APPROVAL SHEET

Title of Dissertation: A COMPARATIVE EFFECTIVENESS EXAMINATION OF ASTHMA TREATMENTS IN THE MARYLAND MEDICAID POPULATION: THREE ESSAYS

Name of Candidate: Jennifer Kitlas Smith
Doctor of Public Policy, 2018

Dissertation and Abstract Approved: _____)
Nancy A. Miller
Professor
School of Public Policy

Date Approved: 11/29/18

ABSTRACT

Title of Document: A COMPARATIVE EFFECTIVENESS EXAMINATION OF ASTHMA TREATMENTS IN THE MARYLAND MEDICAID POPULATION: THREE ESSAYS

Jennifer Kitlas Smith, Doctor of Public Policy, 2018

Directed By: Professor Nancy A. Miller, Public Policy

This is a three-paper dissertation on the comparative effectiveness for asthma treatments. While it has been repeatedly demonstrated that inhaled corticosteroids (ICS) are more clinically efficacious than leukotriene receptor antagonists (LTRA) for the treatment of persistent asthma, it has also been established that adherence to ICS treatment is low yet LTRA adherence is high. This dissertation investigates whether a lower efficacious/high adherence treatment is as effective as a highly efficacious/low adherence treatment for the treatment of mild to moderate persistent asthma. The first paper (Comparison of Leukotriene Receptor Antagonists and Inhaled Corticosteroids for the Treatment of Asthma: A Systematic Literature Review) systematically reviews the current literature to assess two aspects of the comparative effectiveness asthma research of LTRA and ICS monotherapy. First, the paper addresses whether the literature identifies similar outcomes for the two treatments as evidenced by emergency department (ED) visits and inpatient hospitalizations. Second, the method of grading the quality of the evidence is also examined. The second paper evaluates the generalizability of previous research findings by conducting a comparative-effectiveness study of ICS and LTRA in the

Maryland Medicaid population. The third paper examines whether medication adherence for LTRA and ICS affects the comparative-effectiveness of the treatments for the Maryland Medicaid population.

Keywords: leukotriene receptor antagonist, inhaled corticosteroid, comparative-effectiveness

A COMPARATIVE EFFECTIVE EXAMINATION OF ASTHMA TREATMENTS IN THE MARYLAND MEDICAID POPULATION: THREE ESSAYS

By

Jennifer Kitlas Smith
University of Maryland, Baltimore County

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore County, in partial fulfillment
of the requirements for the degree of
Doctor of Public Policy
2018

Dedication

For Logan and Noah: I hope that watching me over the years slowly work towards the completion of this degree you may learn to never give up on the dreams closest to your heart.

For my friends at Hilltop: You always reminded me that I had the intellect and determination to achieve my goal.

For Christopher: I love you for always telling me that I was too close to quit. Your commanding encouragement helped drive me to see my dream. Thank you for never giving up on me.

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Dissertation Introduction

This dissertation is the result of inspiration generated from two articles. The first reported on several pharmaceuticals soon available for a generic option, of which Singulair, a leukotriene receptor antagonist (LTRA) used for the treatment of asthma, was one (Moeller, 2011). The second article reported on studies conducted in the United Kingdom comparing LTRA with inhaled corticosteroids (ICS) for the treatment of persistent asthma[1] (Kelland, 2011). The two studies concluded that the LTRA pill was as effective in treating asthma as the ICS.[2] Upon reading these articles, several policy-related questions come to mind:

(1) Would best practices for asthma treatment change if a pill version of asthma treatment is made more financially available?

(2) Are the limitations of ICS stated in the article referring to the UK studies accurate?

(3) Is there a growing controversy among doctors regarding the use of LTRA and ICS as initial monotherapy for persistent asthma, as suggested in the article?[3]

(4) Is the burden of asthma in the United States (US) great enough that policy-makers would be interested in these articles and their possible impact?

From the investigation into the above questions, and others that follow, a three-paper dissertation for the evaluation of the comparative effectiveness of two asthma treatments was developed.

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[1] Asthma may be either acute or chronic in nature. Furthermore, chronic asthma, or as it is more commonly stated, persistent asthma, can range from mild to severe. In the following discussion the term 'asthma' refers to persistent asthma, whether mild or severe.

[2] Both LTRA and ICS refer to a class of drug. The studies consider all drugs within these classes.

[3] The terms LTRA and ICS not only denote the class of drug, but also indicate the type of monotherapy being used in asthma treatment.

Background

Best Practices Guidelines: Overview

Understanding current policy initiatives and programs for asthma treatment, management, and quality of care assessment requires a requisite knowledge of various aspects of asthma. Much of the necessary information is found in current national and international best practice guidelines for the diagnosis, treatment, and management of asthma.[4] The establishment of best practice guidelines for the treatment of asthma is thought to aid practitioners in providing the best and most effective care for patients, thus reducing costs associated with avoidable healthcare visits and treatments, and thereby reducing the overall burden of the disease. Policy-makers use guidelines for various policy initiatives, including developing performance measures for assessing quality of care and evaluating how the current program—in this case, Maryland Medicaid—is doing at addressing various issues related to the management of asthma.

In 1991, the National Asthma Education and Prevention Program (NAEPP), coordinated by the National Heart, Lung, and Blood Institute (NHLBI), developed and released guidelines for the diagnosis and treatment of asthma (Guidelines) (*Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* 2007). These Guidelines were updated in 1997, 2002, and 2007 by a panel of experts who systematically assessed asthma literature in order to determine the best way to diagnose and treat it. In 2012, the National Heart, Lung and Blood Advisory

[4]While many in the world-wide community use the Global Initiative for Asthma (GINA) guidelines, the healthcare system in the United States primarily uses the National Asthma Education and Prevention Program (NAEPP) guidelines. GINA is an international "network of individuals, organizations, and public health officials" (Global Initiative for Asthma 2016, pg. i) who collaborate to improve the diagnosis, treatment, and management of asthma. Although the National Heart, Lung, and Blood Institute (NHLBI) collaborate in this effort, they do not support the adoption of all products and decisions by GINA for policy decisions in the US (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015). Ramifications of this decision are discussed at further length later in this document.

Council (NHLBAC) recommended the continued "production of clinical practice guidelines" (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015, pg. 1). It was determined the current Guidelines "be updated on selected topics, with the NHLBI continuing to support and coordinate the production of the Guidelines through the NAEPP" (pg. 1).

Recognizing "health care societies, patient organizations and government agencies rely on guidelines to inform their decision making …. the NAEPP agreed a review [of the Guidelines] should be made" (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015, pg. 2). Unlike the previous version, the updated Guidelines would result from collaboration between the NHLBAC and NAEPPG. In April 2014, the NHLBAC Asthma Expert Working Group outlined various areas to consider for revision, which in turn determined the focus of the updates to the Guidelines. The Asthma Expert Working Group met again in January 2015 to further iterate the importance of an update and finalize the assessed needs for the Guideline update.

Between the April 2014 and the January 2015 meetings, the Asthma Expert Working Group collected comments pertaining to 187 recommendations for updates to the current Guidelines (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015, pg. 3). Such groups included the members of the 2007 Expert Panel, NAEPP Coordinating Committee, Guidelines Implementation Panel Members, Members of the National Asthma Control Program Projects, those affiliated with the NAEPP Coordinating Committee, and public comments (pg. 3 - 4). From these comments, the Working Group identified the following areas as highest priority for a systematic literature review: the role of adjustable medication dosing in recurrent wheezing and asthma; the role of long acting anti-muscarinic agents; the role of

bronchial thermoplasty in adult severe asthma; the role of fractional exhaled nitric oxide in diagnosis, medication selection, and monitoring treatment response in asthma; the role of remediation of indoor allergens (house dust mites/pets) in asthma management; and the role of immunotherapy in the treatment of asthma. Within each of these areas, additional sub-categories of interest are also identified.

The Working Group noted areas such as adherence/compliance[5], medication additions, and removal from medication charts, as well as medications currently recommended for step-wise therapy (of which LTRA is one), but did not deem those as the highest priority for the current update (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015, pg. 12 and 13). During the June 2015 meeting, the Working Group revealed a proposed timeline for completing the updates (The National Asthma Education and Prevention Program Coordinating Committee 2015, slide 14). The systematic review for the six identified areas began in 2016 and concluded in 2017. The updated Guidelines are proposed to be published in 2018, however, as of November 2018 the Guidelines remain to be updated.

The role of the NHLBI, through the NHLBAC, is to "ensure the impartiality, credibility and widespread acceptance of the product" (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015, pg. 7). The NAEPP provides a diverse foundation from

[5] This dissertation will use the terms compliance and adherence interchangeably. According to the World Health Organization, adherence implies an agreement between the patient and provider on the recommended treatment protocol (World Health Organization 2003, pg. 4). Compliance, however, does not include acknowledgement of any agreement. There are also other ways to differentiate the two terms. For example, adherence may refer to filling/re-filling a prescription while compliance means taking the medication as prescribed (National Stroke Association 2012, pg. 2). Finally, some researchers use the two terms interchangeably (Cramer et al., 2008). This dissertation will follow that last protocol, although it is recognized that the theoretical ideas being discussed refer to compliance while the discussions pertaining to the quantitative measurement of the act use the term adherence.

which to draw asthma experts from a variety of healthcare specialties. NAEPP consists of "over 37 organizations," including both primary care and sub-specialties, educational organizations and "lay voluntary groups" (pg. 7). These two groups then strive to make the Guidelines comprehensive enough to inform a wide variety of healthcare professionals.

As a result, the Asthma Expert Working Group has differentiated, in the above cited working documents, the difference between the NAEPP Guidelines and other guidelines. The Working Group specifically discussed the Global Initiative for Asthma (GINA) guidelines, which were recently updated in 2015 (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015; Global Initiative for Asthma 2016). Although GINA is developed via an international group, to include NHLDBI, the NHLBI/NAEPP documents have cited several issues for using the guidelines in the United States. Some of the concerns regarding the GINA guidelines include funding from pharmaceutical companies, a predominance of European and Canadian experts, and that "the literature reviews and drafting processes do not incorporate all guidelines development methods promulgated by the Institute of Medicine" (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015, pg. 8). For these reasons, the NHLBI will update the NAEPP Guidelines for decision-making use in the US healthcare system rather than adopting the recently updated GINA guidelines. As this research is focused on Maryland Medicaid data, which falls under the Department of Health and Humans Services, as does the National Institutes of Health, the NAEPP Guidelines will be used and discussed rather than GINA.

Best Practice Guidelines: Efficacy versus Effectiveness

The proposed update to the Guidelines, as stated above, does not include the assessment of LTRA versus ICS. Moreover, the current Guidelines prioritize efficacy studies over

effectiveness studies. These factors signify the necessity of this evaluation. First, much research has been done comparing LTRA versus ICS since 2007. While this research only considers two outcomes, many studies have compared various aspects of the effect these two asthma treatments have on asthma and related healthcare outcomes. Second, the systematic review of literature performed for the proposed update to the Guidelines will be conducted by the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015). Specifically, it will be performed by the Evidence-based Practice Centers (EPCs). As will be discussed in the first paper, the EPCs have developed a way to examine the evidence found in literature which differs from traditional methods, as well as the methods in the 2007 Guidelines and all GINA guidelines. The two methods prioritize efficacy[6] studies differently. Researchers and methodologists have postulated that the difference in prioritizing efficacy studies might affect conclusions important to the determining of real-world effectiveness of a treatment.

The current methods employ weighting efficacy studies over pragmatic and observational studies to determine the most effective treatment. Healthcare decision-makers, including both policy-makers and providers, use the Guidelines to aid in various tasks: design programs, develop healthcare quality measurements and goals, develop coverage packages for insurance policies, pharmaceutical co-payment tiers, and treat patients ("Principles of a Sound Drug

[6] A distinction must be noted between the terms efficacy and effectiveness. According to a thesaurus, the two terms are synonyms. However, in the current use, they differ in meaning significantly. The term efficacy refers to "whether an intervention produces the expected result under ideal circumstances", such as done in a controlled trial (Gartlehner 2006, Introduction, paragraph 2). Effectiveness, however, pertains to "the degree of beneficial effect under 'real world'…settings" (Introduction, paragraph 2). Efficacy studies seek not to compromise internal validity, and thus may not be generalizable to the overall population. Effectiveness studies, though, seek to be as generalizable as possible, thereby concede, to varying degrees, the internal validity of the study.

Formulary System," 2000; “UnitedHealthcare Community Plan Preferred Drug List for Maryland," 2015). Thus, healthcare policy decisions related to asthma are based on how a possible asthma treatment performs in controlled clinical studies.

