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Drug Interaction Profiling in Aging Populations Using Compartmental Pharmacology Models

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Abstract

Older people often have chronic illnesses and take multiple medications, which makes them more at risk of experiencing harmful impacts from drug interactions. This research examines the profiling of drug interactions in elderly patients using compartmental pharmacology models, which simulate the ADME (absorption, distribution, metabolism, and excretion) processes of drugs within the body. The study employed a multi-compartmental approach to capture age-related changes, such as decreased hepatic clearance, altered renal function, and shifts in body composition, that affect drug distribution and pharmacokinetics. Key pharmacokinetic parameters were obtained from clinical metrics, and simulations were conducted to analyze drug-drug interactions (DDIs) in commonly prescribed classes, including antihypertensives, antidiabetics, and central nervous system (CNS)-active drugs. Model outcomes revealed that aging significantly prolongs drug half-life and alters peak plasma concentrations, heightening the risks of toxicity and subtherapeutic attenuation. Furthermore, interaction profiles exhibited both synergistic and antagonistic effects based on the drug combinations and physiological conditions. The research underscores the importance of compartmental models for predicting geriatric-specific DDIs and advocates for their use in personalized medicine aimed at improving prescribing safety. Incorporating pharmacological modeling alongside clinical perspectives provides a foundational framework for evaluating drug interactions among the aging population, improving therapeutic strategies, and reducing unintentional adverse drug reactions.

Keywords: Drug Interaction, Profiling, Aging Populations, Compartmental Models, Pharmacokinetics, Pharmacology, Simulation.

1 INTRODUCTION

1.1 Definition of Drug Interaction Profiling

Drug interaction profiling is the systematic analysis of how two or more drugs affect their absorption, distribution, metabolism, and elimination, as well as their therapeutic or adverse effects on a patient. The goal of drug interaction profiling is to identify synergistic, antagonistic, and additive effects of drugs when used in combination (Tatro, 2020). Drug interaction profiling involves analyzing both chemical drug interactions and interactions that occur through the modulation of drug metabolism (via the cytochrome P450 enzymes), transporters, and/or the influence on target receptors (Zhou et al., 2007). Drug interaction profiling can take place in in vitro studies, clinical studies, and increasingly, via in silico drug interaction modeling approaches.

1.2 Importance of Assessing Drug Interactions in Older Adults

As one ages, ongoing physiological changes primarily attributable to the aging process modify how drugs behave in the body. These changes of aging can impact all pharmacokinetic processes (that is, absorption, distribution, metabolism, and excretion), thus impacting the therapeutic level of the drug in the patient. For example, hepatic and renal clearance is often decreased with aging. Gastrointestinal motility is slower, the levels of plasma proteins have changed, and there are overall changes in the amount of water and fat in the body (Mangoni & Jackson, 2004; Sánchez-Ancajima et al., 2023). These changes can easily impact drug absorption and elimination, potentially putting older adults at risk of adverse drug reactions (ADR) and drug-drug interactions (DDI). In addition, the prevalence of polypharmacy is not only far higher in older adults, but definitionally polypharmacy is considered when a person is taking five or more medications, which is not uncommon as older adults often have multiple chronic conditions such as hypertension, diabetes, cognitive disorders, and so forth (Maher et al., 2014). Because of all of this, it would stand to reason that as older adults take more medications, they are more likely to have predictable and unpredictable DDIs. Adverse outcomes from drug interactions can be especially concerning for older adults, particularly when one takes into account their impact on hospitalizations, morbidity, and mortality, as older adults constitute more than one-third of all emergency hospital visits due to drug-related complications (Budnitz et al., 2011; Sreevidya & Supriya, 2024). Despite this, older adults have historically been underrepresented in clinical trials, which manifests itself in it being very difficult to reliably predict DDIs in this population based solely on empirical data (Cherubini et al., 2011; Pragadeswaran et al., 2024). Therefore, to better understand DDIs in older adults, utilizing a model-based approach will help to address this gap.

