Eur J Clin Pharmacol (2008) 64:159–166
DOI 10.1007/s00228-007-0430-1

REVIEW ARTICLE

Clinical utility of drug measurement and pharmacokinetics – therapeutic drug monitoring in psychiatry

Christoph Hiemke

Received: 21 November 2007 / Accepted: 22 November 2007 / Published online: 15 January 2008

Abstract Based on the assumption that a relationship between blood levels and clinical effects (therapeutic effects, adverse events and toxicity) can be defined and considering that after equal doses plasma concentrations vary markedly between individual patients, therapeutic drug monitoring (TDM) can assist to personalize dose adjustment. Taken together, drug levels and a knowledge of the pharmacological profile of the administered drugs can enable the optimal dosage to be tailored according to the need of the individual patient. Therapeutic drug monitoring has been established for a limited number of drugs. In psychiatry, it has a 40-year-long history, which started with nortriptyline. Evidence has accumulated which shows that TDM is a valid tool for the optimization of psychopharmacotherapy. When used adequately, TDM is helpful for many patients and in many situations. Combined with pharmacogenetic tests, the metabolic status of a patient can be well characterized. Several new observations have been made during routine TDM that have stimulated clinical pharmacological research, such as investigations on inherited differences in drug metabolism that are closely linked to TDM in psychiatry. The contributions of individual forms of cytochrome P450 (CYP) to the metabolism of drugs was elicited by clinical observations on pharmacokinetic drug interactions. Therapeutic drug monitoring requires a close collaboration between the prescribing physician, the laboratory specialist, the clinical pharmacologist and the patient. This complexity may result in errors which can be detected by analysing the appropriate use of TDM in clinical practice. More education has to be provided to the prescribing clinicians on the pharmacology of the drugs and the algorithm of TDM. Moreover, clinical trials should include measurements of blood concentrations during drug development to generate valid data on the relationships between drug concentrations and clinical outcomes under well-controlled conditions. This would merely increase the amount of work and costs, as high-throughput methods are now available in many laboratories. Any progress in TDM has direct benefits for the treatment of many individual patients.

C. Hiemke (✉)
Department of Psychiatry, University of Mainz,
Untere Zahlbacher Str. 8,
55101 Mainz, Germany
e-mail: hiemke@mail.uni-mainz.de

Introduction

Therapeutic drug monitoring (TDM) is defined as the measurement of drug levels that, with appropriate clinical pharmacological interpretation, will directly affect prescribing procedures [1, 2]. Commonly, it is the measurement of a prescribed drug in the blood or plasma, but it may also refer to the determination of an endogenous compound used as replacement therapy in an individual patient who is deficient of that compound. Therapeutic drug monitoring is primarily recommended for drugs with a narrow therapeutic index and with high interpatient pharmacokinetic variability, and it is based on the assumption that a relationship between blood levels and clinical effects (therapeutic effect, adverse events and toxicity) can be defined.

It would be inappropriate to replace blood pressure monitoring by the determination of drug concentrations in blood as the means to control the treatment with an antihypertensive drug. For hypnotic drugs as well, TDM does not make sense for most patients and most situations, since the expected therapeutic effect is rapid in onset and proven by an evident physiological reaction. However,

TDM is informative in the case of a lack of hypnotic efficacy under recommended therapeutic doses. It can then clarify whether non-response could be due to abnormalities in drug absorption or metabolism. When levels are in the expected range with respect to drug dosage, resistance or tolerance towards the drug may be suspected. As such, TMD is beneficial when it shortens the time to remission of a depressed patient or when it helps to prevent the occurrence of convulsions. It is even obligatory when drugs may be harmful, such as in the case of overdosing, which may occur with digoxin, lithium or tacrolimus. Therapeutic drug monitoring has been established for antifungal, antiretroviral, anticonvulsant and immunosuppressant drugs, for theophylline, aminoglycosides, psychotropic drugs, such as antidepressants, antipsychotics and mood stabilizers. It is applied clinical pharmacology that combines the results reported by the laboratory and theoretical knowledge on the pharmacological profile of the administered drugs and, subsequently, the optimal dosages according to the characteristics of the individual patient can be tailored.

In terms of psychoactive drugs, TDM has a 40-year-long history that started with the publication of a method for the determination of nortriptyline in plasma [3]. Today, TDM is more or less widely available for a large number of psychotropic drugs. High interindividual variabilities in the pharmacokinetics of all psychoactive drugs have been proven. Recently, consensus guidelines [2] have been worked out for psychoactive drugs by the TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP). A number of specific situations have been defined in which the determination of plasma concentrations of psychoactive drugs has been proven useful, such as control of compliance, identification of drug interactions or genetic peculiarities of drug metabolism. However, it is still a matter of debate to which extent TDM has beneficial effects when used more or less regularly for treatment optimization. The aim of this review is to show why and how TDM provides clinical pharmacological knowledge for patient treatment, taking psychoactive drugs as an example.

