug concentration and therapeutic outcome is lacking for tetracyclic antidepressants (maprotiline, mianserin and mirtazapine), trazodone and reboxetine, the monoamine oxidase inhibitors moclobemide and tranylcypromine [110], and also for SSRIs [21,124,217], but recent data from Sweden revealed that TDM of SSRI is cost-effective (see above) since it helps to use minimum effective doses [160]. Therefore, data on the plasma concentrations at therapeutic doses may be clinically useful (Table **2**). They must be regarded as preliminary target ranges for TDM in cases of non-compliance, non-response, adverse effects or intoxication.

TDM of antipsychotics
Antipsychotic drugs belong to multiple chemical classes. All of them block the dopamine D2 receptor but to varying degrees. The usefulness of TDM is established for typical antipsychotic drugs such as haloperidol, perphenazine and fluphenazine, and for atypical antipsychotics including clozapine, olanzapine, and risperidone (Tables **3** and **4**). Compared to tricyclic antidepressants and in spite of toxic effects of old and new antipsychotics, safety is so far of minor concern in using TDM for antipsychotics. Overdosing may lead to irreversible extrapyramidal side effects or epileptic seizures, especially in the case of clozapine, and the latter are strongly related to plasma concentrations. Avoiding overdosing by TDM is for the majority of patients a matter of quality of life rather than safety. For antipsychotic drugs such as clozapine, plasma concentration data are in good agreement with in vivo measurement of dopamine D2 receptor occupancy using positron emission tomography (PET) [94]. Receptor occupancy rather than dose correlates with antipsychotic drug concentrations and are markers of drug concentrations at the target site [134]. Optimal response was seen at 60 to 80% receptor occupancy, and 80% receptor occupancy was defined as the threshold for the occurrence of extrapyramidal side effects [94]. It therefore seems that PET studies may add important information for the determination of optimal plasma concentrations of antipsychotics [123]. However, when using this approach, which is available in only a few PET centres, the nature and the binding characteristic of the radioligand have to be considered [96,237].

TDM of antipsychotics is particularly useful when medication is switched from the oral to the depot form, or vice versa.

TDM of mood stabilizers
Mood stabilizers and/or antimanic drugs comprise compounds, which vary widely in their chemical structure and kinetics; besides lithium, valproic acid and carbamazepine, other anticonvulsants and atypical antipsychotics are now increasingly used [138]. Lithium's therapeutic ranges and toxic levels are well documented (Table **4**) and TDM is standard. For its long-term

Table **2** Dose related steady-state plasma concentrations of antidepressants

Antidepressant	*Active metabolite (or metabolite recommended for TDM)*	*Dose related steady-state plasma concentrations* *			
		Dose mg/day	*parent compound ng/ml*	*metabolite ng/ml*	*References*
Amitriptyline	nortriptyline	150	102 ± 59 (34 – 278)	85 ± 60 (16 – 326)	Baumann et al., 1986 [24]
		150	122 ± 62	84 ± 48	Jungkunz and Kuss, 1980 [132]
		150	76 ± 30	84 ± 38	Breyer-Pfaff et al., 1982a [48]
		150	100 ± 41	71 ± 38	Breyer-Pfaff et al., 1982b [47]
		200	146 ± 21 (s. e. m.)	129 ± 23 (s. e. m.)	Kupfer et al., 1977 [147]
Citalopram	demethylcitalopram	40	86 ± 38	35 ± 11	Baumann et al., 1996 [28]
		40 i. v.	70 ± 23	30 ± 12	Baumann et al., 1998 [27]
Clomipramine	demethylclomipramine	75 b. i.d	63 md (22 – 230) (1)	148 md (51 – 331)(1)	Kramer Nielsen et al., 1992 [144]
		50	24 md (5 – 69) (1)	15 md (6 – 78) (1)	DUAG, 1999 [70]
		75	38 md (9 – 78) (1)	43 md (5 – 102) (1)	DUAG, 1999 [70]
		125	83 md (31 – 224) (1)	105 md (41 – 335) (1)	DUAG, 1999 [70]
		200	202 md (50 – 340) (1)	283 md (138 – 446)(1)	DUAG, 1999 [70]
		100 i. v.	122 ± 73	145 ± 118	Müller-Oerlinghausen and Fähndrich, 1985 [185]
		150	74 – 310	69 – 267	Burch et al., 1982 [54]
Desipramine		200	173 (28 – 882)		Friedel et al., 1979 [98]
		186 ± 24	188 ± 152		Amsterdam et al., 1985 [6]
		75 – 250	16 – 502		Nelson et al., 1985 [191]
Dothiepine	dothiepine-SO	150	95 ± 67	323 ± 191	Maguire et al., 1982 [164]
	northiaden	150		16 ± 12	Maguire et al., 1982 [164]
	dothiepine-SO	3.22 ± 0.99 mg/kg	67 (4 – 258)	352 (45 – 953)	Ilett et al., 1993 [126]
	northiaden	3.22 ± 0.99 mg/kg		37 (0 – 230)	Ilett et al., 1993 [126]
Doxepin (DOX)	demethyldoxepin (DDOX)	250	484 ± 251 nmol/L (6)		Adler et al., 1997 [1]
	demethyldoxepin	250	130 ± 113	132 ± 94	Deuschle et al., 1997 [75]
	trans-demethyldoxepin	250		72 ± 60	Deuschle et al., 1997 [75]
	cis-demethyldoxepin	250		60 ± 45	Deuschle et al., 1997 [75]
		143 ± 30	89 ± 75 (6)		Leucht et al., 2001 [152]
Escitalopram (9)	S-demethylcitalopram	10 (9)	27 ± 14	14 ± 5	Bondolfi et al., 1996 [40]
		10 (9)	28 ± 9	11 ± 3	Bondolfi et al., 2000 [42]
Fluoxetine	norfluoxetine	20	80 (9 – 265) md	126 (30 – 300) md	Lundmark et al., 2001 [161]
		40	195 (40 – 496) md	221 (20 – 449) md	
		20	97 ± 51	128 ± 49	Amsterdam et al., 1997 [7]
Fluvoxamine		100	90 ± 29 (f)		Härtter et al., 1998 [120]
		100	59 ± 22 (m)		Härtter et al., 1998 [120]
		200	274 ± 73 (f)		Härtter et al., 1998 [120]
		200	237 ± 90 (m)		Härtter et al., 1998 [120]
		229 ± 47	142 ± 108 (20 – 417)		Kasper et al., 1993 [136]
		200	162 ± 144 (13 – 833)		Gerstenberg et al. 2003 [104]
Imipramine	desipramine	225	(6 – 268)	(18 – 496)	Reisby et al., 1977 [220]
Maprotiline	(demethylmaprotiline)	150	116 ± 47		Gabris et al., 1985 [101]
		236 ± 32	202 ± 134 (12 – 428)		Kasper et al., 1993 [136]
Mianserin	demethylmianserin	30	22 (12 – 48)	9 (3 – 24)	Otani et al., 1991 [198]
(MIA)	(DMIA)	30	14 (6 – 37) (S-MIA)		Mihara et al., 1997 [177]
		30	9 (4 – 18) (R-MIA)		Mihara et al., 1997 [177]
		60	37 ± 19 (14 – 67)(S-MIA)	10 ± 5 (6 – 23)(S-DMIA)	Eap et al., 1999 [87]
		60	19 ± 11 (10 – 51) (R-MIA)	21 ± 15 (10 – 52)(R-DMIA)	Eap et al., 1999 [87]
Mirtazapine	(demethylmirtazapine)	15	7.3 ± 3.2		Timmer et al., 1995 [252]
		30	18 ± 7		Timmer et al., 1995 [252]
		45	28 ± 12		Timmer et al., 1995 [252]
		60	38 ± 16		Timmer et al., 1995 [252]
		70	46 ± 16		Timmer et al., 1995 [252]
Moclobemide		100 t. i. d.	216 ± 55		Schoerlin et al., 1987 [233]
Nortriptyline		150	141 ± 48 (48 – 238)		
		75 – 225	90 ± 40 (32 – 164)		Åsberg et al., 1971 [10]

Table **2** cont.

Antidepressant	*Active metabolite (or metabolite recommended for TDM)*	*Dose related steady-state plasma concentrations* *			
		Dose mg/day	*parent compound ng/ml*	*metabolite ng/ml*	*References*
Paroxetine		30	36.3 (1.7 – 60.8)		Lundmark et al., 1989 [162]
		30	27 md (12 – 45) (1)		Sindrup et al., 1992 [241]
		30	36 (9 – 70)		Kaye et al., 1989 [137]
Reboxetine		4	50 ± 20		Pellizzoni et al., 1996 [202]
Sertraline	(norsertraline)	50	12 ± 17 gm (3 – 134)	30 ± 24 gm (7 – 143)	Lundmark et al., 2000 [160]
		100	19 ± 18 gm (3 – 109)	45 ± 35 gm (10 – 273)	Lundmark et al., 2000 [160]
		150	31 ± 29 gm (8 – 145)	65 ± 47 gm (7 – 138)	Lundmark et al., 2000 [160]
		200	29 ± 18 gm (9 – 82)	87 ± 43 gm (40 – 189)	Lundmark et al., 2000 [160]
		50	12 ± 8 (4 – 32)		Axelson et al., 2002 [12]
Trazodone	m-CPP	150	624 (271 – 1 062)	65 (34 – 108)	Otani et al., 1998 [199]
		150	680 ± 257 (4)	65 ± 21 (4)	Mihara et al., 2001 [176]
		150	541 ± 277 (5)	56 ± 21 (5)	Mihara et al., 2001 [176]
Trimipramine	demethyltrimipramine	200	277 ± 67	169 ± 51	Cournoyer et al., 1987 [65]
(TRI)	(DTRI)		21 ± 11 (7 – 47)(L-TRI)(8)	7 ± 6 (1 – 23)(L-DTRI)(8)	Eap et al., 2000 [82]
			18 ± 6 (8 – 32)(D-TRI)(8)	10 ± 7 (2 – 29)(D-DTRI)(8)	Eap et al., 2000 [82]
Venlafaxine	O-demethylvenlafaxine	75 b. i. d.(2)	56 ± 31	194 ± 75	Troy et al., 1995 [257]
		75	75 ± 93 (5 – 427)	116 ± 65 (16 – 260)	Reis et al., 2002 [219]
		150	109 ± 232 (4 – 1903)	186 ± 94 (16 – 411)	Reis et al., 2002 [219]
		225	178 ± 283 (9 – 1 421)	232 ± 132 (63 – 736)	Reis et al., 2002 [219]
		300	155 ± 109 (21 – 438)	249 ± 121 (104 – 516)	Reis et al., 2002 [219]
Viloxazine		300	1 200 (ca 400 – 1 600)		Müller-Oerlinghausen and Ruether, 1979 [186]

*: Generally, arithmetic means ± sd are given; md: median value; gm: geometric mean.; numbers in (): ranges
m: males; f: females
(1): EM (CYP2D6)
(2): Concentrations show very little differences when given 50 mg/day t. i. d.
(3) drug concentrations measured after a 8-week treatment
(4) and (5): non-smokers and smokers, respectively
(6): Doxepin + desmethyldoxepin
(7): trans-doxepine
(8): concentrations given in ng x kg/ml x mg, in EMs (CYP2D6)
(9): patients were treated with 20 mg/day citalopram, and S-citalopram and its metabolite were measured

use, plasma concentrations of 0.5 – 0.8 nmol/L are recommended, but it may be justified to increase its concentrations up to 1.2 mmol/L [103,234]. For the classical anticonvulsants valproate and carbamazepine, therapeutic ranges are poorly defined (valproate) or not established at all in psychiatric situations. Concentrations established for antiepileptic treatment are used as a guideline for patients with bipolar disorder. For these drugs, TDM is primarily recommended for safety reasons to avoid intoxications.

TDM of antidementia drugs

Drugs that have been shown to be effective in the treatment of dementia are tacrine, donepezil, rivastigmine, galantamine and memantine. With the exception of memantine, which is a weak antagonist of glutamate receptors, antidementia drug are inhibitors of acetylcholine esterase. TDM is not used for the treatment of dementia. However, there is good evidence that TDM can be useful. For donepezil, it has been shown that the patients' improvement was significantly better when their plasma concentrations were above 50 ng/ml than in patients with lower drug concentrations [226].

TDM of anxiolytics and hypnotics

Most anxiolytic and hypnotic drugs belong to the class of benzodiazepines. They act by enhancing the inhibitory effect of gamma-aminobutyric acid (GABA). Anxiolytic and hypnotic effects are rapid and correlate with plasma concentrations. The metabolism of these drugs is as variable between individuals as for other psychoactive drugs. Because of the rapid onset of action, anxiolytic and hypnotic drugs can be dosed by clinical signs. TDM should be restricted to few indications, e. g. for alprazolam, to suppress panic attacks [114].