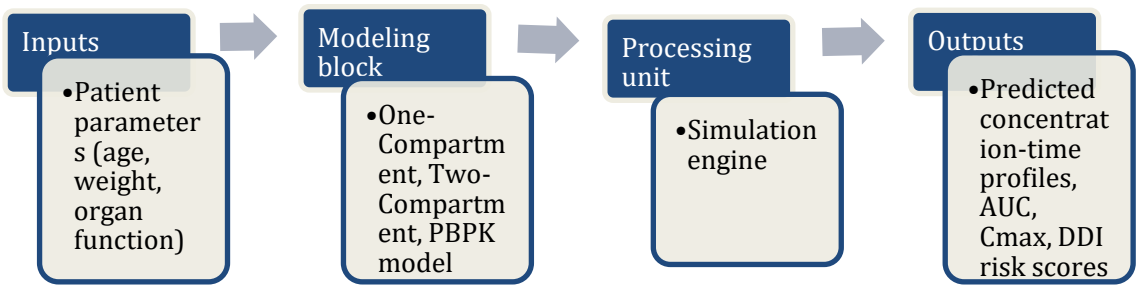


Figure 1: Architecture of a Compartmental Pharmacokinetic Modeling Framework for Aging Populations

Figure 1 presents an organized pharmacokinetic modeling framework for use with aging populations, illustrated in a block diagram. The process begins with input parameters that describe elderly patients so that the model can include the considerations of the patient-specific variables associated with absorption, distribution, and excretion (e.g., age, weight, organ function). Using the previously selected variables, the flow combines them into a modeling block (one compartmental, two compartmental, or physiologically-based pharmacokinetic (PBPK) models) with varying levels

of detail describing drug kinetics. The selected flow model is coupled to a simulation engine that computes the pharmacokinetic parameters used to develop the output data. The output consists of predicted concentration-time profiles, Area under the curve (AUC), maximum concentration (Cmax), and drug-drug interaction (DDI) risk scores. The exact specifications support the systematized and flexible approach to how pharmacokinetic evaluations are made for older adults, improve the dosing decision process, and, in general, support personalized medicine in geriatric pharmacotherapy.

1.3 Overview of Compartmental Pharmacology Models

Compartmental pharmacology models provide a model-based approach to understand how a drug behaves in relation to time through the body, using compartments structured to be bodies of water with compartments often representing groups of organs or groups of tissues (Gibaldi & Perrier, 1982; Sayad Bourani et al., 2023). These models can be categorized as either one-, two-, or multi-compartment based on the complexity of the model and the number of the physiological compartments. With regard to drug interaction profiling, such compartmental models can profile how multiple drugs are absorbed, distributed, metabolized, and excreted in the body (in one or more physiological states), including physiological states caused by aging. One important feature of compartmental models is the ability to utilize age-dependent physiological parameters (e.g., decreased glomerular filtration rate (GFR), altered activity hepatic enzymes, etc.) within the simulation to obtain and predict individual pharmacokinetics (Rowland Yeo et al., 2012). Compartmental models can be used to simulate a population of virtual patients, therefore potentially allowing high-throughput assessment of drug interactions without the ethical or logistical restrictions of conducting clinical trials. High-throughput assessment of drug interactions using compartmental models, such as Simcyp and PK-Sim, has been reported for DDI predictions in older populations, along with the effectiveness and safety of drug co-administration (Jamei et al., 2009). In addition, these models offer assistance with dose adjustments and identification of high-risk combinations before encounters with clinical use. For example, when modeling warfarin with specific antibiotics and elderly patients, simulations can determine there is a risk of increased INR and bleeding and meaningful pre-emptive management in outpatient before exposing patients to therapy (Mallet et al, 2016; Papadopoulos & Christodoulou, 2024). The synergetic use of real-time clinical data and compartmental modelling has provided some unique opportunities for precision medicine especially in geriatric patients where little is known from empirical trial data.

The paper is organized as follows. Section II discusses pharmacokinetic changes as a result of aging, including changes in drug absorption, distribution, metabolism, and excretion, and the role that polypharmacy plays in drug interactions. Section III presents an overview of compartmental pharmacology models detailing their structure, types, and utility with respect to drug interaction profiling in older adults (e.g. model applications). Section IV provides case studies demonstrating ways these models can be used in practical applications and the consequences of age-based

pharmacokinetic changes and drug interaction considerations in scenarios ranging from drug use in older adults to renal impairment and comorbidities. Section V discusses future areas of potential development and implications, and highlights the value of personalized medicine and makes several recommendations about needed research and development. Section VI concludes with a summary, clinical relevance, and a call to develop more model-based approaches to pharmacotherapy in aging.

