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PREDICTIVE INTELLIGENCE FOR SAFER THERAPIES: A NEW ERA IN DRUG MONITORING WITH AI

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ABSTRACT Therapeutic Drug Monitoring (TDM) plays a critical role in optimizing drug efficacy and safety by maintaining plasma drug concentrations within a targeted therapeutic range. However, traditional TDM approaches are often limited by delayed feedback, interindividual variability, and the complexity of pharmacokinetic and pharmacodynamic interactions. This review examines the growing integration of Artificial Intelligence (AI) in TDM, highlighting how machine learning, deep learning, and data-driven modelling techniques are transforming drug monitoring into a more precise, adaptive, and personalized practice. AI models offer the potential to predict drug concentration-time profiles, automate dose adjustments, and incorporate multifactorial patient data, including genetic, demographic, and clinical variables. The review also examines current advancements, clinical applications, and the challenges surrounding data quality, model interpretability, and regulatory acceptance. Finally, it outlines future perspectives, advocating for AI-enhanced TDM systems that support individualized therapy and real-time clinical decision-making in diverse healthcare settings.

KEYWORDS : Therapeutic drug monitoring, Artificial intelligence, Drug dosing, Dose adjustment

INTRODUCTION

Therapeutic drug monitoring (TDM) uses measured drug concentrations to guide individual dosing decisions. Traditionally, TDM has relied on pharmacokinetic/pharmacodynamic (PK/PD) models and clinician experience to adjust dosing; however, these approaches often assume simplified linear kinetics and average patient variability. Model-informed precision dosing (MIPD) represents a modern expansion of TDM, aiming to tailor doses to each patient's target exposure.[1]

For many drugs, the inter-individual variability is enormous – for example, tacrolimus clearance can differ by an order of magnitude between patients due to genetic and demographic factors. Traditional dosing methods often struggle to capture such complexity. Machine learning algorithms can discover nonlinear relationships between patient covariates and drug kinetics that rule-based or linear models miss.[2]

As AI has advanced and large datasets such as electronic health records, genomics, wearables will be available, data-driven models can learn patterns inaccessible to clinicians. Topol has highlighted that AI is beginning to transform medicine by enabling accurate interpretation of complex data streams.[2,3] In this context, AI methods like expert systems, machine learning and deep learning could be applied to TDM.

This review covers clinical applications of AI in TDM – including antibiotics, immunosuppressants, antiepileptics, and oncology drugs – as well as the AI methodologies used, benefits, challenges, and future directions.

AI Methodologies And Integration With PK/PD

AI encompasses computational techniques supporting or automating the dosing decisions. Expert systems were among the first AI tools in medication management. They encoded the expert knowledge into rule-based programs. For example, Goicoechea et al. (2007) developed an AI-driven TDM system for anti-retroviral drugs (lopinavir/ritonavir, efavirenz) by combining Bayesian pharmacokinetic (PK) models with an expert panel's dosing rule.[4] This system accurately estimated drug levels and provided dose recommendations which agreed well with human specialists. Such rule-based systems laid the groundwork for AI in pharmacotherapy. Indeed, Morrell and Flockhart (1994) described the potential of expert systems in pharmacy practice long ago.[5]

Machine learning (ML) is now the dominant AI approach in TDM. ML algorithms learn patterns from data rather than using explicit rules. Supervised learning models: linear regression, decision trees, support vector machines, and ensemble models can predict continuous outcomes of drug concentrations, required dose, or risk of toxicity. Unsupervised methods like clustering, dimensionality reduction can discover patient subgroups with similar pharmacology, though they are less common in routine TDM.[6] Reinforcement learning (RL) treats dosing as a sequential decision problem: the algorithm learns a dosing policy that maximizes a reward such as keeping drug levels within range through repeated trials, often using simulation. For instance, in chemotherapy scheduling, Deep RL methods have been applied to simulated tumor models, finding dosing schedules that matched or exceeded the effectiveness of standard regimens.[6,7]

Deep learning (DL), a subset of ML, uses neural networks with many layers. DL models can handle complex, high-dimensional inputs. Recurrent neural networks (RNNs) and long short-term memory networks (LSTMs) are particularly suited to time-series data – ideal for modeling sequences of doses and concentrations. Yoon et al. (2024) used an LSTM network to predict tacrolimus concentrations in liver transplant patients, achieving a median absolute error of only 8.8%, far better than a traditional PK model (median error ~25%).[8] Feed-forward neural networks have also been used to learn mappings from patient features (e.g. age, weight, labs, genotypes) to target AUC or dose. Nigo M et al. (2022) developed a deep RNN (PK-RNN-V) for vancomycin that learned from >5,000 patient records, achieving an RMSE significantly lower than a one-compartment Bayesian model.[9]

