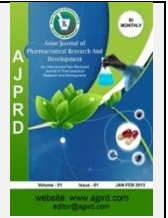


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Review Article

A Descriptive Analysis of Therapeutic Drug Monitoring In India

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ABSTRACT

Therapeutic drug monitoring (TDM) has evolved into therapeutic drug management throughout the past three to four decades, becoming a crucial facet of precision medicine. Even though India has one of the fastest-growing economies in the world, TDM is not widely used there. At the moment, it is restricted to a small number of teaching hospitals and academic medical institutes. Other therapeutic domains, such as anticancer, antifungal, antibacterial, and antitubercular medications, have shown considerable promise to enhance patient outcomes in Indian settings, aside from immunosuppressive pharmaceuticals. The population of this subcontinent is unique in terms of the importance of TDM due to factors like the higher prevalence of nutritional deficiencies, tropical diseases, the widespread adoption of alternative medicines, unlike pharmacogenomics, and the scarcity of population-specific data on the therapeutic ranges of multiple drugs. TDM has not gotten the interest it merits in India, despite its vast applicability and influence on clinical science. This study aims to present a SWOT (strength, weakness, opportunity, and threats) analysis of TDM in India so that suitable measures for promoting TDM growth can be envisaged. Forming a collaborative group with all the stakeholders—including TDM experts, physicians, and the government—and coming up with a National Action Plan to support TDM are urgent needs. To determine the country's TDM focus areas, nodal TDM facilities should be formed, and pilot programmes should be launched. Capacity development and awareness rising are also important steps towards integrating TDM into traditional clinical practice.

Keywords: Therapeutic drug monitoring, TDM, Therapeutic range, Sampling, Monitoring, adverse effects.

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INTRODUCTION

A branch of clinical pharmacy or clinical pharmacology associated with drug or drug metabolite levels in the blood are therapeutic drug monitoring. The reason for the monitoring is because when the dosage is raised from a low to a high level, the patient may have hazardous symptoms as a result of the high dose. Depending on the patient's health and state of illness, different responses occur to the same dosage [1,2]. The results of the assessment may be either acceptable or unpleasant for the patient, or they could have therapeutic or unbearable consequences [3]. The medication monitoring will let the doctor customise the patient's dose schedule, which is based on the patient's medical history and includes elements like age, food, smoking, and illnesses that affect the kidney, liver, heart, and thyroid gland. Target concentrations will be produced by dose individualization in order to avoid certain medical disorders [4]. For example, the dosage of lithium to prevent manic episodes, the dosage of phenytoin to avoid seizures following neurosurgery or

trauma, and the dosage of cyclosporine to prevent transplant rejection.

There are two main scenarios when drug monitoring is employed. The first is the adoption of preventative measures to ensure that there are no clinical disorders present, such as organ rejection, cardiac arrhythmia, depression or manic episode recurrence, or seizures [5]. The second purpose of amino glycoside antibiotics is to prevent major toxicity, such as nephrotoxicity. There are two guiding concepts for drug monitoring [6]. Most medications used for monitoring have a graduated dosage response relationship, meaning that the drug's therapeutic response does not abruptly shift to the higher limit of its therapeutic range or abruptly switch off from its lower limit or toxic response. In order to assess the medication's plasma $t_{1/2}$ during steady state, the drug is administered at regular intervals in order to maintain a therapeutic level in circulation [7,8]. To acquire the dose regimen modifications, the drug's pharmacokinetic data are obtained. The patient's physiological condition, dietary changes, or the prescription of additional medication that

would affect the dosing regimen might all be contributing factors to an alteration in pharmacokinetic characteristics. The two most important factors for monitoring therapeutic medications are the therapeutic range and the sample time [9].

