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The Significance of Therapeutic Drug Monitoring: Investigating Clinical And Forensic Toxicology

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Therapeutic Drug Monitoring (TDM) is a vital tool in clinical and forensic toxicology, assessing drug levels in biological samples to optimize therapy or investigate drug-related incidents. TDM, a field that combines clinical pharmacology and forensic toxicology, provides valuable insights into drug therapy management and forensic investigations. This paper studies the role of TDM in clinical conditions, focusing on its effectiveness in guiding dosage adjustments, ensuring therapeutic efficacy, and minimizing adverse effects. The study explores how TDM aids forensic investigations by providing valuable insights into drug-related fatalities, abuse, and compliance monitoring. This study observes current methodologies, challenges, and trends in TDM, emphasizing its crucial role in promoting patient safety, enhancing drug efficacy, and facilitating forensic analyses in toxicology practice. This review studies the role of TDM in clinical conditions, highlighting its potential benefits and limitations in optimizing drug therapy. The widespread adoption and effectiveness of drug metabolism testing are hindered by challenges like variability, assay limitations, and interpretational complexities. TDM is crucial in forensic toxicology for identifying drug-related fatalities, assessing drug abuse patterns, and verifying medication regimen compliance. Postmortem redistribution, analytical sensitivity, and drug concentration interpretation in non-traditional matrices necessitate cautious interpretation and integration with comprehensive forensic investigations. TDM faces challenges in clinical and forensic domains, requiring ongoing research, methodological advancements, and interdisciplinary collaboration to fully realize its potential in patient care and forensic analyses.

Keywords: Therapeutic drug monitoring, Forensic toxicology, Analysis, Pharmacokinetics, Pharmacodynamics

1. Introduction

Human toxicological symptoms have been known since antiquity, with toxins and medications made from plant extracts, animal venoms, and refined mineral combinations. Arsenic, often used in the Renaissance for fortune-seeking, earned the nickname "the inheritance powder." Swiss physician Paracelsus developed the basic theory of toxicology in the 16th century. Forensic toxicology was founded by pioneering work in the 16th and 17th centuries, with the Marsh test used to determine arsenic poisoning in Charles LaFarge's 1840 murder (Ketha and Garg, 2020). Phases I through IV are developmental steps in creating a novel medication, with Phase II or III studies investigating dosage response and tolerance. However, research on therapeutic drug monitoring (TDM) in Fig. 1. effectiveness for these medications is limited. TDM is useful when drug concentration and effect are strongly correlated, in small therapeutic windows, with no clear clinical parameters, documented

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interactions, tracked drug compliance, and significant variability in pharmacokinetic parameters (Neef et al., 2008). Hyphenated mass spectrometry (MS) is widely accepted and utilized in the fields of TDM, computed tomography (CT), and Fourier transform (FT). Multiple mass spectrometry (MS) devices can be used in combination with various entry systems, including chromatography, electrophoresis, MALDI, or paper spray, for varied applications in these domains. Tandem MS, when combined with ultra-high-pressure liquid chromatography (LC), is currently considered the standard method in TDM. HRMS devices are highly versatile and can be used for a wide range of applications, including human toxicity, particularly in CT and FT, as well as TDM. HRMS is expected to gain widespread acceptance due to cost reduction and user-friendly software packages, offering exceptional identification capabilities and simple qualitative and quantitative approach development. Hyphenated mass spectrometry offers superior selectivity and sensitivity, enabling the creation of new techniques and parameter additions. HRMS allows for novel research, reduces analysis time, and discovers new medications, but requires deep understanding and expertise to avoid potential problems (Maurer, 2018). Clinical pharmacology posits that only free medications are pharmacologically active, as they interact with specific receptors, and unbound concentrations determine their harmful and effective responses. The equilibrium of a drug's free percentage in plasma and saliva is crucial for assessing medicines in oral fluid, despite over 70 years of studies on saliva's organic solutes. Salivary monitoring requires a consistent, predictable link between saliva and plasma drug concentration, despite various assumptions about saliva drug level monitoring. Measuring oral fluid drug levels can aid in treating patients and adjusting dosages for some medications, but not for most therapeutically supervised medications. Research on antipsychotic drugs suggests that changes in metabolic status, influenced by pharmacogenetic variations or clinical conditions, can be reflected in the parent drug-to-metabolite ratio (Langman, 2007). MS is a powerful technology used in research and clinical laboratories for identifying and quantifying compounds. Its specific identification, high sensitivity, and simultaneous analysis of multiple analytes have led to its rapid expansion in routine clinical practices, particularly in therapeutic drug monitoring, drugs of abuse, and clinical toxicology (Garg and Zhang, 2016, Praveen, 2024). This reviews data on drug stability in blood, plasma, or serum, focusing on newer drugs of abuse and therapeutic drugs. Key information about stability experiments and evaluations is provided. Most drugs are stable under typical laboratory conditions, except for those with ester moieties or easily oxidized structures. However, specimens should be stored in the refrigerator at -20°C or lower to avoid degradation. Results from biosamples stored at room temperature should be interpreted carefully (Peters, 2007). Over the past 50 years, forensic toxicology has grown dramatically, adding 8–9 divisions. New specimens like hair, oral fluids, blood, and urine can now be used, thanks to the development of instruments like benchtop GC-MS and immunoassays. The development of excellent standards and guidelines for medications and poisons in biological specimens has also been a focus of international efforts. Autopsy results, details from the crime scene, and medical history are now taken into account when interpreting toxicological results. An important factor in the advancement of forensic toxicology is societies such as TIAFT (Chung and Choe, 2017, Praveen, 2024). A μ-opioid receptor agonist called methadone is used to treat heroin addiction. Individual differences in its metabolomics have a substantial impact on the toxicological profile and dose response. The liver metabolizes methadone via isoenzymes of cytochrome P450. Comprehending the metabolomics of methadone can aid in the development of customized treatment plans and offer essential case files for legal and medical settings (Dinis-Oliveira, 2016; Buko, 2017). LC combined with MS has become crucial in doping control, clinical and forensic toxicology. High-resolution MS analysis and improved techniques for LC-MS(/MS)-based toxicological studies have improved. Multi-target screening and quantification of medications, toxins, and metabolites are also being explored (Peters, 2011). This essay examines the relationships between clinical and forensic toxicology, focusing on seven areas of analytical toxicology: drug control, brain death, prenatal drug exposure, drug-facilitated crimes, intoxications by new psychoactive substances, and sudden infant death syndrome. Forensic laboratories investigate situations like SCD, SIDS, and doping control, while clinical laboratories handle issues like FAS and drug exposure during pregnancy. Both fields share common topics, fostering communication and enhancing the expansion, dependability, and robustness of both types of laboratories (Barcelo et al., 2018). The findings of a comprehensive study that investigated the varied applications of TDM in forensic and clinical contexts are presented in this article. The outcomes highlight the critical role that TDM plays in modern forensic research and healthcare, providing insightful information on toxicological analyses, drug therapy management, and medico-legal questions. Clinicians and forensic scientists can expand the study of drug-related

phenomena in both clinical and legal contexts, improve drug safety, and improve patient care by utilizing TDM methodology and technology.