2 PHARMACOKINETICS IN AGING POPULATIONS

2.1 Changes in ADME for Older Adult Pharmacokinetics

Pharmacokinetics (PK) refers to the transportation of drugs through the body involving four areas (absorption-distribution-metabolism-excretion (ADME). In older adults, there are physiological changes that effect each of those areas. Absorption is probably the least impacted Area of PK, but factors like gastric emptying, decreased splanchnic blood flow, and changes to gastrointestinal pH can influence the rate of absorption (not extent) of drug absorption (Chinnasamy, 2024). For example calcium carbonate, a drug that requires an acidic pH for dissolution, might have less bioavailability in older adults than in younger populations (Seymour & Routledge, 2012). Changes in distribution are of greatest importance because changes in body composition. Body's composition changes with age increasing body fat and decrease total body water and lean body mass. The potential implications of those changes depends on the properties of the drug. A lipophilic drug like diazepam would accumulate in fat tissue resulting in an extended half-life and potential toxicity, whereas a hydrophilic drug like aminoglycosides would be distributed in smaller volume and suggest higher plasma concentrations (Rao & Menon, 2024). Due to reduced hepatic blood flow and lower activity of Phase I enzymes (e.g., cytochrome P450), metabolism commonly slows down. This leads to slower biotransformation and higher levels of drugs in plasma, especially, theophylline, propranolol (Kinirons & O'Mahony, 2004). However, the Phase II conjugation pathways (e.g., glucuronidation) are generally preserved in the elderly (Cotreau et al., 2005). Excretion decreases markedly with age due to reduced renal function. After age 40, glomerular filtration rate (GFR) decreases about 1 mL/min annually; this affects elimination of medications that are renally cleared, such as digoxin, aminoglycosides and lithium (Burtis et al., 2012; Abdullah, 2024). Drugs without dose adjustments are prone to accumulation, risking toxicities.

2.2 Influence of Polypharmacy on Drug Interactions in Elderly Patients

Polypharmacy is common in the elderly, with some patients taking five or more medications at the same time. Although polypharmacy is often appropriate to control multimorbidity, it greatly increases the overall risk of drug-drug interactions (DDI) both medically as well as the toxicological risks (Gnjidic et al., 2012). Polypharmacy puts patients at risk for competitive inhibition of drug-metabolizing enzymes, displacement from plasma protein binding sites, and saturation of renal transporters which can cause altered drug concentrations and increased adverse drug reactions (Hanlon et al., 2004). Polypharmacy often results in DDI concerns that are patient-specific, in elderly

patients, a common DDI worth noting includes the use of NSAIDs and anti-hypertensives, which can blunt blood pressure control and increase risks of renal impairments (Bhupesh et al., 2023). One notable concern includes polypharmacy when combining opioids, benzodiazepines, and anticholinergics which have cumulative CNS depressant effects that may lead to falls, cognitive decline (Campbell et al., 2009; Sathish Kumar, 2024). Any DDI and polypharmacy must be carefully profiled, especially when managing geriatric drug therapy.

2.3 Utility of Compartmental Pharmacology Models for Drug Interaction Predictions

Compartmental pharmacology models describe drug kinetics in compartments of the body (central (blood/plasma), peripheral (tissue) and sometimes organ-specific compartments) using mathematical functions. Pharmacology models can be adjustable to describe changes for aging populations such as reduced GFR (elimination), reduced hepatic enzyme activity, and altered volumes in tissues (Rowland & Tozer, 2011; Delshad et al., 2017). Multi-compartmental models allow researchers and clinicians to predict (in terms of concentration-time profile, half-life, peak plasma concentration) pharmacokinetics, drug interactions in a simulated virtual elderly patient. This use of patient drug simulations can be particularly useful when developing safer dose adjustment regimens or assessing potential drug-drug interactions prior to clinical use (Carter & Zhang, 2025; Sharif, 2018). For example, by using a pharmacokinetic model for warfarin and SSRIs, the current bleeding risk from CYP2C9 inhibition from warfarin could be predicted—a risk particularly relevant for elderly patients with polypharmacy (Ahmed, 2022). Recent advancements in computer software including Simcyp, NONMEM, and PK-Sim offer new areas of research with incorporation of physiological and clinical data into pharmacokinetics modeling as identified by Bouzom & Walther (2008), assisting on informing clinically based individualized therapy drug regimens. Compartmental pharmacokinetic models are likely used for assessing regulatory decisions on new agents where the intended population was geriatric patients (Bouzom & Walther, 2008; Mansuri & Topkanlu, 2018).