Interpretations:

A clinical pharmacologist can assist in the interpretation of an outcome and will typically request additional segment and clinical data. Information to keep in mind when applying for an accommodation includes [10,11]:

- Species, age, and orientation
- Justification for accommodation: remedial disappointment versus support versus new definition versus harmfulness
- Seen drug adequacy
- Any additional prescriptions the patient is receiving, including any home-grown or healthy enhancements [12]

- Dosing detailing, portion, and dosing stretch

A few decision-making recipes can be used to alter the measurement in addition to interpreting the results in the context of the provided data [13]. A simple PK recipe can be used to modify patient portions while adhering to the purposeful PDC over the long term. The existence of hepatic or renal sickness, which may modify discharge, treatment disappointment, or medication interactions are among the explanations given for portion changes. A few well-chosen recipes can be used to alter portions in addition to interpreting outcomes in light of the provided data [14]. A simple PK equation may be used to adjust the patient's share by using the purposeful PDC over an extended period of time. Reasons for the portion change include the possibility of a medication interaction, treatment failure, or the existence of a hepatic or renal infection that might affect discharge [15].

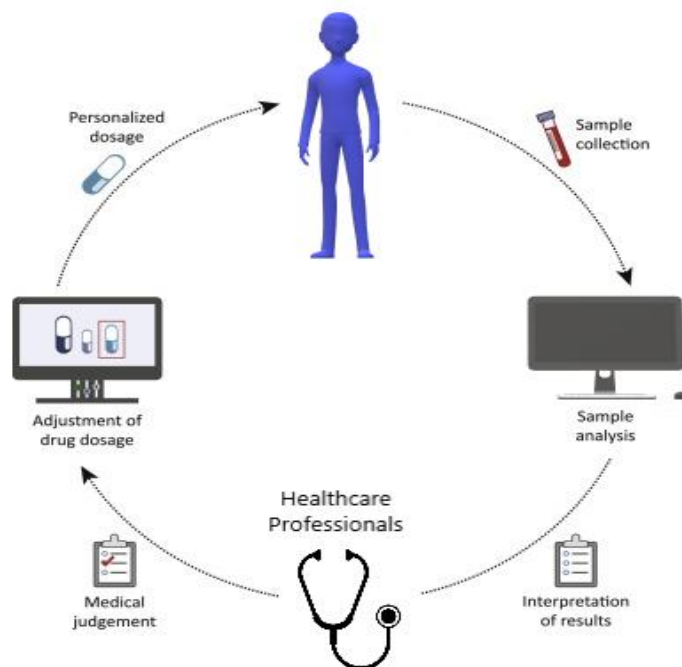


Figure 1: Procedure of Therapeutic drug monitoring

Therapeutic Range:

The blood concentration range that most patients would respond to most successfully and with the fewest adverse effects is known as the therapeutic range. In this range, there are few side effects and a comparatively strong clinical response [16]. The therapeutic range is affected by the degree to which a medication is bound to a protein and in its unbound form, the patient's age, the illness condition, and any drug interactions when the patient is receiving combination therapy, and the sensitivity of the technique used to assess the drug's concentration. In vitro medication combination treatment, such as the infusion of an amino glycoside antibiotic solution with penicillin, can also impact the therapeutic range by causing degradation [17]. Occasionally, the active metabolite of the medication is utilised to evaluate the therapeutic range of the parent drug; for example, n-acetyl procainamide (NAPA) is utilised for

drug concentration measurements rather than procainamide. Digoxin-like immune reactive substance (DLIS), which imitates digoxin in neonates, is produced when digoxin is administered [18-20].

Indications:

The list of benefits of tracking medication usage has grown to include assessing how effectively drugs are functioning, ensuring patients are taking their prescriptions as directed, averting negative drug interactions, and even determining when to stop using them. It is possible to monitor drug concentrations in plasma independently, which is helpful in some circumstances even if not all medications work with all indications [21-23]. On the other hand, measuring plasma levels could be useful. There's been no recent therapy or conformance when performance is low. It is reasonable to assume which a patient is not adhering to their treatment

plan every time their plasma concentration is low even after receiving a dose that could not be expected to produce such a result, or whenever previous readings demonstrate that the plasma concentration ought to have proven greater for the quantity administered [24,25].

That being said, it's plausible that the low concentration isn't being caused by the prescribed dosage [26]. When starting pharmacological therapy, it might be helpful for the physician to keep an eye on the patient's blood concentration of the medication and modify the dosage as necessary. This advice can help all drugs, but the ones with poor therapeutic indices will benefit the most [27]. Examples of therapies that fit within this category are aminoglycosides, lithium, and cyclosporine. Later in the course of treatment, the dosage schedule should be adjusted under any circumstances. Recalculating plasma fixations could prove helpful for those experiencing renal disappointment [28]. If inadequate clinical responses are observed, under treatment of the specified conditions may be assumed.

