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Therapeutic Drug Monitoring (TDM) in Clinical Practice

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Abstract

Therapeutic drug monitoring (TDM) is an ever-evolving process that consists of two components: measurement of drug levels, and interpretation of the values obtained by clinicians. It has mainly been used for optimizing treatment, assessing efficacy of drugs, ensuring patient safety, screening for drug-drug interactions, monitoring compliance, etc. In order to unmask the true potential of TDM, clinicians need to have adequate knowledge of the correct matrix, correct time of sample collection, and the correct analytical method to be used. As beneficial as TDM is, it is important to understand that it should be done only for a handful of drugs that fulfill previously established criteria. The practice of TDM has advanced greatly with the introduction of pharmacogenomics, pharmacogenetics, and artificial intelligence, progressing towards the development of personalised medicine.

Key words: Therapeutic drug monitoring, TDM, patient safety, drug efficacy, drug concentration.

Introduction

Therapeutic drug monitoring (TDM) may be defined as a process that involves drug concentration measurement in biological fluids and interpretation of the obtained values by physicians. This multidisciplinary process requires the application of knowledge of pharmaceutic, pharmacokinetic and pharmacodynamic principles that facilitates safety and efficacy assessment of the drug in question, which in turn helps in personalizing drug treatment regimens for patients[1].

Albader *et al*[2] define TDM as "the measurement of serum drug and/or anti-drug antibody (ADA) concentrations."

Almukainzi defines TDM as, "detecting concentrations of a drug in a biological fluid at a single or several periods following a drug intake for adjusting and customizing drug dosage and administration"[3].

Zijp *et al* define TDM as "the quantitative measurement of drug concentrations to assess adequate exposure, resistance, or side-effects to medication"[4].

Kang *et al* define TDM as "the clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures"[1].

Since the introduction of TDM during the 1960s and 70s, the primary focus behind the concept has been to improve patient outcome by decreasing adverse drug reaction (ADR) rates and toxicity incidences; however, the scope of TDM has been broadened and now includes compliance monitoring, individualisation of therapy, efficacy assessment, drug-drug interactions monitoring, assessing response to new treatment, monitoring abuse and investigating unusual treatment responses and adverse reactions[1,3].

Although the process of TDM is based on the assumption that drug levels correlate with pharmacodynamic effects of a drug[5], it is worth remembering that measurement of drug levels is one of the two components of TDM. It is the combination of drug concentration measurement and clinical interpretation of the obtained values that make TDM an invaluable tool, that can be used to personalise drug treatment[6].

Evolution of TDM

Even though the profession of medicine has, since long, known how minute differences in dosing can lead to undesired outcomes (toxicity, therapeutic failure due to subtherapeutic dosage), it was not until 1932 that drug monitoring was introduced[7]. In the following decades, significant events occurred that lead to the introduction of the concept of TDM[7]: 1.) Scientists started questioning the "one-size-fits-all" approach, as applied to drug administration, 2.) Serum level measurement for drugs like Penicillin and Streptomycin was made possible for the first time, in 1948, 3.) A study by Finney DJ, that talked about the importance of drug monitoring, was published in 1965[8]. All these events led to discussions on drug pharmacokinetics, drug-drug interactions, and the importance of monitoring drug levels, which ultimately brought the concept of TDM into existence. The period between 1970 and 1990 was of particular significance in the history of therapeutic drug monitoring, as multiple