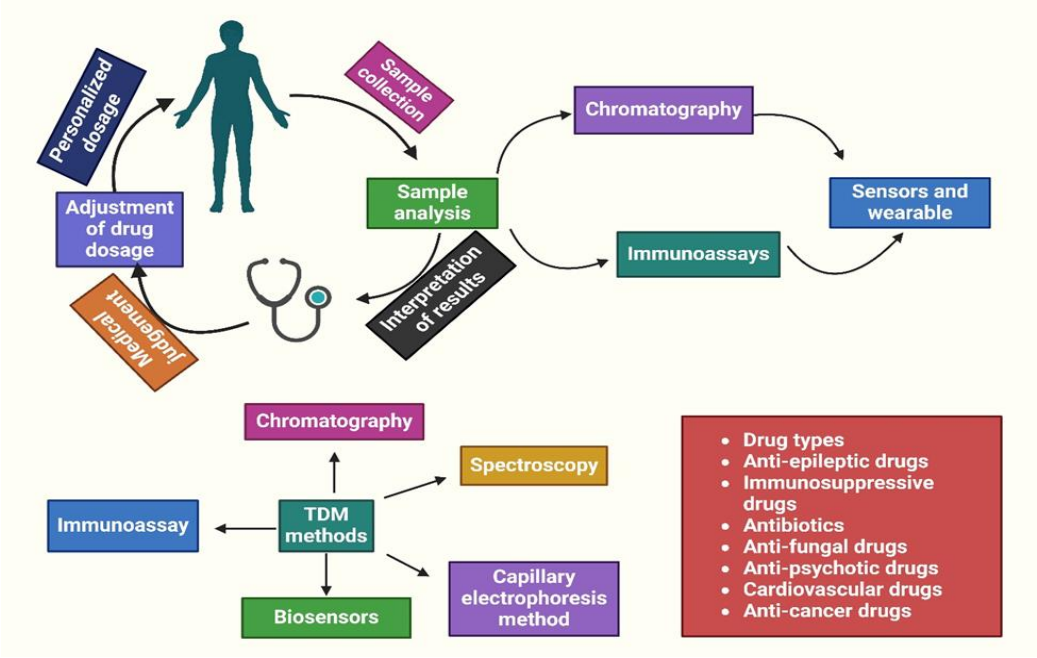

Fig. 1. Therapeutic Drug Monitoring Process and Methods

The rapid growth of clinical pharmacy in China has led to the importance of therapeutic drug monitoring (TDM), a strategy that optimizes individualized drug therapy by combining pharmacokinetic and pharmacodynamic knowledge. TDM aims to reduce drug-drug toxicity, prevent drug resistance, and improve treatment outcomes. Accurate analytical procedures are crucial for successful implementation.

2. Pharmacokinetics and pharmacogenetics

2.1. Pharmacokinetic aspects

2.1.1. Absorption, distribution, and elimination of neuropsychiatric drugs

This list of typical pharmacokinetic characteristics does not include all of the outliers. Aripiprazole and fluoxetine, on the other hand, have lengthy elimination half-lives (3–15 days for fluoxetine and 72 hours for aripiprazole, accounting for its active metabolite norfluoxetine). Examples of medications with short elimination half-lives are tranylcypromine, trazodone, venlafaxine, or agomelatine. Patients with weak liver function may benefit from the fact that sulpiride, gabapentin, memantine, milnacipran, or amisulpride are primarily eliminated really and only poorly metabolized in the liver. The reason for the non-linear pharmacokinetics of paroxetine is that it inhibits its metabolism by the binding of a metabolite that inactivates the enzyme irreversibly (Bertelsen et al., 2003). The enantiomers of many neuropsychopharmacological medications, which are utilized as racemic substances, have markedly different pharmacodynamic and pharmacokinetic characteristics (Baumann et al.,, 2002, Smith, 2009). However, TDM of the enantiomers has only been introduced for two racemic psychoactive substances thus far: methadone and methylphenidate (Balant et al.,, 1989, Eap et al.,, 2002). Racemic methylphenidate has an active enantiomer called (R)-methadone. Its therapeutic action is mainly attributed to l-methylphenidate, also known as levorotary methylphenidate. Flupentixol decanoate in its depot formulation contains only the cis-isomer of flupentixol. In contrast, the oral form of flupentixol is administered as an equal mixture of the geometric isomers, specifically the cis- (Z-isomer) and trans- (E-isomer) forms. As demonstrated by clinical investigations, the latter is the only one deemed pharmacologically active in terms of its affinity for receptors of serotonin and dopamine. Cis-flupentixol efficacy (Z-flupentixol;α-flupentixol) appears to be greater than the effect of trans-flupentixol (Baumann et al.,, 2012). The different activities of enzymes involved in the metabolism of drugs are the cause of inter- and intra-individual variations in concentrations of neuropsychopharmacological medications in the blood. Age may cause a decline in enzyme activity (Klotz, 2009), and hepatic and renal disorders may alter it. CYP enzymes are primarily responsible for catalyzing phase 1 reactions. These proteins are members of a superfamily that act as terminal oxidases in electron transfer chains and include

heme as a cofactor. The spectrophotometric peak at 450 nm, which is the peak wavelength at which CYP enzymes, when in their reduced state and bound to carbon monoxide, absorb the lightest, is the source of the word P450. Phase 1 reactions, catalyzed by CYP enzymes, introduce polar functional groups, allowing for subsequent phase 2 reactions where highly polar substances like sulfuric acid or glucuronic acid are conjugated. Glucuronidation of a hydroxyl group (as seen with oxazepam or lorazepam) or an amine group to form N-glucuronides (such as with olanzapine) is a key metabolic pathway for neuropsychopharmacological drugs with these functional groups. The CYP enzyme family is organized into 18 families and 43 subfamilies based on their amino acid sequences. In humans, different gene clusters encode 57 functional CYP genes and 58 pseudogenes (Zanger and Schwab, 2013). Important isoenzymes for the metabolism of neuropsychopharmacological drugs are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 (Zanger and Schwab, 2013; Backman et al., 2016; Zhou, 2009; Zhou et al., 2009). It is possible that additional enzymes function as metabolic key factors of pharmacological and harmful effects of drugs (Barski,). Ketone or aldehyde group reduction in endogenous and exogenous substances is catalyzed by enzymes belonging to the AKR superfamily, including aldo-keto reductases (AKRs). Thirteen AKR proteins have been found in humans (Barski et al., 2008). It was demonstrated that they convert naltrexone to naltrexol (Breyer-Pfaff and Nill, 2004) and ziprasidone to its dihydro derivative (Beedham et al., 2003). Citalopram undergoes stereoselective deamination by monoamine oxidase subtypes A and B (MAO-A and MAO-B), resulting in an acidic metabolite that appears to be inactive (Rochat et al., 1998). In actuality, phase 2 enzymes are becoming more and more characterized in terms of substrate selectivity. Regarding their affinity for substrates, the isoenzymes overlap significantly (Court, 2010; Oda et al.,, 2015) . The liver is the primary site of drug metabolism, with some metabolism also occurring in extrahepatic tissues. like the brain or intestinal mucosa (Benedetti et al., 2009*;* Gervasini et al.,, 2004; Meyer et al., 2007). Pharmacokinetic drug-drug interactions may arise when medications that inhibit or induce drug-metabolizing enzymes are combined (Abernethy et al., 1985), provided that the medication is a substrate of the enzyme that is either inhibited or stimulated. TDM has discovered numerous interactions through either accidental or retrospective examination of TDM databases (Castberg et al.,, 2007; Hefner et al., 2015; Paulzen et al.,, 2016; Rasmussen and Brøsen, 2000). Smoking is one of the environmental factors that has the greatest therapeutic significance for medications that are CYP1A2 substrates (Ereshefsky et al.,, 1985; Faber et al.,, 2005) Polycyclic aromatic hydrocarbons of cigarette smoke stimulate CYP1A2 in a dose-dependent manner. CYP1A2 activity is enhanced by 1.2, 1.5, and 1.7 while 1-2, 6-10, and more cigarettes smoke each day, respectively (Faber and Fuhr, 2004). Three days after quitting smoking, the elevated activity returns to baseline. Therefore, when smoking more than ten cigarettes a day, smoking consequences should be taken into account (Faber et al., 2005). When using a CYP1A2 substrate in Table 1, for therapy, such as olanzapine (Zullino et al., 2002), duloxetine (Fric et al., 2008), or clozapine (Bondolfi et al., 2005) (van der Weide et al., 2003), stopping heavy smoking may need dose decrease, which TDM should regulate. Drug transporters are engaged in the distribution of pharmacokinetics of pharmaceuticals in addition to Enzymes participating in metabolism phase 1 and phase 2 (Bruhn and Cascorbi, 2014; Dong et al.,, 2009; Ufer et al.,, 2011; Wolking et al.,, 2015) . These proteins, called ATP-binding cassettes (ABCs), are found in membranes of cell, and serve as efflux transporters that shield organs from outside substances. The major factors that determine the distribution kinetics of most neuropsychopharmacological drugs have been identified as ABC transporters including breast cancer resistance protein (BCRP) which is encoded by ABCG2, multidrug resistance protein (MRP) which is encoded by ABCC1 and P-glycoprotein (P-gp) which is the gene product of ABCB1 (Wolking et al., 2015). Substances that are ABC transporters substrates enter cells by passive diffusion and are then released into the extracellular space by ABC transporters through conformational changes that are dependent on ATP. Due to its strong expression in the small intestine and the blood brain barrier (BBB), P-gp is (Wolking et al., 2015) a crucial regulator of drug trafficking into and out of several organs (Wolking et al., 2015). Research on animals indicates that P-gp regulates the brain's availability rate of numerous antipsychotic and antidepressant medications, such as risperidone, citalopram, and nortriptyline (Doran et al.,, 2005*;* Suzuki et al.,, *2014;* Uhr et al.,, 2003). It has been proposed that ineffective concentrations are caused by high P-gp function, and tolerability issues and high drug concentrations are linked to poor P-gp activity (Bet et al.,, 2016; Breitenstein et al.,, 2015; Breitenstein et al.,, 2016; Brückl and Uhr, 2016; De Klerk et al.,, 2013, Nikisch et al.,, 2011; Ray et al.,, 2015; Praveen et al.,, 2024; Uhr et al.,, 2008). ABC transporters have been found to have several genetic mutations, much like CYP enzymes (Wolking et a., 2015). Furthermore, there are numerous mechanisms to up- or down-regulate the expression of ABC

