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NSAIDs and Oral Drug Absorption: Ibuprofen through a Pharmacokinetic Lens

Courtney Gant
cgant@gardner-webb.edu

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Courtney Gant

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Dr. Venita Totten, Thesis Advisor	Dr. Wilson Hawkins, Director of Univ. Honors
Dr. Robert Bass, Honors Committee	Dr. Elizabeth Amato, Honors Committee

Abstract

Human pharmacokinetics is the study of how administered medications move throughout and behave within the body. Absorption, distribution, metabolism, and excretion are four integral parts of this field of study and are commonly known as the ADME principles of pharmacokinetics, but other processes are studied within the field. For orally administered drugs, the absorption process lies within the small intestine and colon, two components of the gastrointestinal (GI) tract; this bodily system is associated with many variables—many of which must be considered in the study of oral drug absorption. Often administered orally, non-steroidal anti-inflammatory drugs (NSAIDs) make up a group rich in history that includes a plethora of drugs available today. NSAIDs are typically known for their treatment of inflammation, pain, and fever, and ibuprofen is a well-known NSAID that treats all three of these afflictions. Ibuprofen is a relatively recent component of the NSAID group, but published research regarding this drug's associated adverse reactions and pharmacokinetic behavior is plentiful. Important factors in ibuprofen's pharmacokinetic behavior include age, biological sex, and body composition; most importantly, the impact of food consumption on oral ibuprofen absorption is an essential consideration when this drug is administered, for a common belief surrounding ibuprofen is that it must be taken with food. Overall, this literature review aimed to compile published information necessary to understand the pharmacokinetics of ibuprofen, discuss important variables in this NSAID's pharmacokinetic behavior, and evaluate ibuprofen's associated food effect—and apply it to patient safety and treatment efficacy.

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1. Human Pharmacokinetics

1.1 Introduction

An often-overlooked topic, the field of human pharmacokinetics is vast and concerns many varying topics. Often serving to analyze the course of medications, pharmacokinetics is a topic that researchers today still strive to accurately quantify (Fan and De Lannoy 94; Stillhart et al. 2). In humans, pharmacokinetics involves many factors that concern researchers, patients, and providers alike. With a multitude of applications, it is still pertinent in medicine today to understand pharmacokinetics. Pharmacokinetics can be defined most simply as the study of four processes undergone by administered drugs: absorption, distribution, metabolism, and excretion (Hughes 2014a and 2014b, as cited in Kawedia 191). Varying definitions of pharmacokinetics exist across scholarly literature, especially when the four ADME principles are considered (absorption, distribution, metabolism, and excretion), and a multitude of measurable factors are involved in building the pharmacokinetic profile of a drug, but the span of components and applications spans as vastly as the field itself.

1.2 Definition

1.2.1 On a Broad Scale

A multitude of ways to classify and define the field of pharmacokinetics can be utilized. First, pharmacokinetics is known to study drug and pharmaceutical compound movement throughout a patient's system following the initial dosing (Abdel-Rahman and Kauffman 2004, as cited in Fan and De Lannoy 94). While providing insight into the field of pharmacokinetics, this definition also shows how broad the area is. After all, countless methods for compound administration exist along with pharmaceutical compounds to be administered. Some scholars

have described the pharmacokinetics of a pharmaceutical compound as a study of its concentration in the human body versus time; in a clinical setting, pharmacokinetics can, therefore, be used to adjust how much of a given drug is given to a patient as well as how frequent (Loucks et al. 903). Pharmacokinetics not only is the study of drugs in the body but also their relationship with time. In this field, all eyes are on the course of a chemical entity as it travels through the body as well as how time fits into the mix. Pharmacokinetics fits under the hypothetical umbrella of pharmacology and can examine how quickly the processes impacting drug plasma concentration take place, thus allowing quantitative study of a pharmaceutical compound's journey throughout the body in relation to time (Pea iv). By relating pharmacokinetic processes to time, speed (velocity) is given, which allows for a logical, numerical study of the course of a pharmaceutical compound. However, this broad topic may be described as the area of study regarding four processes experienced by administered compounds: absorption, distribution, metabolism and excretion (Hughes 2014a and 2014b, as cited in Kawedia 191). By far, these are the most common words used to describe pharmacokinetics. In countless pieces of literature, such terms are referred to as ADME components (for absorption, distribution, metabolism, and excretion). ADME components represent a logical way of breaking down pharmacokinetic studies into four observable regions of a drug's bodily course. Certainly, the field of pharmacokinetics is of interest to providers and researchers alike; with many definitions in use, pharmacokinetics concerns a broad range of processes carried out on an administered drug, but these processes can be simplified into four main principles: absorption, distribution, metabolism, and excretion (ADME).

1.2.2 ADME Principles

1.2.2.1 Absorption

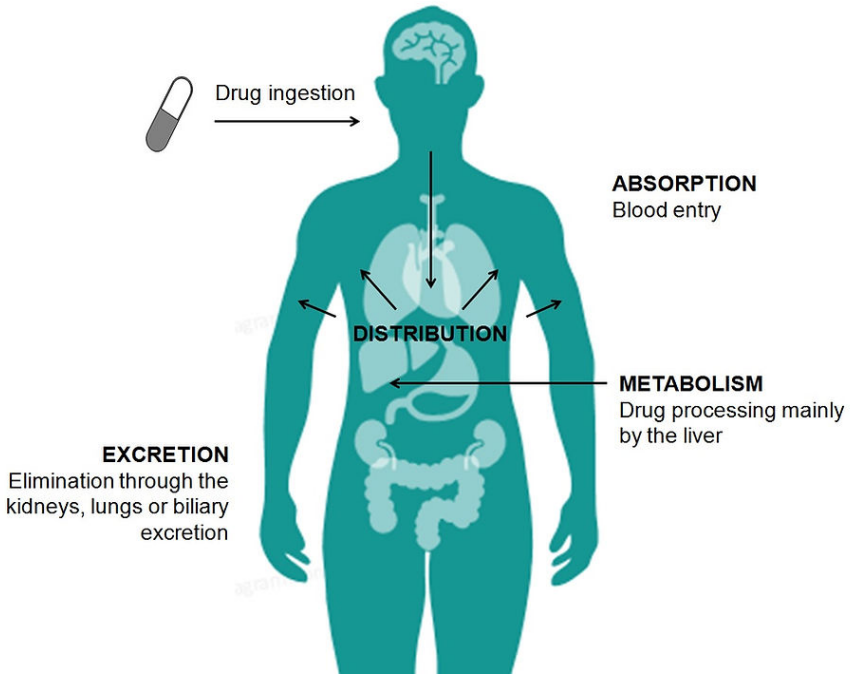

Fig. 1. "The four stages of Pharmacokinetics are represented by the acronym ADME."

Represented by the first letter in the acronym ADME (absorption, distribution, metabolism, and excretion), absorption is chronologically the first pharmacokinetic process to be studied after a drug is given to a patient. In other words, the term absorption may be used to denote the course taken by a chemical entity to reach the blood circulating in the body (Pea 69). This must happen before the other three steps—distribution, metabolism, and excretion—can be considered. Some scholars note that absorption determines the speed and magnitude at which a compound arrives at its target area of the body (Kawedia 191). Evidently, there is more to the absorption stage than simply reaching the bloodstream. In reaching the bloodstream, a pharmaceutical compound can begin performing its intended action within a time frame dictated

by the absorption process itself. To express this principle of pharmacokinetics more quantitatively, absorption can also be described as the movement of a drug from where it is applied to where it will be measured. There is a plethora of ways for a compound to be absorbed, with the most crucial area for absorption being the GI tract for oral drugs; other absorption sites include the skin, nasal lining, and respiratory lining, with the site depending on the drug's administration method (Fan and De Lannoy 95). Undoubtedly, a compound can be absorbed in many ways, with some being more common than others. However, the theme of absorption remains the same: the pathway taken by a drug from administration to its final measure of concentrations. Another noteworthy piece of information is that the process of absorption can be either biologically active or passive (in terms of the use of energy) (Loucks et al. 903). While absorption can be described in terms of a drug arriving at the bloodstream as well as the time it takes to do so and how much of the drug arrives, it can also be defined as the course of a medication from administration to the targeted area of measurement. This area of measurement may very well be the systemic circulation, but the definition at hand adds a broader sense of understanding, for the blood concentration is not always what is measured. The pharmacokinetic process of absorption, represented by A in the ADME principles of pharmacokinetics, represents the various courses of a drug to travel from the place of dosing to its final place of study, typically the bloodstream; this process begins with a compound being absorbed into the body through varying bodily structures.

1.2.2.2 Distribution

The second letter in the ADME acronym represents the pharmacokinetic process of distribution, which is considered to follow the process of absorption by beginning its course in the circulatory system. The distribution process can be simply defined as the procedure

undergone by a pharmaceutical compound to travel from the circulation to bodily tissues (Pea 69). Distribution begins when a drug reaches the bloodstream and ends when it reaches bodily tissues. Such a definition makes sense when the ADME acronym is considered, for absorption is most often referred to as ending in the bloodstream; as with the acronym, this would mean that distribution directly follows absorption. Once a drug enters the circulatory system and the process of distribution begins, it does not get absorbed by a specific region of tissues but is effectively "distributed" to many tissues throughout the body—a wide outreach thanks to the efficiency and power of the bloodstream (Kawedia 191). As soon as a chemical entity reaches the bloodstream, it is immediately on a fast track around the entire human body. The process of distribution, therefore, is where a drug can truly make an impact. As opposed to studying an instantaneous measurement of a drug in the tissues, distribution is also described as the rate at which a chemical entity builds up in the bodily tissues (Doogue and Polasek 6). Using this definition, distribution is a dynamic process—that is, a process full of change. In this way, distribution can be sensibly expressed as a relationship between variables rather than just studying one variable. Additionally, some definitions represent distribution as happening after absorption as well as at the same time, for it involves a compound's movement "to and from the site of measurement" (Loucks et al. 903). Because the site of measurement for absorption is typically the bloodstream, and the beginning setting of a drug in the distribution process is the bloodstream, the two can potentially be considered to overlap. However, not all studies of ADME principles consider this potential overlap. The distribution process includes the transportation of a drug from the bloodstream to the various tissues supplied by it as well as the measurement of the drug's rate of amassing in such tissues; depending on what definition is

consulted, distribution may be considered as both separated from and overlapping with the preceding process of absorption.

