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Review Article

Precision dosing using AI and TDM: integrating data driven prediction with individualized Pharmacotherapy

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ABSTRACT

Precision dosing is an emerging approach that focuses on tailoring of medicine to optimize the drug exposure in individual patient levels, helps to reduce toxicity and increasing efficacy. In precision dosing the Therapeutic drug monitoring (TDM) plays a major role in ensuring the right dose are given to reach the maximum therapeutic efficacy and decreases the adverse effects in precision medicine. TDM is one of the best practices to determine the plasma drug concentration in the biological fluids and also helps to identify the margin between the minimum effective concentration and minimum toxic concentration (narrow Therapeutic index). Even small alterations in the blood levels can be determined the difference between the treatment and adverse effects. Although Pharmacokinetics (PK), pharmacodynamics (PD) modeling and TDM are well-established approaches for individualized dosing, integration of artificial intelligence and machine learning (AIML) can further enhance dose optimization by analyzing complex data of the specific-patient. So, it improves the prediction of drug exposure and therapeutic response.[1] Based on the data collected from patients such as drug metabolism is combined with genetic and Real time physiological factors to support the individual dose optimization. To improve treatment outcomes and reduce toxicity AI based clinical decision supports the system and also help personalized dosage through EHR integration in this system. However, these advances in technology face challenges like poor quality of data, non-interpret ability of models, regulatory challenges and several ethical dilemmas in the clinical areas. So, this review discussed detailed about the principles of precision dosing, their role in AI and ML in TDM, clinical applications, Pharmacotherapy, advantages, limitations, future perspectives and role of pharmacist in precise dosing in TDM And AIML to ensure the safe and effectiveness of the precise dosing.[2]

Keywords: Precision dosing, Therapeutic Drug Monitoring (TDM), Explainable Artificial Intelligence (XAI), Machine Learning (ML), Pharmaceutics, Thermodynamics, Electronic health record (EHR), Reduce Toxicity, Enhance efficacy, Narrow therapeutic index (NTI)

INTRODUCTION:

Precision dosing is an emerging approach in modern health care, that helps to optimizing the disease prevention and drug therapy by selection and adjustment of the dose for individual patient characteristics to achieve the desired therapeutic response while minimizing Adverse effects. Unlike a conventional dose it is based on the generalized dosage recommendation. Whereas, a precision dose takes into account of any variation in Absorption, distribution, metabolism, Elimination and biological variations.

Hence, the individual drug therapy is required for the patients to respond differently with the same medications and dosage regimen. Sometimes Standard dose may fail to provide an optimal therapeutic outcome in every patient, particularly it is seen in the patients with complex medical conditions, impaired organ functions, or the use of multiple medications. There are several factors are included for the needs of individual drug therapy, such as Age, Gender, Body weight, genetic variations, disease conditions, drug interactions, Renal and hepatic functions. So the individual drug therapy mainly focuses on tailoring of drug treatment to each patients requirements for improving therapeutic outcomes and reducing the preventable Adverse drug reactions, and to support appropriate medical use.[3]

The cause of variability in Drug response is either due to pharmacokinetics and (or) pharmacodynamics response in individual patients. Pharmacokinetic drug response variability can occur when the drug varies difference

between patients or changes with time. Whereas, pharmacodynamic variability can occur when pharmacological activity is based on the target binding of molecules differs between the patients or changes with time at the same drug concentration. And also, variability in Drug response differs in the Therapeutic effect and Adverse reactions are observed among the patients receiving the same medications at comparable doses. The cause of this variability may be genetic, physiological, environmental, and clinical factors. It may be due to intraindividual variability may be due to variation in drug absorption, distribution, metabolism, and elimination. It also exists in the same patients over time, which is due to variability in organ function, disease severity, nutritional status, drug interactions, medications use and compliance.[4]

Pharmacokinetics, pharmacodynamics and Therapeutic drug monitoring (TDM) are the foundation of precision dosing and an important aspect of optimizing drug therapy according to the specific patient. The science of understanding and explaining the effects, mechanisms of action, and dosage of drugs; the science of the relationship between drug concentrations and their effects in the body is known to be Pharmacokinetics. The Clearance, volume of distribution, half-life, Area under the curve (concentration vs time) are the known pharmacokinetic parameters which helps to provide valuable information about drug exposure and elimination. Whereas Pharmacodynamic describes what the drug does to the body in contrast, it is concerned with physiological and behavioral consequences produced whenever the drug binds to the target site receptors during their journey through the body. Pharmacodynamic parameters helps to know the relationship between the drug exposure and clinical response variations among the patients can influence treatment effectiveness and risk the of toxicity, highlighting the importance of individualized dose selection.[5]

Therapeutic drug monitoring is a clinical practice used for measuring the drug concentrations in biological samples for dosage adjustments in individual patient therapy. It is particularly useful in the drugs with a Narrow therapeutic index (NTI), even small changes in drug concentration may lead to severe toxicity or therapeutic failure. Such as the drugs like Antibiotics (erythromycin), Anticonvulsants (phenytoin), aminoglycosides, Antiarrhythmic(digoxin), and immunosuppressive agents (tacrolimus) are the examples for narrow therapeutic index.[6]

TDM provides more information about actual drug exposure, along with certain limitations. The Drug concentration measurements may be affected by inappropriate sampling time, analytical errors, and variability in sample handling. For more accurate results requires knowledge on pharmacokinetics, pharmacodynamics, clinical conditions, and the limitations of the selected therapeutic range.[7]

Artificial intelligence (AI) has emerged as a promising technology in precise medicine because it has a high ability to analyze the large and complex data to a simple database, and helps to identify patterns to support the individual clinical decision making. AI along with ML can be used with this patient specific information such as Demographic patient information; DNA and genomic information; Lab results; Patient history; Renal and hepatic function tests; Pharmacokinetic-Pharmacodynamic analysis. In precision dosing, it can be used to predict the concentration of the drug in single dose of the individual which can minimize the toxicity and thus increasing the effectiveness of that drug.[8]

AI combined with TDM can assist to establish the concentration of drugs for individual patients in order to enable more accurate and optimized dosing decisions. And also helps to improve dose prediction, identify and reduce the toxicity risk, particularly for the drugs with Narrow therapeutic index such as vancomycin. However, drugs need to be more importantly validated clinically and with reliable data before safe use. Therefore, AI-assisted TDM can helps to support the healthcare professionals to optimize individualized pharmacotherapy y.[9]

METHODOLOGY / LITERATURE SERACH STRATEGY:

This qualitative systematic review is an exhaustive and transparent process of search, selection and synthesis of relevant literature on AI-TDM for precision dosing in a way reproducible by others. Lll Literature search, screening, and reporting follow the requirements of the PRISMA 2020 statement and its extension for scoping reviews (PRISMA-ScR), which implies that the rationale for each decision can be tracked and replicated. Note that the below methods reflect how the literature was selected and assessed, not any experimental procedures, as this did not occur. Our literature search was for articles published from January 2015 to October 2026 in which machine learning, deep learning or reinforcement learning was first used in large scale dose individualization.

Databases Used:

Five sources were searched so that clinical pharmacology, pharmacometrics, computer science and engineering literature were all covered.

Additionally, forward citations of seminal publications were examined in Web of Science, and reference lists of included research and pertinent prior reviews were manually searched (backward citation searching).

Search Terms:

Search terms were grouped into three concept blocks. Blocks were combined using AND, and terms inside a block were joined using OR. Free-text keywords found in titles, abstracts, and keywords were mixed with controlled vocabulary (MeSH in PubMed).

The Pub Med search strategy used in this study consisted the following: "artificial intelligence" machine learning", "deep learning", and "reinforcement learning" combined with "drug monitoring “OR”, "therapeutic drug

monitoring" and "plasma concentration". The search also combined "individualized medicine", precision dosing, "single dose" or "optimal dose*". The string was modified for every search engine to correspond with the syntax and field tags accepted by the individual database. Limits such as language (English), human studies, and publication date (from 2015 to date) were applied.

Inclusion Criteria:

For studies to be included, they had to meet all of the following:

All papers considered were peer reviewed original research, including clinical, retrospective, prospective and simulation studies, in addition to systematic reviews/meta-analyses. Conference abstracts and preprints were included if the full results and methods were available. The study utilized machine learning (ML) or artificial intelligence (AI) approaches, which may have included hybrid approaches that leverage population PK models for dose prediction and/or optimization, concentration prediction, etc. TDM data (defined as drug concentrations in patients). Input, comparator or outcomes. All studies were required to report at least one quantifiable outcome (e.g., accuracy of prediction, extent of goal attainment, clinical effectiveness, harm or usefulness). All studies were conducted on human patients or human data; however, in silico studies were included if consistent with clinical data.

Exclusion Criteria:

Studies were excluded based on the following criteria:

Anyone who uses artificial intelligence for the purpose of diagnosis, imaging, or drug discovery without any dosing component. Individuals working on therapeutic drug monitoring or dosing without any artificial intelligence or machine learning components. From studies on animals, for example animal studies, in vitro studies, or theoretic studies without any clinical component. Editorials, letters, commentaries, case reports, abstracts of conferences without full papers, duplicate studies. Research that did not disclose enough information to assess the model, sources, or validation procedures. Those not obtained in full text after purchasing attempts. Research not published in English.

Study Selection Process:

The retrieved records by which stage of the studies selection process can be seen in the flow diagram PRISMA diagram.

1. Deduplication: References exported to reference management tools (End Note, Zotero). Duplicates were removed using manual and automated methods. Two reviewers independently reviewed each record based on inclusion criteria.

2. Full Text Review: The abstracts of papers identified as satisfying the inclusion criteria were reviewed in full text by two reviewers. Reasons for exclusion were recorded.

3. Final Inclusion: In case of dissent, consensus was sought through discussion and a third reviewer was approached in case of persistent disagreements.

PRISMA flow diagram for study selection describes the number of records identified, screened, excluded (with reasons), and included as follows: [n] records identified; [n] duplicate records removed; [n] records screened; [n] full-text articles assessed for eligibility; [n] studies included in qualitative synthesis. Inter-rater reliability for this task was obtained with Cohen's kappa.

Data Extraction and Synthesis:

Data were extracted with a standardized form piloted on a few studies and then applied to all included papers. One reviewer extracted the data and a second reviewer checked it.

The judgement of risk of bias and applicability for prediction-model studies was performed with PROBAST when applicable, and for other study types with appropriate tools like for example Newcastle-Ottawa Scale. Due to heterogeneity of the trials (drugs, algorithms, endpoints) we considered the use of quantitative meta-analyses impossible. Therefore, we provided a narrative summary for results, classified into drug groups, by AI algorithms and by clinical setting, in tables.

BACKGROUND:

Foundations of Stratified Medicine

Treatment was individualized first, since clinical trials showed that differences between patients caused wide variation in treatment responses. Conventional dosing Flat dosing was the norm unless a simple clinical factor called for an adjustment, such as weight, body surface area, or organ function (clearance(cl)). In oncology and critical care, these broad adjustments often lead to dangerously high toxicity or too little exposure because of unmeasured physiological differences.

In the late 1960s and 70s, Lewis Sheiner and Roger Jelliffe pioneered computer simulations and mathematical modeling to improve dosage regimens. At about the same time in the early 1980s, the growth in immunoassays made routine therapeutic drug monitoring (TDM) feasible. But traditional TDM was reactive (comparing measured trough concentrations to population-derived therapeutic windows) and not proactive in predicting future concentration profiles.[2]

While precision medicine in the past has focused on identifying genomic tumor targets and finding new drugs, doctors realized that starting the right medicine is no use without tailoring the dose to the individual. This previously triggered a change in pharmacology type as users advanced from traditional TDM to what is now known as model-informed, precision-based dosing (MIPD), an expression formed in the mid-2010s. MIPD combines population pharmacokinetic-pharmacodynamic (popPK/PD) models with Bayesian prediction, enabling clinicians to forecast exposures and individualize regimens among individuals to sparse or nontime-based biological examples. It soon turned into crucial in medicine managing, for instance, traveling drug administration from trough tracking to customized AUC/MIC target.[25]

Dynamic Living Twins and Algorithmic Adaptation:

Recent developments have moved MIPD into real-time, mechanistic, closed-loop prescribing systems, 4. Conventional popPK models typically assume clinical covariates are frozen, which breaks in fast-changing environments such as young children, or septic shock. To address this, dynamic living digital twins are used to fuse high-frequency data streams from electronic health records and continuous biosensors using state-space filters.[49]

Additionally, pharmacometricians are combining RL with systems pharmacology. Training individual RL experts to interact with virtual patient models, these systems will also characterize the changing impact of multiomic biomarkers on sequential dose modification. Although the technology is proving powerful, widespread routine use will need prospective randomized clinical validation, user friendly clinical decision support, and constrained regulatory guidance.

