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Model-Informed Precision Dosing: Background, Requirements, Validation, Implementation, and Forward Trajectory of Individualizing Drug Therapy

Adam S. Darwich,[1] Thomas M. Polasek,[2,3,4] Jeffrey K. Aronson,[5] Kayode Ogungbenro,[6] Daniel F.B. Wright,[7] Brahim Achour,[6] Jean-Luc Reny,[8,9] Youssef Daali,[8] Birgit Eiermann,[10] Jack Cook,[11] Lawrence Lesko,[12] Andrew J. McLachlan,[13] and Amin Rostami-Hodjegan[4,6]

[1]Logistics and Informatics in Health Care, School of Engineering Sciences in Chemistry, Biotechnology and Health (CBH), KTH Royal Institute of Technology, SE-141 57 Huddinge, Sweden

[2]Department of Clinical Pharmacology, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia

[3]Centre for Medicine Use and Safety, Monash University, Melbourne, Victoria 3052, Australia

[4]Certara, Princeton, New Jersey 08540, USA

[5]Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX2 6GG, United Kingdom

[6]Centre for Applied Pharmacokinetic Research, The University of Manchester, Manchester M13 9PT, United Kingdom; email: amin.rostami@manchester.ac.uk

[7]School of Pharmacy, University of Otago, Dunedin 9054, New Zealand

[8]Geneva Platelet Group, Faculty of Medicine, University of Geneva, CH-1211 Geneva, Switzerland

[9]Division of General Internal Medicine, Geneva University Hospitals, CH-1211 Geneva, Switzerland

[10]Inera AB, Swedish Association of Local Authorities and Regions, SE-118 93 Stockholm, Sweden

[11]Drug Safety Research & Development, Pfizer Inc., Groton, Connecticut 06340, USA

[12]Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando, Florida 32827, USA

[13]School of Pharmacy, The University of Sydney, Sydney, New South Wales 2006, Australia

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Abstract

Model-informed precision dosing (MIPD) has become synonymous with modern approaches for individualizing drug therapy, in which the characteristics of each patient are considered as opposed to applying a one-size-fits-all alternative. This review provides a brief account of the current knowledge, practices, and opinions on MIPD while defining an achievable vision for MIPD in clinical care based on available evidence. We begin with a historical perspective on variability in dose requirements and then discuss technical aspects of MIPD, including the need for clinical decision support tools, practical validation, and implementation of MIPD in health care. We also discuss novel ways to characterize patient variability beyond the common perceptions of genetic control. Finally, we address current debates on MIPD from the perspectives of the new drug development, health economics, and drug regulations.

ADR: adverse drug reaction

Precision dosing: tailoring drug therapy to the needs of an individual, or group, informed by pertinent intrinsic, lifestyle, and environmental factors

Model-informed precision dosing (MIPD): prediction methods for optimizing treatment benefit-to-harm balance, based on individual characteristics of the patient, disease, treatment, and other factors

Precision medicine: tailoring medical treatment to the individual characteristics of each patient

INTRODUCTION

Prescribing medicine is one of the most challenging responsibilities in health care. The principles are simple: Choose the appropriate dosage regimen for the right drug, at the right time, and then monitor the outcomes. In practice, it is much more difficult. An increase in the number and efficacy of drug therapies has led to positive gains in life expectancy. However, this means that patients are generally older, suffer from multiple comorbidities, and are medically more complex than they were a generation ago. Failed drug therapies are therefore common, albeit difficult to quantify, and adverse drug reactions (ADRs) continue to cause significant patient harm and financial burden (1). Smarter ways to use limited health-care resources are needed to create long-term sustainable systems that improve patient outcomes. Greater attention to selecting the appropriate dose, rather than the default registered dose, for a patient is therefore a public health priority (2, 3). This is commonly termed precision dosing (also known as personalized or individualized dosing) (4, 5).

The idea that modeling and simulation could inform precision dosing dates back to the late 1960s with the work of Sheiner (6) and Jelliffe (7). There is currently a resurgence in the field and a new acronym, MIPD (model-informed precision dosing) (8), which may be defined as the use of computer modeling and simulation to predict a drug dosage regimen that is most likely to yield a better benefit-to-harm balance than traditional dosing for a given patient, based on their individual characteristics (9). A groundswell of enthusiasm for MIPD occurred in the years following President Obama's State of the Union Address on precision medicine in January 2015 (**https://obamawhitehouse.archives.gov/precision-medicine**). A health-care summit on MIPD was held in Manchester, England, in May 2016 (10); an Asian symposium on precision dosing was presented in Busan, South Korea, in December 2018 (11); and the US Food and Drug Administration (FDA) convened a public workshop on the topic in Bethesda, Maryland, in August 2019 (12). Some landmark advances for MIPD have recently been published, including the virtual twin concept to predict pharmacokinetics (13), liquid biopsy technologies to quantify the activities of hepatic drug-metabolizing enzymes in vivo (14) and account for interindividual

variations in measurements that are not related to the abundance of enzymes and transporters (15), quantitative systems pharmacology and toxicology models to better describe pharmacodynamics (PD) (16), and randomized controlled trials showing superior clinical outcomes with MIPD compared with traditional dosing (17).

The aim of this review is to further advance the debate and discussion on MIPD by defining an achievable vision for MIPD in clinical care. It begins with a historical perspective on variability in dose requirements and then addresses technical aspects of MIPD, including the clinical need for dosing decision support tools, practical validation, evaluation, and implementation of MIPD in health care, and novel ways to characterize patient variability for modeling and simulation. The final parts of the review discuss the latest approaches to MIPD from the perspectives of the new drug development, health economics, and drug regulations.

