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Review Article

LC–MS/MS in Therapeutic Drug Monitoring (TDM): Advances and Clinical Applications

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ABSTRACT

Therapeutic Drug Monitoring (TDM) is a cornerstone of individualized pharmacotherapy, aiming to optimize drug efficacy while minimizing toxicity through precise measurement of drug concentrations in biological matrices. Over the past two decades, liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) has emerged as the gold-standard analytical platform for TDM, superseding conventional immunoassays by virtue of its superior sensitivity, specificity, and multiplexing capabilities. This review article comprehensively examines the fundamental principles of LC–MS/MS as applied to TDM, recent technological advances including microsampling strategies, automation, and high-resolution mass spectrometry, as well as the growing body of clinical evidence supporting its implementation across key drug classes—immunosuppressants, antimicrobials, antiepileptics, psychotropic agents, and targeted anticancer drugs. Current challenges, regulatory considerations, and future prospects in the integration of LC–MS/MS with pharmacokinetic modelling and artificial intelligence are also discussed.

INTRODUCTION

The concept of Therapeutic Drug Monitoring (TDM) revolves around the measurement of drug concentrations in biological fluids—most commonly whole blood, plasma, or serum—combined with dose individualization based on pharmacokinetic (PK) and pharmacodynamic (PD) principles. The overarching goal of TDM is to maintain drug exposure within a pre-defined "therapeutic window," i.e., the concentration range associated with maximum clinical benefit and minimum risk of adverse effects. TDM is particularly critical for drugs characterized by: (i) a narrow therapeutic index; (ii) high inter- and intra-individual pharmacokinetic variability; (iii) concentration-dependent toxicity; and (iv) situations where clinical endpoints of efficacy or

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toxicity are difficult to assess directly. [1] The drug classes most extensively subjected to TDM include aminoglycoside antibiotics, antiepileptics, mood stabilizers, antipsychotics, cardiac glycosides, and immunosuppressants. [2] Historically, immunoassay techniques—including enzyme multiplied immunoassay technique (EMIT), fluorescence polarization immunoassay (FPIA), and chemiluminescent microparticle immunoassay (CMIA)—dominated clinical TDM laboratories due to their speed, ease of use, and amenability to automation. However, these methods suffer from significant cross-reactivity with drug metabolites and structurally related compounds, often leading to overestimation of drug concentrations. [3] Over the past two decades, liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) has progressively emerged as the reference analytical technology for TDM in clinical and research laboratories. LC–MS/MS offers unparalleled selectivity and sensitivity, the ability to simultaneously quantify parent drugs and their metabolites, and freedom from cross-reactivity limitations inherent to immunoassays. [1,4] Furthermore, advances in mass spectrometer design, chromatographic column technology, automation, and micro sampling have considerably reduced the complexity and cost burden associated with LC–MS/MS, accelerating its adoption in routine clinical settings. [5,6] This review aims to (1) describe the fundamental principles of LC–MS/MS relevant to TDM; (2) highlight recent methodological and technological advances; (3) survey clinical applications across major drug categories; (4) address current challenges; and (5) project future directions, with particular emphasis on integration with pharmacometrics and digital health technologies.

Fundamental Principles Of Lc–Ms/Ms In Tdm

Instrumentation Overview

An LC–MS/MS system consists of three core modules: (i) a liquid chromatography unit for analyte separation; (ii) an ionization source for generating gas-phase ions; and (iii) a tandem mass spectrometer for ion selection, fragmentation, and detection. The most widely used mass analyzer configuration for TDM is the triple quadrupole (QqQ), which operates in multiple reaction monitoring (MRM) mode—selecting a precursor ion in Q1, fragmenting it in Q2 (the collision cell), and detecting one or more characteristic product ions in Q3. [4] This targeted approach confers extraordinary selectivity and sensitivity, typically achieving lower limits of quantification (LLOQ) in the low ng/mL to pg/mL range. [5]

