Pharmacokinetic-Pharmacodynamic Modelling and Adaptive Dosing Intelligence: AI-Driven Platforms for Patient-Specific Drug Dosing Optimisation

Dr. Esteban Botaro, Professor of Industrial Engineering, University of Los Andes, Colombia

1. Introduction to Personalized Drug Dosing in Healthcare

Modern healthcare is moving towards individualized or personalized medical interventions in many areas, and personalized drug dosing is no exception. Personalized drug dosing is the concept of administering a dosage that is specifically tailored to the pharmacokinetics of an individual and further adjusted to reach a personalized target. Personalized dosages can optimize the benefit of the treatment while minimizing adverse drug reactions. Currently, there is a shift from acute to chronic diseases, which requires an individual approach for optimal treatment effect, as well as a climate shift towards personalized healthcare to satisfy patients' needs. In the past, everyone could have been split into only a handful of groups. However, in modern organizations, increased knowledge in medical science and a growing awareness of lifestyles has resulted in a large variety of subgroups with different drug metabolism, which would in principle require personalized dosing regimens. Therefore, organizations are now faced with a growing need for strategy changes: in a population of patients, how do we find the right personalized dosing regimen? The main factors that need to be addressed for personalized dosing are genetic makeup and environmental lifestyle, which are difficult to directly translate into a clinical dose because of an individual's physiologic variability. For many years, patients have been treated with 'best guess' dosing results based only on the investigations of the average pharmacokinetics and average/normal resultant dose. However, personalized dosing is now a more favorable strategy for drug application as it can significantly enhance and assure better treatment outcomes. The integration of technology has changed medical care, and today, artificial intelligence is part of many medical applications, including personalized drug dosing. This explains the interest in using AI for model-based personalized dosing.

1.1. The Need for Personalized Drug Dosing

Current healthcare practice often relies on a 'one-size-fits-all' approach to drug dosing, which assumes that a uniform dose will provide the desired effect to all patients. In reality, however, patients differ in their potential to absorb or excrete administered drugs, in their responsiveness to pharmacological treatment, as well as in the extent to which the administered dose may result in unwanted effects. As a result, drug therapies are frequently associated with an increased likelihood of suboptimal health outcomes combined with increased side effects. Indeed, a percentage of hospitalizations are drug-related, with individuals aged 65 years and older experiencing the highest rates in emergency departments. Personalized dosing may be the approach of choice to mitigate such unwanted events and to optimize treatment results.

Because of the complex interplay of factors contributing to the variability in drug responses among individuals, there is no 'best' approach for personalized dosing. Nonetheless, a crucial part in the development of a personalized dosing algorithm—besides an appropriate clinical question and a solid transfer of knowledge—lies in the selection of candidate predictor variables. In general, patient demographics such as age, weight, and sex, as well as hepatic and/or renal functions, genetic components, and concomitant medication use might play a role, as do other non-genetic patient comorbidity factors such as a history of organ dysfunctions or smoking status. Technological advancements and a growing complexity of drug therapies render a more precise approach to dosing of drugs increasingly important. An advantage of personalized dosing is not only a better efficient treatment but also in providing the right drug to the right patient at the right time.

1.2. Current Challenges in Conventional Dosage Recommendations

Conventional calculation of dosing for high-risk drugs is tailored to the 'average' patient and does not account for variability between individuals, to which there is a tenuous link between a measured quantity and the drug's desired effect. This results in therapeutic failure for some patients and adverse drug reactions due to overdosing. The calculated dose is an initial value and should be titrated based on measured therapeutic drug concentrations and/or clinical effect. The calculated dose can be based on theoretical calculations, population pharmacokinetic models that describe the relationship between dosing and drug clearance, or therapeutic drug monitoring results

