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A Quantitative Analysis of Postmarketing Safety Events of Breakthrough Medicines

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This is to certify that the doctoral dissertation by

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and that any and all revisions required by
the review committee have been made.

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Walden University
2025

Abstract

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MS, Johns Hopkins University, 2016

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Dissertation Submitted in Partial Fulfillment

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Abstract

Adverse events to medicines pose a risk to the public health of patients. Breakthrough therapy medicines are designed to address unmet medical needs and are often approved on an expedited timeline; however they are also criticized for lacking an adequate understanding of their risk profile at the time of approval. This study examined the relationship between the number of concomitant medicines, as well as the approved therapeutic indication, and the outcomes of reported adverse events associated with medicines approved under the breakthrough therapy designation. The conceptual framework applied in this retrospective, cross-sectional, quantitative study is the process of pharmacovigilance, which involves studying the postmarketing safety profile of approved medicines. Adverse event reports to non-oncology breakthrough therapy indications (n = 394,706) were obtained from the FDA Adverse Event Reporting System (FAERS) Database from the inception of the program (2012) through 2024. Adverse event report outcomes were analyzed using multinomial logistic regression. The results indicate a modest but significant relationship between the number of concomitant medicines and the reported outcome of adverse events. In addition, the approved therapeutic indication was found to be associated with the outcome of reported adverse events, indicating that the risk of experiencing an adverse event may be disease specific. The results of this study have implications for contributing to social change by protecting public health through informing patients about the potential risks associated with breakthrough therapy medicines, improving future clinical guidelines for the clinical trials of these medicines, and informing future regulatory guidelines of these medicines.

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Dedication

I dedicate this dissertation to my wife and my son, who have provided me with tremendous love and support throughout this process. A very special thank you to my wife, who has supported my love of learning and stood by me through all the challenges and was my rock during the times I doubted myself. I hope my son inherited my love of learning and will earn a graduate degree someday. If not, that is perfectly okay. You are loved immensely, and I thank you for being by my side while I completed this study and for providing me with hugs whenever I needed one.

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It is impossible to complete a journey like this without a great team, and I have been lucky to have a stellar committee. I am deeply grateful to my committee members, Jennifer Oliphant and Richard Palmer, for their valuable input and guidance on this study. I would like to extend a special thank you to Jennifer Oliphant for her help and patience, and for working with me throughout the dissertation journey. I would like to thank Julia Leischner for providing input during the prospectus stage.

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Chapter 1: Introduction to the Study

Introduction

In this study, I conducted an epidemiological analysis of the outcomes of adverse reactions to medicines approved under the breakthrough therapy designation. A cross-sectional study examining the frequency of emergency room visits in the United States from 2017-2019 found that visits that result from a drug-related adverse reaction occur at a rate of 6.1 per 1000 annually (Budnitz et al., 2022). The outcomes of adverse events have the potential to impact the quality of life of patients. While previous reports have examined the adverse reactions reported for medicines approved under expedited pathways, an analysis of the outcome of adverse events reported by patients who received breakthrough therapy medicines has yet to be conducted.

A detailed analysis of the safety of a marketed medicine begins at the approval process, where its safety and efficacy are supported by several clinical trials conducted throughout its development (Beau-Lejdstrom et al., 2019). However, the study of the safety profile of a medicine does not stop at approval. Through the process of pharmacovigilance, it is the sponsor's responsibility to continually monitor the safety of medicines in the post-approval setting (Kugener et al., 2021). The risks and benefits of medicines approved under the standard approval process are supported by data collected from several clinical trials often involving thousands of participants (Beau-Lejdstrom et al., 2019). In contrast, medicines approved under the breakthrough therapy designation are often supported by less clinical data; approval is frequently based on a single study, which has led researchers to question whether the safety profile of these medicines has been adequately assessed (Ribeiro et al., 2020).

In this chapter, I provide a background on the purpose of this study. I then identify the problem to be addressed by this research study, provide the conceptual framework for the study, describe the nature of the study, and state the study's questions and hypotheses. I then list the critical definitions of the terms used in this study, discuss the study's assumptions, scope, delimitations, and limitations, and describe the significance of the study's results.

Background

The practice of pharmacovigilance is an essential responsibility for drug developers to protect the public health that extends throughout the lifecycle of a medicine (Kugener et al., 2021). Pharmacovigilance is a multi-disciplinary activity that monitors the rate and incidence of adverse reactions as well as the outcomes of adverse reactions to establish the safety profile of these medicines, which help to identity which patients would most benefit from a medicine as well as those patients at a greater risk of experiencing an adverse safety event (Kugener et al., 2021). One of the most critical aspects of the pharmacovigilance practice involves monitoring adverse reactions in the postmarketing setting, as a more diverse patient population is exposed to the medicine in greater numbers than was studied during clinical development (Kugener et al., 2021). Pharmacovigilance is a regulatory requirement and is expected following marketing authorization from all relevant regulatory agencies, including the United States Food and Drug Administration (FDA) (Kugener et al., 2021). Data from pharmacovigilance practices are reported to regulatory agencies on a yearly basis, and the safety labeling is updated accordingly (Kugener et al., 2021).

Adverse drug reactions have the potential to negatively impact public health. A cross-sectional study of emergency room visits in the United States from 2017-2019 found that visits due to drug-related adverse reactions occurred at a rate of 6.1 per 1000 annually, and 38.6% of these visits were severe enough to result in hospitalization (Budnitz et al., 2022). A useful tool for monitoring the epidemiology of these adverse events is the FDA Adverse Event Reporting System (FAERS) Database, where demographic capabilities including age, gender, ethnicity, number of concomitant medicines, the seriousness of reported adverse events, and the outcome of the adverse event can be obtained (Chen et al., 2022). The FAERS Database tool has successfully helped monitor the epidemiology of adverse drug reactions of newly approved medicines and has proven valuable as a tool; the risks identified through the database have been found to statistically align with those identified during clinical development (Beau-Lejdstrom et al., 2019). Additionally, the identification of safety signals and the tracking of adverse drug reactions through the FAERS Database are significant drivers of post-marketing labeling changes, including numerous updates to the safety sections of drug labels (Croteau et al., 2022).

Data indicate that one impact on the public health is the serious outcomes of adverse drug reactions which often strain the healthcare system. Adverse drug reactions are responsible for ten to thirty percent of hospital admissions among elderly patients (Park & Luu, 2021). Deaths resulting from adverse drug events exceeded one hundred thousand in 2016 (Park & Luu, 2021). In addition, adverse drug reactions often result in an increase in a hospital stay of up to two days and an increase of up to $2500.00 in medical costs relating to the hospital stay (Park & Luu, 2021). In 2016, adverse drug reactions accounted for approximately 16% of all U.S. healthcare expenditures ($528.4 billion) (Park & Luu, 2021). It is therefore essential to understand if specific patient populations are at an increased risk of experiencing an adverse reaction that will likely require medical intervention. For example, it is known that older adults in the U.S. are at a significantly greater risk of suffering adverse reactions from medicines that are considered high-risk or when medicines are used in a way that is not consistent with their intended approval (Park & Luu, 2021). In addition, older adults in the United States are more likely to experience an adverse event resulting from the use of concomitant medicines (Park & Luu, 2021).

The FAERS Database was implemented in 2007, following the passage of the Food and Drug Administration Amendments Act, which requires the FDA to establish a system for collecting data on adverse drug reactions. This system aims to provide data on the safety of approved medicines in the postmarketing setting (Beninger & Murray, 2021). The FAERS Database allows patients or caregivers to report information regarding an adverse drug event (Beninger & Murray, 2021). The data collected in the FAERS Database enable the monitoring of adverse drug events and the identification of patterns associated with these events, as well as aid in the identification of patient populations with an increased risk of experiencing these events (Beninger & Murray, 2021). The FAERS Database has been an effective tool in the identification of previously unidentified risks associated with approved medicines (Beninger & Murray, 2021). The data collected through FAERS has resulted in labeling changes, including class labeling language (Beninger & Murray, 2021). These changes in safety labeling language have included the addition of language to the Warnings and Precautions sections, the inclusion of events in the Adverse Reactions section, the identification of Contraindications, and the addition of Boxed Warnings (Beninger & Murray, 2021). Findings from the FAERS Database have also led to communications with healthcare professionals aimed at improving the safe use of medicines by communicating changes to the safety profile, dose and administration directions, populations identified to be at an increased risk of experiencing adverse events, as well as identifying concomitant medicines that may increase the risk of adverse events occurring (Beninger & Murray, 2021).

Congress has implemented several expedited designations to encourage the development of medicines addressing critical and unmet medical needs (Hermosilla, 2024). One of these designations is the breakthrough therapy medicine designation, approved in 2012, to expedite the development and approval of medicines that substantially improve the current standard of care (Hermosilla, 2024). Most medicines approved under the breakthrough therapy designation target oncology indications; however, therapies targeting non-oncology indications for which there were often no approved medicines or medicines that provide a significant improvement in clinical efficacy above the current standard of care have also been developed under this designation (Hermosilla, 2024).

However, the breakthrough therapy designation has also received criticism. One criticism of the breakthrough designation pathway is that it has the potential to cause confusion by labeling a medicine as a breakthrough (Herinck et al., 2022; Paquin et al., 2022). Critics point to studies that have found both caregivers and the public reporting an impression and expectation that medicines approved under the breakthrough therapy designation may be a game-changer in treating their disease or even hold potential cures (Herinck et al., 2022; Paquin et al., 2022).

A significant criticism of the breakthrough therapy designation is the characteristics of the trials used to support the approval of these medicines. While medicines approved under the breakthrough designation are required to meet the same standards as those approved under the standard approval therapy, the breakthrough medicine approval pathway allows for a timeline for approval that is often much shorter and permits testing in fewer patients (Ribeiro et al., 2020). The gold standard for the approval of medicines in the U.S. is two well-controlled, randomized, and placebo-controlled clinical trials, often involving thousands of participants (Ribeiro et al., 2020). However, trials supporting the approval of breakthrough therapy medicines often lack randomization, double blinding, the use of control groups, and often utilize surrogate endpoints as the primary study endpoints to determine efficacy (Ribeiro et al., 2020).

While critics point to the characteristics of these trials as limiting the confidence in the efficacy measures demonstrated, they also raise significant concerns about the safety of medicines developed and supported by trials with these characteristics under an expedited program like the breakthrough therapy designation (Ribeiro et al., 2020). The concern with breakthrough therapy medicines is that the characteristics of the clinical trials that support marketing authorization, including the limited sample sizes, likely result in a safety profile that is not as complete and thorough compared to medicines approved under the standard approval process (Shepshelovich et al., 2019). To support this argument, critics have pointed to the increase in postmarketing safety-related labeling changes that occur with medicines approved under expedited pathways compared to medicines approved under the standard approval process (Shepshelovich et al., 2019). Critics claim that the greater number of changes to the labeling language relating to safety in the postmarketing setting is evidence that the safety profile of these medicines is not well understood at the time of approval and, therefore, breakthrough therapy medicines may provide a greater risk to the public health (Shepshelovich et al., 2019). While studies have examined the safety of medicines approved under the accelerated approval pathway, no studies have focused on the postmarketing safety of medicines approved under the breakthrough therapy designation.

In this study, I evaluated the FAERS Database to determine whether a relationship exists between the number of concomitant medicines taken and the outcome of adverse drug reactions to drugs approved under the breakthrough therapy designation, while controlling for demographic variables. Furthermore, I examined whether there is a relationship between the therapeutic indication of breakthrough therapy medicines and the reported outcomes of the adverse events to these medicines while controlling for demographic variables. Different therapeutic indications often represent patient populations that differ in their co-morbid conditions and medical history, which has the potential to contribute to placing these patients at differing risks of experiencing an adverse reaction to medicines.

Problem Statement

The problem I addressed in this study is understanding whether medicines approved under the breakthrough therapy designation pose a greater public health risk to patients on concomitant medicines or treated for certain therapeutic indications. Critics of the breakthrough therapy designation have raised significant concerns regarding the properties of the trials used to support the marketing authorization of these medicines due to the questions regarding the thoroughness of the safety information available at the time of approval (Ribeiro et al., 2020). However, while postmarketing safety analyses have been conducted for medicines approved under other expedited pathways, an epidemiological analysis of the postmarketing safety events of medicines approved under the breakthrough therapy designation is lacking. An understanding of whether the potential risks of medicines approved under the breakthrough therapy designation to the public is warranted. This results of this study have the potential to help healthcare professionals identify patients who are at a potentially greater risk of experiencing a poor outcome in response to an adverse reaction from these medicines. Furthermore, the results from this study have the potential to inform patient education to improve the understanding of the risks these medicines may pose to their health.

