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Identifying Unexpected Inflammation Resulting from Drug-Drug Interactions

Keegan Jolly
keeganjolly@gmail.com

IDENTIFYING UNEXPECTED INFLAMMATION RESULTING FROM DRUG-DRUG INTERACTIONS

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Keegan Jolly

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ABSTRACT

IDENTIFYING UNEXPECTED INFLAMMATION

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Adverse drug events result in nearly 1.3 million emergency room visits per year in the United States of America. As much as 30% of these adverse events are a result of drug-drug interactions (DDI's). There is a gap in knowledge concerning these DDI outcomes especially when it comes to inflammation. Inflammation is linked to a variety of chronic health conditions and non-infectious diseases such as cancer. **Purpose**: The goal of this study was to examine how many active drug ingredients from FDA's Adverse Event Reporting System (FAERS), when combined (in groups of two or more), elicit an inflammatory response and if drug pairs were identified as causing inflammation what were the symptoms? **Methods**: In this study secondary data was analyzed from the publicly available FAERS database. Cases that involved any of the five symptoms of inflammation (swelling, pain, chills, headache, red coloration) ranging from 1980 to August 5, 2022, were retrieved (n= 23,964). Followed by the removal of all cases not reported by healthcare professionals and those that only occurred once (n= 11,957) (See figure 1). **Results**: The data suggested that all these cases were related to 549 different drugs and 37 different drug combinations. Out of these combinations, three-drug

combinations did not contain an active ingredient that elicited an effect alone (See Table 1). **Discussion**: Sense inflammation is associated with long-term disorders; Betamethasone Sodium Phosphate and Betamethasone Acetate which are used to treat long-term disorders, may lead to cancer.

Keywords: Public health, Drug-Drug interactions, Inflammation, Cancer

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CHAPTER I

INTRODUCTION

Introduction to Chapter One

Adverse drug events result in nearly 1.3 million emergency room visits per year in the United States of America (CDC, 2023). As much as 30% of these adverse events are a result of drug-drug interactions (Iyer et al., 2014). While drug-drug interactions (DDIs) are already hard to study, things get monumentally more difficult when these interactions are subtle, non-immediate threats, such as inflammation. There are quantitative methods that use large complex data sets to scan for complications these mainly focus on the adverse events they deem as potentially dangerous rather than those that might cause risk in the long term (Bate & Evans, 2009). There is a gap in knowledge in regards to these DDI outcomes especially, when it comes to inflammation. Inflammation is linked to a variety of chronic health conditions and non-infectious disease such as cancer (Coussens & Werb, 2002; Conroy et al., 2013; Agnoli et al., 2017; Pine et al., 2011; Grivennikov et al., 2009; Holmer et al., 2014; Powell et al., 2021; García-Closas et al., 2007). Therefore, this secondary analysis of data study will mine data from Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) and use predictive pharmacoepidemiology techniques to identify drug-drug-interactions that result in inflammation markers.

Background of the Problem

While the FDA requires pharmaceutical manufacturers to perform clinical trials to establish the safety of their product by themselves, the pharmaceutical company does not typically examine how their drug interacts with other drugs (van der Heijden et al., 2002).

Some DDI's can be predicted through meticulous examination of metabolic pathways (YAP et al., 2011). Other DDI's are predictable because both drugs are metabolized by the same enzyme, in the case of simv'statin and itraconazole (Neuvonen et al., 2006). This relies on knowing the biokinetics of both drugs involved, which becomes more difficult when a drug reacts with proteins that were not their main target causing an unforeseen reaction (Tatonetti et al., 2012). To combat this issue most focus on focus on the adverse events they deem as potentially dangerous rather than those that might cause risk in the long term (Bate & Evans, 2009). This is especially problematic when it comes to inflammatory effects. Inflammation has been linked to multiple types of cancer, including breast, colorectal, lung, bladder, esophageal, pancreatic, and non-Hodgkin Lymphoma (Conroy et al., 2013; Agnoli et al., 2017; Pine et al., 2011; Grivennikov et al., 2009; Holmer et al., 2014; Powell et al., 2021; García-Closas et al., 2007).

Statement of the Problem

Adverse drug events are responsible for nearly 1.3 million emergency room visits each year in the United States alone (CDC, 2023). Out of these 1.3 million visits, as much as 30% of these adverse events are attributed to drug-drug interactions (Iyer et al., 2014). While the FDA requires pharmaceutical manufacturers to perform clinical trials to establish the safety of their product by themselves, the pharmaceutical company does not typically examine how their drug interacts with other drugs (van der Heijden et al., 2002). This leads to a gap in the knowledge of these DDIs effects especially, when it comes to inflammation which is associated with cancer and other diseases in the long run (Coussens & Werb, 2002; Conroy et al., 2013; Agnoli et al., 2017; Pine et al., 2011; Grivennikov et al., 2009; Holmer et al., 2014; Powell et al., 2021; García-Closas et al.,

2007). The prevalence rates for cancer have been slowly increasing United States from 1999 when there were over 1.3 million cancer cases to 2019 when there were over 1.7 million cancer cases (CDC, 2022). As our understanding of both DDI's and inflammations linked to cancer grows, the need to understand if long-term drug interactions can lead to cancer does as well.

Aim of the Study

This quantitative study will examine the relationship between drug-drug interactions and inflammatory effects in the United States.

Research Question

RQ1. *How many active drug ingredients from FEARS when combined (in groups of two or more) elicit an inflammatory response.*

RQ2. *If drug pairs were identified as causing inflammation what were the symptoms?*

Theoretical Framework

This research study is based on a multitude of different theoretical frameworks and models. Explaining the theoretical framework behind DDI's, before exploring the theories of inflammation. To fully understand DDI one must look at the drugs themselves and their pharmacokinetics in the body separately before they can understand their combined effects. When trying to figure out the pharmacokinetics of a drug researchers would start with Lipinski's Rule of Five. Lipinski's Rule of Five is a set of five general rules used when creating a drug to predict its bioavailability when taken orally (Doak et al., 2014). These rules include having a molecular weight of less than 500, no more than five hydrogen bond donors and no more than ten hydrogen bond acceptors, and finally

having a hydrophobic representations log p value not exceeding 5 (Lipinski et al., 1997). These rules are often used because if a molecule meets all five criteria, then it will have greater pharmacokinetic properties (Chen et al., 2020). Even when a drug has high bioavailability, what enzyme will break it down is also required. The majority of pharmaceuticals are broken down by the enzyme class P450, this class contains over 50 different enzymes within it (Lynch & Neff, 2007). This allows us to understand the initial biokinetic issues that may arise as a result of drug interactions. However, once the drugs are downstream, other models are used to understand their effects.