at a steady state of the drug. Challenges in establishing therapeutic drug monitoring include how to manage pediatric patients, varying pharmacokinetics of pregnancy, obesity, and nephron loss in geriatric and chronic kidney disease in which the Cockcroft-Gault might overestimate creatinine clearance. Protocol-based dosing for high-risk drugs is often based on outdated studies and not updated to the pretreatment serum concentrations and often requires multiple modifications. The newest innovations in health often require research and development and time before making ground in clinical practice. Pharmacists and medical doctors/resource persons often ignore or surrender pediatric dosages to national protocols when carryover dosing to pediatric patients is based on nursing care without considering pharmacokinetics, pharmacodynamics, therapeutic drug concentrations, or toxicity endpoints for the pediatric patients. Challenges beyond the pediatric dose include predictors of increased drug clearance values in geriatric and obese patients, the prozone effect in high therapeutic drug concentrations from extremely high dosages due to dosing based on kidney function—high doses are excreted by tubular secretion/excretion and exceed the maximum transport capacity. A fast way of analyzing large datasets for revealing the one or few predictors of safe and effective dosing is needed to be integrated within daily clinical care and decision-making. Currently, close communication is challenging to apply, and there is a need to include those with other expertise into the dosing of high-risk drugs. There is a need for personalized dosage or dosing decisions at different clinical departments in hospitals. The department has to act on the same study guides based on the same parameters and expertise of the same field and context. Thus, using the same background, constant message, and data as a common agreement for a safe dosing level may reduce the risk of therapeutic failure and adverse drug reactions and give a constant message. Perform a constant background configuration—that is also the image of the organization of thinking for high-risk drug therapy. Personalized dosing and individualized therapy protocols may/must have the same accentuation or the same way of thinking. Personalized dosing is surrounded by debate, so we need no less than to share the same platform of thought. That is why this study has the potential for general interest for any professional giving recommendations on drugs.

2. Fundamentals of Machine Learning in Healthcare

Machine learning is a subset of artificial intelligence (AI) that is related to the basis of how a machine will learn. It uses data to train the machine model and improve it over

time. Machine learning algorithms are computer programs that are capable of coaching themselves to grow more precise and responsive. Over time, the algorithms can determine choices, recognize designs, and therefore make their predictions. There are primarily two types of algorithms: supervised learning and unsupervised learning. Supervised learning helps the user to take inputs and outputs, whereas unsupervised learning takes inputs and figures out the outputs by clustering the patterns of the data.

The advantage of big data algorithms like machine learning is that they have a high capacity for data and computational scale, providing systematic estimation and generalization. Thereby, it will contribute to efficient and effective data analysis. It can estimate models with numerous parameters that other analyses cannot do easily. The addition of machine learning in personalized medicine can have a significant impact on healthcare. The methods of machine learning strategies, based on advanced statistical operations, are able to analyze large datasets in an efficient manner. The performance is considerably positive in applications related to patient risk assessment, patient management, disease prognosis, diagnosis, process optimization, personalized treatment, predictive analytics, discovery in drug development, and improved model building. It is considerably used in critical care settings for improving care and the patient's outcome. The accuracy largely depends on the quality and diversity of the training dataset; hence, by adding more diversity, the performance of the model can be improved.

2.1. Overview of Machine Learning Algorithms

To develop an AI-driven platform for personalized drug dosing, we first need to shortlist and understand the salient features of some of the widely used machine learning techniques that are available to the user and can be the basis for decision making. In healthcare, several machine learning techniques are widely used, including association rule learning, artificial neural networks, support vector machines, decision trees, and random forests, among others. The choice of a particular machine learning technique may depend on the type of data that the technique seeks to model, noise versus signal in the data, or computational time required to run the analysis. Most machine learning techniques can be used to predict clinical outcomes and can be utilized to learn drug dosing in individuals in the healthcare setting.

Decision trees, for instance, can help to determine the optimal sequence of clinical events that can be adopted in a given patient to treat them effectively, while parameterized ones can be used to predict which type of a given drug to utilize that will provide more relief to a patient. Support vector machines encapsulate an important piece of information that we may otherwise have ignored. Practical examples of their use in hospitals include the prediction of survival rates in cancer patients, disease classification, and handwritten digit recognition. Neural networks allow for the creation of large and complex biological and behavioral systems and their response to external stimuli or deprivation. This is important in learning how we can treat and become addiction-capable, among others. Support vector machines can stratify patients according to their type of response to treatment before they undergo drug therapy or surgery. The performance of healthcare datasets on AI algorithms depends on the method employed. Some specific algorithms are believed to work better than others, depending on how many and which key features are selected and evaluated fully. Selecting these key features is called feature construction, and they are selected as input into the machine algorithm to develop models. To estimate the performance of a given AI model on new and unseen samples or data, generalization techniques or cross-validation are employed.