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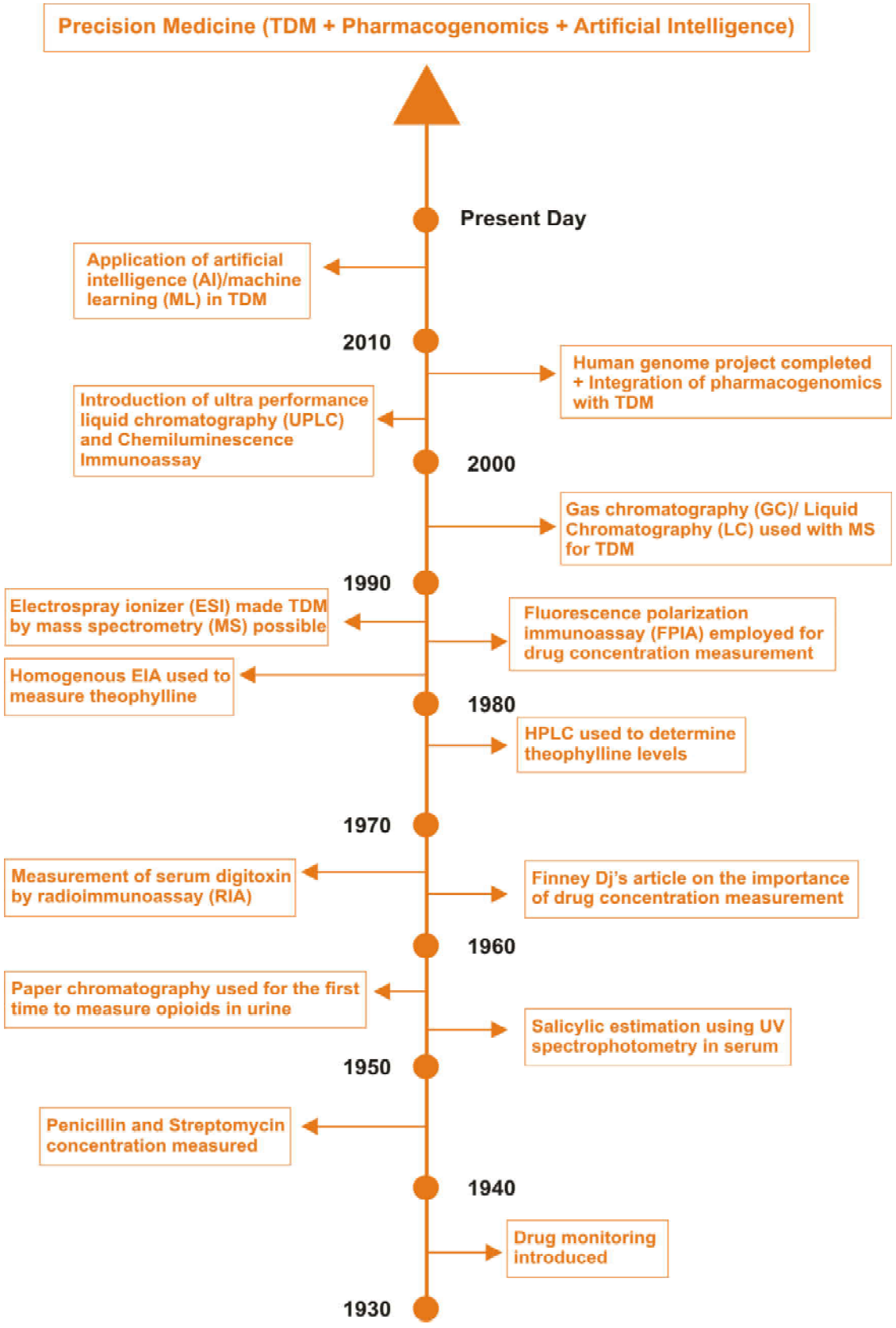

Fig. 1: *Evolution of TDM.*

analytical techniques, such as gas chromatography, high performance liquid chromatography (HPLC), and different types of immunoassays[9] were introduced for the purpose of measuring serum drug concentrations. 1990s onwards, there was introduction of better chromatographic techniques, combination of chromatographic techniques with mass spectrometry (MS), and invention of non-invasive modalities (such as wearable biosensors), for the purpose of measuring drug levels, that led to an increase in the TDM practices. Advancement of pharmacogenomics and pharmacogenetics, brought about by completion of the human genome project in early 2000s, has given rise to the fields of pharmacogenomics and pharmacogenetics, which when combined with TDM can lead to a significant improvement of patient outcomes and improve our understanding of various therapeutic responses[1].

Criteria to be fulfilled by drugs for TDM

While all drugs used may require monitoring, classical TDM is done for drugs that follow the following criteria[1,7,10,11]:

1. Presence of inter-individual variability

   This is seen mainly due to various pharmacokinetic factors. Drugs showing significant inter-individual variability include phenytoin, amitriptyline, chlorpromazine, warfarin, tacrolimus, etc[12,13].

2. The drug has a narrow therapeutic index

   Blix *et al* define Narrow Therapeutic Index (NTI) drugs as the ones "with small differences between their therapeutic and toxic doses, implying that small changes in dosage or interactions with other drugs could cause adverse effects[14]."

   Classic examples of NTI drugs include lithium, aminoglycosides, digoxin, rifampicin, theophylline, warfarin, phenytoin, phenobarbital, etc[14].

3. Existence of correlation between plasma concentration of the drug and clinical response/toxicity

   This criterion is fulfilled by majority of drugs and is essential for drugs undergoing TDM. A classic example of drugs that fall into this category are aminoglycosides (e.g., gentamicin). Drugs belonging to this group mediate clinical efficacy by employing concentration dependent killing, which essentially translates to these drugs having better antimicrobial activity at peak concentrations[15].

4. Interpretation of therapeutic and toxic effect of the drug not possible clinically or with the aid of a biomarker

   Drugs used in psychiatry (e.g., lithium, anti-psychotics, tricyclic antidepressants, etc), immunosuppressants (e.g., tacrolimus, cyclosporine, etc.) and digoxin are some of the drugs that do not have established biomarkers and necessarily require maintenance of concentration within set limits[16].

5. Consistent administration of the drug for a duration long enough to justify treatment modification

   Except in life-threatening conditions, the patient should have been taking the drug for long enough to reach steady-state concentration (i.e., for a duration long enough to cover at least five half-lives), before doing TDM.