transporters, including pathophysiological stresses, xenobiotics, hormones, and nutritional factors (Miller, 2015). The pharmacokinetics of neuropsycho pharmacological medications have also been found to differ between genders (Aichhorn et al., 2006; Marazziti et al., 2013, Sigurdsson et al., 2015; Soldin and Mattison, 2009). This is most likely because female sex hormones have an impact on the absorption, distribution, metabolism, and excretion of pharmacokinetic processes (Damoiseaux et al., 2014; Kokras et al., 2011). The results continue to be inconsistent, and it's unclear how applicable they are clinically. Some investigations indicated that the influence of body mass was lower than expected by pharmacokinetic principles (Aichhorn et al.,, 2006, Sigurdsson et al.,, 2015, Soldin and Mattison, 2009, Praveen and Morales-Bayuelo, 2023), despite the fact that body mass should be a key predictor of the concentration of a medicine in blood following administration of a given dose (Steimer, 2004). In these domains, systematic research is still necessary.

2.1.2. Blood drug concentrations

Drug intake equals drug elimination during a predetermined period of time at a steady state. Concentrations will change during the day, particularly for medications having brief elimination half-lives (<12 hours) and based on the dosage regimen, which is important to take into account when interpreting TDM data (Steimer, 2004). For the great majority of medications in TDM, trough steady-state (treatment with continuous dose for not less than 4 to 6 half-life) concentrations (Cmin) have been the accepted practice. For practical reasons, the method of trough sampling just before the subsequent dose has been selected. The time curve of concentration is almost horizontal towards the end of the dosing period (terminal ß-elimination phase) and deviations from the right sampling time immediately before the next dose are less critical for trough samples than for the other phases after dose administration.

2.2. Pharmacogenetic features

More and more research has shown the clinical significance of pharmacogenetic variables in the pharmacodynamics and pharmacokinetics of neuropsychiatric medications (de Leon, 2006; Evans and M. V. Relling, 1999; Mrazek, 2010; Samer et al., 2013). Drug-metabolizing enzymes, particularly CYP isoenzymes, display genetic diversity, as was previously reported (Zhou, 2009; Zhou et al., 2009). Wild-type individuals with two active alleles are referred to as extensive metabolizers (EM). PMs are those who do not have functional alleles. Genetically heterozygous for both inactive and active alleles, or with one or two alleles with decreased activity, are the two types of intermediate metabolizers (IM). Alleles with enhanced activity or functional allele multiplications are carried by ultrarapid metabolizers (UM) (Bergmann et al., 2001). Clinical significance arises from drug-metabolizing enzyme genetic variations. On the one hand, elevated blood concentrations in PM can lead to unforeseen toxicities and severe medication reactions. Conversely, subtherapeutic blood concentrations in UM may lead to non-response (Jose de Leon et al., 2005). CYP enzymes participate in the metabolism of prodrugs, such as CYP2D6, which converts morphine from codeine and desmethyltramadol from tramadol (Ortiz de Montellano, 2013; Huttunen et al., 2011). Under these circumstances, PM patients won't have the capability to generate metabolites that are pharmacologically active, and UMs run the danger of experiencing unpleasant medication reactions. Determining the mRNA encoding CYP1A2, CYP2C9, and CYP2C19 in leukocytes is a novel and promising method. Parallel probe drug phenotyping of CYP enzymes demonstrated a strong correlation between mRNA levels and hepatic CYP activity (Temesvári et al., 2012). In the past, probe medications like midazolam for CYP3A4/5, metoprolol or dextromethorphan for CYP2D6, omeprazole for CYP2C19, or caffeine for CYP1A2were used to ascertain the metabolizer status. (Tanaka et al., 2003; Liu et al., 2009; Skogh et al., 1999). These phenotyping assays allow for the detection of metabolic alterations by measuring the patient's metabolic state during the test. Thus, they can be used to investigate how CYP activities are affected by environmental factors like smoking or prescription drugs (Faber et al., 2005; Zullino et al., 2002; Skogh et al., 1999). The availability of CYP genotyping has increased during the past few years. The undeniable benefit of genotyping is that it serves as a "trait marker" and is unaffected by external circumstances. Its outcome has a lifelong worth and can be executed in any circumstance. However, the presence of rare genetic variations contributes to a notable amount of variation, making it possible to forecast one's enzyme activity by genetic analysis that specifically focuses on prevalent alleles (Matthaei et al., 2015). This is true even though the functioning importance of the genetic variants for CYP enzymes has been thoroughly described (Gaedigk et al., 2008). Though their clinical significance in pharmacotherapy and for adjusting doses is not as clearly established as that of CYP polymorphisms (Stingl et al.,, 2003), alternative metabolic systems of enzymes, like UDP glucuronosyltransferases (UGT), also exhibit genetic variations (Court 2010, De Leon, 2003). It has been proposed that the ABCB1 genotype influences the response to antidepressant and