The work to move from qualitative drug selection to continuous, monatomic dosage regulation illustrates that establishing the 'five rights' of precision medicine ultimately hinges on quantitative precision dosing.[16]

A widely accepted scientific consensus is that normal cytotoxic-driven dose selection is no longer sufficient for modern targeted drugs and immunotherapeutics and that these dose selection approaches regularly lead to disproportionate toxicities.[17]

Principles of the Traditional Framework:

Prior to the use of novel methods, dose-finding was traditionally based on the MTD (maximum tolerated dose) approach, which made use of rule-based designs (e.g., the standard 3+3 design) . This approach was developed for cytotoxic chemotherapies, following a simple monotonic "more is better" paradigm in which higher exposure leads to higher toxicity and efficacy.

Dose escalation decisions generally assess DLTs over an acute observation period limited to the first one or two cycles of treatment.[25]

In toxicology during preclinical development, first in human doses are also used to determine a safe margin of exposure and to determine a no-observed-adverse-effect level (or NOAEL) using repeat-dose animal studies. Clinical translation often involves fixed regimens or body size-based normalizations (e.g., weight or body surface area) that are based on a limited number of participants.

Upon declaration of an MTD, sponsors frequently incorporate that one regimen into confirmatory studies without thoroughly assessing the overall exposure-response relationship.[47]

Shift to Rational Dose Optimization:

A growing body of data shows that there are significant discrepancies between approved doses and real-world clinical needs, leading to a major regulatory initiative-the FDA Project Optimus. A review of 31 anticancer drugs approved from 2020 to 2023 identified 65% as potentially needing optimization via dose reduction or scheduling changes.[50]

In the past, lack of optimization resulted in post-marketing requirements for multi-year, resource-draining clinical trials. Contemporary drug discovery and optimization: going beyond empirical approaches to a paradigm of model-informed drug development using exposure-response modeling and randomized multi-dose comparisons pre-registration. Dose Determination: Trial runs of several candidate cohorts before definitive trials defines the non-linear dose-response profile and prevents excess.

The combination of pharmacodynamics, target saturation, and biomarker kinetics – creating an optimal biological dose as opposed to finding toxicity limits.[43]

Trial Design with Model Assistance Bayesian adaptive models like BOIN, CRM, and MCP-Mod will lead to more accurate estimation than rule-based approaches. Longitudinal Tolerability Tracking. LONGITUDINAL TOLERABILITY TRACKING With patient reported outcomes beyond acute cycle 1 toxicities, protects chronic compliance and patient quality of life. The complexity of contemporary pharmacology illustrates that selection of conventional doses does not reflect the mechanistic nature of non-cytotoxic agents, and highlights the systematic need for rational model-based dose optimization.[15]

Sources of Interindividual Variability:

Demographic and Anthropometric Factors

Age and body weight set the major physiological volumes of distribution and intestinal absorption characteristics. In a simulation that modeled 1,801 individuals' body conditions and chemical concentrations, body features explained about a 5-fold difference in chemical levels inside a person.

Increasing age reduces total body water and increases fat mass, which shortens the hydrophilic distribution but lengthens lipophilic elimination half-lives.[39]

Gastrointestinal pH, fluid volumes and gastric emptying are pediatric maturation and could lead to variations in oral absorption. Organ Clearance and Disease State, Renal and hepatic excretion pathways determine total systemic clearance but significant organ failure and metabolic differences occur in Acute and Chronic pathologies. One pooled population analysis of 18 drugs has shown that hepatic clearance of unbound drug declines 0.80%/year after the age of 40 due to reductions in the volume of the liver and blood flow. Decline of inulin renal clearance with age follows declines in renal blood flow, which in turn decreases at a rate of 0.97%/year. Decompensated cirrhosis reduces cytochrome P450 expression, changes plasma protein binding, and diminishes the magnitude of reversible enzyme inhibition interactions.

Genetics and Drug Interactions. Inherited pharmacogenomic polymorphisms, polypharmacy and differences in pharmacodynamic receptors alter clearance rates and general clinical response.[43]

Functional variants in CYP2C9 and VKORC1 together can be responsible for approximately 30% of the dose variation seen with low to moderate therapeutic index drugs, such as warfarin.

Concurrent intake of enzyme inducers or inhibitors leads to gross alterations of cytochrome P450 function, either resulting in toxicity or in treatment failure. 2.6% of 227 FDA-approved drug label summaries examined combined intrinsic and extrinsic perturbations to be effective, although these combined intrinsic and extrinsic perturbations were often observed to increase exposure risk.

These physiological, clinical, and molecular factors need to be incorporated into quantitative pharmacometrics models in order to compensate for interindividual variability and develop safe, personalized dosing regimens.[47]

Principles and Parameters of Therapeutic Drug Monitoring and Precision Dosing

The systemic concentration of drugs in biological matrices is measured to define a therapeutic window (a concentration range between toxicity and efficacy) for therapeutic drug monitoring (TDM). TDM allows for the correct exposure to be achieved in order to maximize response with minimizing concentration related toxicity. The next step in how to shift from empirical concentration targets to dynamic precision dosing includes modeling important pharmacokinetic and pharmacodynamic parameters to refine target exposures on a patient-specific basis.

Instead of depending on a snapshot of the trough, the model predicts best biological response by using factors such as individual physiology, exposure measures.

The two key disposition metrics which explain broad between-subject variation in exposure for aging, critical illness and obesity are clearance and volume of distribution.[25]Achievement of the optimal PK/PD targets of anti-infectives is a function of class-specific indices: Time above the MIC value (values are divided by the mean for their class) which is expressed as ($fT {> \text {MIC}} $) for beta lactams, AUC/MIC ratio for glycopeptides and, the peak concentration relative to the MIC ($C{max} / \text {MIC}$) for the aminoglycosides.[39]

Dynamic response modeling uses effective concentration biomarkers to connect systemic concentrations through the half-maximum effective concentration ($\text {EC}_ {50} $), receptor occupancy levels, between toxicity and efficacy for all doses and combination ratios.

Clinical application involves multiple sequential steps: candidate selection, selective blood sampling and high-throughput/mass-spectrometric quantitation and subsequent clinical interpretation of results in terms of covariates. TDM is mainly indicated for drugs that have a narrow therapeutic index and/or a nonlinear clearance and/or if there is no good correlation between dose and clinical response.

Monitoring of glycopeptides, immunosuppressants, antiglycolytic, antiepileptics and certain targeted anti-neoplastic agents has become standard practice. Dose adjustment is based on the trough value of steady-state concentration ($C_ {min, ss} $) measured just before the next planned dose; however, non-standard sampling times can be analyzed with computer software. The ability to combine lab-based drug concentrations with mathematical PK/PD data enables a translation from passive concentration measurement to prospective model based therapeutic individualization.[43]

CURRENT EVIDENCES:

Concentration and Dose Prediction:

The machine learning algorithms can discern the non-linear hidden relationship in high dimensionality of clinical and chemical data to infer the system's exposure and dosage. XG Boost and Random Forest ensemble models demonstrated the most accuracy as measured by root mean squared error in multi-algorithm evaluation of four antiepileptic agents. Models that use 800 compounds can predict the IV exposure in humans within a two-fold error for between 40% and 60% of the test molecules using machine learning combined with a physiologically based pharmacokinetic model.

Deep-PK and neural ordinary differential equations are deep learning models that can accurately predict multiple ADMET endpoints and time- series concentrations profile without assuming any analytical equations. [11]

Incorporation of Patients' Data into Treatment Monitoring:

Modern precision dosing systems use streaming electronic health record data to manage interindividual variability with therapeutic drug monitoring.

If there are unstable period post transplantation, integrated systems are able to use laboratory data including organ function and longitudinal data, CYP3A5 genotypes for dose adjustment of the immunosuppressants.

Automated retrieval of clinical covariates from records allows algorithms to derive important covariates such as time after last dose to help with optimally managing therapeutic concentrations

External evaluation illustrates that patient covariates and TDM observations obtained from dynamic forecasting are essential to guiding the clinical dose adjustments in this cohort of critically ill subjects.[42]

Bayesian Optimization and Competing Method Performance:

With population pharmacokinetic methods, AI can take the mechanistic monstrosity of big machine learning alone off your hands, and still not provide the wrong Bayesian prior.

For pediatric Crohn's disease patients on infliximab, XG Boost-corrected Bayesian model lowered root mean square error (4.8 μg/mL to 3.78 μg/mL) when compared to standard Bayesian estimation. ML algorithms increase execution speed to seconds or minutes rather than hours.

Reduce the cost of training on simulated data with nonlinear mixed-effects modeling.

Such hybrid models can be realized with clinical decision-support systems such as Insight Rx Nova or AID-Tac that outperform trough-based monitoring by 15% to 35% in terms of higher target attainment.[2]

CLINICAL APPLICATIONS:

Correct dosing will ensure optimum use of the drug and decreases its toxicity. By knowing what happens to the drug in the body by pharmacokinetics and Pharmacodynamic processes. This report will look into how drugs are used in different areas of medicine. Including Infectious diseases, Neurology, Transplantation, Oncology, Cardiology and Psychiatry. These drugs are used for the therapeutic range of drug concentrations, monitoring and dosing regimens. Aminoglycosides e.g. gentamicin, tobramycin and amikacin have high peak levels (gentamicin should be 5-10μg/ml). Because of this high peak to trough ratios, they have low trough levels (<1μg/ml). The drug is dependent concentration and will be more effective at high concentrations. Transplant drugs such as tacrolimus and cyclosporine are inhibitors. They have a small therapeutic window. Tacrolimus should be kept to between 5-15ng/ml in blood. Cyclosporine should be kept to trough levels of between 100-300ng/ml. Another drug used is sirolimus which is an mTOR inhibitor. It has a long half-life (60hrs) so should be kept to trough levels of between 5-15ng/ml.High dose methotrexate needs to be handled with care. Patients will be given fluids and alkalinization to help protect their kidneys. Leucovorin resistance is given depending on plasma levels. Plasma levels should be <0.1μM at 72hrs.Digoxin has a large Vd (~7L/kg) in cardiology. In heart failure the dose should be kept to 0.5-0.9ng/ml, especially in Antiarrhythmic drugs.[15]

Antibiotics:

Vancomycin has a long half-life in renal impairment. PD Target – AUC 24/MIC >400-600 (Assuming minimum inhibitory concentration (MIC) of 1mg/l). Traditionally target troughs 15-20mg/l in severe infections. Current consensus is to target AUC to reduce nephrotoxicity. Therapeutic Target – Often target troughs – easy to achieve. 15-20mg/l = approx. 400-600 AUC. Lower troughs (10-15) may be sufficient in less severe infections (Susceptible MIC). >20mg/l will increase risk of toxicity. Risk of toxicity (Nephrotoxicity) significantly increased with >~600 AUC. Monitoring – Steady state trough levels on 3rd/4th dose (30 mins prior to dose). AUC is ideally measured by 2 measurements (peak and trough) and calculated by methods (Trapezoid, Bayesian). Target troughs in severe MRSA infections are 15-20. AUC is similar to pediatric patients (Guidelines contain pediatric). Monitor renal function and adjust dosing. Dosage – Can be calculated by PK. Clearance increased in pediatric patients. Often administered every 6-8hrs. Obese patient – Adjusted body weight. Drugs – Concurrent use of nephrotoxins will increase risk of nephrotoxicity. (Aminoglycosides, NSAID's, Piperacillin-Tazobactam).[30]