TDM is not done if a drug's effects can be observed clinically, like in case of anti-hypertensives, anti-diabetics, etc., or if the drug has measurable biomarkers that can serve as clinical outcome surrogates (e.g., Prothrombin time (PT) - International Normalised Ratio (INR) for warfarin)[17]. Additionally, it is not recommended for drugs that do not have a well-established concentration-clinical effect relationship. Drugs having a delayed onset of action (e.g., selective serotonin reuptake inhibitors (SSRIs), prodrugs (e.g., clopidogrel) and those taken via non-systemic routes for local action (e.g., steroids taken via inhalational route) do not have an established concentration-effect relationship, which makes the utilisation of TDM for these drugs non-beneficial[18].

In the context of inflammatory bowel disease (IBD), TDM has often been described to be of two types: Proactive and Reactive. While proactive TDM includes measurement of drug concentration at pre-determined intervals irrespective of the disease status, reactive TDM involves drug level monitoring in presence of active disease/flare-ups. Table I summarises the differences between proactive and reactive TDM.

Biological samples(/matrices) used in TDM

Usage of blood-based matrices (whole blood, plasma or serum) has been the gold standard practice due to an established relationship between therapeutic efficacy of drugs and their concentration in blood/serum, but due to the invasive nature of collection, usage of other matrices such as hair, urine, sweat, saliva and also the relatively less invasive finger prick sampling technique, has been on the rise.

Table II lists the different matrices, drugs they have been employed for, and their advantages and disadvantages.

Table I: Differences between Proactive and Reactive TDM

	Proactive TDM	Reactive TDM
Time of measurement of concentration[19]	At pre-determined intervals	Levels are measured because of presence of active disease or during flare-ups
Presence of active disease[19]	No	Yes
	Done in asymptomatic patients/patients in remission[20]	Done in patients with symptoms or findings suggestive of active disease
Goal[21]	To ensure that therapeutic drug levels are being maintained	To check if disease persistence/flare-up is due to ADAs or subtherapeutic concentration or in spite of having optimal concentration
	To decrease the incidence of anti-drug antibodies (ADAs), and subsequent loss of response	
Reduction of development of ADAs and drug failure	More	Less
Cost effective[22]	More	Less

Table II: Matrices used for TDM.

S. No.	Type of matrix	Drugs	Advantage(s)	Disadvantage(s)
1.	Whole blood	Immunosuppressants (Tacrolimus[23], Sirolimus[24], Everolimus[24], Cyclosporine[24]) Anti-psychotics (Quetiapine[25])	Allows for measurement of drugs that get sequestered inside blood cells[24]	1. Hematocrit and plasma protein level variations can affect results[26] 2. Anticoagulants used might interfere with the results[27]
2.	Plasma	Direct oral anticoagulants (Apixaban, Rivaroxaban)[28], Immunosuppressants (Mycophenolic acid[24])	1. Relatively larger volume can be obtained, as compared to serum, from a blood sample[29] 2. Less time consuming (clotting of blood not required)[29] 3. Sample can be used for whole blood analysis as well[29]	1. Anti-coagulants might interfere with the results by affecting protein binding (heparin causes lipolysis which causes an increase in the concentration of non-esterified fatty acids that displace drugs bound to plasma proteins) and disturbing the stability of the matrix[29] 2.Preservatives added to anticoagulants may affect results[29]
3.	Serum	Direct oral anticoagulants (Apixaban, Rivaroxaban)[28] Anti-psychotics (Quetiapine[25])	Since anti-coagulants are not used, there is less interference with results	Clotting of blood is time consuming[29]
4.	Liquid finger prick blood (LFB)/Dried Blood Spot (DBS) sampling	Immunosuppressants (Tacrolimus[30], Cyclosporine[31]), tyrosine kinase inhibitors[32], adalimumab[33]	1. Less invasive as compared to other blood-based matrices 2. Longer shelf life of sample	1. Less precise and accurate[33] 2. Dependence on spot homogeneity in DBS[33]
5.	Sweat	Beta lactams(flucloxacillin, imipenem, and cefepime)[34], Levodopa[35]	Non-invasive[36]	1. Contamination of samples is very common[35] 2. Concentration of drugs might vary depending on rate of sweating[35] 3. Dilution with respect to plasma is variable across different drugs[37]
6.	Urine	Polymyxin B[38], Angiotensin receptor blockers (ARBs)[39], opioids[40]	1. Non-invasive[40] 2. More economical[40] 3. Fast results[40]	1. Dilution (due to diuretics) may interfere with results[40] 2. High false positive rates[40]
7.	Saliva[41]	Immunosuppressants (Cyclosporine[42], Mycophenolic acid[43], Prednisolone[44]) Anti-microbials (Gentamicin[45]) Anti-epileptics (Levetiracetam[46], Carbamazepine, Phenytoin and Phenobarbital[47])	1. Non-invasive 2. Frequent sampling possible 3. Self-sampling possible 4. More economical	1. Levels affected by flow rate of saliva[48] 2. Salivary pH may alter levels[48] 3. Blood contamination affects results
8.	Hair	Anti-tubercular drugs[49], anti-retroviral drugs[50,51], antihypertensive drugs[52]	1. Long duration of growth allows study of compliance[52] 2. Easy availability[52] 3. Easy to store samples[52]	1. Pigmentation variability affects drug incorporation[53] 2. Drug diffusion from sweat might interfere with results[54] 3. External contamination might alter findings[54]
9.	Cerebrospinal fluid (CSF)	Anti-retroviral drugs[55], Venlafaxine[56], Vancomycin[57]	Good indicator of brain tissue exposure to drug(s)[55]	1. Ageing is associated with an increased permeation of drugs into CSF[55] 2. Neuroinflammation disrupts BBB and allows for more drug to enter CSF[55] 3. Invasive[55]
10.	Vitreous fluid	Anti-epileptics (carbamazepine, phenytoin, phenobarbital)[58], Opioids[59]	1. Does not undergo postmortem redistribution (PMR) like blood[58,59]	1. Invasive and limited to usage in investigations done postmortem 2. Vitreous levels do not correspond to serum levels in most cases