The current Guidelines emphasize the primary use of daily ICS ("National Asthma Education and Prevention Program - Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma - Summary Report 2007," 2007). Over the years, many studies have documented the clinical efficacy of the ICS as a daily treatment for the relief of asthma symptoms. However, studies have also revealed issues with patients complying with the treatment (Elkout, Helms, Simpson, & McLay, 2012; Lasmar et al., 2009). Compliance issues relate to many aspects of the inhaled treatment: improper use, patient doesn’t like to use the inhaler, does not like the taste, difficult to use (Finkelstein, Lozano, Farber, Miroshnik, & Lieu, 2002; Haughney et al., 2008). As a result, education programs have been developed and encouraged in order to teach patients how to use the inhaler properly, as well as to impress upon the patient the value of using this treatment on a regular basis ("Healthy People 2010: Understanding and Improving Health," 2000, sections 24-6 and 24-7; Department of Health and Humann Services n.d.; Fisher et al., 2009; Haughney et al., 2008). While these programs have helped, compliance with the inhaled medication remains low (Ducharme et al., 2012; Haughney et al., 2008; Price et al., 2011b).

As a result of the difficulties in getting patients to comply with the ICS treatment, many practitioners have argued for the daily pill treatment of LTRA (Lee et al., 2010; Lipworth & Jackson, 2011; Price et al., 2011b). Efficacy studies have compared LTRA to the ICS, where repeatedly LTRA has proven to be less clinically efficacious in controlled trials (Mahr & Mumm, 2011; Price et al., 2011a; Sadatsafavi, Lynd, Marra, Bedouch, & Fitzgerald, 2013;

Zeiger et al., 2005). As a result, guidelines have repeatedly placed LTRAs as a lower level of acceptable asthma treatment. This has resulted in insurance policies requiring physicians to try the ICS for several months prior to being able to gain approval for the LTRA ("UnitedHealthcare Community Plan Preferred Drug List for Maryland," 2015) and various educational programs instituted to encourage and inform patients on taking ICS medication (Fisher et al., 2009; Haughney et al., 2008; Lawson & Flocke, 2009). However, studies have demonstrated patients who take LTRA are highly compliant with the medication (Lee et al., 2010; Li et al., 2014; Tan et al., 2009). While providers are aware that ICS is far more efficacious, the argument is to provide a treatment the patient will comply with.

Thus, an interesting policy question emerges: is clinical efficacy more important than compliance? In other words, does a highly clinically efficacious/low compliance treatment produce better results in an uncontrolled environment than a less clinically efficacious/highly compliant treatment? Or do the treatments react similarly in a real world setting? Answers to this line of query are important as the current Guidelines focus primarily on clinical efficacy for evaluation. However, if patient compliance affects how effective a clinically efficacious treatment will be in society, then policy and programs regarding the treatment of the disease ought to account for patient compliance in the policy initiatives.

This dissertation assesses issues surrounding the treatment of asthma in three distinct evaluations. The first paper (Comparison of Leukotriene Receptor Antagonists and Inhaled Corticosteroids for the Treatment of Asthma: A Systematic Literature Review) considers current available methods to evaluate the published evidence for comparative-effectiveness research on asthma treatments—specifically ICS and LTRA. The second paper (A Comparison of Health Care Outcomes for Inhaled Corticosteroid versus Leukotriene Receptor Antagonist Use in the

Maryland Medicaid Population) focuses on how ICS and LTRA compare within a single population by evaluating utilization rates for emergency department visits and hospitalizations due to mild to moderate persistent asthma. The third paper (Assessing the Impact of Adherence on Health Care Outcomes for Inhaled Corticosteroids Compared to Leukotriene Receptor Antagonists: Analysis of Maryland Medicaid Data) examines the effect of adherence on the impact of either treatment on asthma outcomes by categorizing the level of adherence of the population used in the second paper. These three papers shed light on various aspects of this issue in order for policy-makers, no matter the program level, to ascertain the appropriate strategy for asthma treatment.

The Problem of Asthma

One of the initial questions has not been addressed: what is the burden of asthma in the US? Asthma is a chronic condition that significantly impacts healthcare costs and utilization (Congressional Budget Office 2005; Druss et al., 2001; Thorpe, Ogden, & Galactionova, 2010). Over the years, the impact has grown. Unfortunately, statistics on asthma lag several years, however, it is known that asthma prevalence has been increasing in the US since 1980. As a result, asthma is also often discussed in terms of period prevalence, which measures the prevalence of asthma during a specific time period. Measurement of asthma during the period of 1980 through 1996, for example, indicates that "asthma period prevalence grew from 3.5% to 5.5%," with an average increase of 3.8% (Akinbami et al., 2011, pg. 3).

Changes in the way asthma is measured after 1997 do not allow for a comparison of trends.[7] Period prevalence of asthma since 1997 has increased from 7.4% to 8.2% in 2009, with an average annual increase of 1.2% (Akinbami et. al., 2011, pg. 3). This prevalence translates to approximately 25 million people currently diagnosed with asthma (Akinbami et al., 2011, pg. 2; Akinbami et al., 2012, pg. 2). The associated healthcare costs total more than $56 billion annually, lost school/work days, and pre-mature deaths ("Asthma's Impact on the Nation," n.d.). These healthcare costs include "1.75 million [emergency department] visits (ED) and 456,000 asthma hospitalizations" that occur annually for asthma (Akinbami et al., 2011, pg. 5).

The impact of asthma, though, is different based on race and socio-economic status (SES). Stratification by race indicates Asians have the lowest prevalence at 5.3% (Akinbami et al., 2011, pg. 3). The prevalence for non-Hispanic Whites mimics that of the national average, at 7.8%, while non-Hispanic Blacks have a higher prevalence at 11.1%. Overall, Hispanics have a lower prevalence rate at 6.3%, but Hispanic Puerto Ricans have an elevated prevalence of asthma at 16.6%. Hispanic Mexicans have the lowest at 4.3%. Furthermore, analysis indicates Blacks are more likely than Whites to have asthma related ED visits, hospitalizations and death (pg. 5).

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[7] Asthma prevalence and incidence rates are mainly obtained via the National Health Interview Survey (NHIS). This is an annual survey that collects information on various health topics each year. The NHIS is developed and the data is maintained by the National Center for Health Statistics (NHCS) within the Centers for Disease Control (CDC). In 1997, the survey design underwent major changes. As it pertains to asthma, major design changes were made to how data was collected for children with asthma. Prior to 1997, approximately one sixth of the households with children were asked "During the past 12 months, has anyone in the family had asthma?" (Centers for Disease Control and Prevention 2000, paragraph 2). After 1997, data was collected on "a randomly selected sample child in every household containing a child". Furthermore, the question was changed to "Has a doctor or other health professional ever told you that your child has asthma?" (paragraph 2). If the response is affirmative, it was followed up with inquiring "During the past 12 months, has your child had an episode of asthma or an asthma attack?" (paragraph 2). These changes altered the way data on asthma in children was collected and the resulting statistics, as the overall prevalence numbers decreased significantly due to the increased sample size and more specific query.

Children are more likely than adults to have asthma related ambulatory visits, ED visits and hospitalizations (pg. 5).

Stratification also reveals important differences between SES groups. Prevalence rates of asthma are inversely correlated with the federal poverty line (FPL). Those living below the FPL have the highest rate, then those 100-200% FPL, and those above 200% FPL (11.6%, 8.5%, and 7.3% respectively) (Akinbami et al., 2011, pg. 3). Stratifying SES with race indicates poor Blacks and Whites have a further increased asthma prevalence of approximately 12%, while poor Puerto Rican Hispanics are around 22%.

Since the lower SES brackets are associated with more of the burden of asthma, the Medicaid program is essential for the treatment of asthma. As utilization and costs related to asthma rise, the burden will fall more on Medicaid programs than on commercial insurance. While co-payments may not be of interest as policy or treatment options, legislators and Medicaid directors will be interested in promoting asthma programs and policies to limit the asthma costs for the Medicaid program.

Asthma in Maryland

Two of the three papers for the dissertation focus on asthma in the Maryland Medicaid population. There is not a plethora of published statistics and data analysis on asthma in Maryland Medicaid. However, data relating to the entire state is publicly available. Some reports and statistics also include sub-analyses on the Maryland Medicaid population, and those will be referred to if they are relevant and available. Understanding the impact of asthma in the State of Maryland and the corresponding recognition of asthma's impact as a public health concern underlie the foundation for this research: "In 2002, the Maryland Legislature passed HB 420, which established the Maryland Asthma Control Program (MACP) in statute to address asthma

through surveillance, planning and interventions" Maryland Department of Health and Mental Hygiene, 2009, pg. 2). The "Maryland Asthma Control Plan" is the document that directs various policies and programs in Maryland to address the burden of asthma (pg. 2); its full title is The Maryland Asthma Control Plan: An Action Agenda to Reduce the Burden of Asthma in Maryland 2010 – 2015.

While the Action Plan reports on data from 2006, the Maryland Department of Health and Mental Hygiene Asthma Control Program reports State of Maryland data from 2009. "[A]pproximately 389,000 (9.1%) adults and 159,000 (11.9%) children" have asthma (Bankoski, Hess-Mutinda, McEachern, & De Pinto, 2011, pg. 11). The prevalence of asthma has risen from 2000 to 2009, going from roughly 7.3% to 9.1% (pg. 11). The current prevalence in the State of Maryland (9.1%) is above the national average (8.4%) (pg. 11). A total of 39,834 ED visits and 11,474 hospitalizations related to asthma were documented (pg. 11). ED visits and hospitalizations cost approximately $26 and $73 million respectively (pg. 11). One-third of children with asthma missed three or more days of school and two in ten adults missed at least one day of work annually due to asthma.

As seen in the nation-wide data, the burden of asthma in State of Maryland is greater in lower SES groups. Between 2007 and 2009, those with annual household income less than $15,000 have an asthma prevalence rate of 13.9% while those over $75,000 annually have a prevalence rate of 7.8% (Bankoski, Hess-Mutinda, McEachern, & De Pinto, 2011, pg. 19). However, the racial picture looks much different for the State of Maryland. Those reporting a race/ethinicity of 'Other' had the highest prevalence rate (15.6%) compared to Black, non-Hispanic (9.7%), White, non-Hispanic (8.8%) and Hispanic (6.2%) (pg. 18). Blacks are more

likely than Whites to visit the ED and be hospitalized for asthma. Maryland did not report on combined SES and race stratification.

Information on payments for asthma is not reported for the State of Maryland. As stated above, the total charges for ED visits in 2009 were approximately $26 million and $73 million for hospitalizations (Bankoski, Hess-Mutinda, McEachern, & De Pinto, 2011). The Maryland Medicaid program (Medicaid) is responsible for the largest portion of ED visits, covering roughly 41% of ED visit costs (pg. 64). In 2009, Medicaid paid over $10 million for ED visits, while private insurers paid for nearly $9 million. Hospitalizations were similar (pg. 64). Medicaid is, once again, the largest payer of asthma related hospitalizations in the State of Maryland (34%) (pg. 65). Private insurers and Medicare are the next two largest payers for asthma related hospitalizations (30.6% and 26% respectively) (pg. 65). Medicaid's total payment for asthma hospitalizations in 2009 was approximately $25 million.

The Added Value of This Dissertation to Maryland

While the Guidelines have aided practitioners and policy-makers immensely, the burden of asthma on the healthcare system and in people's lives continues to rise beyond what was expected, revealing the complexity of treating a chronic disease. As such, Maryland has been active in addressing the asthma health concern. Understanding how the use of various treatments impacts ED visits and hospitalizations due to asthma will aid policy makers at every level in defining next steps in addressing issues relevant to asthma statewide. Grasping the complexities of how the population's behavior impacts asthma treatments will aid in ensuring that current treatments are used in the most efficient manner.

Conclusion

The impact of two significant articles on the healthcare world can create a shift in public health policy, especially when the articles relate to a health concern such as asthma, which has a great impact on the population. While it is tempting to make knee-jerk policy reactions to headlines, evaluating various aspects of the topic is always advisable. This dissertation attempts to look at three distinct areas related to guidelines and policy programs pertaining to the treatment of persistent asthma, focusing on pharmaceutical treatment using ICS and LTRAs. First, the available literature is systematically reviewed to evaluate what is currently known regarding the effect of ICS and LTRA on asthma ED visits and hospitalizations. The second paper tests whether findings found within the literature review hold true for the Maryland Medicaid population. Specifically, are LTRA and ICS prescribed as a primary asthma treatment equally within the population and do they result in similar outcomes for the population? Finally, the third paper investigates issues of adherence to both ICS and LTRA within the Maryland Medicaid population, and how adherence impacts outcomes. In the complex world of asthma, this research represents a small portion of considerations a committee such as the MACP contemplates. However, research such as in this dissertation is vital toward any program MACP may put forward.