PD: pharmacodynamics

Virtual twin: a computer-based simulation model that integrates physiological and biological information to mimic an individual patient

PK: pharmacokinetics

A PHYSICIAN'S PERSPECTIVE ON VARIABILITY IN DOSAGE REQUIREMENTS: SOURCES OF VARIABILITY, TERMINOLOGY, AND STRATEGIES

Although doctors have recognized the variability in human responses to pharmacological interventions since medical practice efforts to treat patients began, only in the 1970s did the sources of such variability start to be elucidated (18, 19). Variability in drug response can arise from different sources, some of which are determined genetically and some nongenetically. (*a*) Pharmaceutical variability reflects differences in pharmaceutical formulations, drug amount, rate of release, or a combination thereof. This variability is nongenetic. (*b*) Variability in pharmacokinetics (PK) arises from differences in the rate and extent of drug absorption, distribution, and clearance. Many patient attributes determining drug absorption (e.g., bile release and gastrointestinal motility) and the conditions upon drug administration (e.g., concomitant drugs or food) are nongenetic. Drug disposition is determined by a mixture of genetic (e.g., drug metabolism and transport) and nongenetic (e.g., renal function) factors. (*c*) Pharmacodynamic variability arises from differences in the responses at the site of action, at targets for both beneficial and harmful effects, and is largely genetic in origin.

Genetic factors that determine variability in dosage requirements may result from single gene polymorphisms but are more often polygenic. Nongenetic factors may be endogenous (physiological or pathological) or exogenous (diet or other medicines). Few pharmacological outcomes can be fully explained by a single genetic test.

Since the 1970s, clinicians have sought ways of devising individual dosage regimens to achieve a favorable balance between benefit and harm. Terms such as individualized, personalized, stratified, and precision have arisen and have variously been coupled with terms such as medicine and treatment.

Individualized, a term in use for many years (20), implies tailoring treatment to individual needs, taking account of contributory variables. It suggests no assumptions about the methods used or sources of variability. Personalized originally meant much the same as individualized (21). However, in the 1980s it was applied to the use of genetic polymorphisms in preventive medicine, purportedly creating "medicine that will be more efficient and less burdensome for the community than the present mass system" (22, p. 1474). It then started to be used to refer specifically to the supposed usefulness of genetic tests in predicting individual responses to treatment (23). The realization that purely genetic factors were insufficient for determining individual doses or predicting outcomes in most cases, coupled with the desire to use pharmacogenetics predictively, led to the idea of stratified medicine (24), in which individuals would be grouped according to common

characteristics, often a shared biomarker, rather than treated individually. The term precision emerged in the 1990s (25). However, it is imprecise, because both accuracy and precision are needed in drug therapy. Nevertheless, the meaning has converged with other terms and is the current buzzword. A committee of the US National Research Council defined personalized and precision medicine using the same words (26, p. 124): "the tailoring of medical treatment to the individual characteristics of each patient"; it then contradicted itself by saying that this means "the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease."

We believe that whichever term is used, and individualized is the least value laden, they can all be circumscribed in a definition that recognizes that the factors that produce variability are both nongenetic and genetic, endogenous and exogenous: "tailoring of drug therapy to the needs of an individual or group of individuals, informed by intrinsic genetic and nongenetic characteristics, lifestyle, and pertinent environmental factors."

Delineating genetic variability has four major applications: The first is diagnosis, which has been achieved for some rare conditions, exemplified by the 100,000 Genomes Project (27). The second is dosage determination, which has not been achieved for any drug. For example, none of the 112 polymorphisms in 25 genes predicted opioid dosage requirements in patients with cancers (28). Combining three polymorphisms and two nongenetic variables produced a model that explained 67% of warfarin dosage variability (29); if, as this result suggests, each factor explains on average 20% of the variability, it would take 10 independent factors to explain 90% of variability. Third, avoiding ADRs has been achieved for single adverse reactions to a few drugs (e.g., abacavir) (30). Last, targeting drugs for beneficial outcomes has been achieved for some cancer chemotherapy agents.

Clinicians deal with variability in several ways. (*a*) They ignore it, applying a one-size-fits-all approach. This is appropriate in preventive medicine (e.g., vaccines, hormonal contraceptives, and polypills) (31). However, prescribers may be forced to adopt this method because trials often test only one dosage. (*b*) They titrate the dosage and monitor outcomes (32). This is generally difficult to do because of a lack of time, the difficulty of measuring true outcomes, and the inadequacy or lack of clinically relevant biomarkers (33). (*c*) They use computerized reminders, which are often ignored because of alert fatigue (34). (*d*) They use pharmacogenetics to target benefits and avoid harm. This is still restricted in practice to a few cases such as targeted therapies in cancer; genetic markers rarely predict doses with high certainty and phenotype does not always reflect genotype (e.g., thiopurine metabolism) (35).

POPULATION PHARMACOKINETICS- AND PHARMACODYNAMICS-GUIDED DOSING

During the 40 years since its introduction to the field of pharmacology, the population approach to data analysis (mixed-effects modeling) has been increasingly applied to PK and PD during drug development and in clinical practice. Population PK/PD (pop-PK/PD) is the study of variability in drug concentration-time and drug effect-time profiles between individuals following drug administration (36). The models analyze individual data, typically using compartmental models, whose individual parameters are related to the population mean and its variability. The uniqueness of this approach is that the variability in the data can be explained by group- or individual-specific covariates. Analysis of covariates has been more common in pop-PK than in PD and can include demographic, pathophysiological, and lifestyle variables. For a given data set, a pop-PK model describes a typical individual profile, whose variability can be explained by known covariates, the remaining unexplained variability of model parameters, and random error.

Once established, pop-PK models inform dosing by determining regimens for individual patients using different contributions of the covariates that will achieve the same target concentration. The aim is to reduce the variability in a target concentration for a particular patient. A model can be used to guide dosing at either the group or the individual level (37). Group-guided dosing involves the use of covariates in a model to predict the dose required to achieve a target concentration. The individual groups can be identified on the basis of a categorical covariate, such as the cytochrome P450 (CYP) enzyme genotype, and it is also possible to categorize continuous covariates depending on the effect of the covariate on the parameter. Important advantages of this approach are the ease of implementation, depending on the number of groups, and no requirement to measure the response (concentration), unless there is a narrow therapeutic index. There are examples of group-guided dosing to inform dosage adjustment, based on the results of clinical trials, as recommended on the label (38), and there are examples of this approach used for clinical dosage recommendations for licensed drugs to improve benefit, particularly in special populations in which drugs are used off-label. In general, pop-PK is suited to drugs with high PK variability. **Figure 1** provides an example of the workflow for implementing such an approach (38).