1.2.2.3 Metabolism

The third letter in the ADME acronym of pharmacokinetic processes is indicative of metabolism, a process that changes an administered pharmaceutical compound into a separate chemical product with different characteristics and primarily occurs in the gastrointestinal (GI) tract and liver; especially due to its biphasic process, metabolism heavily influences drug elimination, among other pharmacokinetic factors. A process noted as occurring in the GI tract and liver, metabolism can be described as the alteration of a chemical to form a different one (Loucks et al. 903). Just as absorption concerns the sites of administration and final measurement, and distribution concerns the bloodstream and surrounding tissues, metabolism is most often noted in the liver and GI tract. It is here where the chemical entity in question undergoes a change resulting in a separate chemical product. Other scholars define this chemical change as the breaking down of a pharmaceutical compound "into chemically distinct" products; the endpoint of this chemical change is the drug's elimination from the system (Kawedia 191). Certainly, metabolism is a step along a broad pathway to the total elimination of a given chemical entity. This elimination seems to be the purpose of the deconstructive process that is metabolism. For the products of metabolism to be expelled from the body, the overall process carries out the transformation of a lipophilic drug or chemical into a hydrophilic product with the help of enzymes (Fan and De Lannoy 95). Such transformation is necessary to reach the elimination goal, for lipophilic compounds would be quite difficult to remove from the body via defecation and urination because they will not be attracted to the components therein (Fan and De Lannoy 95). Thanks to the role played by enzymes, the remnants of a pharmaceutical

compound are made hydrophilic and can be excreted successfully. Also described as biotransformation, this transformative process of metabolism is made up of two phases; the first phase is nonsynthetic and called “phase I,” and the second phase is synthetic and known as “phase II” (Pea 70). These two phases make the above deconstructive transformation possible. In other words, the biphasic design of metabolism allows for the conversion of a lipophilic chemical entity to a hydrophilic one. The two phases of metabolism each encapsulate their own reactions, with reactions from Phase I focusing on the introduction of functional groups to the chemical entity and Phase II reactions facilitating the joining of said functional groups to hydrophilic reactants (Fan and De Lannoy 95). The addition of functional groups makes up the synthetic phase, and the combining of the chemical entity in question with hydrophilic materials makes up the non-synthetic phase. By studying the reactions making up the two phases of metabolism, the sheer extent to which a drug is transformed within the process is made evident. Metabolism is a crucial process in the study of pharmacokinetics; after all, it facilitates clearance of a drug from the body, promotes bioavailability when compounds are administered orally, and is in charge of the activation of some select compounds (Doogue and Polasek 6). While the end of the process of metabolism is marked by elimination, the latter also performs many other important duties regarding pharmacokinetics. Among other duties, it is responsible for activating some drugs and is crucial in the proper function of oral pharmaceutics; metabolism is, certainly, a multifaceted process (Doogue and Polasek 6). Overall, the process of metabolism is represented by the M in the pharmacokinetic acronym ADME and is responsible for the breaking down and transformation of an administered chemical entity into a separate product that can be ejected from the body; It occurs typically in the liver and GI tract, is made up of synthetic first-

phase reactions and nonsynthetic second-phase reactions, and plays a central role in many pharmacokinetic aspects of a drug, including elimination.

1.2.2.4 Excretion

The final letter in the ADME acronym stands for excretion, which generally describes a drug irreversibly leaving the body through various processes and is often confused with elimination. Commonly defined as an "irreversible" process, excretion is often described as encompassing the loss of a drug through actions like urinating, sweating, respiration, or defecation (via bile) (Evans, Schentag, and Jusko 1992 and Atikinson et al., as cited in Loucks et al. 903). Once a drug has left the body, it cannot be captured and administered again; intuitively, excretion is an irreversible process. While urinating and defecation most definitely come to mind when one thinks of excretion pathways, respiration and perspiration can also be outlets for the excretion of an administered chemical entity. Excretion can also be put into more quantitative terms by defining it as the rate of removal of a pharmaceutical compound as well as how much of that compound is removed at a given time of measurement (Kawedia 191). The process of excretion can, then, be quantitatively represented as either a rate or an instantaneous measurement. Some scholars also define excretion in terms of elimination, which is the aforementioned endpoint of the preceding process of metabolism; through this lens, excretion is the elimination of a chemical entity through outlets like urination and defecation (Pea 70). Therefore, excretion is a route of elimination. However, this definition can cause confusion, for elimination and excretion are often incorrectly used interchangeably. Some published scholars set these two terms apart by expressing that, while they are both irreversible, elimination is used to describe a chemical entity moving away from the specific site of measurement, but excretion is used to describe the total loss of an "unchanged" pharmaceutical compound (Rowland and

Tozer 2011, as cited in Doogue and Polasek 6). In other words, when a drug has been eliminated, this means it is considered gone from merely the measurement site; excretion, on the other hand, denotes total loss of the original form of the drug from the whole body. Excretion can be the reason for elimination, but elimination is not entirely made up of excretion. The fourth and final letter in the ADME acronym, excretion is noted in literature as an irreversible process in which a drug exits the body through processes like urination, defecation, or even perspiration; this process can be quantitatively represented by both rates and instantaneous measurements, and while excretion is typically confused with the process of drug elimination, the former is merely one way a drug can be eliminated from a bodily site of study.

1.2.3 Other Components

The ADME principles exhibit a typical and revered approach to studying the pharmacokinetics of a chemical entity, but they fail to encapsulate all components in the pharmacokinetic sphere of study; two important components that should also be noted are the alternative acronym ABCD as well as the process of drug elimination. First, it is important to note that scholars have recently coined the acronym ABCD for pharmacokinetics, which stands for administration, which concerns the amount administered and dosing compliance; bioavailability, which considers the part of an active pharmaceutical compound that makes it to the body's circulation of blood; clearance, which involves this active part of a drug exiting the blood; and distribution, which describes the compound's arrival at its intended destination (Doogue and Polasek 5). While distribution is also included in the four ADME principles of pharmacokinetics, administration, bioavailability, and clearance are not present in this formalism. However, bioavailability can be compared to the ADME process of absorption, and clearance can be compared to the processes of metabolism and excretion (Doogue and Polasek

5). There is value in using both acronyms, however, in studying pharmacokinetic processes, for ADME can be considered a mechanistic approach while ABCD places more focus on the active component of an administered chemical entity (Doogue and Polasek 7). This evidence may be used to distinguish ABCD as a narrower lens through which pharmacokinetics can be studied. On the other hand, since ADME is more concerned with the overall mechanisms associated with its four represented processes, it can provide a broader scope of study. In addition to there being another acronym in use, a discussion of pharmacokinetic processes should include drug elimination; however, as discussed above, the ADME principle of excretion is often incorrectly equated to this process (Doogue and Polasek 6). While these processes are related, they possess individual characteristics that should not be overlooked. Certainly, it is important for a scholar of pharmacokinetics to set them apart from one another. One way of distinguishing the two processes lies in a common definition: the elimination of a chemical entity takes place when the combined effects of excretion and metabolism are greater than that of absorption (Loucks et al. 903). Only when the amount of an unchanged drug being excreted from the body combined with the amount of the drug being altered via metabolism can elimination be considered an active process. In other words, metabolism and excretion must both occur for there to be an irreversible loss of administered drug from the measurable area under study. In essence, while the main processes of human pharmacokinetics can be summarized using the ADME principles, there are other components of pharmacokinetic study that are important to note, including the more recent acronym ABCD as well as the process of elimination, which is different from but related to the ADME process of excretion.

1.3 Measurable Factors

1.3.1 Half-Life

Additionally, there are multiple important measurements that can quantify various pharmacokinetic aspects of a pharmaceutical compound, with the half-life of a drug being one pertinent example. Half-life is simply how much time has elapsed when half of the original concentration of a drug remains in the drug's area of measurement; as with the process of absorption, plasma is most often the medium measured, but, depending on the drug, other mediums such as tissue may be the focus (Fan and De Lannoy 96). Half-life is paramount in the pharmacokinetic understanding of a drug. It quantitatively expresses how a drug behaves over time with respect to concentration; such expression is pertinent to drug dosage and clinical research, among other applications. When the measured elimination of a drug from the study site is greater than the measured absorption at that same site, terminal elimination is said to occur; in other words, elimination takes place when a drug is being chemically altered in the body and permanently lost via excretion more than it is being absorbed (Loucks et al. 905). Using this phase to calculate a compound's half-life yields a value called the terminal half-life, which is sometimes noted as "the true elimination half-life of the drug" (Loucks et al. 905). Even though half-life is a simple concept, not all half-life calculations are created equal. Instead, placing focus on different phases of elimination can put forth half-lives with slightly differing applications. Since one broad application of half-life is the study of oral drug development and use, it is relevant to consider the fact that half-life is not directly impacted by absorption, especially when studying oral drugs with coatings that delay their initial release for various reasons (Loucks et al. 906). While absorption is considered when determining the phase of elimination used to study half-life, absorption does not directly influence the half-life measurement. In studying half-life,

absorption is only relevant in defining the classification of drug elimination used to calculate the half-life value. An important quantitative factor in the study of pharmacokinetics, half-life can be described as the time required for a chemical entity's concentration to decrease by half, with plasma concentration typically being studied; additionally, using different definitions of elimination puts forth different types of half-life, but half-life remains uninfluenced by the process of absorption.

1.3.2 Plasma Concentration

Plasma concentration is both an integral part of measuring a compound's half-life as well as an important measurable factor in the pharmacokinetic field. In fact, some scholars classify plasma concentration as an important foundation of pharmacokinetics, for basic pharmacokinetic processes such as absorption and distribution are studied in some relation to plasma concentration (Pea iv). Plasma concentration must, therefore, be a large part of pharmacokinetic study, for the main principles of pharmacokinetics are often explained in terms of a studied drug's plasma concentration over time. As for a specific definition, plasma concentration is typically used to describe how much of a drug is in the body after administration (Fan and De Lannoy 98). This quantitative measurement is necessary for studying the behavior of a pharmaceutical compound in the body, and it provides the basis of many calculations associated with the pharmacokinetics of a drug. However, plasma concentration is a different measurement from blood concentration—while they both concern the circulation of blood throughout the body and directly depend on the distribution of a drug outside of the circulatory system, the measurement of plasma concentration does not include concentration found in erythrocytes or lymphocytes while the measurement of blood concentration considers both (Fan and De Lannoy 95). These two measurements quantify two different phenomena that are important to

distinguish. However, their relation may make confusion of the two measurements more likely, for they both involve the concentration of a drug in circulating blood. One notable way that plasma concentration is utilized in the pharmacokinetics of a drug is its relationship with time, and scholars identify this relationship as a required component in studying the absorption, distribution, metabolism, and excretion of a drug (Fan and De Lannoy 96). Instead of taking an instantaneous measurement of the plasma concentration of a drug, this factor is typically measured and reported in relation to the time that has passed since administration. For a given pharmaceutical compound, the graphical representation of this relationship is known as the compound's pharmacokinetic curve (Loucks et al. 905). In addition to determining the half-life of a drug, plasma concentration is a paramount concept in studying the overall pharmacokinetic processes of any drug as well as a measurement separate from blood concentration, and it is used to quantify how much of a drug is present in the body after its dosing, usually in relation to time.