Even yet, it is absurd to anticipate screening responses in cases when the drug is used as a preventive measure. Similarly, a physician can select measures that yield clear, objective plasma fixations [29]. This adage is especially true with lithium, which prevents extremely stressful attacks, phenytoin, which prevents seizures following neurosurgery or injury, and cyclosporine, which prevents unit discharge. However, early on in a patient's course of therapy, plasma fixation predictions help physicians avoid potentially hazardous plasmafocuses [30]. It is frequently possible to analyse drug poisoning clinically. Intense phenytoin poisoning, for example, is quite easy to identify, and plasma focus estimation may not be essential for diagnosis but rather useful for portion modification down the road [31].

May reflect particular adverse consequences of heart disease, and measuring plasma concentrations can help confirm the conclusion, if poisoning is taken into consideration. Through the estimation of plasma digoxin foci in 260 patients receiving C, beta-methyl digoxin, we were able to screen for certain outcomes that were not in any way apparent. In particular, the technique's use in determining the harmfulness of digitalis is limited by the key cross-over between "poisonous" and "non-harmful" plasma fixation levels. However, in individuals receiving treatment for digitalis whose harmfulness is associated with levels of digitalis plasma less than 2.0 ng/mL, this approach can identify digitalis defenselessness [32]. According to Aronson and Hardman, portion selection based on the evaluation of the drug's plasma focus reduced the toxicity of digitalis to less than 4% of its original level. This method isn't widely used just yet. Thus, the elderly, patients with severe atrial fibrillation who need large doses of digitalis to regulate pulse, and patients receiving digitalis therapy with renal impairment should all undergo continuous assessment of their plasma fixations. It should be noted that an assessment is necessary [33].

Sampling Time:

Early sample collection following the start of medication therapy can provide information on the patient's unique pharmacokinetic characteristics. The dose regimen can be adjusted and specified to yield the patient-specific

pharmacokinetic characteristics. By connecting the serum level to a desired concentration range, the steady state values may be determined [34].

Factors affecting the timing of sample:

- i. Missing data on medication status and clearance occurs if the sampling is done too soon after the dosage.
- ii. Organ harm may result from delaying medication sampling for potentially dangerous substances until steady state is reached. For example, gentamicin is used to treat clinical disorders including ascites and edoema. Over 90% of the plasma is present at steady condition [35]. After two half lives, the next dosage is halved and sampling is done. The next dose is halved and sampling is done after two half lives if the desired concentration is not reached with this dosage.
- iii. Distribution kinetics
 - a) Sampling is done two hours after the oral dose if the medication is absorbed orally during the first two hours following dosage. Absorption is impacted by the patient's posture, food consumption, and physical condition at the time of sample.
 - b) Sampling is carried out two hours after the oral dosage if the medication is quickly dispersed, such as gentamicin or kanamycin. Lithium is sampled right before the last dosage and digoxin is sampled six hours after the treatment if the medication distribution is sluggish [36].
- iv. The sample time in this scenario will be at two half-lives if the medication is administered at a constant maintenance dose without a loading dose and the dosing is done on a regular basis [37].
- v. The dose of medications having shorter half-lives than the dosing interval, such gentamycin, is assessed using the Peak and Trough level instead of the dosing interval.

Characteristic of Therapeutic Drugs Applicable For Monitoring:

- i. The observational clinical scenario, or the medication's end point, serves as the basis for monitoring therapeutic medications. The outcome might be intermiate, poisonous, or therapeutic, for example. Prothrombin time is an intermediate end objective, whereas renal failure and arrhythmia are toxic end points. The prevention of stroke, pulmonary embolism, and seizure episodes are therapeutic end points [38]. A feasible intermediate end goal may be employed in the absence of readily visible hazardous or therapeutic end points. Higher dosages of digoxin are needed to return the heart rate to normal in individuals on digoxin treatment, elderly patients, patients with fast atrial fibrillation, and patients with borderline renal function.
- ii. The monitoring is done using medications with a limited therapeutic range. There is a therapeutic index for these medications will be 2-3 the therapeutic index. It is the therapeutic range's top-to-bottom ratio of serum concentration [39].
- iii. Substances with an erratic PK/PD relationship: A medication dosage that causes a subtherapeutic response in a single individual may have a toxic impact in a