			2. Easy to collect[58]	
11.	Synovial fluid	Opioids[60], Cocaine[60], Vancomycin[61], Meropenem[61], Non-steroidal anti-inflammatory drugs (NSAIDs)[62]	1. Good representatives of local concentration	1. Invasive 2. Limited volume available 3. Joint disorder might affect drug levels[62]
12.	Bone	Anticonvulsants (Carbamazepine[63]), Anesthetics, Antidepressants (Duloxetine, Venlafaxine, Amitriptyline)[64], Antihypertensives (Atenolol, Bisoprolol)[65], Antipsychotics (Quetiapine[66]), Benzodiazepines, NSAIDs, opioids	Useful for postmortem studies	1. Invasive 2. Not beneficial for drugs used for a short time period

Timing of sample collection for TDM

In most cases, drug concentration measurement is done after steady-state concentration has been attained, i.e., when the rate of administration of a drug equilibrates with its rate of elimination. This state is typically achieved after 5 half-lives, but may be achieved earlier, if a loading dose has been administered. However, in patients with metabolism or excretion impairments, measurements may be done prior to reaching steady state concentration, to avoid toxicity development especially if the patient is receiving drugs with long half-lives[5].

Table III lists the suitable time of blood collection based on the indication.

Table III: Blood sample collection for TDM.

S. No.	Indication	Time of blood collection
1.	Suspected toxicity	Immediately[5]
2.	Poor therapeutic control in life-threatening conditions	Immediately[5]
3.	Levels of antibiotics that employ concentration dependent killing (aminoglycosides)	1 - 2 hours after oral administration (to obtain peak values, i.e., maximum concentration of drug attained post-administration)[5] and once trough levels, i.e., minimum concentration post-administration (usually attained just before the next dose) have been achieved[67]
4.	Routine plasma concentration (aminoglycosides)	Immediately prior to administering next dose (to obtain trough levels)[5]
5.	Antibiotics by intravenous route	30 minutes post-infusion[5]

Sample collection, storage and processing

After determining the best time for sample collection, for measuring drug levels in serum, venipuncture is performed and the blood obtained is collected in plain gel-free vacutainers and allowed to clot.

Gel containing vacutainers were commonly used previously, as the gel enabled faster separation of serum from other blood components[68]. But in many cases, it was observed that usage of such vacutainers, during storage, yielded a false low drug concentration due to absorption of drugs on the gel[69,70]. Steuer *at al* also noted that this finding was more pronounced in cases of lipophilic and highly plasma protein bound drugs[68,71].

Once the serum is separated, the sample is centrifuged, following which the serum is pipetted and put in polypropylene tubes for storage. The temperature at which samples are stored varies from drug to drug, but most commonly, for short-term storage, samples are kept at –20°C, and for long-term storage at –80°C[72].

Assay methods employed for performing TDM

Considering that TDM is used for many time-sensitive indications, such as dose adjustment and toxicity diagnosis, an ideal assay method is one that can generate results fast, thereby allowing physicians to make therapeutic modifications in a timely manner, that can affect outcomes[73].

Analytical methods commonly used for performing drug assays can be divided into three broad categories: Spectrophotometry, Chromatography and Immunoassays.

i. Spectrophotometry: It a technique based on the central principle that molecules and atoms, when exposed to light of different wavelengths, absorb a portion of it. This method relies on measuring the amount of light absorbed by a compound, which is considered to be proportional to the concentration of the said compound in a solution, as explained by Beer Lambert's law.

ii. Chromatography: This method, currently the gold standard technique, may be defined as a separation technique that relies on the principle that different constituents of a solution react differently with the stationary and mobile phases, based on their physical and chemical characteristics, which allows for their identification, separation, and quantification[74]. Three types of chromatographic techniques that are currently being used for measuring serum concentration of drugs are thin layer chromatography (TLC), gas liquid chromatography (GLC), and high performance liquid

chromatography (HPLC). While TLC is a simple method that yields fast results, is cost effective, and may be used for on-site TDM,[75] GLC and HPLC are the more commonly used techniques that are usually combined with mass spectrometry (MS) or ultraviolet (UV) to yield more advanced and reliable results.

iii. Immunoassays: rely on antigen-antibody reactions to quantify an analyte[76]. Different types of immunoassays, such as, radio immunoassay, enzyme immunoassay and fluorescent immunoassay, are being used in therapeutic drug monitoring.