This is where Compartmental Modeling for pharmacokinetics comes into play. This model uses linear differential operations to help describe the path of a drug (Bassingthwaighte et al., 2012). Within this model, there are three different models to describe different layers of examination. The first is single- compartment model, in this model a drug enters and exits either highly vascular tissue like the lungs or plasma and does not recirculate (Creative Biolabs Therapeutics, 2022). Next is a two-compartment model, in this model the body's tissues are split up into two groups, peripheral and central with the drug decay denoted by multiple exponential phases. The final model is the three-compartment model, in this, the three compartments are made up of plasma, highly vascularized tissue (such as lungs, kidneys, and brain), and low vascular tissue (epithelial tissues, cartilage) (Creative Biolabs Therapeutics, 2022).

Significance of the Study

This study will help shed some light on DDI's potential long term effects on the human body. In doing so this will not only help the pharmaceutical field in drug development but also help better inform physicians on prescribing risks. This will in turn help the general population by reducing the chances of having a DDI.

Definitions and Key Terms

Drug-Drug interactions: when one pharmaceutical drug interacts with another pharmaceutical drug or substance creating a new unforeseen reaction.

Pharmacokinetics: how a drug moves through the body including but not limited to when first take to the side products its produces when broken down.

Metabolize: the process of the body using enzymes to breakdown substances

Organization

This thesis will examine DDI's linked to inflammation. Chapter two will be discussing the literature around DDI, followed by inflammation, and finish with the theoretical framework of DDI. The next chapter will discuss how the data was collected and analyzed. In chapter four, the results will reveal what DDI's induce an inflammatory effect and the frequency in which they occur. Proceeding this the discussion section will explain the implications of the results. The final chapter wraps up the study and considers the limitations and what future studies could do to expand upon the findings.

CHAPTER II

LITERATURE REVIEW

Introduction to the Literature Review

To truly understand the issue and its importance, the background behind each of them is needed. First, I will examine drug-drug interactions (DDI's) from the basis of what they are to why they matter. Next, I will dive into inflammation and the long-term effects this has on the human body and the importance of addressing it. Finally, I illustrate the theoretical framework behind the research and the rationale behind it.

Drug-Drug Interactions

To understand drug-drug interactions, first an understanding of what is classified as a drug and the normal effects of one is required. According to the FDA, a drug is defined as a substance that is intended for diagnostics, treatment, and prevention purposes other than food that affects the function or structure of either an animal or a human body (Federal Food, Drug, and Cosmetic Act, 2022). These effects on the body can trigger both intended and undesired effects these undesired effects are more commonly known as side effects (FDA, 2022). To determine these, pharmaceutical companies must have their drug pass a series of trials to determine the efficacy of the medication. In the first phase of the trials, the pharmaceutical company tries to "determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted" (FDA, 2017). The next phases just look at the effectiveness and safety of the medication. The final phase looks at the medication in a diverse population often spread throughout the country, all with the same condition. Then the data is sent to the FDA for review before the company can distribute the medication. While this does help illustrate some of the

side effects, there are always more that are not found in these trials. Due to this, the FDA requires all medication to be labeled with a number to call to report any side effects (Morelli, 2022).

While the FDA requires pharmaceutical manufacturers to perform clinical trials to establish the safety of their product by themselves, the pharmaceutical company does not typically examine how their drug interacts with other drugs (van der Heijden et al., 2002). When a drug interacts with another drug (s) is known as a drug-drug interaction (DDIs) (FDA, 2013).

The first major drug interaction was noted in the 1960s when Blackwell (1963) noticed that patients who took tranylcypromine and cheese suffered a cardiac episode. This is because cheese has tyramine, which causes an increase in blood pressure, while tranylcypromine is a type of monoamine oxidase inhibitor that inhibits the breakdown in the intestinal tract (Sjöqvist & Böttiger, 2010). Subsequently, after this occurred, animal research was performed to examine how different drugs may interact with each other to either increase or decrease the metabolic response to each other (Burns & Conney, 1965). While the mechanism behind some DDIs are discovered shortly after the interaction, other take years to figure out. One example of this is Christensen et al. (1963) who noted that five diabetic patients who were treated with the chemotherapy tolbutamide would become hyperglycemic shortly after they were also given the antidiabetic drug sulphathiazole. Years later, the reason behind the interaction was discovered. Sulphathiazole acts as a powerful inhibitor of the enzyme P4503A, which normally acts as catalysis in the hydroxylation of tolbutamide (Baldwin et al., 1995). Even when the biokinetics of the medication is known there are other variables that can affect how the

drug interacts with the body. Some of these variables included the person's genetics and environmental effects. These were found by Alexanderson et al. (1969), who used 39 sets of twins, 19 identical and 20 fraternal. All were given nortriptyline and a drug history background. They also examined drug history and plasma concentration in all the participants. What they found was that identical twins who were not given other drugs along with nortriptyline had similar concentrations in their plasma however, fraternal twins not given other drugs did not have similar concentrations (Alexanderson et al., 1969). Nowadays, many more DDIs are known but they're still harder to detect.

While some of these DDIs can be predicted through meticulous examination of metabolic pathways (Yap et al., 2011), other times DDIs are predictable if the drugs are metabolized by the same enzyme; such as the case with simvastatin and itraconazole (Neuvonen et al., 2006). This issue is not just limited to DDIs though, some supplements also cause similar effects. Most notably this can be seen with grapefruit juice which is thought to inhibit P-glycoprotein which increases the amount of drug that is absorbed into the body while simultaneously inhibiting the enzyme CYP3A4, which helps remove drugs from the body in the intestinal tract (Bailey & Dresser, 2004; Huang et al., 2004). Even without taking herbal supplements like grapefruit juice, the pharmacokinetics are complex. This is seen when a drug reacts with proteins that were not its main target causing an unforeseen reaction (Tatonetti et al., 2012).

This has led to a better understanding of what drugs may cause deadly effects. One of these examples is the antibiotic Clarithromycin and a calcium blocker often used to treat high blood pressure has been shown to result in critical kidney injury (Gandhi et al., 2013). This occurs because calcium-channel blockers are broken down by the enzyme

CYP3A4, and Clarithromycin acts as an inhibitor of this enzyme (Gandhi et al., 2013). Another famous drug interaction that is affected by the same enzyme is the blood thinner Warfarin and the herbal supplement St John's Wort. However, the pharmacokinetics behind this is still unclear because while Obach (2000) has reported that St John's Wort hindered CYP3A4, Gurley et al (2002) found St John's Wart stimulated CYP3A4. While the Sinister form of warfarin is broken down by the enzyme CYP2C9 the Rectus form of warfarin is broken down by the enzyme CYP3A4. St John's Wort appears to significantly increase the metabolism of both forms (Jiang et al., 2004). This combination causes Warfarin to become less effective compared to when taken by itself, which may lead to blood clots (Jiang et al., 2004).