3 COMPARTMENTAL PHARMACOLOGY MODELS

3.1 Description of Compartmental Pharmacology Models and Applications in Pharmacokinetic Modeling

Compartmental pharmacology models represent a mathematical framework for understanding drug distribution and movement throughout the body. Compartmental pharmacology models "divide" the body into conceptual "compartments" representing body regions, for example, central compartments (blood, liver) versus peripheral compartments (muscle, fat). The distribution of the drug to each compartment and elimination from the central compartment is determined by rate constants and is modeled with systems of differential equations. For example, a two-compartment model shows how the concentrations of drug in the central $C1$ and peripheral $C2$ compartments will change over time:

$$\frac{dC_1}{dt} = -(k_{10} + k_{12})C_1 + k_{21}C_2 + \frac{D}{V_1}\delta(t) \quad (1)$$

$$\frac{dC_2}{dt} = k_{12}C_1 - k_{21}C_2 \quad (2)$$

Here, k_{10} is the elimination rate constant from the central compartment, k_{12}, and k_{21} are the transfer rate constants, D is the administered dose, and V_1 is volume of distribution for the central compartment. The delta function $\delta(t)$ implies that the drug is administered instantaneously (e.g., IV Bolus). These equations can be used to make predictions about the time to therapeutic effect, the duration of therapeutic effect, and how those times would alter with drug interactions.

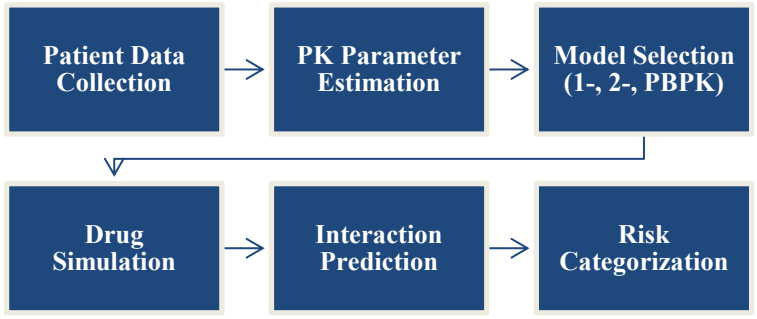


Figure 2: Drug Interaction Profiling Using Compartmental Models

This workflow diagram (Figure 2) shows a step-by-step process of drug interaction profiling in older people using compartmental pharmacodynamics modeling. The drug interaction profiling methodology boils down into a workflow diagram that follows the bei-e project questioning process we have developed for decades. The first step in the process is to collect patient data where individual parameters will be collected (age, weight, renal function, or other comorbidities). Patient data will then be used in PK parameters estimation where various relevant pharmacokinetic variables (clearance, volume, etc.) are derived. The measured or assumed pharmacokinetic parameters will inform model choice (one-compartment to PBPK) which will then be employed in drug simulation where we can examine different drug behaviors in the body virtually under a variety of circumstances. This step will be followed by interaction prediction, which will assess the likelihood and magnitude of potential drug-drug interactions and identify potential risk. Finally the results will be categorized by levels of concern through a consideration of risk to patient safety. At this stage a clinician can then consider an alternative therapeutic strategies as compared to standard prescribing habits. The structured way of thinking outlined in the diagram is an example of how compartmental modeling of pharmacokinetics or pharmacodynamics can improve our ability to make good decisions in geriatric pharmacology by identifying risk of drug-drug interactions before the result precedes issues in clinical practice.

3.2 Types of Compartmental Pharmacology Models in Drug Interaction Profiling

The various types of compartmental models that would be considered in drug interaction profiling include a one-compartment model which assumes that the drug is evenly (in an instantaneously

uniform fashion) distributed in the body. The equation for concentration of drug $C(t)$ for an IV bolus dose is:

$$C(t) = \frac{D}{V} \cdot e^{-k \cdot t} \quad (3)$$

where D is the dose, V is the volume of distribution, k is the elimination rate constant, and t is time. This model is simple, but does not address the potential for delayed distribution reasoning nor the potential for tissue-unit variability in distribution effects. The two-compartment model, as already discussed, consists of a central compartment for the distribution phase and a peripheral compartment for the disposition phase. The two-compartment model is beneficial for drugs that are either lipophilic or distribute slowly. Multi-compartment models consist of additional compartments to account for complex tissue distributions or disposition that are organ-specific, per se. Lastly, physiologically-based pharmacokinetic (PBPK) models capture integrated distribution and disposition of drugs in the body by incorporating anatomical and physiological data such as blood flow rates, organ size, and enzyme metabolism rates for both drug clearance, and plasma concentration changes. These tables and assessment from PBPK models are of great importance in examining interactions in geriatric populations, where physiological parameters are not adhered to as frequently as in younger adults.