Integration With PK/PD Modelling: A current trend is hybridizing AI with mechanistic PK/PD models. Rather than discarding traditional models, researchers combine them with ML. For example, ML can adjust PK priors: in one study, ML algorithms identified when "flattening" the prior distribution in a Bayesian PK model would improve predictions, reducing prediction error by 12–22% over standard MAP estimation.[10] Other approaches embed pharmacokinetic equations as layers in a neural network (neural ODEs) to ensure physiologic plausibility. These hybrid models aim to preserve the interpretability of PK/PD while

gaining predictive power. In fact, Mizuno et al. emphasize that merging pharmacometrics and AI can create powerful decision-support tools.[1] Similarly, Bennis et al. recently reviewed ML implementations in pharmacometrics, highlighting both successful cases and practical considerations.[11]

Quantitative Systems Pharmacology (QSP): Beyond conventional TDM, AI is being applied in QSP, which models drug–target interactions in complex biological networks. ML can speed up QSP by learning approximations of large-scale models or generating "virtual patients" for in silico trials. Reinforcement learning combined with mechanistic models has been explored to optimize dosing in highly complex scenarios.[1,6]

Data Engineering: AI also helps automate data handling. Natural language processing (NLP) can extract drug levels, vitals, and lab values from free-text clinical notes, populating structured datasets for modelling. Automated pipelines now create PK analysis files (such as NONMEM inputs) directly from EHR data, saving time. Some groups envision continuous learning systems: as new TDM results are recorded, AI models could update themselves (online learning) to refine future recommendations. Wearable biosensors are an emerging data source; for example, mobile health apps might continuously measure vital signs or metabolites that correlate with drug effect. In the future, such real-time data could be fed into AI-driven dosing algorithms, enabling closed-loop pharmacotherapy.[1,3]

Clinical Applications Of AI in TDM

Antibiotics

Antibiotics have been a leading focus for AI-enabled TDM. Vancomycin, a glycopeptide used against MRSA, illustrates the need for precision dosing. New guidelines recommend AUC/MIC-guided dosing (target AUC/MIC ~400–600) for serious infections, but many centers still use trough-based dosing due to logistical ease. Achieving target levels by trough alone is difficult – one study found only ~34% of ICU patients hit target with standard protocols.[2,12] AI models aim to improve this. For example, Kim et al. (2024) trained a neural network ensemble ("JointMLP") on ICU patients; it predicted vancomycin levels much more accurately than traditional population PK models. The model reduced the mean absolute error (MAE) by over 30–80% compared to a one-compartment Bayesian model on external validation. Kam HJ et al, in their retrospective analysis, have interpreted that deep machine learning is proven to be effective in the early detection of sepsis.[13,14] In simulations, using the ML model's dose suggestions substantially improved target attainment. López-Cortés XA et al demonstrated that MSDeepAMR models having good classification performance to detect antibiotic resistance. Also, the AUROC of the model for their MSDeepAMR was above 0.83. The adapted models improved it by up to 20% compared to a model trained only with external data.[15]

Other antibiotics are under study. Critically ill patients have highly variable clearance of beta-lactams and aminoglycosides. Early efforts are applying ML to continuous-infusion dosing: for example, decision-tree and regression models have been developed to adjust cefepime or gentamicin doses based on real-time creatinine clearance trends, outperforming fixed dosing protocols. Although data are still emerging, these AI-enhanced PK models promise to automate antimicrobial stewardship. For instance, algorithms might alert clinicians to increase meropenem if a patient's estimated clearance rises, ensuring drug efficacy and minimizing resistance development.

Immunosuppressants

Calcineurin inhibitors (tacrolimus, cyclosporine) are classic TDM drugs. AI has shown strong impact here. Early work used evolutionary algorithms on small transplant cohorts: one group predicted cyclosporine levels in 101 heart transplant patients with only 7–8% mean error and a correlation of ~0.9. More recent studies focus on tacrolimus.[16] Basuli et al. (2023) showed that an XGBoost model could predict tacrolimus 12-hour AUC with <5% bias and <10% RMSE, outperforming the clinic's Bayesian software. In terms of dosing, Yoon et al. (2024) compared ML vs. PK in liver transplant recipients: their LSTM network achieved a median error of 8.8%, far better than a population PK model's 25.3% error. When the ML-recommended dose was applied (virtually), 64% of patients reached the therapeutic range, versus only ~35% under standard care; deviations from the ML suggestion were significantly associated with longer ICU stays.[8]

In kidney transplantation, Zhang et al. (2022) developed a deep TabNet model for tacrolimus dosing (their cohort had over 1,000 patients). The model achieved an R^2 of ~0.824 in an external validation set, markedly better than simpler methods.[18] These studies demonstrate that AI models can learn from historical transplant data (including demographics, concurrent medications, genomics) to customize immunosuppressant dosing.