While the biokinetics of the enzyme interaction plays a key role in understanding the potential for DDIs, the target of the medication is just as crucial. This is where another issue lies. Currently, researchers have identified approximately 500 key targets medication may interact with (Drews, 2000). These targets fall into categories such as receptors, enzymes, nuclear receptors, hormones and factors, DNA, and ion channels. Although these targets only account for about 93% of the FDA-approved drugs, 7% of the drug's primary targets remain unknown (Drews, 2000). Although 7% may not seem like that much in the grand scheme of things, the FDA has approved more than 20,000 drugs for marketing (FDA, 2021). This means that scientists are still unsure how 1,400 different prescription drugs work in the body.

One reason for this could be how each drug is metabolized. This can be seen with the pharmaceutical Adrafinil which is broken down into its bioactive form which happens to be the drug modafinil, which in turn gets broken down further (Lu et al., 2009). While

the metabolization of the drug may be clear modafinil pathway is not. This is because modafinil interacts with a wide variety of areas including the catecholaminergic system, tuberomammillary nucleus, neocortex, nucleus accumbens, and striatum (Milgram et al., 1999; Dell'Osso et al., 2014; Sousa & Dinis-Oliveira, 2020).

This issue is not just limited to drugs with unknown biokinetics, but this is also seen in drugs having a compounding effect on each other. Some very well-documented drug interactions are related to toxic serotonin syndrome. Toxic serotonin syndrome or just serotonin syndrome is a potentially fatal condition that occurs when there is an excess of serotonin (Dunkley et al., 2003; Boyer & Shannon, 2005; Gillman, 2006; Foong et al., 2018). This is commonly caused by either a combination of two different drugs that both increase serotonin levels in distinct ways or by an overdose of just one serotonin-promoting medication (Dunkley et al., 2003; Boyer & Shannon, 2005; Gillman, 2006; Foong et al., 2018). Serotonin syndrome causes symptoms ranging from nervousness, insomnia, tremors, and nausea on the mild side to delirium, rhabdomyolysis, fever of 101.3oF, and death (Foong et al., 2018). Due to this, serotonin elevating drugs are closely monitored and now understand some potentially deadly DDI's. For instance, monoamine oxidase inhibitors should never be combined because this may cause a serotonin overdose. Not only this but combining monoamine oxidase inhibitors with: other classes of antidepressants, opioids that are not pain medication, MDMA, cocaine, amphetamine, St. John's Wort, or dextromethorphan may also cause serotonin syndrome (Foong et al., 2018).

Even though serotonin syndrome is fatal, DDI that causes it can monitor because many of these drugs are prescriptions. Other fatal DDIs are harder to monitor because

they are caused by over-the-counter medications. One such example is diphenhydramine which was involved in about 10% of all fatal overdoses in the U.S. from 2019-2020 (Dinwiddie, 2022). To understand how this occurs, an examination of the biokinetics of diphenhydramine throughout the body is necessary. This first-generation drug class is not very specific and works on many areas of the body such as the gastrointestinal tract, cardiac tissue, and central nervous system (Sicari & Zabbo, 2021). Having such a wide effect on the body means both a wide range of therapeutic uses and side effects if overdone. In the Nishino et al. (2018) case study they examined how an overdose of diphenhydramine caused the death of another wise healthy 45-year-old male. The male had taken an unknown quantity of the medication and suffered a fatal heart attack. This is due to diphenhydramine inhibiting fast sodium channels and delaying potassium channels of the heart at the same time (Nishino et al., 2018). This is not the only potentially deadly side effect caused by diphenhydramine interacting with other drugs. When first-generation antihistamines like diphenhydramine are taken with other anticholinergic medication, the interaction may lead to toxic megacolon, seizures, rhabdomyolysis, and respiratory failure (Wiseman, 1983; Broderick et al., 2018).

DDI's have not only been limited to just two drugs interacting with each other but it also been denoted between three different medications. One notorious example of this is known as the triple whammy. The triple whammy consists of angiotensin-converting enzyme inhibitors (blood pressure medication), non-steroidal anti-inflammatory (naproxen), and diuretics (Harężlak et al., 2021). The combination of non-steroidal anti-inflammatory and angiotensin-converting enzyme inhibitors has been correlated with

acute kidney injury and when combined with diuretics this correlation is increased (Harężlak et al., 2021).

Another DDI that has been well-documented is between statins and fibrates (Corsini & Davidson, 2005). While both statins and fibrates are used to lower cholesterol, statins lower low-density lipoproteins (LDL) cholesterol, while fibrates lower triglycerides and raise high-density lipoproteins (HDL) (Staels et al., 1998; Stancu & Sima, 2001). Statins work by targeting liver cells and alter the enzyme "3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase" which breaks down HMG-CoA into a precursor for cholesterol (Stancu & Sima, 2001). This in turn causes a series of changes inside and outside the cells. This affects more than just the liver cells though, statins also affect the surface of leukocytes and can reduce the number of macrophages as well (Stancu & Sima, 2001). Fibrates on the other hand are not as specific and have multiple mechanisms of action. Fibrates work by increasing lipoprotein lipolysis which breaks down triglycerides (Staels et al., 1998). Fibrates also work in the liver in a few different ways, first it increases fatty acid conversion to acetyl coenzyme A (acyl-CoA) which in turn lowers the available fatty acids available for triglyceride synthesis. Fibrates also stimulate the creation of apolipoprotein A1 and apolipoprotein A2 within the liver which are components critical components of HDL (Staels et al., 1998). Not only do both play a role in liver function but are also metabolized by CYP3A4. This combination has correlated to myopathy and rhabdomyolysis (Corsini & Davidson, 2005). Although there has been extensive study on DDI these studies have not examined the long-term effects of DDI on inflammation or the effects this may lead too.

Inflammation

To understand why inflammatory effects are an issue, an understanding of what inflammation is within the body is necessary. This will include scrutinizing some causes of inflammation. Followed by signs and symptoms of inflammatory effects. Finally, end with the mechanism behind inflammation leading to the symptoms and the long-term effects this has on your body.

There are many different causes for inflammatory effects some are due to external factors such as getting burned or having surgery, while others are caused by internal factors such as the case of lupus (Sherwood & Toliver-Kinsky, 2004). While inflammation due to external factors tends to be acute in nature, these may lead to intense medical emergencies such as sepsis or death (Sherwood & Toliver-Kinsky, 2004). Internal factors tend to be related to more chronic inflammatory effects. This is because acute inflammation is the body's attempt to repair damaged cells while chronic inflammation is the body's attempt to stop the cause of the inflammation (Kawasaki et al., 2012). Internal factors can include an overabundance of adipose tissue and multigene expression, just depending on where the inflammatory effects are transpiring (Temann et al., 1998; Kawasaki et al., 2012). However, no matter the cause of the inflammation the mechanism of action is relatively similar.