The history of TDM in psychiatry

In 1970, Åsberg and coworkers [4] found a correlation between subjective side effects and the plasma concentrations of nortripyline and, 1 year later, the same authors reported a plasma concentration-dependent clinical improvement [5]. In 1970, phenobarbital was found to affect the pharmacokinetics of chlorpromazine [6]. Alexanderson and co-workers [7] observed that genetic factors influenced their therapy with nortriptyline, and Bertilsson and coworkers [8] described a patient exhibiting a genetic deficiency of debrisoquine hydroxylation that was associated with unusually high plasma concentrations of nortriptyline and severe adverse effects. In 1972, the clinical pharmacologists Gram and Overø [9] reported inhibitory effects of neuroleptics on the metabolism of tricyclic antidepressants. Subsequently, evidence has grown rapidly that TDM should be used when treating patients with tricyclic antidepressants [10, 11].

For antipsychotic drugs, it was long believed that TDM is not required despite established correlations between plasma concentrations and clinical improvement [12–15]. The typical antipsychotic drugs exhibited little toxicity. Overdosing lead to extrapyramidal symptoms (EPS) which were of no vital significance; in fact, EPS were even considered to be an intrinsic feature of antipsychotic activity and used in practice to titrate patients up to their maximally tolerable dose. The dose was increased until EPS appeared and then slightly reduced. However, EPS are highly uncomfortable for the patient and thus initiated the development of new antipsychotic drugs. With the discovery of clozapine in 1958 [16], a neuroleptic drug with an atypical profile almost devoid of EPS became available. After the introduction of clozapine, agranulocytosis was soon identified as a severe adverse reaction. Nevertheless, clozapine was found to be therapeutically advantageous in comparison with established typical antipsychotic drugs [16,17]. Because of its haematotoxicity, however, regular blood cell counting became an obligatory part of its prescription. Moreover, therapy with clozapine may result in the appearance of other critical symptoms, such as convulsions or delirium. Therefore, TDM was suggested to be useful as the means to improve the safety of clozapine [18]. Experiences with clozapine have changed the opinion that TDM is not necessary for antipsychotic drugs. The finding that fluvoxamine co-medication can increase clozapine concentrations in the blood up to tenfold the baseline level [19, 20] provided another reason to use TDM. For combinations with fluvoxamine, TDM became an obligatory part of any treatment with clozapine.

Convincing evidence that TDM is useful in psychiatry was provided by the pioneering work of the Scandinavian clinical pharmacologists Folke Sjöqvist (together with Marie Åsberg), Leif Bertilsson and Lars Gram, primarily on tricyclic antidepressants, since 1972 by the multiple activities of Pierre Baumann in Switzerland, who worked with various old and new psychotropic drugs [2], and later by important contributions by the group of Finn Bengtsson in Sweden [21]. Interestingly, TDM has been combined recently with pharmacogenetic tests [22].

Despite the obvious advantages of TDM, its use has been limited to few patients, mostly inpatients, and only a few indications. The reasons for this are as follows:

- Assays of psychoactive drug concentrations in blood with sufficient accuracy, specificity, selectivity and reproducibility can be carried out by very few laboratories.
- The time lag between a TDM request and the reporting of results is often too long; 1 week or even more is not acceptable for treatment optimization.
- For many psychotropic drugs their target ranges are not well defined.
- Valid recommendations on the appropriate use of TDM in psychiatry are lacking. A report of the Task Force on the Use of Laboratory Tests in Psychiatry (1985) was restricted to TDM of tricyclic antidepressants.
- With the introduction of new drugs on the market, it has been claimed, such as for new antidepressants, that TDM is not necessary.

The situation has changed significantly during the last years. Many findings and developments in the field of clinical pharmacology had and still have consequences for TDM and thus for patient care (Table 1). Rapid and reliable methods that enable the reporting of results within a single working day have become available [23–27]. Imaging studies using positron emission tomography (PET) or single photon emission tomography (SPET) have shown that plasma concentrations are closely related with the extent of blockade of target structures in the brain [28–39]. Target ranges have also been for new psychotropic drugs [2, 40–42]. Last not least, literature-based guidelines for TDM in psychiatry have been published [2].