Aminoglycosides show synergism with certain Gram-positive organisms. PK/PD has Low volume of distribution (approx 0.2-0.3L/Kg). Minimal plasma protein binding. Rapid redistribution into extracellular space. Renally excreted (Almost entirely). Clearance is approximately equal to GFR. Half-life is approximately 2hours. Prolonged in renal failure. Pharmacodynamics – Concentration dependent with post antibiotic effect. Gentamicin – Peak 5-10mg/L, Trough <1-2mg/L (Traditional regimen). Tobramycin is similar. Amikacin – Peak 20-30mg/L, Trough <5mg/L (Single dose regimen). Peak approx. 20-30mg/L, Trough undetectable. Peak – 30mins after infusion. Trough – Prior to dose. If multiple doses are given per day. Random level or prolonged interval nomogram if prolonged regimen. Periodically monitor renal and auditory functions. Gentamicin/Tobramycin Traditional regimen – 1-2mg/kg IV 8hrly (Synergistic regimen). 7mg/kg IV OD. (Prolonged regimen). 15-20mg/kg OD. Adjustments – Nomograms (Hartford nomogram for single dose regimen). Toxicity Nephrotoxic (Raised creatinine). Ototoxic (Irreversible deafness & Vestibular issues). Risk increased with high trough levels. Avoid prolonged regimens with high trough levels. Regular monitoring.[30],[47]

Antiepileptic Drugs:

Phenytoin consists of High protein bound (90%) Free active. t 1/2 1/2 = 7-42. Dose dependent (longer half-life with higher concentrations). CYP 2C9/2C19. Strong inducer of CYP. Clearance decreased with higher doses. Plateaus. Therapeutic 10-20ug/ml. Free 1-2ug/ml. Often effective in patients with levels of at ≥10 ug/ml. Common toxicity with >20ug/ml. Patients with hypoalbuminemia will have increased free levels. Correct concentrations can be calculated using the Sheiner-Tozer equation. Corrected total = Measured Conc (mg/L)/ 0.2x Albumin Conc (g/L) + 0.1 Monitor trough concentrations. Steady state achieved within 5-7days. If albumin < is <3.5gdL/renal failure use free/corrected concentrations. Monitor for CYP interactions. Loading dose 15-20mg/kg IV. Max 50mg/min. Should be administered as fosphenytoin (150mg PE/min). Maintenance dose 300-400mg daily. Non-linear dose response curve. Small increases/decreases in high concentrations will lead to large changes. Calculated maintenance dose: Est New Dose = Old dose x (New conc +Km)/ (Current conc + Km) (Varies within populations) Interactions Strong enzyme inducer. Decreases OCs, warfarin and other AEDs. Neurological (nystagmus, ataxia, confusion), dysrhythmias and CNS depression are the main toxic effects we observed. Discontinue if any symptoms develop. (At>20 ug/ml). May require dialysis after massive overdose IV.[15], [32]

Sodium Valproate is used as a Prophylactic therapy in cases of Migraine, Mania and Bipolars disorders. PK/PD: Vd: 0.1-0.5L/kg. Highly protein bound (85-95%). Metabolized by glucuronidation and beta oxidation in liver. T-1/2: 9-16hrs. Increased in overdose. Linear

kinetics. Clearance dose and saturation dependent. Free fraction may increase with large doses. Therapeutic levels: Total: 50-100μg/ml (some to 125). Free: 5-10μg/ml. Take troughs after stabilized (3-5 days). When starting new regimes, in pregnancy (levels will be lower) and toxicity suspected. Monitoring: Ammonia and LFT. Dosage/Titration: 10-15mg/kg/day PO. Titrate to therapeutic levels. Max: 60mg/kg/day. Loading dose can be administered in mania/status epileptic seizures. If you have high total levels and suspect toxicity then measure free levels. Can cause displacement of other drugs (phenytoin/carbamazepine). Many drug interactions (lamotrigine/warfarin etc.). Toxicity: Hepatotoxicity (Monitor LFT). Hyperammonemia (encephalopathy). Pancreatitis. Weight gain. Teratogenic (Neural tube defects). Overdose may require support and L carnitine.[31]

Immunosuppressants:

Tacrolimus is a Calcineurin inhibitor. This drug has a large volume of distribution within RBCs. 99% high protein binding (erythrocyte), oral bioavailability (20-25%) and High inter-patient variability Target levels will depend on risk of rejection. Monitor Trough levels should be taken at 12 hrs. post dose. Initial levels should be monitored twice weekly to reach steady state concentrations. Steady state levels can be taken weekly and then monthly. Patients on interacting drugs and those with graft dysfunction should be closely monitored. Monitor renal function, BP and glucose. The dose should be adjusted to 0.1-0.2mg/kg/day in divided doses (Higher mg/kg required in pediatric patients). Adjust dose to achieve desired trough levels in the Patients who are extremely sensitive to CYP3A5. Individuals with the 3/3 genotype are non-expressers therefore need approximately 50% less than expressers. 1mg of PROGRAF (tacrolimus) is equivalent to 1mg ADVAGRAF (ER) as it has high bioavailability. Interactions: Highly sensitive to CYP3A4/5 enzyme inhibitors (azoles, macrolides, calcium blockers and grapefruit). This will increase levels. Rifampin, phenytoin and St John's Wort are inhibitors Toxicity: Dose dependent toxicity. Nephrotoxicity (acute tubular damage) and Neurotoxicity (tremor, headache and fits). Can cause hypertension, hyperglycemia, dyslipidemia and hair loss. Reduce dose or switch to non-nephrotoxic agent. Cyclosporine. special care should be taken in patients with Prophylaxis of organ transplant rejection; also, autoimmune diseases (off-label). [53]

Sirolimus (Rapamycin) is Rarely used in vascular proliferative disorders. It blocks the mTOR pathway. It has a Poor oral bioavailability (14%) and Large Vd (~12-15L/kg). Metabolized through CYP3A4. Long elimination half-life (~60h). Therapeutic levels: Should be between 4-12ng/ml. In early periods of graft rejection prevention higher levels are needed. For example, in the first 3 months of renal treatment you might want 12-20ng/ml. This depends on protocol and CNI use. Due to the long half-life, it can take 2-4 weeks to reach a steady level after changing dose. Should monitor; Lipids (often have hyperlipidemia) Platelets for adult dosing 1-2mg orally daily. Renal failure is reduced by 15%. Monitor trough levels. Interactions may cause increased levels with CYP3A4 inhibitors (azole anti fungi's). Often, I need to reduce the dose by 50%. Decreased levels with inducers (Rifampicin/Phenytoin). Increased dose will lead to toxicity of hypersensitivity reactions.[32]

oncology:

Methotrexate (HD-MTX) Low dose treatment of high dose (>1000mg/m2). Pharmacokinetics/Pharmacodynamics: Folate antagonist. Cleared mostly Renal. 90% remains unchanged in blood stream for up to 30h in renal failure. Prone to cause Renal tubular precipitation Monitoring: Needs to be monitored closely on high dose of methotrexate. Usually level needs to be kept below 0.1micromolar (0.03mg/L). Toxic levels (LD50) are roughly 100micromolar. Monitor at 24, 48 and 72h. Also monitor Creatinine. Leucovorin (folic acid) Rescue: Started after 24h of the methotrexate Dose is 0.01-0.1g/m2 6-8 hourly. Dose is based on methotrexate levels If >10micromolar give according to Bleyer nomogram. If levels of methotrexate are >1 micromolar give rescue dose more frequently (3 hourly). Examples are 3×10-7M - give double rescue dose and 3×10-7 M - give triple rescue dose as this would be his nomogram with this level.72h after the rescue give 15mg/m2 of Leucovorin every 6h. Dose is based on methotrexate level, if levels of >1x10-7 M (0.1micromolar) then give double dose, if 3×10-7M then give triple dose. Many patients will be using a standardized nomogram (see table).[53]

Methotrexate in high doses:

Day -1: Sodium bicarbonate (PO). X24h. IV fluids.

Day 0: High dose Methotrexate.

24h: Commence Leucovorin rescue.

Days 1-3: Monitor MTX levels at 24,48,72h.

If over threshold, Give extra leucovorin. Interactions: NSAID's, penicillins and probenecid all decrease the clearance of MTX. PPI may cause a small decrease in clearance.

Toxicity: Dose limiting. Myelosuppression Mucositis. Nephrotoxic (precipitation) Hepatotoxic and Neurotoxic (rare). Rescue at high doses with more aggressive hydration, alkalization and more leucovorin. In severe overdose consider Carboxypeptidase which is an FDA approved rapid breakdown of MTX.[53]

Targeted Anticancer Drugs: Principles Correct dosing is important for many targeted therapies Many oral TKI have a narrow therapeutic window. Variability in absorption and metabolism. They are greatly affected by genetic differences (CYP polymorphism and transporters) and drug interactions. BCR-ABL TKIs Therapeutic window is greater than 1000ng/ml. Patients will have a better response to treatment for their CML. Patients with a high BMI and diarrhea should have a dose increase EGFR/ALK inhibitors Patients taking enzyme inducers of CYP3A4 enzymes (Phenytoin/Rifampin) will have less drug levels. Grapefruit juice can also reduce drug levels mTOR inhibitors for oncology treatments target trough level of 3-8ng/ml. LAM patients receiving Sirolimus target

0.5ng/ml Antibodies (Rituximab) No TDM is needed, fixed or weight based Targeted agents (Imatinib) TDM should be performed on the Imatinib and other targeted agents (sunitinib/pazopanib) within IATDMCT consensus (2021). Evidence of a correlation between dose and response has been shown for Imatinib. Variability in levels between individuals is 40-60%. Patients with levels >1μg/ml will have a better outcome. Other targeted TKIs such as sunitinib also show dose limiting toxicity in relation to levels (Imatinib 400mg QID). Drug levels can be monitored for research purposes. Correct dosing can be based on genotype, for example DPYD dosing of fluorouracil Use algorithms where they are available Use PK modelling/Bayesian software Interactions Many drugs are substrates to CYP3A (imatinib/everolimus). Strong inducers/inhibitors will require dose adjustment (see package insert). Acid suppression (gefitinib) TKI can reduce levels of some Toxicity High levels of imatinib can cause myelosuppression. Dose adjustment would be needed if platelets drop Everolimus can cause toxicity (mucositis or hyperglycemia). This can be reduced by titrating down dose depending on trough levels.

Cardiovascular Drugs:

Digoxin Indications: Heart failure with systolic dysfunction (added to decrease hospitalization) and Ventricular rate control in atrial fibrillation/flutter (when other measures inadequate).PK/PD: Cardiac glycoside. Vd ~7 L/kg (massive tissue binding). ~25% renal excretion (filtration + secretion), 75% hepatic/biliary. Protein binding ~30%. Oral bioavailability ~75%. Half-life ~36 h (elevates in renal failure).CL correlates with CrCl: CL (mL/min) 1.3×CrCl + Cl (40 mL/min if no CHF). Target concentrations: Heart failure stabilization – steady-state trough 0.5-0.9 ng/ml. Atrial arrhythmia – use higher levels 1.0-2.0 ng/mL to slow rate. Toxicity rises dramatically >2.0 ng/mL (50% of patients are toxic at 2.5 ng/mL). Monitoring: Always check trough 8-12 h post-dose (after distribution) after reaching steady state (7-10 days). Monitor more closely if changes in renal function. Also check K and Mg, as hypokalemia can amplify toxicity. Loading dose (acute rate control): 10-15 mcg/kg orally or IV (max 1 g) q 6-8 h; intravenous doses can be as high as 50-100 mcg/10 mL for bolus injection (do not use >200 mcg without consultation). Maintenance: Usually 0.125-0.25 mg daily (doses >2.0 mg/d rare and associated with toxicity). Maintenance dose (μg/day): (Steady-state digoxin concentration × CL digest k f/t) / bioavailability where: f = bioavailability (0.75), k = 1.303 CrCl + 20 (mL/min), p = duration of dosing interval. Example: 80-kg elderly (CrCl 30) with heart failure target steady state of 0.8 ng/mL would need ~250 μg/d. Use IBW in obese patients. Renal dosing: Adjust doses based on CrCl Decrease dose or extend interval if CrCl <50 mL/min. Drug interactions: Amiodarone, verapamil, quinidine levels (reduce digoxin dose by 25-50%) Rifampin, antacids, level. Use caution in patients taking loop diuretics, as hypokalemia potent toxicity. Toxicity: GI: anorexia, nausea, vomiting; CNS: confusion, vision change (yellow halos), Cardiac: any arrhythmia (AV block, VT Tach). Use digoxin-specific Fab fragments to treat overdose.[53]

Antiarrhythmic Drugs Principles: Most I-IV (Vaughan-Williams) antiarrhythmics have narrow therapeutic ratios (ESP Class I & III). Several require individual titration and/or special monitoring. Class Ia (procainamide, quinidine): Procainamide NAPA (acetyl metabolite) can build-up; therapeutic combined P + NAPA 10-30 ug/mL (per "reference" labs). Both agents require renally-based dosage. Quinidine: goal ~ 2-5 ug/ml. Watch ECG for QRS, QT changes.