Purpose of the Study

In this retrospective, cross-sectional, quantitative study, I examined whether there is a relationship between the number of concomitant medicines taken and the outcome of the reported adverse event to breakthrough therapy medicines. Certain demographic factors are expected to be associated with a higher likelihood of experiencing an adverse event and the outcome of an adverse event. This analysis controlled for the patient's age and gender. I also examined the relationship between the approved therapeutic indication of a breakthrough therapy medicine and the outcome of the reported adverse event. The outcome of a reported adverse reaction may vary across therapeutic indications due to the severity of illnesses and co-morbid conditions present. The reported demographic characteristics (gender, age), the Number of Prescription Medicines taken, and the Therapeutic Indication (infectious diseases, immunology, neurology, gastroenterology, cardiovascular, genetic/metabolic, other) are the independent variables. The Outcome of the adverse reaction is the dependent variable. The unit of analysis is the reported outcome of the adverse event (serious, not serious, hospitalization, or death).

Research Questions and Hypotheses

Research Question 1: Is there a statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024?

$H_0 1$: There is no statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

$H_1 1$: There is a statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

Research Question 2: Is there a statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024?

$H_0 2$: There is no statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

$H_1 2$: There is a statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

Conceptual Framework for the Study

The conceptual framework most applicable to this study is the pharmacovigilance framework as discussed by Brown and Babri (2019). The process of pharmacovigilance involves identifying and assessing the risks associated with medicines based on an analysis of reported adverse drug events and associated pharmacoepidemiological data (Brown & Babri, 2019). An important aspect of this framework is the collaborative engagement of the researchers, physicians, and regulators (Brown & Babri, 2019). A key aspect of engagement among these stakeholders involves the exchange of information and knowledge collected during pharmacovigilance (Brown & Babri, 2019). This study was designed to investigate and communicate an epidemiological analysis of the outcomes of adverse reactions to medicines approved under the breakthrough therapy designation to an academic, medical, and regulatory audience (Brown & Babri, 2019). Data from the use of breakthrough medicines in the postmarketing setting including reports of the outcomes of adverse reactions was analyzed to help inform regulators, caregivers, and patients of the potential risks of the medicines and to inform potential engagement interactions for patients taking concomitant medicines as well as patients prescribed the breakthrough therapy medicines to treat specific therapeutic indications (Brown and Babri, 2019). The aim of this study is to communicate the findings to prescribers and regulators in a way that ensures and improves upon the safe and effective use of these breakthrough therapy medicines (Brown & Babri, 2019). It is anticipated that the study's findings can help inform and guide additional research (Brown & Babri, 2019).

Nature of the Study

This retrospective, cross-sectional, quantitative study included a secondary analysis of the outcomes of adverse drug reactions as reported in the FAERS Database for medicines approved under the breakthrough therapy designation from 2012 to 2024. This quantitative analysis was designed to determine whether an association existed between the number of concomitant medicines and the outcomes of reported adverse events, while considering the patient demographic variables of age and gender. In addition, this analysis examined whether an association existed between the therapeutic indication of breakthrough therapy medicines and the reported outcomes of adverse drug events, while considering patient demographic variables of age and gender. This cross-sectional design examined whether a statistical relationship existed among and across the independent variables identified (Beau-Lejdstrom et al., 2019).

Definitions

According to the WHO (2012), the following is a brief listing of key terms and phrases utilized in this study that may be considered ambiguous, controversial, or that are operational terms:

Adverse drug reaction (ADR): A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. It is characterized by the suspicion of a causal relationship between the drug and the occurrence.

Adverse Drug Reaction (ADR) Case Report: A notification relating to a patient with an adverse event (or laboratory test abnormality) suspected to be induced by a medicine.

Adverse event: Any untoward medical occurrence that may present during treatment with a pharmaceutical product but does not necessarily have a causal relationship with this treatment.

Benefit-risk analysis: Examination of the favorable (beneficial) and unfavorable results (risk) of undertaking a specific course of action.

Effectiveness/risk: The balance between the rate of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.

Postmarketing setting: The state when a drug is generally available on the market.

Regulatory authority: The legal authority in any country with the responsibility of regulating all matters relating to medicines.

Serious adverse event or reaction: A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death;
- requires inpatient hospitalization or prolongation of an existing hospitalization;
- results in persistent or significant disability or incapacity;
- is life-threatening;
- results in a congenital anomaly or birth defect.

Spontaneous reporting: System whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority.

Unexpected adverse reaction: An adverse reaction, the nature of severity of which is not consistent with domestic labeling or market authorization or is not expected from the characteristics of the drug.

Assumptions

For this study, it was assumed that the data collection and analysis from the FAERS Database over the specified timeframe of 2012 to 2024 was adequate to conduct this study. In addition, it was assumed that the FAERS Database was sufficient for this study to provide the appropriate amount of data. In terms of data quality, this study assumed that all the reports on the FAERS Database from patients or caregivers were similar in content and accuracy to those of reports made by physicians.

Scope and Delimitations

This quantitative study examined whether a significant relationship existed between the number of concomitant medicines and the outcome of the reported adverse events approved under the breakthrough therapy designation. This study also examined whether a significant relationship existed between the approved therapeutic indication and the reported outcomes of the adverse events for these breakthrough medicines. While previous studies have investigated the safety of medicines approved under other expedited approval pathways, a study examining the outcomes of the reported adverse events to medicines approved under the breakthrough therapy designation is lacking. This identified gap in the literature is the focus of this study.

This study is limited to the adverse reactions reported through the FAERS Database. Due to the inherent safety issues associated with many chemotherapeutic medications, oncology medicines have been excluded from this analysis. In addition, since this study utilized secondary data, no subjects were recruited, especially any subjects representing a vulnerable population, including, but not limited to: minors;

students; residents of nursing homes; mentally impaired individuals; individuals with disabilities; emotionally impaired or disabled individuals; immigrants; victims of violent crime or trauma; military personnel; and any other individuals who are not able to protect their rights or interests (Walden University, n.d.).

Limitations

Anticipated limitations of working with secondary data should be acknowledged. The reported events in the FAERS Database are unlikely to represent all adverse events experienced in the postmarketing setting. Furthermore, the accuracy of the data reported to the FAERS Database is unknown. The potential for duplicate reporting is also possible, especially when a caregiver and a patient or family member potentially report the same event. Therefore, it is impossible to reliably calculate an event's incidence rate or risk from data obtained from the FAERS Database (FDA, 2018b).

The quantitative design of this study prevents obtaining any subjective reporting or direct patient experience of adverse reactions. Additionally, recall bias, information bias, and misclassification can affect the validity of cross-sectional data (Gualano et al., 2015). The use of secondary data also limits the type and amount of information available for analysis (Gualano et al., 2015). Cross-sectional study designs also prevent the determination of a causal relationship between the medicine and the adverse reaction; therefore, the report needs to be trusted as it is captured in the database (Frankfort-Nachmias, 2014). Finally, it is essential to remember that any relationship found does not imply any causation between the variables studied (Frankfort-Nachmias, 2014).

In an effort to overcome some of the limitations of this study's design, statistical analyses and summary representations of the results can address these limitations (Frankfort-Nachmias, 2014). With the data properly characterized and represented, the reader can draw their own contrasts and conclusions from the observations (Frankfort-Nachmias, 2014).

Significance

To date, there has been no analysis of the outcomes of adverse events experienced with medicines approved under the breakthrough therapy designation. I, therefore, chose to study the relationship between the number of concurrently prescribed medicines and the outcome of reported adverse events, while controlling for demographic variables. Additionally, I examined whether a relationship existed between the therapeutic indication for which the breakthrough medicine was approved and the reported outcomes of the adverse events, while controlling for demographic variables. Taken together, these results can help to identify patient populations who may be at a greater risk of experiencing a serious outcome from an adverse event associated with a medicine approved under the breakthrough therapy designation. This research study fills a gap in the literature by providing caregivers and patients with information that may help reduce the risk of a poor outcome to an adverse event and therefore help protect the public health. This study's findings may enable caregivers and patients to make more informed decisions about whether a medicine's risk-to-benefit ratio is acceptable given their specific circumstances. This study's findings also provide a deeper understanding of the overall risk associated with medicines approved under the breakthrough therapy designation.

By utilizing data from the FAERS Database, reports from caregivers and patients are integrated, providing potentially greater signal detection and, therefore, a potentially more comprehensive study. The data from this study could inform potential future clinical studies aimed at mitigating risk in the identified patient populations, as well as help further identify risk factors associated with the use of concomitant medicines or a specific patient population treated for a given therapeutic indication. That is, the results of this study have implications for positive social change by informing caregivers and patients about the safety of medicines approved under the breakthrough therapy designation, which has the potential to lead to improvements in future pharmacovigilance systems and processes used to study these medicines. Overall, there is potential for patients to receive improved care by enhancing the safety of medicines approved under the breakthrough therapy designation, thereby potentially enhancing the public health of patients who receive these medicines.

Summary

In Chapter 2, a literature review on breakthrough therapy medicines and the epidemiology of adverse reactions in the United States is presented. The gap in the existing literature is identified, and the theoretical framework most applicable to this study is presented and discussed. In Chapter 3, a review of the methods used to conduct a secondary analysis of the data obtained from the FAERS Database is presented. In Chapter 4, the results of the study are presented. Finally, in Chapter 5, the results are discussed, study limitations are identified, recommendations are made for future research, and the implications for social change are reviewed.

Chapter 2: Literature Review

Introduction

Drug-related adverse events have the potential to significantly impact patient safety and, therefore, represent a public health risk that requires consistent monitoring and study through pharmacovigilance. For example, in the United States, emergency room visits due to drug-related adverse events from 2017 to 2019 occurred at a rate of 6.1 per 1,000 annually; 38% of these visits were severe enough to require hospitalization (Budnitz et al., 2022). While drug-related adverse events can result from patients misusing or abusing medication, many of the adverse events occur due to the use of medication for its intended therapeutic benefit (Budnitz et al., 2022). In the United States, the FDA is responsible for evaluating the safety and effectiveness of medicines prior to granting marketing authorization (Dhruva et al., 2022). To aid in the study of the safety of medications in the postmarketing setting, the FDA, under Title IX, § 921 of the FDA Amendments Act of 2007, is required to implement an adverse events database (FAERS) to monitor the incidence of drug-related adverse events (Beninger & Murray, 2021). Physicians, caregivers, and patients have the ability to post information regarding an adverse event to the FAERS Database, including the seriousness of the event, the outcome of the adverse event, as well as basic demographic information about the patient experiencing the event (Beninger & Murray, 2021).

Drug development is a costly and time-consuming endeavor, and there remains a significant unmet need for many diseases with a high rate of morbidity and mortality, many of which are considered rare (Hermosilla, 2024). In an effort to encourage the development of medicines that treat a serious or life-threatening condition or that provide a substantial improvement over currently approved medicines, Congress created the breakthrough therapy designation (Hermosilla, 2024). However, expedited pathways such as the breakthrough therapy designation have received significant criticisms. A principal criticism of the breakthrough therapy designation is that marketing authorization of these medicines often relies on fewer trials (Ribeiro et al., 2020). In addition, critics are concerned that these pivotal trials often enroll a smaller number of patients (Ribeiro et al., 2020). Furthermore, the clinical trials for breakthrough therapy medicines often lack design characteristics consistent with the gold standard of clinical trials, including a lack of randomization, double blinding, a reliance on surrogate markers as endpoints, and often the lack of a control group (Ribeiro et al., 2020). These criticisms of the breakthrough therapy designation all identify the concern of whether there is a thorough understanding of the risks associated with these medicines at the time of approval (Shepshelovich et al., 2019).

In the remainder of this chapter, I first outline the literature search strategy used for this study. I then explain the theoretical foundation, based on the conceptual framework of pharmacovigilance, which guides the assessment of post-marketing safety in diverse patient populations (Kugener et al., 2021). A brief history of food and drug law follows, with an emphasis on how FDA pharmacovigilance practices and regulatory actions aim to ensure the safety and efficacy of medicine. I summarize expedited pathways and their requirements and conclude by reviewing the main benefits and criticisms of the breakthrough therapy designation. This study specifically aimed to evaluate the criticism that the safety risks of breakthrough therapy medicines is not adequately understood at the time of approval. Determining whether breakthrough therapy medicines are safe for their intended patient populations is a key public health issue addressed by this research.

This study addressed two primary objectives. First, I examined whether there is an association between the number of concomitant medicines and the outcomes of reported adverse events for medicines approved under the breakthrough therapy designation, controlling for age and gender. Second, I evaluated whether the therapeutic indication of breakthrough therapy medicines is associated with the outcomes of reported adverse events, while controlling for age and gender. The findings from this study aimed to identify patients who may be at a higher risk of adverse events associated with these medicines and to inform future pharmacovigilance efforts for breakthrough therapy-designated drugs.

Literature Search Strategy

The MEDLINE, Embase, and ProQuest databases were reviewed. Drug-related adverse events and safety reporting for breakthrough therapy designation were specifically searched. Key search terms included: *adverse drug reactions, drug-related adverse events, FDA, clinical trials, breakthrough therapy designation,* and *expedited approval pathways*. The date range of reviewed published literature falls from 2019 to 2024, inclusive.

Due to the limited number of relevant articles on breakthrough therapy medicines, the search was broadened to include all FDA expedited pathways, yielding a small number of additional relevant articles. The results from these literature searches highlighted the lack of publications in this area. Similar dissertations guided the search, but they frequently led to manuscripts published more than 5 years ago and did not yield additional information specific to the breakthrough therapy designation.