Table IV summarises the advantages and disadvantages of some commonly used techniques used for measuring serum concentration of drugs.

Table IV: Advantages and disadvantages of commonly used analytical methods

Method	Advantage(S)	Disadvantage(S)
Spectrophotometry[77]	• Simple to use • Cost effective • Small amount of sample required	• Excipients and sample matrix variations may interfere with the results • Non-selective
High-Performance Liquid Chromatography (HPLC)[78]	• Sensitive • Specific • Small sample amount required • Minimal sample processing	• High cost • Specialised staff and training required
Gas-Liquid Chromatography (GLC)[79]	• Cheaper reagents, making it cost effective	• Sample processing and analysis are time consuming
Radio Immuno Assay (RIA)[76,80]	• Precise • Sensitive	• Harmful effects of radiation • Higher cost of waste disposal • Cross-reactivity
Enzyme Immuno Assay (EIA)[81]	• Specific • Cost effective	• Cross reaction with other drugs and compounds • False negative result due to established thresholds
Fluorescence polarisation Immunoassay (FPIA)[76,82]	• Simple • Precise • Easy to perform	• Interference by matrix components • Less sensitive than other immunoassays

After a method is selected, it requires validation before being employed for drug concentration measurements. Factors such as accuracy, precision, detection limits, reproducibility, and robustness are some of the parameters considered while performing validation[1,83].

Guidelines for TDM

The need for conducting TDM for various indications has prompted multiple agencies and regulatory bodies to develop guidelines and consensus panel recommendations. These agencies include:

1. *Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (*AGNP)

   AGNP is a Germany-based "interdisciplinary association" that primarily conducts research on neuro- and psychopharmacology[84].

   The AGNP-TDM working group released its consensus guidelines on therapeutic drug monitoring of psychiatric drugs in 2004, which was later updated in 2011[85] and 2017[86] to include drugs used in neurology as well.

2. International League Against Epilepsy (ILAE)

   ILAE is an organization that primarily aims to "ensure that health professionals, patients and their care providers, governments, and the public world-wide have the educational and research resources that are essential in understanding, diagnosing, and treating persons with epilepsy"[87].

   ILAE does not support routine TDM of antiepileptics.

3. International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

   IATDMCT is an international organisation that mainly works to "to promote the related disciplines of therapeutic drug monitoring and clinical toxicology worldwide"[88].

   The organisation has multiple committees that focus on different groups of drugs, such as biologics, anti-infective drugs, immunosuppressants, etc., and releases consensus guidelines and panel recommendations for or against conducting TDM of drugs.

4. World Anti-doping Association (WADA)

   WADA is an organisation that works to "develop, harmonise and coordinate anti-doping rules and policies across all sports and countries"[89]. The organisation has developed a list of drugs that all participants are screened for, prior to and during tournaments, to determine their eligibility for participation.

5. Regional and national bodies

6. Independent studies

Table V: Drugs and their TDM recommendation status

Group	Drugs	Comments	TDM recommendation status	Recommended matrix
Drugs used in psychiatry (as per AGNP-TDM guidelines, 2017 update[86])	Mood stabilisers • Lithium, Carbamazepine • Valproate and Lamotrigine	**Lithium:** Low therapeutic index. TDM done to ensure patient safety. **Carbamazepine:** TDM done for safety issues **Valproate:** high incidence of drug-drug interactions, TDM recommended every 3 - 6 months/if there are changes in doses **Oxcarbazepine:** required for optimisation at extremes of age, pregnancy, renal insufficiency, suspected non-compliance, etc[90]	Strongly recommended Recommended	Blood-based matrices
	Typical antipsychotics • Haloperidol, Fluphenazine,Thioridazine • Chlorpromazine	High rate of serious ADRs	 Strongly recommended Recommended	-do-
	Atypical antipsychotics • Clozapine, Olanzapine • Aripiprazole, Quetiapine, Risperidone	**Clozapine:** Side-effects and inter-individual variability, significant drug-drug interactions **Olanzapine:** significant drug-drug interactions **Aripiprazole:** levels above a certain level are associated with better clinical efficacy	Strongly recommended Recommended	-do-
	Tricyclic antidepressants • **Amitriptyline, Imipramine, Clomipramine** • **Desipramine**	TDM done for safety concerns (serious cardiac ADRs)	 Strongly recommended Recommended	-do-
	Serotonin Norepinephrine Reuptake Inhibitors: Duloxetine, Venlafaxine	TDM required for dose adjustments	Recommended	-do-
	Selective serotonin Reuptake Inhibitors: • Citalopram • Escitalopram, Fluvoxamine, Vortioxetine	**Citalopram:** maintaining levels is associated with lesser rates of hospitalisation Others: to check for compliance	Strongly recommended Recommended	-do-
Drugs used in neurology/ neurological conditions (as per AGNP-TDM guidelines, 2017 update[86])	**Anti-convulsants** • **Carbamazepine, Phenobarbital, Phenytoin, Valproic acid** • **Lamotrigine, Oxcarbazepine, Zonisamide, Tiagabine, Stiripentol, Rufinamide**	**Carbamazepine:** The metabolite also contributed to ADR development **Phenytoin:** follows "dose-dependent pharmacokinetics"[91] **Lamotrigine:** Half-life variable in presence of other anti-epileptics	Strongly recommended Recommended	Blood-based matrices
	Anti-dementia drugs • Donepezil	These is a positive association of clinical improvement with drug level	Recommended	-do-
Drugs used in cardiology/ cardiovascular conditions (as per Japanese Circulation Society (JCS) TDM guidelines[92])	**Vancomycin** in infective endocarditis **Aminoglycosides** for Infective endocarditis **Digoxin**	To reduce ADR development rates and to adjust dose in case of non-responders To reduce ADR development rates To decrease the incidence of digoxin intoxication and to bring down ADR development rates	Strongly recommended[92] Recommended[92] Recommended[92]	Blood-based matrices -do- -do-
	Amiodarone	Usually done to screen for compliance, and to check the safety and efficacy when dose or form is changed	Recommended[92]	-do-
	Bepridil (class 4 anti-arrhythmic)	For safety reasons (higher doses are associated with QT prolongation) and to screen for compliance	Recommended[92]	-do-
Drugs used in pulmonology/ respiratory conditions	**Theophylline** Caffeine	Narrow therapeutic index, significant drug-drug interactions[93] Recommended under certain conditions: [94]	Recommended[93,94] Might be recommended[94]	Plasma -do-