Starting with the process behind acute inflammatory effects. To best describe the steps behind acute inflammation, the example of having a cut that becomes infected with bacteria will be used. When bacteria enter the body, the cells recognize these pathogens by the molecules they secrete called "pathogen-associated immunostimulants" which trigger an immune response (Alberts et al., 2002). This causes macrophages to flood the

area. While macrophages normally are reasonable for clearing dead cells, they also recognize and eliminate pathogens (Rosales & Uribe-Querol, 2017). Macrophages first use different receptors that do not normally bind with things in the body to identify the target. Once, bound a sequence of events occurs in the cytoskeleton allowing the macrophage to form a pseudopod that encases the target. Then the macrophage surrounds the target before completely engulfing it (Rosales & Uribe-Querol, 2017). Macrophages also produce inflammatory cytokines such as Interleukin 1 and 6 (IL-1, IL-6) and Tumor Necrosis Factor-alpha (TNF-a) (British Society for Immunology, n.d). The cytokines released by the macrophages cause an increase in the diameter of the blood vessels allowing more blood flow to the affected region (Janeway Jr et al., 2001). This is what causes the tissue to appear red and warm to the touch. This helps drive neutrophils into the area. The bacteria contain peptides with Formyl methionine which act as a powerful attractor for the neutrophils which proceed to engulf and eliminate the bacteria (Alberts et al., 2002). This is not the only way neutrophils fight off the infection though neutrophils also produce oxidizing molecules that damage the DNA of most bacteria (Döhrmann et al., 2016). After this occurs the cells lining the blood vessel walls begin to disjoin causing fluid filled with protein to flow into the site (Janeway Jr et al., 2001). This is the cause of the swelling along with the pain that is also associated with inflammation. This all helps activate the complement system which produces inflammatory effects through the peptide C5a. This peptide has several effects, including attracting neutrophils, changing the permeability of the blood vessels, and activating mast cells. The mast cells in turn, release the molecules histamine and TNF-a (Janeway Jr et al., 2001). If the blood vessel was also damaged, then the kinin and coagulation systems are both activated as well. The

kinin system is an enzyme-based cascade that produces triggers different inflammatory responses. This includes the production of the peptide bradykinin which acts as a vasodilator causing an influx of fluid to the site along with pain from the swelling. The coagulation system is also an enzyme-based cascade, but the coagulation system is responsible for the formation of blood clots (Janeway Jr et al., 2001).

While chronic inflammation is similar in nature to acute, chronic inflammation where is caused by damaged tissue without an acute cause (Furman et al., 2019). Chronic inflammation is associated with numerous diseases such as cancer, hypertension, cardiovascular disease, and other diseases (Coussens & Werb, 2002; Conroy et al., 2013; Agnoli et al., 2017; Pine et al., 2011; Grivennikov et al., 2009; Holmer et al., 2014; Powell et al., 2021; García-Closas et al., 2007; Furman et al., 2017; Furman et al., 2019). Chronic inflammation is marked by higher levels of circulating cytokines and inflammatory gene expression (Furman et al., 2019; Furman et al., 2017). There is a myriad of different risk factors that play a role in chronic inflammation. Some of these include genetic subspeciality, chronic infection, and obesity (Ferrucci & Fabbri, 2018).

The genetic subspeciality appears to be caused by the gene IL1RN haplotypes, which is correlated to a higher concentration of both IL-6 and C-Reactive Protein (CRP) (Reiner et al., 2008). Another risk factor is chronic infection such as Human Immunodeficiency Virus (HIV). Although current medication has allowed patients with HIV to live with the disease they're is still a depletion of CD4 T-cells which causes the intestinal tract walls to become more permeable allowing microbiome into the bloodstream and causing inflammation (Brenchley et al., 2006). The final risk factor to be discussed is obesity. Proinflammatory effects have been strongly correlated to obesity

(Vandanmagsar et al., 2011; Hotamisligil et al., 1983; Kojta et al., 2020; Pérez-Pérez et al., 2020). These proinflammatory effects are seen more in the adipose tissue of obese individuals, due to obesity altering adipose tissue (Weisberg et al., 2003). One of the proinflammatory mechanisms that occur is adipocytes secreting TNF-a (Hotamisligil et al., 1983). Other proinflammatory molecules released by adipose tissue in obese individuals include IL-6, C- reactive protein, inducible nitric oxide synthase, and monocyte chemotactic protein-1 (Weisberg et al., 2003). While obesity comes with its own disease prognosis, some of them are comorbid with chronic inflammation.

Chronic inflammation has been correlated with a wide variety of diseases, such as cancer, heart disease, diabetes, lung disorders, and chronic kidney disease (Pahwa et al., 2021). This is not just limited to one type of cancer either. Chronic inflammation has been associated with breast, lung, pancreatic, colorectal, esophageal, bladder, prostate cancer, and Non-Hodgkin Lymphoma (Coussens & Werb, 2002; Conroy et al., 2013; Agnoli et al., 2017; Pine et al., 2011; Grivennikov et al., 2009; Holmer et al., 2014; Powell et al., 2021; García-Closas et al., 2007; Imayama et al., 2012; Fujita et al., 2019). Along with lung cancer chronic inflammation is thought to be the driving mechanism behind chronic obstructed pulmonary disease (COPD) (Yi et al., 2018). The inhalation of toxic molecules triggers an abnormal inflammatory response causing an incase in IL-1 and IL-6 along with an immune response which may contribute to the restructuring of the physical airway (Silva et al., 2018; Yi et al., 2018; Wang et al., 2018; Dima et al., 2019). Chronic inflammation has also been noted to lead to chronic kidney disease and potentially lead to end-stage renal disease (Cobo et al., 2018; Mihai et al., 2018; Ruiz-Ortega et al., 2020; Niewczas et al., 2019).

Although obesity is a risk factor for both type 2 diabetes and cardiovascular disease, research has demonstrated a strong association between inflammatory monocyte and cardiovascular diseases (Steven et al., 2019; Ndrepepa. G, 2019; Chait & Den, 2020; SahBandar et al., 2020). Along with this chronic inflammation in obese individuals has been cited as one of the factors in developing insulin resistance and type 2 diabetes (Burhans et al., 2018; Tsalamandris et al., 2019; Oguntibeju. O, 2019; Halim & Halim. 2019; Burgos-Morón et al., 2019; Kojta et al., 2020).