antipsychotic drugs due to its involvement in ABCB1 transporters and the gene product P-gp has an essential function in the transport of drugs throughout the body. Antidepressant treatment outcomes can be enhanced by ABCB1 genotyping, and individuals may exhibit varying responses to antidepressants that are substrates of P-gp. In the meanwhile, more than 30 studies have looked into the possibility that human antidepressant clinical efficacy and/or tolerability may be predicted by genetic variations in ABCB1. Antidepressant effects have been reported to affect minor allele carriers more frequently than major allele carriers of specific single nucleotide polymorphisms (SNPs): rs2032583 and rs2235040 (Breitenstein et al.,, 2015; Breitenstein et al.,, 2016; De Klerk et al.,, 2013; Ray et al.,, 2015; Uhr et al.,, 2008; Roberts et al., 2002; Sarginson et al.,, 2010). However, several additional studies (Dong et a., 2009; Bet etal., 2016, Perlis et al., 2010; Schatzberg et al., 2015) did not find that minor allele carriers had more adverse medication reactions or greater response rates than non-carriers. Carriers of the minor allele of rs2235083 had greater efficacy at doses within the optimal dosage range in an initial clinical trial using various doses of P-gp substrates antidepressants (Breitenstein et al.,, 2016; Brückl and Uhr, 2016). Apart from the pharmacokinetic elements discussed earlier, there is mounting evidence that genetic variables influencing pharmacodynamic processes—like how drugs interact with enzymes, transporters, receptors, structural proteins, or ion channels—are essential in determining how well a treatment works for mental health conditions. The most studied gene in relation to affective disorders is the serotonin transporter gene (5HTT; SLC6A4). But the results are still inconclusive (Kato et al., 2015; Serretti et al., 2007; Taylor et al., 2010). GWAS has been conducted using a hypothesis-free approach on the STARD, MARS, and GENDEP datasets. However, these investigations were unable to find genome-wide significant markers of response to antidepressant treatment (Hohmann et al., 2015, Laje and McMahon, 2011). The greatest meta-analysis to date has examined the response to lithium in a cohort of over 2,500 individuals from 22 research centers worldwide. The findings are not currently significant for clinical decision making, even though they could serve as a foundation for a deeper comprehension of lithium mechanisms (Hou et al.,, 2016; Laje, 2013; McCarthy et al.,, 2010; Schulze et al.,, 2010). The DRD2, DRD3, and DRD4 genes have been widely studied in relation to psychotic disorders and their response to antipsychotic treatments. But these studies have not been able to produce consistent replicable results (for a review see Brandl et al., 2014). Recent meta-analysis studies suggest that the A118G polymorphism of the μ opioid receptor gene (OPRM1) is a significant predictor of the response to naltrexone in alcohol-dependent patients (Chamorro et al., 2012). Future studies are needed to establish the clinical effectiveness (e. g., diagnostic accuracy, positive and negative predictive values) of pharmacogenetic testing for alcohol use disorders based on OPRM1 genotypes (Hendershot, 2014). At the pharmacodynamic level, pharmacogenetic investigations produced encouraging preliminary findings about the underlying genetics of pertinent adverse drug reactions to psychoactive medications. Patients of Asian descent who are treated with carbamazepine have a consistently greater chance of developing Stevens-Johnson syndrome when their human leukocyte antigen markers, HLA-B1502 and HLA-A3101, are present (Wu et al., 2015; Ferrell and McLeod, 2008). A few pharmacogenetic assays, such the PGxPredict: CLOZAPINE test, which was intended to predict the risk of agranulocytosis based on HLA-DQB1 gene variant, were tested in clinical settings. Despite having a high specificity of 98.4% and a poor sensitivity of 21.5%, the test has since been discontinued (Ho and Reddy, 2011). Antipsychotic-induced weight gain has been demonstrated to be mediated by 5-HTR2C, leptin gene variants, neuropeptide Y (NPY), melanocortin 4 receptor (MC4R), cannabinoid receptor 1 (CNR1), and neuropeptide Y (NPY) (for review see Gressier et al., 2016). In antipsychotic-induced dystonia/tardive dyskinesia, well-replicated gene variations have been reported: variations in the serotonin receptor genes HTR2C (Al-Janabi et al., 2009; Hadithy et al., 2009; Segman et al., 2000) and possibly also HTR2A (Lerer et al., 2005; Segman et al., 2001), as well as variations in RGS2 (regulator of G-protein signaling 2), a gene that modulates dopamine receptor signal transduction (Greenbaum et al., 2009; Greenbaum et al., 2007) . Negative symptoms in schizophrenia that respond well to antipsychotic treatment are linked to a polymorphism in the serotonin receptor gene HTR1A (rs6295; C-1019G) (Mössner et al., 2009; Takekita et al., 2016). In an effort to address the shortcomings of earlier research, the following tactics have been suggested: Concentrating on a single pharmacologic class and precisely delineated phenotypes (e.g., ISPC (Biernacka et al., 2015, Azad et al., 2024), factors related to the environment (Klengel and Binder, 2013) and pharmacokinetic parameters (e.g., blood levels (Proft et al., 2014; Unterecker et al., 2015), Enhancing genetic analysis by incorporating structural variation (e.g., copy number variation (O'Dushlaine et al., 2014), examining the combined effects of multiple risk genes ('epistasis', e.g., (Mas et al., 2015; Domschke et al., 2014), and incorporating epigenetic variation

(Domschke et al., 2014; Menke et al., 2012). In this vein, sizable global consortia, such as the International Consortium on Lithium Genetics (ConLiGen) (Schulze et al., 2010), are being formed in an effort to carry out extensive pharmacogenetic research using cutting-edge methods like exome sequencing and genome-wide association studies.

3. Utilizing blood drug concentrations for Neuropsychopharmacotherapy direction

TDM considers both pharmacodynamic and pharmacokinetic factors to direct neuro psychopharmacotherapy. To ensure therapeutic efficacy and acceptable tolerability, it is necessary to determine whether the concentration of a drug is within the therapeutic reference range and, if so, whether the blood concentration matches the recommended dosage. The latter determines whether the medication is taken as directed and, if not, whether there are irregularities in the pharmacokinetics. As such, it is necessary to distinguish between predicted dose-related drug concentrations and therapeutically effective drug concentrations (Haen, 2011, Haen et al., 2008).

3.1. The range of therapeutic reference

Pharmacologic effects are thought to be concentration-related according to the rule of mass action (Aronson and Ferner, 2016). This premise underpins TDM in terms of both therapeutic betterment and unfavorable drug responses. TDM also presupposes that an array of medication concentrations in blood, known as the "therapeutic reference range," are necessary for both acceptable safety and maximum efficacy. Since the 1960s, research on the connections between blood drug concentration and clinical improvement has substantiated this idea about antidepressants that are tricyclic, lithium, and first-generation antipsychotic medications. Nortriptyline, imipramine, and desipramine—drugs linked to a high probability of response—have been shown to have a substantial correlation with blood drug concentration in connection to clinical outcomes in meta-analyses and systematic reviews based on well-designed research (Baumann et al., 2004). A meta-analysis of 45 studies using amitriptyline as a model molecule revealed that different statistical techniques produced nearly equivalent therapeutic reference ranges (Ulrich and J. Läuter, 2002; Ulrich et al., 1998). New antipsychotic medications such as olanzapine (Perry et al., 1997), risperidone (Yasui-Furukori et al., 2010), and aripiprazole (Sparshatt et al., 2010) have been shown to have connections between their blood concentration and clinical effectiveness (Lopez and Kane, 2013). When using TDM-guided medication, the therapeutic reference range is a critical zone that needs to be targeted. Determining the lower and upper bounds of medication concentrations in the blood that are both therapeutically efficacious and tolerated is necessary for its estimate. There isn't a widely used technique to calculate these limits, thus methodological constraints like treatment resistance or placebo response need to be taken into account (Aronson and Ferner, 2016; Preskorn, 2014). The terms “orienting therapeutic range," "target concentration," "target range," "effective plasma concentration," "optimal plasma concentration," "therapeutic range," and "therapeutic window," which was the phrase utilized in the initial TDM consensus (Baumann et al., 2004), are many synonyms for "therapeutic reference range." The AGNP TDM task force determined in 2011 to employ the phrase "drug concentration in blood," which encompasses plasma level or serum concentration, plasma concentration, blood level or serum level, and to use the term "therapeutic reference range," adhering to the publication of TDM recommendations for antiepileptic medicines is a common practice (Patsalos et al., 2008). The evidence-based therapeutic reference ranges were obtained from the literature through the above-described structured review approach. Only 17 neuropsychiatric medications had therapeutic reference ranges according to randomly assigned clinical studies identified in the literature. Reference ranges for the majority of medications came from research using dosages that were therapeutically efficacious. Generally speaking, the reference ranges for the principal indication are those found in. However, numerous medications are advised for multiple purposes. For instance, antipsychotic medications are licensed for the treatment of affective disorders, and antidepressant medications are used to treat anxiety, obsessive compulsive disorder, and chronic pain. The ideal blood medication concentrations for various indications are not well understood. Carbamazepine, lamotrigine, and valproic acid (valproate) are the exceptions, and as a result, they are occasionally included twice. Research to assess therapeutic reference ranges for patients who are juveniles or adolescents is currently underway (Egberts et al., 2011; Gerlach et al., 2016; Koelch et al., 2012; Taurines et al., 2013; Wohkittel et al., 2016).

3.1.1. Determining the therapeutic reference range's lowest limit

When feasible, research assessing the correlation among a drug's blood concentration and clinical efficacy should serve as the foundation for determining the lower bound of the therapeutic range. The effects of the medication are not appreciably different from a placebo below the minimum threshold. A potential study that follows

a double-blind trial with a randomized control with patient doses that produce a predetermined range of blood concentrations of the drug is the best study design to assess the minimum threshold. It used an essentially perfect research design on clozapine-treated individuals (VanderZwaag et al., 1996). The blood was titrated to 50–150 ng/mL, 200–300 ng/mL, or 350–450 ng/mL clozapine concentrations. When compared to low quantities of clozapine, intermediate and high concentrations showed a significant therapeutic advantage. Blood level research contrasting mirtazapine and imipramine was conducted using a similar approach (Bruijn et al., 1996). However, carrying out these investigations presents a significant logistical difficulty. For the assessment of the lower limit, fixed dosage studies are more practical and desirable (Ulrich and Läuter, 2002; Ulrich et al., 1998). Receiver operating characteristic (ROC) analysis has shown usefulness in estimating the therapeutic reference range lowest value (Hanley and McNeil, 1982). A ROC plot analyzes the accuracy and precision of the variable "drug concentration in blood" and enables the determination of a cut-off value that distinguishes responders from non-responders. For some antipsychotic and antidepressant medications, the value of ROC analysis has been established (Müller et al., 2007; Perry, 2001, Perry et al., 1994; Waldschmitt et al., 2009).