		1. Clinical effect not evident 2. Toxicity is suspected		
Immuno-suppressants	**Tacrolimus**[23]	High inter-individual variability[24]	Recommended[95] by IATDMCT	Whole blood
	Cyclosporine[24]	High inter-individual variability[24] +		-do-
	Sirolimus[24]	drug-drug interactions[24]		-do-
	Everolimus[96]	High inter-individual variations and a narrow therapeutic index[96]	Recommended[96] by IATDMCT	-do-
Drugs used in chemotherapy (anti-cancer drugs)	**Methotrexate**	Significant inter- and intra-individual variations, several drug-drug interactions, and unpredictable renal clearance[97]	Recommended	Plasma
	Busulfan	Associated serious adverse drug reactions, drug-drug interactions, and inter-individual variation with high doses[97]	Recommended	-do-
	5 Fluorouracil	Serious adverse drug reactions, significant	Recommended[98]	-do-
		intra- and inter-individual variability[97]	(Study "endorsed" by IATDMCT)	
	Imatinib	Significant inter- and intra-individual variability[99]	Recommended[99] by IATDMCT	-do-
	Paclitaxel	Inter-individual variations[100]	Recommended[100] by IATDMCT	-do-
Drugs used in chemotherapy (anti-microbial agents)	**Aminoglycosides**	Reduced ADR rates and a shorter length of hospital stay	Recommended in critically ill patients[101] by a panel consisting of members nominated by International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), European Society of Intensive Care Medicine (ESICM), International Society of Antimicrobial Chemotherapy (ISAC), and Pharmacokinetic/Pharmacodynamic (PK/PD) and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	Blood-based matrices
	Beta-lactams	To achieve desired levels and decreasing ADR rates		-do-
	Linezolid	Significant inter- and intra-patient variability		-do-
	Teicoplanin	High inter-individual variability		-do-
	Vancomycin	Volume of distribution and clearance of Vancomycin are altered in critically ill patients		-do-
	Voriconazole	Drug shows significant intra- and inter-individual variability in terms of pharmacokinetics	Recommended[102]	Serum
	Itraconazole	Unpredictable bioavailability and presence of significant drug-drug interactions	Recommended[102]	-do-
	Posaconazole		Mandatory under certain conditions such as: [102] • GI pathology affecting absorption • Compliance issue • Doubt of invasive fungal infection	-do-
	5-FC (5-flucytosine)		Mandatory to avoid toxicity development[102]	-do-

Implications of TDM

1. Efficacy assessment and treatment optimisation

Lim *et al* and Rane *et al* observed that utilizing TDM for determining drug doses in patients on anti-epileptic drugs provided a reduction in frequency of seizure episodes and ADR development rates[103,104]. Similarly, Vande *et al*, demonstrated that for biological agents, such as TNF-alpha inhibitors, TDM-guided dosage regimen was associated with fewer flares during the course of treatment[105], and a study conducted by Syverson *et al* concluded that proactive TDM in patients receiving Infliximab provided better disease control as compared to non-TDM guided treatment, in

inflammatory bowel disease patients[106].

Braal *et al* performed a cost-effective analysis of employing TDM-guided tamoxifen therapy in early breast cancer cases and concluded that the TDM intervention was associated with a higher number of life years and quality adjusted life years (QALYs), and relatively lesser healthcare expenses[107].

2. Ensuring patient safety

Since the introduction of TDM in the 1960s, one of the common indications for its use has been prevention of adverse drug reactions and toxicity development. For instance, in their studies, Steetman *et al*, and Darko *et al* utilised TDM to determine doses that helped reduce the incidence of nephrotoxicity development in patients taking aminoglycosides and vancomycin respectively[108,109].