3.3 Benefits and Limitations of Compartmental Pharmacology Models in Determining Drug Interactions in the Aging Population

There are a number of advantages of using compartmental models when thinking about drug interactions in an older population. Compartment models are capable of simulating altered drug behavior resulting from age-related changes in drug disposition due to bedrock alterations in renal function, hepatic function or clearance, protein binding, or tissue proportions and composition. They can allow us to consider the interactions, design optimal dosages, and minimize the occurrence of adverse clinical effects, and they will allow us to do this without having to do a formal clinical study in the older population for implanting high-risk patients. They also have limitations. They usually incorporate the assumptions of linear kinetics, that what's in the compartment is homogenous and is distributed homogeneously, which may or may not be reflective of biologic realities in the geriatric patient with multi-morbidities or failing organs. More critically, and relevant to Campbell's pharmacokinetics, the quality of the model and its capabilities when applied, would rely heavily on parameters being accurately estimated or derived. Compartmental models, due to their simplicity, will always be among our arsenal for predicting and/or managing drug interactions—we may be a more or less powerful tool when geared toward geriatric pharmacology in general but easily adaptable to that particular sub-group within pharmacokinetics.

4 CASE STUDIES: DRUG INTERACTION PROFILING IN AGING POPULATIONS

4.1 Case Study 1: Drug A and Drug B Interactions in Older adults - Compartmental Pharmacology Models

In this instance, an older patient receives a prescription for Drug A, which is a beta-blocker metabolized by the liver, and Drug B, which is an antidepressant shown to be a cytochrome P450 CYP2D6 inhibitor. When simulated through the pharmacokinetics models that showed two-compartment kinetics, Drug B inhibited the hepatic metabolism of Drug A, leading to an increased half-life of Drug A and increased plasma Drug A concentration. When looking at drug interactions with older adults, particularly those on many medications such as this patient, the effect seen from this interaction is compounded by the loss of hepatic enzyme activity. As a result, the person may experience bradycardia or hypotension. The model provided specific predictions of increases in systemic exposure by comparing AUC values with AUC defined as:

$$AUC = \int_0^\infty C(t)\, dt \qquad (4)$$

The increase in AUC for Drug A with Drug B was substantial enough to indicate a very probable interaction. Additionally, the peak concentration (Cmax) can be monitored to characterize the risk of toxicity:

$$C_{max} = \max\{C(t)\} \qquad (5)$$

The simulation predicts that Cmax is above the therapeutic window. The next step is either to reduce the dose of Drug A or space the timing, whichever will minimize the likelihood of adverse outcomes in the elderly.

This bar graph (Figure 3) shows how much the co-administration of Drug A and Drug B changes the pharmacokinetic processes of Drug A in older patients. For patients who take drug A alone, the Area Under the Curve (AUC) is 220 mg·h/L, and peak plasma concentration (Cmax) is 15mg/L. However, with the introduction of Drug B, which is a known hepatic enzyme inhibitor, both AUC and Cmax sharply increase to 410 mg·h/L and 28 mg/L respectively. This sharp increase indicates that Drug B inhibits the metabolism of Drug A. In older patients, where there is already reduced liver function, this interaction is more likely to result in adverse effects such as toxicity or cardiovascular complications. The graph demonstrates how important it is to change the dosage or use a different medication instead when a secondary medication that inhibits enzymatic functions are used in aging patients.

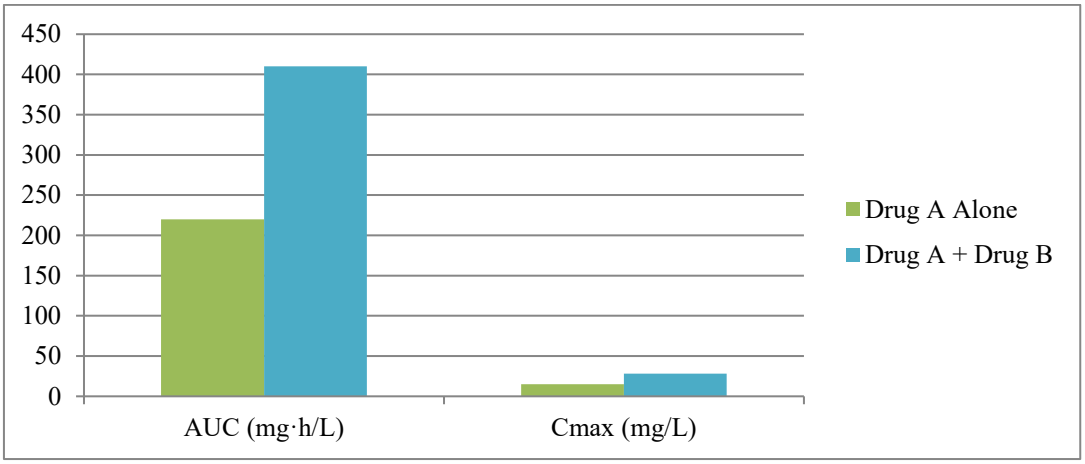


Figure 3: AUC and Cmax Comparison (Drug A With and Without Drug B)