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Comparison of Leukotriene Receptor Antagonists and Inhaled Corticosteroids for the Treatment of Asthma: A Systematic Literature Review

Asthma has been noted as a chronic condition that significantly contributes to rising healthcare costs and utilization (Congressional Budget Office 2005; Druss et al., 2001; Thorpe, Ogden, & Galactionova, 2010). In 1996, it was estimated asthma affected roughly 3.9 percent of the population and cost roughly $27 billion annually in healthcare costs (Druss et al., 2001, pg. 235). Since then, asthma prevalence and costs have dramatically risen. Researchers report that currently, roughly 8% of the United States (US) population, or 25 million people, have asthma (Akinbami, Moorman, & Liu, 2011). Furthermore, the Centers for Disease Control (CDC) estimates asthma to cost more than $56 billion annually in medical costs, lost school/work days, and pre-mature deaths ("Asthma's Impact on the Nation," n.d.). Included in this cost estimate is "1.75 million [emergency department] visits (ED) and 456,000 asthma hospitalizations" that occur annually for asthma (Akinbami et al., 2011, pg. 5). Many hospitalizations and ED visits are considered avoidable if the asthma had been better controlled with proper treatment or compliance to treatment protocol.

Given the burden of asthma on both the US population and healthcare system, various strategies have been attempted to curtail rising prevalence rates and healthcare costs. One such strategy is the National Asthma Education and Prevention Program (NAEPP) guidelines for the diagnosis and treatment of asthma. The first guidelines were published in 1991, with updates

published in 1997, 2002, and 2007[8] (*Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* 2007, pg. 2). The guidelines are created by extensively reviewing all evidence pertaining to asthma, including its diagnosis, treatment and management. Assessment of various efficacious treatments creates the published guidelines. Over the years, many methods have been used to assess the literature. The 2007 NAEPP guidelines and the Global Initiative for Asthma (GINA) guidelines, to include the most current, have used a simplified method of ranking data (Table 1).[9] Other techniques include the method developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPCs), and the Grading of Recommendations Assessment, Development and Evaluation method (GRADE), both of which evaluate the strength of scientific evidence. Once the evidence related to the treatment of asthma is evaluated, it is then used to aid in developing recommendations for the most effective treatment. Logically, it follows that adhering treatment protocols to published guidelines would result in a decrease in uncontrolled asthma, thereby decreasing utilization and costs associated with prevalent persistent asthma. Unfortunately, though these guidelines have aided in more effectively treating and managing asthma, they have not stemmed the rising costs and utilization as expected.

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[8] In 2015, a working group formalized a plan to update the current NAEPP guidelines (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015). Per the outlined timeline, the literature review would begin in 2016 and complete in 2017. Drafting of the new guidelines would occur throughout 2017, with publication during 2018.

[9] Identical information found in both the 2007 NAEPP guidelines and the 2016 GINA guidelines (*Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* 2007, pg. 7; Global Initiative For Asthma 2016, pg. viii). Table 1 is a direct quote from the NAEPP guidelines.

Table 1: Levels of Evidence

(*Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* 2007, pg. 7)

Evidence Category A: Randomized controlled trials (RCTs), rich body of data. Evidence is from end points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
Evidence Category B: RCTs, limited body of data. Evidence is from end points of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B pertains when few randomized trials exist; they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
Evidence Category C: Nonrandomized trials and observational studies. Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
Evidence Category D: Panel consensus judgment. This category is used only in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel consensus is based on clinical experience or knowledge that does not meet the criteria for categories A through C.

Thus, research in asthma continues to update guidelines, develop new drugs, increase patient education of the disease and medication use, and attempt to understand factors contributing to the continual rise in prevalence, healthcare costs and utilization. This systematic

review attempts to contribute to the growing asthma literature by evaluating two aspects of the guideline process. First, this review uses the currently published asthma literature to evaluate how two existing asthma treatments impact ED use and inpatient hospitalizations due to asthma: leukotriene receptor antagonists (LTRA) and inhaled corticosteroids (ICS). Second, in this literature review, two methods of evaluating the evidence will be compared in order to identify any differences in evaluating the literature and the resulting possible impact on decision making for healthcare policy.

Research Questions

1) Do the asthma treatment guidelines need to be altered to include the use of LTRA monotherapy as a first-line treatment for asthma, as confirmed by similar or better patient outcomes compared to those resulting from ICS monotherapy?[10]

a) Does the use of LTRA for the treatment of asthma produce similar healthcare outcomes when compared to ICS, as defined by a reduction in emergency department visits and/or hospitalizations due to asthmatic exacerbation?

2) Does the method of grading the quality of the evidence, specifically the GRADE versus the AHRQ EPC method, impact the conclusion arrived at for the above research questions?

Why this research is important

The last update to the best practice recommendations for the diagnosis and treatment of asthma was published in 2007 (*Expert Panel Report 3: Guidelines for the Diagnosis and*

[10] This paper uses the terms LTRA and ICS to not only denote the class of drug, but to also indicate the type of monotherapy being used in asthma treatment.

Management of Asthma 2007). Research pertaining to LTRA, as well as LTRA compared to ICS treatment, has expanded in the past nine years, yet it remains unclear how clinicians ought to proceed using the two in treatment.[11] As a result, it is important to update the evaluation of evidence and the resulting analysis of best treatment options (Blais et al., 2011; Cao et al., 2012; Lipworth & Jackson, 2011; Price et al., 2011). Furthermore, although recent asthma literature questions the primary role of randomized controlled trials (RCT), it is unclear as to whether altering the method by which evidence is graded will impact the overall analysis of the evidence and the resulting conclusion (Ducharme 2011; Owens et al., 2010; Price et al., 2011; Rawlins 2008). This systematic review seeks to assess the asthma treatments not only in light of new evidence since 2007, but also to evaluate whether alternative grading methods would result in a different understanding of the current recommendations. [12]

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[11] The NAEPP guidelines are not the only guidelines used for the diagnosis, treatment, and management of asthma. GINA is an international organization that also published asthma guidelines. The most recent GINA guidelines were published in 2016 (Global Initiative for Asthma 2016). These guidelines re-evaluated the literature and found that LTRA may be used as an alternate treatment, but note that "[l]eukotriene receptor antagonists…are less effective than ICS" (pg. 33). The guidelines then suggest LTRA "may be appropriate for initial controller treatment for some patients who are unable or unwilling to use ICS; for patients who experience intolerable side-effects from ICS; or for patients with concomitant allergic rhinitis" (PG. 33). This is different from the current study as this paper distinguishes between efficacious and effectiveness. It is the position of this paper that solely because a medication is more efficacious in clinical trials, it should not be assumed the treatment will be more effective in real-life settings. Thus, this paper seeks to evaluate whether ICS and LTRA are equally as effective in a real-world setting and therefore can be used interchangeably without pause.

[12] The literature review for the new update, due out in 2018, will be conducted AHRQ Evidence-based Practice Centers (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2015). As such, the EPC method will be used for evaluating the literature for the NAEPP guidelines. The guidelines developed by GINA do not use the EPC method. GINA has also chosen not to use the GRADE method due to the "major resource challenges that it would present" (Global Initiative for Asthma 2016, pg. vi). Thus, the two most recognized and used current sets of guidelines for asthma will use different methodologies to construct recommendations for the diagnosis and treatment of asthma. Currently, neither published set of guidelines uses the methods applied in this article.

Conceptual Framework

A brief examination of some of the known weaknesses of RCTs, as they pertain to the development of asthma guidelines, is essential to understanding why LTRAs might aid in controlling asthma as well as why other methodologies for evaluating scientific evidence may be necessary. The study design for RCTs provides adequate numbers of study participants, "maximize[s] internal validity…[and] establish[es] an unequivocal cause-and-effect relationship between an intervention and an outcome" (Price et al., 2011, pg. 527). The study design "provide[s] some information of the 'strength' of underlying evidence" that is used by experts to develop guidelines; recommendations are placed in a hierarchy based on the perceived strength of the study (Rawlins 2008, pg. 579). As a result, the guidelines appear to appropriately "evaluate the safety profile and efficacy of emerging therapies" (Price et al., 2011, pg. 527). This type of evaluation is the essence of evidence-based medicine (EBM), as the burden of proof must be met to ensure the public of the safety and efficacy of the recommended treatment. However, the safety and efficacy of treatment are not the only concerns in health care. Hence, a current trend in clinical standard of care guideline literature points to the limitations of RCTs and calls for a new understanding of evidence to be employed in the establishment of guidelines.[13]

In the treatment of asthma, evidence from RCTs is disadvantaged due to "the null hypothesis, probability, generalisablity and resource implications" (Price et al., 2011; Rawlins

[13] Safety and efficacy concerns are evaluated by the Federal Food and Drug Administration (FDA) in order to determine if a drug or treatment is safe for distribution and use in the United States of America (U.S.). Even after FDA approval, safety and efficacy continues to be monitored and studied. The emerging call to evaluate literature beyond safety and efficacy implies a next step in evaluating the literature. Evaluation ought to go beyond issues of safety and efficacy and begin to look at a broader picture of how medical treatments, to include medications, interact within the complex world.

2008, pg. 580). First, study participants involved in RCTs are monitored and provided a treatment regimen the general population does not have access to. Specifically, both poor inhaler technique and non-compliance with inhaler use by asthma patients are barriers to achieving treatment success (Ducharme 2011; Finkelstein, Lozano, Farber, Miroshnik, & Lieu, 2002; Haughney et al., 2008, pg. 1681; Price et al., 2011, pg. 529). Participants in a RCT receiving sufficient education and monitoring for inhaler technique and use will exhibit a different response to treatment than the general asthma population which does not receive such attention and guidance (Bousquet et al., 2007). As a result, findings from RCTs may not be replicated in general patient settings, reducing the real life effectiveness of ICS over other therapies. Recent studies have indicated compliance with LTRA may be higher than with ICS (Ducharme 2011; Price et al., 2011, pg. 1704). Increased compliance with a clinically less efficacious treatment (LTRA) may be more effective in a real-life setting at reducing asthma exacerbations than non-compliance with a clinically more efficacious treatment (ICS). Furthermore, studies have documented ICS is less effective in controlling asthma for populations with co-morbidities such as smoking and allergic rhinitis (Haughney et al., 2008); this effect has not been reported for LTRA use. Thus, LTRA treatment may be more effective than ICS in treating asthma symptoms for those with co-morbidity of allergic rhinitis or for a known smoker.[14,15]

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[14] Although LTRA seems to be more effective for those with either allergic rhinitis or a smoking habit, the reasons behind the effectiveness are vastly different. One hypothesis for the increased effectiveness for those with allergic rhinitis is that the patient population is more apt to be compliant with the medication on a daily basis as LTRA is being used to treat allergy symptoms as well as asthma. As for the smoking population, smoking appears to decrease the efficacy of ICS, but does not affect the pathway of LTRA within the body. Since both groups are routinely excluded from RCTs, the phenomenon was not identified earlier in comparison studies.

[15] Current GINA guidelines only indicate LTRA "may be appropriate for initial controller treatment or for patients with concomitant allergic rhinitis" (Global Initiative for Asthma 2016, pg. 33).

Second, RCTs involve studying a select group of patients meeting specific inclusion criteria. Thus, the results of the RCTs may not be relevant to the entire asthma population. Multiple studies have identified subgroups of the asthma population who are not addressed adequately in RCTs. Patients who smoke or have co-morbidities are often not included in RCTs (Haughney et al., 2008, pg. 1685-1686; Price et al., 2011a, pg. 527). Travers et al. (2007) surveyed asthma patients and found only 6% of study participants on asthma medication would meet eligibility criteria for the RCTs used by GINA to develop guidelines (pg. 219). Given external validity is an issue with RCTs, current guidelines for standard of care for the general asthma population may not be appropriate for a substantial part of the population. If one of the reasons guidelines in general are used is in an attempt to reduce overall health care costs by increasing quality of care, the weight of RCTs in the creation of guidelines is problematic.

Study Methodology

Inclusion Criteria

Inclusion criteria were defined *a priori* to searching for articles. This provides systematic parameters for the selection of articles, ensuring articles are not being selected due to the findings reported. The list below outlines the criteria all studies must meet for inclusion into this review.

- Published between 1996 – Present
- Have one of the following study designs
    - Randomized control trial (RCT)
    - Pragmatic trial
    - Historical controlled trial
    - Non-randomized contemporaneously controlled trial
    - Retrospective cohort study
    - Retrospective case-control study
    - Before-and-after design
    - Case-series
- Contains a statistical analysis of the evidence
- Has an outcome of hospitalization/inpatient stay and/or emergency department visit (ED)
- Available in English
- Published in a peer-review journal
- Compares LTRA with ICS directly

- Only evaluates asthma populations (e.g. excludes COPD, cystic fibrosis, emphysema, etc.)

The time frame of 1996 to present was decided on, as 1996 was the year LTRA came on the market after Food and Drug Administration (FDA) approval for the treatment of asthma. Articles evaluating additional asthma medications will be accepted as long as analyses are conducted directly comparing LTRA directly with ICS. Studies which compared LTRA and ICS for disease populations other than asthma were excluded in order to minimize confounding.[16] Asthma is defined based on specific physiological responses which may differ from other lung diseases or conditions. As such, treatments may affect physical pathways in asthma patients differently than populations having other diseases. For this reason, only studies examining asthma-only populations will be considered.