Class I B (lidocaine, mexiletine): Lidocaine IV if new arrhythmia (no routine levels no chronic use, sf half-life 1.5hr) Mexiletine: oral (no routine TDM, half-life 10-12 hrs.) Class III (amiodarone, sotalol, Dofetilide) Amiodarone shows pulmonary toxicity, liver toxicity, handful of others, very long half-life 60 days (primary fat depot), requires longer loading. Post basal doses 100-400mgdaily for long term (QID, BID, TID). Trough 0.5-2.0 mg/L sometimes done (use for premature beats, adherence assessment). Amiodarone dose exceed 1600mg before initiation should not be started in the outpatients (handful of exceptions). QT prolongation (risk for torsades),monitor baseline and during treatment. QT >500 ms, notify provider. QT normally 350-440ms, average.100ms longer in female. Sotalol: renally cleared, adjust for CrCl. Half-life is 12 hours (half of that.05 is circa 4-8 hour delay). Troughs are collected regularly or if common new arrhythmias. Dosing (8to 80 mg bid) adjusted for CrCl 0if CrCl is <60 or is unknown (Eg:weight <12kg),dose should be reduced (dilutional). Amiodarone: loading dose 800 1600 mg/day divided in 2-3 doses, then 200 400 mg/day for maintenance (achieve steady state 13 days). Amiodarone accumulation results in pulmonary fibrosis, liver toxicity. QT measurement is essential as amiodarone blocks QT, prevalence of dementia, and other organ system toxicity. [32]

Psychiatric Drugs:

Lithium Absorption, eliminated unchanged; 100% excreted in urine (free filtration). Half-life ~ 18–36 hrs (slower in elderly, ~36–48 hrs). Excretory half-life is longer in older adults. Therapeutic window for lithium: serum trough 12 hours after intake is 0.6– 1.2 mol/l. For long-term therapy. 0.8–1.2 mol/l. For acute manic phase. Li level > 1.5 mol/l. Can be toxic in the acute phase. Monitoring: Measure titers 5–7 days after starting or increasing dose. After stable dose titers: q1–3 month (T4, renal function, serum TSH). Dosing / Dose adjustment: Initiate at 300 mg BID, increase dose by 300 mg. – Dose adjusted for serum CrCl: If CrCl < 30 mL/min – take half dose or increase interval if Dose titration: New dose = current dose × (target dose/ current dose) Assume linear function 600 mg/day has no serum Li of 0.3 mol/l target serum lithium concentration of 0.8 mol/l Calculate desired new dose 600×0.8/0.3 1,600 mg/day depending on use single or multiple doses. Interactions: Thiazides, NSAIDs (reduce Li dose by 25–50%). ACE inhibitors (Reduce Li dose by 25%–50%) (use in combination with class B diuretics) Caffeine, osmotic diuretics reduce Li.

Antipsychotics (Selected)

Routine TDM is not established for the majority of antipsychotics, although may be used for some (e.g.

Clozapine, possibly haloperidol in research). Subject to plasma level response for some drugs and safety monitoring (e.g. WBC in clozapine). Clozapine: Used for treatment resistant schizophrenia. Extensive metabolism (CYP1A2, 3A4). Half-life 12-16 hrs; smoking increases clearance (dose by 25%). Therapeutic level: Trough >350-400 ug/L (~0.35-0.4 mg/L) is generally recommended for response (wide individual variation). Levels >1000 ug/L increase risk of seizure. Monitoring: Essential ANC monitoring (risk of agranulocytosis). Levels checked for therapeutic monitoring or adequacy of compliance; not used to titrate dose routinely (except in some complex cases). Dosing: Starting dose 12.5mg/day titrated to 300-600mg/day (some patients >800mg/d). Increasing dose to target trough (with concomitant ANC monitoring) or combining with CYP1A2 inhibitor (fluvoxamine) to increase plasma levels (not confirmed in literature) if adequate plasma level with no effect. Toxicity: Agranulocytosis (1-2%), myocarditis, seizures (dose-related), weight gain, dyslipidemia. Haloperidol: Typical high potency agent. No ready TDM value, dose effect most relevant. Plasma levels ~2-10 ng/mL have been reported for clinical effect in schizophrenia although levels associated with side effects overlap. Excessive salivation, EPS, QT prolongation.[34]

Pediatric and Neonatal Precision Dosing:

Antibiotics: e.g. Vanco: (use actual BW): LD 20 mg/kg; LD given q6-8h in some cases Target AUC 400-600 mg/L in children (minimize toxicity, optimize effect). Aminoglycosides: gentamicin 2.5 mg/kg q8h (total BW), use now extended-interval dosing 1 dose/mg/kg/24hrs, with level at 6-14hrs after dose for clearance calculation. Antiepileptics: phenobarbitone IV: 15-20 mg/kg loading dose, target 10-40 mg/l; the t½ is ~4-5 days in neonates; may need lower initial dose in neonates based on enzyme immaturity. Valproate: avoid in <2 years due to hepatotoxicity. Cardio/Sedatives: phenytoin: Clearance ~mg/kg in children, in neonates may have immature enzyme systems necessitating initial maintenance dose for 10-15 mg/kg. Lignocaine: shorter t½ in children so doses can be higher and more frequent. Digoxin: clearance/kg greater in children so lb=8-10 µg/kg+1 for neonates (versus 6-8 in adults); rarely used in children under 12. Theophylline: clearance greater in children so o/l in neonates is greater than in older children. Examples: Neonates with septicemia/gentamicin: 4-5 mg/kg q24h; phenobarb in neonates: LD 15-20 mg/kg, maintenance 5 mg/kg/d.

Geriatric Precision Dosing:

General principles: Decreased renal (even Cr "normal") and hepatic metabolism, increased sensitivity. Common principles: Start low, go slow. Polypharmacy raises interaction potential. Watch for orthostatic hypotension (antipsychotics, antiarrhythmic drugs) and cognitive effects (anticholinergic psychotropics). Renal modifications: Many drugs listed need dose reduction. For example, in the elderly (CrCl <50 mL/min) digoxin dose should be 50-75% of normal. Aminoglycosides in q24h or lower dose. Lithium: use 0.4-0.8 mmol/L to avoid toxicity. Hepatic changes: serum albumin lower (higher free level of drugs which are highly albumin bound – e.g. phenytoin). Start at 50-75% of usual dose of drugs eliminated through CYP enzymes (e.g. Carbamazepine, valproate).

8.9 Patient(s) with Renal and/or Hepatic Dysfunction

Renal impairment: Reduce dosage of drugs cleared by the kidney. Digoxin: give less 50% of the daily dose if the patient has a creatinine clearance of than 50 ml/min (e.g. Give 0.125mg per day). The maintenance dose should equal the patient's creatinine clearance. Use equations previously shown. Aminoglycosides: Extend the interval between the doses to every 36 to 48 hours. Watch blood levels carefully. Lithium: Dose should equal 0.3 of the creatinine clearance % of dose (e.g. If the creatinine clearance is 30 ml/min use 30%). Carbamazepine and phenytoin: These are mainly liver drugs so they are safe to give in kidney failure. Check free levels as uremia may displaced phenytoin. Sirolimus: These drugs have some renal clearance but mostly liver; in kidney disease no adjustment is required. There is a slight buildup of minor metabolites in kidney disease. Hepatic impairment: Reduce doses or dosing frequency of drugs metabolized by the liver. Phenytoin: Reduce the dose by 25% to 50% if the patient has cirrhosis. VPA: Avoid in liver failure because of the risk of life-threatening liver damage. If it must be given reduce the dose by 25% to 50%; check liver function tests regularly. Carbamazepine: Avoid or use the appropriate dose. Metabolism is. The half-life can double or triple. Tacrolimus, Cyclosporine and Sirolimus: These are mostly liver metabolizers; in liver failure the Child-Pugh class C or B state that these drugs should be given in a reduced dose-e.g. 0.03 mg/kg in tacrolimus-and levels monitored carefully. Digoxin: Liver metabolizers; no dose change in liver failure. Dosing adjustment: Use the Cockcroft-Gault equation to calculate the creatinine clearance for dose adjustment. For liver-adjusted dose we use the Child-Pugh classes to decide the dose reduction e.g. 50% reduction in cirrhosis.[35]

SAFETY LIMITATIONS AND CONSIDERATIONS:

Prediction Errors and Patient Safety:

AI can also guide doctors and pharmacists on a dose of medicine. AI has, however, occasionally chosen a dose without considering all relevant patient information, or with incorrect information. Before selecting a dose, doctors and pharmacists should always consider the patient's medical history, kidney function, their current condition and other medicines being taken, as an improper dose may result in treatment being ineffective or the adverse effects of medication.

The dose chosen by an AI system can be affected by the data given to it to make this decision. For example if the patient's condition after treatment or lab results were not available the AI system's recommendation may not have addressed the patient's requirements. For example a patient's kidney function may alter a drug's effectiveness to be processed by the body. If that information is not

taken into account during dose selection the recommendation will not be appropriate.[32]

A different concern is that an AI model may be successful during training but may not always produce accurate results on other patients. Accuracy can depend on the drug, data type used to train the AI model, and the patients that the model predicts about. A systematic review of machine learning based dose individualization suggested that many of the studies had limitations and did not include external validation or testing of clinical utility.

Medicines should be assisted, not replaced, by AI. Doctors and pharmacists need to audit the output and determine whether it's right for that individual patient – to ensure, for instance, that a patient is actually in a health condition that allows them to take certain medication, and to consider insights from other medical data to identify any potential issues.[34]

Data Quality and Bias:

Recommendation. AI-based dose prediction is based on data quality and accuracy. If the data fed to the AI system is out of date, inaccurate, or inconsistent, the AI may generate a poor recommendation. The quality of training data is equally important since the AI takes learning based on data patterns; if the data is unrepresentative of its patient populations, the AI may make less accurate predictions. [49]

A review of machine learning based dose individualization studies pointed out their emphasis on special populations such as pediatric patients. The same review identified a lack of validation and assessment of clinical utility as leading limitations in the current studies [1]. These reports indicate that more evidence is needed before presuming that an AI model will perform well across all patient groups.[35]

Different patient groups can vary in age, weight, health status, organ function, and other factors that affect medication dosing. An AI model built on one population of patients may not work as well with others. For this reason, it is important to determine whether the data used to build an AI model is relevant to how it will be used. Extra attention may be needed to AI models for children and other excluded populations.[38]

Incorrect, unreliable or incomplete patient data can lead to erroneous advice. Information about the treatment, current medication and key lab results are important for dose selection. When that data isn't available, doctors and pharmacists have to. Cross check first and provide proper assessment of it if they want to use the dose suggested by AI.[26]

Oversight and Implementation Issues:

AI can help doctor and pharmacists to select the right dose of a medication but AI recommendation still needs to be verified before using in patient care. Direct interaction, the one-to-one contact between a patient and a healthcare professional is very important as every patient may have different health conditions and treatment requirements. Doctors and pharmacist can check on the patient's history previous treatment, current health conditions and other medications to assess whether an AI recommendation is suitable. Ai may provide recommendation only. It should not replace personalized patient assessment, and the clinical judgment of health care professionals.[8]

There can be difficulties in using AI based dosing systems in hospitals. Some hospitals lack the computers, equipment, technology or resources that an AI based dosing system needs. Staff have to know how to input a patient's data into an AI based dosing system and how to interpret a dosing system's suggestion, if either of these are lacking then an AI based dosing system will not be effective. For an AI based dosing system to work well the data used must be complete, accurate and clear, the resources and staff need to be of a high standard.[35]

Another issue is to see if the model is reliable for a medicine, disease, or set of patients. The model may perform differently in another hospital because the patients, the data, and the ways that doctors treat people may vary. External validation allows other investigators to check if the model performs well at sites other than the original development site. Evidence of the benefit of using the model is also needed because a model that makes good predictions does not necessarily improve patient care.