1.4 Clinical Applications

1.4.1 Drug Development

A multitude of applications of pharmacokinetics exist, including the field of drug development. Many models have been built to analyze the pharmacokinetics of a new drug, such analysis can be beneficial in multiple ways in the development and testing of new compounds. In the development of a new chemical entity, the pharmacokinetics of the compound must be predicted, with one way of accomplishing such being the use of recently developed "physiologically based pharmacokinetic (PBPK) modelling software tools"; in studying a drug's pharmacokinetics through the lens of anatomical mechanisms, many different health scenarios are able to be studied, but PBPK software will likely require more research in order to increase knowledge of the mechanisms involved and ensure accuracy of the models' findings (Peters et

al. 2016, as cited in Stillhart et al. 2). The study of pharmacokinetic processes is so crucial in the development of new drugs that scholars in the field are still developing new and improved ways to accurately predict these processes' impacts on a drug. Recent efforts have included a focus on physiological processes and how they impact the pharmacokinetic behavior of novel pharmaceutical compounds, for the pharmacokinetics of a drug can often depend on the internal environment in which it is administered. The physiological factors impacting a drug's pharmacokinetic processes include food intake and gastrointestinal pH levels—these can impact the absorption of an orally administered medication, but there are numerous models utilized to build understanding of the absorption, plasma concentration, and other pharmacokinetic aspects of oral pharmaceuticals in various settings. (Abuhelwa et al.; Food, GI pH, and Models; 235). These factors are examples of the many ways that pharmacokinetic profiles can be altered on a case-by-case basis, making it even more important to continue the development of models that take such important factors into account. Accuracy of these models is of the essence to build accurate pharmacokinetic profiles, which is paramount in drug development. Pharmacokinetic knowledge of drugs similar to a novel compound in question can provide insight into what changes should be made in the latter, and building knowledge of an up-and-coming drug's pharmacokinetic behavior can conserve resources and time spent testing drug forms that may not be safe or effective by ruling them out early in the development process (Kola and Landis 2004, as cited in Fan and De Lannoy 94-95; Fan and De Lannoy 95). Evidently, pharmacokinetics is relevant to the development of new drugs because studying such processes can lead to quicker and cheaper development. Additionally, the development of new forms of an existing drug can benefit from a pharmacokinetic understanding of the existing compound, for comparisons can be made between the drugs' processes that assist in deciding what aspects should be changed or

kept the same. In addition to these uses, studying the pharmacokinetics of a new compound can aid in the understanding of results yielded by clinical human trials, for plasma concentration is not the sole process dictating the body's response to a drug; with the many variables presented by pharmacokinetics, it is important that researchers weigh all of the reasons for a subject's response to a new drug so as not to equate correlation with causation (Fan and De Lannoy 94). Even though the plasma concentration of a substance after administration is a grand factor in its pharmacokinetic behavior, it is not the only aspect that should be considered when developing a new drug. Having an accurate understanding of all the pharmacokinetic processes of a novel drug can provide valuable insight into why it yields the physiological responses it does, thus furthering the ability to develop safe and effective compounds. Overall, the study of pharmacokinetics is incredibly important in drug development, and there are many models used to understand the pharmacokinetic profiles of new pharmaceutical compounds in a variety of scenarios; implications of pharmacokinetics in this field include saving time and money in developmental stages, aiding in the development of new forms of existing compounds, and increasing understanding of data found in clinical human trials.

1.4.2 Therapeutics

1.4.2.1 Oncology

In addition to drug development, many applications of pharmacokinetics regarding individual therapeutic treatments are practiced, including in oncology. In the world of oncology, chemotherapy is very prevalent, but many of these compounds balance a fine line between undesirable toxicity and effective cancer treatment; such a line is known as a narrow therapeutic range, which describes the very specific blood concentration of a drug necessary to create the desired therapeutic balance. (Kawedia 191). Therefore, providers in the field of oncology must

be very careful when navigating a drug with a narrow therapeutic range. Failing to do so could, after all, result in dangerous outcomes for patients undergoing treatment. Plasma concentration is often monitored when chemotherapeutics are utilized, but accurate monitoring is of utmost importance, for a reading that is erroneously high carries the potential to warrant lower than necessary administration, and an inaccurately low measurement may warrant high doses that lead to toxicity (Kawedia 196). Previously mentioned as the foundation of pharmacokinetics, the plasma concentration of a drug is an important measurement that can explain how a compound behaves in the body. Understanding this pharmacokinetic principle is, obviously, of utmost importance in oncological treatment, especially chemotherapy, to ensure safe and effective treatment. In fact, this therapeutic index monitoring is referred to as pharmacokinetic monitoring and is necessary for a wide range of drugs used in this field; these drugs include—but are certainly not limited to—methotrexate, tacrolimus, and vancomycin (Kawedia 191). These drugs that must utilize pharmacokinetic monitoring are common options for the general treatment of cancer. On the whole, the utilization of pharmacokinetic principles is a common requirement in the field of oncology, for drugs associated with chemotherapy possess a very narrow range for therapeutic treatment and require pharmacokinetic monitoring, especially of plasma concentration, to ensure productive treatment and minimal toxicity.

1.4.2.2 Transplant Recovery

Yet another application for pharmacokinetic study arises in transplant recovery, where patients and their doctors must navigate proper immunosuppression to combat organ rejection—without the help of an all-inclusive therapeutic index or diagnostic test for immune system function. For instance, the pharmacokinetic processes of absorption and metabolism are important in the field of transplantation, for common drugs used in transplant recovery called

calcineurin inhibitors can react differently based on the patients to which they are administered due to an individual's varying factors like gastrointestinal pH, food intake, and the presence of intestinal enzymes (Loucks et al. 903). While the gastrointestinal tract is an important absorption site, the presence of such enzymes in the intestines allows metabolism to occur there (Loucks et al. 903). It is important for each patient to be monitored to study the pharmacokinetics of a drug over the course of treatment. In this setting, the processes of absorption and metabolism are certainly overlapping, providing a clear need for pharmacokinetic monitoring. A common drug in transplant care, tacrolimus exhibits a rudimentary therapeutic range that leaves much to be desired; the suggested therapeutic use in common literature does not apply to all patients and is, due to a lack of defined standards in the associated research, considered null for all patients that were not direct subjects of the trials at hand (Loucks et al. 905). This shows that no two cases of transplant recovery are created equally, and the suggested therapeutic use of immunosuppressive drugs is just that—a suggestion. Thus, the treatment plan for each patient must be designed for that patient alone to produce ideal results without causing more harm. In addition to the lack of a therapeutic range fit for all patients, there is also no simple way to test a patient for ideal immunosuppression (Loucks et al. 904). Because every patient's immune system operates differently, no known single factor can be used to measure a drug's immunosuppression (Loucks et al. 904). Without an overarching test for immunosuppression, accurate treatment can be difficult to achieve. This evidence is yet another testament to the importance of monitoring each patient's pharmacokinetic response to treatment. In fact, plasma concentration, half-life, and the drug-removal rate from plasma (clearance) are cited as important pharmacokinetic factors to note when immunosuppressive therapies are utilized, for every case of post-transplantation care is different, and many cases differ significantly from those documented in immunosuppressive

studies; studying these pharmacokinetic factors on a case-by-case basis helps providers in the transplantation field to ensure the proper extent of immunosuppression (Loucks et al. 905). As each patient's case varies widely from the next, the monitoring of these pharmacokinetic factors for each case is of utmost importance. With much of the literature only applying to the subjects included in trials, the lack of an overarching test for immune function, and an incompletely documented therapeutic range, treatment utilized in the field of transplant recovery must rely heavily on pharmacokinetic measurements such as plasma concentration, half-life, and clearance to ensure ideal immunosuppression for recovery on a case-by-case basis.

1.4.2.3 General Treatment

In addition to specified fields of medicine, a need for pharmacokinetic knowledge in the general field of medical treatment is apparent, and many factors related to the pharmacokinetic field that a provider should consider when prescribing a treatment. In most studies of patient pharmacokinetics, only healthy subjects are included, so patients presenting to their general provider with any illness or other affliction could experience drug effects different from those expected, for "pharmacokinetic behavior" has the potential to change in the presence of many diagnoses (Pea 3). Just as the fields of oncology and transplant recovery suggest the need for case-by-case pharmacokinetic monitoring, the same has the potential to hold true for general health practice. Many patients seeing a medical professional for an undesired health condition will exhibit unpredictable pharmacokinetic changes in how a drug performs. More specifically, patient age is an important factor in a drug's pharmacokinetic processes upon administration, for as a patient's age increases, body composition and excretory functions may be drastically altered; for this reason, some literature suggests that clinical studies of the pharmacokinetics of a drug should pay specific attention to the varying age groups, with researchers presenting their data by

age group (Pea 29). With few resources available that document how a drug's pharmacokinetic processes change when administered to patients of varying age groups, difficulty arises for general practitioners when determining the appropriate treatment for patients whose ages are not represented in literature. Carrying out studies in terms of age group instead of utilizing a general population may, therefore, be important for those in the field of pharmacokinetic research. Furthermore, obesity could potentially change pharmacokinetic behavior as there is little literature on the topic, so when a practitioner prescribes treatment with a narrow therapeutic range to an obese patient, monitoring the plasma concentration of the drug and proceeding with caution is advisable (Cheymol 216). Drugs with narrow therapeutic indices arise in all fields of medical practice, so knowing how to proceed with them when a patient is obese—or has an adult body mass index (BMI) that is greater than or equal to 30.0—is important ("Defining Obesity"). The pharmacokinetic variable of plasma concentration is incredibly important for practitioners to monitor in this scenario. Certain types of drugs call for pharmacokinetic monitoring, including non-steroidal anti-inflammatory drugs (NSAIDs); many factors unique to each patient are present that can alter the pharmacokinetics of an NSAID when administered, so medical professionals should study the full pharmacokinetic profile of some NSAIDs when prescribing them and take into account factors like drug interactions and half-life (Davies and Skjodt 390). A very common class of medications, NSAIDs can sometimes exhibit narrow therapeutic ranges, making it pertinent that providers take pharmacokinetic factors into account when prescribing them (Davies and Skjodt 390). Undoubtedly, there is plenty of room for pharmacokinetics in the practice of clinicians in non-specialty fields. Yet another factor potentially impacting a pharmaceutical compound's pharmacokinetic behavior is the time of day at dosing, and drugs like ketoprofen exhibit such a phenomenon; due to mechanisms tied to circadian rhythm,

ketoprofen specifically treats pain best when taken in the morning, for it is then that elimination is decreased and absorption is increased (Kowanko IC et al. 1981, as cited in Davies and Skjodt 381). Thus, it may be helpful to examine the pharmacokinetics of a drug when deciding when it should be dosed. When deciding administration times, medical providers should take the complete pharmacokinetic profile of a drug into account to take advantage of effects like these. Overall, there are many ways pharmacokinetics can be applied in the general sphere of medicine, and individual pharmacokinetic monitoring may be helpful when a patient is not totally healthy or obese or a drug has a narrow therapeutic index; additionally, it should be considered that the pharmacokinetics of a drug can vary based on patient age as well as the time of day at the time of dosing.

1.5 Conclusion

Ultimately, a multitude of definitions of human pharmacokinetics are used today, with the most rudimentary being the analysis of a drug's travel throughout a patient's body after dosing (Fan and De Lannoy 2). The field of pharmacokinetics is most often simplified into the four categories of absorption, distribution, metabolism, and excretion, and these processes are typically referred to as the ADME principles. Absorption and distribution respectively denote the way a drug gains access to the circulatory system and makes its way to the surrounding tissues (Pea 69). Metabolism and excretion are closely related processes, with the former describing the decomposition of a compound for its eventual eviction from the system, and the latter describing the rate of irreversible removal of a compound from the body (Kawedia 191). Of course, these four principles are not the only ones included in the field of pharmacokinetics, and multiple measurable factors are at play, including plasma concentration and half-life. Overall, applications of human pharmacokinetics include drug development, oncology, transplant recovery, and

general medicine as a whole. By both facilitating the prediction of a drug's behavior in the body as well as aiding in the care of patients with varying afflictions, the importance and pertinence of pharmacokinetics in the pharmaceutical field is undeniably timeless.

2. Oral Drug Absorption

2.1 Introduction

The first of the ADME principles of pharmacokinetics, absorption is an incredibly important factor in how a drug performs after dosing. Absorption can typically be described as the means taken by a drug to reach the bloodstream, where the other ADME principles can begin (Pea 69). While there are many routes associated with absorption, the absorption route of an oral drug is essentially confined to the gastrointestinal tract, with the small intestine being the most notable site (Stillhart et al. 2). Because of the sheer variability of GI tract conditions, many important factors and variables determine oral drug absorption and, therefore, must be studied to increase the understanding of oral drug behavior. When honing in on oral drug absorption, it is important to note the location in which it takes place as well as factors like GI pH, oral drug pH, and the time it takes a drug to travel through the gastrointestinal tract; additionally, there are multiple ways of examining the absorptive behavior of oral drugs that are pertinent to this field.