Theoretical Framework

While there are many different theories behind how drugs interact with the body this paper will focus on the Compartmental Modeling for pharmacokinetics. This model uses linear differential operations to help describe the path of a drug (Bassingthwaighte et al., 2012). Within this theory, there are three different models to describe different layers of examination. The first is single- compartment model, in this model a drug enters and exits either highly vascular tissue like the lungs or plasma and does not recirculate (Creative Biolabs Therapeutics, 2022). Next is the two-compartment model, in this model the body's tissues are split up into two groups, peripheral and central with the drug decay denoted by multiple exponential phases. The final model is the three-compartment model, in this, the three compartments are made up of plasma, highly vascularized tissue (such as lungs, kidneys, and brain), and low vascular tissue (epithelial tissues, cartilage) (Creative Biolabs Therapeutics, 2022). The methods of this study used Compartmental Modeling for pharmacokinetics however, it used the social ecological model to apply to public. Sense the social ecological model can help address an issue on every level from

individual to policy this study will serve to educate patients, professionals, and legislators (McCormack et al., 2017).

Summary

Drug-Drug Interactions have been known since the 1960s with Blackwell (1963) research that showed tranylcypromine and cheese caused cardiac episodes. Since then, knowledge of DDI's has increased substantially to include many different substances as well. However, DDI's involving inflammatory effects have not been examined. Since chronic inflammation has been associated with a wide variety of diseases, such as cancer, heart disease, diabetes, lung disorders, and chronic kidney disease (Pahwa et al., 2021). If a DDI causes an inflammatory effect, then this could result in long-term diseases.

CHAPTER iii

RESEARCH METHODS

Introduction

The purpose of the chapter is to introduce and explain the research method of the study. To answer the research question How many active drug ingredients from FEARS when combined (in groups of two or more) elicit an inflammatory response? A secondary analysis of data will be used to answer this question.

Research methodology

The second data analysis is using the previously collected data sources that have been collected for a different intent from a specific demographic but have not been examined for specific research questions. This data has been approved for collection from human subjects for a different purpose. This saves time and money along with being clean and structured in an easier-to-use format (secondary data, 2021). In particular, using publicly available data sets such as FEARS or VAERS are reliable and valid. These can also be compared to find new insights into previously conducted studies for different hypotheses.

Source of Data

The source of all the data used in this study comes from the FDA's Adverse Event Reporting System (FEARS). FEARS is a publicly available database made up of adverse events related to medication reported voluntarily by healthcare professionals, consumers, and manufacturers using electronic forms online (FDA, 2021). Each event submitted to FEARS is encoded with a unique case number and no identifying information. If manufacturers receive adverse event reports from either patients or healthcare workers,

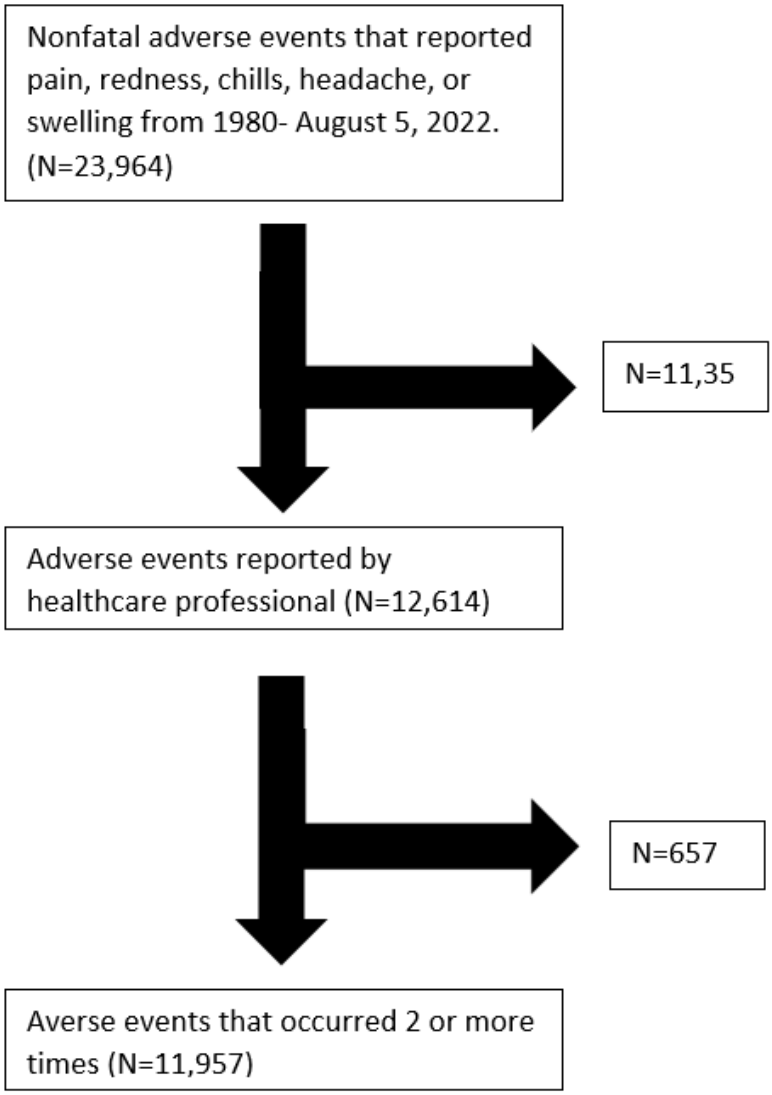
they are required to report this to the FDA (FDA, 2021). FEARS reports include case ID, suspect product names, suspect product active ingredients, the reason for use, reaction, the severity, outcome, sex of the patient, the date the event occurred, the latest date the FDA received the report, patient age, patient weight, who reported it, reporter type (healthcare professionals, consumers, or manufacturers), report source, and more. Due to the nature of the reporting system, there are some issues that occur. These include multiple entries for the same case if reported by different parties such as healthcare professionals and patients (FDA, 2021). Another issue is there is no way to tell if the response is due to the medication or an external factor not reported (FDA, 2021).

Participants and Sampling

Deidentified cases from FEARS will be the source of all the data for this project. In total 23,964 nonfatal adverse events that reported pain, redness, chills, headache, or swelling (from 1980 through August 5, 2022) were retrieved from the FDA's publicly available FEARS database. For internal validity only reports that were stated to have come from a healthcare professional (N= 12,614) were used. Doing so would help ensure more reliable reporting of symptoms because they would be able to diagnose these symptoms. Then examined the frequency in which each active incident(s) was reported to cause any of these side effects. If the ingredient(s) was only reported cause an inflammatory effect once, then it was eliminated from the data (N= 11,957) (See figure 1). The research looked at active ingredient(s) rather than the drugs themselves due to the fact different drugs may contain the same active ingredient that may elicit an effect. One example of this is Glassia vs. Zemaira vs. Prolastin vs. Aralast Np all of which have the active ingredient, Alpha.1-Proteinase Inhibitor, and are used for the same purpose.