different patient. The PD indices, which show the link between dosage and plasma or blood drug concentration and pharmacodynamic effects, include plasma lipid level, blood glucose, blood pressure, and plasma clotting time. Additionally, there is significant inter-patient heterogeneity in PK characteristics, including distribution, metabolism, excretion, and absorption [40]. Most medications have different PKs and PDs in adults and children. There is a restricted sampling volume in children. As a result, extremely sensitive analytical techniques are needed for measuring the drug sample.

- iv. The therapeutic medication being monitored may be hazardous or ineffective, putting the patient at serious danger.
- v. The drug's effects, whether acute, brief-term, or intermittent, are not accurately controlled by the drug's plasma concentration. Sometimes a drug's pharmacological effects last longer than expected.
- vi. There is a larger correlation between the therapeutic effect and the drug's plasma concentration than there is between the drug's given dose and the therapeutic impact.
- vii. Drug plasma concentration measurements have to be taken at regular intervals and at the proper times. Measurements made at erroneous intervals will be considered technique abuse [41].
- viii. Drug monitoring is incomplete without the use of precise, sensitive, sensitive, and accurate assay techniques for measuring drug concentration in biological fluids.

Methods Used For Monitoring Of Therapeutic Drugs

The tools for testing therapeutic monitoring, the credentials of the laboratory and clinical personnel, the administrative structure, and the supervisor are the structural elements of monitoring. Appropriate serum drug level indications, sample collection timing, results communication to the clinician, and monitoring for a suitable clinician response to treatment recommendations, patient response to treatment, and the output are all examples of the process component of the monitoring measurements. Assessment of drug-induced adverse effects, cure rates, death rates, and cost savings related to monitoring are some examples of measuring components [42]. Although whole blood is utilised for medications like cyclosporine, where there is a significant drug shift among red blood cells and plasma due to temperature changes and storage, plasma or serum samples are often used.

Three distinct markers are employed in drug surveillance:

- a. Tracking the clinical outcomes, such as blood sugar decrease, migraine prevention, and inflammation reduction.
- b. The observation of biochemical effects that occur before physiologic impacts, such as insulin's control of glucose. a reduction in CRP (c-reactive protein) levels preceded by an anti-inflammatory action [43].
- c. Measurements of plasma drug concentration and their relationship to biological therapeutic effects. Digoxin causes cardiac arrhythmia, whereas phenytoin causes seizures.

Analytical methods for monitoring of therapeutic drugs Fluorometry and Spectrophotometry:

These techniques have a sensitivity level in the region of $\mu\text{g/ml}$. Thin layer chromatography is a technique for drug identification and quantification. It is less sensitive and takes more time, though [44].

HPLC with GLS: This approach has exceptional specificity, precision, and sensitivity. Nevertheless, after time, column degradation and extraction are needed. GLC is not as favoured as HPLC.

Radioimmunoassay (RIA): This technique needs radio nucleotides but is very sensitive and accurate. Unlike RIA, enzyme-linked immunoabsorbant assays (ELISA) do not require radioactive trace [45].

Fluorescence polarisation immunoassay (FPIA): FPIA provides a direct assessment without the need for separation by combining fluorescence polarisation with competitive protein binding.

Dose Adjustment Due To Unpredictable Drug Serum Concentration

Changes in protein binding in patients with hepatic and renal diseases, noncompliance, inappropriate dosing, malabsorption, insufficient bioavailability, and multidrug regimens are the reasons behind variations in serum concentration. Pharmacokinetic medicines can be used to obtain the newly adjusted dosage.

Adjusted new dose = Usual dose X desired drug concentration/ usual dose concentration

Quality Assurance, Criteria of Evaluation and Compliance of Drug Monitoring

Assurance of quality

Precise scheduling, blood sample collection, medication concentration reporting, measurement consultation with senior team members, and patient compliance are all necessary for ensuring the quality of drug monitoring [46].