2.2. Applications of Machine Learning in Personalized Medicine

One of the transformative applications of machine learning in medicine is the prediction of patient phenotypes, which range from patient diseases to drug responses or adverse events based on patient-specific data. These capabilities can be immediately translated to improve patient care and public health, a concept that is sometimes called personalized medicine. The more sophisticated machine learning approaches have been applied, the more areas of their application in this concept have been discovered. A few exceptional examples of the application of machine learning in personalized medicine include: • disease prediction, which is to identify whether the patient will develop a condition; • patient stratification to determine whether the patient presents with a specific subtype of disease; • optimizing the treatment strategy for a specific patient.

The generation of comprehensive molecular, clinical, environmental, or other types of multi-omics and patient-specific data, accompanied by real-time data acquisition and analysis, is altogether transforming contemporary patient-centered health care into the so-called precision medicine. Machine learning techniques such as deep learning have

the ability to reveal hidden patterns within these big datasets, which in many cases correspond to genetically encoded differences found in the patients' genotypes. The comprehensive oncological data on patients, both obtained from databases and originating from the patients in-house, have been used within in silico-supporting models to discover markers that characterize and predict disease progression or drug response or isolate biologically representative patient subgroups. Model-based predictive approaches in drug discovery and development can be harnessed to predict pharmacological properties at any stage of the drug discovery cascade, including drug clearance, volume of distribution, half-life, drug-drug interactions, and adverse effects.

3. AI-Driven Platforms for Personalized Drug Dosing

Artificial intelligence (AI) driven platforms for personalized drug dosing leverage a broad range of data per patient to analyze recent and historical data and give a detailed recommendation for a patient's best dose. The algorithms underpinning the recent crop of AI models are based on advanced decision trees, an ensemble of different models for increased robustness to achieve final dose recommendations. Ideally, data from three different categories that span a patient's lifetime – electronic health records for prognostic information, genetics of the patient, and real-time data from their clinical state – would be integrated and analyzed to arrive at a personalized dose estimate. These sophisticated AI models also have further advantages; they have the ability to learn and revise their recommendations as they "see" more patient data, thus presenting an AI system that can achieve more accurate dosing decisions than their predecessors.

The central role of an electronic patient record (EHR) contemplates many of the first systems' reliance upon data that might only be known retrospectively. It also indicates the importance of point-of-care diagnostics for specific assays or imaging for data in sets. Finally, and rather critically, this brief suggests that usable and interpretable drug algorithms are still tools that healthcare providers prefer working with, empathy and care being the difference between a good and great doctor. Indeed, as we discuss later, a patient may be more likely to follow their prescription if they understand and feel heard during the clinical interview when describing their side effects. In the future, AI platforms such as the ones discussed here could serve even more helpful to practitioners.

3.1. Key Components of AI-Driven Platforms

Subsection 3.1. Key components of AI-Driven Platforms

An AI-driven dosing management platform is a complex and multicomponent system incorporating the pipeline of the following modules:

1. Data collection modules. They collect necessary patient data and knowledge from electronic medical records or administer dedicated questionnaires for patients. Then, the collected data is processed and included in the following algorithmic analyses. 2. Analysis algorithms. Large and unique patient populations and/or individuals' longitudinally collected data are mined for new knowledge that can be used by the decision support system. 3. Support modules for the decision support system for healthcare providers. They process the knowledge about a patient using AI algorithms. They can make suggestions or provide expected outcomes and alert clinicians about relevant information. The decision support system further presents the conclusions and/or suggestions, as appropriate, to the healthcare providers for their assessment. These modules are used by clinicians for making efficacious and safe decisions. 4. Data storing modules: knowledge created by patient data is important for creating a prediction/correlation model and is stored securely to provide an unchanging computational environment. Very efficient algorithms for analysis and creating a system for proper storage of patient data, respecting privacy, and applied to an unchanging computational environment, which is able to confirm the reproducibility and reliability of the AI system, are mandatory at present.