CYP: cytochrome P450

Individualized dosing involves measuring the concentration of drug in plasma to tailor the dosing regimen. Thus, the approach estimates individual PK parameters using a pop-PK model as prior information and then fine-tunes it further with a few individual measurements. Because this approach requires individual measurements, therapy can begin with group-guided dosing. This

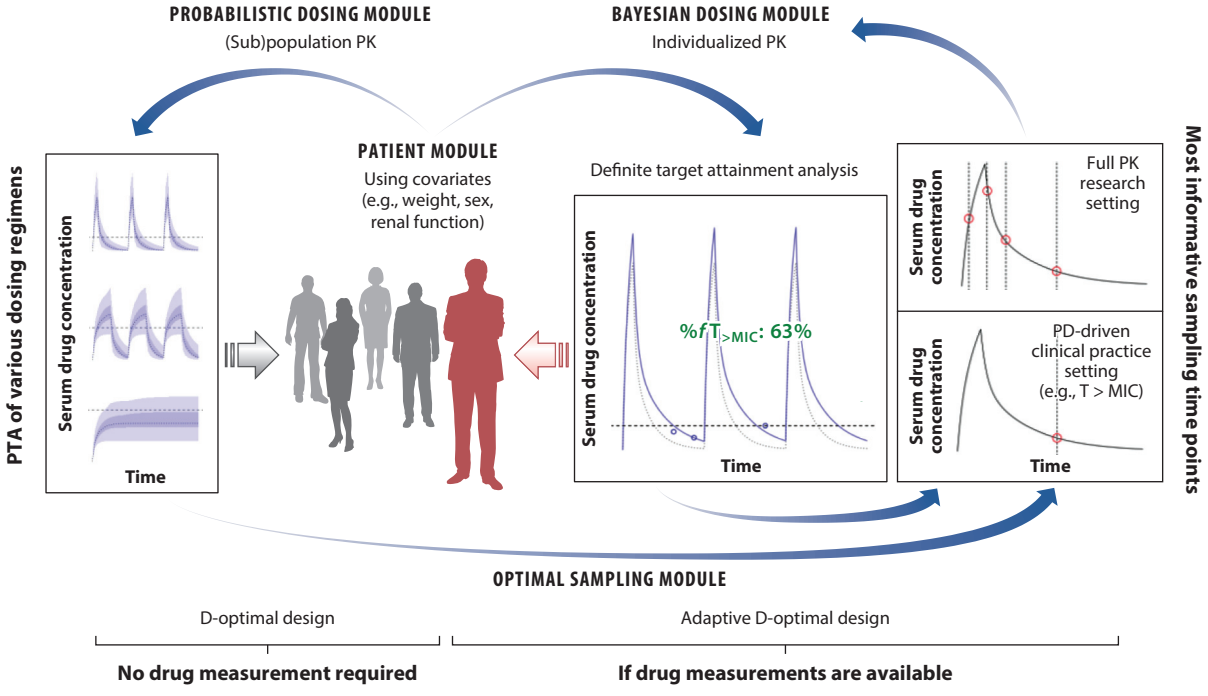

Figure 1

Example of a workflow for population PK/PD precision dosing. Dose personalization can be carried out using covariates either alone, to predict so-called subpopulation PK, or together with therapeutic drug monitoring and Bayesian feedback of PK or PD. Figure adapted with permission from Reference 38. Abbreviations: MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; PTA, probability of target attainment; T > MIC, time above MIC.

approach is also termed therapeutic drug monitoring (TDM) and target concentration intervention and has been implemented in commercially and freely available software (see the section titled Bayesian Feedback and Dose Adjustment as Opposed to Trial and Error for further information).

TDM: therapeutic drug monitoring

CDSS: clinical decision support system

EHR: electronic health record

For a pop-PK model to be used to adjust doses in clinical practice, it must be developed appropriately and validated adequately. Such models should at a minimum contain the most relevant physiological and biological attributes determining the drug's disposition and enough attributes to explain a substantial portion of observed variability. Although attributes related to body size and age (the most commonly tested covariates) are essential, they are not adequate. A pop-PK model can be validated internally, externally, or prospectively to diagnose misspecifications (39). Prospective evaluation can be included in studies designed to evaluate the potential benefit of the method, or device, over current practices used for dosage adjustment. Notably, these models cannot address the impact of covariates that were not part of the original data set.

BAYESIAN FEEDBACK AND DOSE ADJUSTMENT AS OPPOSED TO TRIAL AND ERROR

Bayesian theory provides a statistical framework to formalize the intuitive process of trial and error for dose optimization. In clinical practice, prior expectations about a drug's response at a given dose are updated by monitoring the patient for outcomes. A Bayesian dosing system works much the same. The setup includes a prior model, a system of patient data inputs, a search algorithm, a means of outputting individualized parameter estimates from the model, and individual response predictions. The model provides the prior population estimates for each of the parameter values. Individualized estimates of the parameters are usually obtained by searching for the parameter values that satisfy the observed data for both each individual and expected prior values by minimizing a maximum a posteriori (MAP) objective function (40). The prior is usually fixed, with the predictions updated on the basis of new data (see 41 for an exception). Time weighting penalties are often incorporated to down-weight older observations. Most methods provide point estimates of parameters rather than a full Bayesian posterior.

Implementation

Bayesian forecasting tools for dose individualization were first proposed by Sheiner et al. (40, 42) and have since been developed for several therapies (43–45). Many are developed as software, such as Mediware (**http://www.mediware.cz/en/mwpharm/**) and DoseMeRx (**https://doseme-rx.com/**), and some tools, such as BestDose (**http://www.lapk.org/bestdose.php**), use nonparametric methods. Increasingly, web-based dashboards, such as Tucuxi (**http://www.tucuxi.ch/**), InsightRX (**https://www.insight-rx.com/**), NextDose (**https://www.nextdose.org/**), and TDMx (**http://www.tdmx.eu/**), and integrated clinical decision support systems (CDSSs) (see the sidebar titled Integrating MIPD with EHRs) in electronic health records (EHRs) or e-prescribing systems (e.g., InsightRX) are being proposed.