Chromatographic Separation

Reversed-phase chromatography using C18 or C8 bonded silica columns is the most commonly employed separation mode for small-molecule drug analytes in TDM. Ultra-high performance liquid chromatography (UHPLC) systems operating at pressures up to 1000–1200 bar with sub-2-µm particle columns have shortened run times to under 5–10 minutes while maintaining resolution. Column dimensions of 50–150 mm × 2.1 mm with 1.7–1.8 µm particles are standard in modern TDM workflows. [1,6]

Ionization Sources

Electrospray ionization (ESI) is the dominant ionization mode for TDM applications owing to its compatibility with a wide range of polar and semi-polar drug molecules and LC mobile phases. Atmospheric pressure chemical ionization (APCI) is employed for less polar compounds, and atmospheric pressure photoionization (APPI) finds niche applications for compounds with aromatic chromophores or for lipophilic drugs like

cannabinoids. Heated ESI (H-ESI) or turbospray variants further enhance sensitivity at higher flow rates commonly used in clinical laboratory workflows.

Materials And Methods

Sample Preparation

Because biological matrices (blood, plasma, urine, saliva) contain complex mixtures of proteins, lipids, salts, and endogenous metabolites, sample preparation is a critical determinant of method performance in TDM. The three principal strategies are:

1. **Protein precipitation (PPT):** The simplest and fastest technique, using organic solvents (acetonitrile, methanol) or acids (trichloroacetic acid, perchloric acid) to denature and precipitate plasma proteins. Though rapid and suitable for automation, PPT may leave residual phospholipids that can cause matrix effects. [7]

2. **Liquid–liquid extraction (LLE):** Partition of analytes between an aqueous biological matrix and an immiscible organic solvent. Provides cleaner extracts with lower matrix effects compared to PPT, but requires careful solvent selection and optimization.

3. **Solid-phase extraction (SPE):** Analyte retention on a sorbent bed (C18, mixed-mode, ion exchange) followed by selective elution offers the highest level of sample clean-up, reduced matrix effects, and potential for analyte enrichment. Phospholipid removal (PLR) plates represent a hybrid PPT–SPE approach gaining popularity in high-throughput TDM laboratories. [8]

Internal Standards

Stable isotope-labelled (SIL) internal standards (ISs) are universally regarded as the gold standard for LC–MS/MS quantification in biological matrices. Deuterium- or $^{13}C/^{15}N$-labelled analogues of the target drug compensate for matrix effects, extraction variability, and ionisation fluctuations, thereby ensuring high assay accuracy and precision across patient sample batches. [1,4]

Matrix Effects And Method Validation

Matrix effects (ME), predominantly ion suppression or enhancement in the ESI source caused by co-eluting phospholipids and other endogenous components, remain the foremost analytical challenge in LC–MS/MS-based TDM. Regulatory guidelines from the US FDA and EMA mandate systematic assessment of ME during method validation, with acceptance criteria of ±15% for matrix factor variability. [9] Method validation parameters including linearity, selectivity, accuracy, precision (intra- and inter-assay), carry-over, dilution integrity, and stability (freeze-thaw, bench-top, long-term) must be rigorously documented in compliance with the EMA Guideline on Bioanalytical Method Validation (2011, revised 2024) and FDA BMV guidelines.

Recent Technological Advances

Microsampling Technologies

Dried Blood Spot (DBS) sampling—whereby a small volume (typically 10–30 µL) of capillary blood is deposited onto a filter paper card and dried—has attracted considerable attention as a minimally invasive, patient-centric alternative to conventional venepuncture for TDM. DBS samples are stable at ambient temperature, reducing cold-chain logistics, and can be collected by patients at home, facilitating remote monitoring. [10,11] A key limitation of traditional