Figure 1

Data Flow diagram



Note. Illustrates the flow process of taking out cases at each step of the process and the total number left after each step. Starting with 23,964 cases 11,350 of which were taken out to help control for internal validity by only counting ones that were reported by healthcare professionals. Next 657 cases were removed because the active ingredient(s)

only occurred once and would not be as reliable. This left 11,957 reported cases of drugs and drug combinations that elicited a nonfatal inflammatory response in the U.S.A.

Data Analysis

First, the suspected active ingredients were separated in Excel, then visually analyzed for any active ingredient that occurred both by itself and with something else. Once the active ingredients that only elicited an effect when combined were isolated, the drugs were examined to see if they contained both ingredients or only one. Next, the molecular structure of the active ingredients was examined; to determine if there was a correlation between the backbone of the molecules and the effects they cause.

Ethical Approval

This study has been approved for the exemption of human subjects by Central Washington University's IRB.

CHAPTER iV

RESULTS

Introduction

After careful analysis, we discovered the 11,957 cases could be attributed to just 549 different drugs, and 37 were from drug combinations. Out of these 37 drug combinations, only four drug combinations were found to elicit an inflammatory effect only when combined. While the other 33 combinations contained one or more drugs that created an inflammatory effect independently. These four combinations contained active ingredients which were not found to create an inflammatory response independently. These four-drug combinations resulted in thirteen reported cases (see Table 1). These cases were made up of 6 males and 7 females with an average age of 49 years old. Symptoms experienced by these DDI's consisted of chills, tenderness, cold sweats, akathisia (2%), erythema, swelling, fatigue (5%), headache (7%), pain (14%), with the last 57% consisting of non-inflammatory symptoms (see figure 2).

Table 1.

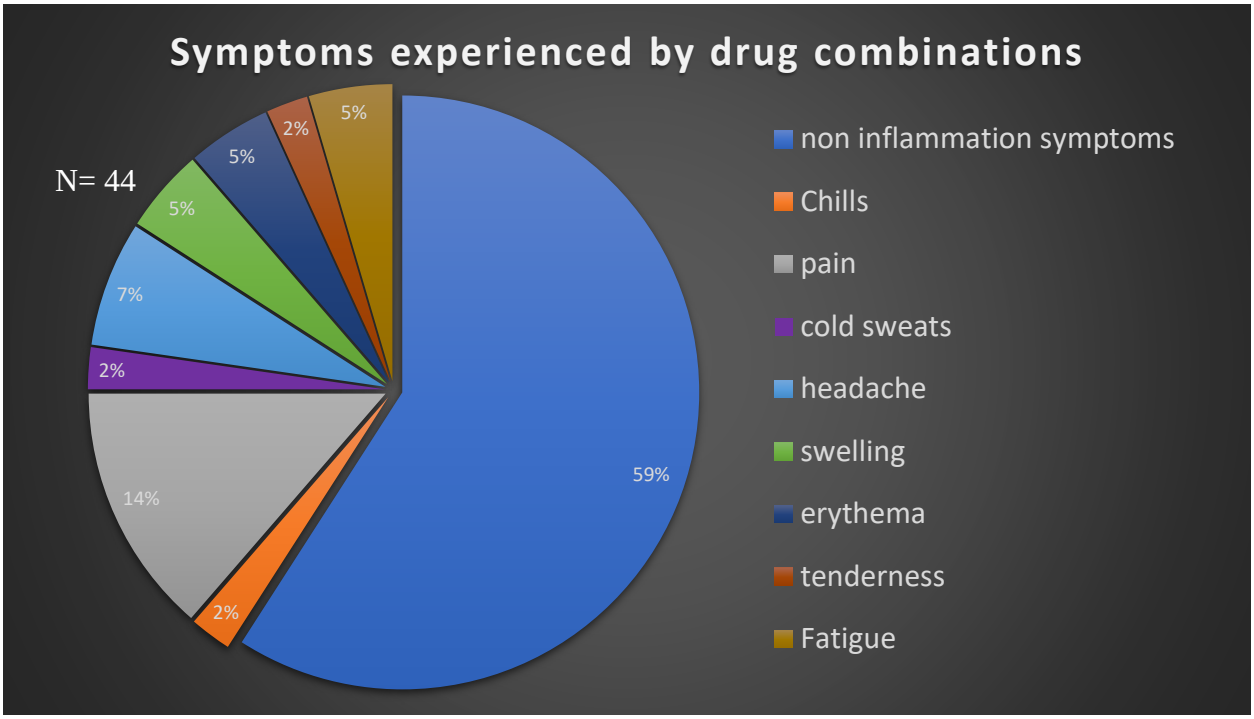
Cases of Drug-Drug interactions that elicited an inflammatory response.

Product Names	Active Ingredients	Reactions	Sex	Age	Weight
Braftovi; Mektovi	Binimetinib; Encorafenib	Chills; Cold Sweat; Face Discolored; Abdominal Pain	Male	62 YR	Not Specified
Braftovi; Mektovi	Binimetinib; Encorafenib	Pain	Female	62 YR	58.5 KG
Hydrocodone Bitartrate and Acetaminophen	Acetaminophen\Hydrocodone Bitartrate	Headache; Product Quality Issue	Male	58 YR	Not Specified
Hydrocodone Bitartrate and Acetaminophen	Acetaminophen\Hydrocodone Bitartrate	Product Substitution Issue; Pain; Therapy Non-Responder; Inadequate Analgesia	Female	56 YR	150 LB
Hydrocodone Bitartrate and Acetaminophen	Acetaminophen\Hydrocodone Bitartrate	Pain; Drug Ineffective; Therapeutic Response Unexpected	Female	30 YR	130 LB
Hydrocodone Bitartrate and Acetaminophen	Acetaminophen\Hydrocodone Bitartrate	Therapeutic Response Unexpected; Therapeutic Product Effect Decreased; Pain	Male	48 YR	Not Specified
Hydrocodone Bitartrate and Acetaminophen	Acetaminophen\Hydrocodone Bitartrate	Headache; Drug Ineffective	Male	41 YR	Not Specified
Hydrocodone Bitartrate and Acetaminophen	Acetaminophen\Hydrocodone Bitartrate	Drug Ineffective; Headache	Male	41 YR	Not Specified
Betamethasone Sodium Phosphate And Betamethasone Acetate	Betamethasone Acetate\Betamethasone Sodium Phosphate	Erythema; Pain; Swelling	Male	46 YR	234 LB
Betamethasone Sodium Phosphate and Betamethasone Acetate	Betamethasone Acetate\Betamethasone Sodium Phosphate	Erythema; Swelling; Tenderness	Female	49 YR	138 LB
Pondimin; Ionamin	Phentermine; Fenfluramine Hydrochloride	Pain; Akathisia; Nervousness; Thirst; Dry Mouth; Tachycardia; Chest Pain	Female	37 YR	273 LB
Pondimin; Ionamin	Phentermine; Fenfluramine Hydrochloride	Mitral Valve Incompetence; Chest Pain; Vomiting; Nausea; Dyspnoea; Alopecia; Drug Ineffective; Palpitations; Vision Blurred; Fatigue	Female	36 YR	125 LB
Pondimin; Ionamin	Phentermine; Fenfluramine Hydrochloride	Sedation; Fatigue; Blood Pressure Decreased	Female	47 YR	150 LB