A retrospective study conducted by Charfi *et al* revealed that TDM of digoxin played an important role in prevention of toxicity development especially in older adults[110].

3. Compliance monitoring

Utilizing TDM especially in cases where inadequate response to treatment is being observed, can help us understand if the reason underlying therapeutic failure is related to compliance before other causes are considered.

Gerona *et al* used Isoniazid concentrations in hair to assess adherence to ATT in people living with HIV[111].

Avataneo *et al* utilised TDM to monitor adherence in cases of resistant hypertension and screen for factors that contributed to poor compliance in such patients. This study revealed that a total of 42 per cent of enrolled patients were not adhering to the prescribed treatment, which was perceived as "drug resistance" due to inadequate response[112].

Similarly, Kylleso *et al* performed a study in treatment resistant schizophrenia cases and discovered a significant percentage of people who were diagnosed with this condition had undetectable levels of previously used antipsychotics, which strongly pointed towards a lack of compliance on patients' part[113].

4. To monitor drug-drug interactions

A review study conducted by Spina *et al*, on drug-drug interactions associated with second generation antipsychotics (Clozapine, Risperidone, Quetiapine, etc), recommended utilizing TDM when a cytochrome P450 inducer or inhibitor was to be given concomitantly, especially for drugs with a narrow therapeutic index (risperidone, sertindole)[114].

Gagno *et al* uncovered a case of drug-drug interaction when a patient who was on Imatinib for a gastrointestinal stromal tumour, presented with tumour growth and TDM revealed subtherapeutic levels of the drug due to concomitant consumption of carbamazepine, a CYP3A4 and P-gp inducer[115].

Gex-Fabry *et al* emphasized on the importance of including TDM database for monitoring drug-drug interactions during post-marketing surveillance[116].

5. To reduce healthcare costs

A systematic review article by Marquez-Megias *et al* demonstrated that "TDM strategy" of dosing anti-tumour necrosis factor (TNF) drugs in inflammatory bowel disease (IBD) patients was more cost saving as compared to an "empiric strategy"[117.]

And a meta-analysis by Ricciuto *et al* similarly concluded that reactive TDM provided a better "cost benefit" as compared to empiric treatment in IBD patients receiving Infliximab[118].

6. In forensic studies and toxicology

In the current scenario, with many matrices available for performing TDM, it has become possible to screen for drugs and other substances post-mortem. Bone has been used as a TDM matrix in post-mortem studies to screen for anticonvulsants, antidepressants, opioids, etc[63,64]. Similarly, vitreous fluid has been used in forensic studies to screen for cocaine and opioid misuse.

TDM can also aid in suspected cases of homicide and suicide resulting from administration/intake of drugs in lethal doses. For instance, in 2007, a 24-year-old woman was murdered by administration of a toxic dose

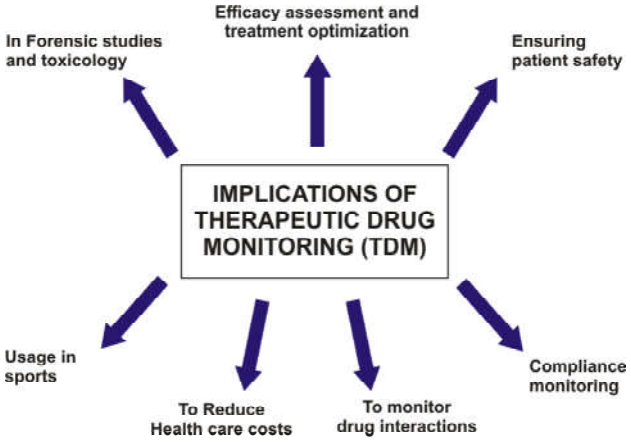

Fig. 2: *Implications of therapeutic drug monitoring.*

of propofol. Blood propofol concentration measurement was pivotal in solving this case[119].

Similarly, three members of a family were given toxic doses of colchicine which initially caused all the three individuals to develop non-specific symptoms, like vomiting and diarrhoea, and later turned out to be fatal for all three patients. Measurement of colchicine in the serum and urine of the third patient helped the clinicians reach the diagnosis of colchicine toxicity[120].

Homicide by Arsenic poisoning is yet another scenario that is commonly diagnosed, post-mortem, using TDM. Duncan *et al* reported a case of a patient who presented with non-specific features to a hospital. The patient succumbed to the illness before the correct diagnosis could be made. On performing routine post-mortem toxicology screening on liver, urine, blood and hair samples, a diagnosis of arsenic poisoning was made by the treating physicians[121].

7. Usage in sports

TDM is used in sports to detect doping amongst athletes. World Anti-doping Association (WADA) utilizes drug/substance concentration monitoring in different matrices to screen for potential abuse[122].