DBS is the hematocrit (HCT) effect, which influences spot area and analyte concentration. Volumetric absorptive micro sampling (VAMS) devices (e.g., Mitra™, Capitainer®) absorb a fixed, precisely defined volume of blood (typically 10 µL) irrespective of HCT, substantially mitigating this error. A 2025 study validated VAMS and quantitative DBS (qDBS) LC–MS/MS methods for everolimus TDM in 33 solid organ transplant recipients, demonstrating excellent agreement with venous whole blood reference measurements. [12] Dried plasma spot (DPS) and volumetric absorptive microsampling combined with LC–MS/MS have also been applied successfully for antifungal TDM in paediatric patients, where minimally invasive sampling is of particular ethical importance. [13] Furthermore, DBS LC–MS/MS methods have been validated for CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) and PARP inhibitors (olaparib, rucaparib, niraparib) in oncology TDM, with samples collected by patients at home and mailed to centralised laboratories. [14,15]

Automation And High-Throughput Workflows

The historically greater complexity of LC–MS/MS relative to immunoassay has been addressed by automation. Fully automated sample preparation modules directly coupled to LC–MS/MS (e.g., the CLAM system, Shimadzu) allow complete sample work-up including pipetting, protein precipitation, and injection without manual intervention. A prospective clinical validation of CLAM-LC–MS/MS for tacrolimus and cyclosporin A monitoring demonstrated high correlation with commercial immunoassays, lower inter-assay precision values, reduced pre-treatment time, and avoidance of cross-reactive interference. [16] Robotic liquid handlers operating in 96-well plate format, online SPE integrated with LC–MS/MS, and multiplexed MRM acquisition have collectively transformed TDM throughput. A fully automated method for simultaneous quantification of clozapine, mycophenolic acid, sunitinib, N-desethylsunitinib, and voriconazole using an automated pretreatment LC–MS/MS system has been described for routine clinical use. [17]

Multiplex Analysis

One of the most clinically transformative advantages of LC–MS/MS over immunoassay is the ability to quantify 10–20 analytes simultaneously in a single analytical run without the need for separate assay kits. A 2023 multiplex LC–MS/MS platform from Zhongnan Hospital of Wuhan University simultaneously quantified 14 antibacterial and antifungal agents—including beta-lactams, beta-lactamase inhibitors, vancomycin, linezolid, tigecycline, daptomycin, and azole/echinocandin antifungals—in plasma of ICU patients, with the entire workflow completed in under 10 minutes. [18] Similarly, an LC–MS/MS method for simultaneous quantification of ten antimicrobials in human plasma was validated for routine TDM in critically ill patients. [19] A method simultaneously analyzing five major immunosuppressants (tacrolimus, cyclosporin A, everolimus, sirolimus, and mycophenolic acid) in only 2.8 µL of whole blood, compatible with various microsampling devices, has been developed to streamline post-transplant TDM workflows and support precision medicine in telemedicine applications. [20]

High-Resolution Mass Spectrometry (Hrms)

While triple-quadrupole instruments dominate routine TDM practice, high-resolution mass spectrometry (HRMS) platforms—including Orbitrap and time-of-flight (TOF) analysers—are increasingly applied in research-oriented TDM and pharmacometabolomic studies. HRMS allows retrospective data mining for unexpected

metabolites or co-administered drugs, acquisition of accurate mass data for structural elucidation, and untargeted pharmacovigilance surveillance. Emerging data-independent acquisition (DIA) approaches on HRMS instruments may eventually enable comprehensive, simultaneous monitoring of multiple drug classes without pre-specified MRM transitions, offering a paradigm shift in clinical TDM laboratory practice.

Clinical Applications

Immunosuppressive Drugs In Organ Transplantation

With over 100,000 solid organ transplants performed worldwide annually, TDM of immunosuppressive drugs (ISDs) is arguably the most established and high-volume clinical application of LC–MS/MS in any hospital pharmacy laboratory. [2,21] The five most commonly monitored ISDs are cyclosporin A (CsA), tacrolimus (Tac), sirolimus (Sir), everolimus (Eve), and mycophenolic acid (MPA). All exhibit narrow therapeutic windows, high inter-individual PK variability driven by CYP3A4/3A5 and P-glycoprotein polymorphisms, and severe concentration-dependent toxicity (nephrotoxicity, neurotoxicity, infections). [3,22] Immunoassays systematically overestimate CsA and Tac concentrations due to cross-reactivity with metabolites; LC–MS/MS, by contrast, measures parent drug exclusively with typical inaccuracy and imprecision of <10% CV. Reference LC–MS/MS methods for all five ISDs are now well-established and internationally proficiency-tested through schemes such as those coordinated by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT). The development of simultaneous multiplex LC–MS/MS methods for all major ISDs from microvolume samples represents the current frontier, enabling home-based remote TDM for transplant outpatients.