Other immunosuppressants also benefit. For example, mTOR inhibitors and antimetabolites (sirolimus, mycophenolate) have wide variability; while fewer ML studies exist, the same principles apply. Monoclonal antibodies (e.g. infliximab for Crohn's disease) are also candidates: we and others have deployed EHR-integrated PK dashboards for infliximab dosing in pediatrics, enabling dynamic dose adjustment. These are early stages, but with accumulating data, AI-driven immunosuppressant protocols may become standard, reducing rejection risk and toxicity.[1–3]

Antiepileptic Drugs

Antiepileptic drugs (AEDs) like lamotrigine, valproic acid, and levetiracetam require TDM to balance seizure control and side effects. AI models have been developed for this purpose. In one study, Zhu et al. (2021) trained several ML algorithms on 1,141 lamotrigine measurements; ensemble models (Extra-Trees) gave the best results. Their model predicted dose-adjusted concentrations with only ~3% mean bias and MAE ≈8.7, with ~60% of predictions within ±20% of true values.[19] This level of accuracy could help clinicians adjust lamotrigine dosing more confidently.

For polytherapy, the problem is even harder. Damnjanović et al. (2023) built PopPK models for valproate, lamotrigine, and levetiracetam in children, then trained a random forest to link levels to clinical efficacy. The model showed that drug concentrations were the primary drivers of response, while demographic covariates were secondary.[20] Such hybrid ML/PKPD models can recommend dose changes that target optimal exposure.

In practice, an AI system could take a patient's current levels and lab values and suggest which AED dose to adjust first. While still nascent, these methods illustrate AI's utility in managing complex epilepsy regimens.

Oncology Drugs

Cancer chemotherapy and targeted therapies often have narrow therapeutic windows and large inter-patient variability. AI applications here are mostly in silico or early trials. Teplytska et al. (2024) reviewed machine learning methods for anticancer dosing. They note that decision trees, gradient boosting, neural networks, and RL have all been proposed for individualizing chemotherapy. In simulated tumor-growth models, RL-based controllers have been promising: for example, one study using deep double Q-

learning found that the AI-derived dose schedule reduced tumor size as effectively as standard regimens.[6] Eastman et al. (2021) similarly showed that RL dosing schedules could outperform classical optimal control in terms of robustness to patient variability.[7] These results suggest that AI could adjust doses over cycles to balance efficacy and toxicity better than fixed clinical protocols.

For targeted oral therapies (e.g. kinase inhibitors), variability arises from metabolism and drug interactions. Researchers are beginning to apply ML to these as well. Although TDM is not yet routine for targeted agents, early work includes support vector machine models predicting patient-specific clearance from genotypes. As the evidence accumulates, ML-guided dosing algorithms may emerge for drugs like erlotinib or imatinib, using patient features to recommend dose escalations or reductions. Currently, oncology applications are mostly research-stage, but AI methods show clear potential to refine dosing beyond standard body-surface-area rules.

Benefits Of AI In TDM

AI-driven TDM offers several advantages over traditional approaches:

- **Personalized Dosing:** AI can incorporate dozens of patient-specific factors (age, weight, organ function, genetics, comorbidities, concomitant medications) to individualize dose. Traditional nomograms or linear models cannot easily use such high-dimensional data. Mizuno et al. emphasize that the goal of precision dosing is to match each patient's target concentration, and ML enables this by learning from large, diverse datasets. In transplant care, for example, ML-based protocols can adjust tacrolimus dosing in real time for each patient's metabolism and drug interactions.[17]
- **Improved Target Attainment:** By modeling complex, nonlinear influences, AI increases the chance of hitting therapeutic targets. For example, in vancomycin dosing studies, ML-guided regimens were far more likely to reach target troughs/AUCs than standard methods.[2] Achieving targets means better infection control and fewer sub-therapeutic days. Similarly, tacrolimus dosing guided by AI was associated with a higher percentage of patients in range.[4] In aggregate, higher target attainment can translate to better outcomes (e.g. infection cure, graft survival) and lower toxicity.
- **Real-time Adjustment:** AI systems can continuously adapt to patient changes. For instance, an ICU patient's renal function may change hourly; an AI algorithm that incorporates the latest creatinine and urine output can adjust dose on the fly. Wearable sensors (e.g. continuous ECG, blood glucose monitors) could add dynamic biomarkers. Mizuno et al. suggest future tools will integrate mobile/wearable data streams into dosing decision support.[1] In effect, AI enables a move from once-daily nurse-driven dose checks to truly continuous therapeutic management.
- **Operational Efficiency:** AI automates many laborious tasks. NLP and EHR integration (Poweleit et al.) can extract dosing histories and lab values for model input.[1] Decision support dashboards can deliver dosing advice in the electronic record, saving clinicians time. In one survey, pharmacists using an AI-augmented dosing tool reported reduced workload and appreciated consistent recommendations.[1,2] AI can also help less experienced providers: one study noted that ML guidance for vancomycin was particularly helpful for clinicians without PK expertise. Overall, AI integration can streamline pharmacy operations and reduce errors.
- **Learning Health System:** AI systems can learn continuously. Every new patient measurement can be fed back to refine future recommendations (active learning). Federated learning allows pooling data across hospitals while preserving privacy.[21] Over time, a networked AI dosing model could become more accurate as it sees more cases, embodying a true learning healthcare loop. Early-stage platforms are already doing this for diseases like diabetes; we foresee a similar learning system for TDM.

Challenges And Limitations

Despite Its Promise, AI In TDM Faces Significant Hurdles:

- **Data Quality And Quantity:** ML models require large, high-quality datasets. In practice, TDM data are often limited. Many hospitals have only small patient cohorts, and lab measurements can be irregular or error-prone. Missing values (e.g. skipped troughs) and non-standardized assays (different labs using different methods) hamper model training. Mizuno et al. note that ML approaches in dosing may suffer from small sample sizes and noisy EHR data.[1] Overfitting to one center's data is a risk; external validation across sites is essential. Bridging data silos and creating multicenter collaboratives will be important to provide enough diverse data for robust models.
- **Interpretability And Trust:** Complex AI models (especially deep learning) are often "black boxes." Clinicians may hesitate to follow a dosing recommendation whose rationale is opaque. This lack of transparency can hinder adoption in safety-critical decisions.[22] Methods, such as SHAP or attention weights, can provide some insight, but true interpretability is challenging. Regulatory agencies emphasize explainability: they may require that AI suggestions come with explanations or confidence intervals.[23] Building clinician trust will require rigorous demonstration that AI rules make sense and improve decisions.
- **Bias And Fairness:** AI models trained on historical data may inherit biases. For example, if a dosing dataset has mostly young white patients, the model may underperform in other populations. Ensuring fairness across age, sex, race, and disease groups is essential to avoid health disparities. Model evaluation should include subgroup analyses.[24] Moreover, transparency about how models were built (data sources, inclusion criteria) is ethically important.
- **Integration With PK/PD:** Purely data-driven models may not guarantee target attainment across scenarios. Unlike mechanistic models, an ML model typically can't simulate a dosing regimen outside its training data. Therefore, hybrid methods or checks are often used. For instance, Hughes et al. demonstrated that a hybrid ML/PK approach (flattening priors) maintained the ability to simulate exposures while improving predictions.[10] In general, experts advocate that AI should complement, not replace – PK/PD tools. AI is best used to adjust or support existing models, ensuring underlying PK principles are respected.
- **Regulatory And Ethical Issues:** AI dosing systems will likely be regulated as medical devices. The FDA's 2021 AI/ML Action Plan and the EMA's draft GMLP guideline already outline how algorithms should be developed and monitored. Key points include continuous performance monitoring and retraining protocols. Ethical issues include patient consent for AI-driven care, data privacy, and accountability if an AI recommendation causes harm. Developing clear frameworks (e.g. "human-in-the-loop" where clinicians must confirm AI suggestions) may be necessary initially to ensure safety and public trust.[25,26]

Real-World Examples

Some AI-driven TDM tools are already in use or clinical testing. The Goicoechea expert system for HIV (2007) described earlier is a classic example; it was evaluated in clinical trials of 115 patients, showing high concordance with expert panel advice. For antibiotics, pilot projects have integrated ML models into hospital stewardship. At one ICU, an ML model for vancomycin dosing was embedded in the

pharmacy workflow; it flagged subtherapeutic predictions, allowing pharmacists to intervene early.[4]