WADA tests for drugs such as anabolic steroids, beta 2 agonists, glucocorticoids, diuretics (such as acetazolamide, furosemide, bumetanide, spironolactone), vaptans (such as tolvaptan, conivaptan), desmopressin, erythropoietin receptor agonists (such as darbopoetin), TGF-β antagonists (such as Luspatercept, Sotatercept), GnRH analogues (such as goserelin, busurelin), GH analogues, GHRH analogues (such as sermorelin and tesamorelin), growth factors (such as IGF-1, FGF, PDGF, VEGF), aromatase inhibitors (such as letrozole, anastrolozole), SERMs (such as Clomifene, Fulvestrant, Raloxifene, Tamoxifen), stimulants (such as cocaine, amphetamine, mephentermine), opioids (such as morphine, tramadol, methadone), beta blockers (such as propranolol, sotalol, esmolol), etc[122]. The most commonly used matrix is urine, and abuse is determined on the basis of limits set by previous studies.

TDM and precision medicine

Precision medicine, also referred to as personalised medicine, has been introduced as the successor of evidence based medicine with both the fields opposing the concept of "one size fits all" approach to drug therapy[10]. This branch of medicine requires physicians to take genetic, environmental and lifestyle factors into account while prescribing drugs[123].

TDM which is considered to be a "snapshot" of drug exposure and the effect of genetic, environmental, nutritional factors, concomitant drug use, etc., on drug levels[124], can significantly contribute towards development of precision medicine by improving our understanding of pharmacokinetics and pharmacodynamics at individual level[125].

While pharmacogenomics and pharmacogenetics are being advocated as potential aids in the development of personalised medicine[126], concurrent usage of TDM can help achieve target concentrations more effectively. In this combined setup, pharmacogenomics can help determine the initial dose, and TDM can be used to monitor and adjust subsequent doses according to concentrations and pharmacodynamics characteristics[127].

For example, TDM and pharmacogenomics are being increasingly employed together to develop personalised medicine for Isoniazid (INH) in patients suffering from Tuberculosis[128]. A study conducted by Jing *et al*, in Chinese pulmonary tuberculosis patients, utilised analysis of N-acetyltransferase 2 (NAT2) gene polymorphisms to categorize subjects into fast, intermediate, and slow acetylators. On the basis of this information, patients were given different doses of isoniazid. Drug concentrations were then measured and assessed for each patient, which led to development of a model that helped in estimation of appropriate doses for all the three groups[129].

Underdosing of tacrolimus has been historically associated with graft rejection while overdosing increases the risk of development of ADRs. Studies have shown that in patients who express CYP3A5, tacrolimus levels are lower than non-expressors, which results in a higher proportion of graft rejection cases[130]. A study conducted by Schönfelder *et al* revealed that administration of genotype-guided tacrolimus therapy led to attainment of equivalent trough levels in transplant patients, which in turn resulted in similar incidences of graft rejection, nephrotoxicity, and development of anti-HLA antibodies amongst CYP3A5 expressors and non-expressors[131].

TDM and Artificial Intelligence (AI)

Machine learning (ML), a subset of AI may be used for designing prediction models. While this can help in bringing down the number of samples required for TDM, large training sets are required for development of such models[132]. Pioneering work in this field was done by Woillard *et al*, who developed prediction models for tacrolimus and mycophenolic acid, which provided better results than the existing Bayesian estimation approach[133]. Advantageous usage of ML in TDM was further proven by Huang *et al*, who used an ML model to accurately predict trough vancomycin

levels in children[134].

Similarly, machine learning may aid in the development of population pharmacokinetic models. These models are usually developed to understand how patient-specific factors can alter various pharmacokinetic parameters. When compared with traditional pharmacometrics models for selection of covariates, the ML models provided comparable results in a short amount of time[132].

Based on the findings of their study, Dijkman *et al* concluded that an integrated approach, utilizing both TDM and dosing algorithms, can be used to create personalised treatment, for patients on antiepileptic medication, which helps in more effective target attainment than using TDM alone[135].

TDM in India

TDM is carried out in either large tertiary care teaching hospitals or corporate hospitals. While multiple labs have set up drug concentration measurement facilities, their lack of association with physicians who might be able to clinically interpret the findings, disqualifies them from being considered as TDM centers[136].

There are certain issues specific to India that hamper the growth of TDM in the country[136]:

1. The therapeutic ranges are usually taken from studies conducted in developed countries, many of which fail to take ethnic factors unique to Indians into consideration.
2. TDM requires expensive resources and setups, which is difficult to achieve in India. Justifying these expenses in addition to the enormous healthcare burden is one of the major challenges that hamper TDM development in the country.
3. Skilled manpower is needed to set up and run TDM facilities and currently, there are no official programs that equip individuals with the desired set of skills.
4. There is lack of awareness amongst healthcare workers regarding the application and utility of performing TDM.
5. There are quality standard issues due to lack of regulations regarding mandatory standard maintenance in the country.

Conclusion

Therapeutic drug monitoring can help improve treatment outcomes and safety profile for patients. It is a complex process that requires a multidisciplinary approach comprising of clinicians, pharmacologists, as well as other healthcare workers involved in patient care. Quality TDM requires adoption of standard operating procedures which must be implemented thoroughly.

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