Bayesian forecasting has traditionally been linked with TDM, and more recently MIPD, and is often used for drugs with a narrow therapeutic index, such as antibiotics (46, 47), antifungals (48), immunosuppressants (44, 49, 50), and oncology drugs (17, 51, 52), and for special populations (10). The approach has also been applied to PD end points, including international normalized ratio (INR) monitoring for warfarin (53, 54).

Bayesian dosing tools have not been widely implemented in health care. Free downloadable software are often developed in academic settings with sporadic uptake. Commercial software can be scaled more consistently to a larger user base but are often expensive and require support, local expertise, and buy-in from funders. The widespread implementation of Bayesian dosing tools

INTEGRATING MIPD WITH EHRS

Integration of clinical decision support systems (CDSSs) that are capable of automated communication with electronic health record (EHR) systems for model-informed precision dosing (MIPD) is straightforward. What is often forgotten is the availability, quality, and understanding of relevant information that characterizes the patient, treatment, and outcomes. Genetic information about patients is still missing in most EHR systems after decades of debate over their usefulness and value. Hence, the adoption of additional omics information will take time for EHR integration, even though the scalability of these measures is not an issue, unlike the therapeutic drug-monitoring assays, which are specific to a single drug. Approval of a dosing strategy as opposed to approval of certain dosage regimens will make it essential to have MIPD as a companion tool for the drug itself, using the regulatory process for new drug approval.

faces several challenges (8, 10, 11, 55, 56), mainly the regulatory requirements associated with software as a medical device (learning devices may prove particularly problematic) (57) and limited prospective evaluation studies. If clinical and economic benefits can be demonstrated in well-conducted evidence-generating studies, then funding bodies and health authorities will have more incentive to support implementation.

Scalability and Other Technical Issues

In theory, if the prior model is sufficiently informative and scalable across populations, a Bayesian forecasting tool for a given drug could predict response in multiple clinical settings. In practice, this is difficult to achieve. The prior model will usually be an empirical model, often developed with data from a particular population that may not predict well into other populations. MAP parameter estimates can be thought of as a weighted average of the prior model and the likelihood of the data; if the prior model is uninformative or biased, the Bayesian system will struggle. Sampling designs (number and frequency) are not routinely explored, meaning that the optimal sampling to estimate individual parameters for a patient is often not known. This becomes particularly important with more complex models, suggesting that a Bayesian dosing system is clinically practical for scenarios where observations are collected infrequently.

Ongoing Efforts and Future Direction

Bayesian dosing systems have never been short of interesting technical advances. Artificial intelligence and machine learning (AI/ML) are already being implemented in some Bayesian algorithms. Technical innovations suggested over 20 years ago, including the use of updating prior models, are long overdue for reexamination and a move away from MAP estimation to a full Bayesian posterior.

The challenge for Bayesian dosing to progress is clinical acceptability. Indifference from the medical and health-care communities is understandable. Pharmacometrics is completely absent from medical school programs. Commercial providers rely largely on marketing to sell the concept. Until Bayesian dosing is accepted by the health-care community as a decision support tool for some drugs, until funders see the economic and clinical benefits, and until regulatory agencies clarify the status of these systems from a regulatory/legal perspective, the future remains uncertain. Integration of Bayesian tools into EHRs and CDSSs available at scale is a reasonable goal.

PATIENT CHARACTERIZATION STRATEGIES: GENOTYPING, ENDOGENOUS PROBES, AND LIQUID BIOPSY

OATP: organic anion transporting polypeptide

UGT: UDP-glucuronosyltransferase

SULT: sulfotransferase

P-gp: P-glycoprotein

BCRP: breast cancer resistance protein

OCTN: organic cation transporter novel

The use of pop-PK and Bayesian approaches for MIPD in health care today relies heavily on feedback-control-facilitated TDM of drug concentrations or response measurements. However, the difficulties in setting up multiple TDM assays for each specific drug are considerable barriers to wider use and have led many researchers to follow a different avenue that is less drug dependent. The philosophy behind this is to define the most influential patient characteristics that determine the fate of drugs in the body and then use a select set of these characteristics, in combination with modeling, to optimize drug therapy. Various approaches have recently been adopted. Genotyping for drug-metabolizing enzymes, transporters, and receptors is the first line of such common targets, and it can explain large differences in activity; for example, CYP2C9*2 has reduced activity and occurs in approximately 11% of Caucasians but CYP3A5*3 is inactive in approximately 85% of Caucasians (58, 59). When a single nucleotide polymorphism occurs in an enzyme or transporter dominant in a key clearance step, it can affect drug exposure, efficacy, and toxicity. However, population variability is better reflected by phenotyping. Administration of a cocktail of specific exogenous substrates (e.g., the Cooperstown cocktail) is used as a phenotyping tool in patients, but the approach is invasive. Recent efforts have therefore been directed to identifying, characterizing, and validating endogenous compounds as probe substrates for individual enzymes and transporters. These compounds include endogenous metabolites or metabolite-to-parent ratios in plasma or urine [e.g., the ratio of 4β-hydroxycholesterol to cholesterol in plasma, the ratio of 6β-hydroxycortisol to cortisol in urine for CYP3A activity, and the use of plasma coproporphyrin I as a biomarker for organic anion transporting polypeptide 1B (OATP1B) function] (60). Efforts to develop models for such endogenous compounds are currently under way with a view to apply this to drug–drug interaction (DDI) risk assessment and patient selection for clinical trials (61). Only a limited number of sufficiently selective biomarkers have been identified so far (60), and these compounds tend to explain only a fraction of the variability in activity (62). Robust liquid biopsy assays have been proposed to complement these techniques.

Liquid biopsy involves collection of biofluid (e.g., blood or urine) from patients at defined intervals followed by extraction and characterization of exosomes. Exosomes are small extracellular vesicles (~50–100 nm) constitutively released into the bloodstream (or urine) via exocytosis by different tissues at variable rates under physiological or pathological conditions. These vesicles enclose functional transmembrane and nonmembrane proteins and nucleic acids sampled from the cellular biochemical pool. They are therefore believed to reflect the functional state of their tissue of origin. Historically, exosomes have been used extensively in disease biomarker research (63, 64). More recently, exosome data can be used to construct a snapshot of enzymes expressed in a particular tissue (14, 15).