Antimicrobial Agents

TDM of antimicrobials—particularly beta-lactams, glycopeptides (vancomycin), aminoglycosides, and azole antifungals—has grown substantially in the context of antimicrobial stewardship and the global antimicrobial resistance crisis. In critically ill ICU patients, pathophysiological alterations (augmented renal clearance, hypoalbuminaemia, volume redistribution) dramatically alter PK, rendering fixed standard dosing regimens inadequate. Empirically prescribed regimens may result in sub-therapeutic or supra-therapeutic exposure, perpetuating poor clinical outcomes and resistance selection. [18,23] Vancomycin TDM has traditionally been based on trough concentrations, but contemporary guidelines from ASHP, IDSA, and SIDP (2020 onwards) advocate AUC-guided dosing using Bayesian estimation tools, necessitating two-sample PK strategies that require precise, timely measurement methods. [24] LC–MS/MS offers critical advantages over immunoassays in this setting: absence of cross-reactivity with vancomycin crystalline degradation products (VCDPs), simultaneous quantification with concomitant antibiotics, and suitability for low-volume paediatric samples. [18] For azole antifungals (voriconazole, posaconazole, itraconazole, isavuconazole), significant PK variability linked to CYP2C19 and CYP3A4 polymorphisms mandates individualized dosing guided by TDM, for which LC–MS/MS multiplex methods are the method of choice, enabling simultaneous monitoring in patients receiving prophylactic or therapeutic antifungal combinations. [25] An LC–MS/MS method for omadacycline—a novel aminomethylcycline antibiotic—quantification in human plasma,

developed and validated in accordance with FDA and EMA guidelines, has been applied to population PK modelling in Chinese patients, informing dosing optimization. [26]

Antiepileptic Drugs

TDM of antiepileptic drugs (AEDs) has an established history spanning more than 50 years. The 2018 IATDMCT consensus guidelines updated target reference ranges for both established (phenytoin, carbamazepine, valproic acid, lamotrigine, levetiracetam) and newer-generation AEDs (lacosamide, brivaracetam, perampanel). [27] LC–MS/MS is now preferred over immunoassay for simultaneous monitoring of multiple AEDs, enabling detection of polytherapy regimens without separate assay protocols. [5] Particular clinical utility exists in paediatric epilepsy (where weight-based dosing and developmental PK changes require frequent adjustments), pregnancy (where AED clearance increases significantly in the second and third trimesters), and the elderly (with altered protein binding and renal clearance). In all these populations, the ability of LC–MS/MS to measure both total and free (unbound) AED concentrations from the same sample run—by analysing ultrafiltrate alongside whole plasma—provides clinically actionable information unavailable from immunoassays.

Psychotropic Drugs

Antipsychotic and antidepressant TDM is recommended by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) consensus guidelines for optimizing treatment of psychiatric disorders. LC–MS/MS has demonstrated superiority over immunoassay for clozapine monitoring, a drug whose active metabolite norclozapine exerts both therapeutic and toxic effects and cannot be differentiated from the parent compound by immunoassay. [28] Simultaneous multiplex LC–MS/MS panels covering 20–30 psychotropic drugs and metabolites in a single analytical run have been validated for clinical application, enabling comprehensive TDM in patients receiving polypharmacy regimens—a common situation in psychiatric practice. The CYP2D6 genotype–phenotype relationship for paroxetine dose adjustment, integrating LC–MS/MS TDM data with pharmacogenomics, exemplifies the evolving synergy between precision analytics and genomic medicine.