TDM of drugs used in the treatment of substance abuse and dependence

Methadone, R-methadone, buprenorphine, l-α-acetylmethadol (LAAM) and slow-release formulations of morphine are used for the treatment of opioid addiction. TDM is indicated for patients treated with methadone or R-methadone [84,85]. It may also be useful for other drugs such as acamprosate, which has been introduced as an "anti-craving" substance for the treatment of alcoholism.

Table **3** Dose related steady-state plasma concentrations of antipsychotics

Antipsychotic	*Active metabolite*	*Dose related steady-state plasma concentrations*			
Drug	*(or metabolite recommended for TDM)*	*Dose mg/day*	*parent compound*	*active metabolite*	*Reference*
Amisulpride		100	55.8 ± 3.6 (1)		Puech et al., 1998 [214]
		400	212.7 ± 21.7 (1)		Puech et al., 1998 [214]
		800	536.2 ± 61.9 (1)		Puech et al., 1998 [214]
		1 200	655.4 ± 51.1 (1)		Puech et al., 1998 [214]
		679 ± 229	317 ± 270		Müller et al., 2003 [183]
Clozapine	norclozapine	384 ± 42	374 ± 233 (84 – 1 088)	116 ± 65 (25 – 272)	Perry et al., 1991 [205]
	norclozapine	451 ± 200	348 ± 244 (4)	245 ± 176 (4)	Hasegawa et al., 1993 [121]
	norclozapine	410 ± 133	437 ± 290 (5)	346 ± 221 (5)	Hasegawa et al., 1993 [121]
	norclozapine	202 ± 36	188 ± 71	101 ± 41	Wetzel et al., 1998 [275]
	(clozapine N-oxide)	202 ± 36		26 ± 11	Wetzel et al., 1998 [275]
Haloperidol	(reduced haloperidol)	16	7.1 ± 3.7 (1)		Puech et al., 1998 [214]
		12 ± 12	7.3 ± 5.5 (2)	2 ± 2 (2)	Brockmöller et al., 2002 [50]
		40	20.6 ± 8.9 (6.2 – 43.7)		Ulrich et al., 1999 [262]
Olanzapine		10	20.2 ±16.9		Perry et al., 1997 [206]
		16 ± 7	34 ± 21		Weigmann et al, 2001 [274]
		10 md (2.5 – 30)	27.7 md (1.6 – 122)		Gex-Fabry et al., 2003 [107]
Perazine	(desmethylperazine)	100 – 1 000	34 – 397		Müller-Oerlinghausen and Schley, 1988 [187]
		200 – 600	78 – 383	92 – 1 119	Breyer-Pfaff et al., 1983 [45]
Quetiapine		600 md	93 md (41; 170)(3)		Sachse et al., 2003 [230]
		3 × 150	147 ± 61		Strakowski et al., 2002 [247]
		209 (50 – 267)	42 (17 – 90)		Small et al., 1997 [242]
		360 (50 – 566)	68 (22 – 169)		Small et al., 1997 [242]
Risperidone	9-OH-risperidone	6	10.7 ± 19.8	40.1 ± 24.7	Aravagiri et al., 1998 [8]
		6	7.3 ± 7.6	42.4 ± 7.7	Lane et al., 2000 [148]
		4	3.21 ± 2.95	26.3 ± 9.23	Bondolfi et al., 2002 [41]
		6.3 ± 1.2 (4 – 8)	6.6 ± 7.4 (0.8 – 27)	52 ± 27 (10.7 – 138)	Spina et al, 2001 [244]
Sulpiride		531 ± 279	376 ± 246		Müller et al., 2001 [184]
Thioridazine	mesoridazine	400	383 ± 200 (92 – 803)	458 ± 201 (132 – 873)	Baumann et al., 1992 [26]
	sulforidazine	400		137 ± 59 (64 – 242)	Baumann et al., 1992 [26]
		100	308 ± 193 (80 – 670)(2)		Eap et al., 1996 [86]

(1): Means ± SE
(2): Patients phenotyped or genotpyed as extensive metabolisers (EM; CYP2D6)
(3): 25th and 75th percentile, resp.
(4) and (5): Smokers and non-smokers, respectively

Specific indications for TDM in psychiatry

Optimal therapeutic plasma concentrations for an individual patient may differ widely from the established ranges, depending on clinical features. The plasma concentration range recommended for lithium depends on whether the patient is in an acute manic episode or needs maintenance therapy (cf TDM of mood stabilizers). Low levels are discussed for haloperidol in first-episode patients [163] and for doxepin if sedation and not antidepressant treatment is the main therapeutic goal [152]. Therapeutic windows should therefore be interpreted in the context of the clinical situation before deciding to change the treatment strategy.

Other indications such as "problems occurring after switching from an original preparation to a generic form (and vice versa)" should not be overemphasized. There are few data available which support the hypothesis that such problems may occur frequently [25,174,231,258].

For some groups of patients, such as children, adolescents and elderly patients, especially very old patients, TDM may be useful when data on the pharmacokinetics of the drugs in these populations are lacking. In elderly patients, who frequently present age-related sensitivity to medication, TDM may help to distinguish between pharmacokinetic and pharmacodynamic factors in the occurrence of adverse effects.

"TDM in forensic psychiatry" has to be considered as a special indication as it is mostly not carried out for therapeutic purposes.

TDM of psychotropic drugs in blood of pregnant or lactating women may help to minimize drug exposure of the fetus or newborn infant [4,57,61,92,157].

Pharmacokinetic measurements are strongly recommended in Phase III and IV studies. As stated in the document published by the European Agency for the Evaluation of Medicinal Products

Table **4** Recommended target plasma concentration ranges for psychoactive drugs and levels of recommendation for routine monitoring

Drug and active metabolite	*Recommended therapeutic range (consensus)* [1]	*Level of recommendation* [2]	*References*	
			Reports on therapeutic ranges	*Reports on intoxications*
Antidepressant drugs				
Amitriptyline plus nortriptyline	80 – 200 ng/ml	1	Ulrich & Läuter 2002 [260], Pedersen et al. 1982 [201]	Preskorn & Jerkovich 1990 [209]
Citalopram	30 – 130 ng/ml	3	Bjerkenstedt et al. 1985 [38], Leinonen et al. 1996 [150]	Jonasson & Saldeen 2002 [131]
Clomipramine plus norclomipramine	175 – 450 ng/ml	1	DUAG 1999, Gex-Fabry et al. 1999 [106], Mavissakalian et al. [169]	McIntyre et al. 1994 [171]
Desipramine	100 – 300 ng/ml	2	Perry et al. 1994 [207], Pedersen et al. 1982 [201]	Preskorn & Jerkovich 1990 [209]
Doxepin plus nordoxepin	50 – 150 ng/ml	3	Leucht et al. 2001 [150], Rodriguez de la Torre et al. 2001 [225]	Preskorn & Fast 1992 [212]
Escitalopram	15 – 80 ng/ml	4	SPC	
Fluoxetine plus norfluoxetine	120 – 300 ng/ml	3	Lundmark et al. 2001 [161], Amsterdam et al. 1997 [7]	
Fluvoxamine	150 – 300 ng/ml	4	Gerstenberg et al 2003 [104], Goodnick 1994 [110]	Kasper et al. 1993 [136]
Imipramine plus desipramine	175 – 300 ng/ml	1	Perry et al. 1994 [207]	Pedersen et al. 1982 [201]
Maprotiline	125 – 200 ng/ml	3	SPC, Kasper et al. 1993 [136]	Pedersen et al. 1982 [201]
Mianserin	15 – 70 ng/ml	3	Montgomery et al. 1978 [181]	Isacsson et al. 1997 [128]
Mirtazapine	40 – 80 ng/ml	3	Timmer et al. 2000 [253]	Velazquez et al. 2001 [130]
Moclobemide	300 – 1 000 ng/ml	4	Fritze et al. 1989 [99], Gex-Fabry et al. 1995 [105]	Hernandez et al. 1995 [19]
Nortriptyline	70 – 170 ng/ml	1	Perry et al. 1994 [207], Åsberg et al. 1971 [10]	Åsberg et al. 1970 [9]
Paroxetine	70 – 120 ng/ml	3	Lundmark et al. 2000a [160], Tasker et al. 1989 [248]	
Reboxetine	10 – 100 ng/ml	4	Ohman et al. 2001 [194]	
Sertraline	10 – 50 ng/ml	3	Lundmark et al. 2000b [160]	Milner et al. 1998 [178]
Tranylcypromine	0 – 50 ng/ml	5	Burke & Preskorn 1999 [56]	Iwersen & Schmoldt, 1996 [129]
Trazodone	650 – 1 500 ng/ml	3	Monteleone et al. 1989 [180], Goeringer et al. 2000 [109]	
Trimipramine	150 – 350 ng/ml	3	Cournoyer et al. 1987 [65], Isaccson et al. 1997 [128]	
Venlafaxine plus O-desmethylvenlafaxine	195 – 400 ng/ml	2	Veefkind et al. 2000 [269], Levine et al.1996 [153]	
Viloxazine	20 – 500 ng/ml	3	Norman et al. 1980 [193], Altamura et al. 1986 [3]	Falcy et al. 1983 [93]
Antipsychotic drugs				
Amisulpride	100 – 400 ng/ml	3	Moulin et al. 1991 [182], Müller et al. 2003 [183] Bergemann et al. 2004 [35]	
Benperidol	2 – 10 ng/ml	3	Furlanut et al. 1987 [100], Seiler et al.1994 [238]	
Chlorpromazine	30 – 300 ng/ml	2	van Putten et al. 1991 [266], Rivera-Calimlim et al. 1976 [221]	Rivera-Calimlim et al. 1973 [221]
Chlorprothixen	20 – 200 ng/ml	3	Schulz & Schmoldt 1997 [235]	
Clozapine	350 – 600 ng/ml	1	Perry et al. 1991 [205], VanderZwaag et al. 1996 [267]	Broich et al. 1998 [51]
Fluphenazine	0.5 – 2 ng/ml	1	van Putten et al. 1991 [167]	
Flupentixol	> 2 ng/ml	2	Balant-Georgia et al. 1985 [15]	
Haloperidol	5 – 17 ng/ml	1	Ulrich et al. 1998a [263], van Putten et al.1991 [266], Ulrich et al. 1998b [261]	Bjorndal et al. 1980 [39]
Melperone	50 ng/ ml	4	Molander & Bergstrom 1983 [179]	Stein et al. 1980 [246]
Levomepromazine	15 – 60 ng/ml	3	SPC, Tokunaga et al. 1997 [255]	
Olanzapine	20 – 80 ng/ml	1	Perry et al.2001 [204], Kapur et al. 1998 [135]	Zullino et al. 2002 [278]
Perazine	100 – 230 ng/ml	2	Breyer-Pfaff et al. 1983 [45]	Kieferstein et al. 2000 [133]
Perphenazine	0.6 – 2.4 ng/ml	2	van Putten et al. 1991 [167], Hansen & Larsen 1985 [118]	
Pimozide	15 – 20 ng/ml	4	The Scottish first Episode Schizophrenia Study, 1987 [249]	