2.2 Location

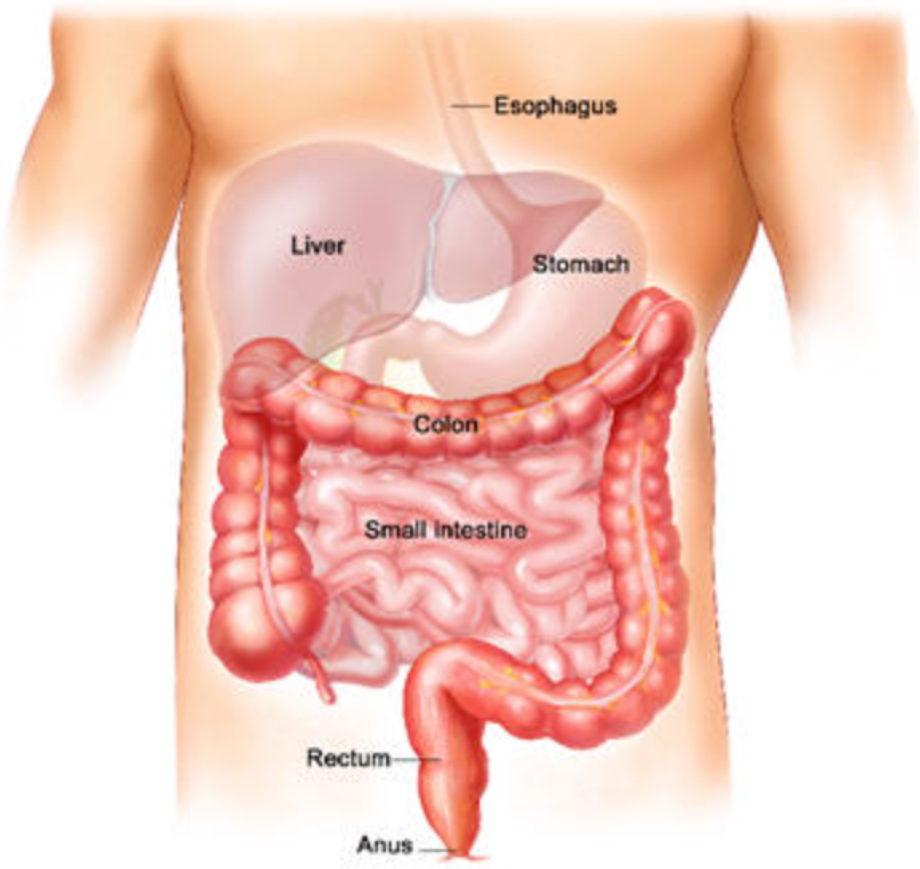

Fig. 2. "Anatomy of Your Digestive System."

In studying the absorption of an orally dosed drug, it is pertinent to identify the area in which absorption takes place. With drug administration routes spanning from the skin to the respiratory system, wide variety of ways for a drug to undergo absorption exist, but orally administered drugs are, by far, the most popular in the medical field, so the GI tract is the foremost path of drug absorption (Fan and De Lannoy 95). The GI tract is by no means the sole path of drug absorption. However, when the focus is placed on oral pharmaceutical drugs, the gastrointestinal tract becomes the sole mode of absorption. The specific location of such absorption is most typically noted as the small intestine, but certain drugs experience continued

absorption in the colon, which is typically due to a lack of prior absorption or the specific design of a drug to do so (Stillhart et al. 2). While there are many gastrointestinal regions traveled by a drug, the small intestine remains a popular target. However, as is presented by evidence, the colon is capable of drug absorption as well. Additionally, many variables of absorption intensity and frequency arise from the gastrointestinal tract, including the stomach's pH, absorptive surface area, and the time it takes ingested material to travel the GI tract (Evans, Schentag, and Jusko 1992 and Atikinson et al., as cited in Loucks et al. 903). Thus, even though oral drug absorption depends fully on the GI tract, it is anything but a simplistic absorption site, for it boasts many factors that vary based on the conditions at hand. Thus, oral drug absorption may be difficult to predict. Ultimately, oral drug absorption is confined to the gastrointestinal tract and most often takes place in the small intestine, but the colon is also an absorption site, and the GI tract itself presents many complex variables that impact the absorption process.

2.3 Factors

2.3.1 Gastrointestinal pH

2.3.1.1 Normal Levels

	Baseline (fasted) pH	Fed pH
Stomach	1.56-2.20	4.66-5.31
Whole Duodenum	5.85-6.35	5.90-6.40
Small Intestine (sans duodenum)	6.87-7.18	6.87-7.18
Whole Colon	6.22-6.72	6.22-6.72

Table 1. Comparison of fasted and fed pH levels in specific GI regions (Abuhelwa et al., Quantitative Review Part I, 1313).

Among the factors of oral drug absorption along the GI tract is gastrointestinal pH. For example, one scholarly source notes this relation and attributes it to variables such as drug solubility, how well a drug releases, and even the permeability of a drug across intestinal membranes, among others (Abuhelwa et al.; Food, GI pH, and Models; 237). With a long list of ways oral drug absorption can be impacted by GI pH, the latter must be considered when studying the absorption of an orally administered compound. The normal pH levels within the gastrointestinal tract depend on the region being measured, and some regions such as the colon exhibit more room for variation from person to person; for instance, fluids present in the stomach exhibit an approximate pH of 1.5-3.5, those in the duodenum an approximate pH of 5-6, those in the distal jejunum and ileum an approximate pH of 7-8, and those in the colon an approximate pH of 6. (Evans et al. 1988 and Koziolek et al. 2015, as cited in Stillhart et al. 2). Although these are only approximate pH ranges, the variation from acidic to basic throughout the gastrointestinal tract is made quite clear. The jump in value from a relatively acidic stomach to a weakly acidic duodenum nearing basic levels is most shocking. In adding specificity, as recently as 2016, researchers have documented the approximate pH ranges of various GI locations, with one source citing pH values for the whole stomach as 1.56-2.20, the whole duodenum as 5.85-6.35, the whole small intestine sans duodenum as 6.87-7.18, and the whole colon 6.22-6.72; also, it should be noted that the former two ranges are in the fasted state, with such a condition not applying to the latter two (Abuhelwa et al., Quantitative Review Part I, 1313). This further shows the variability present in the normal pH levels of the GI tract. Additionally, some regions exhibit different pH values in the presence and absence of food while others yield no difference. As for the physiology associated with oral drug absorption and GI pH, such levels are responsible for how charged a chemical entity becomes after ingestion, which directly impacts the drug's

absorptive behavior; additionally, the formulations of some oral drugs rely on the pH of the stomach to dictate appropriate delivery and release (Stillhart et al. 2). Thus, gastrointestinal pH is an important factor in oral drug absorption, with baseline pH levels in the GI tract varying by region; such levels may be necessary for the proper function of some compounds.

2.3.1.2 Food Effect

While the normal pH of the GI tract is relatively predictable, the presence of recently consumed food within the gastrointestinal tract can impact the pH values at hand—this phenomenon is called food effect. First of all, some literature has noted that, after one consumes an FDA-approved breakfast meal, the pH of the stomach immediately climbs to a more weakly acidic level around 4-5; since about 6 hours is required for this meal to be evacuated from the stomach, "several" hours must elapse for the stomach's pH to return to a typical, strongly acidic state (Koziolek et al. 2014 and Koziolek et al. 2015, as cited in Koziolek et al. 11). This evidence demonstrates food effect on gastrointestinal pH. However, the stomach is not the only GI region that can experience a shift in pH. More specifically, the pH of the stomach in the presence of consumed food has been noted as 4.66-5.31, of the whole duodenum as 5.90-6.40, the whole small intestine sans duodenum as 6.87-7.18, and the whole colon 6.22-6.72; the former two ranges are in the fed state, but this condition does not apply to the latter two (Abuhelwa et al., Quantitative Review Part I, 1313). By comparing these fed values to the baseline values previously discussed, the presence of food increases the stomach's pH while slightly increasing the pH of the duodenum; however, there is no change exhibited in the small intestine (when excluding the duodenum) and the colon (Abuhelwa et al., Quantitative Review Part I, 1313). The caloric content of the consumed meal within this study had a direct impact on these pH levels, and the small decrease in pH noted in the fed-state duodenum may be underestimated because of

the wide pH range exhibited in the presence and absence of food (Abuhelwa et al., Quantitative Review Part I, 1320). Certainly, this food effect should be considered when a drug is being administered. However, not all drugs experience decreased absorption in the presence of food; for example, a drug called felbamate exhibits increased permeability due to its low solubility, and though the presence of food could be assumed to increase its solubility, its weakly basic formulation can balance out this effect by precipitating when pH levels are increased (Custodio, Wu, and Benet 2008 and Carver et al. 1999, as cited in Gatarić and Parojčić 11). Therefore, only some pharmaceutical drugs experience a negative impact on absorption in the presence of food. Knowledge of the chemical entity being administered is necessary to determine if food effect will alter absorption. Ultimately, the pH of the gastrointestinal tract is susceptible to food effect, for the consumption of a meal has been shown to alter baseline pH levels, but complete knowledge of a drug being prescribed is necessary to predict how this food effect impacts absorption, for it is not the only acting factor.

2.3.2 pH of Oral Drugs

The pH of an oral drug itself is also an important variable in predicting its absorption within the GI tract. An article published by Surofchy et al. notes that when a weakly basic drug is administered orally, its solubility is highest in the stomach but decreased when it leaves the acidity of the stomach, and when a weakly acidic drug is orally dosed, it experiences the most solubility when it exits the highly acidic stomach (Surofchy et al. 155). Using this evidence, one can conclude that drugs with weakly acidic formulations undergo most of their absorption in the basic regions of the GI tract following the stomach, and drugs with weakly basic formulations are most absorbable while still in the stomach. Since weakly acidic drugs are most soluble in the more basic regions of the GI tract, a positive food effect can be noticed with the administration

of such a drug, for the stomach's pH increases in the fed state and allows for an oral drug to be better absorbed in the stomach (Surofchy et al. 155; Deng et al. 1839). This food effect allows for a weakly acidic drug to be absorbed more quickly and, overall, to a greater extent (Deng et al. 1839). As the pH of a drug can dictate its absorption, knowing the pH of a prescribed oral drug can provide insight as to whether it should be taken with a meal to maximize absorbency. Also important to mention is that the increased solubility of a weakly basic drug in the stomach is due to its ionization, so when the stomach is made less acidic by the presence of food, an orally administered weakly basic drug experiences decreased dissolution because it will "become unionized" (Abuhelwa et al.; Food, GI pH, and Models; 155). This evidence further exemplifies how the relative pH of a drug can determine how well it is absorbed, especially when food effect is taken into consideration. While the pH of some drugs causes them to absorb better following food consumption, some drugs experience the opposite effect. Overall, the pH of an oral drug can determine the region in which it is best absorbed, and it can also provide insight as to how its absorption changes in the presence or absence of food.