3.1.2. Determining the therapeutic reference range's top limit

An inverse U-shaped connection among clinical activity and blood concentrations was observed for nortriptyline in the first investigation on TDM in psychiatry (Åsberg et al., 1971). The tricyclic antidepressant drug's method of action on monoaminergic neurons was blamed for the lack of therapeutic improvement at high dosages. But based on what is now known, it is more plausible that the side effects of nortriptyline are what are causing the decreased amelioration at high dosages. As a result, even under these guidelines, the upper bound of the therapeutic range is frequently determined by the elevated risk of adverse medication reactions. Antipsychotic medication motor symptoms (Rao et al., 1980) and tricyclic antidepressant drug side effects (Dawling, 1982; Gupta et al., 1999) have been linked to blood drug concentrations. The blood content of paroxetine was observed to positively correlate with symptoms of serotonin syndrome (Hegerl et al., 1998). It was demonstrated that the clearance of citalopram was inversely linked with adverse medication responses (Yin et al., 2006). ROC analysis can be used to determine the top limit of the therapeutic range when such data are available (Müller et al., 2007). However, there is insufficient reliable data regarding the blood levels and the frequency of adverse drug reactions for several of the neuropsychiatric medications included. Most case reports on intoxications or tolerability issues omit measurements of drug concentrations. Reports of intoxications and fatal instances that appear sporadically are not very useful. The medication level is typically significantly above the threshold linked to optimal therapeutic effects when recorded blood concentrations have resulted in death (Reis et al., 2007; Stead and Moffat, 1983). Additionally, post mortem drug redistribution into or out of the circulation can cause abrupt changes in blood levels (Kugelberg et al., 2004; Pounder and Jones, 1990), and the change's direction is not always consistent (Kennedy, 2010).

3.2. The reference range linked to dosage

A second concentration range, known as the dose-related reference range, exists in addition to the therapeutic reference range for the purpose of interpreting TDM results. The therapeutic reference range is a pharmacodynamic method that is used. Pharmacokinetics is the application of the dose-related reference range. It makes a comparison between a drug's measured concentration and its theoretically predicted range. These studies are preferably conducted on a population of normal patients. In pharmacokinetic studies, the average steady-state concentration (Cav) of a drug in a normal patient can be determined when we know the bioavailability (F), total clearance (CL), dosing interval (di), and daily maintenance dose (Dm),

$$Cav=(F/CL)\ x(DM/di) \text{ ---------- } (1)$$

The prescription specifies the dosage and the interval between doses, while pharmacokinetic trial data provides the pharmacokinetic parameters. Cav±SD (ng/mL) can be calculated by Eq. (1) utilizing the standard deviation (SD) of the total apparent clearance CL/F (mL/min), the daily dose (1 mg/24 h = 10^6 ng/1440 min). The dimensions of the various factors must be taken into account throughout the computation, and all doses, volumes, and time periods must be translated to ng, mL, and min, respectively. The coefficient of variation is 50% when the CL/F value is provided as 100±50 mL/min. This means that for a dose of 20 mg/day,

$$\text{Cav} = \left(\frac{20{,}000{,}000\ ng}{1440\ min}\right)\left(\frac{1ml}{100min}\right) = 139\ \text{ng/mL}$$

The standard deviation is 69 ng/mL. So, Cav±SD varies from 70 to 208 ng/mL. By Haen and colleagues (, Landmark et al., 2016), the Cav±SD range was recommended as a dose-dependent

reference range, assuming a 24-hour dosing interval. Within this range, the mean - SD was regarded as the lowest bound and the mean + SD as the maximum threshold. According to statistics, this range includes 68% of the quantities seen in the blood of a population of people aged 18 to 65 under typical circumstances. Apparent total clearance (CL/F) data±SD for 83 neuropsychiatric medications were taken from the literature for the 2011 guidelines (Hiemke et al., 2011) in order to calculate dosage factors. Dose-dependent reference ranges were computed and utilized for the analysis of TDM findings by multiplying the daily dose with these factors ± SD. A patient's drug concentration was considered normal when it was determined by TDM to be within the reference range associated to their dosage. Concentrations that were either above or below the range were seen as indicators of possible anomalies, such as partial non-adherence, interactions between drugs, genetic variations in the enzymes that metabolize drugs, or illnesses of the organs that remove drugs.

The dose-dependent reference range concept was effective. It was possible to identify a large number of individuals who were either pharmacokinetically abnormal or incompletely adherent (Haen, 2011). When the drug's elimination half-life (t1/2) is longer than the dosage frequency, the equation for Cav is accurate and helpful. Nevertheless, values determined by Eq. (1) are not very indicative of the Cmin values used for TDM when the half-life is brief and the time between doses is larger than the half-life. With a t1/2 of 14 hours and valproic acid administered once or twice daily.

The dose-related reference range of valproic acid, as determined by Eq. (1), is 94±35 μg/mL when administered daily in dosages of 900 mg, regardless of the interval between doses. Time to concentration curves, on the other hand, indicate that if the dosage regimen consists of a single 900 mg dose every day, the concentrations in the trough are less than Cav, 49±15 μg/mL. If a regular dosage of 900 mg per day is given in two equal doses of 450 mg each, it equals 69±25 μg/mL. For dosage intervals less than 14 hours, the Cav±SD and Cmin±SD ranges correspond. As a result, calculated Cav can be regarded as a reliable indicator of the anticipated concentration of drugs in the bloodstream. However, Cmin is 54% lower than Cav 24 hours after the last dosage while following a single dose per day schedule. This constraint needs to be taken into account when utilizing Eq. (1) based computations of dose-related reference ranges, as valproic acid is used as an example to illustrate. This restriction may apply to several medications, such as naltrexone, atomoxetine, venlafaxine, paroxetine, or duloxetine, depending on the dose interval. The values calculated are reduced by over 30% for Cmin than for Cav when dosage intervals exceed t1/2. In total, 32% of the compounds included in fall into this category.

Additionally, there exists an additional constraint for Cav-based computations. TDM is predicated on measuring the minimum concentration of a drug in bloodstream; in contrast, Cmin allows for easy measurement verification of the accuracy of the dose-related reference range. Cav is defined as the area under the dose interval divided by the area under the time to concentration curve (AUC). It cannot be linked to a specific moment in time, such as Cmin, which is required for venipuncture timing. Neglecting daily variations in drug levels, which might be significant for a medication's tolerance and efficacy (Chenu et al., 2009), is another drawback of Cav-based computations.