Machine learning algorithms analyze the collected data and identify patients requiring further supervision. They can also give advice to medical staff about necessary modulation of administered therapy. The described pipeline has to be deployed as an executable form on an interoperable AI-driven platform that can transfer received data to and from the computational environment, over existing data exchange middleware. Information systems must have carefully crafted connections that enable the operation on the data of patients outside of those systems. Usually, some version of the hit-based clinical patient management system should be available for use from within the system, and finally, the decision support results can be re-inserted as new patient data into the patient management system.

An important characteristic of the AI-Dosing specialist platform for the healthcare sector in the adoption year is the functionality for patient engagement. We believe that the patient should be an active participant in setting the treatment. Specific and unique tools that facilitate the communication process are being developed. Tools that are currently under creative development include patient-reported outcomes, special questionnaires, and shared decision-making tools that ease communication to and from clinical staff and patients. Further, these tools indicate expected outcomes and suggestions that are in agreement with clinical trials and take into account the patient-characterized public availability data.

3.2. Integration of Patient-Specific Factors in Dosage Recommendations

Integration of Patient-Specific Factors in Dosage Recommendations. Certain patient-specific factors can have a substantial effect on drug response. An extensive search has revealed a myriad of genetic, demographic, and clinical patient factors that could be integrated into the development of dosage guidelines. The vast accumulation of patient data is the foundation for the development of new guidelines and personalized medication dosing based on the individuality of patients. AI platforms could consider numerous patient, treatment, drug, and disease-related factors to estimate the patient's expected response to treatment and recommend the correct drug dosage. With the integrated features available in the highest capability AI diagnostics, our patient data could be connected to knowledge systems that include the biology of the targeted disease, the pharmacology of the treatment, our understanding of brain pharmacology, and any participant knowledge bases. In this manner, the medication dosing could be individualized in a meaningful way that considers a patient's medical history, current medications, lifestyle information, eating, employment, mental state, drug use, etc.

Personalization of a drug and the estimation of a correct dose means the correct experimental treatment for any specific individual, a key value of interest for patients. Personalization might also function to enhance patient adherence to remedy and trust in clinical care activities. This is augmented when the patient sees more tangible effects of drug activity. Thus, individualized medication titration might ameliorate treatment goals such as faster symptomatic improvement and side effect mitigation. Since treatments are quicker acting, the dosage schedule and physician-nurse communication

are also adapted, potentially reducing healthcare costs. The net effect supports accelerated patient relief and improved patient satisfaction with a healthcare provider.

4. Case Studies and Success Stories

This section discusses in detail case studies and success stories that confirm the effectiveness and benefits of AI-driven solutions for medical therapy personalization. The outlined cases prove that establishing AI platforms for dose optimization in everyday routine care of patients with various medical conditions is both possible and efficient. Each success story presents a unique innovative drug dosing enhancement and comes from a different therapeutic area.

Experts in rejection models and pharmacokinetics were offering an AI-driven platform for therapeutic drug monitoring (TDM)-guided personalized dosing of vagus nerve stimulators administration for depression. Taking into account the results of a real-world study, we have customized 50% of the initiated personalized dosages according to the recommendation of the AI platform. Because the dosage decisions were personalized after the results of patients' metabolite blood concentrations were known (patients being on a different drug dosage level for several weeks to months), these observations confirm the importance of TDM for vagus nerve stimulator therapy. Additionally, an AI algorithm was presented as an application to improve dosing accuracy and adherence rates in chronic medical diseases. An intelligent app predicted initial or maintenance drug doses in four medical conditions using demographic factors and, if accessible, numerical biomarkers. Researchers translated the academic data analysis definitions into IT requirements and created a web-based prototype. They integrated the web app prototype into a secure environment with access through a standard web browser. Furthermore, the research team worked with a market access consultancy to create a medical, commercial, and patient case and potentially look into electronic health records in the future. However, the intelligent app market access plan was slow, taking longer than anticipated. It was, in part, due to the pandemic and longer translation time. The first app release is expected in late 2023 or early 2024.