Article Selection Methodology

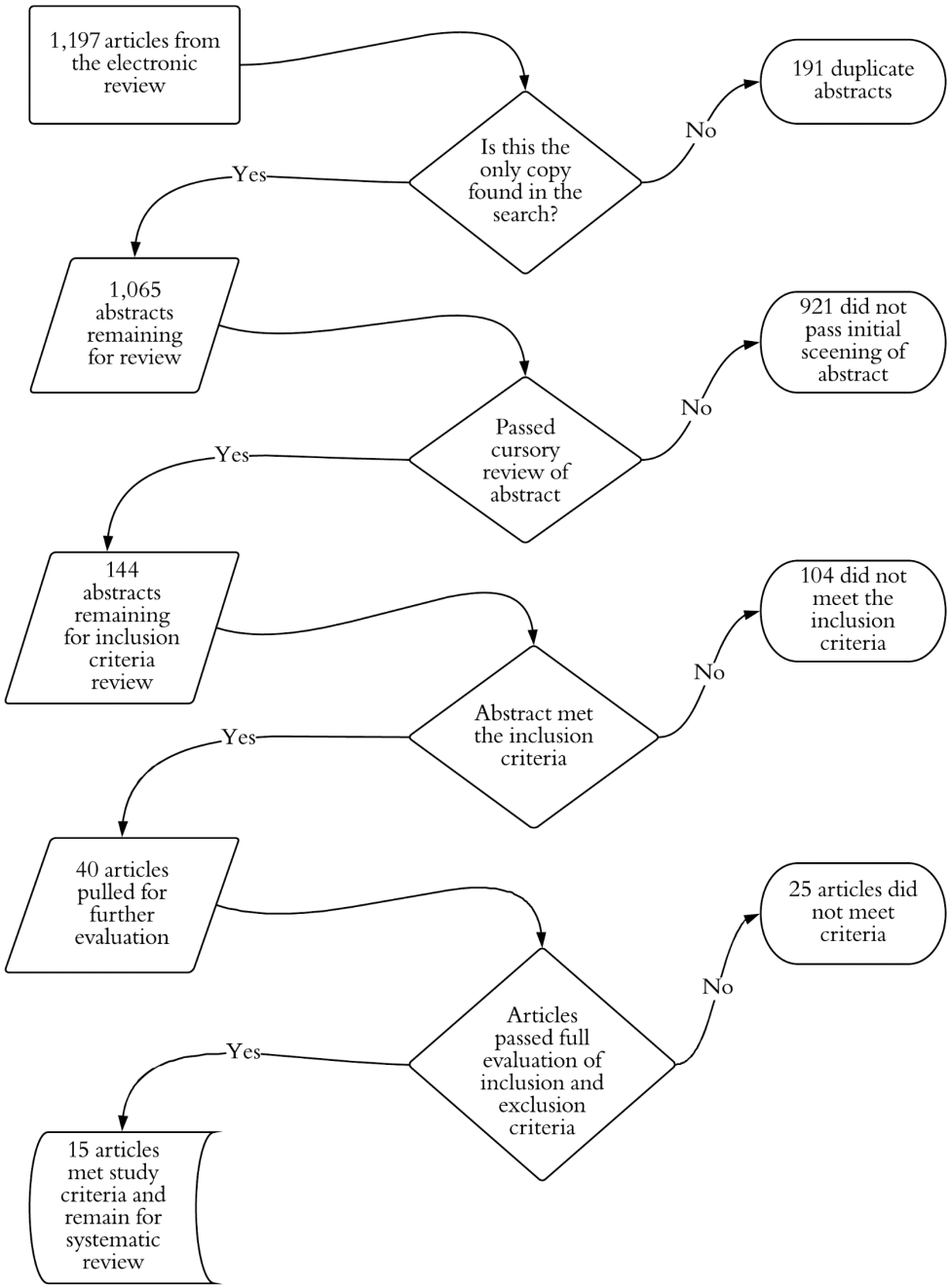
An electronic search of the asthma literature was initially performed in March and April 2014. The search included seven databases: Academic Research Premier, MEDLINE, CINAHL, Academic Search Complete, Science Citation Index Expanded, Social Sciences Citation Index and Arts and Humanities Citation Index. Articles were limited to those published in English during 1996 – 2014 and in a peer-reviewed journal. The keywords used in the electronic search were ("leukotriene" AND "asthma" AND ("corticosteroid" OR "adrenocortical" OR "glucocorticoids"). The literature search was updated in January 2016, using the same

[16] Treatment with LTRA and ICS are also used for other pulmonary diseases, such as congestive-obstructive pulmonary disease (COPD), cystic fibrosis and emphysema. This study only considers the treatment of asthma.

parameters and methods as described above, in order to discover if any additional articles meeting the criteria need to be added to this study. The updated search was conducted for the time frame of January 2014 through January 2016. Chart 1 depicts the flow of articles through the ensuing levels of review.[17]

[17] The literature has continued to be monitored for future research. Only studies available at the writing of this research were used for this essay.

Chart 1: Flow Chart of Article Selection



This search resulted in 1,256 articles. An initial screening of the identified references was performed to limit articles to those that mentioned a leukotriene antagonist and an inhaled corticosteroid, evaluated only asthma (not COPD, exercise-induced asthma, wheezing), and contained a statistical evaluation of the study. A total of 1,112 were excluded from further evaluation. The elimination of these 1,112 articles is further detailed in Chart 1, specifically those excluded after the initial screening and second abstract screening.[18]

Those articles which continued on for evaluation experienced a detailed examination of the abstracts; the abstracts were compared against parts of the inclusion criteria. Initially, the abstracts were reviewed to ensure the study was published after 1996, when the first LTRA gained FDA approval for sale. Only including studies published after 1996 allows for evaluation to include prescribing and compliance issues pertaining to the treatment. Furthermore, it was confirmed the study must be published in English and in a peer-reviewed journal.

Next, the study must indicate specific aspects in the design. Included articles must have one of the following study designs: randomized control trial, pragmatic trial, historical controlled trials, non-randomized contemporaneously controlled trials, case-control studies, before-and-after designs, case-series, retrospective studies, or observational studies. These study designs allow for a statistical analysis of the evidence evaluating each treatment. The study design must also directly compare LTRA with ICS. Finally, add-on designs, where the control group consists

[18] Of the 1,112 articles, 191 were excluded due to being duplicate articles; due to the search occurring in multiple databases, articles may have been identified and pulled more than once. When a more detailed examination of the abstract revealed the article did not refer to either LTRA or ICS, or did include one or more of the discussed inclusion and exclusion criteria, 921 articles were excluded from the study. As a direct comparison between the two is necessary, many of these articles were eliminated from this analysis.

of patients taking only one medication (typically ICS) and the comparison group consists of patients taking both medications (ICS and LTRA), were not considered.

Articles passing a second level of screening must only consider treatment of asthma. Other conditions, such as chronic obstructive pulmonary disease (COPD), emphysema, and exercise-induced asthma follow different physiological pathways and medical considerations. As these groups of patients require different clinical considerations so only studies examining asthma patients will be considered in order to minimize confounding results. Finally, the study outcome should include healthcare utilization as the evaluated measure. Healthcare cost may also be included, however, given one of the most common LTRAs available (Singulair) is now available as a generic (montelukast), cost-effectiveness analyses must not include pharmacy costs or the study must be conducted after the generic is available.

Examining the remaining 144 study abstracts against the above criteria resulted in excluding 104 studies. The full text of the article was pulled for the remaining 40 studies. A more in-depth analysis of the study designs was conducted resulting in an additional 25 articles being excluded from the final review analysis. Although the research question of this study refers to hospitalizations and/or ED visits due to asthma exacerbation, not all studies were able to differentiate the reason for the visit. As such, only studies with a specified outcome of hospitalization/inpatient visit and/or ED visit were entered into the review. Appendix A provides detailed information on each study selected. Listed below are the 15 remaining articles included in this review, listed in alphabetical order of the article title:

1. A comparison of confounding adjustment methods for assessment of asthma controller medication effectiveness (Li et al., 2014).
2. Asthma costs and utilization in a managed care organization (Zeiger et al., 2008).

3. Asthma hospitalization risk and costs for patients treated with fluticasone propionate vs. montelukast (Orsini, Limpa-Amara, Crown, Stanford, & Kamal, 2004).
4. Clinical effectiveness of inhaled corticosteroids versus montelukast in children with asthma: Prescription patterns and patient adherence as key factors (Ducharme et al., 2012).
5. Costs and resource use of mild persistent asthma patients initiated on controller therapy (Colice et al., 2008).
6. Effect of montelukast for treatment of asthma in cigarette smokers (Price et al., 2013).
7. Impact of asthma controller medications on clinical, economic, and patient-reported outcomes (Tan et al., 2009).
8. Impact of asthma controller medications on medical and economic resource utilization in adult asthma patients (Lee et al., 2010).
9. Inhaled corticosteroids vs. leukotriene receptor antagonists: Health care costs across varying asthma severities (O'Connor, Parasuraman, Roberts, & Leibman, 2006).
10. Inhaled corticosteroids vs. Leukotriene-receptor antagonists and asthma exacerbations in children (Blais et al., 2011).
11. Observational study of the effects of using montelukast vs. fluticasone in patients matched at baseline (Allen-Ramey, Duong, Riedel, Markson, & Weiss, 2004).
12. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: A randomized controlled trial (Zeiger et al., 2005).
13. The risk of hospitalization in patients with asthma switched from an inhaled corticosteroid to a leukotriene receptor antagonist (Stempel, Pinto, & Stanford, 2002).

14. Treatment effectiveness of inhaled corticosteroids and leukotriene modifiers for patients with asthma: An analysis from managed care data (Allen-Ramey et al., 2003).
15. Use of Leukotriene Receptor Antagonists Are Associated with a Similar Risk of Asthma Exacerbations as Inhaled Corticosteroids (Wu et al., 2014).

Overall, the majority of identified articles were excluded as a result of not being a study of the treatments, but rather commentary or review of existing information and articles. Second, articles were excluded as a result of not directly comparing LTRA with ICS. Third, many articles evaluated diseases or conditions that were not solely asthma. These conditions included exercise-induced asthma, COPD, Churg-Strauss[19], wheezing, and asthma-like symptoms. Finally, the remaining articles were excluded based on other inclusion criteria not being met. Table 2 displays the frequency of reasons why articles were excluded from this review.

[19] Churg-Strauss is a vascular disorder where the blood vessels are inflamed (Mayo Clinic n.d.). This disorder restricts blood flow, often causing permanent damage to vital organs and tissues. Asthma is often the most common symptom of Churg-Strauss disorder.

Table 2: Excluded Articles

Reason for Exclusion	Number of Articles Excluded at Each Level of Article Review (After Duplicates have been removed.)		
	Abstract Did Not Pass Initial Screening	**Abstract Did Not Meet Inclusion Criteria**	**Article Did Not Meet Study Criteria**
Not an included study design	415	17	5: CEA 2: Not studies
Did not compare LTRA vs. ICS	283	35	3: Ran separate analyses for LTRA and ICS 5: Compared a treatment of interest with a LTRA-ICS combination
Did not evaluate asthma population only	193	7	-
No Abstract	20	-	-
Not published in English	8	1	-
No statistical analysis	2	-	-
Does not have included outcome measure	-	44	2: Quality of Life 6: Clinical markers 1: Evaluates add-on of additional allergy medications 1: Measured outcomes of interest only pre-index date

Characteristics of Studies Selected

Most of the studies meeting the inclusion criteria, and thus selected for this review, are observational studies. Thirteen studies are retrospective observational studies. The remaining two studies are randomized control trials (Price et al., 2013; Zeiger et al., 2005). Of the observational studies, six use propensity score matching to create treatment groups that were statistically

similar (Allen-Ramey et al., 2003; Allen-Ramey et al., 2004; Li et al., 2014; O'Connor et al., 2006; Wu et al., 2014; Zeiger et al., 2008). One of these studies also uses the instrumental variable technique to control for confounding in the analysis (Zeiger et al., 2008). All studies were published between the years 2002 – 2014. Most studies use data from the United States, while two studies use data from Canada (Blais et al., 2011; Ducharme et al., 2012) and one uses data from 29 various countries (Price et al., 2013).

Overall, sample size varies greatly, from a total of 227 people (Ducharme et al., 2012) to over 96,000 people (Zeiger et al., 2008). Eight studies include both adult and children asthmatics, four evaluate children only (Blais et al., 2011; Ducharme et al., 2012; Li et al., 2014; Wu et al., 2014), and three only consider adult populations (Tan et al., 2009; Lee et al., 2010; Price et al., 2013). Of the three evaluating adult populations, one only includes adults who smoke regularly (Price et al., 2013). As adherence to medication is vital to the treatment of asthma, every study references adherence, although only eight studies attempt to control or evaluate adherence levels.