Security of data is a further concern. Because AI uses and records data from such systems might contain information such as medical notes, medical history, hospital protocols, lab work, and information about medical treatments. Medical institutions have to keep this data secured so that they are not exposed to people who are not supposed to see it, and they need to be safeguarded through the use of security so that they remain private.

Modeling-informed precision dosing applications may require some new workflows at hospitals. Healthcare staff need to understand how the system works, how to interact with the system and how to interpret the dosing advice it provides. The system needs to be integrated into practice so that the healthcare professional is able to easily access the dosing advice without getting confused or waiting for it. A systematic review of challenges in the implementation of model-informed precision dosing found issues such as limited data for model validation, poor standardization of modeling methods, vague guidelines from regulators and additional blood level samples in some settings. They also found that simple and intuitive tools, team work and training of healthcare staff were helpful.[8]

AI-based dosing systems should be thought of as tools, not as replacements, for doctors and pharmacists. AI can assist with dose decisions. Take some of the burden off doctors' shoulders, but that doesn't mean doctors and nurses should ever neglect the doctoring and check the advice before taking action. Judicious testing, good data, trained personnel, compatible technology, secure data management and prudent clinical judgment are all essential to safely using dosing systems.35

EMERGING ADVANCES:

Machine learning and deep learning:

Artificial intelligence (AI) and machine learning (ML) are transformative technologies that can be utilized to advance therapeutic drug monitoring (TDM) and model-informed precision dosing (MIPD). The concept of precision dosing encourages incorporation of various components including, but not limited to, the degree of exposure to the drug and the response of the patient to the developed treatment regimen in order to determine the optimum dosage of a drug. Previously, scientists have attempted to individualize the drug regimen through the implementation of pharmacokinetics and pharmacodynamics (PK/PD) model which aimed to predict the relationship between the administered doses, the route and frequency of administration, the metabolism of the drug in the body, and elimination in order to achieve the desired therapeutic effect. It is important to note that the response of the patients to the treatment regimen varies depending on age, body mass, liver and renal function, disease status, genetic makeup, concurrent drugs, and several other factors.AI and ML methods complement conventional models by analyzing the complex patient data to identify patterns that could be of value to make individualized treatment decisions.[8]

Applications in Therapeutic Drug Monitoring and Precision Dosing:

One important application of ML is to predict drug concentration and exposure. TDM typically involves the measurement of drug concentrations in biological samples and the interpretation of these results in relation to the prescribed dose, the time since the dose was administered, treatment response, and potential adverse effects. ML algorithms can complement this process by using the available information about the patient to predict exposure to the drug or aid in the interpretation of the drug concentration measurement. The review by Poweleit al. describes research using extreme gradient boosting (XG Boost) models to predict exposure to tacrolimus and mycophenolic acid as well as the use of ML predictions in combination with pharmacokinetic models for vancomycin.[8]

Integration of Machine Learning with Pharmacometrics Models:

Traditional pharmacometrics approaches and ML methods have different but complimentary advantages. Pharmacometrics models typically integrate pharmacological and physiological principles to describe a drug's behavior and estimate clinically relevant parameters while ML methods focus on recognizing patterns in the data and minimizing the difference between predicted and observed values. These methods could be combined into a hybrid model in which ML methods identify potentially informative patterns or improve the predictions while pharmacometrics models describe drug behavior and provide a mechanistic basis for interpreting drug exposure. The review highlights several applications in which such an integration could enhance TDM and MIPD.[8]

Real-Time Therapeutic Drug Monitoring: -

Real-time therapeutic drug monitoring is a strategic approach that provides timely information about the drug concentration in order to personalize treatment. Real-time therapeutic drug monitoring generally involves collecting biological samples and sending those samples to the lab in order to determine drug concentrations followed by interpreting those results to adjust the drug dose. Although real-time therapeutic drug monitoring is essential for personalizing drug therapy the delays involved in sample collection and processing the need for equipment and the necessity to account for the time of drug administration before the blood sampling can limit its usefulness. Intelligence and machine learning can estimate drug concentrations based on patient information and model-informed precision dosing to support real-time therapeutic drug monitoring. However, AI-based prediction methods complement rather than replace laboratory-based TDM. [8]

Zhu et al. describe the development of an interpretable machine-learning framework to predict olanzapine concentrations using electronic health record data from 927 patients including 2,142 olanzapine concentration measurements and 472 patient-related features. The authors developed a stacking ensemble model that utilized multiple ML algorithms to improve prediction accuracy. Nine features were identified for the final model that included the daily dose of olanzapine, age, sex, body weight, concomitant valproic acid use, selected laboratory parameters, and the time of blood sampling relative to the first dose administration. These examples illustrate how information from a patient's EHR including demographics, concomitant medications, laboratory measurements, and sampling related factors can be used to estimate drug concentrations. The model had a mean relative error of 13% and an ideal rate of 63.4% (defined by the authors as predictions within ±30% of the measured concentration) and a coefficient of determination (R^2) of 0.5355. [10]

Wearable and Point-of-Care Drug Monitoring: -

Therapeutic drug monitoring (TDM) plays an important role in ensuring drugs are accurately dosed. TDM allows drugs to be tailored to individual patients by looking at how much drug there is and its relevance to that individual. Generally, this is done by sending a blood sample into the laboratory for examination and recommending dosage modifications on the results of tests. Despite the relevance of the TDM strategy in therapeutic management, it is associated with several limitations. The approach requires multiple steps thereby demanding more time for execution. Advanced technologies such sensors and point-of-care devices have the potential to individualize TDM and improve its overall efficacy.[8], [11]

Wearable Sensors for Therapeutic Drug Monitoring:

Wearable sensors can be used to measure biological/chemical information continuously or repeatedly. They have been investigated for measuring drug molecules or metabolite levels in bodily fluids such as sweat, saliva, tears and interstitial fluid. These sensors

are usually electrochemical, optical or other analytical methods. Continuous or repeated measurements using wearable sensors could enable drug monitoring outside of a conventional laboratory setting.

These approaches may be of value for patients who require frequent monitoring or long-term treatment, for instance, in case of changes in drug exposure may affect therapeutic efficacy or safety. The applicability of any sensor will depend on the drug being monitored and the analyte being sampled. It will also rely on the correlation between the analyte concentration and the clinical levels of drug present.[3]

Point-of-Care Therapeutic Drug Monitoring:

Therapeutic drug monitoring that occurs at the point of care (POC) involves carrying out in vitro tests in situations such as hospital wards. POC technologies aim to reduce the turnaround time for results to be obtained so clinicians can make decisions about drug treatment quicker. POC technologies may include portable testing devices, miniaturized sensing systems and simple testing techniques.

There is an interest in obtaining drug concentrations quickly for drugs with a narrow therapeutic window or if it is essential to make decisions regarding treatment quickly to avoid prolonged exposure to potentially toxic concentrations. Research has been undertaken to explore the potential of POC technologies for the administration of certain drugs such as vancomycin, carbamazepine, methotrexate, tobramycin, clozapine and infliximab.

However, the level of clinical development can vary between drugs and technologies. A fast, portable test may not be accurate enough and not appropriate for routine use.[3]

Digital Health and Remote Monitoring:

Digital health technologies have the potential to improve precision dosing by helping collect connect and understand patient-clinical data. Electronic health records (EHRs) tools that engage patients home-monitoring devices and mobile health (mHealth) apps can gather extra information on a patient's health condition, medication use, lab results and treatment history. When this data is combined with model-informed precision dosing (MIPD) it can help doctors make personalized dosage decisions based on changes in a patient's health and treatment needs.[9]

Therapeutic drug monitoring (TDM) is a useful method to fine-tune drug therapy especially for medicines that have a narrow safety range vary a lot from person to person in how the body handles them or can cause harm at high levels. TDM usually involves measuring drug levels in a blood sample and using those results in light of the patient's health. MIPD builds on TDM by using measured drug exposure data, population-based models and Bayesian forecasting to predict how a patient will respond and to decide the dose adjustment. Digital health tools can help gather and use patient data such as age, weight, kidney function, other medicines being taken and general health status all of which support MIPD models. Systems that monitor patients remotely and at home provide data which usually provides a truer representation of their health status. This can be used in conjunction with MIPD systems to help clinicians make decisions regarding treatment if it has been correctly standardized and interpreted. The usefulness of these tools is increased when MIPD software is built directly into the EHR. This removes the need for documentation and reduces the risk of mistakes.[9]

Pharmacogenomics-Integrated Precision Dosing:

Pharmacogenomics is about how people are different in their genes and how these differences change the way they react to medicines. These differences can cause people to respond differently to medicines. They can also change how likely someone is to have bad side effects from medicine. This information can help doctors figure out which patients might need a medicine or a different dose.[12]

Genetic test results can help doctors pick the medicine or change the dose of a medicine. For example there is information that shows that changes in the genes CYP2C9 and VKORC1 are linked to how much warfarin a person needs and changes in CY2PC19 are linked to how well clopidogrel works. Changes in CYP2D6 are linked to how some medicines work. There are chances for test results to help doctors make better choices when it comes to treating patients. However, it is important for doctors to understand what the genetic changes mean and to make decisions based on the information available.[12],[14]

Many studies have looked into the benefits of using information to choose medicines. These studies have used ways like looking at lots of studies at once doing experiments where some people get one treatment and others get another and combining results from many studies.[13]

Like with dosing pharmacogenomic testing can help avoid serious side effects from medicines. Testing can help find patients who're at risk of bad reactions to certain medicines, like abacavir. Testing for the HLA-B57:01 gene can stop a reaction to abacavir. Also changes in the genes TPMT and NUDT15 can help find patients who might have reactions to thiopurine drugs and can help decide how to treat patients with azathioprine or mercaptopurine.[12], [14]

Digital Twins for Individualized Drug Therapy:

Digital twin technology is an idea in precise drug treatment. Digital twin uses a computer model of one patient to help doctors choose the medicine. Digital twin combines kinds of data such as patient records, lab tests, DNA information, data from many people and math models that show how drugs move in the body to create an up-to-date image that belongs only to that patient. The main advantage of twin is that it keeps getting fresh data. Digital twin lets doctors see how different people absorb and react to medicines.[15]

Using a twin allows doctors to make the best choice when treating patients with drugs. A digital twin can take into account many factors which affect how drugs behave within our bodies such as gender, age, weight, liver and

kidney functions, DNA differences, comorbidities, and other drugs. Using this information the digital twin can predict how well a patient will respond to a drug and choose the most effective dosage. Digital twin can also work together with drug level checks and special dosing calculations to give the result for the patient. [15],[17]

Using a twin model for precise medicine is best especially when it is hard to pick the right drug plan. In a made-up case doctors can think about changing the plan may be adding a medicine or changing the dose and then see what happens. This change can be used for a patient who's less likely to have liver failure because the liver works less well. Digital twin predictions are only as good as the data and the rules used to build the model. So digital twin should only be used for the group of people it was made for. [15], [16]

To create a twin doctors gather many pieces of patient data: records from computers, lab tests, medicine lists, drug levels and other important facts. They then use methods, like simulations to make a model that fits that single patient. Examples of these methods are drug movement models and Bayesian prediction. Digital twin is not the same as model-informed precision dosing, which also uses data and math to pick the plan.[15],[16],[17]

Large Language Models and Clinical Decision Support:

Large language models are intelligence tools that can understand and create human language. In the healthcare field they have been suggested as help for making decisions. These tools can summarize data read documents find important advice and share details about medicines and how much to take. These models could help with giving the dose of medicine by putting together information about a specific patient and showing the right evidence to doctors. There is a chance that these models can be used for checking medicines and looking at drug levels in the blood. By looking at the medicines a patient's on test results, drug levels and rules a model could spot problems with the medicines that need more checking. Using these models in checking medicines has looked at finding doses seeing possible bad interactions between medicines and looking at how dose changes are suggested.[18]

These models can be used to help doctors within decision support systems. This is by identifying patterns and information around medicines. A method called retrieval augmented generation is used where the model queries a database to obtain information to generate a response. If these systems are connected to up-to-date medical resources they can give correct and relevant answers. How good the answers are depends on the quality of the information in the database how the information is fetched.[19]

Using these models to help with the right dose of medicine is limited because they might create information that sounds right but is wrong miss important interactions or not take into account important details about the patient. Also different models can give answers and the information given and the situation can change how reliable the advice is, especially for patients with less working organs or those taking many medicines and for medicines that have a small range of safe doses.[18],[19],[20]