Despite general interest in integrating liquid biopsy with PK/PD modeling, liquid biopsy remains a specialist technique. Isolation of exosomes employs various methods (e.g., ultracentrifugation, immunocapture, or polymer-based precipitation) that require optimization for the type of tissue or biofluid, followed by confirmation with electron microscopy, size distribution, and immunolabeling of particular surface proteins (e.g., CD63 or CD81). Finally, the exosomal cargo is analyzed, which requires genotyping and multiple omics methods to quantify the composition of nucleic acids and proteins within the vesicles (61). Further validation is required for each protein. Available literature (14, 65, 66) demonstrates that enzymes such as CYPs, UDP-glucuronosyltransferases (UGTs), and sulfotransferases (SULTs) are shed in plasma exosomes. Several transporters [e.g., P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter novel 2 (OCTN2)] are also present in plasma and urine

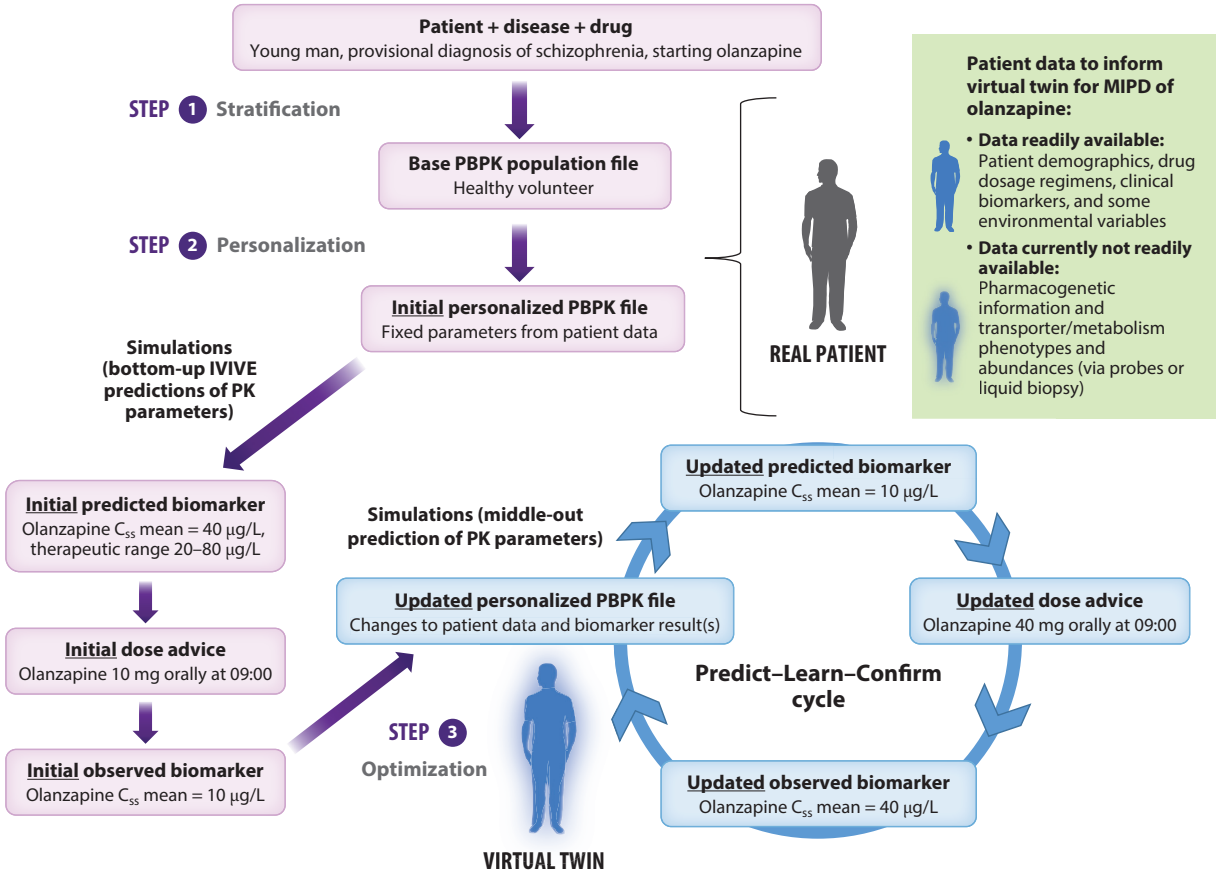

Figure 2

Workflow for MIPD using the virtual twin framework exemplified with olanzapine. A priori stratification of dose to a subpopulation level can be done using patient, disease, and drug data. Personalization of dose can be done using health-care data of the individual patient. Readily available data in EHRs may include patient demographics, drug dosage regimens, clinical biomarkers, and some environmental variables. Data that are seldom available in EHRs include pharmacogenetic information and transporter/metabolism phenotypes and abundances (via probes or liquid biopsy; see text for additional details). Predictions can then be optimized using patient data in a predict–learn–confirm cycle. Figure adapted with permission from Reference 70. Abbreviations: EHR, electronic health record; IVIVE, in vitro–in vivo extrapolation; MIPD, model-informed precision dosing; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics.

(67–69). Correlations between the expression of CYPs and UGTs in exosomes and liver tissue have recently been established (14, 15), and current efforts are extending this approach to transporters. Establishing such assays enables the use of biofluid analysis to support pharmacological phenotyping in disease and special populations. The utility and applications of this multifaceted strategy remain to be explored.

It is envisaged that incorporation of such new individual data into EHR systems will take a long time. This is based on the experience with the genetic information, which has been available for over two decades yet is not a routine component of any EHR systems beyond those of a few leading university hospitals (10). Nonetheless, the infrastructure to use such information as part of a virtual twin of a patient is in place and could be operationalized when the data become part of EHRs, as illustrated in **Figure 2** (70).