Targeted Anticancer Therapies

TDM of cytotoxic chemotherapy has historically been limited by practical challenges (short elimination half-lives, requirement for multiple sampling timepoints). However, the advent of orally administered targeted therapies—tyrosine kinase inhibitors (TKIs), CDK4/6 inhibitors, mTOR inhibitors, and PARP inhibitors—has created a new paradigm for TDM in oncology. [29] These agents are dosed chronically, exhibit high inter-patient PK variability (up to 10-fold), and have defined exposure–response relationships supporting dose individualization. [30] A 2024 bibliometric analysis covering 1990–2024 confirmed that TKIs (imatinib, dasatinib, sunitinib) and detection methods including LC–MS/MS and mass spectrometry dominate current TDM research in oncology, underscoring the clinical importance of TDM for agents with high interpatient variability used in chronic settings where sustained drug exposure is critical to prevent resistance. [31] A comprehensive review of LC–MS/MS methods for cytotoxic anticancer drugs—retaining 90 analytical methods from 88 articles—highlighted critical remaining barriers: limited reference range consensus, absence of

decision algorithms integrating PK data into dose modification protocols, and inadequate pharmacist/oncologist awareness of TDM utility. [32] An advanced automated monolithic C18 pipette-tip SPE method coupled with LC–MS/MS for simultaneous quantification of eleven TKIs in biological samples has been described, representing a significant step toward high-throughput oncology TDM workflows compatible with real-world clinical laboratory volumes. [33]

Antituberculosis Drugs

Tuberculosis (TB) remains a leading global infectious cause of mortality. LC–MS-based TDM and pharmacometabolomics for anti-TB precision dosing have been advocated as essential tools for managing multidrug-resistant TB (MDR-TB) and drug-susceptible TB in resource-limited settings. [34] Simultaneous quantification of first-line agents (isoniazid, rifampicin, pyrazinamide, ethambutol) by LC–MS/MS in human plasma enables identification of patients with subtherapeutic exposures who are at risk of treatment failure and resistance emergence.

Summary Of Key Clinical Applications

Table 1. Summary of key LC–MS/MS clinical TDM applications by drug class.

Drug Class	Key Agents	Clinical Indication	LC–MS/MS Advantage
Immunosuppressants	Tacrolimus, CsA, Sir, Eve, MPA	Solid organ transplantation	No metabolite cross-reactivity; multiplex analysis; microsampling compatibility
Antimicrobials	Vancomycin, beta-lactams, azoles, linezolid	Sepsis, ICU, immunocompromised patients	Multiplex 10–14 agents; rapid turnaround; AUC-guided dosing support
Antiepileptics	Phenytoin, levetiracetam, lamotrigine, lacosamide	Epilepsy; pregnancy; paediatrics	Simultaneous polytherapy monitoring; free drug measurement
Psychotropics	Clozapine, risperidone, lithium, antidepressants	Schizophrenia; bipolar disorder; depression	Metabolite discrimination; broad polypharmacy panels
Oncology TKIs/targeted agents	Imatinib, sunitinib, palbociclib, olaparib	Chronic oncology; resistance prevention	DBS home sampling; multiplex TKI panels; PK/PD modelling integration
Anti-TB drugs	Isoniazid, rifampicin, pyrazinamide, ethambutol	Drug-sensitive and MDR-TB	Simultaneous first-line drug monitoring; identification of sub-therapeutic exposure

Challenges And Limitations

Standardization And Harmonization

Despite its analytical superiority, LC–MS/MS-based TDM suffers from a lack of standardization across laboratories. There are no universally certified reference materials for most TDM drugs, contributing to between-laboratory variability in reported concentrations. External quality assurance (EQA) schemes organized by IATDMCT and regional proficiency testing programs are essential, but participation remains uneven globally. [35]

Regulatory And Accreditation Requirements

Clinical TDM laboratories must comply with regulatory frameworks including ISO 15189 (medical laboratories) and in many jurisdictions, clinical laboratory improvement amendments (CLIA) or equivalent national standards. Full bioanalytical method validation per FDA/EMA guidelines is required before clinical implementation, representing a significant investment of time and resources compared to the simpler validation requirements for immunoassays.