Conceptual Framework

The conceptual framework for this study is the pharmacovigilance framework. Pharmacovigilance is a crucial process in drug development that ensures the safety of medicines. A key part of pharmacovigilance is the monitoring and studying of the safety profiles of medicines after marketing approval. A key aspect of the investigation of the relationship between patient demographics and adverse events to identify those patients at an increased risk for experiencing an adverse event (Kugener et al., 2021). Retrospective studies are a standard method utilized in pharmacovigilance to examine drug-related adverse events in the postmarketing setting, consistent with this study (Kugener et al., 2021). Brown and Babri (2019) proposed that the pharmacovigilance framework can be strengthened through engagement from researchers, stakeholders, and regulators. The results of this study address the interests of researchers developing breakthrough therapy medicines, stakeholders who depend on these medicines, and regulators who aim to protect public health by ensuring that medicines approved under the breakthrough therapy designation are used safely.

The first step in the conceptual framework of pharmacovigilance is to define the depth of engagement (Brown & Babri, 2019). This retrospective, cross-sectional, quantitative study analyzed the relationship between the number of concomitant medicines and outcomes of reported adverse events to breakthrough therapy medicines. This study also analyzed the relationship between the therapeutic indication and outcomes of the reported adverse events. Since this is the first study to examine adverse event outcomes in medicines approved under the breakthrough therapy designation, the engagement level is relatively shallow. The engagement level of this study focused on a one-way form of gathering and communicating information (Brown & Babri, 2019). Study findings from this initial level of engagement may warrant deeper engagement and help guide future stakeholder interactions (Brown & Babri, 2019). However, deep engagement is not required for the outcome to have great depth and influence (Brown & Babri, 2019). This study's level of information engagement involved collecting adverse reaction reports (Brown & Babri, 2019). For this study, reports of adverse reaction outcomes and patient demographic characteristics were collected from the FAERS Database.

Determining the outcome of this information engagement includes considering the depth of knowledge obtained (Brown & Babri, 2019). It also involves identifying the target audience and the breadth of engagement for these findings (Brown & Babri, 2019). The outcome of this engagement is this dissertation report. Findings are reported to academics, clinicians, and regulators. The aim is to communicate results and implications as clearly and concisely as possible to ensure the greatest impact. Finally, the outcome is to inform future studies on the safety of breakthrough therapy medicines and to identify therapeutic indications that require further research to understand their potential risk to the public health.

History of Food and Drug Law in the United States

Throughout the history of drug regulation in the United States, significant threats to public health from dangerous and ineffective medicines are what led to the prompting of the passage of acts to improve and ensure the safety and efficacy of medicine. Prior to 1800, investigations into the efficacy of potential medicines were not conducted in a controlled fashion and instead relied on observation and assumption (Darrow, 2020). The beginning of drug regulation based on controlled trials in the United States can be traced to the Vaccine Act of 1813, which was enacted in direct response to a small trial conducted in 1800 by Harvard University (Darrow, 2020). This trial was designed to test the efficacy of a new smallpox vaccine (Termini, 2022). Because the data from this trial led many physicians to adopt the vaccine, demand increased, resulting in the production of counterfeit vaccines that often lacked efficacy and posed a risk to the public health (Termini, 2022). To address this risk to public health, President Madison signed the Vaccine Act in 1813, ensuring access to efficacious smallpox vaccines.

Ineffective medicines given to troops in the Mexican American War drove the Drug Import Act of 1848 (Termini, 2022). The Act required the Secretary of the Treasury to appoint specialists to examine the quality and purity of imported medicines (Termini, 2022). The law was effective in reducing the importation of adulterated medicines. However, an unintentional consequence of the law was an increase in domestically produced adulterated medicines, which continued to pose a threat to public health (Termini, 2022).

The Biological Products Act of 1902 followed a New Jersey tetanus outbreak caused by a contaminated smallpox vaccine (Termini, 2022). The act was crucial for enhancing medical regulation and public safety. It prohibited interstate shipment of biological products intended to treat or cure diseases unless the products were labeled truthfully and made by a licensed establishment (Termini, 2022). For the first time, a premarket safety review of biological products was required. Civil and criminal penalties could be imposed for violations (Termini, 2022).

The FDA originated as the Chemical Division of the US Department of Agriculture (USDA) in 1906, created in response to two major incidents of food and drug adulteration that threatened public health. Although a bill to form such an agency was first introduced in Congress in 1858 after a fatal incident in England involving arsenic in throat lozenges, it was not until Upton Sinclair's novel The Jungle brought attention to poor conditions in the meat industry that the Federal Food and Drugs Act passed in 1906 (Termini, 2022). The act officially defined the misbranding and adulteration of medicines, granted the FDA the power to examine food and drug products, and gave the Department of Justice the authority to enforce these regulations (Termini, 2022).

In 1938, the Food and Drug Cosmetic Act further advanced drug safety. The Act required drug developers to demonstrate that their medicines were safe for their intended uses. It was a response to the "Elixir Sulfanilamide," which was contaminated with diethylene glycol and killed 120 people (Termini, 2022). The Act mandated safety tests for new drugs and further protected public health (Termini, 2022).

Efficacy requirements for drugs were introduced after the 1962 amendments to the Food and Drug Cosmetic Act. For the first time, drugs needed "adequate" and "well-controlled" trials to show safety and efficacy (Termini, 2022). The FDA could now regulate new medicines before marketing approval. The 1962 amendments also established Good Manufacturing Practices to ensure that medicines met quality standards, provided consistent dosing, and were free of contaminants (Termini, 2022).

Expedited Approval Pathways in the United States

The FDA aims to ensure that drugs are both safe and effective for their intended use, while also accelerating the approval of medicines addressing unmet medical needs (Ch et al., 2021). To address patient and caregiver needs and improve public health, the U.S. Congress has enabled the FDA to establish several expedited approval pathways (Ch et al., 2021). These pathways introduce flexibility in drug development to increase speed, but critics argue that this sometimes results in approvals based on less comprehensive testing compared to the standard approval pathway (Ch et al., 2021). After expedited approvals, additional safety information is typically gathered postmarketing to confirm a medicine's safety in a broader population (Ch et al., 2021). Some argue that expedited pathways lead to insufficient understanding of the safety profile of drugs, and therefore pose an increased safety risk, as evidenced by a higher rate of postmarketing safety labeling changes (Ch et al., 2021).

Fast Track Designation

The FDA introduced the fast track designation in 1997 to expedite the development of drugs that treat a serious condition and fulfill unmet medical needs (Cox et al., 2020). Fast track designation can also be awarded to a drug in which available therapies are available but in conditions in which the drug provides an improvement in the efficacy or safety, an improvement in the diagnosis of a disease, a decrease in current toxicity, or that addresses an anticipated public health need (Cox et al., 2020). Benefits to the fast track designation includes more frequent meetings with the FDA, more frequent communication with the FDA, and the opportunity for a rolling review, a process in which a company can submit sections of an approval package to the FDA for review instead of waiting for the preparation of a complete submission (Cox et al., 2020). While the fast track designation does not guarantee a shorter review period, drugs that receive this designation are considered for priority review when submitted for marketing authorization, which could result in a shorter review period (Cox et al., 2020).

Accelerated Approval

The accelerated approval pathway was introduced in 1992 in an effort to help make therapies still under development available to patients diagnosed with AIDS (Cox et al., 2020). To qualify for accelerated approval, a drug must treat a serious condition, provide a meaningful advantage over approved therapies for the same indication, and demonstrate efficacy on a surrogate endpoint that will predict a clinical benefit (Cox et al., 2020). While drugs granted accelerated approval demonstrate efficacy on a surrogate endpoint, they must meet the same safety and efficacy standards as medicines approved under the standard approval pathway (Cox et al., 2020). Because the approval of drugs under the accelerated approval pathway relies on measuring a surrogate endpoint, they must complete postmarketing trials to verify their safety and efficacy on an established clinical endpoint (Cox et al., 2020). Drugs approved under the accelerated approval pathway include a statement in their labeling that discloses the uncertainty regarding their clinical benefits and any limitations to their use (Cox et al., 2020).

Breakthrough Therapy Designation

Drugs under development can qualify for breakthrough therapy designation if they either alone or in combination with another drug treat a serious or life-threatening condition, and preliminary clinical data indicate that there is substantial improvement in efficacy, as demonstrated in one or more relevant endpoints, compared to existing therapy (Cox et al., 2020). Often, drugs that achieve breakthrough therapy designation treat a life-threatening condition without an approved treatment (Cox et al., 2020). There is also an opportunity for a drug to receive breakthrough therapy designation if there is evidence that it treats the underlying physiological condition or reverses or inhibits the progression of a disease, where the standard of care is limited to treating the symptoms of the disease (Cox et al., 2020). In addition to a rolling review, drugs that receive breakthrough therapy designation also qualify for priority review, which can reduce the review period substantially (Cox et al., 2020). If, at any time during development, clinical data indicates the drug no longer meets these criteria, the FDA can rescind this designation.

Priority Review

The standard review period for drug approval in the US takes at least twelve months (Cox et al., 2020). The review period can be shortened to six months if a drug qualifies for a priority review (Cox et al., 2020). Priority Review is granted for drugs intended to treat a serious condition and will provide a significant improvement in the safety and efficacy profile compared to the currently approved standard of care medicines (Cox et al., 2020). To meet the criteria for demonstrating that a drug significantly improves the standard of care, the medicine must demonstrate increased efficacy, elimination or reduction in an adverse reaction, have an improved safety profile, or demonstrate efficacy within a new subpopulation, or improve compliance in the current population compared to the standard of care (Cox et al., 2020). A sponsor can request that a drug receive a priority review designation at the time of submission for marketing approval (Cox et al., 2020). Receiving the priority review designation does not guarantee a medicine's approval or approval within a six-month time frame, as deficiencies identified during the review process can result in additional delays or requests for more data (Cox et al., 2020).

Benefits of Breakthrough Therapy Designation

Breakthrough therapy designation is designed to benefit both the developer of the drug and the patients. Sponsors of drugs that receive breakthrough designation benefit from more frequent meetings with the FDA to aid in developing the drug, including inputs on clinical trial design (Cox et al., 2020). Senior leadership within the FDA often review applications for breakthrough therapy designation (Cox et al., 2020). Drugs granted breakthrough designation have also benefited from significantly shorter development times, averaging approximately 4.9 years (Hermosilla, 2024). The review period for breakthrough designations is also significantly shorter, averaging 6.9 months (Hermosilla, 2024). Shorter development and review times benefit both the developer and the patients as these medicines treat serious and life-threatening indications that often lack effective treatments (Hermosilla, 2024). Current data indicate that patients are benefiting from medicines that received breakthrough designation, as they are more likely to help meet the program's goals of substantially improving the treatment of serious diseases and enhancing patient quality of life (Hermosilla, 2024).

Criticisms of Breakthrough Therapy Designation

While drugs approved under the breakthrough designation meet the criteria of providing a substantial improvement over existing therapies or treating a serious disease, they have also received criticism that focuses on their potential for increased safety risks due to their substantially shortened development timelines and smaller trials supporting approval. The leading criticism of drugs approved under the breakthrough therapy designation is that a single pivotal clinical trial is often the only source of safety and efficacy data for the approval of these medicines (Hermosilla, 2024). In addition, trials supporting approval under the breakthrough therapy designation also lack many of the properties of trials that support medicines approved under the standard approval pathway, which some critics consider important in identifying a drug's safety risks. For example, drugs approved under the breakthrough therapy designation often lack randomization, double-blinding, and the use of a control group (Hermsosilla, 2024). Taken together, the concern is that the shorter clinical development timelines and smaller clinical trials pose the potential for inadequate safety exposure and a decreased ability to identify the risk for significant but rare adverse event in the patient populations (Hermosilla, 2024).

Critics point to the significantly higher rate of postmarketing safety labeling changes for drugs approved under the breakthrough designation, compared to medicines approved under the standard approval therapy, as evidence that there is a lack of a thorough understanding of the safety risks of these medicines at the time of approval (Shepshelovich et al., 2019). Consistent with this finding, drugs approved under expedited approval pathways, which were developed using trials that lack randomization and have fewer participants, are also associated with a higher rate of postmarketing safety labeling changes (Shepshelovich et al., 2019). However, what is lacking is an investigation of whether there is an increase in safety risks associated with drugs approved under the breakthrough therapy designation. A potential explanation for the lack of studies examining the safety of medicines approved under the breakthrough therapy designation is that it is the most recent expedited pathway implemented by the FDA.

Epidemiology of Adverse Drug Events

Adverse events to medicines have the potential to negatively impact public health, with some population groups at a greater risk of experiencing harm. For example, patients over sixty-five years of age experience a greater number of adverse events that require hospitalization compared to younger patients (Budnitz et al., 2022). This is concerning given that patients over 65 years of age represent the most rapidly growing portion of the patient population (Hadia et al., 2022). Patients over 65 years of age are also more likely to suffer from multiple diseases and, therefore, are more likely to take multiple medicines to control their diseases or treat their symptoms (Hadia et al., 2022).