Guidelines for optimal use of TDM

The interdisciplinary TDM group of the AGNP has worked out consensus guidelines for optimal use of TDM in psychiatry [2]. Five levels of recommendation were defined for routine use of TDM: (1) strongly recommended (e.g. for lithium or nortriptyline); (2) recommended (e.g. for risperidone or methadone); (3) useful (e.g. for citalopram or alprazolam); (4) probably useful (e.g. for reboxetine or melperone); (5) and not recommended (e.g. for tranylcypromine or clomethiazol). Therapeutic drug monitoring has been strongly recommended when controlled clinical trials have shown a

Table 1 Major findings and developments of clinical psychopharmacology research and their impact on therapeutic drug monitoring (TDM) on patient care

Major findings/developments since 1967	Impact on routine TDM
Analytical techniques	
High-performance liquid chromatography with ultraviolet detection	Preferentially used in most TDM laboratories
Liquid chromatography with mass spectrometric detection	Rarely used to date (<20% of the laboratories), increases gradually
Immunoassays	Used for some tricyclic antidepressants, critical for quantitative determination, of decreasing importance
Radio–receptor assays	Used for some antipsychotic drugs in the past
Pharmacokinetics	
Evaluation of pharmacokinetic properties of multiple new drugs	Basic information, e.g. for calculation of dose-related drug concentrations
Drug–drug interactions	Indication to use TDM
Pharmacogenomics	
Inherited differences in drug metabolism	Highly relevant to explain interindividual variability of drug metabolism
Genetic polymorphism of drug metabolizing enzymes	Highly relevant to explain interindividual variability
Phenotyping assays	
Single probe assay (e.g. spartein)	Used primarily in research and for special indications
Cocktail approach (two to five probe drugs)	Not widely used
Genotyping assays	Increasing used in addition to TDM
Clinical studies	
Phase I to phase III trials	Availability of new drugs, mostly without information related to TDM
Evaluation of optimal plasma concentrations	Definition of target ranges for TDM
Positron and single photon emission tomography (PET and SPET)	Evaluation of drug concentrations in blood and in vivo receptor occupancy
Drug–drug interactions (often accidental finding, case reports), pharmacovigilance programs	So far, programmes did not include drug concentration measurements regularly; these are becoming of increasing importance for drug safety in association with TDM

benefit of TDM; for example, when toxic effects were associated with "supratherapeutic" plasma concentrations. Likewise, at "subtherapeutic" plasma concentrations, the expected response should be similar to placebo, and at plasma concentrations higher than the recommended target range there is an increasing risk of adverse effects. TDM was rated as "probably useful" when publications on TDM of the drug were lacking and when the suggested therapeutic ranges were derived only from steady-state pharmacokinetic studies with therapeutically effective doses. Nevertheless, TDM can be useful to control whether plasma concentrations are plausible for a given dose.

The authors of the consensus guidelines carefully reviewed and evaluated the literature for 65 psychoactive drugs, defined the individual levels of recommendation for their monitoring and suggested therapeutic ranges. Moreover, indications were defined for TDM, such as uncertain compliance, lack of response, adverse effects, suspected drug interactions, relapse prevention, presence of a pharmacogenetic peculiarity, comorbidity, forensic cases or other problems that might be clarified by TDM. The specific indications do not necessarily require the existence of clearly defined "therapeutic windows". The knowledge of expected plasma concentration ranges at a given dose may efficiently alert the clinician. According to the guidelines, blood has to be collected under steady-state conditions (five half-lives after changes of dosing) and at a time representing trough levels. A request form indicating co-medications, diagnosis, dose, treatment duration, sex, age, body weight and reason for the request should accompany the blood sample. Interpretation of a drug concentration and context information of the treated patient is essential to obtain the full clinical benefit of TDM.

TDM as part of drug therapy

Before the application of any drug, the patient must have been well diagnosed. It must be evident that a beneficial effect can be expected under drug treatment. Psychiatric disorders cover a wide spectrum of symptoms that can range from close to normal at one end to severely abnormal at the other. The a priori selection of the most suitable drug among the more than 50 antidepressants and antipsychotics for an individual patient is actually not possible. Clinical trials have shown a similar efficacy (50–60 % response rates) for the majority of antidepressant drugs [43, 44], and it is a matter of debate whether the new atypical antipsychotic drugs are really advantageous [45–47]. In terms of an individual patient, biomarkers with predictive validity are currently lacking for treatment response to psychotropic drugs. The best predictor is the change in the psychopathology [44, 48–51]. Therefore, it is common sense that drug selection relies primarily on the patient's history. Psychopharmacotherapy, which aims to reach the highest possible level of functioning, is a stepwise trial and error process starting with a first drug and often ending with a combination of drugs (Fig. 1). In accordance with the guidelines [2, 43], TDM should be implemented regularly for those drugs with high levels of recommendation (strongly recommended or recommended). In the case of treatment failure or less than 20% improvement under a sufficiently high dose and for a sufficiently long time of treatment of 2–4 weeks, an augmentation treatment (e.g. lithium in addition to an antidepressant drug) or a switch to another drug is recommended. However, the medication is changed, it should be shown that the plasma concentration was sufficient.