Explainable Artificial Intelligence and adaptive drug dosing system:

Explainable Artificial Intelligence (XAI) includes methods that make the way an artificial intelligence system makes decisions easy for healthcare workers to understand. In the world of dosing AI systems might look at things like a patient's age lab results, medicines they are taking and other medical details to suggest the right amount of medicine for that person. [21],[22]

Role of XAI in Precision Dosing:

When making choices for precise dosing it is important to think about all the things that affect how a drug works in a person's body and how that person reacts to the treatment. AI tools can be trained to find patterns in all these factors. With the help of XAI it is possible to find out which patient or drug factors the model thinks are important. Depending on the type of model that is used important factors might include age, weight how well the kidneys and liver are working, other medicines being taken and results from tests that check drug levels.[21]

XAI in Therapeutic Drug Monitoring:

As part of a plan to make drug treatment better therapeutic drug monitoring (TDM) is when the level of a drug in the body is checked to help decide the right dose. When AI is used with TDM data it can help explain how a patient's drug levels relate to their body and what changes in dose might be needed. By helping doctors and nurses understand why a model suggests a dose XAI can help them work better together in dosing.[22]

Common Methods of Explainable AI:

There are many ways to make an AI model easier to understand. Some models, like decision trees and rule-based systems can explain their choices naturally by showing how the input leads to the output. For models special methods can be used to show how each part of the input affects the final result. These methods can also help understand how different parts of the input are connected to the output. The right method to use depends on the model itself. [23], [24]

Adaptive drug dosing system:

Time adaptive dosing systems offer a way to improve pharmacological therapy. These systems adjust the dose as treatment continues using information about the patient. They rely on data such as drug levels, patient response and other health details. By adapting the treatment based on real-time data these systems allow for a personalized approach to care. Common methods include /pharmacodynamic models, therapeutic drug monitoring, machine learning techniques and clinical decision support tools.[10], [11]

The working principle of adaptive dosing systems:

An adaptive dosing system involves combining patient data with a mathematical algorithm. This helps predict what drug exposure or treatment outcomes will result from dosing plans. Factors like weight kidney function, lab results, drug levels and how the patient is responding

can be included. As new data comes in the algorithm updates the drug exposure. Suggests a new dose. The suggested change must be checked against the treatment goal, safety limits and the patient's health.[10],[11]

Role of Artificial Intelligence and Machine Learning:

Artificial intelligence and machine learning are key to these systems. They use algorithms to analyze many variables and make predictions or suggestions. One area of interest is reinforcement learning, a type of machine learning. It allows an algorithm to learn from repeated decisions and improve over time. This method has been tested in pharmacodynamic models to find the best dose for a patient. To work well these approaches need datasets and careful testing before they can be used in real medical settings.[24]

ROLE OF CLINICAL PHARMACIST:

Interpretation of TDM Results:

Evidence based protocols will be designed by clinical pharmacists and pharmacologists. This will include when to monitor, optimal drug levels and interpreting results. This can be adapted for different patient groups. Interpreting Results As TDM can be a complex process, clinical pharmacists and Pharmacologists will have knowledge of pharmacology, individual patients and situations. They can interpret results that can advise what changes can be made. This may include changes to medication, drug type and further investigations. Multidisciplinary Team A multidisciplinary team will be required to undertake TDM. Doctors, Nurses and Lab staff will all be involved. Clinical pharmacists and pharmacologists will provide the team with information so they can make informed decisions.[36] They can advise any drug related issues. Education of Patients and Family Patients and family members are vital when undertaking TDM. Clinical pharmacists and pharmacologists will provide education to patients to ensure they understand the importance of TDM, their results and how we can assist them. This builds up trust and empowers individuals. Research and Quality Improvement TDM is an ever changing field with new drugs and tests being available. Clinical pharmacists and pharmacologists will be leading the research into TDM. This will allow us to determine if TDM is effective and identify areas for improvements to increase care in areas where TDM can be used more. They will look at outcome data to improve processes., identify new applications for TDM, and improve the overall quality of patient care.[34]

Evaluation of Patient-Specific Factors:

There are several factors to consider. Clinical Pharmacists will tailor the drug accordingly.

The most likely factors to be considered are recent height/weight measurements. Recent creatinine and liver function results will also be considered to give the pharmacist an accurate dosage to prescribe. If the patient has a GFR of 20mL/min then Enoxaparin will be prescribed in a reduced dosage or less frequently. If Warfarin needs to be prescribed and the patient has knowledge that they have a variant in CYP2C9/2 or 3 then it will also be prescribed in a reduced dosage.[49]

There are many factors that cannot be easily calculated. Factors such as frailty and creatinine depend on muscle mass so there can be variation depending on what equation is used (Cockcroft-Gault or CKD-EPI). Genetic testing may not be available or covered by insurance. There will be many factors to consider by the pharmacist. Elderly patients with renal impairment and multiple medications are more likely to have drug interactions so they will be prescribed a reduced dosage.

Validation of AI-Generated Dose Recommendations:

Advice could come from machine learning models or advanced population pharmacokinetics. All data should have been obtained from the patient including demographics, lab results and medication. Weight should be within the range of 100-120kgs. Ensure units are correct (mg/mcg/mL/min). Does this advice make sense? You could look at guidelines to help answer this question. If not then it is invalid. However, the pharmacist would know and ensure the advice isn't too extreme. Context: How sick is the patient? The AI doesn't know if the patient is pregnant or on dialysis. The pharmacist will use their knowledge to ensure it does make sense.[37] Interactions: The pharmacist would want to know what medications the patient is taking. Starting new medications can impact drug metabolism. Starting an antifungal can cause an increase in tacrolimus. Safety: Is this a safe dose? Are the troughs toxic? Are they too low to make any impact? Any changes should be planned and monitored. Limitations: Many AIs use black box so we won't know why they came to that conclusion. There will be some bias. If the model hasn't been validated on elderly patients then it may not be as accurate. Has the model been tested on similar patients? Team: Discuss with physicians/care team why you have accepted/rejected the advice. It could be difficult but many clinical pharmacists will use data driven decisions to alter the dose.[34]

Dose Optimization and Medication Safety:

Advice will be provided. Adjustments will be made to the dose, frequency and division of medication. Administration routes were also adjusted. Where appropriate, advice will be given to convert IV medications to oral medication. Advice will also be given to discontinue any unnecessary medication. Advice will be given about high risk/high narrow therapeutic index medications. Advice will be given about key medications such as serious infections and anticoagulants.[37]

Aminoglycosides- Advice will be given to change the regimen to a high once daily bolus to improve kill rate and monitoring. Advice will be given to change the dose of warfarin based on INR. Advice will be given about diet changes if they are taking anticoagulants. LMWHs should be advised to be used as bridging therapy if warfarin hasn't worked well in this instance. Advice will be given about transferring care. Medication will be reconciled on admission and discharge. This will give a full list of what medications they are taking at home. This will prevent duplication, omissions and errors.[32]

RESEARCH GAPS:

Artificial intelligence has opened ways to improve precision dosing. It helps doctors look at details and predict the right drug dose. When used with drug monitoring AI can assist in reading drug levels. Suggest dose changes for individual patients. This is especially important for drugs with a range, where even small differences in drug levels can lead to poor results or harm. Still the evidence available today is not strong enough to support the use of AI-based precision dosing in healthcare. Much of the research far has been about building algorithms using past patient data and comparing how well different machine-learning methods work. While this work is helpful it often does not show if using AI really leads to health outcomes for patients.[32]

An algorithm might give dose predictions in a controlled research setting. Its performance may drop when used in a hospital or with a different group of patients. Also a model that works well with data may not perform the way when information is missing clinical routines change or lab tests are done in a different way. These problems matter a lot in precision dosing because the final advice can directly affect treatment.[38] A systematic review by Li and colleagues found that machine-learning-based dose personalization is still in stages. The review showed weaknesses in study design a lack of testing in settings and limited proof that these tools help patients in life. The review also noted that most studies focus on types of drugs and pay attention to special groups like children. Another recent review on drugs with an index found big differences in study methods, validation approaches and how well models worked. Most of these studies were done in one hospital. Used past data. Because of these gaps more research is needed before we can say that AI-based precision dosing is reliable and effective. Future studies should not improve the accuracy of the algorithms but also test how well they work in real hospitals how useful they are for doctors and patients and how safe they are. The main research gaps are discussed below.[15]

Limited Clinical. Real-World Evidence:

One of the challenges in this field today is the lack of clinical validation for AI-based precision-dosing models. Many studies have created machine-learning models using data. Tested how well these models predict drug doses or blood concentrations. These studies are useful during the development phase. Good performance on data does not mean the model will work well when used in hospitals with real patients.[37]

Another problem is that many studies use data. These studies rely on information already stored in records, lab databases or past research projects. They can help find patterns between a patient's traits the dose given and the treatment outcome. The accuracy of these studies depends on how complete and accurate the records. Important details like when a drug was given, when a blood sample was taken changes in dose, missed doses or other medicines being taken may be. Recorded wrong. This issue is especially important in drug monitoring. The meaning of a blood drug level isn't about the lab result. It also depends on when the sample was taken relative to the dose. If the timing or dosing history is wrong the drug level could be misinterpreted. An AI model trained on data might learn the relationships and give incorrect predictions. So, with datasets there's no guarantee that the model is safe or reliable in real-world settings. Real-world evidence is essential to see how these AI tools work outside of research environments. In hospitals patients often have illnesses. They may take medicines. Their kidney or liver function can change quickly during treatment. In care units health can shift fast. A dosing model must be able to adapt to these changes. It shouldn't just perform well on controlled research data.[47]

Another major gap is the number of studies that look at how AI recommendations affect outcomes. Many studies focus on prediction accuracy—like how close the predicted dose or drug level's to what was actually observed. While these metrics are helpful they don't tell us whether the model truly improves care. A model might predict well. Still, it may fail to reduce side effects help patients reach target drug levels or shorten the time it takes to find the dose. For this reason future research needs to focus on outcomes.[38] Depending on the drug these could include how many patients reach the desired drug concentration how often toxic effects happen how often treatment fails how long patients stay within the target range how long they are in the hospital and other patient-centered results. Researchers should also compare the model's recommendations to methods and see if it helps doctors make better decisions. [34]

The need for validation has also been emphasized in studies on model-informed precision dosing. Dibbets et al. Pointed out that limited validation data is a barrier to using these models in care. Their review also stressed the importance of collaboration between groups and training for healthcare workers who will use these tools. Another key requirement is validation. Internal validation tests a model using the dataset it was built on. This is often done by splitting the data into training and test sets or using cross-validation. External validation however tests the model using a dataset from a hospital, region or healthcare system. It shows whether the model works in environments.

For example , an AI model that predicts tacrolimus doses for transplant patients might work well in the hospital where it was developed. Patients at another hospital may differ in age, health status, genetics, other medicines they take or how often they are monitored. Testing the model in a setting helps confirm whether it still performs well when conditions change.[49]

Clinical validation should also look at the real-world impact of errors. In precision dosing a prediction is not a number difference. The wrong dose could lead to treatment failure or dangerous side effects depending on the drug and the patient. So , validation studies must examine how big the prediction errors are and whether they matter clinically—beyond reporting accuracy. In

sum the current evidence shows promise for AI-based precision dosing. Clinical and real-world testing is needed. Future studies should go beyond building algorithms. They should focus on whether these tools make a difference when used by doctors and nurses in practice.

Lack of Standardized Models and Datasets:

AI-based precision dosing has a problem with no ways to create and test models. Different groups of researchers use kinds of patient data different machine-learning methods different ways to define outcomes different lab measurements and different ways to check their work. This variety is good for exploring ideas. It makes it hard to compare results or see which model works best in real situations.

Models for AI-based dosing depend a lot on the data they are built with. The important factors change depending on the medicine and the situation in the hospital. Things like age, weight, kidney function, liver function, genetic details how sick the patient is, medicines, current medicines, dose history and drug levels in the blood can all matter. Not every study includes all of these. Some models use data like age and lab results. Others include information like genetic makeup or very specific medical details.

This difference makes it hard for the models to make predictions. For example , two models that try to predict the right dose of a medicine might use patient features and different ideas about what the target dose should be. One study might try to guess what a doctor actually prescribes. Another might focus on what dose leads to the level of the drug in the body. These are goals so it's not fair to compare them.