It is estimated that in the United States, over 90% of patients over 65 years of age are on at least one medication, with 10 to 25% of these experiencing an adverse event (Hadia et al., 2022). These elderly patients are twice as likely to require a hospital visit for their adverse event and seven times more likely to require hospitalization to resolve the event (Hadia et al., 2022). Hospital stays for these patients averaged 11 to 25 days (Hadia et al., 2022). Therefore, while breakthrough medicines may provide a significant advancement in the treatment of diseases affecting the elderly, this population may be at a greater risk of a negative impact on their public health due to the increased likelihood of using concomitant medicines, as well as the higher prevalence of co-morbid conditions in this population.

Gender differences in weight, height, body surface area, and volume are also believed to contribute to differences in the incidence of adverse events (Sportiello & Capuano, 2024). Studies have also demonstrated that women have been traditionally underrepresented in clinical trials, resulting in a limited understanding of the risks of medicines to women at the time of their approval (Sportiello & Capuano, 2024). In addition, certain classes of medicines are prescribed more often in women compared to men (Sportiello & Capuano, 2024). Women were found to be at a greater risk of experiencing adverse events to cancer therapies, including immunotherapies, targeted therapies, and chemotherapies (Sportiello & Capuano, 2024). A contributing factor to the difference in the risk of experiencing an adverse event between genders is the presence of differences in pharmacogenomics between men and women, which can result in variations in metabolism rates and pharmacokinetics of medicines (Sportiello &

Capuano, 2024). Taken together, these differences between the genders can contribute to women being at a 1.5 to 1.7 greater risk of experiencing an adverse event compared to men, with women more likely to have an outcome resulting in stopping treatment of a medicine due to an adverse event (Sportiello & Capuano, 2024). However, men are more likely to experience a serious or fatal adverse outcome to an adverse event to medicine, especially immunomodulatory agents (Sportiello & Capuano, 2024). The differences in pharmacogenomics, gender representation in therapeutic areas, and disparities in outcomes between genders, coupled with the underrepresentation of women in clinical trials, underscore the importance of considering gender as a variable in examining the outcomes of adverse drug reactions to medicines approved under the breakthrough therapy designation.

While it is often necessary to treat an individual with multiple medicines to control a disease or to use multiple medicines to address the presence of multiple health issues, the use of multiple medicines does lead to an increased risk of a patient experiencing an adverse drug event in patients across age groups (Delara et al., 2022). The risk of multiple medicines to a patient in terms of negative outcomes to adverse drug events also increases with the number of medicines the patient is taking (Delara et al., 2022). Given the known risks of taking multiple medicines across age groups, as well as the risk of experiencing an adverse event between genders, it is important when investigating outcomes of adverse events to control for age and gender.

Summary and Conclusions

The findings from the literature review indicate there is a substantial concern that drugs approved under the breakthrough therapy designation may pose a greater safety risk to the public health. Researchers identify the smaller clinical trials supporting marketing authorization, which often lack the characteristics of trials approved under the standard pathway, as the key concern that is likely contributing to a lack of a thorough understanding of the risks associated with these medicines (Hermosilla, 2024; Shepshelovich et al., 2019). Whether the rate of postmarketing labeling changes in drugs approved under the breakthrough therapy designation translates to an increased risk for certain patient populations has yet to be examined, likely due to the relatively recent implementation of this expedited pathway designation (Shepshelovich et al., 2019).

A greater understanding of the adverse events to drugs approved by the breakthrough therapy designation is essential. The process of pharmacovigilance allows a postmarketing analysis of the use of medicines in a more diverse patient population, allowing for a better understanding of whether key risks, such as the number of concomitant medicines, or therapeutic area, are associated with a greater risk of experiencing a poor outcome from an adverse event. Hospitalizations due to adverse drug events have a negative impact on public health, with the risk of requiring hospitalization in response to an adverse event differing across genders, medical conditions, and the number of concomitant medicines (Budnitz et al., 2022).

However, to date, there have been no studies examining adverse event outcomes of medicines approved under the breakthrough therapy designation. Therefore, in this study I examined whether a relationship existed between the number of concomitant medicines taken and the reported outcome of the adverse event, while controlling for age and gender, as reported in the FAERS Database, in an effort to fill this gap in the literature. Additionally, I investigated whether a relationship existed between the approved therapeutic indication and the reported outcome of the adverse event to breakthrough therapy medicines, while controlling for age and gender. In Chapter 3, I provide a description of the research methodology utilized to perform a secondary analysis of the data contained in the FAERS Database. In Chapter 4, I provide the results of this quantitative study. Lastly, in Chapter 5, I provide a discussion of these results, identifying and acknowledging the limitations of this study, provide recommendations for future research in this area, and discuss the implications of this research for social change.

Chapter 3: Research Method

Introduction

In the previous chapter, I presented a review of the limited literature available that examined the safety properties of the expedited approval pathways implemented by the FDA, particularly the breakthrough therapy designation. Additionally, I identified the risks to public health resulting from adverse events to medicines and the demographic variables associated with an increased risk. I also focused on identifying the criticisms of the breakthrough therapy designation that previous researchers have identified as having the potential to contribute to an elevated risk to the public health. In this study, I assessed whether an association existed between the number of concomitant prescribed medicines and the reported outcomes of adverse events to medicines approved under the breakthrough therapy designation. I also examined whether an association existed between the therapeutic indication for these approved medicines and the reported outcome of the adverse events.

The independent variables for this study were the number of concomitant medicines taken, and the therapeutic area for which the medicine is approved. The dependent variable was the reported outcome of the adverse events. This chapter describes the statistical methodology that was employed in this study. The design of this study, data collection, and analysis, as well as potential threats to validity, are also discussed in this chapter.

Research Design and Rationale

The proposed study is a cross-sectional secondary analysis of the outcomes of adverse events reported in the FAERS Database. Studies utilizing a cross-sectional analysis of reported adverse events to medicines in the post-marketing setting have yielded results that aid in the identification of patient populations who have a greater risk for experiencing adverse events similar to those results identified in the randomized, controlled trials used to support marketing authorization of medicines (Beau-Lejdstrom et al., 2019). This cross-sectional designed study examined the relationship between the number of concomitant medicines and the outcome of the reported adverse events. Additionally, the relationship between the therapeutic area of the medicines and the outcome of the reported adverse events was also examined. The independent variables for this study were the number of medicines taken and the therapeutic indication; the reported outcome of the adverse events was the dependent variable.

This study utilized quantitative methods to determine whether a relationship existed between the independent and dependent variables. A multinomial logistic regression analysis was conducted to determine if an association existed between the number of concomitant prescribed medicines and the reported outcome of adverse events, as well as to investigate whether an association existed between the therapeutic indications of the breakthrough therapy medicines and the reported outcome of adverse events. The statistical significance of the association between the independent variables and the outcome of the adverse reaction is indicated by a *p*-value of less than 0.05.

Methodology

Population

The target population for this study were patients and caregivers who submitted adverse event reports to the FAERS Database. Patients receiving breakthrough therapy medicines approved for oncology indications were excluded from this analysis. The FAERS Database serves as a resource that the FDA, academics, and drug companies can use to monitor new risks and safety information regarding approved drugs as they are used in the postmarketing setting (Beninger & Murray, 2021). The Database was established to enhance the postmarketing safety monitoring of medicines as they are administered to a more diverse and extensive patient population (Beninger & Murray, 2021). The FDA has used the information obtained from the FAERS Database to update safety labeling language, identify potential drug interactions, and protect the public health by ensuring the safe use of these medicines (Beninger & Murray, 2021). While potential action by the FDA typically occurs following the monitoring of multiple safety reports, a single safety report may be sufficient to launch an FDA investigation (Beninger & Murray, 2021).

Sampling and Sampling Procedures

The FAERS Database is an online repository where clinicians or patients can submit adverse events to all FDA-approved medicines (Beninger & Murray, 2021). A list of medicines approved under the breakthrough therapy designation was available on the FDA Website (FDA, 2024). The reported information for each medicine in FAERS was extracted from the FAERS website as an Excel spreadsheet for each approved breakthrough therapy medicine product. This analysis included all non-oncology medicines approved under the breakthrough therapy designation since its implementation in 2012 through 2024 inclusive.

A well-powered study samples an adequate number of responses to detect significance given the predefined power and significance level. However, a multinomial logistic regression analysis does not have a true power analysis calculation (de Jong et al., 2019). The number of predictor variables in the study is an important consideration when determining the ideal sample size for a multinomial logistic regression (de Jong et al., 2019). The minimum sample size for conducting a multinomial logistic regression is 10 samples per variable, with predictive performance improving up to 50 samples per variable (de Jong et al., 2019).

Procedures for Data Collection

This study examined the reported outcomes of adverse events reported by patients and caregivers to the FDA's FAERS Database. The latest data files available were extracted for analysis. Data for this experiment were collected from the FAERS Database following approval by the Institutional Review Board (IRB) on 30 January 2025. The data collected contained the adverse event reports from the period 01 April 2008 through 03 September 2024 based on the reported date of the adverse event. The file formats are available in both ASCII and SGML. The ASCII data files are $ delimited (FDA, 2018a). The SGML files conform to ICH guidelines (FDA, 2018a). The variables included in the data files were as follows: demographic information, ID number, drug information, reported event, patient outcome following the event, source of the report, and information on the file itself, contained in a "README" file (FDA, 2018a). No personal identification is included in the information for the adverse reaction event (FDA, 2018a).

Instrumentation and Operationalization of Constructs

Adverse events were coded consistently with how they are reported in the FAERS Database. The codes for the outcomes of the adverse reactions were: H = Hospitalized; OO = Other Outcomes; CA = Congenital Anomaly; D = Died; DS = Disabled; LT = Life Threatening; NS = Non-Serious; RI = Required Intervention. Patient age was coded as: 1 = 18 – 25 years, 2 = 26 – 30 years, 3 = 31 – 35 years, 4 = 36 – 40 years, 5 = 41 – 45 years, 6 = 46 – 50 years, 7 = 51 – 55 years, 8 = 56 – 60 years, 9 = 61 – 65 years, 10 = 66 – 70 years, 11 = 71 – 75 years, 12 = 76 – 80 years, 13 = 81 years or more, 14 = not specified. Subject gender was coded as: 1 = female; 2 = male; 3 = not specified. The number of concomitant medicines the subject was taking was coded continuously. The eight different therapeutic indications for this study were coded as follows: Autoimmune (AI), Cardiovascular (CV), Endocrine (EN), Gastrointestinal (GI), Infectious (I), Neurological (NS), Rare Diseases (RD), Respiratory (RP), or Other (O).

Data Analysis Plan

In this study, I analyzed secondary data on reports of the outcomes of adverse events to drugs approved under the breakthrough therapy designation obtained from the FDA's FAERS Database. The data contained the adverse event reports for all drugs approved under the breakthrough therapy designation pathway since its inception in 2012. A total of 394,706 adverse events were analyzed. Adverse events experienced by patients taking a medicine approved under the breakthrough therapy designation were analyzed to determine if a relationship existed between the number of concomitant medicines and the reported outcomes of adverse events experienced. The relationship between the approved therapeutic indication and the reported outcomes of the adverse event was also examined. Statistical relationships were determined utilizing statistical software (SPSS v.27).

Prior to conducting the secondary analysis, approval from the IRB was obtained (01-30-25-0726704). Once approved, I extracted adverse reactions for breakthrough therapy medicines from the FDA's FAERS Database (February, 2025).

The following research questions are to be addressed:

Research Question 1: Is there a statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024?

$H_0 1$: There is no statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

$H_1 1$: There is a statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

Research Question 2: Is there a statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024?

> $H_0 2$: There is no statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.
>
> $H_1 2$: There is a statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

The primary objective of this study was to investigate whether a relationship existed between the number of concomitant medicines and the outcome of the reported adverse event, while controlling for patient age and gender. Data from the FAERS Database for breakthrough therapy medicines approved between 2012 and 2024 were examined for patient age, gender, number of concomitant medicines, and the outcome of the reported adverse event. Breakthrough therapies approved for oncology indications were excluded from this analysis, as well as any patients receiving oncology medications concurrently. The second goal of this study was to determine if there is an association between the therapeutic indication of the approved breakthrough medicine and the outcome of the reported adverse event while controlling for patient age and gender. The independent variables were the number of concomitant medicines, patient age, and gender. Patient age is coded as: 1 = 18 – 25 years, 2 = 26 – 30 years, 3 = 31 – 35 years, 4 = 36 – 40 years, 5 = 41 – 45 years, 6 = 46 – 50 years, 7 = 51 – 55 years, 8 = 56 – 60 years, 9 = 61 – 65 years, 10 = 66 – 70 years, 11 = 71 – 75 years, 12 = 76 – 80 years, 13 = 81 years or more, or 14 = not specified. Gender is coded as: 1 = female, 2 = male, or 3 = not specified. The eight different levels of the outcome variable are: Hospitalized (H), Other Outcomes (OO), Congenital Anomaly (CA), Died (D), Disabled (DS), Life-Threatening (LT), Non-Serious (NS), and Required Intervention (RI). The number of medicines the patient was taking was coded continuously. Therapeutic indications are coded as follows: Autoimmune (AI), Cardiovascular (CV), Endocrine (EN), Gastrointestinal (GI), Infectious (I), Neurological (NS), Rare Diseases (RD), Respiratory (RP), or Other (O). Statistical software (SPSS v.27) was utilized to manage the data and perform the statistical analysis. A multinomial logistic regression analysis was performed to determine if a statistically significant association existed for both research questions posed.