Table **4** **cont.**

Drug and active metabolite	*Recommended therapeutic range (consensus)* [1]	*Level of recommendation* [2]	*References*	
			Reports on therapeutic ranges	*Reports on intoxications*
Quetiapine	70 – 170 ng/ml	3	Small et al. 1997 [242]	Belen et al. 2001 [32]
Risperidone plus 9-hydroxyrisperidone	20 – 60 ng/ml	2	Olesen et al. 1998 [195]	Nishikage et al. 2002 [192]
Sulpiride	200 – 1 000 ng/ml	3	SPC, Müller et al. 2001 [184], Tokunaga et al. 1997 [255]	Nishikage et al. 2002 [192]
Thioridazine	200 – 2000 ng/ml	2	van Putten et al. 1991 [266]	
Zotepine	12 – 120 ng/ml	3	Kondo et al. 1994 [142], Tokunaga et al. 1997 [255]	
Ziprasidone	50 – 120 ng/ml	4	Wilner et al. 2000 [276]	
Zuclopentixol	4 – 50 ng/ml	3	Kjolbye et al. 1994 [140]	
Mood stabilizers				
Carbamazepin	6 – 12 μg/ml	2	Petit et al. 1991 [208]	Tibballs 1992 [251]
Lithium	0.5 – 1.2 mmol/l	1	APA Guidelines 2000 [5]	Bailey & McGuigan 2000 [13], Dyson et al. 1987 [80]
Valproate	50 – 100 μg/ml	2	Bowen et al.1996 [46], Vasudev et al. 2000 [268]	Ingels et al. 2002 [127]
Anxiolytics/ Hypnotics				
Alprazolam	20 – 40 ng/ml	3	Greenblatt et. al. 1993 [115], Wincor et al. 1991 [277]	
Buspirone	3 ng/ml	4	SPC	
Clonazepam	20 – 40 ng/ml	3	Beauclair et al. 1994 [30]	
Diazepam plus Metabolites	300 – 400 ng/ml	3	Dasberg et al. 1974 [71]	Divoll et al. 1981 [77]
Lorazepam	10 – 15 ng/ml	4	Ellinwood et al. 1985 [89]	
Midazolam	6 – 15 ng/ml	4	Garzone et al. 1989 [102]	
Zolpidem	90 – 325 ng/ml	5	Salva & Costa, 1995 [232]	
Zopiclone	60 – 75 ng/ml	5	Houghton et al. 1985 [125]	
Antidementia Drugs				
Donepezil	30 – 75 ng/ml	2	Rogers & Friedhoff 1996 [226], Tiseo et al. 1998 [254]	
Galantamine	30 – 100 ng/ml	3	SPC	
Memantine	7 – 159 ng/ml	4	Kornhuber & Quack, 1995 [143]	
Tacrine	7 – 30 ng/ml	2	Roberts et al. 2000 [222]	Ford et al 1993 [97]
Drugs for Addiction				
Acamprosate	30 – 75 ng/ml	3	Mason et al. 2002 [168]	
Bupropion	< 100 ng/ml	4	Preskorn et al. 1990 [213]	
Clomethiazol	100 – 5 000 ng/ml	5	Ulrich et al. 2002 [260]	
Disulfiram	2400 ng/ml	5	Johansson 1992 [130]	
Methadone	400 – 600 ng/ml	2	Eap et al. 2000 [84], Torrens et al. 1998 [256]	
Methadone	R-meth. 250 – 400 ng/ml		Eap et al. 2000 [84]	
Naltrexone	< 9 ng/ml	4	SPC, Comer et al. 2002 [64]	

[1] *Therapeutic ranges* indicate trough concentrations of drugs in serum or plasma of patients under steady state medication

[2] Level of recommendation:

1 : Strongly recommended (for lithium TDM should be a standard of care): Established therapeutic range

2 : Recommended: Suggested therapeutic ranges obtained from plasma concentrations at therapeutically effective doses (fixed dose studies)

3 : Useful: Suggested therapeutic ranges are plasma concentrations at therapeutically effective doses obtained from steady state pharmacokinetic studies

4 : Probably useful: Suggested therapeutic ranges from steady state pharmacokinetic studies at therapeutically effective doses

5 : Not recommended (explanations see text)

SPC: Summary of Product Characteristics

(1995), an established concentration-response relationship is the basis to forecast chance of toxicity due to pharmacokinetic differences or drug-disease or drug – drug interactions. Well-controlled and randomised concentration – response studies with different fixed dose levels will help to define a "therapeutic window". On the other hand, pharmacokinetic studies, which are submitted by the pharmaceutical companies for drug registration, should be more readily available for scientists and clinicians.

Pharmacogenetic tests in addition to TDM

It is beyond the scope of these consensus guidelines on TDM to comprehensively treat pharmacogenetics, but some procedures are suggested in cases where pharmacogenetic tests could ad-

vantageously be combined with TDM [36,69,139,175,236]. Some authors wonder whether pharmacogenetics have to be considered as the TDM of the future [90]. However, there is still a need for prospective studies of pharmacogenetics-oriented TDM to determine its efficacy and cost-effectiveness in optimising therapeutic effects while minimizing toxicity. Some of the most important indications for phenotyping and/or genotyping are the following [90,245], and it is strongly recommended to carry out these tests in combination with TDM: the metabolism of the medication (or its active metabolite) is governed to an important extent by the enzyme, which is considered to be phenotyped or genotyped;

- the patient is treated with a substrate the metabolism of which shows a wide interindividual variability as demonstrated by TDM;
- a drug is characterized by a small therapeutic index: risk of toxicity in the case of a genetically impaired metabolism, or on the other hand, risk of non-response due to an ultrarapid metabolism and the inability to reach therapeutic drug levels;
- the patient presents unusual plasma concentrations of the drug or its metabolite(s) and genetic factors are suspected to be responsible;
- the patient suffers from a chronic illness, which requires lifelong treatment.

TDM by itself has to be considered as a phenotyping procedure, but it may be advantageously combined with pharmacogenetic tests. Actually, phenotyping is carried out most frequently with test probes specific for certain isozymes, such as debrisoquin, spartein or dextromethorphan for CYP2D6. Genotyping, when available, has some advantages in comparison to phenotyping, in that its result has a life-long significance for a particular patient and its results are not influenced by comedications. Therefore, both phenotyping and genotyping are recommended in some circumstances, in combination with TDM.

Practical aspects of TDM

A study on the clinical use of TDM of tricyclic antidepressants in a psychiatric university hospital showed that between 25 and 40% of the requests for TDM were inappropriate and the interpretation of the results led to about 20% of inappropriate therapeutic adjustments [273]. The criteria for inappropriate requests included an inappropriate indication for TDM, absence of steady state conditions and transcription errors on the request form. Among the inappropriate interpretations of the TDM result was the lack of adjustment of the dose of the antidepressant. A recent study on TDM of antidepressants confirmed the relative "lack" of clinicians to follow the recommendations [183]. Therefore, some practical recommendations may be helpful for the optimal use of TDM, as illustrated in Fig. **1**.

Recommendations for the treating physician

Preparation of TDM

TDM is not available for all psychotropic drugs. Therefore, for patients who most probably would benefit from TDM, a drug should be recommended for which TDM is available, either to minimize adverse effects or to optimise clinical efficacy of a treatment. A well-defined "therapeutic window" for this drug (Table **4**) or at least known plasma concentration ranges for clinical doses (Tables **2** and **3**) would be an optimal condition for TDM in an individual patient. The physician should be aware that laboratories differ in their capacity to carry out analyses: the delay to a result may vary between 1 and 7 days.

TDM is based on trough steady-state plasma concentrations. Blood should therefore be collected at least 5 drug half-lives after changes of dose and during the terminal β-elimination phase. For most psychotropic drugs, the half-lives are between 12 and 36 hours (fluoxetine and norfluoxetine, and venlafaxine and risperidone are examples of drugs with exceptionally long and short half-lives, respectively). In clinical practice, the appropriate sampling time for most psychoactive drugs is one week after stable daily dosing and immediately before ingestion of the morning dose i.e. about 12 – 16 hours (or 24 hours if the drug is given once daily) after the last medication. If for organisational reasons and blood can be collected only later in the morning, the patient should not be medicated before blood collection. In an outpatient setting, it can be problematic to measure trough levels. Under these conditions it is important to indicate the time of administration of the last dose to enable interpretation. In patients treated with a depot preparation of an antipsychotic drug, blood should be sampled immediately before the next injection.

Both, after a modification of the dose and after prescription of a comedication, which may inhibit or enhance the metabolism of the drug to be measured, TDM should be delayed until steady-state conditions are reached again. Of course, TDM should be carried out earlier if unexpected side effects are observed.

Technical recommendations given by the laboratory need to be taken into account when blood is collected for TDM (anticoagulant, conditions for mailing, influence of light, temperature). The preferred material is serum or plasma, i.e. blood containers without additives or with EDTA, respectively. With few exceptions, psychoactive drugs are stable in serum or plasma for at least 24 hours [122]. If mailing to the laboratory is necessary, plasma or serum can be sent without freezing if the sample is likely to arrive within the next two days. The laboratory should give instructions on the request form how to collect (plasma volume, labelling of the samples), store and mail the sample.

The quality of the analysis may be considerably influenced by comedications (and their metabolites!). Precise information on comedications may help the laboratory to avoid analytical problems (interferences with other drugs), except when LC/MS/MS is used for analysis. When a laboratory also offers an interpretation of the results, it is absolutely necessary to fill out the request forms adequately and completely (diagnosis, comorbidities, comedications, treatment duration, doses, sex and age of the patient, reasons for the request).

Diagnosis and drug dose are important information for the laboratory, since it enables a judgement on whether a result is plausible or not. Moreover, most analytical methods are developed for samples collected under usual clinical conditions. However, a patient may be medicated with unusually high doses (non-responder, suspected ultrarapid metabolizer status). As a consequence, the drug concentrations may be too high for the es-

tablished calibration curve, and time will be lost for repeating the assay with a diluted plasma sample.

Critical appreciation of the results

The choice of pharmacological treatment should mainly be guided by sound clinical judgment, taking into account patients' drug history. TDM is, if used appropriately, an additional and useful tool for optimising therapy.

Laboratories use different methods for analyses of drugs which may differ in their quality (e.g., sensitivity, robustness with regard to the influence of disturbing factors (e.g. comedications)), and the physician should be aware that some laboratories may not accurately measure drug levels, as shown for an apparently "simple" parameter, lithium [158]. Most laboratories have introduced a quality program, and some of them are accredited (e.g., ISO 17025) or certified. However, as shown by worldwide external quality control programs, there is considerable interlaboratory variability in the results on analysis of control samples. This should be considered when a drug was monitored several times in a patient but the measurements were carried out in different laboratories.

The laboratories vary in the presentations of their results. The clinician should take account of the units (ng/ml, µg/L, µmol/L, nmol/L) in which the results of the analysis are expressed (cf Table **5** for conversion factors). This is especially recommended for comparisons of TDM values obtained from different laboratories or with those in the literature. A list of conversion factors for most psychotropic drugs used is given in Table **5**.

In the case of suspected non-compliance, especially when plasma concentrations are low suggesting irregular drug intake, it may be useful to repeat TDM. In case of CYP2D6 substrates, low plasma concentrations may be explained by an ultrarapid metabolism, but genotyping identifies only about 30% of ultrarapid metabolizers.

Finally, it may be advantageous for the clinician to involve a laboratory for TDM, which offers pharmacological consultation. This is always recommended, when due to the result of TDM, a pharmacogenetic test is advised.

TDM-interpretation and patient treatment

Expert interpretation of a drug concentration measurement and the adequate use of the information are essential to ensure full clinical benefit of TDM. A TDM result is a guide to proper dosing of the individual patient. The physician has to be aware that reporting of results with inclusion of dose recommendations and other comments by the laboratory must be guided by the best available evidence, but also that the laboratory has only a very restricted knowledge of the clinical situation. For the interpretation of the results, the physician should take in consideration whether the "reference plasma concentrations range" reflects only "drug plasma concentrations at clinically relevant doses" (Tables **2** and **3**), or whether they are "therapeutic ranges" (Table **4**). In addition, it is certainly wise to take into account the level of recommendation for TDM of the particular drug (Table **4**). It should be considered that in Tables **2** and **3**, it is not indicated whether in a particular study, the daily drug dose was given as a simple or a multiple dose. If the plasma concentration of the drug is within the therapeutic range, an adaptation of the dose is, of course only recommended when clinical reasons, as adverse effects or non-response clearly justifies such a decision. Evidently, the treating physician has to decide whether the treatment strategy is to be changed or not, as he alone knows his patient. On the other hand, when the advice given on the TDM report is not followed, the reason must be substantiated to evaluate the decision of the treating psychiatrist if the consequences for the patient retrospectively turned out to be unfavourable.

Recommendations for the laboratory

Analytical procedures

To ensure quality and reliability of plasma concentrations assays, internal and external quality control procedures are mandatory. It can be advantageous (but the relative importance varies from country to country) that the laboratory is accredited, e.g., according to ISO 17025. Briefly, methods should be sufficiently precise, accurate and robust. Within the therapeutic range, the lack of precision should not exceed 15% (coefficient of variation) and accuracy should not deviate more than 15% from the nominal value. Each assay needs to be validated for linearity, selectivity, accuracy, precision, recovery and sensitivity (limits of detection (LOD) and quantification (LOQ)). This must be documented and assessed regularly. Each series of samples should contain internal control samples. They should be prepared by personnel other than those performing the assays and by separate weighing of reference material. Reporting of results requires that the results of the quality controls are within the expected range. If quality controls are outside the expected range, the reason underlying the outlier needs to be clarified and documented. In addition, whenever available, the laboratory should participate in an external quality assurance program by commercial interlaboratory tests [53, 60, 239].

The laboratory should not only analyse the drug but also its active metabolites (e.g. clomipramine + desmethylclomipramine; fluoxetine + norfluoxetine; risperidone + 9-hydroxyrisperidone (Table **2**, Table **3**, Table **4**). For some drugs, the determination of metabolites that most probably contribute little to their overall clinical effect (e.g. norclozapine, norsertraline) may also be useful to ensure compliance of the patients or to get information on his or hers capacity to metabolise drugs.