4.2 Case Study 2: Illustration of Drug-Drug Interactions in an Elderly Population and the Impact of Renal Impairment

An elderly patient is prescribed two renally excreted drugs (an aminoglycoside and a diuretic) that have the potential to precipitate adverse effects in the setting of chronic kidney disease (CKD). A multi-compartment model was used to simulate these diseases of elderly patients while taking into account decreased renal clearance due to the impaired glomerular filtration rate (GFR). Following dosing and resulting in the accumulation of drug (most notably the aminoglycoside) that creates the potential for nephrotoxicity and ototoxicity. Renal clearance (CL_{renal}) was calculated using:

$$CL_{renal} = \frac{Ke \cdot V_d}{f} \qquad (6)$$

where Ke is the elimination rate constant, V_d is the volume of distribution, and f is the bioavailability. In the setting of renal impairment, Ke is drastically lower, which reduces clearance and increases systemic exposure to the drug. The model demonstrates that the second drug (the diuretic) will reduce renal perfusion, which further reduces elimination. Modifications in dosing intervals and therapeutic drug monitoring adjustments can be made to ensure patient safety in this population based on the model predictions.

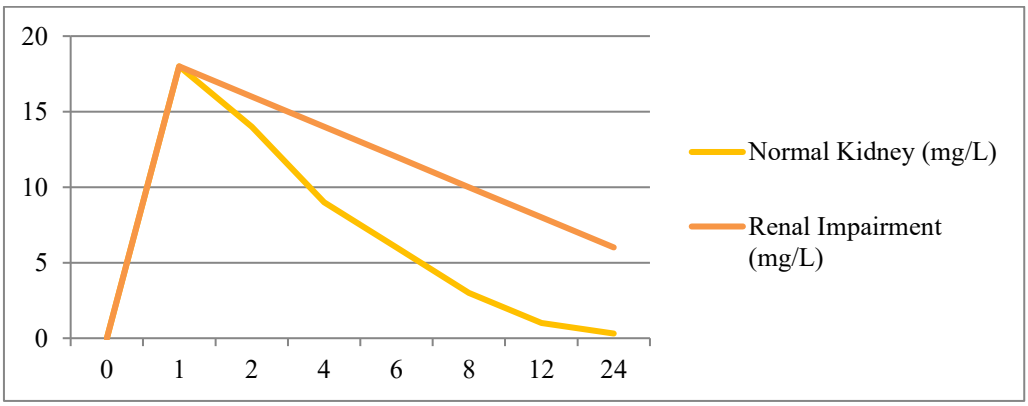


Figure 4: Drug Concentration vs. Time in Renal Impairment

Figure 4 shows the plasma concentration of an aminoglycoside antibiotic given over a 24 hour period to elderly patients with normal renal function and those with renal impairment. For patients without renal issues, the drug concentrations peak at 1 hour with a value of 18 mg/L and drop to 0.3 mg/L by the 24 hour mark showing effective clearance. Within the renal impairment group, the concentration does decrease but much more slowly reaching only 6 mg/L after 24 hours. This demonstrates the increasing factor of a reduced elimination rate stemming from decreased glomerular filtration. The increased time exposed to the drug increases the chances of nephrotoxicity and ototoxicity, particularly when taking other drugs that damage the kidneys. This emphasizes the need of simulation through compartmental models to estimated clearance and adjust dosage in elderly patients with reduced renal function.

4.3 Case Study 3: Predicting Drug Interactions in Older Adulthood with Comorbidities using Compartmental Pharmacology Models

In this case, there is an older patient with diabetes and hypertension, mild cognitive impairment, who takes a combination of metformin, ACE inhibitors and an anticholinergic agent. A physiologically-based compartmental model is implemented to take into account reduced renal function, altered motility in the gut (i.e. gastroparesis), and increased body fat content. The model is used to describe the pharmacokinetics of each drug including drug potential to alter gastrointestinal transit time and liver blood flow. The measures of interactions are quantified by measuring bioavailability (F) and apparent clearance (CL/F) and defined by:

$$CL/F = \frac{D}{AUC} \tag{7}$$

Where D is the dose given, and AUC is drug exposure (total drug concentration over time). A decrease in CL/F for the anticholinergic suggests there is impaired elimination; however, the ACE inhibitor increases the absorption of metformin only slightly in this model because of hemodynamic effects. Anticholinergic medications, and the ACE inhibitor in this case, may not create acute toxicity on their own but they can, over time, impede glycemic control or cognitive control. Our model provides evidence in support of optimizing dose and time with contingencies for identifying which drugs are better to substitute for to limit cumulative risk for patients with more complicated health profiles.