This study utilized a quantitative method. A multinomial logistic regression was the most appropriate statistical method to determine the relationship between a nominal or continuous independent variable and a nominal dependent variable. The statistical significance of the association between the independent variable and the reported outcome of the adverse event is demonstrated by a p-value of less than 0.05. The multinomial logistic regression assumes that the observations are independent and that the dependent variable has categories that are mutually exclusive and exhaustive of one another (Laerd, n.d.). The observations in FAERS represent reports for individual patients, and while both patients and physicians can report adverse events, it is assumed that the risk of this occurring is low. The categories for the dependent variable represent exhaustive outcomes. The multinomial logistic regression also assumes that there is no multicollinearity among the independent variables (Laerd, n.d.). Multicollinearity occurs when two or more independent variables are highly correlated (Laerd, nd). Multicollinearity in SPSS is determined by examining the Variance Inflation Factors (Laerd, nd). It is also assumed a linear relationship exists between continuous independent variables and the logit-transformed value of the dependent variable (Laerd, n.d.). The final assumption of this analysis is that there are no outliers in the data (Laeard, nd). The linear relationship between the continuous independent variables and the logit-transformed dependent variable, as well as the presence of any statistical outliers, is also determined in SPSS (Laerd, n.d.).

After conducting bivariate analyses, the data are presented in tables. Table format provides the most concise and precise representation of the data. All results that relate to the hypotheses are noted. The results are summarized without assuming the implications of the effects or making any speculations.

The primary research question for this study was whether there is a relationship between the number of concurrent medicines taken and the reported outcome of adverse events, while controlling for patient age and gender. In addition, this study examined whether there was an association between the approved therapeutic indication for breakthrough medicines and the reported outcome of the adverse event while controlling for patient age and gender.

Threats to Validity

Utilizing secondary data to examine an association between an outcome and an exposure posed some inherent risks to the validity of the analysis (Cox et al., 2009). It should be noted that the level of control over data collection is less thorough and rigorous when utilizing secondary data compared to data collected by the gold standard, randomized controlled trials (Cox et al., 2009). Determining an accurate outcome linked to drug exposure is one challenge faced when utilizing secondary data. Often, patients will switch from one drug to another due to a lack of efficacy or an inability to tolerate the medicine (Cox et al., 2009). Changing medicines can complicate the ability to accurately determine whether an outcome to an adverse event is linked to exposure to a given medicine given the outcome could be confounded by the potential for previous medicines remaining at a physiologically active level (Cox et al., 2009). Therefore, there is a possibility that the observed outcome to an adverse event is the result of a complex drug-drug interaction or potentially the result of a higher exposure than intended if the drug-drug interaction results in an effect on drug metabolism and exposure levels of either medicine (Cox et al., 2009).

Classification bias is another threat to the validity of findings from studies using secondary data. Errors in the reporting of exposure to a drug or the potential for the misidentification of a drug when concomitant medicines are present can cause adverse reactions, which is a risk with databases similar to the FAERS Database (Cox et al., 2009). The potential for misclassification of the outcome of an adverse event is also a concern if the outcome could be attributed to a long-term condition (Cox et al., 2009). Misclassification of the outcome of drug exposure occurs at different risks across various diseases and should be considered before making recommendations based on findings from secondary data analyses (Cox et al., 2009).

A secondary analysis of data from a database like FAERS is also prone to potential confounding. Confounding, in this instance, occurs when an independent variable in the patient's background or treatment leads to a distortion of the exposure-outcome relationship (Cox et al., 2009). While some sources of confounding can be measured and represented in databases like FAERS, others cannot be measured or identified (Cox et al., 2009). This experiment controlled for patient age and gender to minimize confounding from these demographic variables. Secondary data is also prone to time-dependent confounding. For example, the use of concomitant medicines prior to the adverse event is one example that can easily confound the potential for the outcome of the adverse event (Cox et al., 2009).

Determining the causal effect of drug exposure and an outcome to the adverse event can be challenging when analyzing secondary data, such as that found in the FAERS Database (Cox et al., 2009). However, statistical analyses can enhance the ability to identify a potential relationship, which, with appropriate limitations, could be a useful measure to draw inferences from (Cox et al., 2009).

Nevertheless, secondary data analyses provide potential advantages. Secondary data provides a convenient and inexpensive method of obtaining large cohorts (Cox et al., 2009). In addition, utilizing a large cohort can often provide data from a more diverse population than the population sampled in the trials used to support marketing approval of the medicine (Cox et al., 2009).

Ethical Procedures

Any form of identification was removed from the adverse event reports before being posted on the FAERS Database. Therefore, it is not possible to determine the identity of the patient or reporter from the report itself. Ensuring that personal information is removed from the data before releasing it as secondary data ensures compliance with the Health Insurance Portability and Accountability Act (HIPAA) (Xiang & Cai, 2021). In addition, this study did not require the recruitment of participants, which would include individuals who are members of a vulnerable population, including minors, mentally, emotionally, or physically impaired or disabled individuals, undocumented immigrants, or victims of a violent crime or trauma (Walden University, nd).

Because this study did not involve direct interviews with subjects, it avoids sensitive topics that require ethical consultation, such as behaviors affecting employment, substance abuse, self-incrimination, or distressing personal issues (Walden University, n.d.). Additionally, race or ethnicity was not used as an inclusion variable (Walden University, nd).

Nevertheless, doctoral research projects involving secondary data analysis do require IRB review, as defined in Code of Federal Regulations 45 CFR 46.102(f), which defines a ‘human subject’ as a living individual about whom a researcher collects data via intervention or interaction with the individual or identifiable private information for the purpose of research (U.S. Department of Health & Human Services, 2021). Since the data from the FAERS Database is publicly available, no additional approval beyond the approval from the Walden University IRB was needed. Hence, prior to commencing secondary data collection and analysis, approval from the Walden University IRB was sought and obtained (01-30-25-0726704).

Summary

This retrospective, quantitative, cross-sectional research study utilized secondary data to examine whether an association existed between the number of concomitant medicines and the reported outcomes of adverse events associated with drugs approved under the Breakthrough Therapy Designation between 2012 and 2024, while controlling for patient age and gender. In addition, this study examined whether there is an association between the approved therapeutic indication of the medicine and the outcomes of adverse events reported for drugs approved under the breakthrough therapy designation. The secondary analysis utilized a multinomial logistic regression analysis, utilizing a statistical software package (SPSS v.27). In this chapter, I reviewed the methodology and provided additional insight into the importance of examining these variables. The outcomes of adverse reaction data were obtained from the FAERS Database as reported by clinicians or patients. In Chapter 4, I will provide the results of this study. In Chapter 5, I discuss the results and limitations of this study, provide recommendations for future research in this area, and present some implications for social change.

Chapter 4: Results

Introduction

The purpose of this retrospective, cross-sectional, quantitative study was to examine whether an association existed between the number of concomitant medicines and the reported outcome of adverse events for drugs approved under the breakthrough therapy designation between 2012 and 2024 while controlling for patient age and gender. The number of concomitant medicines was the independent variable, and the number of concomitant medicines was coded continuously. A second purpose of this study was to examine whether there is an association between the approved therapeutic indication of the breakthrough therapy medicine and the reported outcome of the adverse events to breakthrough therapy medicines, while controlling for age and gender. The therapeutic indication of the approved medicine was the independent variable and consisted of nine levels: autoimmune, cardiovascular, endocrine, gastrointestinal, infectious, neurological, rare disease, respiratory, or other. For both research questions, the unit of analysis was the reported outcome of the adverse events (serious, non-serious, hospitalization, or death). The findings of this study are summarized in tables in this chapter. The following research questions and hypotheses were addressed during the analysis:

Primary Research Questions

Research Question 1: Is there a statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024?

$H_0 1$: There is no statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

$H_1 1$: There is a statistically significant association between the number of concomitant medicines and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

Research Question 2: Is there a statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024?

$H_0 2$: There is no statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

$H_1 2$: There is a statistically significant association between the therapeutic indication and the reported outcome of adverse events while considering the age and gender of the patient for medicines approved under the breakthrough therapy designation between 2012 and 2024.

Data Collection

This study was a secondary analysis of publicly available data obtained from the FAERS database. The reported outcomes of the adverse events were coded to align with the FAERS database. The FAERS Database reports data in a table format under the following topics: Demographics, Outcomes, Report Sources, Reactions, Drugs, Therapies, and Indications (FDA, 2018b). The data utilized in this study were obtained by searching for the approved drug by name.

The data analyzed in the analyses are the outcomes of the adverse events reported from 2012 (the inception of the breakthrough therapy designation) through the end of 2024. The analyses were performed from the case perspective (case-based analyses). The use of a case-based analysis was necessary due to the potential for multiple events for each case. Therefore, the samples used in the analyses are those cases with only one event. In addition, since the intent of the analyses was event outcome-based and there was potential for multiple reactions associated with a case, the analyses were limited to those events with only a single outcome reported. The FAERS Database includes input for suspect product names and suspect product ingredients that were believed to be the cause of the reported adverse event. The analyses were limited to those adverse events in which the suspect product name and suspect product ingredient were limited to the breakthrough therapy medicine. Finally, breakthrough therapy medicines can be approved for multiple indications before losing patent protection and exclusivity. The analyses were limited to those adverse events experienced for the indication for which the medicine received the breakthrough therapy designation. These analyses were therefore based on approximately 395,515 adverse events (31.3% of the total reported adverse events for drugs approved under the breakthrough therapy designation (Table 1). Of the reported adverse events, 59.2% were reports involving male patients (n = 211,681), 40.8% involved female patients (n = 145,928), and 9.4% (n = 37,906) did not indicate the gender. Among those reports that reported age, the most represented age groups were 56-60 years (9.7%), 18-25 years (9.6%), and 51-55 years (8.6%). Reports of adverse events were classified by therapeutic indication, with the most frequent being rare diseases (36.2%, n = 142,947), autoimmune conditions (34.8%, n = 137,505), and neurological conditions (24.0%, n = 94,783). Less common categories included infectious diseases (2.7%, n = 10,662) and cardiovascular (n = 464), endocrine (n = 134), gastrointestinal (n = 197), or other (collectively <3%, n = 8,013). Outcomes of adverse events reported were categorized as non-serious (66.6%, n = 263,056), hospitalized (11.0%, n = 43,554), death (7.4%, n = 29,087), other outcomes (14.5%, n = 57,167), life-threatening (0.1%, n = 521), disability (0.3%, n = 1,173), required intervention (n = 109), and congenital anomaly (n = 38). The number of concomitant medicines was reported for 111,968 cases (28.4%). The number of concomitant medicines ranged from 1 to 54 (M = 5.45, SD: 5.03), with a median of 4.00 (interquartile range: 2.00 to 8.00).

The data was cleaned, and data integrity checks were conducted to assess the completeness and quality of the demographic variables prior to analysis. A substantial portion of the dataset exhibited missing demographic information, specifically age (51.2%, n = 202,241) or gender (9.4%, n = 37,096).

Table 1

Descriptive Characteristics of FAERS Reports by Demographic Reporting Status

Study variables	*n* (%)
Gender	
Male	211,681 (59.2)
Female	145,928 (40.8)
Not indicated	37,906 (9.4)
Age	
18-25	18,489 (9.6)
26-30	11,488 (6.0)
31-35	12,614 (6.6)
36-40	12,800 (6.7)
41-45	13,013 (6.8)
46-50	14,316 (7.4)
51-55	16,564 (8.6)
56-60	18,582 (9.7)
61-65	18,037 (9.4)
66-70	14,789 (7.7)
71-75	13,990 (7.3)
76-80	12,928 (6.7)
81+	14,854 (7.7)

Table 1 (continued)

Study variables	*n* (%)
Therapeutic indication	
Autoimmune	137,505 (34.8)
Cardiovascular	464 (0.1)
Endocrine	134 (0.0)
Gastrointestinal	197 (0.0)
Infectious	10,662 (2.7)
Neurological	94,783 (24.0)
Rare Diseases	142,947 (36.2)
Other	8,013 (2.0)
Adverse event outcome	
Died	29,087 (7.4)
Life threatening	521 (0.1)
Disabled	1,173 (0.3)
Hospitalized	43,554 (11.0)
Required intervention	109 (0.0)
Congenital anomaly	38 (0.0)
Non-serious	263,056 (66.6)
Other outcomes	57,167 (14.5)

Note. Values are frequencies with column percentages (%) in parentheses.