Note. The individual deidentified case with the drug combination they took, the active ingredients those drugs contain, symptoms experienced, age, sex, reported weight.

Figure 2

Symptoms Experienced by Drug-Drug Interactions.



Note. This pie chart depicts the percent of inflammatory symptoms that were experienced in the four DDI combinations combined.

Summary

From the initial 11,957 cases caused by 549 different drugs and 33 combinations, only four combinations (13 cases), were found to elicit an inflammatory effect only when combined. These cases were made up of 6 males and 7 females with an average age of 49 years old. Symptoms experienced by these DDI's consisted of chills, tenderness, cold sweats, akathisia (2%), erythema, swelling, fatigue (5%), headache (7%), pain (14%), with the last 57% consisting of non-inflammatory symptoms (see figure 2).

CHAPTER V

DISCUSSION

Introduction to Chapter

This final chapter will discuss the implications of these results to the public. Followed by an examination of the limitations. This chapter will end by discussing where future research can go using this research paper.

Discussion of Findings

While all four DDIs are used to treat different disorders, three of them are commonly combined. For instance, Braftovi and Mektovi are two different medications that are commonly combined to treat metastatic melanoma which contain the gene mutation BRAF V600E or BRAF V600K (Melanoma Research Alliance, 2021). While Braftovi; works by inhibiting the BRAF protein kinase, Mektovi works as a mitogen-activated protein kinase kinase (MEK) inhibitor (Davis & Wayman, 2022). However, MEK and BRAF are part of the same Ras pathway which is responsible for cellular regulation and rapid division (Sood et al., 2021). While either medication can be taken individually to treat the specific melanoma, the average overall survival rates go from 22.5 months by themselves to 33.6 months when combined (Davis & Wayman, 2022). However, with the average survival time being 33.6 months, understanding the long-term effects of inflammation caused by these drugs would be difficult.

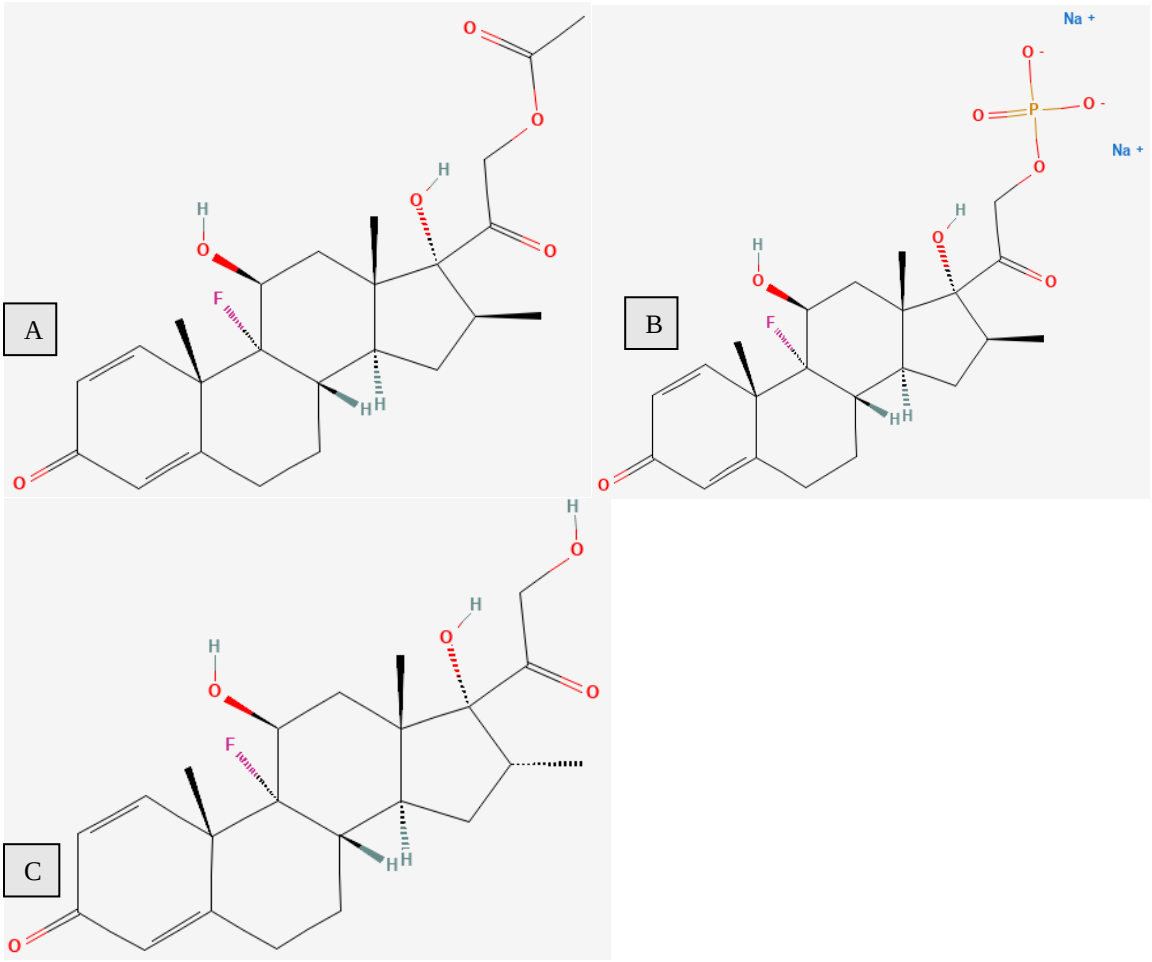
Other commonly combined drugs like Hydrocodone Bitartrate and Acetaminophen do not share this issue. Hydrocodone is a commonly prescribed pain medication used in patients suffering from disorders ranging trauma to cancer (Habibi & Kim, 2019). While Acetaminophen is used to treat pain and fever when used alone; when

combined with other medication, it can treat cough, sleeplessness, and allergies (FDA, 2022). An estimated 5 million Americans that suffer from chronic pain use opioids like hydrocodone for long-term pain management (Reuben et al., 2015). Therefore, of these 5 million individuals who take the combination of Hydrocodone Bitartrate with Acetaminophen and experience an inflammatory adverse event may be at higher risk of developing an inflammatory-related disease.