It was determined to alter the computation of dose-related reference ranges for this update due to these constraints. By extending Eq. (1) and using the Bateman function, steady-state concentrations can be computed without delving into the specifics covered in pharmacokinetics courses (see, for example, Bauer et al., 2008; Dost, 1953). Using this method, Gex-Fabry and colleagues (Gex-Fabry et al., 2003) calculated concentration throughout the elimination phase and provides an objective for the postabsorptive phase, which refers to the period among tmax, the time when the concentration of drug is at its highest, and tmin, Cmin.
For every time point during the postabsorptive phase, a predicted steady-state drug concentration Ct can be calculated as follows, considering a model with only one compartment and a decline that follows an exponential pattern of the concentration of drugs in the bloodstream:

$$Ct=(e^{-ke\times t}) \times[(ke\times di)/(1-e^{-ke\times di})] \times [(F/CL) \times (Dm/di)] \text{ ----------(2)}$$

where t is blood withdrawal time, $t_{1/2}$ is elimination half-life, ke is elimination rate constant, di is dosing interval, CL/F apparent total clearance, and Dm is the dose under steady state conditions

$$ke = \frac{ln2}{t_{1/2}}$$

Using Eq. (3), one may estimate an expected Cmin as follows, assuming,
di = 24 h,
t = time,

Δt = Duration between the most recent consumption of medication and the withdrawal of blood.

$$Cmin = (e^{-ke\times\Delta t}) \times[(ke\times24)/(1-e^{-ke\times24})]\times(F/CL) \times (Dm/24) \text{ ----------(3)}$$

It is therefore possible to calculate the drug concentrations predicted by TDM measurements using the values.
For medications with known CL/F and $t_{1/2}$, a DRC factor can be constructed & calculated, for example, using MS-Excel software, by using part of Eq. (3).

$$DRC\ factor = (e^{-ke\times\Delta t}) \times[(ke\times24)/(1-e^{-ke\times24})] \times (F/CL) \quad (4)$$

Then, by calculating the product of the DRC factor and the daily dose, one can determine the expected Cmin of a given dose. The necessity to apply $t_{1/2}$, that as well differs throughout persons, and the more involved calculation process are the limits for predicting theoretically predicted Cmin in contrast to Cav. The TDM guidelines regard the standard deviation of mean drug concentrations in patients who comply as the normal variability of perceived total clearance, which is probably attributable to comparable reasons. This presumption led to the definition of the relationship between the variation between individual's CL/F and the variation of the Cmin. As was previously done for Cav-based estimates (Haen et al., 2008), the SD provided in the literature for CL/F was thus propagated to Cmin to determine anticipated mean±SD as dose-related reference range. The prediction of expected drug concentrations using this method of calculation was evaluated empirically.

The DRC variables for 172 compounds, including parent medicines, metabolites, and active moiety. Eq. (4) was utilized to calculate factors by utilizing pharmacokinetic data that was published in articles. Recommendations for drug administration regimens were followed for defining Δt. It was 24 hours for a medication like citalopram or extended release (XR) venlafaxine administered once daily in the morning. It was set at 12 hours for medications such as amitriptyline, which is generally administered in the morning and evening. It was fixed at 10 hours for hypnotic medications administered just before bed and blood withdrawal the following morning. By multiplying the DRC factors low (= DRC factor – SD) and high (= DRC factor + SD) by the daily dose, the above factors can be used to calculate the lower and upper limits of the range and to produce the dose-related reference range. DRC factors for Δt at 12 and 24 hours, respectively, for medicines administered once or twice daily. Since blood concentrations are not determined at tmin (no trough levels) for medications such as modafinil or clomethiazole, DRC factors are provided at specific times when blood withdrawal is advised.

For each time point in the postabsorptive phase, anticipated concentrations of drugs can be calculated using Eq. (2) when Δt deviates from the values given.

The dose-related reference range, which was first introduced as the dose-related reference range for average drug concentrations (Haen et al., 2008), is currently understood to be a Cmin range that may be computed using the recommended dosage and pharmacokinetic characteristics.

3.3. Ratio of concentration to dosage

An additional metric to analyze pharmacokinetic anomalies is the proportion of medication concentration to dosage (Cmin/D, sometimes shortened as C/D) (Leon et al., 2013, Hefner et al., 2013; Diaz et al., 2008). C/D can be computed with ease using TDM data. Total clearance has an inverse relationship with C/D ratios ((Leon et al., 2013, Hefner et al., 2013; Diaz et al., 2008)). Drug clearance is accelerated by a low C/D ratio and sluggish by a high C/D ratio. By comparing several patient groups, C/D ratios were utilized to identify drug-drug interactions (e.g., (Paulzen et al., 2016, Burns et al., 2016; Schoretsanitis et al., 2016). Jerling and colleagues assessed intraindividual C/D ratios of nortriptyline and amitriptyline and discovered interaction activity of carbamazepine, perphenazine, and levomepromazine by demonstrating that earlier C/D values were substantiated both on and off concurrent medications (Jerling et al., 1994). As was demonstrated with clozapine (Stieffenhofer et al., 2011), repeated monitoring in the exact patients aids in the detection of partial medication non-adherence. The C/D intraindividual variability should be less than 20%. If the variation is more than 20%, it may indicate pharmacokinetic changes or issues with adherence brought on by interactions between drugs, foods, and diseases. The C/D ratio can also be used to calculate the dose needed to get the drug's blood concentration down to the desired target (Armijo, et al., 1997).

4. Clinical applications

In the clinical laboratory, immunoassays are frequently used techniques for tracking both medicinal medications and drugs of abuse. Due to the possibility of false positive or false negative results from immunoassays. Because immunoassays may not be available for certain medicines and lack

specificity or cross-reactivity, mass spectrometry has been used to confirm immunoassay results (Maurer et al., 2007) and occasionally as a screening tool. Small molecule drug measurement is one of the primary factors propelling mass spectrometry's growing number of clinical practice applications and is also pushing the boundaries of technology development. This volume focuses on toxicology and therapeutic medication monitoring. Another early adopter of mass spectrometry was testing for the confirmation and screening of inborn errors of metabolism, which has been crucial in expanding the uses of mass spectrometry (Garg and Dasouki et al., 2006, Jones and Bennett, 2002). Many advancements have recently been made in novel research areas, especially in the fields of endocrinology and hormone testing in clinical laboratories (Pagotto et al., 2013; Vogeser and Parhofer, 2007; Soldin and Soldin, 2009). Applications of MS are growing in the analysis of big molecules, including peptides, proteins, lipids, polysaccharides, and DNA, even if these are not yet often seen in clinical laboratories (Jimenez and Verheul, 2014; Li et al., 2014; Whiteaker, 2010). The use of matrix-assisted laser desorption/ionization (MALDI) mass spectrometry for quick bacterial identification is another developing field (Ho and Reddy, 2011; Lagacé-Wiens, 2015; Luan et al., 2009).

5. Clinical and forensic toxicology screening

If the proportion of positive outcomes is minimal and large amounts of samples need screening in Fig. 2, IA prescreening for a restricted number of substances of abuse designed for workplace drug testing in the USA is still widespread in CT and FT. Because most NPS are not detectable by IA, and because positive results need to be validated in cases of high prevalence (Yuan et al., 2015; Petrocheilou et al., 2017), hyphenated MS is increasingly being utilized for drug testing in place of IAs (Pasin et al., 2017). While there are just a few known chemicals covered by focused MS drug screening, many hundred analytes can be detected with the use of contemporary multi-analyte LC-MS/MS techniques with selective reaction monitoring (Mbughuni et al., 2016). Naturally, the number of monitored transitions and selectivity both affect identification power (Peters, 2011; Panderi et al., 2017). The powerful search algorithms and well-developed reference libraries including over 10,000 selective electron impact spectra, GC-MS remains a viable option for comprehensive drug screening, which is primarily conducted on urine (Meyer et al., 2010; Maurer et al., 2007; Grapp et al., 2016). Nevertheless, it was determined that LC-MS^n screening using a matching reference library was an appropriate addition to GC-MS (Wissenbach et al., 2011-193]. While this was going on, targeted and thorough screening was also successfully carried out using LC-HRMS/MS with TOF or OT analyzers. This method offered several benefits, including exceptionally strong identifying capability with relatively simple method development, great selectivity, sensitivity, robustness, and flexibility (Maurer and Meyer 2016; Beck and Ericsson, 2014; Concheiro et al., 2015). The advantages and disadvantages of low-resolution mass spectrometry (LRMS) and high-resolution mass spectrometry (HRMS) for NPS screening in hair, blood, urine, and soil that has been soaked with urine gathered throughout rave events have already been covered by Meyer and Maurer (Meyer and Maurer, 2016) elsewhere. Although most writers still create targeted screening processes, they concluded that HRMS could handle non-targeted screening operations (generic unknown screening) more easily. Additionally, they talked about the benefits of using extremely rapid scanning (QTOF) devices for sequential window acquisition of all theoretical fragment ion spectra (SWATH), which is a promising method for non-targeted HRMS screening in clinical and forensic toxicology (Roemmelt et al., 2015; Karastogianni et al., 2017). The first HRMS reference library was created and effectively used for urine screening, concentrating on metabolites (Maurer, 2017). Metabolite detection improves selectivity, permits confirmation of body passage, and, ultimately, reduces the possibility of false-negative LC-MS results that can be brought on by ion suppression of the target analyte (George et al., 2018; Xu, 2016). Examining metabolic trends can even lower the chance of false positive outcomes. Understanding these patterns is necessary to create screening methods based on metabolites. If the metabolites exhibit pharmacologic and/or toxic effects, these studies are also crucial for toxicological risk assessment in drug discovery and development. Because controlled human studies are prohibited, the flood of non-preclinical substances (NPS) has encouraged toxicologists to conduct metabolism studies in animals or human liver preparations, such as primary hepatocytes, cell cultures, S9 fractions, microsomes, or cytosol. NPS are sold and consumed without any preclinical testing (Maurer and Meyer, 2016, Beck and Ericsson, 2014) . Richter et al., (2017) examined NPS metabolism data from research involving human urine, primary human hepatocytes, and liver preparations. They came to the conclusion that human liver preparations, especially the pooled S9 fraction, were a sufficient and more affordable alternative in the context of metabolic investigations and for creating toxicological urine tests, even though hepatocytes offered the widest diversity of metabolites. Because