Reporting of results

The concentration of the psychoactive drug as well as that of active metabolites contributing to the therapeutic action should be reported with the appropriate target range (cf Table **2**, Table **3**, Table **4**). They are reported in either mass or molar units (SI, International System of Units) (cf Table **5** for conversion factors). To relate concentrations with dose, mass units are preferable, though many international journals prefer the use of molar units. When drug concentrations are below the limit of detection (LOD) or quantification (LOQ), these limits should be indicated. The use of LOQ is to be preferred as the aim of TDM is to quantitate drugs. Increasingly, the report of confidence intervals of the measured parameters will be required, as a consequence of accreditation procedures. The results should be available for clinical interpretation within a clinically meaningful time. This is of importance in case of suspected intoxications. A 48-hour TDM service is suf-

Table **5** Molar conversion factors for psychotropic drugs: nMol/L <-> ng/ml (= µg/L). The molar weights of the bases are indicated.

Class of Drugs	*Drug or metabolite*	*Molecular weight*	*Conversion factor (a)*
Antidepressants			
	Amitriptyline	277.5	3.604
	Citalopram	324.4	3.083
	Desmethylcitalopram	310.4	3.222
	Didesmethylcitalopram	296.4	3.374
	Clomipramine	315.0	3.175
	Desmethylclomipramine	301.0	3.322
	Dothiepine	295.5	3.385
	Doxepin	279.4	3.579
	Desmethyldoxepin	265.4	3.768
	Fluvoxamine	318.4	3.141
	Fluoxetine	309.3	3.233
	Norfluoxetine	295.3	3.386
	Imipramine	280.5	3.565
	Desipramine	266.5	3.752
	Maprotiline	277.5	3.604
	Mianserin	264.4	3.782
	Desmethylmianserin	250.4	3.994
	Mirtazapine	265.4	3.768
	Desmethylmirtazapine	251.4	3.978
	Moclobemide	268.7	3.721
	Nortriptyline	263.5	3.795
	Paroxetine	329.4	3.036
	Reboxetine	313.4	3.191
	Sertraline	306.2	3.266
	Norsertraline	292.2	3.422
	Tranylcypromine	133.2	7.508
	Trazodone	371.9	2.689
	m-CPP	196.7	5.083
	Trimipramine	294.4	3.397
	Desmethyltrimipramine	280.4	3.566
	Venlafaxine	277.4	3.605
	O-Desmethylvenlafaxine	263.4	3.797
	N-Desmethylvenlafaxine	263.4	3.797
	N.O-Didesmethylvenlafaxine	249.4	4.010
	Viloxazine	237.3	4.214
Antipsychotics			
	Amisulpride	369.5	2.706
	Benperidol	381.5	2.622
	Chlorpromazine	318.9	3.136
	Chlorprothixene	315.9	3.166
	Clopenthixol	401.0	2.494
	Clozapine	326.8	3.060
	Norclozapine	312.8	3.197
	Fluphenazine	437.5	2.286
	Flupentixol	434.5	2.301
	Haloperidol	375.9	2.660
	Levomepromazine	328.5	3.044
	Olanzapine	312.4	3.201
	Perazine	339.5	2.946
	Perphenazine	404.0	2.475
	Promethazine	284.4	3.516
	Quetiapine	383.5	2.607
	Risperidone	410.5	2.436
	9-OH-risperidone	426.5	2.345
	Sulpiride	341.4	2.929
	Thioridazine	370.6	2.698
	Sulforidazine	402.6	2.484

Table **5** cont.

Class of Drugs	*Drug or metabolite*	*Molecular weight*	*Conversion factor (a)*
	Mesoridazine	386.6	2.587
	Trifluoperazine	407.5	2.454
	Ziprasidone	392.5	2.547
	Zotepine	331.9	3.013
	Zuclopentixol	401.0	2.494

(a) ng/ml x factor = nMol/L; 1000/MW = factor

ficient in most cases, but many laboratories may not be able to respond to this criterion. Shorter intervals may be required in case of intoxications.

We recommend that interpretation and clinico-pharmacological advice are provided with every report. Reporting of results with inclusion of dose recommendations and other comments must be guided by the best available evidence. Therefore, it is advantageous for the clinician to choose a laboratory that offers this service. Otherwise, the treating physician, a clinical pharmacologist or a trained expert of the clinic has to interpret the results. Expert knowledge may be necessary to calculate dose corrections or to analyse drug-drug interactions. For the training in clinical psychopharmacology and pharmacokinetics and to learn the use of TDM, it is most helpful that junior psychiatrists interpret the results under supervision of an expert.

Interpretation of plasma concentrations must be done in the light of sound clinical judgement. Recommendations on dose changes is the most frequent advice. Prompt alerting of drug concentrations above the recommended range will assist in rapid intervention of patients at risk of toxicity. Other information which could be of help for the physician are those related to genetic polymorphisms, risks for pharmacokinetic interactions in situations of polymedications, pharmacokinetic properties of the drug when given to patients belonging to a "special population" (elderly patients, hepatic or renal insufficiency, etc).

A laboratory may also recommend that an additional sample should be provided for TDM, after a certain period, in cases where drug concentrations are unusually low. This may help to decide whether the patient's compliance is variable (irregular intake of the drug) or whether he is an ultrarapid metabolizer. As a consequence, the laboratory may also suggest that a pharmacogenetic test (phenotyping or genotyping) should be carried out.

In a patient who was diagnosed as a PM (CYP2D6), the medication (a CYP2D6 substrate) should not automatically be replaced by another as suggested by some authors [50], but the dose should be adapted as suggested by the same group of authors [139], using clinical judgment and TDM.

Conclusion

During the past decades, knowledge on the fate of psychotropic drugs in the human organism has increased. Pharmacogenetic and environmental factors are better understood. Long-term treatment with psychotropic drugs will be a standard tool in psychiatry. TDM will remain a valuable approach to optimise the often lifelong medication of psychiatric patients with antidepressants, antipsychotics and other compounds [34]. A considerable body of data for plasma concentrations of psychotropic drugs has been accumulated and relationships between plasma concentrations and therapeutic response have been investigated and reviewed in more detail. A re-evaluation of some previous data was performed including an empirical approach to the separation of adequate and inadequate data for important model compounds. This situation has prompted an interdisciplinary collaboration of specialists who brought about this consensus on TDM. The development of precise analytical procedures and the introduction of quality programs provide sensitive and specific assay of the drugs and their main metabolites. Based on empirically obtained evidence, 5 levels of certainty for TDM were to be introduced, depending on the data reported for each individual drug. For some of them, only plasma concentrations observed at defined doses are known from the literature, while for others, numerous studies on the plasma concentration – clinical effectiveness relationship are available, and therapeutic plasma concentrations could be presented, as a result of the consensus. Finally, practical recommendations for the clinicians as well as the laboratory practitioners will help to use TDM optimally from a scientific, clinical and economic point of view.

References

1 Adler L, Hajak G, Lehmann K, Kunert H-J, Hoffmann G, Issinger J et al. On the problems of switching from intravenous to oral administration in drug treatment of endogenous depression – A placebo-controlled double-blind trial with Doxepin. Pharmacopsychiatry 1997; 30: 62 – 69

2 Alexanderson BH, Evans DA, Sjöqvist S. Steady-state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. Br Med J 1969; 686: 764 – 768

3 Altamura AC, Mauri MC, Guercetti G. Age, therapeutic "milieu" and clinical outcome in depressive patients treated with viloxazine. Prog Neuropsychopharmacol Biol Psychiatry, 1986

4 American Academy of Pediatrics. Use of psychoactive medication during pregnancy and possible effects on the fetus and newborn. Pediatrics, 2000; 105: 880 – 887

5 American Psychiatric Association Practice Guidelines. Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry, 2000; 157 Supplement(4)

6 Amsterdam JD, Brunswick DJ, Winokur A, Rickels K. Desipramine and 2-hydroxydesipramine plasma levels in endogenous depressed patients. Arch Gen Psychiatry 1985; 42: 361 – 364

7 Amsterdam JD, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, Michelson D et al. Fluoxetine and norfluoxetine plasma concentrations in major depression: a multicenter study. Am J Psychiatry 1997; 154: 963 – 969

8 Aravagiri M, Marder SR, Wirshing D, Wirshing WC. Plasma concentrations of risperidone and its 9-hydroxy metabolite and their relationship to dose in schizophrenic patients: simultaneous determination by a high performance liquid chromatography with electrochemical detection. Pharmacopsychiatry 1998; 31: 102 – 109

9 Åsberg M, Cronholm B, Sjoqvist F, Tuck D. Correlation of subjective side effects with plasma concentrations of nortriptyline. Br Med J 1970; 4(726): 18 – 21

10 Åsberg M, Cronholm B, Sjöqvist F, Tuck D. Relationship between plasma level and therapeutic effect of nortriptyline. Br Med J 1971; 3: 331 – 334

11 Åsberg M, Sjöqvist F. On the role of plasma level monitoring of tricyclic antidepressants in clinical practice. Comm Psychopharmacol 1978; 2: 381 – 391

12 Axelson DA, Perel JM, Birmaher B, Rudolph GR, Nuss S, Bridge J et al. Sertraline pharmacokinetics and dynamics in adolescents. J Am Acad Child Adolesc Psychiatry 2002; 41(9): 1037 – 1044

13 Bailey B, McGuigan M. Lithium poisoning from a poison control center perspective. Ther Drug Monit 2000; 22(6): 650 – 655

14 Balant-Gorgia AE, Balant L. Antipsychotic drugs. Clinical pharmacokinetics of potential candidates for plasma concentration monitoring. Clin Pharmacokinet 1987; 13: 65 – 90

15 Balant-Gorgia AE, Eisele R, Aeschlimann JM, Balant LP, Garrone G. Plasma flupentixol concentrations and clinical response in acute schizophrenia. Ther Drug Monit 1985; 7(4): 411 – 414

16 Balant-Gorgia EA, Balant LP. Therapeutic drug monitoring – Relevance during the drug treatment of psychiatric disorders. CNS Drugs 1995; 4: 432 – 453

17 Baldessarini RJ, Cohen BM, Teicher MH. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. Arch Gen Psychiatry 1988; 45: 79 – 91

18 Banger M, Hermes B, Härtter S, Hiemke C. Monitoring serum concentrations of clomipramine and metabolites: fluorescence polarization immunoassay versus high performance liquid chromatography. Pharmacopsychiatry 1997; 30: 128 – 132

19 Baptista T, Teneud L, Contreras Q, Alastre T, Burguera JL, de Burguera M et al. Lithium and body weight gain. Pharmacopsychiatry 1995; 28: 35 – 44

20 Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ. World federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, Part 1: acute and continuation treatment of major depressive disorder. World Journal of Biological Psychiatry 2002; 3: 5 – 43

21 Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. Clin Pharmacokinet 1996; 31: 444 – 469

22 Baumann P, Eap CB. Pharmacogenetics of chiral psychotropic drugs. In: Lerer B, editor. Pharmacogenetics of Psychotropic Drugs Cambridge: Cambridge university press, 2002: 181 – 214

23 Baumann P, Hiemke C, Ulrich S, Gaertner I, Rao ML, Eckermann G et al. Therapeutic monitoring of psychotropic drugs – An outline of the AGNP-TDM expert group consensus guideline. Ther Drug Monit 2004; 26(2): 167 – 170

24 Baumann P, Jonzier-Perey M, Koeb L, Le PK, Tinguely D, Schöpf J. Amitriptyline pharmacokinetics and clinical response: I. Free and total plasma amitriptyline and nortriptyline. Int Clin Psychopharmacol 1986; 1: 89 – 101

25 Baumann P, Kahn JM. Les médicaments génériques: quels sont les problèmes et d'où viennent-ils?. Med Hyg 2003; 61(2434): 879 – 884

26 Baumann P, Meyer JW, Amey M, Baettig D, Bryois C, Jonzier-Perey M et al. Dextromethorphan and mephenytoin phenotyping of patients treated with thioridazine or amitriptyline. Ther Drug Monit 1992; 14: 1 – 8

27 Baumann P, Nil R, Bertschy G, Jecker A, Brändli H, Morand J et al. A double-blind double-dummy study of citalopram comparing infusion versus oral administration. J Affect Disord 1998; 49: 203 – 210

28 Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol 1996; 16: 307 – 314

29 Baumann P, Zullino DF, Eap CB. Enantiomers' potential in psychopharmacology – a critical analysis with special emphasis on the antidepressant escitalopram. Eur Neuropsychopharmacol 2002; 12: 433 – 444