Finally, outcome measures vary as well. Nine studies use a composite outcome variable; a composite variable is an outcome variable that requires of a combination of several possible events (Allen-Ramey et al., 2003; Blais et al., 2011; Tan et al., 2009; Lee et al., 2010; Li et al., 2014; Price et al., 2013; Wu et al., 2014; Zeiger et al., 2005, 2008). An example of a composite outcome would be an outcome that requires a patient to have either an ED visit or an inpatient hospitalization. A composite outcome may also include use of a short-acting beta-antagonist (SABA) or presence of a healthcare visit other than ED visits and inpatient hospitalizations. An example of a multifaceted outcome is **"**a day in which there was no inhaled albuterol or oral corticosteroids use and no rescue clinical care, including unscheduled asthma care in the office,

urgent care center, emergency department, or hospital" (Zeiger et al., 2005, pg. 651).[20] Nine studies report specifically on hospitalization and emergency department visits as independent outcomes (Allen-Ramey et al., 2004; Colice et al., 2008; Ducharme et al., 2012; Li et al., 2014; O'Connor et al., 2006; Orsini et al., 2004; Stempel et al., 2002; Wu et al., 2014; Zeiger et al., 2008).

Similar quality issues are addressed in each study. Specifically, issues pertaining to assessing the adherence to treatment, evaluating the level of asthma severity, concerns of patients being misdiagnosed or misclassified as having asthma, and heterogeneity concerning co-morbidities such as allergic rhinitis or smoking are discussed in all studies. Since these concerns pertain to confounding they can greatly affect the interpretation of study results. As such, even the randomized control trials are subject to severe confounding concerns.[21]

Sample size also presents a concern for several studies. Four studies have sample sizes less than 1,000 people, averaging approximately 150 people in the LTRA treatment group and 375 in the ICS treatment group (Allen-Ramey et al., 2003; Ducharme et al., 2012; Stempel et al., 2002; Zeiger et al., 2005). Two studies have less than 75 people in the LTRA treatment group (Blais et al., 2011; Ducharme et al., 2012). Small sample sizes diminish statistical power of the

[20] Studies using composite outcomes were eligible for this study if one of the factors of the outcome included an inpatient stay/hospitalization or an ED visit. Many of the composite outcomes combine hospitalization and ED visit into one outcome. Studies including more than hospitalization, ED, or oral corticosteroids are considered multifaceted composite outcomes.

[21] Zeiger et al. (2008), in post hoc analysis, reports identifying a subgroup of patients who appear to have moderate asthma, rather than mild. This refers to the issue of assessing and classifying severity of disease for asthma. The range of severity, in conjunction with the possible misclassification of severity is cited by the authors as contributing limitations of the study. Likewise, Price et al. (2013) rely on self-report for smoking rather than a more objective assessment. Furthermore, given this study evaluated the treatments in a population which smokes, the possibility of patients having mild COPD rather than asthma exists.

study, making it difficult to adequately detect a difference of effect. Consideration of sample size is used in the assessment of study quality.

Methods of Quality Assessment

The second research question seeks to identify if the two methods of assessing quality of studies provide different guidance in forming a response to the first research question. While the EPC method is based on GRADE methodology, it differs with respect to how evidence from RCT and observational studies are graded (Owens et al., 2010; Slutsky, Atkins, Chang, & Sharp, 2010). GRADE initially assesses RCTs with an initial quality of evidence of HIGH, which can be downgraded based on four domains; observational studies begin with a Low-quality of evidence and can be upgraded based on three additional domains, although upgrading is discouraged in GRADE (Guyatt et al., 2011a). EPC, however, realizes that policy decisions may view internal bias to be more of a risk than external bias, as well as certain outcomes available in observational studies may be preferred for policy considerations (Owens et al., 2010). As such, EPC allows for both the upgrading of observational studies and the downgrading of RCTs to occur over all domains.

The domains of a study both GRADE and EPC consider are as follows: risk of bias, inconsistency, indirectedness, imprecision, publication bias, strength of evidence (effect size/magnitude), dose-response, and residual confounding (Balshem et al., 2011; Guyatt et al., 2011f; Owens et al., 2010). These domains may be assessed for individual studies, however, since the goal for both strategies is to evaluate the overall quality of evidence, these domains are generally assessed for a group of studies. GRADE refers to risk of internal bias only, while EPC considers both internal and external validity concerns equally (Guyatt et al., 2011g; Owens et al., 2010). Both GRADE and EPC generally regard inconsistency and imprecision in the same

manner (Guyatt et al., 2011b, 2011c; Owens et al., 2010). Inconsistency indicates whether the group of studies reports findings consistent with each other. Imprecision is an indication of the precision of the findings, whether an effect is found and if there is a high level of confidence in the effect.

GRADE defines indirectedness by evaluating various aspects of the study design (Guyatt et al., 2011d). First, are the populations similar to each other, and/or do the study populations directly correlate with the population of interest of the review (pg. 1304)? Second, is the intervention present in the studies the same as the intervention of interest? If the studies selected present information similar to, but not precisely of, the intervention of interest conclusions may be made, although they will be indirect (pg. 1305). Third, are the outcomes reported the outcomes of interest? If the outcomes of interest for the review are not directly presented in the selected studies, again conclusions will be drawn using indirect information (pg. 1306). Finally, if the interventions of interest are not directly compared, rather each compared to placebo, any conclusions drawn whether one intervention is better than the other will be indirect (pg. 1307). EPC considers indirectedness as either the direct link between the intervention and outcome of interest (Owens et al., 2010, pg. 516) or whether differing interventions are directly compared with each other (pg. 517).

Finally, publication bias, dose-response association, and residual confounding are similarly assessed in both GRADE and EPC methodologies. Publication bias "indicates that studies may have been published selectively with the result that the estimated effect of an intervention based on published studies does not reflect the true effect" (Owens et al., 2010, pg. 517; Guyatt et al., 2011e). Dose-response association, "either across or within studies, refers to a pattern of a larger effect with greater exposure" (Owens et al., 2010, pg. 517; Guyatt et al.,

2011f). The dose-response could refer to the dose of the treatment, duration the intervention is used, or the level of adherence to the treatment. Residual confounding refers to "plausible confounding factors [that] would work in the direction opposite to that of the observed effect… [and] had these confounders not been present, the observed effect would have been even larger than the one observed" (Owens et al., 2010, pg. 517; Goat et al., 2011f). GRADE will upgrade a low-quality level for observational studies for dose-response and residual confounding, while EPC will adjust the grading of study for these domains.

Quality Assessment of Selected Studies

The assessment of quality for the selected studies was done by outcome reported. As presented earlier, there are five outcomes reported in the selected studies: multifaceted composite, inpatient/ED/oral corticosteroids (OCS), inpatient/ED, inpatient hospitalization, and ED visit. Tables 3 and 4 summarize the studies in terms of the various domains used to assess quality for GRADE and EPC. Tables 5 and 6 present the overall scoring and quality grade for each of the outcomes reported. All study specific details are located in Appendix A. These data are used to aid in the creation of tables 3-6. Publication bias is not assessed for this review as all selected articles are published; this review did not include a search of unpublished literature.

GRADE Grading

Studies are initially evaluated with GRADE methodology based on outcome measures. However, due to diversity of study design within the observational studies, it was decided to stratify GRADE assessment into those that incorporated causal inference techniques (e.g. propensity scoring) and those that did not. Table 3 delineates each stratum in this analysis. Table 4 presents the assessment of quality of studies using the GRADE method. As specified, the two RCTs start with a quality level of HIGH and were evaluated for being downgraded, while the

observational studies begin with a quality level of LOW and are evaluated for possible upgrading.

Table 3: Composite of Stratum Used in Analysis

Outcome Stratum	Number of Studies Included	Total Number of Study Participants	Technique Used to Address Confounding Issues	Included Studies
Composite	2	1,369	Randomized Control Trial	Price et al., 2013 Zeiger et al., 2005
Inpatient/ED/OCS	3	147,502	Causal inference techniques used	Li et al., 2014 Wu et al., 2014 Zeiger et al., 2008
	2	41,231	None	Lee et al., 2010 Blais et al., 2011
Inpatient/ED	1	56,168	Causal inference techniques used	Allen-Ramey et al., 2003
	1	960	None	Tan et al., 2009
Hospitalization	5	185,522	Causal inference techniques used	Allen-Ramey et al., 2004 Li et al., 2014 O'Connor et al., 2006 Wu et al., 2014 Zeiger et al., 2008
	4	3,542	None	Colice et al., 2008 Ducharme et al., 2012 Orsini et al., 2004 Stempel et al., 2002
ED Visit	5	185,522	Causal inference techniques used	Allen-Ramey et al., 2004 Li et al., 2014 O'Connor et al., 2006 Wu et al., 2014 Zeiger et al., 2008
	2	1,510	None	Colice et al., 2008 Ducharme et al., 2012

GRADE documentation states that although there are reasons for upgrading observational studies, "these factors…are encountered infrequently" (Guyatt et al., 2011f, pg. 1315). Furthermore, "although most observational studies, even if well done, yield low-quality evidence, one can consider rating up the quality of evidence when there is a large or very large magnitude of effect, when consideration of all plausible residual confounders and biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect, or when there is an evidence of a dose-response gradient" (pg. 1315). Given these factors were not overwhelmingly met, though some studies employed techniques to control for heterogeneity, it was decided to start all observational studies at the VERY LOW level and upgrade from there. Thus, studies that utilize causal inference statistical techniques were upgraded to a LOW level (Allen-Ramey et al., 2003; Allen-Ramey et al., 2004; Li et al., 2014; O'Connor et al., 2006; Wu et al., 2014; Zeiger et al., 2008).

The RCTs are downgraded from HIGH to LOW for several reasons (Price et al., 2013; Zeiger et al., 2005). Both serious indirectedness and imprecision are evident in both studies. The study by Price et al. (2013) is downgraded for indirectedness based on three factors: the study only considers an adult smoking population, uses a measure which incorporated several asthma outcomes along with hospitalization and ED visits, and primarily assesses outcomes for LTRA and ICS against a placebo. In this study the outcome measure measured the number of days (1) without more than "2 puffs of SABAs[22]", (2) nighttime symptoms, (3) "an unscheduled

[22] A short acting beta-antagonist is often referred to as a rescue inhaler. Many times, a prescription for a SABA is the medication albuterol.

healthcare visit" to include a hospitalization or ED visit, and (4) use of oral corticosteroids (pg. 764). This outcome measure indirectly measures the outcome of hospitalization and ED visits, as they are only a component of the primary outcome measure. Furthermore, effects in the adult smoking population can only indirectly assess what is found in the general asthma population.[23] Finally, the only mention of a direct comparison made between LTRA and ICS was one sentence stating, "a statistical difference between the 2 active treatments was not observed (P = .140)" (pg. 764-765). All other analyses presented in this study are based on comparison between treatment and placebo.

Likewise, the study conducted by Zeiger et al. (2005) is also downgraded because of indirectedness due to the outcome measure. In this study the multifaceted outcome measure is defined as "a day in which there was no inhaled albuterol or oral corticosteroids use and no rescue clinical care, including unscheduled asthma care in the office, urgent care center, emergency department, or hospital" (pg. 651). Again, this does not allow for directly assessing the effect of either LTRA or ICS on hospitalization or ED visits.

Both studies are also downgraded for imprecise findings. The sample size of both studies is a concern, given neither found an effect. It is unclear as to whether there truly is no effect or if the study does not have the statistical power to detect an effect. Price et al. (2013) examine approximately 350 people in both LTRA and ICS treatment arms, whereas Zeiger et al. (2005) has around 175 in each treatment arm. Imprecision is also noted as both studies reported non-

[23] This is the exact opposite of the issue with many RCTs, which often exclude smokers from studies. Excluding part of the general population does not provide a complete picture of what is happening in the population. However, the Price et al. (2013) study does illuminate on an important part of the general population, allowing decision-makers to understand a more complete picture of the whole population.

significant findings. As stated previously, Price et al. (2013) only states a non-significant p-value is found, so it is not possible to assess the confidence interval around the estimate. Zeiger et al. (2005) report an estimate of 1.8% of days, or a difference of ½ day/month, requiring asthma rescue techniques between LTRA and ICS. This finding is not significant and has a confidence interval of -3.2% - 6.8% of days. This interval clearly includes the possibility that either LTRA or ICS may perform better, rendering this effect an imprecise estimate.

As per GRADE guidelines, downgrading significantly in two areas moves the evidence from a HIGH level of quality to a LOW level of quality (Guyatt et al., 2011a). Thus, the RCTs in this review provide similar level of evidence as the well-done observational studies. Additionally, the limitations of the two RCTs do not suggest that any upgrading ought to be considered. The study by Price et al. (2013) does not quantify smoking, but relies on participant self-report. Also, it is reasonable to assume this population might have been misdiagnosed as having asthma, as smoking is also a risk factor for COPD. Asthma severity is not adequately assessed in either study, providing additional confounding issues that might impact the reported effect.