of its exceptional sensitivity and identifying power, HRMS is the industry leader in this area [Maurer and Meyer, 2016, Maurer and Meyer, 2016, Maurer and Meyer, 2012). It also plays a significant role in research on drug transporters or drug binding to proteins (Meyer, 2016 Meyer, 2015 Mardal et al., 2016). Lastly, the high sensitivity of contemporary equipment opens up new research and application domains, such as the miniaturization of drug (of abuse) quantification using dried blood spots (Stove et al., 2012; Verplaetse and Henion, Patteet et al., 2015; Berm et al., 2015; Ambach et al., 2014) or the detection of chemical warfare agent protein adducts as a biomarker of poisoning in innovative micro sampling devices (John et al., 2016). Successfully applied to a dried urine spot LC-MS^n screening are well-established comprehensive urine screening methodologies (Michely, et al., 2017). Of course, some of its drawbacks had to be mentioned, such the fact that some very low-dose medications lacked adequate detection limits. Additionally, this dried urine spot screening was moved to an HRMS without chromatography or extraction. Urine could be directly screened for drugs (of abuse) and their metabolites using paper-spray ionization (Michely et al., 2017).

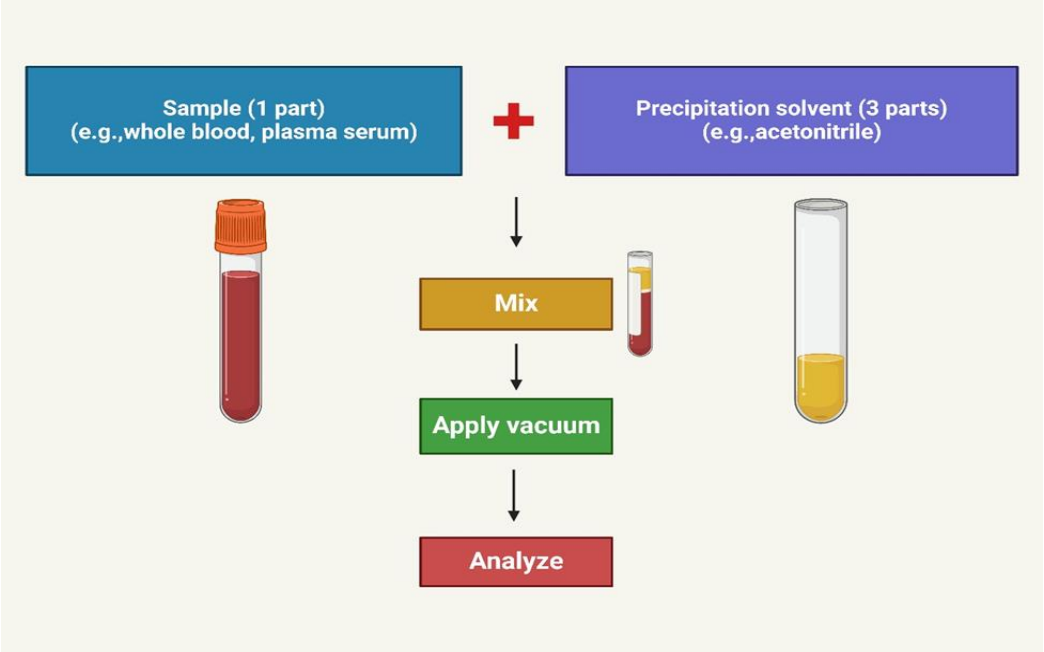

Fig. 2. An investigation of the process of preparing samples in the field of forensic toxicology

6. Clinical toxicology

In emergency clinical toxicology, sample transportation, laboratory analysis, and findings reporting are allotted no more than two hours. Analytical techniques that can be applied in this situation are strictly required by the time constraint. The primary use of urine is in drug testing. Immunoassay methods are widely used in hospital laboratories due to their ease of use and speed. However, it is generally recognized that the present generation of immunoassay techniques can only cover a small portion of compounds that are significant to toxicology. Gamma-hydroxybutyrate, the majority of designer pharmaceuticals, oral antidiabetics, calcium channel blockers, β-blockers, and pregabalin are only a few of the numerous significant ones that are overlooked. A comparative analysis between immunoassay and full GC-MS screening revealed that nearly every other patient had consumed chemicals that the immunoassay had not been able to identify. Furthermore, the results of the GC-MS did not agree with every fifth result (von Mach, et al., 2007). According to certain reports, the majority of acute poisoning patients would not respond well to treatment if substances taken in overdose were quickly identified through thorough drug screening (Pohjola-Sintonen et al., 2000). The same authors did note, nevertheless, that thorough screening would allow for the best possible care for many acute poisoning cases by eliminating the need for expensive medications and supervision and making it easier to identify instances that would need immediate drug-specific treatment (Pohjola-Sintonen et al., 2000). The program has generally been favorably regarded in the centers where comprehensive broad-spectrum drug screening has been organized appropriately. Another problem is that without the toxicologist's assistance and direction, doctors may not always be able to understand the analysis's findings (Hammett -Stabler et al., 2002; Tenore 2010; Flanagan, 2004).

7. Forensic toxicology

There are many different areas in forensic toxicology (Table 1), and each has different requirements for the breadth and depth of screening. Comprehensive screening is ideal in the following areas: drug-facilitated crime; child welfare; driving while intoxicated; post-mortem toxicology; and assault victim and offender investigations. Testing of drug in the penal system, the workplace, and the military forces are among the settings focused on drugs of abuse (Vuori and Ojanperä, 2009). The same kinds of specimens used in clinical toxicology are also used in clinical forensic toxicology. But unlike clinical toxicology, the forensic environment places more value on analytical findings that can be supported in court. As such, a confirmation step ought to be conducted in conjunction with screening in forensic toxicology, either concurrently with the same analytical run or independently. Considering that someone who tests positive for an unlawful drug may face consequences, the treatment of drug-dependent individuals falls between the purview of clinical and forensic toxicology. It is standard practice in post-mortem toxicology to use two distinct specimens and two distinct procedures. Because of the varied and frequently deteriorated character of the specimens as well as the wide variety of specimens accessible for investigation, applying analytical techniques in postmortem toxicology is frequently more challenging than in other forms of forensic toxicology (Drummer et al., 2007). It is important to thoroughly validate methods for the specific postmortem specimen being used. In addition to blood, urine and vitreous humour can be useful specimens. In certain situations, solid tissues like the liver and the contents of the stomach can also be used (Drummer et al., 2007).

Table 1. An overview of the features of a few time-of-flight and Orbitrap Fourier-transform mass spectrometry-based drug-screening techniques for doping control and clinical and forensic toxicology, arranged chronologically by year of publication.