30 Beauclair L, Fontaine R, Annable L, Holobow N, Chouinard G. Clonazepam in the treatment of panic disorder: a double-blind, placebo-controlled trial investigating the correlation between clonazepam concentrations in plasma and clinical response. J Clin Psychopharmacol 1994; 14(2): 111 – 118

31 Beedham C, Miceli JJ, Obach RS. Ziprasidone metabolism, aldehyde oxidase, and clinical implications. J Clin Psychopharmacol 2003; 23(3): 229 – 232

32 Beelen AP, Yeo KT, Lewis LD. Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone. Hum Exp Toxicol 2001; 20(4): 215 – 219

33 Benet LZ, Kroetz DL, Sheiner LB. Pharmacokinetics the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Limbird LE, editors. Goodman & Gilman's The pharmacological basis of therapeutics New York: McGraw-Hill Companies, 1996: 3 – 27

34 Bengtsson F. Therapeutic drug monitoring of psychotropic drugs TDM "nouveau". Ther Drug Monit 2004; 26(2): 145 – 151

35 Bergemann N, Kopitz J, Kress KR, Frick A. Plasma amisulpride levels in schizophrenia or schizoaffective disorder. European Neuropsychopharmacology 2004; 14: 245 – 250

36 Bertilsson L, Dahl ML. Polymorphic drug oxidation – Relevance to the treatment of psychiatric disorders. CNS Drugs 1996; 5: 200 – 223

37 Bertilsson L, Mellström B, Sjöqvist F, Mårtensson B, Åsberg M. Slow hydroxylation of nortriptyline and concomitant poor debrisoquine hydroxylation: clinical implications. Lancet 1981; i: 560 – 561

38 Bjerkenstedt L, Flyckt L, Overø KF, Lingjaerde O. Relationship between clinical effects, serum drug concentration and serotonin uptake inhibition in depressed patients treated with citalopram. A double-blind comparison of three dose levels. Eur J Clin Pharmacol 1985; 28: 553 – 557

39 Bjorndal N, Bjerre M, Gerlach J, Kristjansen P, Magelund G, Oestrich IH et al. High dosage haloperidol therapy in chronic schizophrenic patients: a double-blind study of clinical response, side effects, serum haloperidol, and serum prolactin. Psychopharmacology 1980; 67(1): 17 – 23

40 Bondolfi G, Chautems C, Rochat B, Bertschy G, Baumann P. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. Psychopharmacology 1996; 128: 421 – 425

41 Bondolfi G, Eap CB, Bertschy G, Zullino D, Vermeulen A, Baumann P. The effect of fluoxetine on the pharmacokinetics and safety of risperidone in psychotic patients. Pharmacopsychiatry 2002; 35: 50 – 56

42 Bondolfi G, Lissner C, Kosel M, Eap CB, Baumann P. Fluoxetine augmentation in citalopram non-responders: pharmacokinetic and clinical consequences. Int J Neuropsychopharmacol 2000; 3: 55 – 60

43 Bork JA, Rogers T, Wedlund PJ, De Leon J. A pilot study on risperidone metabolism: the role of cytochromes P450 2D6 and 3A. J Clin Psychiatry 1999; 60: 469 – 476

44 Bowden CL, Janicak PG, Orsulak P, Swann AC, Davis JM, Calabrese JR et al. Relation of serum valproate concentration to response in mania. Am J Psychiatry 1996; 153: 765 – 770

45 Breyer-Pfaff U, Brinkschulte M, Rein W, Schied HW, Straube E. Prediction and evaluation criteria in perazine therapy of acute schizophrenics pharmacokinetic data. Pharmacopsychiatry 1983; 16: 160 – 165

46 Breyer-Pfaff U, Gaertner HJ. Antidepressiva pharmakologie, therapeutischer Einsatz und Klinik der Depression. Wissenschaftliche Verlagsgesellschaft GmbH, Stuttgart: 1987

47 Breyer-Pfaff U, Gaertner HJ, Giedke H. Plasma levels, psychophysiological variables, and clinical response to amitriptyline. Psychiatry Res 1982; 6(2): 223 – 234

48 Breyer-Pfaff U, Gaertner HJ, Kreuter F, Scharek G, Brinkschulte M, Wiatr R. Antidepressive effect and pharmacokinetics of amitriptyline with consideration of unbound drug and 10-hydroxynortriptyline plasma levels. Psychopharmacology 1982; 76(3): 240 – 244

49 Brinkmann U, Eichelbaum M. Polymorphisms in the ABC drug transporter gene MDR1. Pharmacogenomics 2001; 1: 59 – 64

50 Brockmöller J, Kirchheiner J, Schmider J, Walter S, Sachse C, Müller-Oerlinghausen B et al. The impact of the CYP2D6 polymorphism on haloperidol pharmacokinetics and on the outcome of haloperidol treatment. Clin Pharmacol Ther 2002; 72(4): 438 – 452

51 Broich K, Heinrich S, Marneros A. Acute clozapine overdose: plasma concentration and outcome. Pharmacopsychiatry 1998; 31: 149 – 151
52 Brøsen K. Drug-metabolizing enzymes and therapeutic drug monitoring in psychiatry. Ther Drug Monit 1996; 18: 93 – 396
53 Buick AR, Doig MV, Jeal SC, Land GS, Mcdowall RD. Method validation in the bioanalytical laboratory. J Pharm Biomed Anal 1990; 8: 629 – 637
54 Burch JE, Raddats MA. Time course of plasma drug levels during once-daily oral administration of clomipramine. Psychopharmacology 1982; 77: 344 – 347
55 Burchell B. Transformation reactions: glucuronidation. In: Woolf TF, editor. Handbook of drug metabolism New York – Basel: Marcel Dekker, Inc, 1999: 153 – 173
56 Burke MJ, Preskorn SH. Therapeutic drug monitoring of antidepressants – Cost implications and relevance to clinical practice. Clin Pharmacokinet 1999; 37: 147 – 165
57 Burt VK, Suri R, Altshuler L, Stowe Z, Hendrick VC, Muntean E. The use of psychotropic medications during breast-feeding. Am J Psychiatry 2001; 158(7): 1001 – 1009
58 Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. Clin Pharmacokinet 1990; 18: 434 – 459
59 Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine – pharmacokinetic and pharmacodynamic profile. Clin Pharmacokinet 1999; 37: 177 – 193
60 Causon R. Validation of chromatographic methods in biomedical analysis viewpoint and discussion. Journal of Chromatography B 1997; 689: 175 – 180
61 Chaudron LH, Jefferson JW. Mood stabilizers during breastfeeding. A review. J Clin Psychiatry 2001; 61: 79 – 90
62 Chen S, Chou WH, Blouin RA, Mao Z, Humphries LL, Meek C et al. The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry. Clin Pharmacol Ther 1996; 60: 522 – 534
63 Chou WH, Yan F-X, Barnhill J, Rogers T, Cronin M, Pho M et al. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. J Clin Psychopharmacol 2000; 20: 246 – 251
64 Comer SD, Collins ED, Kleber HD, Nuwayser ES, Kerrigan JH, Fischman MW. Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. Psychopharmacology 2002; 159(4): 351 – 360
65 Cournoyer G, De Montigny C, Ouellette J, Langlois R, Elie R, Caille G et al. A comparative double-blind controlled study of trimipramine and amitriptyline in major depression: lack of correlation with 5-hydroxytryptamine reuptake blockade. J Clin Psychopharmacol 1987; 7: 385 – 393
66 Coutts RT, Urichuk LJ. Polymorphic cytochromes P450 and drugs used in psychiatry. Cell Mol Neurobiol 1999; 19: 325 – 354
67 Creese I, Snyder SH. A simple and sensitive radioreceptor assay for antischizophrenic drugs in blood. Nature 1977; 270: 80 – 182
68 Dahl ML. Cytochrome P450 phenotyping/genotyping in patients receiving antipsychotics: useful aid to prescribing? Clin Pharmacokinet 2002; 41(7): 453 – 470
69 Dahl ML, Sjöqvist F. Pharmacogenetic methods as a complement to therapeutic monitoring of antidepressants and neuroleptics. Ther Drug Monit 2000; 22: 114 – 117
70 Danish University Antidepressant Group. Clomipramine dose-effect study in patients with depression: clinical end points and pharmacokinetics. Clin Pharmacol Ther 1999; 66: 152 – 165
71 Dasberg HH, van der KE, Guelen JP, Van Praag HM. Plasma concentrations of diazepam and of its metabolite N-desmethyldiazepam in relation to anxiolytic effect. Clin Pharmacol Ther 1974; 15(5): 473 – 483
72 De la Torre R, Ortuño J, Pascual JA, Gonzalez S, Ballesta J. Quantitative determination of tricyclic antidepressants and their metabolites in plasma by solid-phase extraction (bond-elut TCA) and separation by capillary gas chromatography with nitrogen-phosphorous detection. Ther Drug Monit 1998; 20: 340 – 346
73 De Leon J. Glucuronidation enzymes, genes and psychiatry. Int J Neuropsychopharmacol 2003; 6: 57 – 72
74 De Oliveira IR, Dardennes RM, Amorim ES, Diquet B, de Sena EP, Moreira EC et al. Is there a relationship between antipsychotic blood levels and their clinical efficacy? An analysis of studies design and methodology. Fundam Clin Pharmacol 1995; 9: 488 – 502
75 Deuschle M, Härtter S, Hiemke C, Standhardt H, Heuser I. Doxepin and its metabolites in plasma and cerebrospinal fluid in depressed patients. Psychopharmacology 1997; 131(1): 19 – 22
76 DeVane CL. Pharmacogenetics and drug metabolism of newer antidepressant agents. J Clin Psychiat 1994; 55(suppl 12): 38 – 45
77 Divoll M, Greenblatt DJ, Lacasse Y, Shader RI. Benzodiazepine overdosage: plasma concentrations and clinical outcome. Psychopharmacology 1981; 73(4): 381 – 383
78 Doherty MM, Charman WN. The mucosa of the small intestine – How clinically relevant as an organ of drug metabolism? Clin Pharmacokinet 2002; 41(4): 235 – 253
79 Donoghue J, Taylor DM. Suboptimal use of antidepressants in the treatment of depression. CNS Drugs 2000; 13: 365 – 383
80 Dyson EH, Simpson D, Prescott LF, Proudfoot AT. Self-poisoning and therapeutic intoxication with lithium. Hum Toxicol 1987; 6(4): 325 – 329
81 Eadie MJ. Formation of active metabolites of anticonvulsant drugs – A review of their pharmacokinetic and therapeutic significance. Clin Pharmacokinet 1991; 21: 27 – 41
82 Eap CB, Bender S, Gastpar M, Fischer W, Haarmann C, Powell K et al. Steady state plasma levels of the enantiomers of trimipramine and of its metabolites in CYP2D6-, CYP2C19- and CYP3A4/5-phenotyped patients. Ther Drug Monit 2000; 22: 209 – 214
83 Eap CB, Bender S, Jaquenoud SirotE, Cucchia G, Jonzier-Perey M, Baumann P, Allorge D, Broly F. Nonresponse to clozapine and ultrarapid CYP1A2 activity clinical data and analysis of CYP1A2 gene. J Clin Psychopharmacol 2004; 24: 214 – 219
84 Eap CB, Bourquin M, Martin J-L, Spagnoli J, Livoti S, Powell K et al. Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. Drug Alcohol Depend 2000; 61: 47 – 54
85 Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet 2002; 41(14): 1153 – 1193
86 Eap CB, Guentert TW, Schäublin-Loidl M, Stabl M, Koeb L, Powell K et al. Plasma levels of the enantiomers of thioridazine, thioridazine 2-sulfoxide, thioridazine 2-sulfone, and thioridazine 5-sulfoxide in poor and extensive metabolizers of dextromethorphan and mephenytoin. Clin Pharmacol Ther 1996; 59: 322 – 331
87 Eap CB, Yasui N, Kaneko S, Baumann P, Powell K, Otani K. Effects of carbamazepine coadministration on plasma concentrations of the enantiomers of mianserin and of its metabolites. Ther Drug Monit 1999; 21: 166 – 170
88 Eilers R. Therapeutic drug monitoring for the treatment of psychiatric disorders – Clinical use and cost effectiveness. Clin Pharmacokinet 1995; 29: 442 – 450
89 Ellinwood EH, Jr., Heatherly DG, Nikaido AM, Bjornsson TD, Kilts C, Heatherly DG, Nikaido AM, Bjornsson TD, Kilts C. Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. Psychopharmacology 1985; 86(4): 392 – 399
90 Ensom MHH, Chang TKH, Patel P. Pharmacogenetics – The therapeutic drug monitoring of the future? Clin Pharmacokinet 2001; 40(11): 783 – 802
91 Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry 1996; 57 (suppl. 11): 12 – 25
92 Ernst CL, Goldberg JF. The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. J Clin Psychiatry 2002; 63 (suppl. 4): 42 – 55
93 Falcy M, Riboulet-Delmas G, Efthymiou ML. [Acute poisoning by viloxazine chlorhydrate taken by itself]. Encephale 1983; 9(2): 137 – 144
94 Farde L, Nordström AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Arch Gen Psychiatry 1992; 49: 538 – 544
95 Fawcett J, Stein DJ, Jobson KO, editors. Textbook of treatment algorithms in Psychopharmacology. Chichester (England), New York , Singapore, Ontario: John Wiley & Sons, 1999: 1 – 205
96 Fitzgerald PB, Kapur S, Remington G, Roy P, Zipursky RB. Predicting haloperidol occupancy of central dopamine D_2 receptors from plasma levels. Psychopharmacology 2000; 149: 1 – 5
97 Ford JM, Truman CA, Wilcock GK, Roberts CJC. Serum concentrations of tacrine hydrochloride predict its adverse effects in Alzheimer's disease. Clin Pharmacol Ther 1993; 53: 691 – 695