2.3.3 GI Travel and Time

In addition to the pH of the GI tract and the pH of orally administered drugs, the time it takes for a drug to traverse the gastrointestinal tract also plays a role in its absorption. Since the small intestine, mainly its upper region, is the primary site of oral drug absorption, there is a small window in which absorption must take place, so the transit time of a drug through the GI tract plays a paramount part in determining how well an oral drug is absorbed (Abuhelwa et al.; Food, GI pH, and Models; 238). Whether a drug moves slowly or quickly through this typical region of absorption can, therefore, determine its extent of absorption. GI transit time becomes especially important in the case of drugs like tacrolimus or cyclosporine, for such drugs may be

partially metabolized before reaching the systemic circulation or even possess a specific frame for absorption; in this case, if the drug spends less time in the intestine, absorption may be negatively impacted (Stillhart et al. 13). This shows that, while the time it takes for a drug to pass through the GI tract can impact the absorption of all oral drugs, some drugs are more impacted than others by GI transit time. Some drugs, therefore, require special care when administered to assure that they are properly absorbed. In the cases of some drugs, absorption is directly tied to the emptying of material from the stomach, allowing the transit time of the stomach to either hasten or slow down proper absorption; since gastrointestinal transit time is a factor that is different from one patient to another, the absorption of any compound can wildly vary depending on the patient, and the time a drug spends in each region of the GI tract coupled with the different properties in each region allow for a multitude of unique scenarios (Custodio, Wu, and Benet 2008 and Carver et al. 1999, as cited in Abuhelwa et al., Quantitative Review Part II, 1331). In the study of GI transit time, then, plentiful room for variability is available. Also, some drugs may benefit from a decreased transit time, while others absorb quicker when transit time is decreased. In summary, gastrointestinal transit time is among the factors influencing oral drug absorption, for it determines how long a drug is present in the GI region by which it is absorbed; the absorption of some oral drugs is more easily impacted by this factor than others, and a multitude of ways that such transit time can impact absorption exist, especially when considering each patient's unique situation.

2.4 Means of Study

Just as many factors are at play in the absorption of an oral drug, various means are employed in the field of pharmacokinetics to study and predict the absorption process. First, laboratory-based, in-vitro experiments are often used to study the absorptive behavior of a drug

without administering it to a patient; for instance, one team of researchers developed a system of five physical absorption models representing varying levels of stomach acidity by testing the permeability of two drugs across an in-vitro layer of cells in each pH-based environment (He et al. 71-72). By taking physiological factors into account, this in-vitro method is useful in predicting how an oral drug's absorption can be impacted by the pH of the stomach (He et al. 71-72). An important first step in studying oral drug absorption, experimental methods such as this one can be used to collect data for the study of a drug and how it undergoes absorption. In addition to laboratory studies, oral drug absorption can also be studied using quantitative modeling. The most simplistic approach to quantitatively modeling absorption, empirical models typically focus on the plasma concentration of an oral drug in relation to time in order to quantify absorption, with such models applying zero- and first-order kinetics to simplistically study this relationship; both typical and atypical styles of absorption can be represented by an empirical model, but physiological processes are not taken into account with this approach (Zhou 2003, as cited in Abuhelwa et al.; Food, GI pH, and Models; 242). By representing found data such as plasma concentration over time, empirical models hone in on one of the most important factors of drug absorption. However, many factors that influence the plasma concentration of a drug may be overlooked by these models. Another way of quantitatively modeling absorption lies in the use of mechanistic models, which place focus on both the physiological processes impacting absorption and the characteristics of the drug being studied (Abuhelwa et al.; Food, GI pH, and Models; 242). Both the physiological and drug components of these models are drawn from existing data and theory, so while mechanistic models consider a wide variety of factors, they still apply some amount of simplistic assumption (Gordi et al. 2205, as cited in Abuhelwa et al.; Food, GI pH, and Models; 242). With an array of factors at play in oral drug absorption, it is

certainly helpful to take these into account when studying the absorption of a specific drug. Just as empirical models may lack a complete understanding of such variables, though, mechanistic models can sometimes rely on inferences that also overlook the true degree of variability. Overall, the absorption of oral drugs can be studied by performing in-vitro experiments or by quantifying experimental data in the form of an empirical or mechanistic model.

2.5 Conclusion

In conclusion, the broad site of absorption for oral drugs is the highly variable gastrointestinal tract, with the small intestine and colon being the primary specific absorptive surfaces (Stillhart et al. 2). Among the varying factors of absorption along the GI tract is the pH of the tract itself, which varies by region and can be altered by the presence of food (Abuhelwa et al., Quantitative Review Part I, 1313). The pH of an orally administered drug is also a factor in how it is absorbed, with this factor partially defining the region in which the drug is absorbed, among other characteristics (Surofchy et al. 155). Gastrointestinal transit time is yet another factor that should be taken into account when studying the absorptive behavior of a drug, for it determines how long a drug must be absorbed before it is whisked away from the intended absorptive site (Abuhelwa et al.; Food, GI pH, and Models; 238). In terms of the actual study of oral drug absorption, laboratory experiments can be helpful in studying and predicting drug behavior, as can quantitative presentations of experimental data such as empirical and mechanistic models. With the absorption process of an oral drug essentially determining how well it performs its intended purpose, the study of drugs today and how they can be better administered to patients with varying unique circumstances remain incredibly pertinent outlets for this topic of study.

3. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

3.1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are easy to acquire, treat a wide variety of illnesses, and are incredibly common in today's medical sphere. Available in prescription and over-the-counter forms, these drugs are popular for a multitude of reasons. This group of drugs carries with it a comprehensive and rich history, with the Ancient Sumerians being the first to use a compound that would later become the first NSAID (Ozleyen et al. 2). With many NSAIDs available on the market, this type of drug is known well by the common consumer and even better by the general practitioner. Non-steroidal anti-inflammatory drugs (NSAIDs) have been relied on for centuries, with their general properties tracing back to even earlier times, and this group of drugs is composed of many classes of compounds; in studying NSAIDs, the common knowledge and opinions surrounding them, their proper applications for treatment, and their associated side effects are important to consider.

3.2 Background

3.2.1 History

First, the history of NSAIDs is a long and surprising one. At the beginning of the nineteenth century, a compound called salicylate was under the focus of German scholars for properties that would later characterize the first NSAID—after this, the next time an NSAID would be coined would not be until the mid-twentieth century, but the discovery of such compounds would increase exponentially thereafter (Green 50). Undoubtedly, the number of NSAIDs in use today is incomparably larger than those in use in the early days of development, and the start of clinical NSAID development was certainly a slow yet momentous one. The main

component of aspirin, salicylic acid, traces its roots to the salicylate compound found in willow plants; in the mid-eighteenth century, scientist Edward Stone organized and conducted an experiment collecting data on willow bark and its effect on fever, but the developing use of the compound within willow bark was perfected towards the late 1800s (Ozleyen et al. 3). This bit of history is merely a glimpse at the developments made in the study of aspirin that were chronologically close to its official release. The history of this willow plant derivative, however, goes back much further than this. Evidence exists suggesting that ancient Sumerians used willow leaves to doctor rheumatic afflictions, which also contained this salicylate compound, and Hippocrates was noted to have hypothesized that such willow plants could be used to aid those afflicted with pain and regulate fevers (Ozleyen et al. 2). The dense history surrounding the first NSAID's development is a rich one, and aspirin was centuries in the making. A highly popular and varying group of drugs today, NSAIDs exhibit a rich history, especially surrounding the development of the first NSAID, aspirin; while aspirin has roots in societies as early as ancient Sumeria, its final development was a catalyst in the development of every NSAID since then.

3.2.1 Common NSAIDs

In the twenty-first century, an outstanding number of NSAIDs exist as well as a relatively large group of commonly used ones. As for the wide span of this group, drugs within include classes such as arylacetic acids, arylpropionic acids, fenamates, oxicams, pyrazoles, and salicylates; other sources, however, list other classes like naphthylalkanones, indoles, and phenylacetic acids (Davies and Skjodt 377; Green 51). Instead of just consisting of one class of drugs, these anti-inflammatory compounds included many classes, and important to note is the fact that the comprehensive list of classes depends on the source being referenced. As for specific compounds included in the classification, two very common and favored NSAIDS are

naproxen and ibuprofen; this favor is due to their relatively low risk of cardiovascular reactions (Thomas D et al. 2017, as cited in Varrassi et al. 65). While the list of NSAIDs is long, these two are especially prevalent. In fact, ibuprofen is commonly known as a trustworthy NSAID with few associated adverse reactions, so it makes sense that this compound is quite popular in treating pain, inflammation, and fever (General Practice Notebook, as cited in Rainsford, Pharmacology, Efficacy and Safety, 276). As all NSAIDs carry some level of risk, those with the lowest risk factor are preferred, and ibuprofen is a standup example of such (Thomas D et al. 2017, as cited in Varrassi et al. 65). However, the full list of commonly used NSAIDs is astronomically long and includes well-known anti-inflammatory drugs such as aspirin, ketoprofen, diclofenac sodium, celecoxib, and meloxicam (Green 51). Many varying NSAIDs are in use today, and those most used span a wide range that includes aspirin, ibuprofen, and naproxen.

3.3 Common Beliefs

Since NSAIDs are incredibly popular, multiple common beliefs are circulated publicly. First of all, one taking an NSAID is typically advised to do so with plenty of liquids and in the relative presence of food; this advice is typical regardless of treatment duration and whether the treatment is over-the-counter (Rainsford and Bjarnason 465). Because this advice is common, the concept of taking NSAIDs with food or fluids can be assumed to be a typical belief. While the advice of administration with food is concerned with safety, a harmful expectation that is associated with NSAIDs is that exceeding the recommended dosage results in the quicker treatment of pain; this belief, however, is not true, and some scholars suggest that it may be more helpful to suggest that some NSAIDs be taken in the absence of food in order to speed up results, effectively thwarting a patient's idea of taking too high of a dose (Rainsford and Bjarnason 468).

Thus, while some circulating beliefs are helpful in assuring patient safety, some are erroneous and unapproved by clinicians. Furthermore, a study of young adults in 2014 showed that about 70% of participants were unaware of the side effects associated with taking common NSAIDs, about half of participants saw no need for intervention by a medical professional when NSAIDs are taken over the counter, and less than half suggested that the misuse of NSAIDs is uncommon. (Wawryk-Gawda 177). Yet another common belief is that NSAIDs are generally safer than they truly are. The scholars performing this study suggest that the ease of access to NSAIDs is, in part, to blame for this incorrect assumption of safety (Wawryk-Gawda 177). Certainly, many beliefs circulate in the public regarding NSAIDs; some involve taking extra precautions during administration, but others are harmful and may lead to misuse due to a lack of information.

3.4 Proper Usage

3.4.1 Common Uses

Many uses for the wide range of NSAIDs available are known, possibly explaining their popularity. First of all, NSAIDs are most notably used to combat pain, reduce inflammation, and lower fevers, but they are also sometimes used to reduce the incidence of blood clotting (Wawryk-Gawda 175; Gøtzsche 2). In this way, NSAIDs are multifaceted pharmaceutical compounds, and they treat very common problems experienced by the public. A more specific outlet for the use of NSAIDs lies in the field of sports medicine, where NSAIDs are popular applications in cases of physical injury due to their treatment of both inflammation and pain; however, there is little clinical evidence stating the role of NSAIDs in the athletic sphere (Green 53). Thus, NSAIDs would, theoretically, be helpful in cases of injury involving inflammation and pain. However, it is unclear whether NSAIDs can help heal these injuries due the lack of research on the topic. Yet another outlet for NSAIDs lies in the sphere of infectious disease,

where NSAIDs are cited as decreasing symptoms of those suffering from influenza or the common cold; the specific NSAID ibuprofen can even be taken by adults and children alike (Varrassi et al. 74). By treating symptoms of these common illnesses in patients young and old, NSAIDs like ibuprofen have proven their relevance. Another specific use of ibuprofen is in the treatment of arthritis; rheumatoid arthritis (RA) and osteoarthritis (OA) are two uses that are commonly cited (Rainsford; Pharmacology, Therapeutics, and Side Effects; 27). In fact, OA is the reason behind approximately half of all NSAID prescriptions (Green 53). Though NSAIDs can treat a wide variety of common afflictions, the fact that OA is a huge part of overall NSAID use is quite interesting. Overall, the large group of NSAIDs available are employed in various cases, including inflammation, flu and cold symptoms, and some symptoms of arthritis.