Evaluation standards

The appropriateness of carrying out concentration measurements, the completeness and accuracy of the data that is provided, the suitability of the action taken in response to the results, improvements in scheduling, drawing, and reporting, and the the suitability of the documentation—which involves the measurement of plasma drug concentration, the times at which blood samples were taken and the final dosage was given—are the evaluation criteria for drug monitoring [47].

Factors influencing compliance

- i. Variations in plasma concentration under illness circumstances are one of the factors impacting medication monitoring compliance.
- ii. Using plasma concentration to predict overdose and underdose. For instance, low dosage, weakened small bowel function, and limited medication clearance: While hepatic insufficiency does not impact clearance, renal failure does.

- iii. Greater tissue binding, such as that of chloroquine, will raise the volume of distribution (Vd) by lowering the plasma concentration.
- iv. Digoxin cannot penetrate adipose tissue in obese people, resulting in a drop in Vd.

PRIORI AND POST-PRIORI MONITORING

The first dosing regimen is chosen based on the clinical objective through priori monitoring. The PK/PD relationship data can be used to determine patient subpopulations with varying dose needs. Pre-, analytical, and post-analytical phase data are produced in post-priori monitoring. The identification of the active and/or dangerous forms of pharmaceuticals in biological samples that are gathered at the proper time is done by specialised, accurate, exact, and timely PK monitoring in post-priori TDM. The assessment of biological indicators, such as the plasma concentration of endogenous chemicals, enzyme activity, and gene expression, serves as a surrogate or end point marker impact in post priori TDM PD monitoring [48].

Limitation of Drug Monitoring

- i. The cost of equipment, supplies, technical expertise, biological fluid concentration, data gathering investment, and interpretation for therapeutic drug monitoring is high.
- ii. The monitoring only benefits medications with a wide therapeutic range.
- iii. Information on the population of men with CHF fewer than 50 years old who have normal renal cardiac function is accessible. For female patients with CHF who are older than 70, the values differ and cannot be understood based on the information that is currently available on normal levels.
- iv. Blood pressure and blood coagulation readings are more reliable indicators of a drug's effectiveness than serum concentration levels for some medications.
- v. Drugs having a wide therapeutic range do not need serum concentration data.

PHARMACOECONOMIC EFFECTS OF TDM

Nowadays, pharmacoeconomics is being used in a wide range of fields, including TDM. This is happening as public and medical professionals alike grow increasingly worried about the soaring costs of healthcare and the preparedness that TDM has been shown to produce. Therapeutic drug management, or TDM, is a type of medication designed to lessen the side effects of potentially dangerous drugs while boosting the benefits of life-sustaining drugs. It's likely that the costs incurred by using TDM methods will be covered by advantages like lower hospitalisation rates. TDM therefore serves as a useful technique for calculating the overall cost of treatment.

Donabedian suggests assessing the effectiveness of different medical therapies using the design interaction outcome approach. Structures, equipment, staff, and a variety of affected persons are all things he takes into account while assessing the form figure for this method. The priorities in health care transportation administrations are examined in the first section, and the effects of health care mediation on

affected individuals' outcomes and the financial case for healthcare are examined in the second [49]. When adding TDM to Donabedian's analysis, it's important to take into account the following factors: the existence of a TDM administration, observing management, and regulatory association; the staff's level of expertise at logical and research centres; and the existence of a TDM evaluating offices and staff.

The techniques included in the framework include talking to the doctor about any adverse effects, doing blood draws at the best times, reviewing how the drug is acting, and monitoring the patient's reaction to recommended treatments. To sum up, outcome metrics such as the number of side effects brought on by the medication, the rate of cure, the rate of death, and the cost of providing TDM will be used to assess the viability of TDM. A pharmacoeconomic evaluation found that cycle TDM patients with generalised tonic-clonic epilepsy had significantly better seizure control, fewer catastrophic events, higher salary limits, decreased patient charges, fewer hospitalisations per seizure, and greater potential reduction outcomes.

TDM seems to be especially beneficial for people on digoxin or theophylline, and this study supports the results of a meta-analysis of research. Similar studies found that the percentage of patients with clinically relevant blood concentrations rose dramatically when a clinical pharmacokinetic supplier was added to an analytical drug specialist. TDM may be used to reduce the toxicity of aminoglycosides, which B shows is an essential step in extending the usable life of these medications. placing greater focus on the most inhibiting component and less attention on the least inhibiting component. In several patient-centered TDM studies, it was determined that component individualization was too far along.