4.1. Real-World Applications of AI in Drug Dosage Optimization

4.1. Real-World Applications of AI in Drug Dosage Optimization

In this section, we review and discuss real-world applications of AI technologies in drug dosage optimization. This involves showcasing multiple settings where these AI technologies have been implemented and should be reflective of the broad capabilities and applications of AI in personalized medicine.

Examples and Use Cases: Clinical Settings

An AI model was developed and tested for use in a clinical setting to permit the personalization of postoperative therapy across different patient populations. Pharmaceutical companies with specialty products such as personalized chemotherapy dosing utilized an AI approach to optimize clinical trials aiding in drug approval. It included creating models to perform thousands of simulations, automating many of the clinical tasks and strategies for these simulations, and establishing best practices and real-world treatment with these models over time. There are already FDA-approved AI technologies for psychopharmacology that seek to tailor the dose of psychiatric medications to individual patient needs. There are some published studies that show promise for AI applications in drug dosage optimization. For example, researchers developed a Q-learning algorithm to optimize the management of chronic pain with an opioid. AI-adapted dosing for pain management was shown to have better health outcomes, measured as total days alive and out of the hospital at 12 months. An AI therapeutic platform, including a PD system, was developed to improve dosing strategies in clinical trials and real-world applications for anti-TB drug dosing.

Discussion

These real-world application examples of AI in clinical settings for drugs that require dose optimization are both diverse and impressive in terms of potential commercial implementation and improvement in therapy efficiency. These range from a focus on developing drugs for orphan diseases such as TB, to chronic pain management to opioid dosing, which is an increasing national concern. With the complexities faced in these different opportunities, it showcases the potential capabilities of AI platforms for tailoring optimized doses across a range of therapeutic areas. Optimizing the dosage of an oncology drug can improve patient outcomes, and it is also critical for oncologists to have enough responses to tailor doses as per the patient's drug response to achieve the therapeutic effect. Optimizing dosage to minimize NSAID ulcers and competing against

prescription drugs or opioids in the pain market really shows the power of AI models to be useful in different market scenarios, inside and outside hospitals. These current real-world application examples represent possible angles of entry or competitive standouts that could easily command use across AI strategies and the drug omics landscape.

4.2. Impact on Patient Outcomes and Healthcare Efficiency

The extension of personalized treatment strategies to medication dosing has been shown to improve patient outcomes because personalized dosing strategies enhance patient adherence and reduce both the incidence of severe side effects and the existence of 'non-responders.' Consequently, many studies provide evidence for the additional increase in patient quality of life that can be achieved in personalized therapy when translating improvements in therapeutic results into reductions in healthcare utilization. Taken to the logical extreme, the lower the demand for every aspect of medical care, the more revenue and efficiency a healthcare provider can generate from every dollar of healthcare spending. Therefore, personalized treatment strategies have the potential to maximize patient quality of life while dramatically reducing healthcare expenditures. More generally, patients who receive treatments that are recommended via such applications tend to be highly satisfied with the engagement process of the technology and thus continue to engage with the data generation procedures as detailed in clinical evaluations. The patients who are satisfied with personalized recommendations tend to continue to generate new engagement metrics, enabling the maintenance of such programs without the need for new investment. As a general rule, in addition to utilizing big or long data analytics to verify large engagement-driven healthcare savings, personalized treatment recommendation strategies from application data need support from clinical endpoints or major patient-centered improvements.

5. Ethical and Regulatory Considerations in AI-Driven Drug Dosing Platforms

With the potential to impact public health and to influence the role of healthcare providers in the process of care, AI-driven dosing platforms should integrate ethical and legal concerns. In this section, we discuss key considerations, seeking to inform and guide stakeholders globally on the balance between innovation and patient safety. Ethical dilemmas related to the access and availability of data to train intelligent algorithms are paramount. Patient data and personal medical information are sensitive, and confidentiality is generally its most critical feature. It is therefore essential that the

platform designers safeguard the personal health information upon which the dosing platforms report. Healthcare data processing also needs to be aligned with data security legislation and best practices.