3.4.2 Dose and Treatment Duration

When administering or taking NSAIDs, some specifics regarding dosage and duration should be considered. In the general use of NSAIDs, providers and patients should note that administration of these drugs should be kept to the minimum duration, and the minimum amount of compound should always be prescribed; the minimum amount and duration of treatment depend on the purpose for treatment and denote minimal treatment needed for intended outcomes (Wawryk-Gawda et al. 177). Therefore, a patient should take the smallest amount needed for the shortest period needed to produce the ideal lessening of symptoms. In the cases of some NSAIDs, dosing only needs to occur twice in a 24-hour period; with ibuprofen, indomethacin, diclofenac, and ketoprofen being included in these drugs, the minimum daily dosage interval needed to produce the intended results is twice daily (Jalali S et al. 1986, as cited in Davies and Skjodt 384). Also, in the specific case of ibuprofen (a rarely toxic drug with a broad therapeutic index) 200 or 400 mg is typically the amount taken every six hours, but patients of RA may take

up to 3200 mg in a 24-hour window (Davies 137). In this example, the maximum daily dosage depends on the ailment being treated. As for duration of treatment, France's National Agency for the Safety of Medicines and Health Products (ANSM) says that only one NSAID should be administered in an effective period, and NSAID use should not continue for more than five days when used as an analgesic or three days when used in combatting fever; further, the suggestion is made that when the symptom being treated improves, administration should be halted (Varrassi et al. 62-63). Just as with dosage, the duration of NSAID administration depends on the reason for treatment and how it responds to such treatment. Additionally, NSAIDs may not be concomitantly taken with other NSAIDs. In determining dosage and duration of treatment, NSAID dosage should not be dosed more or used more often than what is necessary to treat the ailment at hand, and the factors of dose and duration depend on both the NSAID being used and the affliction being targeted.

3.5 Adverse Effects

3.5.1 Cardiovascular

As with all drugs, NSAIDs carry with them several potential adverse effects, including the risk of negative cardiovascular impacts. While all NSAID compounds carry the potential risk of heart disease and can increase bleeding, especially when taken by elderly patients, NSAIDs that block the production of the COX-2 enzyme carry the greatest potential for cardiovascular side effects (Davis and Robson 172). In this way, cardiovascular adverse effects caused by NSAIDs can include an increased risk of heart disease, especially in certain formulations. Additionally, NSAIDs that block COX-2 enzymal production have also been associated with negative cardiovascular "events," including heart attack (Gøtzsche 1). This formulation, then, seems to present various concerning risks in the sphere of cardiovascular health. On a more

general note, NSAIDs have been noted to raise patient blood pressure, even going as far as canceling out the desired effects of blood pressure-targeting drugs (Green 56). Even when all NSAIDs are wholly considered, some widespread cardiovascular side effects can be noted. These cardiovascular adverse reactions are more common when a patient has preexisting cardiovascular diagnoses, and the overall risk may be attributed to the blockage of prostaglandin synthesis in the kidneys which can cause "fluid overload" (Moore N et al. 2014 and Gislason GH et al. 2009, as cited in Varrassi et al. 69). Certainly, patients of cardiovascular illnesses should proceed with caution when taking NSAIDs, but a certain level of such a risk is present in all patients taking NSAIDs. Overall, NSAIDs that inhibit the production of the COX-2 enzyme present an especially large risk for declining cardiovascular health, but all NSAIDs can cause cardiovascular-related adverse reactions, partially due to an increase in fluid present in the body.

3.5.2 Gastrointestinal

Gastrointestinal adverse reactions are also associated with NSAID use. In fact, this type of adverse effect is one of the United States' largest sources of side effect reporting (Pelletier JP et al. 2016, as cited in Varrassi et al. 66). Illnesses occurring within the upper GI tract make up most of the adverse reactions stemming from NSAID use, with these reactions including bleeding, ulcers, and overall irritation; the higher the dose taken, the higher the risk of GI distress (Green 54). This type of side effect is certainly important to take into account when administering or taking an NSAID, for such effects are incredibly common. Also noteworthy is that up to 20% of all patients taking NSAIDs will experience general symptoms of indigestion-related discomfort (Green 54). As for the reasoning behind such side effects, published literature shows that NSAIDs have a tendency of increasing the permeability of mucosa in the GI tract due to their harsh effect on such tissue—this phenomenon can specifically explain the increased risk

of ulcers (Somasundaram S et al. 1997, as cited in Varrassi et al. 66). Essentially, NSAIDs have the power to decrease physiological defenses in place in the GI tract. According to author K.D. Rainsford, factors such as greater age, large doses, and the partaking of alcohol drinking and smoking can cause a patient to exhibit an increased risk of ulceration within the GI tract (Pharmacology, Therapeutics, and Side Effects 124). Certain characteristics can increase side effect risk, but all NSAID use can negatively impact one's GI health. GI adverse reactions due to NSAID administration are very common and can include general discomfort, bleeding, and ulcers, and the risk of such effects may be increased due to some preexisting characteristics.

3.5.3 Other Adverse Reactions

Aside from cardiovascular and gastrointestinal side effects, NSAIDs carry the potential to cause many other adverse reactions. First, general abuse of NSAIDs can lead to dangerous conditions of the blood like low platelet count (thrombocytopenia) and further harm to the GI tract (Wawryk-Gawda et al. 175; "Thrombocytopenia"). Thus, some side effects stemming from NSAID use are not typical with proper usage of NSAIDs. Instead, some reactions can stem from the inappropriate use of a compound from this group. NSAID use has also been associated with longer periods of bleeding following initial injury as well as increased difficulty forming blood clots, but true complications in the blood are not very common when an NSAID is used properly (Park et al. 616). Unlike GI and cardiovascular side effects, adverse reactions concerning the blood are not incredibly common with NSAIDs, but such reactions are still possible. In the case of the kidneys, chronic kidney disease may spawn from the use of NSAIDs in high amounts and, furthermore, cause high blood pressure, among other secondary side effects; also, when the duration of treatment is long NSAIDs can further damage the kidneys in terms of blood supply (Weir MR 2002 and Ejaz P et al. 2004, as cited in Park et al. 615-616). In this way, higher

dosages of and longer treatment durations by NSAIDs can lead to damage within the renal system. Many general side effects are possible when NSAIDs are administered, with some stemming from typical use, some from misuse, and some from high dose and long-term use; to name a couple, conditions of the blood and kidneys have the potential to arise in the presence of these compounds.

3.6 Conclusion

Overall, NSAIDs are a staple in the healthcare industry today. This fact is unsurprising; the first of these anti-inflammatory compounds traces its beginnings to the salicylate-containing willow tree, which was known by Hippocrates and ancient Sumerians alike to have analgesic and antipyretic properties; later, this compound would become known as aspirin in the late nineteenth century (Ozleyen et al. 2-3). NSAIDs make up a wide group of drugs containing multiple classes and many individual drugs, including ibuprofen, naproxen, and aspirin (Green 51). Since NSAIDs are so widespread, various opinions and beliefs surround them that are publicly apparent, including those both helpful and harmful. With a grand array of treatment applications including the common symptoms of fever, pain, and inflammation, the preference of these drugs by many patients makes sense (Wawryk-Gawda 175). In the dosing of an NSAID, the consensus is that these compounds should only be administered as necessary, and treatment duration should not exceed the presence of symptoms, but dosing and duration also depend on the specific NSAID being administered (Wawryk-Gawda et al. 177). Important side effects to consider include cardiovascular and gastrointestinal reactions, but there are also many other associated side effects that may arise. Since NSAIDs are so popular and readily available, familiarity with the information published surrounding these drugs is important for both the provider and the average consumer to increase the safety and efficacy of NSAID administration.

4. Ibuprofen: Oral Absorption and More

4.1 Introduction

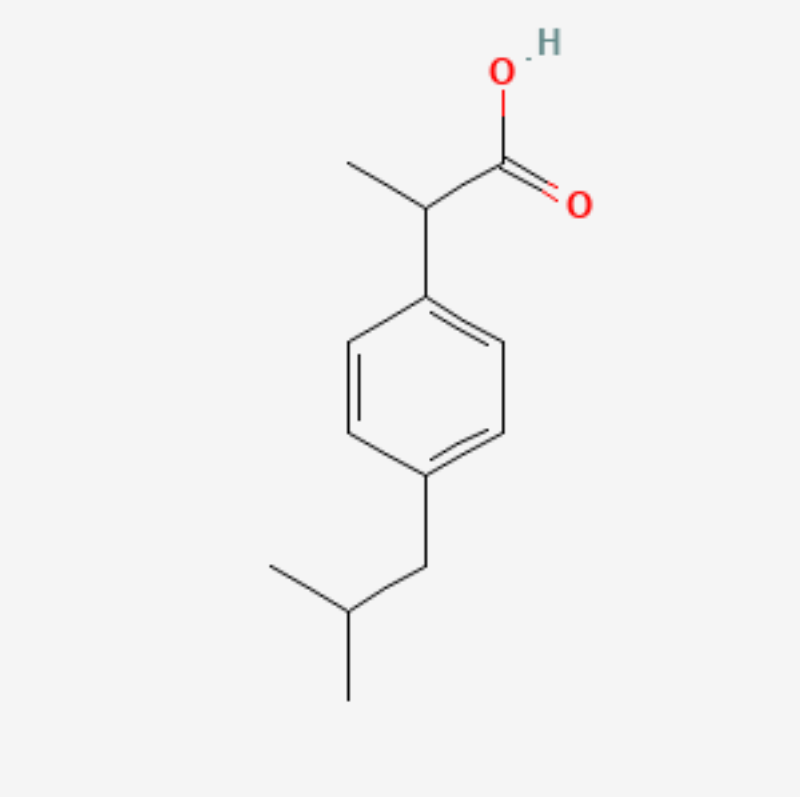

Fig. 3. "Ibuprofen 2D Structure."

An NSAID that is readily available by prescription and over the counter, ibuprofen is a popular treatment for a variety of diagnoses. While NSAIDs are often noted for their widespread treatment of fever, inflammation, and pain, ibuprofen was initially developed as a treatment for rheumatoid arthritis (Wawryk-Gawda 175; Varrassi et al. 62). A quick review of the published literature surrounding ibuprofen suggests that its oral formulations are quite important in medicine. As with any orally administered drug, the absorption of oral ibuprofen is dictated by the gastrointestinal tract (Stillhart et al. 2). While ibuprofen's history is relatively recent in comparison to other NSAIDs, its benefits and costs are well documented by associated literature,

and various factors that impact its pharmacokinetic behavior and overall efficacy have been identified; additionally, the effect of food on ibuprofen is one important component of its study, and the understanding of any food effect may be applicable for clinicians and patients alike.