Another problem is that there are no shared datasets. Patient data is often kept in systems like hospital records, electronic health records, lab databases and pharmacy files. The format and level of detail can be very different. One hospital might record when a medicine was given. Another might only note the dose. Lab results might be in units. Use different testing methods.

These differences make it hard to bring data together. Before using the data for models' researchers often have to clean it change it into a format and check for mistakes. If they don't do this carefully the final dataset might have errors that hurt the model's performance. Data from drug monitoring also needs attention. The level of a drug in the blood depends on when the dose was given and when the blood was taken. A drug level without knowing when the dose was given or when the sample was taken might not help predict the right dose. Making sure this information is recorded in a way would improve the quality of TDM datasets. This would help build models.

The way studies measure success also needs to be more consistent. Some studies show how well a model predicts by using things like error, root mean square error, prediction accuracy or how often predictions are within a range. These measures tell things. Also, the amount of error that's okay can be different for medicines because their safe levels and risks are different. For example, a small error might not matter much for one medicine. It could be a problem for a medicine that has a narrow range of safe doses. Future studies should not just show results. They should also explain what those results mean in life. Making how results are reported more standard would help compare models and decide which are useful for which medicines.

There is also no agreement on how to test AI-based dosing models before they are used in hospitals. Some studies show performance. They don't give info about testing outside the study about how well the model fits the real data or about how useful it is, in practice. Checking how well a model fits the data is important. A model might rank patients well. Still give predictions that're always too high or too low. These mistakes need to be found before the model helps with dosing.

Another issue is that there's no way to mix intelligence with older methods like population pharmacokinetic models and Bayesian methods. These older methods are already used in model-informed precision dosing. Artificial intelligence tools can find patterns in data. People need to think about what role they should play. Researchers should say whether an AI model is meant to replace, help or improve these methods. Comparing with these approaches is needed to see if AI brings benefits.[32]

Poweleit et al. Said that data quality, data working together between hospitals and better ways to share data are needed for intelligence and machine learning in managing drug treatment. These points are important. Models built on data might not represent all patients or all situations.

Standardization doesn't mean every hospital has to use the model for every drug. Different medicines and different patient groups might need models. Instead, researchers should follow rules for collecting data defining variables building models testing them and sharing results. This would help compare models while still letting them be adapted to needs. Future research should work to create easy-to-share datasets. Multi-center studies can help collect data. Researchers should also clearly explain how missing data is handled how variables are picked, how outcomes are defined and how models are tested. These steps would make the research clearer and easier to repeat.[34]

Generalizability Across Patient Populations:

Generalizability: How well does an AI model continue to perform in practice, when used with patients or in an environment that are different than the data source? This is one area that concerns me in precision dosing, because drug effects and concentrations can vary widely between individuals. A dosing model developed in one patient population may not be very accurate in a different population, especially if that patient group is different in such factors as body size, age, and disease. That generalizability is the challenge. A lot of AI-based dosing models are derived from a hospital dataset or a sample of patients, which capture only the attributes of that one group of patients. If we apply the AI model in another area or care environment the differences in attributes and care patterns could alter the model's predictions. This

means the generalizability of the AI model is constrained until we also validate it widely.

Age can influence model applicability changes. Children, adults and old people vary in body composition, organ function, drug metabolism and elimination. Children are not little adults and drug pharmacokinetics and pharmacodynamics can change significantly as a child develops. Many older people with multiple comorbidities are also on many medications. A dosing model developed primarily for adults would have to be validated in these other age groups to determine it is appropriate unless the same model could be shown to be applicable to all age groups.

LI et al. The machine-learning models for dose tailoring examined here have failed to consider groups, e.g. children. This is an important shortcoming as many medications require dose adjustments in children and other special patient groups. Further studies are necessary to investigate the applicability of AI models to these patient populations. Generalizability of the AI model to children is still in question.

Pregnant women are another population that needs to be studied. When women are pregnant, this alters the blood volume, body make-up, kidney function, and drug work. This can impact a drug's levels – the dose required for it to be effective. However pregnant women are rarely included in clinical trials, so an adult model may not account for what occurs during pregnancy.[32]

We may also have to treat patients with organ function. Bad kidney function may cause delay in clearance of drugs that are eliminated via kidney. Liver disease may cause variations in drug breakdown to other body processes that are with proteins playing a role in drug movement. The severity of impairment may vary for each drug. Organ impairment data set may not be enough for this subpopulation to be sure about AI model safety.

Other relevant human data for a drug or drug class Genes matter for how a drug will work in someone. The variation within genes that encodes for drug metabolism (Breakdown or transport genes) or drug targets can alter how much drug a person needs to take. For example, CYP2C9 and VKORC1 genes are relevant for warfarin, while CYP3A5 genes determine Tacrolimus levels. Several AI models incorporate gene data for dose predictions, though gene data may not be evenly distributed for all groups. A model created with one set of gene data may not be as accurate for a group with different gene characteristics. Generalizability of the AI model in terms of genetics is limited.

You may also be able to adapt dosing algorithms to ethnic, geographic and economic differences. Patients who come from different regions and socioeconomic groups eat different foods live in different homes and environments have different access to healthcare and may have different disease prevalence and laboratory test patterns. These can all influence the clinical efficacy of a drug and impact the data available to the AI model. A model trained on data primarily from one area may not be applicable to others. The generalizability of the AI model is undermined.

This is even more important if you consider how, you would use AI dosing across countries with different populations and level of health system performance. You might train an AI model using a hospital that depends on certain laboratory values, extensive records, and special tests. But you might not have those in a hospital or low-resource setting. The model may then be difficult to implement without adaptation and revalidation. Generalizability is an issue.

Size of data set does not determine if a set is generalizable. The more heterogeneity a data set has, the better. Even a large data set may not reflect a certain group if most are from the same age, geographic location or type of disease. The characteristic details of the set should be made available to the researchers, and the model tested in each population subgroup.[34]

Because the overall result can hide differences. A model might work well in general. But on people with kidney problems or certain age it does badly. We will report the overall score but we might miss the limitations. Generalizability needs to be evaluated within each subgroup of the AI model.

Testing models in populations outside of development can find issues that may not show up when the model is developed. It's very important that the model should be applied in practice in hospitals and patient groups that were not used in the training data. If the model performs differently the cause should be investigated. It may be necessary to refit or adjust the model with new data before it is used.

Furthermore, generalizability should be assessed longitudinally. Medical procedures, techniques of prescription, laboratory methods and treatment modalities evolve with time. A model developed some years ago can deteriorate in accuracy if the clinical setting changes. So, the performance of dosing systems should be evaluated continuously after deployment and modifications should be validated prior to deployment.

Overall future research will need to continue to include populations and do separate performance checks in clinically relevant subgroups. Particular emphasis should be placed on children, older adults, pregnant women, patient groups with renal or hepatic impairment, as well as underrepresented groups. Such an approach will reveal the areas where AI-based precision dosing is robust and others where evidence is lacking.[49]

Need for Prospective Clinical Studies:

Clinical studies are key to learning whether the AI approaches to determine the right amount of medicine really benefit patients. The majority of the initial efforts have been directed toward developing models and evaluating how these models perform based on the data. Although it is a step, it doesn't entirely predict how these models will function in clinical practice.

In these studies patients are follows over time as part of a pre-designed plan for the study. This allows

researchers to gather information in a structured way. They can include doses of the drugs given, levels of drugs in the blood, how the patients are and any adjustments to doses during treatment. These studies can show how an AI-based approach to titrating doses works in the real world.

Another advantage of this type of research is that it can study the impact of using AI advice on patient care. Researchers, for example, could compare one group of people who receive a dose of medicine based on a doctor's decision to another group who received a dose based on help from an AI-based tool. The research could then determine whether the AI assistance resulted in bad side effects or quicker achievement of the correct dose.

FUTURE PERSPECTIVES:

Individualized Dose Optimization:

The individualized dose optimization is an approach when the dose of a medication that should be taken by the patient may be different because each patient is unique and may have different response to the same drug the same drug dose. That is why using drug monitoring (TDM) and dose adjustment strategies guided by pharmacokinetics modeling and connected digital therapeutics can help choose doses that work best while keeping side-effects.[8], [24]

I believe this approach is the future of medicine.Model-informed precision dosing (MIPD) is an approach to precision dosing. MIPD uses population PK (PopPK) models, data that's specific to each patient and drug concentration information to forecast how much of a medication will reach a patient. MIPD uses Bayesian forecasting so that doctors can decide on a dose that fits the predicted PK parameters while taking into account each patient's data and drug concentration.[8],[24],[26]

MIPD is especially useful for medicines that have an index, such as vancomycin and lithium because too little or too much drug can cause treatment failure or harm. I see MIPD as a tool for dosing. The promise of dose prediction was shown in a study that built a tool using three PopPK models for vancomycin to predict drug levels in patients. The researchers checked how well the models worked by looking at data from 15 patients and found that the models were hopeful but varied in how accurately they predicted concentrations.[24],[27],[28]

Real-Time AI-Guided Therapeutic Drug Monitoring:

levels from the interstitial fluid of six participants. During the 24-hour period, the device was generating results every five minutes, with the stability of the sensor being primarily tested during the first 12 hours of the experiment. The information gathered from the application of the models identified the characteristics of the distribution and elimination of the drug, offering invaluable data, which cannot be accomplished by conventional laboratory tests.[40]

The application of AI and ML can potentially enhance real-time TDM, as the integration of patient data with drug level results can enable clinicians to make more accurate conclusions. By employing population pharmacokinetics and Bayesian forecasting, AI can predict the response, exposure, and future levels of drugs for an individual patient, which can support the clinicians in identifying the appropriate doses to be administered. The technology is especially beneficial for narrow therapeutic range drugs like vancomycin and immunosuppressants, where the achievement of the appropriate exposure is of paramount importance for the development of a safe and effective treatment regimen.[8],[24],[26],[38],[9]

Integration of Pharmacogenomics Therapeutic Drug Monitoring and Artificial Intelligence:

I think that the combination of pharmacogenomics drug monitoring (TDM) and artificial intelligence (AI) can offer big benefits to making drug doses fit each person. Pharmacogenomics looks at differences that change how drugs work in the body. TDM is about finding out how much of a drug is in the blood. AI, which includes machine learning can look at the data from TDM and group information to make drug doses better suited for each person.[8],[24],[26],[9]

Pharmacogenomics, when used on people can cause differences in how the body breaks down drugs and different amounts of medicine needed. For example changes in the CYP2C9 and VKORC1 genes change how warfarin a person needs. Also the CYP3A5 genetic type changes how tacrolimus works in the body and how much is needed. Adding this information can help make better treatment plans with tacrolimus, including a starting dose.. These genetic factors alone are not enough to know the right dose because other things like age how well the organs work, other medicines whether the person takes the medicine as told and the person's health can also change how the body deals with drugs.[24],[43],[44]

The data from TDM helps doctors understand how a person reacts to a medicine plan. When this data is added with information from pharmacogenomics the way the drug works in groups and TDM it can help figure out why people react differently to medicines. For instance, the genetic type of a person for CYP3A5 is very important for the dose of tacrolimus. The guidelines from the Clinical Pharmacogenetics Implementation Consortium say that doctors should use the CYP3A5 type to decide the tacrolimus treatment.[8],[24],[26],[44]

Ai-enabled clinical decision support systems:

AI-enabled clinical decision support systems are tools made to help doctors and nurses pick the medicines find the best doses and keep patients safe. I notice that doctors and nurses appreciate tools that help them pick the medicines. AI-enabled clinical decision support systems use technology such as intelligence and machine learning and combine it with each patient's health details to give advice that fits that person. In dosing AI-enabled clinical decision support systems can merge health records, lab results, past medicines taken drug-monitoring measurements and models of how the body handles medicines.[37],[39],[9],[45]

One big use for AI-enabled decision support systems is to predict how much medicine a person has in their body

and what dose they need. I see that the system can learn from doses and measured levels. By looking at doses a patient has taken and measured medicine levels AI-enabled clinical decision support systems can find patterns that reveal how the medicine works in the body. When combined with models that show how medicines move through the body and a method of predicting from known data AI-enabled clinical decision support systems can estimate how much medicine is in a person and help adjust the dose. This is very important for medicines that have a safe range, such as vancomycin and tacrolimus because too little or too much can harm the patient.[27],[37],[44]

Digital Twins for Predictive Dosing:

Digital twins are models of each patient that are constantly updated with the patient's biological data. In precision pharmacotherapy digital twins can combine AI, PK/PD models, drug monitoring (TDM) lab tests and other patient data to predict how a drug will work and to tailor dose plans.Unlike fixed dosing strategies digital twins strive to maintain a picture of a patient's changing body.[45] How the patient reacts to treatment. When new clinical information is added digital twins can run simulations of dose schedules and forecast drug levels. This helps clinicians weigh the benefits and risks of various treatment plans.[40]

Future Applications

1. Predictive Dose Optimization: The application of digital twins enables the simulation of doses and intervals in order to identify those most likely to achieve the desired outcome.