Prior to conducting the analyses, the distribution of outcomes of adverse events across therapeutic indications was examined. To ensure sufficient statistical power and interpretability, small and sparse outcome categories were collapsed based on clinical and reporting similarity. Specifically, the serious outcomes category was created by merging three low-frequency AE types: disabled, life-threatening, and required intervention. This decision was made to stabilize estimation and address convergence issues in the multinomial logistic model, while maintaining conceptual integrity. The congenital anomaly category was excluded due to its extremely small frequency and lack of conceptual fit with the other outcome categories. Similarly, therapeutic indications with very small cell sizes—such as cardiovascular, endocrine, and gastrointestinal—were collapsed into a broader "other" category to avoid unstable parameter estimates and improve the robustness of comparisons. These modifications were made prior to multivariate modeling and were applied consistently across all analyses.

Patients with medicines indicated for rare diseases accounted for the largest portion of the reported outcome of death (61.1%). Autoimmune therapies were most frequently associated with non-serious outcomes (58.8%). Reports involving neurological indications were frequently associated with other outcomes (41.8%). The infectious disease category was relatively balanced across all outcome types. However, it accounted for a smaller proportion of overall reports (3.3%; Table 2).

Table 2

Cross-Tabulation of Therapeutics Indications by Adverse Event Outcome

		Adverse event outcome					
Therapeutic indication		Died	Serious outcome	Hospitalized	Non-serious outcome	Other outcome	Total
Autoimmune	*n*	750	223	2,877	72,515	5,744	82,109
	%	5.3	18.1	13.0	58.8	19.0	43.0
Infectious	*n*	238	41	529	4,738	811	6,357
	%	1.7	3.3	2.4	3.8	2.7	3.3
Neurological	*n*	2,860	353	4,494	22,746	12,637	43,090
	%	20.2	28.7	20.3	18.5	41.8	22.6
Rare disease	*n*	8,652	490	13,560	22,644	8,919	54,265
	%	61.1	39.9	61.4	18.4	29.5	28.4
Other	*n*	1,671	122	631	617	2,107	5,148
	%	11.8	9.0	2.9	0.5	7.0	2.7
Total	*n*	14,171	1,229	22,091	123,260	30,218	190,969
	%	100.0	100.0	100.0	100.0	100.0	100.0

Note. *n* = 190,969. Serious Outcomes = Life-Threatening, Disabled, and Required Intervention. Therapeutic indications with small cell sizes (Cardiovascular, Endocrine, Gastrointestinal) were merged into the “Other” category.

Results

Research Question 1

For the first research question, I examined whether a statistically significant relationship existed between the number of concomitant medicines and the outcome of the reported adverse event while controlling for age and gender. A multinomial logistic regression was performed. Since the response variable (outcome of adverse events) contains eight categories, a reference category is needed to compute the odds ratios (ORs) and compare the reported outcomes. Therefore, "Died" was chosen as a reference category. The model was statistically significant (Pearson $\chi 2$ (3204) = 4,480.03, $p < 0.001$). Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Overall, patients with fatal outcomes had the highest medication burden and hospitalized patients also reported elevated counts relative to the other reported outcomes (Table 3).

Table 3

Number of Concomitant Medicines by Adverse Event Outcome Category

	Number of concomitant medications					
Outcome	N	M	SD	Mdn	Q1	Q3
Died	528	6.66	5.49	5.0	2.0	9.0
Serious outcomes	529	4.90	4.23	4.0	2.0	7.0
Hospitalized	9,510	6.33	5.74	5.0	2.0	9.0
Non-serious	32,111	5.04	4.71	4.0	2.0	7.0
Other outcomes	11,337	4.94	4.69	3.0	2.0	7.0

Note. Values reflect descriptive statistics for number of concomitant medications. *M* = mean; *SD* = standard deviation; *Mdn* = median; *Q1* = first quartile; *Q3* = third quartile.

The number of concomitant medicines was significantly associated with all outcome categories. The number of medicines was associated with decreased odds of serious outcomes (OR = 0.95, 95% CI [0.93, 0.97]), non-serious outcomes (OR = 0.96, 95% CI [0.96, 0.97]), and other outcomes (OR = 0.95, 95% CI [0.95, 0.96]) relative to death. The odds of an outcome of hospitalized increased slightly (OR = 1.01, 95% CI [1.00, 1.01]) (Table 4).

Gender was a significant covariate. Compared to males, females had higher odds of experiencing serious outcomes (OR = 2.46, 95% CI [2.05, 2.96]), hospitalized (OR = 1.74, 95% CI [1.62, 1.87]), non-serious outcomes (OR = 2.47, 95% CI [2.31, 2.63]), and other outcomes (OR = 2.61, 95% CI [2.44, 2.80]) (Table 4).

Age group was also a consistent predictor across all categories. Using patients aged 81 years and older as the reference group, younger age groups had a higher likelihood of experiencing non-fatal outcomes following an adverse event. Those aged 18-25 showed increased odds of serious outcomes (OR = 4.02, 95% CI [2.10, 7.71]), hospitalized (OR = 32.85, 95% CI [25.05, 43.08]), non-serious outcomes (OR = 32.37, 95% CI [24.91, 42.07]), and other outcomes (OR = 10.95, 95% CI [8.28, 14.47]). This inverse association with age held across all younger groups, with gradually decreasing odds as age increased. Patients aged 76-80 remained significantly more likely to report non-serious (OR = 1.51, 95% CI [1.36, 1.68]) and other outcomes (OR = 1.36, 95% CI

[1.20, 1.55]) compared to the reference group but were not more likely to experience serious outcomes (OR = 0.97, 95% CI [0.65, 1.46]) (Table 4).

Table 4

Multinomial Logistic Regression Predicting Adverse Event Outcome by Number of Concomitant Medicines, Controlling for Age and Gender

Predictor	Serious outcomes OR [95% CI]	Hospitalized OR [95% CI]	Non-serious outcomes OR [95% CI]	Other outcomes OR [95% CI]
Concomitant Medications	0.95 [0.93, 0.97]*	1.01 [1.00, 1.01]*	0.96 [0.96, 0.97]*	0.95 [0.95, 0.96]*
Gender (*Ref: vs. Male)* Female	2.46 [2.05, 2.96]*	1.74 [1.62, 1.87]*	2.47 [2.31, 2.63]*	2.61 [2.44, 2.80]*

Table 4 (continued)

Predictor	Serious outcomes OR [95% CI]	Hospitalized OR [95% CI]	Non-serious outcomes OR [95% CI]	Other outcomes OR [95% CI]
Age (*Ref: vs 81+*)				
18-25	4.02	32.85	32.37	10.95
	[2.10, 7.71]*	[25.05, 43.08]*	[24.91, 42.07]*	[8.28, 14.47]*
26-30	8.10	23.31	23.96	15.64
	[4.55, 14.40]*	[17.09, 31.78]*	[17.76, 32.31]*	[11.46, 21.35]*
31-35	8.04	16.85	20.57	15,36
	[4.77, 13.54]*	[12.75, 22.27]*	[15.78, 26.83]*	[11.65, 20.26]*
36-40	6.56	13.91	16.77	14.85
	[3.94, 10.93]*	[10.75, 18.01]*	[13.14, 21.40]*	[11.52, 19.16]*
41-45	6.09	8.38	12.74	12.12
	[3.84, 9.66]*	[6.66, 10.54]*	[10.32, 15.72]*	[9.72, 15.13]*
46-50	5.27	7.38	11.57	10.65
	[3.42, 8.12]*	[6.02, 9.04]*	[9.62, 13.90]*	[8.75, 12.94]*
51-55	4.59	5.65	9.65	7.01
	[3.10, 6.79]*	[4.75, 6.73]*	[8.27, 11.25]*	[5.92, 8.30]*

Table 4 (continued)

Predictor	Serious outcomes OR [95% CI]	Hospitalized OR [95% CI]	Non-serious outcomes OR [95% CI]	Other outcomes OR [95% CI]
56-60	3.27	4.60	8.91	5.51
	[2.20, 4.86]*	[3.92, 5.40]*	[7.76, 10.23]*	[4.72, 6.44]*
61-65	2.63	3.31	6.15	3.70
	[1.80, 3.83]*	[2.86, 3.83]*	[5.44, 6.95]*	[3.22, 4.27]*
66-70	2.00	2.38	3.25	2.57
	[1.37, 2.92]*	[2.07, 2.73]*	[2.89, 3.65]*	[2.25, 2.95]*
71-75	1.30	1.53	2.07	1.77
	[0.89, 1.91]	[1.34, 1.75]*	[1.86, 2.31]*	[1.56, 2.02]*
76-80	0.97	1.52	1.51	1.36
	[0.65, 1.46]	[1.33, 1.72]*	[1.36, 1.68]*	[1.20, 1.55]*

Note. Odds ratios (OR) and 95% confidence intervals (CI) are reported for each outcome category compared to the reference group (“Died”). Concomitant medicines were modeled as a continuous variable. Serious outcomes include life-threatening events, disability, and required intervention. Therapeutic indication reference group = “Other”. Gender reference group = Male. Age reference group = 81 years and older, $^{*}p < .05$.

Research Question 2

The second research question examined whether a statistically significant association existed between the therapeutic indication and the outcome of the reported adverse event, controlling for age and gender. A multinomial logistic regression analysis was performed. The dependent variable was the reported outcome of the adverse event, with "died" as the reference category. The model was statistically significant (Pearson $\chi 2$ (448) = 7,167.66, $p < 0.001$).

The therapeutic indication for the breakthrough therapy medicine significantly predicted the outcome of the reported adverse event to the breakthrough therapy medicine. Compared to "other" indications, patients using drugs approved for autoimmune indications had a higher odds of experiencing a serious outcome (OR = 1.59, 95% CI [1.23, 2.06]), hospitalized (OR = 3.45, 95% CI [3.04, 3.92]), non-serious outcome (OR = 76.13, 95% CI [67.49, 85.88]), and other outcomes (OR = 2.12, 95% CI [1.91, 2.36]). Similarly, rare disease indications were associated with an increased odds of experiencing an adverse event outcome of hospitalized (OR = 2.17, 95% CI [1.96, 2.39]) and non-serious outcomes (OR = 3.26, 95% CI [2.95, 3.60]), but a decreased odds of serious outcomes (OR = 0.44, 95% CI [0.36, 0.55]) and other outcomes (OR = 0.44, 95% CI [0.40, 0.47]). Patients using breakthrough medicines approved for neurological indications has lower odds for serious outcomes (OR = 0.58, 95% CI [0.46, 0.74]), but a higher odds of hospitalized (OR = 1.36, 95% CI [1.22, 1.52]) and non-serious events (OR = 5.73, 95% CI [5.16, 6.36]). Patients taking breakthrough therapy medicines approved for infectious diseases were associated with an increased odds of an outcome of hospitalized (OR = 2.28, 95% CI [1.89, 2.74]) and non-serious outcomes (OR = 15.98, 95% CI [13.53, 18.87]), but were not statistically significantly different from the reference group in predicting serious (OR = 0.86, 95% CI [0.58, 1.29]) or other outcomes (OR = 0.96, 95% CI [0.81, 1.13]) (Table 5).

Table 5

Multinomial Logistic Regression of Adverse Event Outcomes by Therapeutic Area

Predictor	Serious outcomes OR [95% CI]	Hospitalized OR [95% CI]	Non-serious outcomes OR [95% CI]	Other outcomes OR [95% CI]
Therapeutic indication (*Ref: vs Other*)				
Autoimmune	1.59 [1.23, 2.06]*	3.45 [3.04, 3.92]*	76.13 [67.49, 85.88]*	2.12 [1.91, 2.36]*
Infectious	0.86 [0.58, 1.29]	2.28 [1.89, 2.74]*	15.98 [13.53, 18.87]*	0.96 [0.81, 1.13]
Neurological	0.58 [0.46, 0.74]*	1.36 [1.22, 1.52]*	5.73 [5.16, 6.36]*	1.07 [0.98, 1.16]
Rare diseases	0.44 [0.36, 0.55]*	2.17 [1.96, 2.39]*	3.26 [2.95, 3.60]*	0.44 [0.40, 0.47]*

Note. Odds ratios (OR) with 95% confidence intervals (CI) are presented for each outcome category relative to death (reference category). Serious outcomes include life-threatening events, disability, and required intervention. Therapeutic indication reference group = “Other”. Gender reference group = Male. Age reference group = 81 years and older. *p < .05.

Summary

The number of concomitant medicines was independently associated with the outcome of reported adverse events to a medicine approved under the breakthrough therapy designation, even after adjusting for patient gender and age. A greater number of concomitant medicines was linked to an increased risk of an adverse event outcome requiring hospitalization. However, the increase in the number of concomitant medicines was also associated with a slightly reduced odds for serious, non-serious, and other adverse event outcomes relative to death.