Cost And Infrastructure

LC–MS/MS instruments are significantly more expensive to procure and maintain than immunoassay analysers, and require specialist expertise in mass spectrometry, chromatography, and method development. This creates significant access inequities, particularly in low- and middle-income countries (LMICs) where TDM needs are often greatest (e.g., for anti-TB, antiretroviral, and antimalarial drugs). Miniaturized, field-deployable MS technologies under development may eventually address this gap.

Turnaround Time

The complexity of sample preparation and the non-automated nature of traditional LC–MS/MS workflows results in turnaround times (TAT) of several hours to days in many clinical settings, limiting their utility for time-critical TDM decisions (e.g., aminoglycosides in acute sepsis). Automated pre-treatment systems, microwave-assisted extraction, and rapid online SPE–LC–MS/MS configurations are actively being developed to bridge this TAT gap with immunoassay methods.

Future Directions

Integration With Pharmacokinetic Modelling And Bayesian Forecasting

The true clinical value of LC–MS/MS-generated drug concentration data is fully realized only when integrated with population PK models and Bayesian dosing optimization tools. Software platforms such as InsightRX, DoseMeRx, and MWPharm++ ingest LC–MS/MS trough or AUC-derived concentrations to generate individualized dose recommendations. For vancomycin, this Bayesian AUC-guided approach is now recommended over trough-only monitoring in major infectious disease guidelines. [24]

Pharmacogenomics Integration

The convergence of LC–MS/MS-based TDM with pharmacogenomic data (e.g., CYP3A5 genotype for tacrolimus; CYP2C19 for voriconazole and proton pump inhibitors; CYP2D6 for codeine, antidepressants, antipsychotics) enables a genotype-informed Bayesian dosing strategy. Pre-emptive pharmacogenomic testing combined with real-time LC–MS/MS monitoring represents the pinnacle of precision pharmacotherapy.

Artificial Intelligence And Machine Learning

Machine learning algorithms applied to LC–MS/MS spectral data, patient demographics, co-medication profiles, and clinical outcomes data have the potential to: (i) automate peak integration and quality control review; (ii) predict individual PK parameters from sparse sampling designs; (iii) identify novel predictive biomarkers of drug response or toxicity; and (iv) flag at-risk samples for matrix effects or adulteration. These applications are moving from proof-of-concept to early clinical implementation.

Point-Of-Care Lc–Ms/Ms

Miniaturized mass spectrometers and paper spray ionization (PSI-MS) techniques that can directly analyse DBS samples without chromatographic separation are emerging as potential point-of-care (POC) TDM tools. While not yet achieving the selectivity of full LC–MS/MS for complex multiplexed panels, these technologies may offer rapid (<2 min) single-drug monitoring at the bedside or in community pharmacy settings, particularly for immunosuppressant and antiepileptic TDM.

CONCLUSION

LC–MS/MS has fundamentally transformed TDM from a technique dependent on imprecise, cross-reactive immunoassays to a high-performance, multiplex analytical discipline capable of underpinning the full promise of precision pharmacotherapy. Its superior selectivity, sensitivity, and flexibility in quantifying parent drugs, metabolites, and simultaneous polypharmacy panels have made it indispensable across immunosuppression, antimicrobial, antiepileptic, psychiatric, and oncologic TDM applications. Advances in microsampling, automation, high-resolution mass spectrometry, and integration with pharmacokinetic modelling continue to reduce operational barriers and expand clinical reach. The ongoing convergence of LC–MS/MS with pharmacogenomics, artificial intelligence, and digital health platforms heralds a new era of data-driven, individualized drug therapy—placing LC–MS/MS at the heart of next-generation clinical pharmacology practice.

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