[98] Friedel RO, Veith RC, Bloom V, Bielski RJ. Desipramine plasma levels and clinical response in depressed outpatients. Comunications in Psychopharmacology 1979; 3: 81 – 87

[99] Fritze J, Laux G, Sofic E, Koronakis P, Schoerlin MP, Riederer P et al. Plasma moclobemide and metabolites: lack of correlation with clinical response and biogenic amines. Psychopharmacology 1989; 99(2): 252 – 256

[100] Furlanut M, Perosa A, Benetello P, Colombo G. Electrochemical detection of benperidol in serum for drug monitoring in humans. Ther Drug Monit 1987; 9(3): 343 – 346

[101] Gabris G, Baumann P, Jonzier-Perey M, Bosshart P, Woggon B, Küpfer A. N-methylation of maprotiline in debrisoquine/mephenitoin-phenotyped depressive patients. Biochem Pharmacol 1985; 34: 409 – 410

[102] Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. Clin Pharmacokinet 1989; 16(6): 337 – 364

[103] Gelenberg AJ, Carroll JA, Baudhuin MG, Jefferson JW, Greist JH. The meaning of serum lithium levels in maintenance therapy of mood disorders: a review of the literature. J Clin Psychiatry 1989; 50 Suppl.: 17 – 22

[104] Gerstenberg G, Aoshima T, Fukasawa T, Yoshida K, Takahashi H, Higuchi H et al. Relationship between clinical effects of fluvoxamine and the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. Psychopharmacology 2003; 167(4): 443 – 448

[105] Gex-Fabry M, Balant-Gorgia AE, Balant LP. Potential of concentration monitoring data for a short half-life drug: Analysis of pharmacokinetic variability for moclobemide. Ther Drug Monit 1995; 17: 39 – 46

[106] Gex-Fabry M, Balant-Gorgia AE, Balant LP. Clomipramine concentration as a predictor of delayed response: a naturalistic study. Eur J Clin Pharmacol 1999; 54: 895 – 902

[107] Gex-Fabry M, Balant-Gorgia AE, Balant LP. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. Ther Drug Monit 2003; 25: 46 – 53

[108] Glassmann AH, Schildkraut JJ, Orsulak PJ, et al. Tricyclic antidepressants, blood level measurements and clinical outcome: an APA task force report. Am J Psychiat 1985; 142: 155 – 162

[109] Goeringer KE, Raymon L, Christian GD, Logan BK. Postmortem forensic toxicology of selective serotonin reuptake inhibitors: a review of pharmacology and report of 168 cases. J Forensic Sci 2000; 45(3): 633 – 648

[110] Goodnick PJ. Pharmacokinetic optimisation of therapy with newer antidepressants. Clin Pharmacokinet 1994; 27: 307 – 330

[111] Gram LF. Plasma level monitoring of tricyclic antidepressants: methodological and pharmacokinetic considerations. Commun Psychopharmacol 1978; 2: 373 – 380

[112] Green M. A practical guide to analytical method validation. Analytical Chemistry News and Features, 1996: 305 – 309

[113] Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. Clin Pharmacokinet 1981; 6: 89 – 105

[114] Greenblatt DJ. Basic pharmacokinetic principles and their application to psychotropic drugs. J Clin Psychiatry 1993; 54: 8 – 13

[115] Greenblatt DJ, Von Moltke LL, Harmatz JS, Ciraulo DA, Shader RI. Alprazolam pharmacokinetics, metabolism, and plasma levels: clinical implications. J Clin Psychiatry 1993; 54: 4 – 14

[116] Greenblatt DJ, Von Moltke LL, Harmatz JS, Shader RI. Human cytochromes and some newer antidepressants: Kinetics, metabolism, and drug interactions. J Clin Psychopharmacol 1999; 19(Suppl. 1)(5): 23S – 35

[117] Hammer WM, Brodie BB. Application of isotope derivative technique to assay of secondary amines: estimation of desipramine by acetylation with H3-Acetic anhydride. J Pharmacol Exp Ther 1967; 157: 503 – 508

[118] Hansen LB, Larsen NL. Therapeutic advantages of monitoring plasma concentrations of perphenazine in clinical practice. Psychopharmacol 1985; 87: 16 – 19

[119] Härtter S, Hermes B, Hiemke C. Automated determination of trimipramine and N-desmethyl-trimipramine in human plasma or serum by HPLC with on-line solid phase extraction. J Liq Chromatogr 1995; 18: 3495 – 3505

[120] Härtter S, Wetzel H, Hammes E, Torkzadeh M, Hiemke C. Nonlinear pharmacokinetics of fluvoxamine and gender differences. Ther Drug Monit 1998; 20: 446 – 449

[121] Hasegawa M, Gutierrez-Esteinou R, Way L, Meltzer HY. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. J Clin Psychopharmacol 1993; 13: 383 – 390

[122] Heller S, Hiemke C, Stroba G, Rieger-Gies A, Daum-Kreysch E, Sachse J, Hartter S. Assessment of Storage and Transport Stability of New Antidepressant and Antipsychotic Drugs for a Nationwide TDM Service (Letter). Therapeutic Drug Monitoring 2004; 26(4): 459 – 461

[123] Hiemke C, Dragicevic A, Gründer G, Härtter S, Sachse J, Vernaleken I et al. Therapeutic monitoring of new antipsychotic drugs. Ther Drug Monit 2004; 26(2): 156 – 160

[124] Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther 2000; 85: 11 – 28

[125] Houghton GW, Dennis MJ, Templeton R, Martin BK. A repeated dose pharmacokinetic study of a new hypnotic agent, zopiclone (Imovane). Int J Clin Pharmacol Ther Toxicol 1985; 23(2): 97 – 100

[126] Ilett KF, Blythe TH, Hackett LP, Ong RTT, Tannenbaum DA, Clarke TMF. Plasma concentrations of dothiepin and its metabolites are not correlated with clinical efficacy in major depressive illness. Ther Drug Monit 1993; 15: 351 – 357

[127] Ingels M, Beauchamp J, Clark RF, Williams SR. Delayed valproic acid toxicity: a retrospective case series. Ann Emerg Med 2002; 39(6): 616 – 621

[128] Isacsson G, Holmgren P, Druid H, Bergman U. The utilization of antidepressants – a key issue in the prevention of suicide: an analysis of 5281 suicides in Sweden during the period 1992 – 1994. Acta Psychiatr Scand 1997; 96: 94 – 100

[129] Iwersen S, Schmoldt A. One fatal and one nonfatal intoxication with tranylcypromine. Absence of amphetamines as metabolites. J Anal Toxicol 1996; 20(5): 301 – 304

[130] Johansson B. A review of the pharmacokinetics and pharmacodynamics of disulfiram and its metabolites. Acta Psychiatr Scand Suppl 1992; 369: 15 – 26

[131] Jonasson B, Saldeen T. Citalopram in fatal poisoning cases. Forensic Sci Int 2002; 126(1): 1 – 6

[132] Jungkunz G, Kuss HJ. On the relationship of nortriptyline: amitriptyline ratio to clinical improvement of amitriptyline treated depressive patients. Pharmakopsychiatr Neuropsychopharmakol 1980; 13(3): 111 – 116

[133] Kaferstein H, Sticht G, Pluisch F. [Poisoning by perazine-organ distribution and interpretation]. Arch Kriminol 2000; 206(3 – 4): 82 – 87

[134] Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. A positron emission tomography study of quetiapine in Schizophrenia – A preliminary finding of an antipsychotic effect with only transiently high dopamine D_2 receptor occupancy. Arch Gen Psychiatry 2000; 57: 553 – 559

[135] Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. Am J Psychiatry 1998; 155: 921 – 928

[136] Kasper S, Dötsch M, Kick H, Vieira A, Möller HJ. Plasma concentrations of fluvoxamine and maprotiline in major depression: implications on therapeutic efficacy and side effects. Eur Neuropsychopharmacol 1993; 3: 13 – 21

[137] Kaye CM, Haddock RE, Langley PF, Mellows G, Tasker TCG, Zussman BD et al. A review of the metabolism and pharmacokinetics of paroxetine in man. Acta Psychiatr Scand 1989; 80 (suppl. 350): 60 – 75

[138] Keck PE, Jr., McElroy SL. Clinical pharmacodynamics and pharmacokinetics of antimanic and mood-stabilizing medications. J Clin Psychiatry 2002; 63 Suppl 4: 3 – 11

[139] Kirchheiner J, Brøsen K, Dahl ML, Gram LF, Kasper S, Roots I et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatr Scand 2001; 104(3): 73 – 192

[140] Kjolbye M, Thomsen K, Rogne T, Rehfelt E, Olesen OV. Search for a therapeutic range for serum zuclopenthixol concentrations in schizophrenic patients. Ther Drug Monit 1994; 16(6): 541 – 547

[141] Kollroser M, Schober C. Simultaneous determination of seven tricyclic antidepressant drugs in human plasma by direct-injection HPLC-APCI-MS-MS with an ion trap detector. Ther Drug Monit 2002; 24: 537 – 544

[142] Kondo T, Otani K, Ishida M, Tanaka O, Kaneko S, Fukushima Y. Adverse effects of zotepine and their relationship to serum concentrations of the drug and prolactin. Ther Drug Monit 1994; 16: 120 – 124

[143] Kornhuber J, Quack G, Danysz W, Jellinger K, Danielczyk W, Gsell W et al. Therapeutic brain concentration of the NMDA receptor antagonist amantadine. Neuropharmacology 1995; 34: 713 – 721

[144] Kramer Nielsen K, Brøsen K, Gram LF, Bech P, Bolwig TG, Sørensen PK et al. Steady-state plasma levels of clomipramine and its metabolites: impact of the sparteine/debrisoquine oxidation polymorphism. Eur J Clin Pharmacol 1992; 43: 405 – 411