4.2 Background of Ibuprofen

4.2.1 History

To discuss ibuprofen as a whole, an examination of the history behind its development is pertinent. While the year 1984 marked the over-the-counter designation of ibuprofen in both the United States and the United Kingdom, this NSAID was first synthesized during the 1960s; its official release for prescription use fell somewhere in between, with its debut being made in the UK in 1967 and in the States seven years later (Adams SS et al. 1967, as cited in Davies 102). Therefore, while many know this drug as an over-the-counter one, it was initially available only by prescription. Creation of ibuprofen was set into motion by scientist Stewart Adams, who, during his close work with John Nicholson, isolated propionic acids from experimental compounds containing carboxyl groups (Varrassi et al. 62). The final isolated chemical entity, 2-(-4-isobutylphenyl) propionic acid, would later become known as ibuprofen (BBC News 2019, as cited in Varrassi et al. 62). As is common in the pharmaceutical field, the study of organic chemistry was heavily applied both in structure and nomenclature. While the maximum daily dosage is now known as 2400 mg, ibuprofen was typically prescribed in "low doses ranging from 400 to 1,200 mg day" upon its US release for prescription applications, most often as a replacement for more dangerous NSAIDs in the treatment of rheumatic conditions (Rainsford, "Pharmacology, Efficacy, and Safety" 276). Thus, ibuprofen was used in much smaller doses upon release than it is today. Over the years, its safety has been increasingly proven. Thanks to scientists like Adams and Nicholson, ibuprofen was able to be clinically applied in rheumatics

about a decade after its invention; its proven safety allowed its over-the-counter sale soon after, and the maximum daily dosage has increased over time as more information became available.

4.2.2 Benefits

Ibuprofen has many applications—a characteristic paramount to its widespread popularity—and many associated benefits. Typical applications of ibuprofen lie in treating inflammation, fever, and generalized pain, with general inflammation and pain (rheumatism) being its greatest applications over the years (Klueglich et al. 1055). By treating common ailments like these, ibuprofen has become a common drug in clinics and households alike. Especially when considering its wide array of applications, its importance is undeniable. Ibuprofen has even boasted positive outcomes similar to other NSAIDs in more specific cases of pain and inflammation management, like rheumatoid, acute gouty arthritis, and osteoarthritis (Davies 102). Evident in its relative preference over similar medications, ibuprofen's scope of treatment possibilities is important in its popularity, but its safety is also incredibly noteworthy, for ibuprofen is traced to very few dangerous complications and deaths—even in comparison to aspirin and acetaminophen (Rainsford, "Pharmacology, Efficacy, and Safety," 276). Certainly, both safety and efficacy are important to prescribers and consumers, and ibuprofen can perform well in both regards. Specifically, clinical research has shown that aspirin produces unwanted side effects in 9% more patients than ibuprofen, and even acetaminophen yields such effects in 4% more patients. (Varrassi et al. 65). Ibuprofen's safety is prominently showcased when compared to these two compounds that are also used for pain management. What's more, in comparison with many clinically pertinent NSAIDs, this compound is associated with a far lower risk for gastrointestinal bleeding, a highly undesirable and dangerous adverse reaction (Sing G et al. 1994, as cited in Davies and Skjodt 379). Safety is paramount when administering NSAIDs,

so the proven safety of ibuprofen makes it a highly preferable treatment of pain, inflammation, and fever. Ibuprofen's wide array of applications and highly preferable safety are illustrative in discussing its associated benefits.

4.2.3 Costs

However, because ibuprofen is an NSAID, its use comes with the risks characteristic of this group of drugs. First of all, as discussed in the previous segment of this review on NSAIDs, people with cardiovascular (CV) conditions or experiencing symptoms of declining CV health may benefit from utilizing NSAIDs as little as possible for the shortest duration or, better yet, avoiding NSAIDs altogether (Pepine CJ et al. 2017, as cited in Varrassi et al. 70). While ibuprofen is an attractive treatment option in many cases, certain patients should proceed with caution when navigating the use of all NSAIDs, and this caution is sometimes in the form of total avoidance. In fact, a patient taking any NSAID has a chance of heart failure-related hospital treatment twice as high as a patient not taking one, and the administration of large doses of ibuprofen specifically has been tied to 2 out of 1000 patients every year dying from a CV reaction and up to 9 patients in the same population experiencing non-deadly yet dangerous CV reactions; these effects are due to the increased blood clotting caused by NSAIDs other than aspirin as well as increased blood pressure and an "increase [in] fluid retention" (Bhala N et al. 2012, as cited in David and Robson 172). While high doses of ibuprofen can only account for up to 0.9% of dangerous CV effects and 0.2% of deadly CV effects yearly, ibuprofen is no exception to the risk factors associated with NSAID administration—and those with preexisting CV conditions should be very cautious when taking ibuprofen. Additionally, while many attempts to research the potential of lasting harm to the stomach have yielded little helpful advice, NSAID adverse reactions in the gastrointestinal tract such as nausea, vomiting, and

diarrhea often drive patients to seek help from a specialist in the field, and these reactions are often cited when a patient discontinues NSAID use (Rainsford; Pharmacology, Efficacy, and Safety; 315). Also discussed in the previous NSAID segment, gastrointestinal symptoms are incredibly common among NSAID users, so ibuprofen carries the potential to enact such distress. On top of cardiovascular and gastrointestinal side effects, research has shown that, especially when a high dose is administered to patients with preexisting conditions of the liver or older adults, ibuprofen poses a risk of liver condition development that may be mild or severe; however, this risk is rare when the aforementioned conditions are not present (Kean et al. 2008, as cited in Rainsford; Pharmacology, Efficacy, and Safety; 324). While the risk of hepatic adverse effects is somewhat uncommon outside of the select populations, it is still present in the administration of ibuprofen, especially in high doses. This theme is common with ibuprofen's associated risks: the risks of some side effects are small yet present, and such risks are often more significant among specific groups of patients. Overall, while ibuprofen is considered to be a relatively safe drug, its NSAID classification carries with it the potential for gastrointestinal side effects as well as more uncommon side effects like the development of cardiovascular and renal conditions, which become more common in specific populations and among patients taking high doses.

4.3 Examination of Factors

4.3.1 Age

One demographic factor that is helpful to consider in the study of ibuprofen is age, for this factor may alter the pharmacokinetic behavior or performance of the drug. First, a 1992 study by scholars Kauffman and Nelson determined that neither the plasma concentration of ibuprofen nor its absorption or elimination rate changed with patient age, and no concentration-

related impact on efficacy was noted. This study would suggest that ibuprofen is relatively unaffected by the factor of age. Additionally, this work seems to confirm a 1984 study of ibuprofen administration in elderly patients, where age was documented as not being associated with a considerable difference in plasma concentration or gastrointestinal absorption as a whole (Greenblatt et al. 1068). Such findings may lead one to believe that the pharmacokinetics of ibuprofen are unrelated to age. However, the same 1984 study by Greenblatt and colleagues states that, while little impact on ibuprofen behavior is attributed to age, elderly patients taking ibuprofen exhibited less clearance of the drug due to metabolism as well as a longer half-life than what is noted among younger patients (1068). Thus, even though absorption and elimination lie fairly unimpacted by patient age, other pharmacokinetic components of ibuprofen in elderly patients may differ from those in younger adults. Additionally, the actual efficacy of ibuprofen can be altered by the age of a patient, for due to a difference in the comparative surface area present, the degree of fever reduction is increased and the time to initial fever reduction is decreased in younger children when compared to that of older children (Kauffman and Nelson 1992). In this way, age can impact the way ibuprofen behaves when applied as an antipyretic therapy. Overall, while some of ibuprofen's pharmacokinetic factors do not change with the age of a patient, others are altered in the presence of elderly patients versus younger patients, and the efficacy of this drug in children can vary with age.

4.3.2 Sex

Another demographic factor that may yield information about ibuprofen when considered is biological sex. In studying this drug's behavior across the sexes, its enantiomeric forms are important to consider; (R)-ibuprofen is inactive in the body while (S)-ibuprofen is the active enantiomeric form, and, because ibuprofen as a drug has both (R)- and (S)-enantiomers present,

any probability of the inactive form's intended inversion being altered is important to study (Day RO and Brooks PM 1987 and Wiliams KM and Day RO 1985, as cited in Knights et al. 153). If this inversion is changed, a potential exists for ibuprofen efficacy to also be changed (Day RO and Brooks PM 1987 and Wiliams KM and Day RO 1985, as cited in Knights et al. 153). Ibuprofen's chirality is the focus in multiple studies surrounding ibuprofen absorption between the sexes. In a 1995 study, little evidence was found to suggest that the pharmacokinetics of the inactive form of ibuprofen were different across men and women; additionally, with inversion between inactive and active forms making up a significant portion of the clearance of ibuprofen, the unchanged clearance of this oral compound between men and women is a testament to the idea that ibuprofen activation is not changed by biological sex (Knights et al. 155-156). This study's results suggest that both ibuprofen inversion and ibuprofen's pharmacokinetic behavior are the same for both women and men. However, a study carried out in 2015 says that women exhibit a lower maximum concentration of the (S)-enantiomer of ibuprofen as well as a greater clearance of this active form than men; in terms of the inactive enantiomer, female participants exhibited a lower maximum concentration and smaller half-life of (R)-ibuprofen than male participants (Ochoa et al. 946). Thus, more recent studies suggest that the factor of sex does, in fact, alter the absorption and other pharmacokinetic factors of ibuprofen. Overall, this 2015 study found that women have a higher clearance rate of both (R)- and (S)-ibuprofen than men, with the pharmacokinetic behavior of both inactive and active forms presenting differently for men and women (Ochoa et al. 945). These recent findings seem to disprove the findings of the 1995 study. Certainly, sex is an important factor when studying the pharmacokinetics of oral ibuprofen. While evidence from the 1990s suggests that biological sex is not a factor in the chiral inversion and pharmacokinetics of ibuprofen, more recent evidence notes the opposite, with the

pharmacokinetic behavior, including absorption, of both ibuprofen enantiomers differing from one sex to the other.

4.3.3 Body Composition

In addition to demographic factors like age and sex, the factor of body composition is pertinent to the study of oral ibuprofen and its pharmacokinetic principles. First of all, some scholars have published that obese patients should receive larger doses of ibuprofen than patients with typical body composition to yield target absorptive factors like plasma concentration (Abernathy and Greenblatt 1120). In this way, body composition can change the way a patient attains the intended effects of ibuprofen, so an adjustment must be made. Furthermore, although there is insufficient data to predict exactly how dosing should be altered, some studies have suggested that a patient's fat mass can alter the pharmacokinetic factors of distribution volume and clearance for ibuprofen (Morse et al. 505). Clearly, there is a relationship between a patient's fat mass and the behavior of oral ibuprofen. Also pertinent to note is that the study of obese patients typically involves more diagnostic variables, so it may be difficult to accurately pinpoint and predict the pharmacokinetic behavior of an administered drug (Cortinez LI et al. 2015, as cited in Morse et al. 505). In other words, obese patients, or patients with a BMI of 30.0 or greater, are associated with more clinical variability than non-obese patients (U.S. Department of Health & Human Services, "Defining Obesity"). Such association is especially true in the study of the pharmacokinetics of a drug. From these pieces of evidence, one can conclude that body composition plays a role in ibuprofen absorption and other pharmacokinetic principles, especially in the case of patient obesity.