Table 4: GRADE - Assessment of Quality by Outcome and Risk of Bias

Outcome # Studies; #Participants	Risk of bias	Consistency of Findings[2]	Directedness of Comparison[2]	Precision of Finding[2]	Finding[1]	Dose-Response	Confounding	GRADE Quality
Composite								
2; 1,369	No serious limitations	No serious inconsistencies	Serious indirectedness	Serious imprecision	NS	-	-	Low
Inpatient/ED/OCS								
2;147,502	-	-	-	-	LTRA OR = 1.23 (1.04-1.45); 2 studies NS	NA	Causal inference techniques used	Low
2;41,231	-	-	-	-	2 95% confidence; 1 NS	Present in 1 study	No technique used	Very Low
Inpatient/ED								
1;56,168	-	-	-	-	LTRA OR = 0.80 (0.72-0.88)	Present opposite result	No technique used	Very Low
1;960	-	-	-	-	ICS OR = 1.85 (0.74-4.61)	NA	Propensity score used; sample size very small	Very Low
Hospitalization								
5;185,522	-	-	-	-	NS	NA	Causal inference techniques used	Low
4;3,542	-	-	-	-	Mostly Significant findings; opposite directions	NA	No technique used	Very Low
ED Visit								
5;185,522		-	-	-	NS	NA	Causal inference techniques used	Low
2;1,510	-	-	-	-	NS	NA	No technique used	Very Low

[1] NS: Not significant at 95% confidence level; Significant: At 95% confidence level; confidence interval found in parentheses
[2] If findings were mixed, the negative was indicated: inconsistent, indirect, and imprecise

EPC Grading

The EPC evaluation is conducted in the same manner as the GRADE evaluation as it pertains to stratifying observational studies into those that incorporated causal inference techniques (propensity scoring) and those that do not. Table 5 presents the assessment of quality of studies using the EPC method. For the risk of bias, though, each group is identified by the design type and level of internal validity (Owens et al., 2010).

Table 6 presents how each stratum is scored and the resulting level of quality grade. Scoring within the EPC methodology is "determined by either a point system for combining ratings of the domains or a qualitative consideration of the domains" (Owens et al., 2010, pg. 520). This determination is left up to the reviewer in order to determine the best method given the current research. For the purposes of this study, where EPC quality is being compared to GRADE, a similar point system has been chosen. Each domain is scored in the positive, where 1 point is given for the preferred outcome and 0 points for the non-preferred. Risk of bias, however, is scored differently. Two points are given for RCT, due to high internal validity, and one point is given for observational studies that employ causal inference techniques. Given external validity is needed for policy decisions in asthma reversing the RCT and causal inference point assessment has been considered. However, it was determined scoring should remain as similar to GRADE methodology as possible.

The scoring for dose-response is done in a two-step process. First, a point is given for those studies that attempt to determine a dose-response. Only two studies indicate a dose-response (Tan et al., 2009; Zeiger et al., 2005). Zeiger et al. (2005) continued the experiment in an open-label arm, where patients using ICS had more rescue free days (6.2% of days) than

patients using LTRA (CI: 0.80% - 11.66%).[24] Tan et al. (2009) conduct analysis for the sub-population of participants that have a high level of adherence, and found patients in the LTRA group are more likely to have a hospitalization or ED visit than those in the ICS group (OR=1.74 CI:1.02-2.99). These results, though, are inconsistent with the overall analysis of each study. Thus, the second step in scoring identifies whether the dose-response effect reinforces the findings from the overall analysis. For this stage of scoring, a dose-response of 1 or -1 is assessed, depending on whether the dose-response supports or contradicts the overall finding. If the dose-response finding reinforces the primary finding, then 1 point is scored. Otherwise, the score is -1. While consideration was given to establish the scoring method similar to the other domains, it was concluded that a dose-response score should not increase the overall score for the quality of the study unless the dose-response results confirmed the primary findings. A dose-response that has a contradictory finding may be indicating the presence of confounding rather than the true effect.

For EPC, the quality may be graded as high, moderate, low, or insufficient. High is given when there is a "[h]igh confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect" (Owens et al., 2010, pg. 519). Moderate reflects "confidence that the evidence [moderately] reflects the true effect… [and where f]urther research may change…confidence in the estimate of effect [or]…the estimate" (pg. 519). Similarly, low confidence indicates "[f]urther research is likely to change the

[24] "Based on the predefined confidence bound" Zeiger et al. (2005) report the double-blind study as a significant finding and the open-label as non-significant (pg.s 652– 653). "[I]f the 95% CI lay entirely below 10%, corresponding to 3 days rescue-free days per month, the conclusion that montelukast is at least as effective as fluticasone would be supported" (pg. 651). Since the upper confidence level in the open-arm portion of the study is above 10%, the hypothesis is not supported.

confidence in the estimate of effect and is likely to change the estimate" (pg. 519). Finally, the evidence is graded as insufficient if "[e]vidence either is unavailable or does not permit a conclusion" (pg. 519).

It was determined a score of 5 would be the highest possible, thus maintaining consistency with the GRADE evaluation. A stratum with RCTs reporting consistent, direct and precise effects would produce a score of 5. Furthermore, it was determined, *a priori*, a score of 5 or 4 would be rated as high, 3 would be moderate, 2 or 1 would be low, and regardless of the score, strata that produced inconsistent findings would be insufficient.

After scoring the domains and tabulating the overall EPC Grade for each stratum, this review identifies 3 moderate quality strata, including studies with multifaceted, hospitalization and ED visit outcomes (Allen-Ramey et al., 2004; Li et al., 2014; O'Connor et al., 2006; Price et al., 2013; Wu et al., 2014; Zeiger et al., 2005, 2008). Four strata are identified as low-quality strata, including studies with inpatient/ED/OCS, inpatient/ED, and ED visit outcomes (Allen-Ramey et al., 2003; Blais et al., 2011; Colice et al., 2008; Ducharme et al., 2012; Tan et al., 2009; Lee et al., 2010). Lastly, two strata are determined to have an insufficient rating (Colice et al., 2008; Ducharme et al., 2012; Li et al., 2014; Orsini et al., 2004; Stempel et al., 2002; Wu et al., 2014; Zeiger et al., 2008). The strata identified as 'Uknown' in the 'Consistency of Findings' domain both have inconsistent results, making it impossible to draw an overall conclusion for the strata.

The insufficient evidence is for both the inpatient/ED/OCS and hospitalization outcomes. The moderate evidence report outcomes of multifaceted, hospitalization, and ED visit. The outcome inpatient/ED is only reported in low-quality studies; low-quality studies also report

inpatient/ED/OCS and ED visit only outcomes. Finally, it is important to note that a study may report on several outcomes, thus being considered in multiple strata.

Table 5: AHRQ EPC - Strength of Evidence by Outcome and Bias Level

Outcome # Studies; #Participants	Risk of bias Design Internal Bias Level	Consistency of Findings[2]	Directedness of Comparison[2]	Precision of Finding[2]	Finding[1]	Dose-Response	Confounding
Composite							
2; 1,369	RCT Low	Consistent	Indirect	Imprecise	NS	Present in 1 study	Present
Inpatient/ED/OCS							
3;147,502	Retrospective Medium	Inconsistent	Direct	Imprecise	LTRA OR = 1.23 (1.04-1.45); 2 studies NS	NA	Causal inference techniques used
2;41,231	Retrospective High	Inconsistent	Direct	Imprecise	2 95% confidence; 1 NS	Present in 1 study	No technique used
Inpatient/ED							
1;56,168	Retrospective High	Unknown	Direct	Precise	LTRA OR = 0.80 (0.72-0.88)	Present opposite result	No technique used
1;960	Retrospective Medium	Unknown	Direct	Imprecise	ICS OR = 1.85 (0.74-4.61)	NA	Propensity score used; sample size very small
Hospitalization							
5;185,522	Retrospective Medium	Consistent	Direct	Imprecise	NS	NA	Causal inference techniques used
4;3,542	Retrospective High	Inconsistent	Direct	Precise	Mostly Significant findings; opposite directions	NA	No technique used
ED Visit							
5;185,522	Retrospective Medium	Consistent	Direct	Imprecise	NS	NA	Causal inference techniques used
2;1,510	Retrospective High	Consistent	Direct	Imprecise	NS	NA	No technique used

[1] NS: Not significant at 95% confidence level; Significant: At 95% confidence level; confidence interval found in parentheses
[2] If findings were mixed, the negative was indicated: inconsistent, indirect, and imprecise

Table 6: AHRQ EPC – Scoring of the Evidence

Outcome # Studies; #Participants	Risk of bias	Consistency of Findings[2]	Directedness of Comparison[2]	Precision of Finding[2]	Dose-Response/ Direction[3]	Confounding	Finding[1]	Score EPC Grade
Composite								
2; 1,369	2	1	0	0	1 -1	0	NS	3 Moderate
Inpatient/ED/OCS								
3;147,502	1	0	1	0	0	0	LTRA OR = 1.23 (1.04-1.45); 2 studies NS	2 Insufficient
2;41,231	0	0	1	0	0	0	2 95% confidence; 1 NS	1 Low
Inpatient/ED								
1;56,168	0	Unknown	1	0	1 -1	0	LTRA OR = 0.80 (0.72-0.88)	1 Low
1;960	1	Unknown	1	0	0	0	ICS OR = 1.85 (0.74-4.61)	2 Low
Hospitalization								
5;185,522	1	1	1	0	0	0	NS	3 Moderate
4;3,542	0	0	1	1	0	0	Mostly Significant findings; opposite directions	2 Insufficient
ED Visit								
5;185,522	1	1	1	0	0	0	NS	3 Moderate
2;1,510	0	1	1	0	0	0	NS	2 Low

[1] NS: Not significant at 95% confidence level; Significant: At 95% confidence level; confidence interval found in parentheses

[2] If findings were mixed, the negative was indicated: inconsistent, indirect, and imprecise

[3]If two numbers are present, the top number is the score for the dose-response analysis and the bottom number is the score for the direction of the dose-response.

Discussion of Results

GRADE versus EPC

Table 7 compares how the GRADE and EPC assessments rate the quality of the studies.[25] Additionally, it is also reports whether the strata outcomes collectively support LTRA as a first-line treatment for asthma due to similar or better outcomes as compared to ICS. Of note is the presence of "insufficient" as an EPC option in the findings table. This immediately allows any decision-maker to recognize the conflicting results of the strata. This is not evident in the overall quality grade in the GRADE system. Rather, in this review, GRADE clusters insufficient evidence along with other low or very low-quality studies. Furthermore, in the EPC column, it appears plausible that observational studies and RCTs could both achieve a high-quality rating, although that is not seen in the current review.

The above observations of Table 7 provide the foundation of addressing the second research question: will conclusions differ depending on whether GRADE or EPC quality assessment is used? In this review, GRADE assesses the quality of all studies to be of low to very low quality of evidence. It is difficult to conceive such a level of evidence would persuade a decision-maker to alter current asthma treatment policy, regardless of the evidence supporting the conclusion of LTRA performing as well as ICS. The presence of only low-quality RCTs further supports the notion the primary hypothesis (LTRA should be used as a first line of

[25] The use of GRADE or EPC is only a tool to assess the quality of available studies. This is not a tool to ascertain what conclusion we can draw from the data presented in the studies. The information drawn from GRADE or EPC, in conjunction with the published results of each study, allows for a conclusion to be drawn regarding the meaning of the body of work. If all studies are determined to have low quality, it is important to understand why it is low. Is the low quality due to the presence of internal bias, are the findings inconsistent or imprecise, or does the body of work not directly address the current research question? The answer to these questions will aid in understanding what the body of evidence illustrates in terms of the current research. The quality of studies within a specific topic is only one consideration in determining the overall findings of the combined literature.

treatment for asthma as outcomes are similar to those achieved with ICS) should be rejected. At the very least, additional data would need to be collected in order for LTRA to be suggested as a first-line treatment.

Table 7: Comparison of GRADE and EPC Rating with Study Findings

Outcome # Studies; #Participants	**GRADE**	**EPC**	**Supports the addition of LTRA to first-line treatment**
Composite			
2; 1,369	Low	Moderate	Yes
Inpatient/ED/OCS			
3;147,502	Low	Insufficient	Cannot draw a conclusion
2;41,231	Very Low	Low	Yes
Inpatient/ED			
1;56,168	Very Low	Low	Yes - with caveat
1;960	Very Low	Low	Yes
Hospitalization			
5;185,522	Low	Moderate	Yes
4;3,542	Very Low	Insufficient	Cannot Draw a conclusion
ED Visit			
5;185,522	Low	Moderate	Yes
2;1,510	Very Low	Low	Yes

The results of the EPC grading, though, provide a different picture. Since the majority of the strata consist of low-quality or insufficient evidence, additional research ought to be done. However, the moderate quality evidence indicates a pattern of LTRA and ICS having similar results in the population. Moreover, moderate quality evidence is seen over varying study designs and outcomes, further supporting the hypothesis that the two treatments may be equally effective in terms of external validity. Finally, the use of "insufficient" as a grade allows for the reviewer to focus on demonstrative findings, permitting the ability to identify possible patterns

while contemplating the possibility further research should occur. Thus, using the EPC method in evaluating the quality of the evidence can alter the conclusions drawn from the evidence.