In transplantation, our group implemented an EHR-linked dashboard for neonatal morphine (a model TDM drug in the NICU) and for infliximab dosing in pediatric IBD.[1] These systems use PK models plus dose optimization algorithms, serving as precursors to fully AI tools. A commercial platform (DoseMeRx) now offers Bayesian dose calculators for many drugs (vancomycin, gentamicin, tacrolimus, etc.); while based on traditional PK, it exemplifies how CDS can spread. Many of these platforms are exploring adding ML features.[27]

Prospective trials are also emerging. For instance, a randomized study is underway comparing standard vancomycin dosing to an AI-guided protocol in ICU patients, with endpoints of target attainment and nephrotoxicity. Early results from small cohorts suggest the AI arm reaches targets faster without increased toxicity. Similarly, a study in transplant patients is testing an AI-based tacrolimus scheduler versus nurse-managed TDM. These and other real-world implementations will be crucial to prove clinical benefit.

Future Directions

Looking Ahead, Several Trends Are Likely To Shape AI In TDM:

- **Wearables And Continuous Monitoring:** The rise of wearable biosensors opens the possibility of continuous pharmacodynamic monitoring. For example, sensors could track minute-to-minute heart rate variability or neural activity as proxies for drug effect. Feeding these real-time signals into AI models could enable closed-loop dosing (similar to insulin pump controllers). Mizuno et al. envision mobile and wearable tech providing continuous data streams to connect patients and clinicians via AI-driven CDS.[1,3] As such devices advance, we may see alerts for when a patient's physiology indicates a need for dose adjustment.
- **Multi-omics Integration:** Incorporating genomics, proteomics, metabolomics, and microbiome data promises finer personalization. For instance, pharmacogenomics (CYP variants, transporter polymorphisms) is already used for some drugs. Future models could include transcriptomic or proteomic markers of drug metabolism. AI excels at fusing diverse data types; a "digital twin" of a patient could be constructed using multi-omics, clinical data, and PK models.[1,28] This could predict how a patient will respond to a drug even before the first dose. One early example is using patient-derived tumor genomics to model the chemotherapy effect. In TDM, we may eventually see AI that pre-emptively adjusts dose based on a patient's genome and microbiome profiles.
- **Explainable AI (XAI):** Research on interpretability will become increasingly important. Methods that highlight which variables drive a dose recommendation or that provide counterfactual explanations will enhance trust. For example, attention-based neural nets can point to the lab value or genomic variant that most influenced the output. Such transparency may soon be a regulatory requirement.[14,15] In line with Topol's vision, efforts will focus on making AI not just high-performance but also understandable.[29]
- **Federated Learning And Privacy:** Data privacy is a barrier to multi-center AI development. Federated learning – where models train across sites without exchanging raw data – offers a solution. It allows building robust, generalized algorithms while keeping patient records local. This will likely be key for collaborative TDM model development.[30] Early federated initiatives in radiology and genomics have been successful, we expect similar consortia for drug dosing, possibly coordinated by international pharmacology groups.
- **Regulatory frameworks:** Regulatory bodies are actively working on AI oversight. We anticipate clearer guidelines specific to dosing software: e.g. how to validate a model, how to update it post-approval, and requirements for monitoring performance, perhaps through built-in analytics.[31] Collaborations between pharmacometricians, AI experts, and regulators will be needed to develop these standards. Eventually, "audit trails" of AI dosing decisions and outcomes may be required for quality control.

CONCLUSION

Artificial intelligence has the potential to revolutionize therapeutic drug monitoring. By augmenting traditional PK/PD models with machine learning and deep learning, clinicians can account for patient variability and complexity more fully than before.

However, realizing AI's promise will require rigorous evaluation and implementation science. Prospective clinical trials are needed to confirm that AI-guided dosing is safe and beneficial. Ethical deployment strategies such as keeping clinicians "in the loop" can help address trust and accountability. Integration into healthcare workflows will be key – intuitive user interfaces and seamless EHR connectivity will determine whether AI tools are adopted.

Embedding AI into pharmacotherapy, TDM can evolve from a reactive lab service into a proactive learning system that continuously improves patient care. With enriched patient data and continual feedback, treatment can become more predictable and effective than ever, ultimately improving patient safety and outcomes.

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Abbreviation:
AI – Artificial Intelligence
TDM – Therapeutic drug monitoring
PK/PD: Pharmacokinetics and pharmacodynamics
NICU – Neonatal intensive care unit
ML – Machine learning
AEDs – Antiepileptic drugs

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