4.4 Food Effect

4.4.1 In the Absence of Food

When considering food effect, ibuprofen administration in the absence of food yields results more attractive than those in the presence of food, and these results are the standard for food effect comparisons. For example, the absorption of immediate-release ibuprofen in the stomach lies unimpacted when administered before food consumption; however, in the cases of all widely available ibuprofen forms as well as novel lysine and salt forms reviewed by K.D. Rainsford in 2012, slower absorption is experienced when taken after eating (Pharmacology, Therapeutics, and Side Effects; 137). While some forms of ibuprofen avoid food effect, immediate-release forms of ibuprofen absorb best in the fasted state. A logical conclusion can be made that such unimpacted absorption in the absence of food is the clinically intended effect. When ibuprofen is taken in the fasted state, for instance, less than two hours elapse before the greatest concentration is noted (Moore et al. 384). This value makes little sense on its own, but comparison to the same measurement taken in the fed state adds context. Thus, fasted state values are, essentially, the baseline when determining food effect. Furthermore, according to Morse and colleagues, the time in which oral ibuprofen reaches maximum concentration is less when taken following a 10-hour fast than in the presence of food; specifically, when studying the absorption of ibuprofen tablets, a difference of approximately 15 minutes was noted (502). In this way, ibuprofen absorption in the fasted state is preferred over that in the presence of food and provides a relative baseline for comparison. Overall, when in the absence of food consumption, studying oral ibuprofen absorption yields standard values that can be used in illustrating relative food effect, with the absorption process itself being noted as much quicker than if food had been present.

4.4.2 In the Presence of Food

Since oral NSAIDs are typically instructed to be taken alongside food (Rainsford and Bjarnason 465), any change in ibuprofen absorption due to the presence of food is incredibly important to both patients and clinicians. Since the maximum concentration of an NSAID can be lessened by decreasing the acidity of the stomach, one important fact to consider is that food consumption carries the potential to raise the stomach's pH range to 3-5 from the baseline range of 1-3; additionally, this food effect may be more noticeable when an NSAID is taken over a short period of time instead of as part of long-term therapy (Davies and Skjodt 381). Thus, orally administered NSAIDs can behave differently in the stomach when food is present, and altered efficacy is far more noticeable in the case of short-term NSAID usage. While orally administered ibuprofen takes less than two hours to climb to its maximum concentration when taken in the absence of food, the presence of food carries the potential to increase this time frame as well as overall absorption time (Moore et al. 384). While factors like the time in which ibuprofen is absorbed are changed in the presence of food, overall bioavailability is not impacted (Moore et al. 384). It should be mentioned that ibuprofen's "poorly soluble but highly permeable" behavior yields an absorption half-life that is far greater than other common analgesics like acetaminophen (Álvarez C 2011, as cited in Morse et al. 505). In other words, ibuprofen experiences a slower absorption process than some pain relievers. One published study has stated that, when taken with food, the absorption half-life of ibuprofen is further increased, with the baseline half-life being at least doubled but sometimes quadrupled (Morse et al. 505). Since ibuprofen absorbs relatively slowly, the presence of food makes this drug absorb significantly slower. This decrease in absorption time is most notable for ibuprofen tablets (Morse et al. 505). With the widespread availability of ibuprofen tablets, this food effect is significant to note, for a

change in absorption time could result in altered treatment outcomes. Morse and co-workers also suggested that the absorption of oral ibuprofen in the fed state may appear differently for patients that are of increased age, exhibit liver complications, or are severely overweight, for their study involved study participants of average health (Morse et al. 505). Thus, the administration of ibuprofen in the fed state is associated with a great deal of variability, especially when considering this drug's absorptive behavior. Even more variables that may impact the efficacy and pharmacokinetic behavior of oral ibuprofen in the fed state include the time between eating and administration as well as what kind of food is consumed (Rainsford; Pharmacology, Therapeutics, and Side Effects; 137). Any consumption of food near the administration time of ibuprofen brings with it a large probability of variation, for there are many ways for both the absorption and noted effect to be altered. Certainly, evidence suggests that ibuprofen's absorption, as well as other pharmacokinetic behavior and efficacy, is impacted by the presence of consumed food; this impact is in part due to the alteration of gastric pH in the fed state, and many variables must be considered when determining this food effect's extent.

4.4.3 Applications

With ibuprofen absorption experiencing a significant food effect in clinical studies, such knowledge can be applied regarding treatment efficacy and patient safety. For instance, since taking ibuprofen in the presence of food can lengthen absorption and lessen the amount absorbed, the documented food effect carries the potential for lessened pain treatment; after all, in the treatment of short-term pain, ibuprofen yields the most effective results when maximum plasma concentrations are reached in a minimal period (Moore et al. 386). By monitoring the altered absorption of ibuprofen in the presence of food, a prediction can be made about treatment efficacy, paving the way for fruitful conversations between providers and patients. Such

knowledge of the food effect on ibuprofen allows those taking ibuprofen to anticipate how this drug will truly perform. Furthermore, researchers Rainsford and Bjarnason have even suggested that providers and medical professionals should begin recommending that patients take NSAIDs like ibuprofen on an empty stomach, for doing so can lead to quicker analgesic effects and halt patients from immediately taking more than prescribed due to any lag in efficacy; additionally, these same researchers call the common instructions to take such drugs with food "unsubstantiated 'safety' information" (468). While these claims are unorthodox compared to typical medical advice, they are built on information regarding the effect of food on ibuprofen absorption. Additionally, these claims suggest that the dangers associated with patients taking more of an NSAID than prescribed due to food effect outweigh the dangers targeted by taking these drugs with food. As noted in the same review, lessened ibuprofen efficacy due to food effect may potentially lead a patient to increase any future doses in an attempt to compensate for any lessened analgesia noticed, for NSAIDs are typically marketed for their fast and effective treatment of short-term pain; for this reason, Rainsford and Bjarnason's review of this food effect states that this lessened analgesic effect is likely not the case in long-term NSAID use but stresses the importance of any food effect on short-term use (Levine MA et al. 1992, as cited in Rainsford and Bjarnason 467). This evidence is yet another testament to how combatting any food effect on ibuprofen may be pertinent to patient safety. In summary, through increased awareness of how ibuprofen performs when administered with food, clinicians and patients benefit from a more accurate prediction of its performance, and clinicians can make informed decisions regarding the common instruction to take ibuprofen with food and what it means for patient safety.

4.5 Conclusion

On the whole, ibuprofen's development is relatively recent. First synthesized in the 1960s, the discovery of ibuprofen is most often attributed to researcher Stewart Adams (Adams SS et al. 1967, as cited in Davies 102; Varrassi et al. 62). While the administration of this drug comes with many benefits, ibuprofen's most notable treatment outlets are fever, inflammation, and pain (Klueglich et al. 1055). However, this compound is also associated with multiple risks, including those of cardiovascular and gastrointestinal significance. In the study of ibuprofen, factors linked to pharmacokinetic variability include age, biological sex, and relative body composition. For example, pediatric age carries the potential to alter the efficacy of oral ibuprofen when used as a treatment for fever, and recent findings have suggested that clearance of this compound is greater in females than in males (Kauffman and Nelson 1992; Ochoa et al. 946). In terms of body composition, multiple studies have been published surrounding the pharmacokinetic behavior of ibuprofen regarding obesity and, more specifically, the fat mass possessed by a patient (Abernathy and Greenblatt 1120; Morse et al. 505). Perhaps the most important discourse surrounding ibuprofen is documenting the effect of food on its absorption; while this food effect takes place in many ways, one example lies within an increased absorption time when ibuprofen is administered with food (Morse et al. 505). Applications of this well-documented food effect include both treatment efficacy and patient safety. Boasting undeniable popularity, ibuprofen's standing in the world of analgesia and beyond seems to be unshakeable, thus making its potential for research endless and solidifying the importance of its understanding.

5. Discussion

The purpose of this review was to study published information regarding the impact of food on ibuprofen after discussing pharmacokinetics and the pharmacokinetic behavior of ibuprofen itself. Pharmacokinetics denotes the study of a pharmaceutical compound's movement through the body, or concentration as it moves throughout the body, typically over time (Abdel-Rahman and Kauffman 2004, as cited in Fan and De Lannoy 94; Loucks et al. 903). Among other processes, the pharmacokinetic behavior of a drug is typically studied in terms of the four ADME components: absorption, distribution, metabolism, and excretion. In true pharmacokinetic fashion, these ADME principles are typically studied in relation to time (as shown by the above review). Absorption is the process undergone by an administered pharmaceutical compound of a drug to travel from the administration site to where it will be measured, often the bloodstream (Pea 69); of the four ADME principles, absorption seems to be the most impacted by oral ibuprofen's food effect, for the absorption of oral drugs occurs in the GI tract (Fan and De Lannoy 95). In general, food effect plays a large role in oral drug absorption, especially due to altered GI pH levels and transit time.

Ibuprofen is part of a group of drugs known as NSAIDs, which typically function as analgesic, anti-inflammatory, and anti-pyretic drugs (Wawryk-Gawda 175). The first NSAID was developed in the late 1800s, but all drugs belonging to this group tend to pose a risk of adverse cardiovascular and gastrointestinal reactions, among others (Ozleyen et al. 3). Developed in the 1960s, ibuprofen is no exception to this commonality, and its associated risk of GI upset is often cited as a reason that this NSAID should be administered with food (Adams SS et al. 1967, as cited in Davies 102; Rainsford and Bjarnason 465). However, when taken in the presence of food, ibuprofen's absorption time is increased, as is the time it takes for its expected effects to

occur (Moore et al. 384; Davies and Skjodt 381). Other factors that can impact ibuprofen's pharmacokinetic behavior include age, biological sex, and relative body composition. However, the negative impact on ibuprofen's efficacy due to food effect is more noticeable when this drug is used as a short-term treatment for pain, which is often how it is marketed (Davies and Skjodt 381; Levine MA et al. 1992, as cited in Rainsford and Bjarnason 467). Researchers Rainsford and Bjarnason suggest that, to prevent patients from exceeding the suggested dose of ibuprofen to make up for any lag in analgesic effect, medical providers should advise patients to take this drug on an empty stomach (468). While this would certainly be an uncommon instruction, published research has boasted ibuprofen as safer than other common analgesics, and this compound is even associated with a very low risk for GI bleeding—an adverse reaction which is the basis of the common instruction to take ibuprofen with food (Sing G et al. 1994, as cited in Davies and Skjodt 379). Therefore, while ibuprofen carries the risks associated with all NSAIDs, its pharmacokinetic behavior is undeniably altered when administered in the fed state, which is a typical recommendation.

Ibuprofen is a well-known and widespread drug, likely due to its over-the-counter treatment of common symptoms. However, the belief that it must be taken with food is also widespread, so if its food effect impacts patient safety more than its associated risk for GI side effects, providers and patients must be made aware. Information in the above review seems to call for a reexamination of ibuprofen's GI-related risks in the context of treatment efficacy; while only one source reviewed calls the suggestion to administer ibuprofen with food "unsubstantiated 'safety' information," its altered pharmacokinetic behavior in the presence of food is extensively documented (Rainsford and Bjarnason 468). Because ibuprofen is often used as a short-term solution, it is important for the time it takes for this drug to impose intended analgesic effect to

resemble patient expectations. NSAIDs should only be taken for the shortest time at the minimum dose necessary for successful treatment, so if a patient were to take more ibuprofen than prescribed/advised to compensate for its well-researched food effect, their safety may be put at risk. Therefore, a logical conclusion to the above literature review would be that more research must be done to determine the validity of the instruction to take ibuprofen after consuming food. After all, it should be determined whether ibuprofen's GI side effects are more dangerous than its decreased efficacy due to food effect; only then can it be decided if a specific focus should be placed on making this food effect more widely known or if medical professionals should change their typical instructions for ibuprofen administration. If the dangers associated with taking ibuprofen on an empty stomach outweigh the potential dangers carried by taking this drug with food, it may be necessary to make patients and consumers aware of the possibility of altered efficacy, especially in the case of short-term treatment; if the food effect is determined to be more dangerous, then providers and patients should be promptly advised to halt concomitant food intake. Overall, reviewing the published research at hand shows that more research is required to evaluate how ibuprofen is best administered for minimum risks and maximum results.

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