LTRA as a First-line Treatment

Nine studies report non-significant findings, meaning the outcomes of populations that use LTRA did not statistically differ significantly from those who use ICS (Allen-Ramey et al., 2003; Allen-Ramey et al., 2004; Blais et al., 2011; Colice et al., 2008; Li et al., 2014; O'Connor et al., 2006; Price et al., 2013; Wu et al., 2014; Zeiger et al., 2005). Four studies report that LTRA treatment results in better outcomes (i.e. less hospitalization and/or ED visits) (Blais et al., 2011; Ducharme et al., 2012; Tan et al., 2009; Lee et al., 2010). Two studies report that ICS treatment results in better outcomes (i.e. less hospitalization and/or ED visits) (Orsini et al., 2004; Stempel et al., 2002). One study reported mixed findings for outcomes. Specifically, when inpatient, ED visits and OCS are considered collectively, ICS treatment results in better outcomes (Zeiger et al., 2008). However, when each outcome is considered individually, LTRA treatment and ICS treatment result in similar outcomes.

By outcome type, both RCTs, which have a multifaceted outcome, report LTRA and ICS treatment are not significantly different. Of the observational studies with a combined outcome of inpatient/ED/OCS, four studies report that LTRA treatment has outcomes similar to or better than ICS treatment and one study reports ICS treatment has a better outcome. The two studies reporting on the combined outcome of hospitalization/ED visit demonstrate that LTRA treatment results in similar or better outcomes than ICS treatment. However, in one study, a sub-analysis of the highly adherent population demonstrates that ICS treatment produces better outcomes. Table 8 illustrates these findings.

Of the non-combination outcome studies, nine report on hospitalization as an outcome. Most of these (7) indicate that LTRA treatment results in similar or better outcomes as compared to ICS treatment. Two report that ICS treatment produces better outcomes than LTRA treatment. Finally, all 7 of the studies reporting on ED visits alone find LTRA treatment to do as well or better than ICS treatment in preventing ED visits in the asthma population studied.

Table 8: Finding by Outcome

Outcome	**LTRA Similar or Better Outcomes**	**ICS Better Outcomes**
Composite	(Price et al., 2013) (Zeiger et al., 2005)	
Inpatient/ED/OCS	(Blais et al., 2011) (Lee et al., 2010) (Li et al., 2014) (Wu et al., 2014)	(Zeiger et al., 2008)
Inpatient/ED visit	(Allen-Ramey et al., 2003) (Tan et al., 2009)	(Tan et al., 2009) * For adherent groups only
Inpatient/Hospitalization	(Allen-Ramey et al., 2004) (Colice et al., 2008) (Ducharme et al., 2012) (Li et al., 2014) (O'Connor et al., 2006) (Wu et al., 2014) (Zeiger et al., 2008)	(Orsini et al., 2004) (Stempel et al., 2002)
ED Visit	(Allen-Ramey et al., 2004) (Colice et al., 2008) (Ducharme et al., 2012) (Li et al., 2014) (O'Connor et al., 2006) (Wu et al., 2014) (Zeiger et al., 2008)	

Conclusions

The majority of the studies indicate that LTRA treatment does at least as well as ICS treatment in preventing hospitalization and ED visits for patients with mild-moderate persistent asthma. Focusing on the fact that only three out of the 14 studies denote that ICS treatment produces better outcomes supports the addition of LTRA as a first-line treatment for asthma; LTRA and ICS produce similar outcomes for those with mild-moderate persistent asthma. However, taking into consideration the GRADE and EPC quality assessments, cautious deliberation seems advisable and requesting additional research is a reasonable response as the quality of the evidence is not high. Certainly, in a world where adherence to ICS is difficult to achieve, it appears that a less clinically efficacious treatment with higher adherence levels might produce satisfactory healthcare outcomes.

Regarding adherence, eight studies attempt to capture some measure of adherence (Allen-Ramey et al., 2004; Blais et al., 2011; Colice et al., 2008; Ducharme et al., 2012; Tan et al., 2009; Lee et al., 2010; Li et al., 2014; Wu et al., 2014). Li et al. (2014) was the only study that does not indicate a finding for adherence in the study population; this study only discusses the method used to calculate the adherence measure for use in the statistical model. Four articles indicate a significantly higher use of LTRA by patients than ICS (Allen-Ramey et al., 2004; Blais et al., 2011; Colice et al., 2008; Ducharme et al.). The three studies did not indicate statistical findings for adherence. Both Lee et al. (2014) and Wu et al. (2014), while discussing the method of calculating an adherence measure for use in a statistical model, state levels of adherence, although do not indicate whether the values are statistically significantly different. Tan et al. (2009) uses an adherence calculation to control for confounding in the regression model and simply mentions the LTRA population was more adherent than the ICS population.

Asthma policy decisions require knowledge and evidence of how the general asthma population interacts with the prescribed treatment and the impact on healthcare utilization. To this end, the analysis of the GRADE and EPC quality assessment indicates that EPC allows for analysis to equally consider study designs that have high internal validity against those that have high external validity. Since RCTs consistently demonstrate that both LTRA and ICS are safe and efficacious treatments for mild-moderate persistent asthma, future research ought to focus on which treatment is effective for producing positive health outcomes for patients in everyday settings and reducing their overall healthcare utilization. Since a causal link between both treatments and clinical asthma outcomes has been repeatedly established, research questions should strive to identify the link between reality-based treatment use and healthcare utilization. Although the goal of achieving a superior clinical outcome for asthma patients is paramount, one must also acknowledge that individual patients may be satisfied with a less than optimal clinical state. If healthcare utilization and pre-mature deaths are reduced using less clinically efficacious treatments, it must be considered as an acceptable alternative in healthcare policy.

The variety of outcomes and results in the selected studies suggest that the consideration of LTRA as a first-line treatment of asthma cannot be rejected. This review finds consistent results across RCT and observational studies, as well as various outcome measurements regarding hospitalization and ED visits. Furthermore, given the complexity of asthma risk factors, levels of severity, and adherence to treatment regimen, weighing studies with high external validity is essential in order to draw conclusions of how LTRA and ICS will affect real-life scenarios. While RCTs have proven useful in demonstrating a causal-effect of both treatments, they provide little insight as to how the general asthma population will react to the treatments. The consideration of data from observational and pragmatic studies demonstrate the

external validity of these treatments. Combined data from various study designs enhance the ability of decision-makers to create effective healthcare policy.

In conclusion, based on this review, LTRA ought to be considered as a first-line treatment option, on par with ICS. However, additional studies are needed to increase certainty of the data. Both raising the quality of the studies as well as providing further evidence in populations not previously studied are essential in evaluating LTRA versus ICS questions. To this end, further understanding of the circumstances LTRA might be most beneficial is also required; studies already indicate LTRA is more beneficial in allergic rhinitis and smoking populations. As such, it may be most efficient to study the effects of LTRA and ICS on smaller community populations, where communities are more homogeneous in terms of prescribing patterns, environmental risk factors, and cultural behavior patterns. This would alleviate some of the concerns of unobserved heterogeneity in the study population. Several more localized studies may provide needed insight into which populations might benefit most from LTRA treatments over ICS treatments, and thus healthcare policy may need to vary depending on population characteristics.

Appendix A

Study: Allen-Ramey 2003

Study Design	Retrospective study with use of propensity score to identify treatment groups
Data Used	Protocare Sciences' Proprietary Managed Care Organization Data
Participants	960 asthmatics; 807 ICS v 153 LTRA
Inclusion Criteria	• A full-year of medical eligibility and pharmacy coverage • Aged 6-55 • Continuously enrolled from 1997 - 1999 • One inp/ed or two opt visits for asthma OR 2 pharmacy claims for an anti-asthma drug • Had index prescription for ICS or LTRA from 7/1998 - 6/1999 • No controller meds in the 6 months prior to index • No other controller med 30 days post index
Exclusion Criteria	Medicare beneficiaries; COPD; Chronic bronchitis; Emphysema; Prescription for Atrovent or Combivent
Outcome Measure	Inpatient visit/ED visit composite
Outcome Reported	OR =1.85 CI: 0.74-4.61 p=0.18 (LTRA Reference)
Adherence Measure	N/A
Statistical Method	Multivariate Regression

Study: Allen-Ramey 2004

Study Design	Retrospective study with use of propensity score to identify treatment groups
Data Used	Claims data from various regions around the United States
Participants	6,160 asthmatic patients; 3,080 in both LTRA and ICS groups
Inclusion Criteria	• At least 1 diagnosis of asthma between 1/1/1998 and 6/30/2001 OR 2 or more claims for an antiasthma medication on 2 different dates within 1 year (fluticasone or montelukast) • "Eligible individuals had to be continuously enrolled in a health plan with pharmacy benefits for the 12 months before the index prescription (the preindex period) and for the 12 months after the index prescription (the postindex period)" pg. 374 • Ages 2-55
Exclusion Criteria	• "Filled a prescription for an asthma controller in the 6 months immediately before the index date." • "Filled a prescription for more than 1 asthma controller in the 30 days immediately after the index date." • Chronic bronchitis; emphysema; bronchiectasis; chronic airway obstruction; cystic fibrosis; bronchopulmonary dysplasia; use of COPD medications during the preindex or postindex period
Outcome Measure	Hospitalization; ED visits
Outcome Reported	Hospitalization: 1.00 CI:0.58-1.72; ED visit: 0.87 CI:0.70-1.08 (LTRA v ICS)
Adherence Measure	Reported on the number of prescriptions filled in a year
Statistical Method	Multivariate logistic regression

Study: Blais 2011

Study Design	Retrospective study
Data Used	Two administrative databases from Quebec, Canada
Participants	27, 355 children; 489 LTRA v 27,288 ICS
Inclusion Criteria	• First prescription 1/1998 - 8/2005 • No dispensed ICS or LTRA in the previous year • At least 1 asthma diagnosis in the prior year • Age between 5-15 at index treatment • Covered by RAMQ Drug Insurance plan for at least 1 year prior to index • A follow-up at least 4 months after index
Exclusion Criteria	Chronic bronchitis; cystic fibrosis; dyspnea; layrngotracheitis; had ICS in the prior year or in the first 90 days of LTRA index
Outcome Measure	Combined inpatient/ED/OCS
Outcome Reported	>1 previous exacerbation in year prior to index: 1.4 (ICS) v 1.6 (LTRA) CI: 0.8 - 3.1 No previous exacerbation in year prior to index: 2.2 (ICS) v 2.3(LTRA) CI: 1.3 - 4.0
Adherence Measure	Proportion of Prescribed Days Covered (PPDC) and Proportion of Days Covered (PDC)
Statistical Method	Poisson regression with confounders entered into the model

Study: Colice 2008

Study Design	Retrospective study
Data Used	Privately insured claims database
Participants	1,283 asthmatics; 550 LTRA v 319 ICS v 414 ICS+LABA
Inclusion Criteria	• Ages 6-64 • Asthma diagnosis of asthma • Continuous eligibility for 1 year prior and 1 year after index • Mild persistent asthma
Exclusion Criteria	COPD; mild intermittent asthma; moderate-to-severe asthma; no more than 2 prescriptions of SABA in year prior to index; no ED or hospitalization asthma related visit 30 days prior to index
Outcome Measure	Inpatient visit; ED visit
Outcome Reported	All p-values were not statistically significant
Adherence Measure	Reported on prescriptions filled; not included in model
Statistical Method	Multivariate GLM with a log-link and gamma distribution

Study: Ducharme 2012

Study Design	Retrospective study
Data Used	Cohort drawn from children who presented to the Asthma Center of a pediatric hospital in Canada. Data was linked to Canadian administrative databases.
Participants	227 asthmatic children; 58 LTRA v 169 ICS
Inclusion Criteria	• Ages 2-17 • Presented to the Center between 1/2000 and 12/2007 • Mild or moderate severity as assessed by an Asthma Center physician • Prescribed either LTRA or ICS • Covered by Quebec medical and drug plans
Exclusion Criteria	Other chronic lung diseases
Outcome Measure	Hospitalization; ED visit
Outcome Reported	ED visits RR: 1.79 CI: 0.96-3.34 (ICS v LTRA) Hospitalization RR: 3.63 CI:1.20-11.03 (ICS v LTRA)
Adherence Measure	Proportion of Days with Supply Prescribed (PDSP), PPDC, PDC
Statistical Method	Generalized Linear Model