THE INCREASING NEED FOR MODEL-INFORMED PRECISION DOSING TOOLS IN CLINICAL PRACTICE

PBPK: physiologically based pharmacokinetics

The abundance and complexity of data in clinical care today, and as envisioned through the precision medicine paradigm, speak to the need for MIPD to facilitate interpretation and decision making. Clinicians are expected to process a significant amount of patient information related to diagnostics, such as medical imaging, laboratory tests, and previous clinical presentations, and to identify multiple risk factors influencing drug efficacy and safety, including pharmacogenomics, DDIs, diet, organ impairment, age, and functional status of the patient. Rapid, optimal integration of all this information, and softer factors such as drug formulary recommendations and patient/caregiver choice, are crucial for making prescribing decisions that result in high-quality patient care. This can be overwhelming, as mistakes can easily be made and ADRs may result (71–73).

Complex drug–drug–gene–disease interactions (DDGDIs) are intricately complicated clinical situations that cannot be identified prospectively but are usually documented retrospectively as case reports of severe ADRs. An example is the tyrosine kinase inhibitor (TKI) class of drugs, which improve survival rates for a variety of cancers. However, many patients experience multiple intolerable adverse effects, after which the TKI must be temporarily stopped or replaced, which in turn increases the risk of developing drug resistance. Many other patients are initially nonresponders or develop drug resistance during treatment due to, for example, TK mutations or polymorphisms of drug-metabolizing enzymes and transporters or to DDIs or dietary changes. Another example of a complex DDGDI is opioid intoxication on low-dose codeine in ultrarapid metabolizers for CYP2D6 (the metabolic pathway producing morphine) in combination with inhibition of CYP3A and acute renal failure in opioid-naive patients (74). The addition of subsequent variabilities related to μ-opioid receptor mutations could also explain rare cases of codeine toxicity.

These ADRs contradict the one-size-fits-all dosing approach supported by an allegedly large therapeutic window for many drugs. Direct oral anticoagulants (DOACs) and the antiplatelet drugs (P2Y12 receptor antagonists) are classic examples. Cardiovascular patients who require these treatments are generally older and more medically complex than they were previously, with multiple comorbidities and polypharmacy. Despite an established relationship between DAOC exposure and risk of major bleeding (75), few formulations allow dose tailoring (e.g., apixaban). To date, no clinical tools are available for selecting the ideal DOAC or antiplatelet drug and optimal dose. The management becomes even more complex when the link between PK/PD and clinical outcomes is distorted by clinical conditions; for example, the relationship between platelet inhibition by clopidogrel and the occurrence of ischemic events is influenced by background cardiovascular risk (76). In practice, a poor response to clopidogrel is clinically relevant in higher-risk cardiovascular patients who may be the sole benefactors of dose adjustment or drug change. Therefore, patient characteristics and conditions are integral to drug-related clinical prognosis.

Predicting optimal drug doses in individual patients a priori represents the holy grail for physicians when using drug therapy. Smart, easy-to-use, and clinically validated MIPD tools would be of tremendous value in improving patient care. This can be facilitated by integration into EHRs. Such tools could combine clinical and demographic information and other biomarkers, electronic prescriptions, and, for example, a physiologically based pharmacokinetics (PBPK) model with validated drug and population databases (77). This requires validation in clinical settings in sufficiently large cohorts. Clinical trials are currently under way to validate a PBPK-based MIPD approach for antithrombotic drug management (**https://clinicaltrials.gov/ct2/show/NCT03477331**), although it should be recognized that this approach may not always be feasible. Currently, there is considerable evidence generation, evaluation, and implementation research in health care, as

well as sociotechnical systems research, health systems engineering, and health economics, that can inform and further develop this process (78–80). Going forward, clinical education on and engagement (such as participatory methods) with MIPD would ensure accurate and critical interpretation of dose predictions and implementation at the point of care. Multidisciplinary efforts are now needed to ensure widespread implementation of these approaches.

Semantic interoperability: the ability of computer systems to share data with unmistakable meaning

IMPLEMENTATION INTO ELECTRONIC HEALTH RECORDS

Implementation of MIPD into EHRs has been discussed in the literature and suggested here as a strategy for wider adoption (3, 10, 11, 81, 82). Practically, CDSSs can be implemented either as stand-alone solutions or into EHRs (11, 81, 82). Stand-alone systems have a usability problem; because the prescriber must enter all patient data manually, these systems require time resources and are vulnerable to potential errors. Linkage to EHRs in which structured patient data are available would overcome these problems. Depending on the model, the availability of data varies. Most EHRs store structured data for demographics, drug treatments, and various laboratory parameters, for example, for kidney and liver function. Patient information on relevant genetic factors is still rare in EHRs and standards are needed to structure the information. There are ongoing efforts in the area of semantic interoperability (the ability of computer systems to share data with unmistakable meaning) through standardization of, for example, genetic information, such as Health Level Seven International's (HL7) Fast Healthcare Interoperability Resources (**http://www.hl7.org/Special/committees/clingenomics/index.cfm**).

These types of initiatives are important for enabling precision medicine in clinical practice. However, it is likely that standardization will be relevant only for a limited core of medical data structures, as the field of medicine is heterogenous and constantly evolving. An alternative approach being developed within the Swedish Origo program (**https://origoprogrammet.org/en/**) is the creation of a language for building semantic data structures within a distributed nonprofit and open-source infrastructure, thereby allowing accelerated user-defined data structures and sharing. This approach may overcome some of the issues around standardization for interoperability.

Today, CDSSs for drug treatment are frequently implemented into EHRs. However, their impact on improved health-care quality and outcome is still unclear (83, 84). These CDSSs build on knowledge bases of various types, such as DDIs, pregnancy, breastfeeding, and renal impairment. These knowledge bases are created as individual databases, and alerts to prescribers are based on the content of the specific knowledge base in relation to the parameters of each individual patient. Some databases exist for pharmacogenomics (85). However, these are rarely implemented into EHRs. All knowledge bases give advice to alter or stagger doses or to switch drugs. It is well recognized that CDSSs can create alert fatigue for the users due to multiple warnings (86).

The existence of various CDSSs within EHRs must be considered whenever a MIPD system is integrated. If the MIPD model has taken account of kidney function or concomitant drug treatment, it must be clear to the user that the possible separate alert from other knowledge bases should be ignored to avoid ambiguity.

This way, MIPD suggestions for dosing based on pharmacogenetics, kidney and liver function, and concomitant drug treatment could replace the information and possible alerts from several CDSSs and diminish the need for other warnings from individual knowledge bases. This coordination would require algorithms in the EHR that would eliminate firing alerts from specific knowledge bases whenever the MIPD-based dose suggestion has already included these patient-specific parameters.