[145] Kratzsch C, Frank TP, Kraemer T, Armin AW, Maurer HH. Screening, library-assisted identification and validated quantification of fifteen neuroleptics and three of their metabolites in plasma by liquid chromatography/mass spectrometry with atmospheric pressure chemical ionization. J Mass Spectrom 2003; 38: 283 – 295
[146] Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001; 27(4): 383 – 391
[147] Kupfer DJ, Hanin I, Spiker DG, Grau T, Coble P. Amitriptyline plasma levels and clinical response in primary depression. Clin Pharmacol Ther 1977; 22(6): 904 – 911
[148] Lane HY, Chiu W-C, Chou JCY, Wu S-T, Su MH, Chang WH. Risperidone in acutely exacerbated schizophrenia: dosing strategies and plasma levels. J Clin Psychiatry 2000; 61: 209 – 214
[149] Laux G, Riederer P, editors. Plasmaspiegelbestimmung von Psychopharmaka: Therapeutisches Drug – Monitoring, Versuch einer ersten Standortbestimmung. Stuttgart (Germany): Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1992: 7 – 128
[150] Leinonen E, Lepola U, Koponen H, Kinnunen I. The effect of age and concomitant treatment with other psychoactive drugs on serum concentrations of citalopram measured with a nonenantioselective method. Ther Drug Monit 1996; 18: 111 – 117
[151] Lerer B, Macciardi F. Pharmacogenetics of antidepressant and moodstabilizing drugs: a review of candidate-gene studies and future research directions. Int J Neuropsychopharmacol 2002; 5: 255 – 275
[152] Leucht S, Steimer W, Kreuz S, Abraham D, Orsulak PJ, Kissling W. Doxepin plasma concentrations: is there really a therapeutic range? J Clin Psychopharmacol 2001; 21(4): 432 – 439
[153] Levine B, Jenkins AJ, Queen M, Jufer R, Smialek JE. Distribution of venlafaxine in three postmortem cases. J Anal Toxicol 1996; 20: 502 – 505
[154] Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics – Clinical implications. Clin Pharmacokinet 2003; 42(1): 59 – 98
[155] Linder MW, Keck PE, Jr. Standards of laboratory practice: antidepressant drug monitoring. Clin Chem 1998; 44: 1073 – 1084
[156] Liston HL, Markowitz JS, DeVane CL. Drug glucuronidation in clinical psychopharmacology. J Clin Psychopharmacol 2001; 21: 500 – 515
[157] Llewellyn A, Stowe ZN. Psychotropic medications in lactation. J Clin Psychiatry 1998; 59(suppl. 2): 41 – 52
[158] Lovell RW, Bunker WW. Lithium assay errors. Am J Psychiatry 1997; 154(10): 1477
[159] Lundmark J, Bengtsson F, Nordin C, Reis M, Walinder J. Therapeutic drug monitoring of selective serotonin reuptake inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients. Acta Psychiatr Scand 2000; 101: 354 – 359
[160] Lundmark J, Reis M, Bengtsson F. Therapeutic drug monitoring of sertraline: variability factors as displayed in a clinical setting. Ther Drug Monit 2000; 22: 446 – 454
[161] Lundmark J, Reis M, Bengtsson F. Serum concentrations of fluoxetine in the clinical treatment setting. Ther Drug Monit 2001; 23: 139 – 147
[162] Lundmark J, Thomsen IS, Fjord-Larsen T, Manniche PM, Mengel H, Møller-Nielsen EM et al. Paroxetine: pharmacokinetic and antidepressant effect in the elderly. Acta Psychiatr Scand 1989; 80(suppl. 350): 76 – 80
[163] Madsen AL, Karle A, Rubin P, Cortsen M, Andersen HS, Hemmingsen R. Progressive atrophy of the frontal lobs in first-episode schizophrenia: interaction with clinical course and neuroleptic treatment. Acta Psychiat Scand 1999; 100: 367 – 374
[164] Maguire KP, Norman TR, Burrows GD, Davies B. Blood and plasma concentrations of dothiepin and its major metabolites and clinical response. J Affect Disord 1982; 4: 41 – 48
[165] Mancama D, Arranz MJ, Kerwin RW. Genetic predictors of therapeutic response to clozapine – Current status of research. CNS Drugs 2002; 16(5): 317 – 324
[166] Mancama D, Kerwin RW. Role of pharmacogenomics in individualising treatment with SSRIs. CNS Drugs 2003; 17(3): 143 – 151
[167] Marder SR, Midha KK, van Putten T, Aravagiri M, Hawes EM, Hubbard JW et al. Plasma levels of fluphenazine in patients receiving fluphenazine decanoate. Relationship to clinical response. Br J Psychiatry 1991; 158: 658 – 665
[168] Mason BJ, Goodman AM, Dixon RM, Hameed MH, Hulot T, Wesnes K et al. A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. Neuropsychopharmacology 2002; 27(4): 596 – 606
[169] Mavissakalian MR, Jones B, Olson S, Perel JM. Clomipramine in obsessive-compulsive disorder: clinical response and plasma levels. J Clin Psychopharmacol 1990; 10(4): 261 – 268
[170] McEvoy JP, Scheifler PL, Frances A. The expert consensus guideline series – treatment of Schizophrenia 1999. J Clin Psychiatry 1999; 60(Suppl. 11): 12 – 18
[171] McIntyre IM, King CV, Cordner SM, Drummer OH. Postmortem clomipramine: therapeutic or toxic concentrations? J Forensic Sci 1994; 39(2): 486 – 493
[172] McManus P, Mant A, Mitchell P, Birkett D, Dudley J. Co-prescribing of SSRIs and TCAs in Australia: how often does it occur and who is doing it? Br J Clin Pharmacol 2001; 51(1): 93 – 98
[173] Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics. Clin Pharmacokinet 2002; 41(5): 329 – 342
[174] Meredith PA. Generic drugs – Therapeutic equivalence. Drug Safety 1996; 15(4): 233 – 242
[175] Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet 2000; 356: 1667 – 1671
[176] Mihara K, Kondo T, Suzuki A, Yasui-Furukori N, Ono S, Otani K et al. Effects of genetic polymorphism of CYP1A2 inducibility on the steady-state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine in depressed Japanese patients. Pharmacol Toxicol 2001; 88: 267 – 270
[177] Mihara K, Otani K, Tybring G, Dahl ML, Bertilsson L, Kaneko S. The CYP2D6 genotype and plasma concentrations of mianserin enantiomers in relation to therapeutic response to mianserin in depressed Japanese patients. J Clin Psychopharmacol 1997; 17: 467 – 471
[178] Milner DA, Hall M, Davis GG, Brissie RM, Robinson CA. Fatal multiple drug intoxication following acute sertraline use. J Anal Toxicol 1998; 22: 545 – 548
[179] Molander L, Borgstrom L. Relationship between plasma concentration and arousal in normal subjects after single oral and parenteral doses of melperone, a butyrophenone neuroleptic. Psychopharmacology 1983; 79(2 – 3): 111 – 114
[180] Monteleone P, Gnocchi G, Delrio G. Plasma trazodone concentrations and clinical response in elderly depressed patients: a preliminary study. J Clin Psychopharmacol 1989; 9(4): 284 – 287
[181] Montgomery SA, Montgomery DB, McAuley R, Rani SJ. Mianserin plasma levels and differential clinical response in endogenous and reactive depression. Acta Psychiatr Belg 1978; 78: 798 – 812
[182] Moulin A, Truffer D, Rauch-Desanti C, Istin M, Grognet JM, Dufour A. Comparison of HPLC and RIA methods applied to the quantification of amisulpride in human plasma. Eur J Drug Metab Pharmacokinet 1991; 3: 507 – 512
[183] Müller MJ, Dragicevic A, Fric M, Gaertner I, Grasmader K, Härtter S et al. Therapeutic drug monitoring of tricyclic antidepressants: how does it work under clinical conditions? Pharmacopsychiatry 2003; 36(3): 98 – 104
[184] Müller MJ, Härtter S, Köhler D, Hiemke C. Serum levels of sulpiride enantiomers after oral treatment with racemic sulpiride in psychiatric patients: a pilot study. Pharmacopsychiatry 2001; 34: 27 – 32
[185] Müller-Oerlinghausen B, Fähndrich E. The relationship between pharmacokinetic data and the clinical response in patients treated with maprotiline or clomipramine by intravenous infusion. Pharmacopsychiatry 2002; 18: 100 – 101
[186] Müller-Oerlinghausen B, Rüther E. Clinical profile and serum concentration of viloxazine as compared to amitriptyline. Pharmakopsychiatr Neuropsychopharmakol 1979; 12(4): 321 – 337
[187] Müller-Oerlinghausen B, Schley J. Serumspiegel von Perazin und seinen Metaboliten: Qualitätskontrolle, Kosten, Interpretation und praktische Bedeutung. In: Helmchen H, Hippius H, Tölle R, editors. Therapie mit Neuroleptika – Perazin New York: Georg Thieme Verlag, Stuttgart: 1988: S27
[188] Murray M. P450 Enzymes. Inhibition mechanisms, genetic regulation and effects of liver disease. Clin Pharmacokinet 1992; 23: 132 – 146
[189] Nakajima M, Yokoi T, Mizutani M, Kinoshita M, Funayama M, Kamataki T. Genetic polymorphism in the 5′-flanking region of human CYP1A2 gene: effect on the CYP1A2 inducibility in humans. J Biochem 1999; 125: 803 – 808
[190] Nelson JC. Current status of tricyclic antidepressants in psychiatry: their pharmacology and clinical applications. J Clin Psychiatry 1991; 52: 193 – 200

[191] Nelson JC, Jatlow PI, Mazure C. Desipramine plasma levels and response in elderly melancholic patients. J Clin Psychopharmacol 1985; 5: 217 – 220

[192] Nishikage H, Nakanishi T, Takamitsu Y, Yamamoto J. Sequential changes in the plasma concentration of risperidone following intentional overdose. Clin Neuropharmacol 2002; 25(6): 307 – 309

[193] Norman TR, Burrows GD, Davies BM, Maguire KP, Wurm JM. Viloxazine plasma concentrations and clinical response. J Affect Disord 1980; 2(3): 157 – 164

[194] Ohman D, Norlander B, Peterson C, Bengtsson F. Bioanalysis of racemic reboxetine and its desethylated metabolite in a therapeutic drug monitoring setting using solid phase extraction and HPLC. Ther Drug Monit 2001; 23: 27 – 34

[195] Olesen OV, Licht RW, Thomsen E, Bruun T, Viftrup JE, Linnet K. Serum concentrations and side effects in psychiatric patients during risperidone therapy. Ther Drug Monit 1998; 20: 380 – 384

[196] Orsulak PJ. Therapeutic monitoring of antidepressant drugs – Guidelines updated. Ther Drug Monit 1989; 11: 497 – 507

[197] Otani K, Aoshima T. Pharmacogenetics of classical and new antipsychotic drugs. Ther Drug Monit 2000; 22: 118 – 121

[198] Otani K, Kaneko S, Sasa H, Kondo T, Fukushima Y. Is there a therapeutic window for plasma concentration of mianserin plus desmethylmianserin. Hum Psychopharmacol Clin Exp 1991; 6: 243 – 248

[199] Otani K, Tybring G, Mihara K, Yasui N, Kaneko S, Ohkubo T et al. Correlation between steady-state plasma concentrations of mianserin and trazodone in depressed patients. Eur J Clin Pharmacol 1998; 53: 347 – 349

[200] Özdemir V, Kalow W, Okey AB, Lam MS, Albers LJ, Reist C et al. Treatment-resistance to clozapine in association with ultrarapid CYP1A2 activity and the C–>A polymorphism in intron 1 of the CYP1A2 gene: effect of grapefruit juice and low-dose fluvoxamine. J Clin Psychopharmacol 2001; 21(6): 603 – 607

[201] Pedersen OL, Gram LF, Kristensen CB, Moller M, Thayssen P, Bjerre M et al. Overdosage of antidepressants: clinical and pharmacokinetic aspects. Eur J Clin Pharmacol 1982; 23: 513 – 521

[202] Pellizzoni C, Poggesi I, Jørgensen NP, Edwards DMF, Paus E, Benedetti MS. Pharmacokinetics of reboxetine in healthy volunteers. Single against repeated oral doses and lack of enzymatic alterations. Biopharm Drug Dispos 1996; 17: 623 – 633

[203] Perry PJ. The relationship between antidepressant response and tricyclic antidepressant plasma concentrations: a retrospective analysis of the literature using logistic regression analysis lin. Pharmacokinet 1987; 13: 381 – 392

[204] Perry PJ, Lund BC, Sanger T, Beasley C. Olanzapine plasma concentrations and clinical response: acute phase results of the North American olanzapine trial. J Clin Psychopharmacol 2001; 21: 14 – 20

[205] Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. Am J Psychiatry 1991; 148: 231 – 235

[206] Perry PJ, Sanger T, Beasley C. Olanzapine plasma concentrations and clinical response in acutely III schizophrenic patients. J Clin Psychopharmacol 1997; 17: 472 – 477

[207] Perry PJ, Zeilmann C, Arndt S. Tricyclic antidepressant concentrations in plasma: an estimate of their sensitivity and specificity as a predictor of response. J Clin Psychopharmacol 1994; 14: 230 – 240

[208] Petit P, Lonjon R, Cociglio M, Sluzewska A, Blayac JP, Hue B et al. Carbamazepine and its 10,11-epoxide metabolite in acute mania: clinical and pharmacokinetic correlates. Eur J Clin Pharmacol 1991; 41(6): 541 – 546

[209] Preskorn S, Jerkovich GS. Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. J Clin Psychopharmacol 1990; 10: 88 – 95

[210] Preskorn SH, Burke MJ, Fast GA. Therapeutic drug monitoring: Principles and practice. Ther Drug Monit 1993; 16: 611 – 641

[211] Preskorn SH, Fast GA. Therapeutic drug monitoring for antidepressants: efficacy, safety, and cost effectiveness. J Clin Psychiat 1991; 52(Suppl.): 23 – 33

[212] Preskorn SH, Fast GA. Tricyclic antidepressant-induced seizures and plasma drug concentration. J Clin Psychiatry 1992; 53: 160 – 162

[213] Preskorn SH, Fleck RJ, Schroeder DH. Therapeutic drug monitoring of bupropion. Am J Psychiatry 1990; 147: 1690 – 1691

[214] Puech A, Fleurot O, Rein W. Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. Acta Psychiatr Scand 1998; 98: 65 – 72