The combination of Betamethasone Sodium Phosphate and Betamethasone Acetate is used to treat a wide range of diseases. Both are synthetic corticosteroids; they share the same chemical backbone but differ in the 17- hydroxyl group (Pub Chem, 2023d) (see Figure 3). Betamethasone Sodium Phosphate is fast acting and used to treat diseases ranging from: skin disorders, kidney diseases, respiratory disorders, and nervous system diseases (Drug Bank, 2018). Betamethasone Acetate is a long-acting corticosteroid that is used to treat skin conditions (Drug bank, n.d). Along with treating skin conditions, Betamethasone Acetate is used in combination with Betamethasone Sodium Phosphate and by itself to help lung maturation in those who are at risk of giving premature birth (Schmidt et al., 2018). The combination of the two is used to treat long-term diseases like; arthritis, blood problems, eye problems, and adrenal problem (Mayo Clinic, 2023). Since this combination is used for these long-term diseases and elicits adverse inflammatory effects, they may experience higher rates of inflammatory-related diseases like cancer.

Figure 3

Skeletal Structure of Cortical Steroids



Note. This depicts the chemical structure for Betamethasone Acetate (A) (Pub chem, 2023a), Betamethasone Sodium Phosphate (B) (Pub chem, 2023b), and Dexamethasone (C) (Pub chem, 2023c).

The last combination of Pondimin and Ionamin is the only combination that was not commonly prescribed together. Although, Pondimin (fenfluramine hydrochloride) does share an active ingredient that is similar to the active ingredient (Dexfenfluramine) which, is used in the discontinued medication Redux (Pub chem, 2023e). Redux was weight loss medication that was discontinued due to cardiovascular issues (cite source). When Pondimin was first approved, it was marketed as a weight loss medication like

Redux. However, later on, it was discovered to be significantly more effective in reducing seizures caused by Dravet syndrome (Lagae et al., 2019). While Ionamin is also a stimulant, Ionamin is used for weight loss (Jeong & Priefer, 2022). In a study by the American Society of Bariatric Physicians, 95% of the physicians who responded reported prescribing Ionamin to their patients (Hendricks et al., 2009). While there is a chance some may be prescribed this combination for long-term use, Ionamin is only recommended for short-term use. In combination, with the rarity of Dravet syndrome means studying these combinations' long-term inflammatory effects would be very difficult. However, while Pondimin is no longer FDA-approved for weight loss, it is feasible that patients may take a combination of these two only for weight loss. Especially if the patient does not change their diet or behavior; this combination may be seen, used long-term, or off-and-on use over multiple years. This could possibly be the reason for the one patient who was 273lb and taking this combination.

Limitations of Study

The major limiting factor in this study was the source of the data. Since the data in FAEARS comes from adverse reactions that were self-reported by either the patient, healthcare provider, or manufacturer to the FDA these cases may not represent the true magnitude of the issue. This combined with the lack of information on the patient's current diseases or symptoms makes it difficult to determine if the symptoms experienced were from preexisting conditions or from the medication itself. This issue arises when it comes to medication used to treat a wide range of different diseases and medications where the mechanism of action is not fully understood. To combat this issue the law needs to change to include preexisting disease as a part of the required reporting system.

However, this will be difficult because the law must balance patients' privacy with creating a better understanding for the general public. The other limitation related to this data source is we do not know if the medication was prescribed off-label (prescribing medication for uses not approved by the FDA). An example of this can be seen in the use of hydroxychloroquine (anti-parasite medication) to treat the viral infection SARS-CoV-2 (Kalil, 2020).

Implications for Practice

Using the social-ecological model in combination with health literacy to work on a personal, interpersonal, and organizational level (McCormack et al., 2017). This study's results can educate healthcare professionals on the long-term effects of different medication combinations. For instance, if a patient has an inflammatory-related disease, their healthcare provider may change the medication they prescribe to avoid aggravating the inflammation. Other times healthcare providers may alter medication, which is for patients who are at high risk of developing cancer. These healthcare providers may also use this information to educate their patients on the signs and symptoms of inflammation along with the long-term effects inflammation may have. This would help empower the patients to take more control of their health and become more Intune to what is going on with their bodies. In turn, the patients could help educate their community and loved ones. While they may take these specific medications, they may know others who do. Along with healthcare providers, the results could help inform the FDA. The FDA then could update its database to inform an even larger audience. The FDA may also add more sections in the reporting system to include the intended use of the medication, preexisting conditions, and history of smoking/ alcohol use. Pharmaceutical companies may also use

these when creating new medications and when examining the effects of existing molecules.

Future Research

Using these results future research should perform a retrospective study on patients who took Hydrocodone Bitartrate and Acetaminophen or Betamethasone Sodium Phosphate and Betamethasone Acetate to see if those who took these combinations have a higher rate of inflammatory-related diseases compared to an age-matched population. Other research can look at the mechanism of action of these DDI for commonality including how they change after metabolizing from P450. If there is found to have a higher rate of inflammatory-related diseases when taking these combinations then, research can examine what proinflammatory cytokines are being elevated in the bloodstream. Along with this looking to see if there is a correlation between the level and combination of different cytokines and the development of different inflammation-related disorders. Other research can look at implementing a program on a medical charting system to collect the same data as FAERS but run an automated examination for DDI to see what other combinations elicit an inflammatory product. Finally future research can compare different sexes, age groups, and weights that took the same medication combinations to see not only if their side effects differed when controlling for the other two variables but also the frequency at which they occurred among these groups.

Conclusions

Out of the initial 11,957 cases, only thirteen were attributed to a combination of two or more drugs that did not contain active ingredients in other drugs (see Table 1). The initial cases were also associated with 549 different drugs and 37 were from drug

combinations. Out of these 37 different drug combinations, only four drug combinations were discovered to elicit an inflammatory effect only when combined. Out of these combinations, only Hydrocodone Bitartrate and Acetaminophen, Betamethasone Sodium Phosphate and Betamethasone Acetate were determined to be probable long-term combinations. Therefore, those who take either of these combinations have an increased risk of developing an inflammatory-related disease.

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