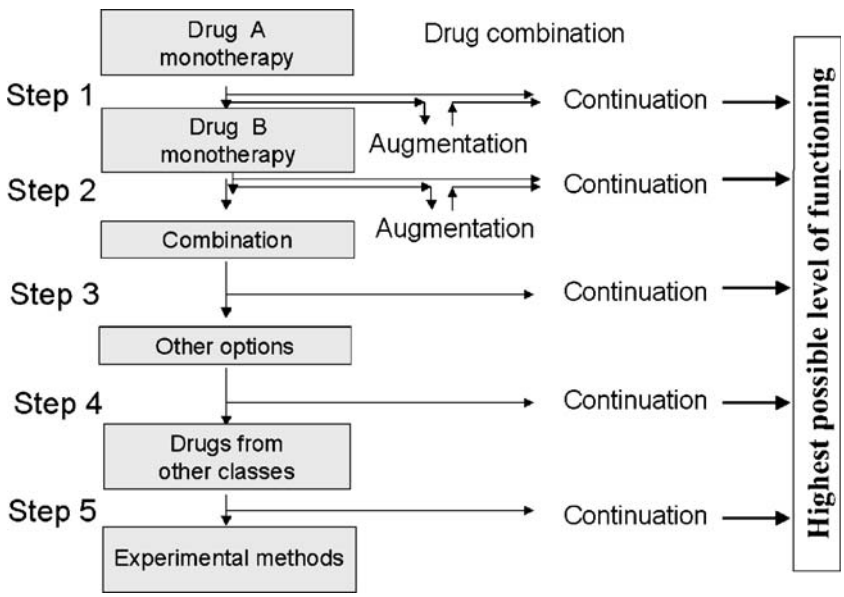

Fig 1 Algorithm for the treatment of psychiatric patients to attain the highest level of functioning. Whenever a treatment option has failed despite a sufficient dose and time, the treatment will be switched to the next step

In terms of the treatment schedule (Fig. 1), information from TDM that plasma concentrations are below, within or above the recommended target range can be sufficient. In many situations and for many cases, however, more information can be gained in association with context variables (Fig. 2). When the plasma concentration is within the recommended target range, but too high in relation to the applied dose, reduced metabolic activity, interaction with co-medication or intake errors may be a possibility. If metabolites of the drug have also been measured, their concentrations and also the ratio of the concentration of the metabolite to the parent compound can help to solve such a problem [21]. Comorbidity may affect the pharmacokinetics, and most patients, especially inpatients, are treated by more than a single drug. Clinical pharmacological knowledge and the adequate use of this information are essential to ensure the full benefit of TDM for many interpretations of a drug concentration. Interpretation can be done by a specialist, either in the laboratory or in the clinic; specialized laboratories with expert knowledge in pharmacokinetics and psychopharmacology are most often preferred. Because of the increasingly high complexity due to the treatment of difficult cases and the use of drug combinations, TDM is an interdisciplinary task between the prescribing physician, the laboratory specialist, the clinical pharmacologist and – last but not least – the patient. In many countries, there is a trend to separate routine laboratory work from research activities; this is primarily driven by economic reasons. Such structural changes will reduce the quality of TDM, since this leads almost automatically to TDM without interpretation. Appropriate interpretation based on clinical pharmacology data is the best approach for applying present knowledge to an improvement in the patient's clinical outcome. Automated interpretation of results is not possible.

Therapeutic drug monitoring represents a tool to phenotype an individual patient with respect to a given drug. When a drug is primarily metabolized by a single enzyme, a phenotyping test may be used to estimate the activity of this particular enzyme and to use this information for calculating a target dose [52–55]. For testing, a probe drug is given as a single dose, which is normally without pharmacological effect. A number of probe drugs are used for in vivo testing, including caffeine and theophylline for cytochrome (CYP)1A2, tolbutamide, phenytoin, warfarin and losartan for CYP2C9, mephenytoin, omeprazole and proguanil for CYP2C19, dextromethorphan, debrisoquin, sparteine and metoprolol for CYP2D6, chlorzoxazone for CYP2E1 and midazolam, nifedipine, dextromethorphan, erythromycin, dapsone and alfentanil for CYP3A (for review see [54]). More recently, a cocktail approach for phenotyping has been introduced [55]. A mixture of probe drugs is administered with the aim of obtaining – in a single experiment – information on the activities of several CYP enzymes. These in vivo tests can be associated with some problems, such as adverse effects, high costs and complicated analyses. Therefore, to date these tests have not been introduced as routine clinical assays; they are still restricted to research purposes.