2. Prediction of Toxicity: In addition, digital twins can recognize increases in exposure to drugs that could be harmful and recommend the necessary adjustments to the dose.

3. Continuous personalization: Digital twins update predictions whenever a patient's condition organ function or treatment response changes.

4. Integration of patient-specific data: Digital twins merge TDM, pharmacogenomic data, lab tests and clinical details to enhance prediction accuracy.

5. Decision support: Digital twins give clinicians and pharmacists patient-specific predictions helping them make dosing decisions.[40],[46]

Home-based and remote therapeutic drug monitoring:

Home based and remote therapeutic drug monitoring (TDM) involves the collection of samples by patients at the comfort of their home to measure drug levels. Conventional TDM is carried out in the hospital. Involves venous blood sampling, a potentially inconvenient process for patients who require regular assessments. Alternative sampling methods, such as dried blood spot (DBS) sampling and volumetric microsampling (VAMS) require volumes of capillary blood and could be useful in facilitating remote TDM monitoring.Such techniques could reduce hospital visits improve convenience and facilitate long-term monitoring for patients taking drugs that require dose individualization.[41],[42]

Role of Artificial Intelligence in Remote TDM Essay

Artificial intelligence or model-informed precision dosing has the potential to improve the interpretation of TDM results by taking into account the patient's individual characteristics such as the concentration of the drug, age, body weight organ function, dose history and laboratory investigations. These strategies could predict drug exposure. Support clinicians in determining whether to adjust a patient's dose. Such digital health technologies could also enable the exchange of test results between patients, laboratories, pharmacists and prescribers.[9]

Future Applications

1. Monitoring of patients via a remote patient management system to allow drugs to be monitored without the need for hospital visits.

2. Optimization of individual dose based on measured drug concentrations and characteristics.

3. Increased patient convenience: Overcoming the inconvenience of repeated blood sampling procedures.

4. Clinical review: Supporting clinicians in identifying drug concentrations requiring evaluation.

5. Healthcare integration: Connecting home-sampling services with health records and model-informed precision dosing.[28],[9],[41],[42]

Expansion into Pediatric and Rare Diseases:

Artificial intelligence assisted precision dosing has uses in situations involving children and people with uncommon diseases, where choosing the right amount of medicine can be hard. The problem is made difficult because as people get older the way their bodies work and how they absorb and break down medicines change; so the dose for a child may not be simply a smaller version of the adult dose.[46],[47]

Role of AI in Pediatric and Rare-Disease Precision Dosing

Artificial intelligence and machine learning combined with knowledge can be used to look at the data that exists about traits. This data can be used to find links between how the body reacts and how the drug works, such as body weight, age of the genetic background how the organs are working, lab results and levels of medicine in the blood. When these methods are properly checked, they can help create medicine and treatment. They can also help with the study of how medicines work in the body and how they affect the body (PK/PD).[46],[47],[48]

Future Applications

1. Dose finding based on age: Finding the amount of medicine that takes into account the changes in the body and how metabolism works as people get older.

2. Customized treatment: Using information about the patient and medicine levels to create a dose that's right for each person.

3. Better prediction: Using real-world data along with models of how medicines work in groups of people and simulations to look at the properties of the drug and how much should be given.

4. Predicting exposure: Creating models of how much medicines in the body and identifying what factors can make that amount more or less.

5. Diseases that are rare: Using models to develop medicines and find the right dosing in studies for patients who have diseases.[46],[47],[48]

Pharmacist-Led AI-Assisted Precision Dosing:

Pharmacist-led AI-assisted precision dosing is a way of thinking that brings together pharmacists' knowledge, artificial intelligence (AI) therapeutic drug monitoring (TDM) and model-informed precision dosing (MIPD). Pharmacists can help with reviews of drug plans looking at drug levels, managing drug interactions, handling side effects and adjusting doses. Also, AI can help pharmacists do precision dosing by looking at data and giving advice based on computer programs.[28],[49]

AI-Assisted Precision Dosing: Role of Pharmacists

Looking at TDM results: pharmacists can check drug levels along with the patient's dose, general health and other lab results to find the way to give the medicine.

Customized dose suggestions: using software for how the body handles drugs and MIPD pharmacists can suggest the way to give the right amount.

Finding drug issues: AI can help find drug interactions, the doses and the risk of bad reactions that a pharmacist needs to handle.

Taking into account each patient's details: pharmacists can look at the suggestions. Think about the patient's weight, age, how well their organs work, their genes if known and other things.

Pharmacist's judgment: the pharmacist can look at the advice and decide if it is right for the patient's overall condition and their own experience.[27],[49]

Future Ideas

AI-assisted precision dosing can be added to health records and pharmacist software to help with decisions by giving details about each patient explaining TDM results and finding which patients could get better from precise dosing. Also, if pharmacists take part in training, checking and using the systems it can make the advice more useful and correct. It can stop the advice from being wrong or misunderstood.[38],[49]

CONCLUSION:

Precision dosing is a breakthrough in personalized pharmacotherapy by aiming to deliver the best possible outcome while causing no harm. The advancement of an intelligent therapeutic drug monitoring (TDM) for dose optimization by coupling combination of clinical data, patient characteristics, patient physiology, pharmacokinetic (PK) / pharmacodynamics (PD) data, patient-specific drug measurements with the aid of artificial intelligence (AI) model showed great potential for individual dose adjustment and risk diagnosis.[1] AI-assisted TDM could predict drug doses, spot dangerous risks, and make early adjustments. This new technology can be critical for a class of drugs with narrow therapeutic index such as vancomycin and tacrolimus that inflict serious renal or central nervous system toxicity when not administered correctly. This innovative monitoring system still faces many challenges, including molecularly precise dose prediction, data heterogeneity, precision prediction capability, model interpretability, and safe implementation and validation. But the use of such algorithms will lead to safer, more efficacious and more tailored individualized treatment of patients.[8]

DECLARATION:

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review article.

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Author Contributions

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Tables and Figures

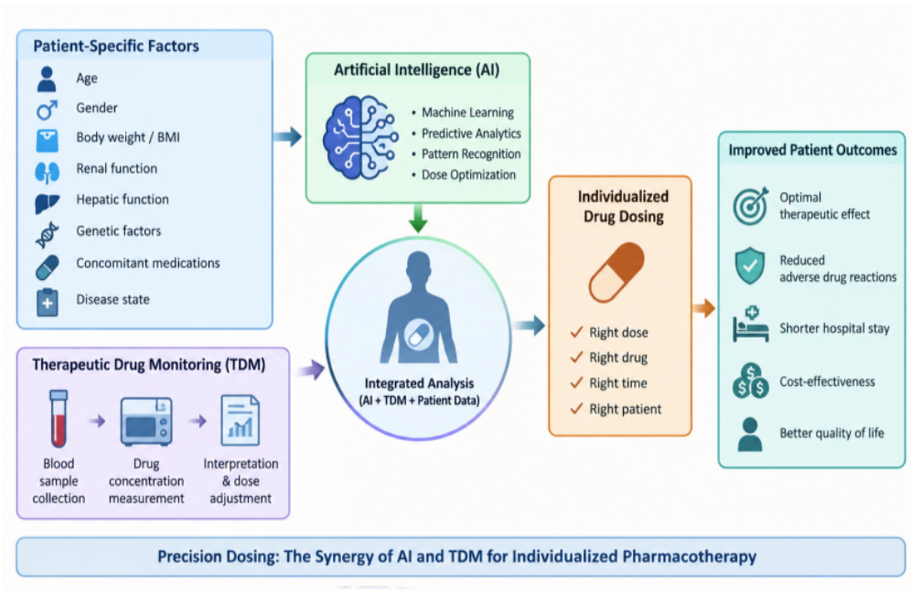

Figure 1. Conceptual framework illustrating the integration of artificial intelligence and therapeutic drug monitoring for individualized precision dosing.

Table 1: -Databases Used and Their Roles in the Literature Review

Database	Role in this review
PubMed/MEDLINE	Primary biomedical resource; searched with MeSH headings and free text
Scopus	A multidisciplinary scope of journals covering engineering and information sciences
Web of Science	Core Collection indexing and citation tracking of important papers
ScienceDirect	Complete volumes of all Open Access journals
Google Scholar	**An additional source for conference papers, preprints and gray literature; up to 200 of the most relevant search results for each individual query will be displayed.**

Table 2: -Search Strategy and Keywords Used for Literature Identification

Concept block	Example terms
Artificial intelligence	"Artificial intelligence" (AI), "machine learning", "deep learning", "neural network", "random forest", "reinforcement learning", "Bayesian", "gradient boosting."
Therapeutic drug monitoring	"Therapeutic drug monitoring"(TDM), "drug monitoring", "plasma concentration", "area under the curve", "model-informed precision dosing" TDM.
Presicion dosing	**Dosing "Precision medicine", "precision dosing", "individualized dose", "dose optimization", "dose adjustment", "personalized dosing", "dosing algorithm".**

Table3: - Data Extraction Domains and Key Parameters

Domain	Items extracted
Study	Authors, year, country, design, setting, sample size
Population and drug	Patient group, drug or drug class, indication.
AI approach	Algorithm type, input variables, training and validation method, software.
TDM component	Sampling strategy, assay, target concentration or AUC
Performance	Accuracy, bias, precision, target attainment, clinical outcomes

Limitations	**External validation, explainability, bias, implementation barriers.**

Table4: - Comparison of Conventional Dosing and Precision Dosing Approaches

Dosing Paradigm	Primary Informing Data	Core Methodology	Key Limitations
Weight / Covariate Dosing	Weight, surface area, serum creatinine	Empirical formulas, identified names	Ignores wide between-subject differences
Conventional TDN	Static trough drug concentrations	Comparing thresholds to population ranges	Reactive adjustments require a steady state.
Model-Informed Precision Dosing (MIPD)	Sparse PK levels, genotypes, clinical covariates	Population PK/PD models, Bayesian forecasting	Static snapshots, requires model qualification
Dynamic Multiomic & RL Dosing	**Continuous biosensors, EHR streams, multiomics.**	**Reinforcement learning, digital twins**	**Interoperability hurdles, SaMD regulatory demands**

Table5: - Flaws of traditional dose selection and its downstream clinical implications

Evaluation Dimension	Conventional Approach	Identified Limitations	Clinical Consequences
Dose-Response Dynamics	Assumes linear monotonicity	Ignores target saturation and plateauing efficacy	Administers excessive doses beyond receptor saturation
Toxicity assessment	Assessed acute DLTs in cycle 1	Misses the cumulative and delayed toxicities	Causes treatment discontinuations and dose reductions
Statistical Design	Uses 3+3 rule-based cohorts	High error rates and poor sample precision	Frequently misidentifies the true recommended dose
Efficacy Integration	**Only considers safety to decide the dose**	**Ignores exposure-response and pharmacodynamics**	**Discards smaller doses which offer better long-term viability**

Table6: - Key Responsibilities of Clinical Pharmacists in Therapeutic Drug Monitoring Interpretation

Task	Key Points
Verify sample timing	Ensure peak/trough correctly timed (e.g. true trough = just before next)
Consider PK parameters	Relate level to expected half-life, CL; use AUC or peal/MIC models
Compare to therapeutic range	Note whether level is therapeutic or supra therapeutic
Adjust dose as needed	Recommend dose or interval changes to achieve target exposure
Account for lab/ assay issues	Confirm units and assay (total vs free); flag implausible values
Correlate with clinical status	**Evaluate patient response, organ function, side effects alongside levels**

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