Analytes	*Work-up*	*Matrix*	*HRMS technique*	*ID procedure*	*Qual/quant*	*Ref.*
637 drugs and metabolites	Mixed mode SPE	Urine	LC–TOFMS	Δm, RT, minimum abundance criteria, and precursor exact mass reverse database search and EIC generation	Qual	(Pelander et al., 2003)
97 doping agents	Mixed mode SPE	Urine	LC–TOFMS	Minimum abundance criteria, Δm, RT, isotope pattern matching, and precursor exact mass reverse database search	Qual	(Kolmonen et al., 2007)
29 doping agents	LLE	Urine	LC–OrbitrapMS	Find the precise masses of the precursor and diagnostic fragments; indicate any unreported criteria.	Qual	(Virus et al., 2008)
10 drugs of abuse and metabolites	LLE	Hair	CE–TOFMS	Generate elemental composition for precursors within specified RT windows, match isotopic patterns, and meet Δm requirements	Qual and semiquant	(Gottardo et al., 2007)
175 drugs	Mixed mode SPE	Whole blood	UHPLC–TOFMS	Primary: Δm, RT, and minimum abundance parameters for searching the target database; additional: matching isotope patterns	Qual	(Dalsgaard et al., 2012)
815 drugs and metabolites	Mixed mode SPE	Hair	LC–TOFMS	Minimum abundance criteria, Δm, RT, isotope pattern matching, and precursor exact mass reverse database search	Qual	(Pelander et al., 2008)
815 drugs and metabolites	Mixed mode SPE	Vitreous humour	LC–TOFMS	Isotopic pattern, precursor precise mass reverse database search, Δm, and RT	Qual	(Pelander et al., 2010)
13 steroids	Dilution	Hormone preparations	LC–TOFMS and LC–QTOFM	Manual: precise mass-based elemental composition of predecessors TOFMS and QTOFMS selected from TIC, UV spectrum DBE criteria, fragment analysis by DDA or ISCID	Qual	(Nielen et al., 2001)

8. The present challenges in forensic and analytical toxicology

The main concerns concern behavioral or human performance toxicology, including drug testing in workplace, abstinence control, postmortem toxicology, impaired driving evaluation, and drug-facilitated crimes (Wyman, 2012). Within living organisms, mostly blood or urine, forensic toxicology primarily involves the quantitative and qualitative examination of poisons, prescription medicines, drugs of abuse (DOA), or ethanol, as well as the interpretation of the corresponding data. Prescreen immunoassays (IA) are frequently used in routine laboratory procedures to screen for the most pertinent DOAs. These IA tests are frequently followed by confirmatory analyses using hyphenated chromatographic methods, like liquid chromatography (LC) -MS (mass spectrometry) or gas chromatography (GC) —MS (Maurer, 2007; Drummer, 2007; Maurer, 2010). As of December 2017, over 800 NPS had been informed to the UNODC Early Warning Advisory, making the use

and abuse of these substances an international issue (United Nations Office on Drugs and Crime, 2018). Of these, the majority (68%) were stimulants and synthetic cannabinoids, which accounted for the majority of newly reported NPS in 2017. In general, there is a dearth of knowledge regarding the harmful impacts and toxicity of NPS, which is becoming a global issue. Furthermore, because of their transience on the drug scene, direct detection and identification continue to be difficult for analysis. Since most of the time common IAs cannot accurately identify entire classes of NPS, thorough screening procedures must be developed to detect them. Although highly sensitive, focused techniques such as multiple reaction monitoring (MRM) require frequent updates and reference standards that are either hard to come by or very expensive. Due to its ability to evaluate data retrospectively and eliminate the requirement for technique adjustment, HRMS has demonstrated great promise (Grabenauer et al., 2012; Shanks et al., 2012). Developing innovative screening techniques that do not specifically target the chemical structures of the analyte or its metabolites is an alternate strategy. This could be quite helpful in providing prompt action in the event of suspected NPS intake and in helping to resolve this intricate analytical problem. The first method demonstrates that an assay that can identify synthetic cannabinoids and their metabolites according to their interaction and activity with cannabinoid receptors may be developed (Cannaert et al., 2017). As a primary urine screening tool, such an activity-based screening test may supplement traditional analytical techniques (both targeted and untargeted). In contrast to targeted techniques, which miss compounds if they are not on the candidate list, this method may result in fewer false negative results even though it is hard to positively identify individual synthetic cannabinoids (Bijlsma et al., 2018). Drug users may turn to NPS not only to obtain legal highs but also, possibly, to avoid testing positive for drugs on drug screening tests. In situations when drug abstinence must be demonstrated, such as driving liability tests, certain psychiatric or jail settings, or workplace pharmacological screening processes, the latter is especially pertinent (Bijlsma et al., 2018). Urine continues to be the preferred matrix in settings for abstinence control (Verstraete, 2004; Phan et al., 2012; Fu et al., 2014). Therefore, labs must identify attempts at urine adulteration that may be made in an attempt to evade positive drug test findings (Wu et al., 1999). Diluting real pee, replacing it with synthetic urine, or chemical adulteration are common manipulation techniques. Because several compounds are known to hide drug detection effects, their use has been documented. Everyday domestic substances like pyridinum chlorochromate (PCC), hypochlorite-based bleach (NaOCl), peroxide (H_2O_2), and peroxidase are often appropriate for chemical urine adulteration (Fu et al., 2014; Uebel and Wium, 2002; Jaffee et al., 2007). Products like Stealth® (consisting of H_2O_2 and peroxidase) (Valtier and Cody, 2002) Klear® (consisting of KNO2) (Peace and Tarnai, 2002), or Whizzies® (consisting of sodium nitrite) (Dasgupta et al., 2004) and "Urine Luck" (consisting of PCC) (Wu et al., 1999; Paul et al., 2000) are easily accessible online (Fu et al., 2014; Jaffee et al., Dasgupta, 2007). Products designed to adulterate urine for commercial use are in particular common in the United States. This also holds for artificial urine products that are sold commercially (Goggin et al., 2017; Kluge et al., 2018). Comprehensive testing is sometimes impeded by time, costs, and resources, even though screening for a wide range of chemical adulterants and artificial urine products should be a requirement for toxicological laboratories. Integrity testing, integrated sample checks, and spot and dipstick tests are quicker and less expensive alternatives to IA systems that are sold commercially. However, these are frequently linked to high percentages of false negative or inaccurate positive outcomes (Fu et al., 2014, Edwards et al., 1993, Matriciani et al., 2018).

9. Conclusions

TDM is crucial in clinical and forensic toxicology as it aids in optimizing drug therapy and identifying drug-related incidents. TDM is a crucial tool in clinical and forensic toxicology, providing valuable insights into drug therapy management and incident investigation. Despite challenges like metabolism variability, TDM optimizes treatment, minimizes adverse effects, and enhances forensic analyses. It reveals that despite providing valuable insights, TDM also faces significant challenges and limitations. The widespread adoption and effectiveness of drug metabolism tests in clinical practice are delayed by variability in drug metabolism, assay inaccuracies, and interpretational complexities. Forensic investigations face challenges like postmortem redistribution and analytical sensitivities, complicating the interpretation of TDM results and requiring careful integration with comprehensive forensic analyses. Future efforts should focus on addressing challenges and enhancing the utility and reliability of TDM in clinical and forensic conditions. Analytical techniques advancements, including the creation of more sensitive and specific assays, are crucial for enhancing the accuracy and precision of drug measurements. Interdisciplinary collaboration between pharmacologists, toxicologists, forensic scientists, and clinicians is crucial for developing standardized protocols and guidelines for TDM

interpretation and integration into clinical and forensic practice. Advancements in pharmacogenomics and personalized medicine provide opportunities to customize drug therapy based on individual patient characteristics, enhancing therapeutic outcomes and minimizing adverse effects. Future research should address TDM challenges by improving assay sensitivity, standardizing interpretation guidelines, adopting LC-MS for accuracy, and integrating pharmacogenomic information for personalized medicine approaches. Emerging technologies like LC-MS and point-of-care testing can enable rapid and reliable drug monitoring in various clinical and forensic conditions. TDM, despite facing challenges, holds great promise for improving patient care, enhancing drug safety, and facilitating toxicology forensic investigations. Point-of-care testing and mobile technologies can improve clinical drug monitoring, while collaboration between forensic scientists and clinicians is crucial for standardized protocols and comprehensive forensic analyses. TDM's future lies in embracing technological innovations, interdisciplinary collaboration, and refining methodologies to enhance patient care and facilitate toxicology forensic investigations.

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