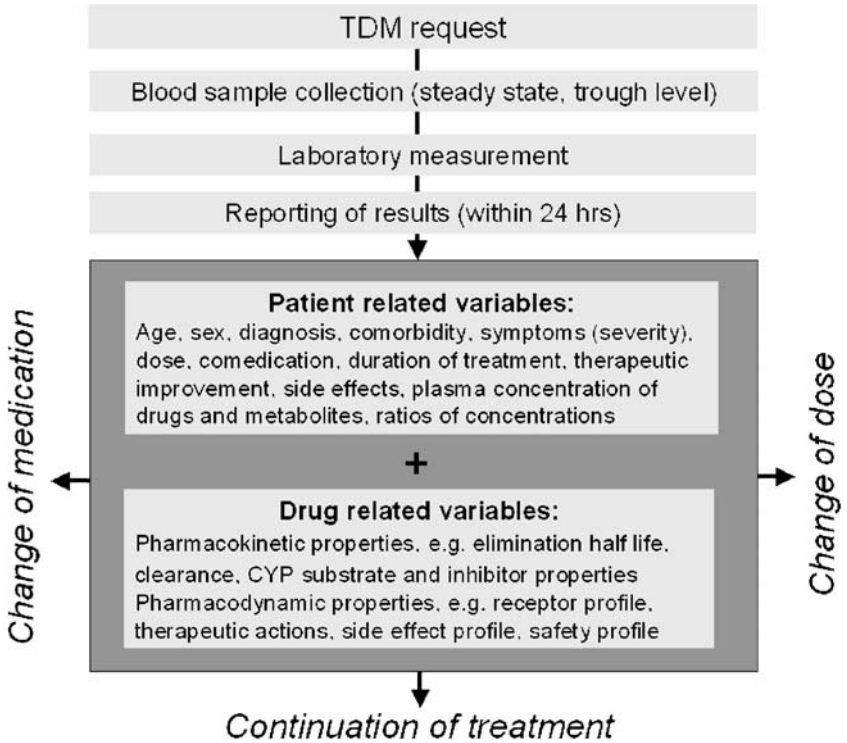

Fig 2 Context variables needed for clinical decision making for treatment of psychiatric patients with inclusion of therapeutic drug monitoring. Clinical decision-making must consider both the patient and drug-related variables

TDM as a base for clinical pharmacological research

In psychiatry, research on inherited differences in drug metabolism is closely linked to TDM. The function of individual forms of CYP450 in drug metabolism was elicited by clinical observations on pharmacokinetic drug–drug interactions. Enormous progress has been made in the area of drug metabolism during the last 40 years. Enzymes of theCYP450 family have been identified as major players in the metabolism of psychotropic drugs. It was found that humans have 57 sequenced CYP genes and 29 pseudogenes [56]. Today, drug development includes the analysis of the involved CYP species. This knowledge enables pharmacokinetic drug interactions to be predicted, and it can be easily decided if a distinct combination should be accompanied by a monitoring of plasma concentrations of the drugs. Moreover, many CYP enzymes have been found to be genetically polymorphic, which can have clinical consequences similar to those reported for the first time by Bertilsson for nortriptyline [8]. Information gained from routine TDM has been an important stimulator of clinical pharmacological research. Poor or ultrarapid metabolizers of CYP2D6 were detected when using TDM. Aranow and co-workers [57] observed an interaction of fluoxetine with tricyclic antidepressants. Another example was the report "Fluvoxamine–tricyclic antidepressant interaction – an accidental finding" [58] in which the authors demonstrated, for the first time, the inhibitory effect of the alternative selective serotonin reuptake inhibitor fluvoxamine on CYP1A2. Similarly, a dramatic increase of clozapine plasma concentrations was observed in patients under co-medication with fluvoxamine [19,59]. These and other TDM-related observations initiated an intensive research on drug interactions, and it was found that these are highly relevant in psychopharmacotherapy. Thus, TDM has gained importance for the handling of polypharmacy.