Research indicates that vancomycin is far less harmful to the kidneys than aminoglycosides. Serum fixation does, however, seem to be connected to both viability and toxicity. Contrary to popular assumption, vancomycin is equally as toxic to the kidneys as aminoglycosides. The pharmacokinetic variability associated with the use of any of the immunosuppressants now on the market is rather high, both across and within persons [50].

SWOT Analysis of Therapeutic drug monitoring in India [51]

Strengths (S):

- **Clinical Utility:**
TDM helps medical practitioners optimise medication doses and enhance treatment results by providing important information about drug concentrations in a patient's bloodstream.
- **Differential Healthcare environments:**
TDM is flexible enough to be used in a variety of healthcare environments, such as clinics, hospitals, and labs.
- **Expanding Pharmaceutical Sector:**
TDM is important for tracking pharmaceuticals with limited therapeutic indices since the pharmaceutical

sector in India is expanding and making a wide range of treatments accessible.

- **Competent Healthcare Workers:**
India boasts a number of proficient healthcare workers who are able to decipher TDM data and make well-informed choices regarding medication dose modifications.

Weaknesses (W):

- **Restricted Access in Rural locations:**
Inadequate infrastructure, a dearth of specialised laboratories, and a paucity of skilled staff may all contribute to limited access to TDM services in rural locations.
- **Cost of TDM:**
Patients who may have to pay for TDM may find it to be costly. This cost barrier may prevent TDM from being widely adopted, especially in environments with limited resources.
- **Healthcare Professionals' Awareness:**
It's possible that some medical practitioners are unaware of the advantages of TDM and how to incorporate it into standard clinical practice.

Opportunities (O):

- **Technological Developments:**
TDM can become more accessible and economical by improving its accuracy and efficiency via the use of automation and analytical technology.
- **Connectivity with Electronic Health Records (EHRs):**
By combining TDM data with EHRs, procedures may be streamlined, data accessibility is increased, and improved decision-making is made easier.
- **Research Collaboration:**
Research on TDM may be pushed by cooperation between academic institutions, pharmaceutical corporations, and healthcare providers. This can result in the creation of best practices and recommendations that are specifically suited to the Indian population.
- **Government Support:**
TDM deployment may be made more widely accepted and integrated into standard clinical treatment by government initiatives and policies.

Threats (T):

- **Regulatory Obstacles:**
Developments in TDM-related technologies and assays may be hampered by regulatory obstacles and delays in the approval process.
- **Healthcare Priorities in Competition:**
Competing healthcare goals may draw focus and resources away from TDM deployment in a setting where resources are limited.
- **Opposition to Change:**
TDM's incorporation into standard clinical treatment may be hampered by healthcare practitioners' and institutions' resistance to implementing new procedures.
- **Data Privacy Issues:**

The incorporation of TDM information into electronic health records may raise privacy and security concerns that might hinder the general acceptance of the practice.

CONCLUSION

Using TDM necessitates a sophisticated approach that combines pharmacokinetic, pharmacodynamic, and pharmacological techniques and analysis. A thorough evaluation of the subject's blood and target region is necessary for the successful use of TDM. Rather, TDM is essential to the development of effective and safe therapies as well as the personalisation of these medications. Furthermore, TDM assists in determining corrective compliance concerns when dealing with non-compliant data subjects. The patient's reaction, the intended medical goals, the dosage history, the sample time and dose, and other factors are taken into account while interpreting the medication adherence index. With the use of these facts, the best dose schedules may be chosen to produce excellent results with the least amount of harm.

In conclusion, TDM in India has a lot of promise to improve medication therapy; nevertheless, there are some issues that must be resolved, such as restricted access in rural regions, financial constraints, and the requirement for more public knowledge. TDM's place in the Indian healthcare system may be strengthened by taking use of possibilities including government sponsorship, research cooperation, and technical advancements to help overcome these obstacles. Sustaining TDM practices in India and ensuring their successful adoption would need ongoing efforts to address vulnerabilities and challenges.

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