[215] Rao ML. Modification of radioreceptor assay technique for the estimation of serum neuroleptic drug levels leads to improved precision and sensitivity. Psychopharmacol 1986; 90: 48 – 553

[216] Rao ML, Staberock U, Baumann P, Hiemke C, Deister A, Cuendet C et al. Monitoring tricyclic antidepressant concentrations in serum by fluorescence polarization immunoassay compared with gas chromatography an HPLC. Clin Chem 1994; 40: 29 – 933

[217] Rasmussen BB, Brøsen K. Is therapeutic drug monitoring a case for optimizing clinical outcome and avoiding interactions of the selective serotonin reuptake inhibitors. Ther Drug Monit 2000; 22: 43 – 154

[218] Regenthal R, Krueger M, Koeppel C, Preiss R. Drug levels: therapeutic and toxic serum/plasma concentrations of common drugs. J Clin Monit Comput 1999; 15(7 – 8): 529 – 544

[219] Reis M, Lundmark J, Bjork H, Bengtsson F. Therapeutic drug monitoring of racemic venlafaxine and its main metabolites in an everyday clinical setting. Ther Drug Monit 2002; 24(4): 545 – 553

[220] Reisby N, Gram LF, Bech P, Nagy A, Petersen GO, Ortmann J et al. Imipramine: clinical effects and pharmacokinetic variability. Psychopharmacology 1977; 54(3): 263 – 272

[221] RiveraCalimlim L, Castaneda L, Lasagna L. Effects of mode of management on plasma chlorpromazine in psychiatric patients. Clin Pharmacol Ther 1973; 14(6): 978 – 986

[222] Roberts CJ, Ford JM, Truman CA, Scott M, Makela PM, Wilcock GK. Assessment of the value of therapeutic monitoring of tacrine in Alzheimer's disease. Eur J Clin Pharmacol 1998; 54(9 – 10): 721 – 724

[223] Roberts RL, Joyce PR, Mulder RT, Begg EJ, Kennedy MA. A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. Pharmacogenomics Journal 2002; 2(3): 191 – 196

[224] Rochat B, Kosel M, Boss G, Testa B, Gillet M, Baumann P. Stereoselective biotransformation of the selective serotonin reuptake inhibitor, citalopram, and its demethylated metabolites by monoamine oxidases in human liver. Biochem Pharmacol 1998; 56: 15 – 23

[225] Rodriguez dlT, Dreher J, Malevany I, Bagli M, Kolbinger M, Omran H et al. Serum levels and cardiovascular effects of tricyclic antidepressants and selective serotonin reuptake inhibitors in depressed patients. Ther Drug Monit 2001; 23(4): 435 – 440

[226] Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. Dementia 1996; 7(6): 293 – 303

[227] Roh HK, Chung JY, Oh DY, Park CS, Svensson JO, Dahl ML et al. Plasma concentrations of haloperidol are related to CYP2D6 genotype at low, but not high doses of haloperidol in Korean schizophrenic patients. Br J Clin Pharmacol 2001; 52: 265 – 271

[228] Rudorfer MV, Potter WZ. The role of metabolites of antidepressants in the treatment of depression [review]. CNS Drugs 1997; 7: 273 – 312

[229] Sachse C, Brockmöller J, Bauer S, Roots I. Functional significance of a C ->A polymorphism in introm I of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 1999; 47: 445 – 449

[230] Sachse J, Härtter S, Müller MJ, Dragicevic A, Hiemke C. Therapeutisches Drug Monitoring von Quetiapin. Psychopharmakotherapie 2003; 10: 19 – 22

[231] Sajbel TA, Carter GW, Wiley RB. Converting patients from brand-name clozapine to generic clozapine. Ann Pharmacother 2001; 35(3): 281 – 284

[232] Salva P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. Clin Pharmacokinet 1995; 29(3): 142 – 153

[233] Schoerlin M-P, Mayersohn M, Korn A, Eggers H. Disposition kinetics of moclobemide, a monoamine oxidase-A enzyme inhibitor: single and multiple dosing in normal subjects. Clin Pharmacol Ther 1987; 42: 395 – 404

[234] Schou M. Forty years of lithium treatment. Arch Gen Psychiatry 1997; 54: 9 – 13

[235] Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 500 drugs. Pharmazie 1997; 52: 895 – 911

[236] Scordo MG, Spina E. Cytochrome P450 polymorphisms and response to antipsychotic therapy. Pharmacogenomics 2002; 3(2): 201 – 218

[237] Seeman P, Van Tol HHM. Deriving the therapeutic concentrations for clozapine and haloperidol: the apparent dissociation constant of a neuroleptic at the dopamine D2 or D4 receptor varies with the affinity of the competing radioligand. Eur J Pharm-Mol Pharmacol Section 1995; 291: 59 – 66

[238] Seiler W, Wetzel H, Hillert A, Schollnhammer G, Langer M, Barlage U et al. Pharmacokinetics and bioavailability of benperidol in schizophrenic patients after intravenous and two different kinds of oral application. Psychopharmacology (Berl) 1994; 116(4): 457 – 463
[239] Shah VP, Midha KK, Dighe S, McGilveray IJ, Skelly JP, Yacobi A et al. Analytical methods validation – bioavailability, bioeqivalence and pharmacokinetic studies. Pharm Res 1992; 9(4): 588 – 592
[240] Simmons SA, Perry PJ, Rickert ED, Browne JL. Cost-benefit analysis of prospective pharmocokinetic dosing of nortriptyline in depressed. J Affect Disord 1985; 8: 47 – 53
[241] Sindrup SH, Brøsen K, Gram LF, Hallas J, Skjelbo E, Allen A et al. The relationship between paroxetine and the sparteine oxidation polymorphism. Clin Pharmacol Ther 1992; 51: 278 – 287
[242] Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CGG, Seroquel Study Group. Quetiapine in patients with Schizophrenia – A high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997; 54: 549 – 557
[243] Spector R. Drug transport in the mammalian central nervous system: multiple complex systems. Pharmacology 2000; 60: 58 – 73
[244] Spina E, Avenoso A, Facciolà G, Salemi M, Scordo MG, Ancione M et al. Relationship between plasma risperidone and 9-hydroxyrisperidone concentrations and clinical response in patients with schizophrenia. Psychopharmacology 2001; 153: 238 – 243
[245] Steimer W, Potter JM. Pharmacogenetic screening and therapeutic drugs. Clin Chim Acta 2002; 315(1 – 2): 137 – 155
[246] Stein S, Schmoldt A, Schulz M. Fatal intoxication with melperone. Forensic Sci Int 2000; 113(1 – 3): 409 – 413
[247] Strakowski SM, Keck PE, Jr., Wong YW, Thyrum PT, Yeh C. The effect of multiple doses of cimetidine on the steady-state pharmacokinetics of quetiapine in men with selected psychotic disorders. J Clin Psychopharmacol 2002; 22(2): 201 – 205
[248] Tasker TCG, Kaye CM, Zussman BD, Link CGG. Paroxetine plasma levels: lack of correlation with efficacy or adverse events. Acta Psychiatr Scand 1989; 80(suppl. 350): 152 – 155
[249] The Scottish Schizophrenia Research Group. The Scottish first episode Schizophrenia study. II. Treatment: imozide versus flupenthixol . Br J Psychiatry 1987; 150: 334 – 338
[250] Thürmann PA, Hompesch BC. Influence of gender on the pharmacokinetics and pharmacodynamics of drugs. Int J Clin Pharmacol Ther 1998; 36: 586 – 590
[251] Tibballs J. Acute toxic reaction to carbamazepine: clinical effects and serum concentrations. J Pediatr 1992; 121(2): 295 – 299
[252] Timmer CJ, Lohmann AAM, Mink CPA. Pharmacokinetic dose-proportionality study at steady state of mirtazapine from remeron tablets. Hum Psychopharmacol 1995; 10: S97 – 106
[253] Timmer CJ, Sitsen JMA, Delbressine LP. Clinical pharmacokinetics of mirtazapine. Clin Pharmacokinet 2000; 38: 461 – 474
[254] Tiseo PJ, Rogers SL, Friedhoff LT. Pharmacokinetic and pharmacodynamic profile of donepezil HCl following evening administration. Br J Clin Pharmacol 1998; 46 Suppl 1: 13 – 18
[255] Tokunaga H, Kudo K, Imamura T, Jitsufuchi N, Ohtsuka Y, Ikeda N. Plasma concentrations of antipsychotic drugs in psychiatric inpatients. Nippon Hoigaku Zasshi 1997; 51: 417 – 422
[256] Torrens M, Castillo C, San L, del Moral E, Gonzalez ML, de laTorre R. Plasma methadone concentrations as an indicator of opioid withdrawal symptoms and heroin use in a methadone maintenance program. Drug Alcohol Depend 1998; 52(3): 193 – 200
[257] Troy SM, Parker VD, Fruncillo RJ, Chiang ST. The pharmacokinetics of venlafaxine when given in a twice-daily regimen. J Clin Pharmacol 1995; 35: 404 – 409
[258] Tse G, Thompson D, Procyshyn RM. Generic clozapine: a cost-saving alternative to brand name clozapine? PharmacoEconomics 2003; 21(1): 1 – 11
[259] Uhr M, Steckler T, Yassouridis A, Holsboer F. Penetration of amitriptyline, but not of fluoxetine, into brain is enhanced in mice with blood-brain barrier deficiency due to Mdr1a P-glycoprotein gene disruption. Neuropsychopharmacology 2000; 22: 380 – 387
[260] Ulrich S, Danos P, Baumann B, Müller D, Lehmann D, et al. Serum concentration of chlormethiazole and therapeutic effect in acute alcohol withdrawal syndrome – an open clinical trial. Ther Drug Monit 2002; 24: 446 – 454
[261] Ulrich S, Neuhof S, Braun V, Meyer FP. Therapeutic window of serum haloperidol concentration in acute schizophrenia and schizoaffective disorder. Pharmacopsychiat 1998; 31: 163 – 169
[262] Ulrich S, Neuhof S, Braun V, Meyer FP. Reduced haloperidol does not interfere with the antipsychotic activity of haloperidol in the treatment of acute schizophrenia. Int Clin Psychopharmacol 1999; 14: 219 – 228
[263] Ulrich S, Wurthmann C, Brosz M, Meyer FP. The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. Clin Pharmacokinet 1998; 34: 227 – 263
[264] Van der Weide J, Steijns LS, van Weelden MJ. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. Pharmacogenetics 2003; 13(3): 169 – 172
[265] Van Putten T, Marder SR. Variable dose studies provide misleading therapeutic windows (Letter). J Clin Psychoparmacol 1986; 6: 55 – 56
[266] van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N. Neuroleptic plasma levels. Schizophr Bull 1991; 17(2): 197 – 216
[267] VanderZwaag C, McGee M, McEvoy JP, Freudenreich O, Wilson WH, Cooper TB. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. Am J Psychiatry 1996; 153(2): 1579 – 1584
[268] Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. Psychopharmacology 2000; 150(1): 15 – 23
[269] Veefkind AH, Haffmans PMJ, Hoencamp E. Venlafaxine serum levels and CYP2D6 genotype. Ther Drug Monit 2000; 22: 202 – 208
[270] Veenstra DL, Higashi MK. Assessing the cost-effectiveness of pharmacogenomics. AAPS Pharmsci 2000; 2(article 29)(3): 1 – 11
[271] Velazquez C, Carlson A, Stokes KA, Leikin JB. Relative safety of mirtazapine overdose. Vet Hum Toxicol 2001; 43(6): 342 – 344
[272] Veuthey JL, Souverain S, Rudaz S. Column-switching procedures for the analysis of drugs in biologic samples. Ther Drug Monit 2004; 26(2): 161 – 166
[273] Vuille F, Amey M, Baumann P. Use of plasma level monitoring of antidepressants in clinical practive – Towards an analysis of clinical utility. Pharmacopsychiatry 1991; 24: 190 – 195
[274] Weigmann H, Gerek S, Zeisig A, Muller M, Härtter S, Hiemke C. Fluvoxamine but not sertraline inhibits the metabolism of olanzapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit 2001; 23: 410 – 413
[275] Wetzel H, Anghelescu I, Szegedi A, Wiesner J, Weigmann H, Härtter S et al. Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. J Clin Psychopharmacol 1998; 18: 2 – 9
[276] Wilner KD, Tensfeldt TG, Baris B, Smolarek TA, Turncliff RZ, Colburn WA et al. Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. Br J Clin Pharmacol 2000; 49(Suppl. 1): 15S – 20
[277] Wincor MZ, Munjack DJ, Palmer R. Alprazolam levels and response in panic disorder: preliminary results. J Clin Psychopharmacol 1991; 11(1): 48 – 51
[278] Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine. Int Clin Psychopharmacol 2002; 17: 141 – 143