CDSS research has shown that recommendations about how to handle a patient's drug treatment regimen are preferred to simple messages containing only information about what not to do. It is therefore important to understand how these recommendations should be communicated through the CDSS. With increasing availability of patient data, the integration of MIPD and CDSS tools is becoming more feasible and important.

AN INDUSTRIAL PERSPECTIVE ON MODEL-INFORMED PRECISION DOSING DURING DRUG DEVELOPMENT

The optimal use of drugs is desired by pharmaceutical companies from both an altruistic and an economic perspective. There is a vested interest in getting the dose right, which is strengthened even more by the ongoing debate by policy makers over the last 10 years about the increasing cost of health care (87) and the possibility of an outcome-based compensation model of any intervention (often called pay-for-performance) (88). It is assumed that this payment approach increases quality of care and reduces health-care costs by removing the expenditures in cases in which the intervention does not provide value, including individualizing the drug treatment regimen.

Pharmaceutical companies routinely collect exposure–response data when developing a drug (89). In addition, drug development routinely characterizes the PK profile of the drug and some of the intrinsic and extrinsic factors that influence the profile, focusing on factors that are mandated in the labeling information (e.g., pediatric) (34) or suggested by regulatory guidance (e.g., hepatic and renal insufficiency) (90). Nevertheless, dosing recommendations for these patient groups are frequently lacking. A survey of 59 new molecular entities approved in 2013 and 2014 found that labeling recommendations lacked information for such populations over 60% of the time; moreover, information for the pediatric population was typically not available at the time of first approval (91). When there are dose recommendations, they usually reflect only a single factor and leave the prescriber guessing about how to integrate the information provided.

Although the field of pharmacokinetics has made significant strides in producing predictive models (e.g., DDIs), much more can be done. Development of predictive models can be facilitated by pooling data across compounds, as done in 2017 for pediatric patients (92). CDSSs could allow the integration of various factors into dosing recommendations to better serve complex patients. Advances in liquid biopsy and exosome science offer researchers the ability to characterize metabolic pathways (14), and this characterization may enable researchers to access data about patient populations from which it was previously too difficult to obtain such information (e.g., pregnancy).

Most of the promise noted above hinges on pooling data, and much of that data reside in industry. To date, there have been few, if any, industry-wide efforts to pool data to facilitate dose recommendations. For example, a proposal to create a framework for dosing recommendations for specific populations using modeling and simulation based on data from prior drugs with similar clearance mechanisms was made through the Innovative Medicines Initiative (**https://www.imi.europa.eu/**) (93). However, the proposal failed to garner the necessary industrial support and therefore did not go forward. Efforts like this may fail because individual companies do not see a return on their investment and fear that competitors will not participate but will reap the rewards. To overcome this, regulatory bodies should consider incentivizing such efforts and making participation mandatory. Before full benefits can be achieved, questions about, for example, when a model is sufficiently predictive need to be considered. A joint effort by pharmaceutical companies and regulatory agencies is consistent with efforts to increase the diversity of patients in clinical trials (94) and would help achieve optimal drug use for all patients.

REVISITING HEALTH ECONOMICS: THE FALSE ECONOMY OF ONE-SIZE-FITS-ALL DOSING

Drug therapy is the most common health intervention, represents a major portion of global health budgets (**https://data.oecd.org/healthres/pharmaceutical-spending.htm**), and has the greatest potential to improve human health and quality of life through the treatment or prevention of disease. Every health intervention has a cost that needs to be weighed against benefits and harm. The increased economic burden of medication-related harm in many health systems has had a negative impact on patients' quality of life (95, 96). This prompted the World Health Organization to name the third Global Patient Safety Challenge *Medication Without Harm* (**https://www.who.int/patientsafety/medication-safety/en/**). Most medication-related harm is preventable, and the challenge aims to reduce preventable harm caused by medication by 50% over five years. Of these instances of preventable medication-related harm, over- and underdosing of medication account for a sizeable portion (97, 98). Judicious drug selection and dose individualization, such as envisioned through MIPD, can lead to improved health outcomes, reduced medication-related harm, and smaller economic burden.

The value that a medicine provides is a reflection of the cost to the health system and the benefit (and harm) it provides to the broader population (99). These data are often derived or extrapolated by modeling approaches from controlled clinical trials conducted during development. Reasonable assumptions about the disease process, cost of care, and clinical pharmacology of the drug are combined to estimate the (economic) value that a medicine provides during treatment (100). A key assumption is that the medicine is administered at the correct dosage regimen. The reality is that at the postmarketing stage, when a medicine is used by the wider patient population, there is increased variability in response (101). Variability in response is most evident when the medicine is used with a fixed dosing strategy, meaning that the expected benefit of the medicine may not be fully realized (102).

Drug policies around the world provide a foundation for drug regulation frameworks (103). These policies acknowledge the need for economically viable and responsible pharmaceutical companies as partners in health care. This acknowledgment recognizes that pharmaceutical sponsors bring medications to market and that their profits are not only distributed to shareholders but also reinvested in research and development of new therapeutic agents to improve human health (104). From a pharmaceutical sponsor's perspective, developing a new medicine with a one-size-fits-all dosing strategy might seem to be economically favorable and therapeutically efficient. In many cases, generating evidence of safety and efficacy, and even cost-effectiveness, is more straightforward if the new medicine is administered at one or a few dose levels. Less formulation work and fewer trials lead to lower development costs and, more importantly, a faster route to market (104). Physicians also tend to prefer medications that are easy to prescribe. Yet this strategy does not ensure the best or optimal outcome for each patient.

Imprecision medicine represents low-value care (105, 106). Medication use and dose optimization must also embrace shared decision-making principles to support the preferences, beliefs, attitudes, knowledge, and social context of individual patients (107).

The impact of the aging population across the globe has been identified as a major economic challenge for health care. The imprecise manner in which medications are used creates an added burden of preventable harm and low-value care (108, 109). Older people are among the most vulnerable to the potential harm of medications, which can add considerable cost to the health-care system (110). Integrating knowledge of clinical pharmacology and physiology (108, 109) and the impact of disease, through approaches such as MIPD, can guide individualized dosing regimens for the elderly (110). This has considerable potential to ensure that when medications are initiated and carefully monitored, clinicians can provide high-value care.