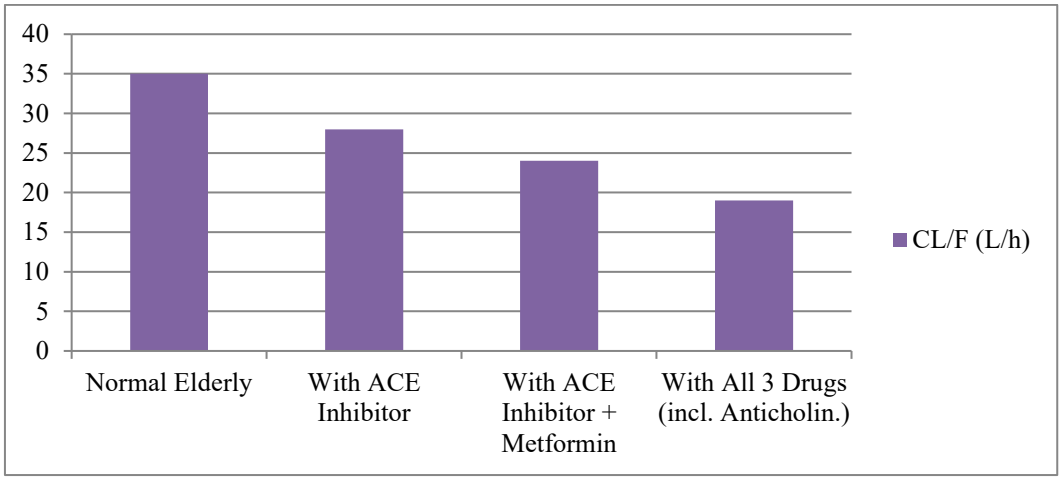


Figure 5: Apparent Clearance (CL/F) of Anticholinergic Agent in Elderly with Comorbidities

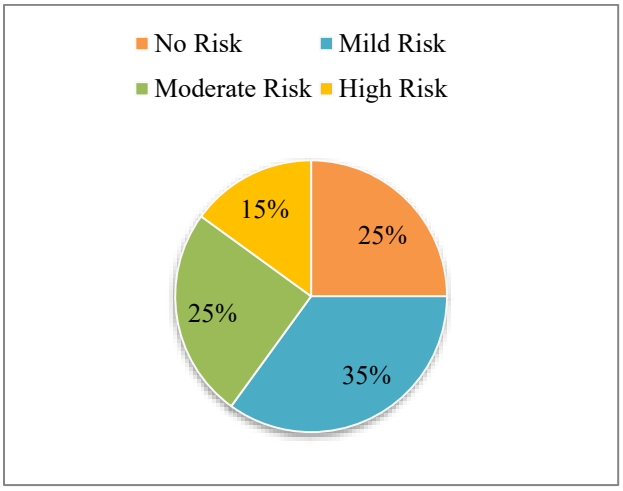


Figure 6: Predicted Risk Index for Multi-Drug Interaction

Figure 5 shows a bar graph that highlights the apparent drug clearance (CL/F) of an anticholinergic medication with different drug combinations in an elderly patient with multiple diseases. With no other medications, the clearance is at 35 L/h. The use of an ACE inhibitor drops clearance to 28 L/h, presumably because of some changes in hepatic blood flow. When metformin is added, clearance further drops to 24 L/h. With the full combination of ACE and metformin and anticholinergic, the clearance drops to 19 L/h. The gradual decline in clearance demonstrates the effects of polypharmacy and increased metabolic strain in elderly patients. The graph also describes the impact of several medications on the rate of hepatic and renal elimination. Compartmental models provide quantifiable precision which aids in developing better dosing strategies and prescribing medications more safely. This pie chart (Figure 6) shows how the predicted risk levels of drug interactions are distributed after simulating common geriatric prescriptions. This model assigns 25% of the interactions to be “No Risk,” 35% to be “Mild Risk,” 25% to be “Moderate Risk,” and 15% to be “High Risk.” The largest section marked “mild risk” indicates that the majority of combinations need oversight, though active management is not essential. Still, the 15% of high-risk interactions present dangerous problems, particularly in those with organ dysfunction or cognitive decline. These

cases might involve medications with a small margin of safety or overlapping toxic effects. This graph reinforces the importance of predictive models not only for classifying drug combinations by risks but also for anticipating harmful interactions in elderly care.