The therapeutic indication for a medicine approved under the breakthrough therapy designation was significantly related to the outcome of the adverse event. Among the therapeutic indications, patients utilizing medicines approved for neurological and rare disease indications had significantly lower odds of fatal adverse event outcomes compared to patients using drugs for “other” indications. In contrast, patients taking breakthrough medicines approved for autoimmune disease indications were associated with elevated odds of death relative to all other therapeutic indications. Gender was also a consistent predictor, with female patients exhibiting significantly higher odds of every non-fatal adverse event outcome category relative to males. Patient age also demonstrated a robust inverse relationship with mortality risk; younger individuals were substantially more likely to experience a non-fatal adverse event outcome to an adverse event, with a strong association observed among patients aged 18-30. Together, these findings suggested that the severity of adverse events varies by the number of concomitant medicines as well as the therapeutic indication.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

To date, there have been limited studies conducted that utilize the FDA's FAERS Database to examine the postmarketing safety profile of medicines approved under the breakthrough therapy designation. This retrospective, cross-sectional, quantitative study investigated the relationships between the number of concomitant medicines as well as the approved therapeutic indication, and the reported outcomes of adverse events to breakthrough therapy medicines, with the aim of filling a gap in the literature. The outcomes of this study provided insight into the potential risk of medicines approved under the breakthrough therapy designation relating to the polypharmacy and the intended patient population.

In this study, a secondary analysis was conducted on the reported outcomes of adverse events obtained through the FAERS database (FDA, 2018a). The data collected were for medicines approved under the breakthrough therapy designation from 2012 (inception of the breakthrough therapy program) to the end of 2024. Outcomes examined were for those adverse events experienced for the indication for which the breakthrough designation was granted. The independent variable for the first analysis was the number of concomitant medicines. The independent variable for the second analysis was the approved therapeutic indication and consisted of four levels: autoimmune, infectious, neurological, and rare diseases. The outcomes of the reported adverse events were the dependent variable for both analyses. Multinomial logistic regression was conducted to examine the relationship of the independent and dependent variables in both analyses.

The findings demonstrated a significant relationship between the number of concomitant medicines and reported outcomes of the adverse events. The results indicated that patients with the highest medication burden were most likely to experience fatal outcomes or require hospitalization. Most comparisons reached statistical significance, likely due to the statistical power provided by the high sample size. However, the effect sizes were small, suggesting differences in nonfatal categories may have limited practical importance. However, the data still indicate that polypharmacy is a risk factor for experiencing a negative outcome from medicines approved under the breakthrough therapy designation.

The findings also demonstrated that the approved therapeutic indication is linked to the reported adverse event outcome. Breakthrough therapy medicines approved for autoimmune conditions had the highest likelihood of experiencing a serious outcomes or hospitalization due to an adverse event. In contrast, those medicines approved for neurological conditions and rare diseases were much less likely to result in a serious outcome due to an adverse event.

Taken together, the results from this study indicated that there is an opportunity to improve the understanding of the risk-to-benefit ratio and safety profile of breakthrough therapy medicines at the time of approval. The data pointed out a potential risk to patient populations receiving medicines approved under the breakthrough therapy designation as well as patients taking concomitant medicines. Patients receiving breakthrough therapy medicines to treat autoimmune conditions were also found to be at an increased risk for negative outcomes to adverse events. Further analysis is required to fully understand the demographic groups within these broad patient classifications that are at an elevated risk from adverse events to breakthrough therapy medicines.

Interpretation of the Findings

To understand the potential risk medicines have to the public health, pharmacovigilance teams study adverse events in the postmarketing setting. The postmarketing setting is a focus of pharmacovigilance to ensure the medicines are not posing an unidentified risk to the population and to help guide future labeling changes and postmarketing safety studies as needed to ensure their safe use (Kugener et al., 2021). The FAERS Database is one source for monitoring postmarketing safety events utilized by regulatory agencies as well as the pharmaceutical industry for pharmacovigilance studies (Beau-Lejdstrom et al., 2019). Critics of the expedited drug approval pathways, including the breakthrough therapy designation, often cite the smaller sized studies used to support marketing approval as a cause for concern that the safety profile of medicines is not thoroughly understood at the time of marketing approval (Puthamana et al., 2018). Shepshelovich et al. (2019) found that postmarketing labeling changes relating to safety were higher for medicines approved under expedited review pathways.

In this study, I focused on examining the safety profile of breakthrough therapy medicines in the postmarketing setting in an effort to provide insight on how well the safety profile of breakthrough therapy medicines is understood following approval and to identify whether these medicines provided an elevated risk to the public health. Currently, no studies have examined the postmarketing safety of medicines approved under the breakthrough therapy designation.

The study performed by Beau-Lejdstrom et al. (2019) employed a similar data collection methodology to this study. Beau-Lejdstrom et al. utilized adverse event reports from the FAERS Database to examine the relationship between the number of adverse events and the size and quality of the clinical trials used to support marketing authorization. Clinical trials utilizing trials of adequate size and that were well controlled were associated with fewer postmarketing safety events (Beau-Lejdstrom et al., 2019). While previous studies have examined the number of reported adverse events, the severity of the adverse event outcome, therapeutic indication, and the effect of concomitant medicines were not examined.

Patients often require multiple medicines to treat the conditions targeted by medicines seeking the breakthrough therapy designation (Hoon et al., 2019). Therefore, one focus of this study is the relationship between the number of concomitant medicines and the outcome of reported adverse events to breakthrough therapy medicines. The use of concomitant medicines has been associated with adverse events outcomes requiring emergency medical intervention, especially in the elderly (Budnitz, Shehab, & Lovegrove, 2022). The relationship between the therapeutic indication and the outcome of the adverse event was a second focus of this study. The breakthrough therapy designation has been used to treat indications across various therapeutic areas, representing unique patient populations (Darrow et al., 2020). Previous studies that have examined the safety of medicines approved under other expedited pathways have not examined the approved therapeutic indication as an independent variable.

Regarding concomitant medicines, this study identified a statistically significant relationship between the number of medicines and the outcome of the reported adverse event. A higher number of medicines was associated with a modest decrease in the odds of serious outcomes (OR = 0.95, 95% CI [0.93, 0.97]), non-serious outcomes (OR = 0.96, 95% CI [0.96, 0.97]), and other outcomes (OR = 0.95, 95% [0.95, 0.96]) relative to death. However, the odds of hospitalization increased modestly (OR = 1.01, 95% CI [1.00, 1.01]). Crescioli et al., (2021) observed a statistically significant increase in the risk of hospitalization due to an adverse event related to the use of multiple medicines. Interestingly, in this study, a reduced risk of hospitalization was also observed with certain medicines across both genders and across age groups, including renin-angiotensin system inhibitors (ROR 0.89, 0.83-0.95 and 0.91, 0.84-0.98, respectively), and a more pronounced reduced risk with angiotensin II receptor blockers (alone and in combination) and ibuprofen (ROR 0.52, 0.36-0.76 and 0.56 (0.34-0.90) (Crescioli et al., 2021).

While modest, the observed decrease in odds of experiencing certain outcomes with polypharmacy could be related to the indication and types of medicines these patients were prescribed. For example, several medication-based risk scores are available for medicines with known risks of affecting balance, impairing physical function, inducing sedation, and those with known effects on the central nervous system (Silva-Almodóvar & Nahata, 2022). While it may be challenging to determine an appropriate risk score for a new breakthrough therapy medicine with limited patient exposure compared to medicines approved under a non-expedited approval pathway, this study found evidence of a reduction in the risk of certain outcomes with breakthrough therapy medicines in patients taking concomitant medicines. The data from this study identify an opportunity to identify which class of medicines, indications, and concomitant medicines contributed to this observed reduction in risk in adverse event outcomes and apply these findings to better classifying the potential for risk of medicines.

The observed reduction in risk for serious outcomes, non-serious outcomes, and other outcomes, as well as the increased risk of hospitalization, could be related to the mechanism of action of the breakthrough therapy medicines and or the concomitant medicines. Understanding the potential risk associated with the pharmacological activity and interactions of concomitant medicines could provide an opportunity to reduce any risk to public health. Kimura et al. (2022) found that pharmacist intervention, focusing on reviewing both prescribed medicine and medical histories, was effective in reducing hospitalizations due to adverse events in patients taking concomitant medicines. The risk of hospitalization due to an adverse event can be reduced in situations where medicines with potential for negative interactions can be proactively identified and deprescribed (Kimura et al., 2022). This approach may be more important in certain patient populations who, due to their condition or age, are at an elevated risk of experiencing adverse events and who require multiple medicines to treat their condition.

This study also demonstrated that the approved indication for the breakthrough therapy medicine predicted the outcome of reported adverse events. Compared to “other” indications, patients prescribed breakthrough therapy medicines for autoimmune conditions had a significantly higher odds of experiencing serious outcomes (OR = 1.59, 95% CI [1.23, 2.06]), hospitalized (OR = 3.45, 95% CI [3.04, 3.92]), non-serious outcomes (OR = 76.13, 95% CI [67.49, 85.88]), and other outcomes (OR = 2.12, 95% CI [1.91, 2.36]). Patients treated with breakthrough therapy medicines to treat rare diseases were also associated with an increased odds of an outcome of hospitalized (OR = 2.17, 95% CI [1.96, 2.39]) and non-serious outcomes (OR = 3.26, 95% CI [2.95, 3.60]), as well as a significant decrease in odds of serious outcomes (OR = 0.44, 95% CI [0.36, 0.55]) and other outcomes (OR = 0.44, 95% CI [0.40, 0.47). Patients receiving breakthrough therapy medicines to treat neurological conditions had a significantly lower odds of serious outcomes (OR = 0.58, 95% CI [0.46, 0.74]) but had a higher odds of experiencing an outcome of hospitalized (OR = 1.36, 95% CI [1.22, 1.52]) and non-serious outcomes (OR = 5.73, 95% CI [5.16, 6.36]). Patients treated with breakthrough therapy medicines to treat infectious indications were associated with an increase in odds of an outcome of hospitalized (OR = 2.28, 95% CI [1.89, 2.74]) and non-serious outcomes (OR = 15.98, 95% CI [13.53, 18.87]), but no significant difference in experiencing a serious outcome (OR = 0.86, 95% CI [0.58, 1.29]) or other outcomes (OR = 0.96, 95% CI [0.81, 1.13]).

Understanding the pathology and organ systems that are responsible for the conditions within these therapeutic indications may provide insight into the differences in the odds of experiencing a given outcome to an adverse event experienced for breakthrough therapy medicines. For example, autoimmune conditions encompass a range of conditions that affect multiple organ systems. Diseases treated by autoimmune therapies include rheumatoid arthritis, inflammatory bowel disease, psoriasis, multiple sclerosis, myasthenia gravis, lupus erythematosus, ankylosing spondylitis, and neuromyelitis optica spectrum disorder (Zong et al., 2024). In addition, breakthrough therapy medicines are often large-molecule antibodies, which often have a more selective targeting profile than traditional immunotherapies (Martins et al., 2022). While traditional immunosuppressants pose a significantly greater safety risk to patients due to their broader inhibitory effect on the immune system, newer biologics still exert an inhibitory effect on the immune system which has the potential to place patients at a greater risk of opportunistic infections, developing other immune related diseases, often resulting in patients living with an impaired ability to mount an immune response to an infection (Martins et al., 2022). While this study found a relationship between breakthrough therapy medicines targeting autoimmune conditions and serious outcomes and hospitalizations, this study found that these patients were at a greater risk of experiencing a non-serious outcome to an adverse event.

Rare diseases often have a prolonged and complicated disease progression, are poorly understood, and have limited clinical study (Skwere-Kuchta, Czerska, & Szaruga, 2023). As a result, rare diseases pose a significant challenge to developing medicines due to the limited understanding of the underlying cause of these diseases as well as the health risks for these patients as a result of the low prevalence of these diseases and the heterogeneity of the patient population (Skweres-Kuchta, Czerska, & Szaruga, 2023). These characteristics also likely contribute to a limited understanding of the safety profile of medicines used to treat these diseases, as well as an increased risk of an outcome of hospitalized observed in this study. However, this study indicated that the breakthrough therapy medicines targeting rare diseases are associated with a lower risk of serious outcomes and an increased risk of non-serious outcomes indicating that while an increased understanding of the risk of these medicines in this patient population is warranted these medicines may not pose an impactful risk to the public health.

Drugs that treat neurological conditions are among the most likely medicines to cause adverse events due to the comorbidities common with these diseases as well as the known risks associated with the concomitant medicines prescribed for neurological diseases (Borges et al., 2024). However, this study found a decreased risk of serious outcomes in addition to an increased risk of experiencing a non-serious outcome. An increased odds in experiencing and outcome to an adverse event that required hospitalization was also found. While these studies demonstrate that the risk associated with breakthrough therapy medicines targeting neurological conditions is complex, the safety risks from these drugs have the potential to change over time as the risk of drug-disease interactions evolves with the progression of a neurological disease (Borges et al., 2024). Therefore, understanding the risk to the public health for this condition should be studied at different stages of disease progression, and patient age.

Infectious disease indications are often associated with a higher risk for severe illness and mortality (Deiana et al., 2024). In addition, patients with infectious diseases are often misdiagnosed, leading to a delay in receiving effective treatment for their disease which increases the potential risk to the health of these patients (Deiana et al., 2024). While this study found patients treated with breakthrough therapy medicines for infectious diseases were at a greater risk for an outcome of hospitalized, there was a more pronounced risk for patients experiencing a non-serious outcome. It is unknown how much of the risk for hospitalization observed in this study is the result of the risk from the disease itself or due to factors like delayed diagnoses and treatments common to these conditions (Deiana et al., 2024).