A REGULATORY PERSPECTIVE ON MODEL-INFORMED PRECISION DOSING

A long-standing goal of regulators has been to ensure that the right drug is given to the right patient at the right dose and time. This is the contemporary concept of precision medicine and has become increasingly possible with regard to matching the right drug to the right patient. It is common in drug development to leverage the power of the human genome to target specific diseases. Cancer therapies that target specific genetic changes in tumors have benefited the most, going back more than two decades when the FDA approved rituximab (111). Since then, more than 150 indications for targeted therapies for 28 cancer types have been approved by the FDA (112).

In contrast, precision medicine has outpaced MIPD. Regulators play a major role in advancing innovative science, and MIPD has been embedded in several FDA initiatives such as the Critical Path Initiative and more than 10 clinical pharmacology guidances for industry. The 21st Century Cures Act, signed into law in 2016, advocated for innovations in individualizing drug therapies. The Prescription Drug User Fee Act (2018–2022) (113) also has a deliverable of advancing model-informed drug development, including MIPD (12).

Model-Informed Precision Dosing for a Regulatory Framework During Drug Development

Unlike the landmark regulatory legislation of 1938 that set in place the Federal Food, Drug, and Cosmetic (FD&C) Act, which required pharmaceutical companies (sponsors) to demonstrate drug safety, and the Kefauver-Harris Amendments of 1962, which required industry to prove drug efficacy, there are no regulations that require industry to enable precision dosing during drug development. The current practice in drug development, expected and supported by regulatory agencies, is to bin patients into subgroups defined by factors that influence pharmacokinetics (e.g., renal impairment, age, smoker status, body weight, or phenotype) as though all patients in the respective subgroups are identical. Precision dosing in these so-called special populations amounts to adjusting standard population doses on the basis of model-driven matching of PK exposure but with the critical assumption of similar exposure–response relationships across the individual subgroups. In this context, MIPD has been hailed as the age of individualization. A few drug development programs have enabled precision dosing by using pharmacodynamics as a guide. For example, the FDA recently approved a recombinant coagulation factor VIII prophylactic treatment for hemophilia A with a companion PK CDSS that, to achieve a target clotting activity, individualized dosing on the basis of trough concentrations of the drug.

Model-Informed Precision Dosing for a Regulatory Framework for the Real World

The promise of MIPD is to individualize dosing at the point of use in health care. Currently, the regulatory oversight of MIPD as a CDSS is a moving target. In 2019, a draft guidance issued by the FDA laid out potential pathways to regulatory approval or clearance. Because of the uncertainty around the regulation of MIPD tools, the pace of development of commercial CDSSs for MIPD has been slow despite the use and demonstrable effect of TDM for more than 40 years. Today, the challenges are that the FDA interprets a CDSS as a device under the FD&C Act, because the software informs clinical management for serious or critical situations or conditions, and that many clinicians are not able to independently and correctly evaluate the basis for the CDSS recommendations. The factors that regulators consider when making benefit–harm determinations of CDSS are, on the efficacy side, the type and magnitude of the benefits and the probability of

a patient experiencing one or more benefits. On the safety side, regulators are interested in the extent of probable risks, including the severity, types, and rates of harmful events, associated with the CDSS if not correctly implemented.

ADDRESSING THE BARRIERS

Timely access to patient-specific information to guide drug dosing has been a major barrier to achieving precision dosing. With the considerable expansion of EHRs, clinicians now have increased access to information about patient factors, such as age, weight, sex, organ function, relevant genotype, concomitant medications, and disease severity, that can be used to better tailor drug dosing. The ability to access relevant biomarker information to monitor and adjust doses according to an individual's pharmacological response in an evidence-based manner is vital to achieve optimal outcomes and ensures that the value of drug therapy can be realized. Combining these data into appropriately developed and evaluated PK/PD models, and other types of modeling regimes such as AI/ML, will provide the stepwise change needed to allow large-scale tailoring of drug doses to meet the needs of individual patients.

SUMMARY POINTS

1. Pharmaceutical companies, regulators, and clinicians recognize the need for model-informed precision dosing (MIPD) supported by clinical decision support systems (CDSSs). However, it is unnecessary to apply MIPD to every drug and every patient.
2. The community must delineate well-defined situations where MIPD provides considerably more effective therapy and less toxicity than traditional dosing.
3. Precision medicine approaches in oncology have transformed the standard of care in less than a decade. The continued evolution of computer technology, regulatory policy, and clinician adoption may allow precision drug dosing to transform the standard of care for other diseases.
4. Drug-related lack of efficacy and adverse reactions produce a significant burden on health-care systems and in many cases are preventable. MIPD can lead to improved health outcomes and reduced economic burden.
5. The economic cost of developing and implementing MIPD strategies to improve the initiation and monitoring of medications should be weighed against the direct economic burden of preventable medication-related harm on the health-care system.
6. Widespread use of MIPD requires a multidisciplinary approach to meet challenges in evidence generation, implementation, and systematic use.

FUTURE ISSUES

1. A shift from drug-specific assays to non-drug-specific patient characterization will be a general trend over the next decade. Patient characterization will go beyond genetics and address proteomics and other elements defining the biology and physiology of the system at each stage of health and disease for each patient.

2. The application of MIPD will reach its full potential and go beyond the classical examples used in therapeutic drug monitoring. Personalized predictive models based on pharmacodynamic targets and patient outcomes will be used for precision dosing. A greater understanding of the mechanisms and variability of disease and treatment, as well as its translation to clinical outcomes, is needed to attain this goal.
3. Artificial intelligence and machine learning are entering the arena of precision dosing. This could be a potential game changer for the utilization of real-world patient and health-care data.
4. The integration of CDSSs with MIPD and electronic health records is important for enabling widespread use. Efforts in standardization, interoperability, and information and communications technology will be essential for this to occur.
5. Evidence generation and implementation of MIPD in health care will require multidisciplinary efforts and collaboration between health care, academia, regulators, patients, and other key stakeholders.

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