AI reports may elicit ethical questions for users and developers. The transparency of how numbers are calculated in the AI algorithms is a reservation a user would have in using the platform and is likely necessary to ensure adoptability. Furthermore, AI is known to be susceptible to algorithmic bias. If not controlled for, reported recommendations from such a model might systematically benefit or hurt certain patient groups. Ensuring from the designers' side that the AI's decisions are transparent and ethical therefore not only guards acceptability and utility but also protects the patient. Lastly, the implications of recommending off-label prescriptions should be considered. Since use cases see drugs used beyond their current licensed conditions, it is appropriate to provide a patient prescription report on this medicine use. Stakeholders can also expect that different levels of healthcare regulations and AI guidelines and codes of practice will be followed. For example, guidelines on how manufacturers of AI medical devices should address the data quality required to assure the performance of the medical device prior to launch. More generic standards include updated regulations and standards. While a standard is helpful as AI becomes an international norm, deploying platforms with the guidance of the most up-to-date and AI-specific medical device regulatory framework will best secure unique patient inclusion. In this way, AI developers can position their products as not only compliant with the law but, more importantly, best aligned with the norms and spirit of the law.

6. Future Direction

Artificial intelligence (AI)-driven platforms for drug dosing depict a paradigm shift toward personalized medicine for a number of clinical applications. While the accuracy of dosing recommendations from these platforms continues to grow, future developments promise to make dosing more precise. Advanced machine learning algorithms and big data analytics can exploit patient-specific pharmacokinetics and pharmacodynamics models to integrate empiric clinical data and further refine dosing recommendations. However, it is equally crucial that AI systems developed for dosing are capable of learning from more examples as new patient data become available. Continuous learning and adaptability to include and adapt to new clinical situations and

unforeseen phenomena are critical for success. In addition, future platforms will likely also incorporate optimizations for data interoperability with electronic health records, including from different vendor systems and settings. A period of transformative innovation lies on the horizon, offering platforms that will refine and optimize drug dosing levels and schedules with an immediacy unmatched by standard-of-care practice.

However, downstream access to and use of AI-driven platforms will be navigated as part of broader research, development, and clinical practice informed by ethical guidelines and regulatory frameworks. As technologists, machine learning scientists, clinical investigators, and regulatory authorities collaborate on AI platforms to personalize medication, efforts to conceive practical, ethical, and grounded guidance will shape the future of this area in healthcare. Pharmaceutical companies and healthcare providers will build on that work to adhere to and help define clinical norms and practice in the AI-augmented application of a core provision of patient care, championed by pharmacology, medicine, and ethics: a personalized approach to drug treatment. This will particularly include treatment strategies for diverse and underserved populations resistant to broad-label regimens, who stand to gain the most from drug therapy personalized to their own clinical and biological profiles. In summary, personalized treatment with the potential to precede upfront adaptation of fast-acting and narrow therapeutic index medication is here. Cross-disciplinary research into ethics, laws, and governance will accompany the rapid growth that is expected in AI-driven personalized drug dosing in answering how we provide the right medical drug to the right patient at the right time.

7. Conclusion

The increasing number of AI drug platforms with personalized drug dosing provides the opportunity to revolutionize the current trial-and-error paradigms in many diseases, including cancers, chronic diseases, metabolic diseases, and infectious diseases. This growing area of research is rapidly improving individual precision in drug prescription, which is the main goal of personalized therapy, allowing the proper drug, in the right dose, at the right time, to be given to an individual patient. This pharmacological management has the potential to increase therapeutic efficacy by maximizing the full benefit of the drug effect while minimizing adverse effects. Despite the advantages of

these precision strategies, several challenges remain unsolved, including the improvement of population-based systems and the deeply rooted ethical, legal, and social hurdles. In conclusion, AI platforms, because of the characteristics described above, are gaining more and more attention and significant investments and are reshaping the health system scenario. It has been calculated that the expected benefits of the use of AI in healthcare consist of improved outcomes, productivity, and personalized medicine solutions. The combination of AI and machine learning with extensive diverse datasets from patients is shaping up a new therapeutic scenario, one that is patient-centered. On the other hand, it is still necessary to set up regulations, develop infrastructures for big data, and solve logistic and seasonal issues to make the implementation on a large scale truly effective.