Problematic use of TDM

Therapeutic drug monitoring starts with the physician's decision to request a plasma concentration analysis and ends with either a change or no change of the pharmacotherapy. A prospective investigation failed to find a clinically significant impact of the TDM of tricyclic antidepressants because in many cases the dose adjustment was inappropriate [60]. Similar observations were made by Zernig and co-workers [61]. Another study on the clinical use of TDM of tricyclic antidepressants in a psychiatric university hospital revealed that between 25 and 40% of the requests for TDM were inappropriate and that the interpretation of the results led to about 20% of the therapeutic adjustments being incorrect [54]. Detailed reviews of TDM tests have analysed the time of blood sampling in relation to the medication process and the consequences of the TDM results for clinical decision-making [62–64]. A total of 748 plasma levels were measured for antidepressants and 370 for mood stabilizers. A minority of TDM tests was performed within an optimal time frame. About one-third of blood samples were taken too early – before steady-state had been reached. The inappropriate use of TDM that has been found in a retrospective analysis indicated that beneficial effects can still be enhanced. Education of the prescribing clinicians on the pharmacology of psychotropic drugs and the TDM strategy are required to improve clinical outcome.

Outlook on TDM

Therapeutic drug monitoring is using clinical pharmacology data and knowledge to improve drug treatment. Progress in clinical pharmacology research will contribute to an improved application of TDM. The background and present status have been outlined for psychotropic drugs. In clinical practice, the application of beneficial TDM is still far from optimal. Moreover, TDM should also be considered during drug development. Although high-throughput laboratory methods are now available, clinical trials do not include measurements of blood concentrations. These should be implemented in the near future to provide valid data on relations between drug concentrations and clinical outcomes under well-controlled conditions. Only a minor increase in the amount of work and costs would be needed to generate many positive consequences for drug treatment.

Acknowledgements The author (C. Hiemke) has received research grants and lecture fees from the pharmaceutical companies Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Lundbeck, Pfizer, Servier, Sanofi-Aventis and Wyeth. The author indicates that no potential conflict of interest exists with products described in this manuscript.

References

1. Touw DJ, Neef C, Thomson AH, Vinks S (2005) Cost-effectiveness of therapeutic drug monitoring. Ther Drug Monit 27:10–17
2. Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, Kuss HJ, Laux G, Müller-Oerlinghausen B, Rao ML, Riederer P, Zernig G (2004) The AGNP-TDM expert group consensus guidelines: Therapeutic drug monitoring in psychiatry. Pharmacopsychiatria 37:243–265
3. Hammer WM, Brodie BB (1967) Application of isotope derivative technique to assay of secondary amines: estimation of desipramine by acetylation with H3-Acetic anhydride. J Pharmacol Exp Ther 157:503–508
4. Åsberg M, Cronholm B, Sjöqvist F, Tuck D (1970) Correlation of subjective side effects with plasma concentrations of nortriptyline. Br Med J 4:18–21