The conceptual framework guiding this study is pharmacovigilance. The framework for pharmacovigilance utilizes monitoring tools, such as the FAERS Database, to study the postmarketing safety profiles of approved medicines (Kugener et al., 2021). Collectively, the findings observed in this study suggest that a better understanding of the effect of polypharmacy combined with breakthrough therapy medicines, and breakthrough therapy medicines targeting autoimmune and rare disease indications require additional studies to better understand their risk to public health.

Limitations of the Study

Despite the advantages of the FAERS Database, the data obtained can be prone to redundant entries, reporter bias, and incorrect information, which have the potential to impact the reliability of the results (Beninger & Murray, 2021). These issues can result in Type I and Type II statistical errors, potentially confounding pharmacovigilance efforts. A causal relationship between the drug and the adverse event cannot be concluded based on the data from the FAERS Database (FDA, 2018a). The results obtained in this study represent an association and cannot be construed as indicating a causality between the breakthrough therapy medicine and the reported outcome of the adverse event (Duan et al., 2024).

The potential for bias in the data should also be considered. Potential for bias in the reports obtained from the FDA's FAERS Database stems from the nature of reports from patients, providers, manufacturers, and caregivers (Duan et al., 2024). The fact that the data is self-reported can affect the ability to determine the true frequency of the outcomes to the reported adverse events (Duan et al., 2024). Previous studies have found that reporting on the FAERS Database is skewed toward more serious outcomes (Duan et al., 2024).

The retrospective, cross-sectional, secondary quantitative design of this study also contributed to the limitations of the study. The study did not employ qualitative analyses to determine the patient experience of the outcome of the reported adverse event. In addition, the potential for reporting and recall bias may have led to the improper classification of serious and non-serious outcomes reported in this study (Duan et al., 2024). Correlational, cross-sectional studies also have the potential for the existence of confounding variables in this study (Kelly et al., 2024).

The study is also limited in the amount of information provided by the FAERS Database (Duan et al., 2024). Additional information on the time course of the adverse event onset is lacking and could provide a better understanding of the likelihood of a causal relationship between the breakthrough therapy medicine and the outcome of the reported adverse event. In addition, more information on the medical history of the patients experiencing the adverse event could provide a better insight into the potential for the identification of other variables potentially contributing to the outcome reported. Hence, in this study, it is not possible to make causal inferences when examining the results on the association between the outcomes of the adverse events reported in the FAERS Database and the breakthrough therapy medicine when considering the relationship between the number of concomitant medicines taken or the therapeutic indication targeted.

Recommendations

This study found a significant association between the number of concomitant medicines and the reported outcomes of the adverse events to breakthrough therapy medicines. An association was also found between the therapeutic indication and the outcome of the reported adverse events to the breakthrough therapy medicine. These data suggest that there is an opportunity to better understand the risk-to-benefit ratio of breakthrough therapy medicines at the time of marketing authorization. Breakthrough therapy medicines address unmet medical needs and often offer improvements over existing therapies; however, critics highlight the smaller studies that often lack randomization and proper controls as potential risks to the safety of these medicines (Puthamana et al., 2018). Shepshelovich et al. (2019) found that medicines approved utilizing studies without proper randomization and control resulted in greater postmarketing safety labeling changes. The data from this experiment potentially supports the conclusion that the risk that breakthrough medicines pose to public health is not adequately understood at the time of approval. Further research is necessary to better understand this risk.

The use of the FAERS Database as a tool for pharmacovigilance has its limitations. There is a significant underreporting of adverse events in the FAERS Database, as the findings from the FAERS Database do not always align well with those from other post-marketing studies (Zhou et al., 2024). The potential for underreporting of adverse event outcomes means that a thorough understanding of the true association between concomitant medicines and the outcome of adverse events, particularly for breakthrough therapy medicines, is lacking. Indeed, the adverse events reported in the FAERS Database are often skewed towards more serious outcomes (Zhou et al., 2024). Underreporting could be best addressed with other pharmacovigilance tools. More focused studies comparing the postmarketing reports of adverse events to breakthrough therapy medicines reported on the FAERS Database to those reported in clinical studies supporting the marketing authorization of these medicines could help inform how significant the effect of underreporting in the post marketing setting is regarding these patient populations.

The data from this study suggested an association between the therapeutic indication and the reported outcome of the adverse event. In particular, breakthrough therapy drugs used to treat autoimmune conditions, and rare diseases were associated with more serious outcomes. More detailed studies are warranted here to understand the variables responsible for the increased risk associated with these medicines when used to treat these conditions. While treating autoimmune conditions often involves inhibiting immune function, and while more advanced therapies accomplish this in a more targeted and selective approach, it appears breakthrough therapy medicines may still pose an increased risk to these patients (Martins et al., 2022). It is inherently difficult to mitigate the risk associated with treating rare diseases due to the poor understanding of the underlying physiology of these diseases and the limited clinical studies of these indications (Deiana et al., 2024). However, the data from this study demonstrate that further studies are warranted to aid in mitigating safety risks in these patient populations.

Concomitant medicines have been found to negatively impact the public health of patients (Budnitz, Shehab, & Kesselheim, 2018). Polypharmacy is a significant risk contributing to the risk of experiencing hospitalizations due to adverse events (Budnitz, Shehab, & Kesselheim, 2018). The outcomes examined in this study were likely experienced by patients who were on a variety of concomitant medicines, given the complicated nature of treating the conditions targeted by breakthrough therapeutic medicines (Hermosilla, 2024). For example, patients treated for neurological conditions often require concomitant sedatives, analgesics, or anxiolytics to treat their symptoms depending on their disease and comorbidities (Borges et al., 2024). Future studies focusing on pharmacovigilance of breakthrough therapy medicines relating to specific indications and disease states are warranted and would be helpful in further understanding how best to protect the public health of these patient populations.

Implications

The results from this study found a significant relationship between the number of concomitant medicines and the outcomes of the reported adverse events to breakthrough therapy medicines. Although modest, this study found a decrease in certain outcomes associated with an increase in the number of concomitant medicines. In addition, this study found a significant relationship between the therapeutic indication and the outcomes of the reported adverse events to breakthrough therapy medicines. Notably, autoimmune conditions and rare diseases were associated with more serious outcomes to adverse events. These findings support concerns that the safety profile of breakthrough therapy medicines may not be adequately understood at the time of marketing authorization which has the potential to pose a risk to the public health of patients receiving these medicines (Puthamana et al., 2018). The FDA requires breakthrough therapy medicines to meet the same standards of safety and efficacy as medicines approved under the standard approval pathway (Darrow et al., 2020). However, this study indicates that there are opportunities to refine the requirements for breakthrough therapy medicines based on their targeted therapeutic indication as well as the intended patient population, especially those likely to be administered concomitant medicines.

This study also found that certain patient groups were at a lower risk of experiencing a serious outcome from an adverse event to a breakthrough therapy medicine. Patients treated with breakthrough therapy medicines for neurological conditions were less likely to experience serious outcomes. In addition, younger patients had higher odds of experiencing non-fatal outcomes, hospitalization, and non-serious outcomes from adverse reactions to breakthrough therapy medicines. Taken together, these data indicate that developing drugs for breakthrough therapy indications among patient populations that include these age groups as well as those targeting neurological indications may not require a more detailed understanding of the safety profile than what is currently required. While the underlying cause for the associations between concomitant medicines and outcomes to reported adverse events is likely complex, this study observed an age effect consistent with other studies. However, additional studies could contribute by controlling for potential confounding factors, including lifestyle, nutrition, health history, and sociodemographic characteristics of these patients (Vennu, 2024; Ye et al., 2022). There may be unidentified opportunities to improve the safety profile of medicines receiving the breakthrough therapy designation by modifying the sample study size requirements based on considerations regarding the intended patient population.

Findings from this study support other the concerns identified by previous studies regarding the safety profile of medicines approved under the breakthrough therapy designation at the time of approval. Patients treated for autoimmune conditions may have an elevated risk of experiencing a negative outcome to adverse events due to the nature of their diseases or the fact that the medicines used to treat these conditions often have suppressive effects on the immune system (Zong et al., 2024). Therefore, autoimmune conditions may represent an area that would benefit from larger, more diverse studies during drug development. The challenge lies in improving the safety of developing drugs to treat rare diseases while addressing the urgency of the unmet needs of these diseases. Due to the low prevalence of these diseases, the lack of information regarding the underlying pathophysiology and natural progression of these diseases are often poorly understood (Deiana et al., 2024).

The breakthrough therapy designation is an expedited pathway implemented by the FDA to improve the speed of drug development and approval of medicines that address unmet need (Ch et al., 2021). The FDA weighs the risks and benefits when considering whether the studies supporting approval have an appropriate design and sample size (Termini, 2022). Critics have voiced concern over the size and design of these studies, as well as the increased occurrence of changes to postmarketing safety related labeling language as evidence of an inadequate understanding of the safety profile of these medicines at the time of approval contributing to a potential risk to the public health of patients treated with these medicines (Puthamana et al., 2018). This study found that while breakthrough therapy medicines may pose a greater risk of certain outcomes to reported adverse events among certain patient populations, this risk is not uniform across all therapeutic indications and does not necessarily rise with the number of concomitant medicines. Therefore, a consideration of the modification of the regulatory requirements for approval of all breakthrough therapy medicines does not appear to be warranted. Rather, it is likely that a risk-benefit analysis should be tailored for indications and the potential for polypharmacy in the intended patient population.

The findings from this study also have implications for societal-level changes. An outcome of hospitalization due to adverse events has a significant impact on the public health of patients, with elderly patients who are often prescribed concomitant medicines being at the greatest risk of requiring medical intervention to treat and monitor their adverse events (Budnitz, Shehab, & Lovegrove, 2022). Clinicians view medicines approved under expedited pathways, such as the breakthrough therapy designation, as having high value for their patients and a greater potential to address their patients' needs (Dhruva et al., 2022). Patients are also more willing to adhere to prescription directions when they perceive their caregivers communicating an improvement in the benefit of these medicines is likely (Minton et al., 2021). It is, therefore, equally important that caregivers and patients understand the risks a medicine may pose. A goal of pharmacovigilance is to effectively share knowledge about the risks of medicines, as well as inform of any changes to the risk profile or identification of new risks to specific patients (Kugener et al., 2021). This study suggests that certain patient populations may benefit from further clinical investigation prior to marketing authorization of breakthrough therapy medicines to better understand the risks associated with concomitant medicine use or the risks to patients prescribed medicines to treat autoimmune or rare disease indications. Communicating the findings from these clinical studies to prescribers, caregivers, and patients should be considered to best inform of the potential risks breakthrough therapy medicines may have to the public health.

The results of this study have implications at the industry level as well. Drug companies benefit from their medicines receiving breakthrough therapy designation by receiving more frequent communication with regulators during development (Darrow et al., 2020). Often, the smaller, less complex trials associated with the breakthrough therapy designation result in a shorter development timeline, as well as an expedited review timeline (Darrow et al., 2020). Shepshelovich et al. (2019) observed a greater number of postmarketing safety-related changes to medicines approved under an expedited pathway, including those designated as breakthrough therapies. This study affirms that for certain therapeutic indications and patient populations treated with concomitant medicines, the safety profile of these medicines may not be thoroughly understood at the time of marketing authorization. While critics have expressed concern about all medicines approved under these expedited conditions, this study indicates that changes to the requirements to demonstrate safety for all breakthrough therapy medicines. A better understanding of which patient populations are at risk can provide the drug industry with an opportunity to design more informative clinical trials while still taking advantage of the speedy development and review timelines, resulting in an improvement in the understanding of the safety risks of breakthrough therapy medicines at the time of approval. Achieving this will help meet the goal of delivering medicine to address the unmet needs of patients in a timely manner while also working to protect public health.

Conclusion

This study analyzed postmarketing adverse event outcomes for breakthrough therapy drugs approved between 2012 and 2024, using data from the FDA FAERS Database. The results showed a modest but significant association between the number of concomitant medicines and the reported adverse event outcomes. This association was independent of age and gender. More concomitant medicines were associated with lower odds of fatal outcomes but higher odds of non-serious events. The therapeutic indication was also related to the outcome, again independent of age and gender. Breakthrough therapy medicines for rare diseases and autoimmune indications were tied to higher odds of hospitalization and non-serious outcomes. Patients taking breakthrough therapy medicines for neurological indications had lower odds of experiencing serious outcomes.

This study represented the first analysis of reported postmarketing adverse event outcomes for breakthrough therapy drugs. Collectively, the findings underscore the need for rigorous pharmacovigilance in patients prescribed breakthrough therapy medicines in combination with other medicines, as well as in those prescribed breakthrough therapies for autoimmune and rare conditions. Further research is needed to clarify the specific risk factors that should inform improvements in the development of breakthrough therapies for the identified patient groups. A clearer understanding of these risks may improve informing both healthcare providers and patients regarding the risk of these important medicines. Enhancing the safety profile and clinical use of breakthrough therapy medicines could ultimately improve public health outcomes by reducing the incidence of serious or fatal outcomes to adverse events.

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