5 FUTURE DIRECTIONS AND IMPLICATIONS

5.1 Potential for Personalized Medicine in Aging Populations Using Compartmental Pharmacology Models

The use of compartmental pharmacology models has significant potential for progressive personalized medicine approaches in aging populations. Older adults frequently exhibit distinct physiological profiles characterized by age-related changes in organ function, body composition, and patterns of co-morbidity. Existing traditional "one size fits all" dosing practices are often inadequate at accommodating these changes. Compartmental models can be tool for simulating drug behavior based on individualized parameters like renal clearance, hepatic metabolism, and volume of distribution (VD). Inputting patient specific information (age, weight, organ function, genetic markers) into these models can help to forecast the behavior of a given drug or drug combination in an individual patient. This development allows for the crafting of more personalized drug regimens to optimize the therapeutic effect while minimizing toxicity, especially in at-risk geriatrics. Additionally, with the potential inclusion of real-time patient monitoring information into model algorithms, future clinical uses may assist and inform real-time dosing adjustments based on individual patients' evolving physiologic states. These approaches could support improved patient outcomes, decreased hospitalizations, and improved quality of life for older adults needing complex treatments.

5.2 Significance of Age-Related Pharmacokinetics in the Study of Drug Interactions

Age-related changes in pharmacokinetics are an important consideration in the evaluation of drug interactions in older adults. Physiologic changes that occur with age can vary significantly and are a consideration, as follows: decreases in hepatic enzyme activity, renal filtration rates, plasma protein binding, and gastric acidity all alter the pharmacokinetics of drugs. If we do not utilize, and justify, the changes made to the pharmacokinetics related to the aging process, we risk inaccurate prediction of drug absorption, distribution, metabolism, and excretion, resulting in adverse drug reactions and therapeutic failure. An example would be a drug with a small therapeutic index, which is eliminated by renal clearance, and would accumulate to a Toxic level in the elderly with unrevealed kidney insufficiency. Pharmacology models of compartmentalization can integrate ubiquitous older adult pharmacokinetic measurements to predict the behavior of drugs in older adults. Understanding age-related presentation and pharmacokinetic change is imperative in polypharmacy, given that drug-drug interactions are so common, and so unanticipated due to the multitude of possible overlapping metabolic and elimination pathways. Thus, there is a need to better understand and apply

agerelated pharmacokinetic changes well, and integrate these changes into innovative, patient-centered and safe therapeutic strategies in the care of older adults.

5.3 Prospects for Future Research on Drug Interaction Profile Studies in Elderly Population with Compartmental Pharmacology Model

Future research needs to continue to modify and enhance compartmental pharmacology models for the appropriate use in the elderly populations. There needs to be significant data collection to apply pharmacokinetic and physiological measurements across very large and diverse groupings of older individuals, even differentiating between elderly adults that are frail or have multiple comorbid conditions. This will allow for actual pharmacokinetic modeling and determination between variability or heterogeneity that cannot be averaged or generalized. Future studies should also examine using machine-learning using compartmental modeling approach where built on drug interaction predictions over time. The development of usable clinical tools designed from these models, can help impact decision making at the point of care. There will be a necessity of collaboration of specific subject matter experts in pharmacology, geriatric medicine, data science and healthcare technology developers to better implement model-based prediction into the clinical practice of healthcare. Additionally, there should be an appeal to regulatory agencies to work with pharmaceutical companies to consider age-appropriate avenue of model-based representation in drug development and eventually post-marketing observational studies on the reception of new medications in an elderly cohort for drug safety and efficacy evaluations.

6 CONCLUSION

In summary, applying compartmental pharmacology modeling to drug interaction profiling in an aging population is a robust and systematic approach to understanding and predicting pharmacokinetic behavior in a challenging and complex evolutionary state of human physiology. Compartmental models can provide a careful simulation of drug absorption, distribution, metabolism, and excretion, while addressing age-induced effects, such as decreased renal function, modified hepatic metabolism, and increased total number of medications. The ability to integrate individualized parameters into compartmental pharmacology enhances the usefulness of these models in setting safe and efficacious drug interventions in elderly patients. Unique findings across cases illustrate how compartmental pharmacology has identified drug-drug interactions that represent higher risk combinations, improved drug dosing individually, and ultimately prevented adverse outcomes during geriatric care. These tools can establish a foundation for evidence-based practice and patient-centered treatment plans clinically. Furthermore, they should lead to safer development of new drugs by considering older adults in clinical trial designs and drug approvals. As the world's population ages, the need for research to make these models more relevant, while coupling with real-time health data, and to develop clinical decision support systems usable at the bedside is outwardly warranted. Progressing this research agenda necessitates collaborative efforts and an increased focus on geriatric

-specific particulars in pharmacology studies. Therefore, we can reduce the number of non-saving medication therapies that are widely accepted in aging.

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