5. Åsberg M, Cronholm B, Sjöqvist F, Tuck D (1971) Relationship between plasma level and therapeutic effect of nortriptyline. Br Med J 3:331–334
6. Curry SH, Davis JM, Janowski DS, Marshall JHL (1970) Factors affecting chlorpromazine plasma levels in psychiatric patients. Arch Gen Psychiatry 22:209–215
7. Alexanderson BH, Evans DA, Sjöqvist S (1969) Steady_state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. Br Med J 686:764–768
8. Bertilsson L, Mellström B, Sjöqvist F, Märtensson B, Åsberg M (1981) Slow hydroxylation of nortriptyline and concomitant poor debrisoquine hydroxylation: clinical implications. Lancet i:560–561
9. Gram LF, Overø KF (1972) Drug inhibition: Inhibitory effects of neuroleptics on metabolism of tricyclic antidepressants in man. Br Med J 1:463–465
10. Perry PJ (1987) The relationship between antidepressant response and tricyclic antidepressant plasma concentrations: a retrospective analysis of the literature using logistic regression analysis. Pharmacokinetics 13:381–392
11. Preskorn S, Jerkovich GS (1990) Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. J Clin Psychopharmacol 10:88–95
12. Baldessarini RJ, Cohen BM, Teicher MH (1988) Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. Arch Gen Psychiatry 45:79–91
13. Perry PJ, Miller DD, Arndt SV, Cadoret RJ (1991) Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. Am J Psychiatry 148:231–235
14. Ulrich S, Wurthmann C, Brosz M, Meyer FP (1989) The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. Clin Pharmacokinet 34:227–263
15. van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N (1991) Neuroleptic plasma levels. Schizophr Bull 17:197–216
16. Hippius H (1989) The history of clozapine. Psychopharmacology 99:S3–S5
17. Kane JM, Honigfeld G, Singer J, Meltzer H (1988) Clozapine in treatment-resistant schizophrenics. Psychopharmacol Bull 24:62–67
18. Perry PJ, Miller DD, Arndt SV, Cadoret RJ (1991) Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. Am J Psychiatry 148:231–235
19. Hiemke C, Weigmann H, Härtter S, Dahmen N, Wetzel H, Müller H (1994) Elevated levels of clozapine in serum after addition of fluvoxamine. J Clin Psychopharmacol 14:279–281
20. Jerling M, Lindström L, Bondesson U, Bertilsson L (1994) Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit 16:368–374
21. Bengtsson F (2004) Therapeutic drug monitoring of psychotropic drugs TDM "nouveau". Ther Drug Monit 26:145–151
22. Jaquenoud Sirot E, van der Velden JW, Rentsch K, Eap CB, Baumann P (2006) Therapeutic drug monitoring and pharmacogenetic tests as tools in pharmacovigilance. Drug Safety 29:735–68
23. Gutteck U, Rentsch KM (2003)Therapeutic drug monitoring of 13 antidepressant and five neuroleptic drugs in serum with liquid chromatography-electrospray ionization mass spectrometry. Clin Chem Lab Med 41:1571–1579
24. Kirchherr H, Kühn-Velten WN (2006) Quantitative determination of forty-eight antidepressants and antipsychotics in human serum by HPLC tandem mass spectrometry: a multi-level, single-sample approach. J Chromatogr B 843:100–113
25. Härtter S, Hiemke C (1992) Column switching and high-performance liquid chromatography in the analysis of amitriptyline, nortriptyline and hydroxylated metabolites in human plasma or serum. J Chromatogr 578:273–282
26. Härtter S, Weigmann H, Hiemke C (2000) Automated determination of reboxetine by high-performance liquid chromatography with column-switching and ultraviolet detection. J Chromatogr B 740:135–140
27. Saint-Marcoux F, Sauvage FL, Marquet P (2007) Current role of LC-MS in therapeutic drug monitoring. Anal Bioanal Chem 388:1327–1349
28. Farde L, Nordström AL, Wiesel F-A, Pauli S, Halldin C, Sedvall G (1992). Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch Gen Psychiatry 49:538–544
29. Farde L, Wiesel FA, Halldin C, Sedvall G (1988) Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry 45:71–76
30. Gründer G, Siessmeier T, Piel T, Vernaleken I, Buchholz H-G, Zhou Y, Hiemke C, Wong DF, Rösch F, Bartenstein P (2003) Quantification of D2-like dopamine receptors in human brain with [^{18}F]desmethoxyfallypride. J Nucl Med 44:109–116
31. Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P (2000) A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. Arch Gen Psychiatry 57:553-559
32. Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA et al (1998) 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. Am J Psychiatry 155:921–928
33. Medori R, Mannaert E, Gründer G (2006) Plasma antipsychotic concentration and receptor occupancy, with special focus on risperidone long-acting injectable. Eur Neuropsychopharmacol 16:233–240
34. Meyer JH, Wilson AA, Sagrati S, Hussey D, Carella A, Potter WZ, Ginovart N, Spencer EP, Cheok A, Houle S (2004) Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. Am J Psychiatry 161:826–835
35. Nordström A-L, Farde L, Wiesel F-A, Forslund K, Pauli S, Halldin C, Uppfeldt G (1993) Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol Psychiatry 33:227–235
36. Talbot PS, Laruelle M (2002) The role of in vivo molecular imaging with PET and SPECT in the elucidation of psychiatric drug action and new drug development. Eur Neuropsychopharmacol 12:503–511
37. Talvik M, Nordstrom AL, Larsen NE, Jucaite A, Cervenka S, Halldin C, Farde L (2004) A cross-validation study on the relationship between central D2 receptor occupancy and serum perphenazine concentration. Psychopharmacology (Berl) 175:148–153
38. Vernaleken I, Siessmeier T, Buchholz HG, Härtter S, Hiemke C, Stoeter P, Rösch F, Bartenstein P, Gründer G (2004) High striatal occupancy of D2-like dopamine receptors by amisulpride in the brain of patients with schizophrenia. Int J Neuropsychopharmacol 7:421–430
39. Yokoi F, Gründer G, Biziere K, Stephane M, Dogan AS, Dannals RF, Ravert H, Suri A, Bramer S, Wong DF (2002) Dopamine D_2 and D_3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): a study using positron emission tomography and [^{11}C]raclopride. Neuropsychopharmacology 27:248–259
40. Hiemke C, Dragicevic A, Gründer G, Härtter S, Sachse J, Vernaleken I, Müller MJ Therapeutic monitoring of new antipsychotic drugs. Ther Drug Monit 26:156–160
41. Lundmark J, Bengtsson F, Nordin C, Reis M, Walinder J (2000) Therapeutic drug monitoring of selective serotonin reuptake

inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients. Acta Psychiat Scand 101:354–359
42. Müller MJ, Regenbogen B, Härtter S, Eich FX, Hiemke C (2007) Therapeutic drug monitoring for optimizing amisulpride therapy in patients with schizophrenia J Psychiatr Res 41:673–679
43. Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ (2002) 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 J Biol Psychiatry 3:5–43
44. Stassen HH, Angst J, Daniel H, Scharfetter C, Szegedi A (2007) Is there a common resilience mechanism underlying antidepressant drug response. Evidence from 2848 patients. J Clin Psychiatry 68:1105–1205
45. Beasley CM Jr, Stauffer VL, Liu-Seifert H, Taylor CC, Dunayevich E, Davis JM (2007) All-cause treatment discontinuation in schizophrenia during treatment with olanzapine relative to other antipsychotics: an integrated analysis. J Clin Psychopharmacol 27:252–258
46. Dolder CR, Lacro JP, Dunn LB, Jeste DV (2002) Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry 59:103–108
47. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–23
48. Chang Y-C, Lane HY, Yang KH, Huang CL (2006) Optimizing early prediction for antipsychotic response in schizophrenia. J Clin Psychopharmacol 26:554–559
49. Leucht S, Busch R, Kissling W, Kane JM (2007) Early prediction of antipsychotic nonresponse among patients with schizophrenia. J Clin Psychiatry 68:352–360
50. Leucht S, Davis JM, Engel RR, Kane JM, Wagenpfeil S (2007) Defining "response" in antipsychotic drug trials: recommendation for the use of scale-derived cutoffs. Neuropsychopharmacology (in press)
51. Szegedi A, Müller MJ, Anghelescu I, Klawe C, Kohnen R, Benkert O (2003) Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. J Clin Psychiatry 64:413–420
52. Frank D, Jaehde U, Fuhr U (2007) Evaluation of probe drugs and pharmacokinetic metrics for CYP2D6 phenotyping. Eur J Clin Pharmacol 63:321–333
53. Faber MS, Jetter A, Fuhr U (2005) Assessment of CYP1A2 activity in clinical practice: why, how, and when? Basic Clin Pharmacol Toxicol 97:125–1234
54. Streetman DS, Bertino JS Jr, Nafziger AN (2000) Phenotyping of drug-metabolizing enzymes in adults: a review of in-vivo cytochrome P450 phenotyping probes. Pharmacogenetics 10:187–216
55. Tanaka E, Kurata N, Yasuhara H (2003) How useful is the "cocktail approach" for evaluating human hepatic drug metabolizing capacity using cytochrome P450 phenotyping probes in vivo? J Clin Pharm Ther 28:157–65
56. Nelson DR (2006) Cytochrome P450 nomenclature, 2004. Methods Mol Biol 320:1–10
57. Aranow AB, Hudson JI, Pope HG Jr, Grady TA, Laage TA, Bell IR, Cole JO (1989) Elevated antidepressant plasma levels after addition of fluoxetine. Am J Psychiatry 146:911–913
58. Bertschy G, Vandel S, Vandel B, Allers G, Volmat R (1991) Fluvoxamine-tricyclic antidepressant interaction. An accidental finding. Eur J Clin Pharmacol 40:119–120
59. Jerling M, Lindström L, Bondesson U, Bertilsson L (1994) Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit 16:368–374
60. Müller MJ, Dragicevic A, Fric M, Gaertner I, Grasmäder K, Härtter S, Hermann E, Kuss HJ, Laux G, Oehl W, Rao ML, Rollmann N, Weigmann H, Weber-Labonte M, Hiemke C (2003) Therapeutic drug monitoring of tricyclic antidepressants: How does it work under clinical conditions Pharmacopsychiatry 36:98–104
61. Zernig G, Lechner T, Kramer-Reinstadler K, Hinterhuber H, Hiemke C, Saria A (2004) What the clinician still has to be reminded of. Ther Drug Monit 26:582
62. Vuille F, Amey M, Baumann P (1991) Use of plasma level monitoring of antidepressants in clinical practive – Towards an analysis of clinical utility. Pharmacopsychiatry 24:190–195
63. Mann K, Hiemke C, Schmidt LG, Bates DW (2006) Appropriateness of therapeutic drug monitoring for antidepressants in routine psychiatric inpatient care. Ther Drug Monit 28:83–88
64. Mann K, Hiemke C, Lotz J, Schmidt LG, Lackner KJ, Bates DW (2006) Appropriateness of plasma level determinations for lithium and valproate in routine care of psychiatric inpatients with affective disorders. J Clin Psychopharmacol 26:671–673