Study: Tan 2009

Study Design	Retrospective study
Data Used	Administrative claims data from 8 commercial US plans
Participants	56,168 adult asthmatics; 11,561 LTRA v 13,725 ICS v 30,882 Other
Inclusion Criteria	• Aged 18-64 • At least 1 medical claim for asthma from 9/1/2002 - 8/31/2006 • Receive monotherapy with ICS, LTRA, LABA or combination of those • Continuously enrolled in a health plan for 12 months pre and post index
Exclusion Criteria	Emphysema; chronic bronchitis; cystic fibrosis; bronchopulmonary dysplasia; other respiratory diseases
Outcome Measure	Hospitalization/ED visit combined
Outcome Reported	Hospitalization/ED: OR=0.80, CI: 0.72-0.88 (ICS reference group) Adherent group: 1.74 CI: 1.02-2.99 (ICS reference)
Adherence Measure	Medication Possession Ratio (MPR)
Statistical Method	Generalized Linear Model

Study: Lee 2010

Study Design	Retrospective study
Data Used	HealthCore Integrated Research Database
Participants	28,074 adult asthmatics; 6,500 LTRA v 7,376 ICS v 14,198 combination
Inclusion Criteria	• Ages 18 - 56 • At least 1 primary diagnosis of asthma in the ED or inpatient setting OR at least 2 outpatient diagnosis for asthma during 1/2004 - 3/31/2009 • At least 1 prescription for asthma controller medication between 1/2005 - 3/31/2008 • Continuous health plan eligibility 1 year prior and 1 year after index prescription
Exclusion Criteria	Patients with a history of asthma controller fills during previous 6 months; pregnant women; COPD; emphysema; other respiratory diseases; cystic fibrosis; bronchopulmonary dysplasia
Outcome Measure	Hospitalization/ED/OCS combined
Outcome Reported	0.82 CI: 0.75 - 0.89 (LTRA v ICS)
Adherence Measure	MPR
Statistical Method	Negative binomial model

Study: Li 2014

Study Design	Retrospective study with use of propensity score to identify treatment groups
Data Used	Population-Based Effectiveness in Asthma and Lung Diseases (PEAL) Network data
Participants	24,680 asthmatic children; 5,867 LTRA v 4,022 ICS (Medicaid) 1,286 LTRA v 13,505 ICS (Commercial)
Inclusion Criteria	• Diagnosis code for asthma during 1/1/04 - 12/31/2010 • Continuous enrollment 1 year prior to index
Exclusion Criteria	diagnosis of cystic fibrosis, immuniodeficiency, bronchietctasis, hereditary/degenerative diseases of the CNS, psychoses, mental retardation, CHF, hypertension, or pulmonary embolism
Outcome Measure	Hospitalization/ED/OCS; hospitalization; ED visit; OCS use
Outcome Reported	No statistical significance reported for any outcome
Adherence Measure	PDC
Statistical Method	Cox regression to analyze time-to-event adjusting for PDC jointly used with one of the following three methods: covariate-adjusted regression; covariate-adjusted regression with groups defined by propensity score; covariate-adjusted regression with groups defined by high-dimensional propensity score

Study: O'Connor 2006

Study Design	Longitudinal, retrospective study with use of propensity score to identify treatment groups
Data Used	Claims data from US managed care plans
Participants	31,860 asthmatics; 7,385 LTRA v 24,475 ICS
Inclusion Criteria	• New prescription for ICS or LTRA between 1/1/1999 and 12/31/2000 • All ages (<18/18+) • Enrolled in plan for at least 12 months prior and 12 month post index date • At least 1 medical claim indicating a diagnosis of asthma during the study period. • Controller naive during pre-index
Exclusion Criteria	COPD; cystic fibrosis; patients who used ICSs, LTRAs, long-acting 2-adrenergic agonists (LABAs), mast cell stabilizers (MCSs; cromones), or theophylline during the 12-month preindex period
Outcome Measure	Hospitalization; ED visit
Outcome Reported	(ICS v LTRA) Hospitalization: OR = 0.94 CI:0.70-1.26 ED: OR = 1.06 CI: 0.93-1.21
Adherence Measure	-
Statistical Method	Logistic regression

Study: Orsini 2004

Study Design	Retrospective study
Data Used	MarketScan Commercial Claims and Encounters
Participants	1,177 asthmatics; 777 LTRA v 400 ICS
Inclusion Criteria	• Aged 4 years and older • At least 1 primary diagnosis of asthma between 1/1/1997 and 6/30/2000 • At least 1 outpatient pharmaceutical claim for fluticasone proprionate or montelukast • Continuous enrollment in plan for 12 months prior and post index
Exclusion Criteria	Cystic fibrosis; COPD; older than 45 years with 2+ prescriptions for ipratropium bromide; any prescription for salmeterol, ICS, or LTRA in 12 months prior to index
Outcome Measure	Hospitalization
Outcome Reported	Univariate/ICS reference: OR=0.382; p=0.13 Multivariate/ICS reference: OR=0.117 p=0.04 Cox/ICS reference: HR=0.13 CI: 0.02-0.95
Adherence Measure	-
Statistical Method	Univariate logit; Logistic regression; Cox proportional hazard

Study: Price 2013

Study Design	Randomized, double-blind, placebo-controlled, crossover study
Data Used	Data collected from 131 sites in 29 countries
Participants	1,019 adult asthmatic smokers; 347 LTRA v 336 ICS v 336 placebo
Inclusion Criteria	• Ages 18-55 • Active cigarette smokers • Smoking history of 30 pack years or less (pack years 5 cigarette packs per day multiplied by the number of years smoking) • Clinical history of chronic asthma for 1 year or more with symptoms including dyspnea, wheezing, chest tightness, and/or cough • Eligible patients were previously unable to quit smoking (pg. 764)
Exclusion Criteria	COPD; emphysema
Outcome Measure	Composite of asthma exacerbation, to include hospitalization and ED visit
Outcome Reported	P=0.140
Adherence Measure	-
Statistical Method	ANOVA

Study: Stempel 2002

Study Design	Retrospective study
Data Used	Administrative claims from 3 US health plans
Participants	855 asthmatics; 285 LTRA v 570 ICS
Inclusion Criteria	• Aged 4-64 • Continuously enrolled for 24 months • Have at least 1 prescription claim for ICS and no LTRA claims in year prior to index • A medical claim for asthma
Exclusion Criteria	None reported
Outcome Measure	Hospitalization
Outcome Reported	ICS Reference OR = 7.1 CI: 2.79-17.95
Adherence Measure	-
Statistical Method	Multivariate regression

Study: Wu 2014

Study Design	Retrospective study with use of propensity score to identify treatment groups
Data Used	Population-Based Effectiveness in Asthma and Lung Diseases (PEAL) Network data
Participants	26,191 asthmatic children aged 4-17; 5,867 LTRA v 4,022 ICS v 735 ICS-LABA (Medicaid) 1,286 LTRA v 13,505 ICS v 776 ICS-LABA (Commercial)
Inclusion Criteria	• Diagnosis code for asthma during 1/1/04 - 12/31/2010 • Continuous enrollment 1 year prior to index
Exclusion Criteria	diagnosis of cystic fibrosis, immuniodeficiency, bronchietctasis, hereditary/degenerative diseases of the CNS, psychoses, mental retardation, CHF, hypertension, or pulmonary embolism
Outcome Measure	Hospitalization/ED/OCS; hospitalization; ED visit; OCS use; composite exacerbation outcome
Outcome Reported	No statistical difference between LTRA and ICS except for allergic rhinitis patients in TennCare (both ED and Composite) HR: 0.44 CI:0.21-0.93 for Cox regression LTRA v ICS
Adherence Measure	PDC
Statistical Method	Cox regression to analyze time-to-event adjusting for PDC jointly used with one of the following two methods: covariate-adjusted regression; and covariate-adjusted regression with groups defined by high-dimensional propensity score.

Study: Zeiger 2005

Study Design	Randomized, double-blind control trial
Data Used	Data collected from the Mild Asthma Montelukast versus Inhaled Corticosteroid Study (MIAMI)
Participants	350 asthmatics; 177 LTRA v 173 ICS
Inclusion Criteria	• Aged 15 to 85 years • mild persistent asthma for at least 4 months • Evidence of airway reversibility or hyper-responsiveness • Treatment with only as-needed albuterol • FEV1 during the run-in period 80% of predicted • "Daytime symptoms and albuterol use on an average of 2 days, but 6 days, per week during the 2 weeks before randomization" (pg. 650)
Exclusion Criteria	Use of other asthma controller medications or systemic corticosteroids within the past month or required recent hospital or urgent care for asthma.
Outcome Measure	Composite measure of asthma control, including hospitalization and ED visits
Outcome Reported	Percent of rescue free days (ICS v LTRA): 74.9% v 73.1% 1.8% or 1/2 day/month CI: -3.2% - 6.8%
Adherence Measure	Monitored medication given in trial
Statistical Method	ANOVA

Study: Zeiger 2008

Study Design	Retrospective study
Data Used	Kaiser Permanente of Southern CA administrative claims
Participants	96,631 asthmatics: 848 LTRA v 26,879 ICS v 68,904 other
Inclusion Criteria	• Aged 5 years and older • KPSC drug coverage • Any hospital discharge diagnosis of asthma OR 2+ asthma-related dispensed drugs OR any ED/outpatient asthma-related diagnosis • Continuously enrolled during 2002 - 2004
Exclusion Criteria	COPD; cystic fibrosis
Outcome Measure	Hospitalization/ED/OCS; hospitalization; ED visit
Outcome Reported	LTRA v ICS (reference) Inpatient: OR = 1.37 CI: 0.67-2.80 ED: OR = 1.20 CI: 0.82-1.73 Any asthma utilization: OR=1.23 CI: 1.04-1.45 p=0.02
Adherence Measure	-
Statistical Method	ANOVA; Multivariate Least Squares Regression

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A Comparison of Health Care Outcomes for Inhaled Corticosteroid versus Leukotriene Receptor Antagonist Use in the Maryland Medicaid Population

Introduction

Background and Significance

Historically, clinical trials have been considered the superior source of information when assessing various medications for standardized asthma treatment guidelines (Price et al., 2011; Rawlins 2008). Clinical studies evaluating both inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) for efficacy in controlling asthma have determined ICS to be the more efficacious medication (Colice, 2008; Ducharme, 2011). Thus, evidence-based guidelines for the diagnosis, treatment, and management of asthma primarily use the clinical studies to derive the guidelines (Bousquet et al., 2007; Global Initiative for Asthma, 2016; National Asthma Education and Prevention Program, 2007). As such, ICS is recommended as the preferred treatment for mild to moderate persistent asthma, while LTRA is suggested as an alternate treatment. However, clinical trials are designed with strict inclusion and exclusion criteria that often eliminate some parts of the general asthma population using either ICS or LTRA, thereby reducing the generalizability of the results. Factors such as human behavior, the environment, and confounding diseases are some of the elements clinical studies fail to consider within a study (Ducharme, 2011; Finkelstein, Lozano, Farber, Miroshnik, & Lieu, 2002; Haughney et al., 2008; Price et al., 2011). Thus, the clinically established efficacy of a treatment may not translate to its effectiveness in actual practice (Gartlehner, 2006).

Several observational studies have considered the use of ICS and LTRA in the general population, specifically against the outcomes of an emergency department (ED) visit or an inpatient hospitalization (INPH) for asthma exacerbation (Allen-Ramey et al., 2003; Allen-

Ramey, Duong, Riedel, Markson, & Weiss, 2004; Blais et al., 2011; Colice et al., 2008; Ducharme et al., 2012; Lee et al., 2010; Li et al., 2014; Tan et al., 2009; O'Connor, Parasuraman, Roberts, & Leibman, 2006; Orsini, Limpa-Amara, Crown, Stanford, & Kamal, 2004; Stempel, Pinto, & Stanford, 2002; Wu et al., 2014; Zeiger et al., 2008). While most of these studies have found that the two treatments do not differ significantly, they do not provide conclusive evidence due to limitations of observational studies (Smith, 2016). Of note when assessing these studies is that they focus on commercial populations rather than Medicaid populations. The Medicaid population carries a substantial burden of asthma due to the number of asthma risk factors in this population versus a commercial population (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, n.d.). Only two studies have specifically evaluated the outcomes of ED visits and INPHs for ICS and LTRA treatment within a Medicaid population, and both of them focused only on the Tennessee Medicaid population (Li et al., 2014; Wu et al., 2014). Results of both studies indicate notable differences between the Medicaid and commercial populations. Of main interest, the percentage of Medicaid recipients using LTRA as treatment was higher in the Medicaid population than in the commercial population (2014).

Due to the lack of focus on Medicaid populations within the area of asthma research and the increased risk and prevalence of asthma within this population, there is a need to expand the research. Thus, the purpose of this study is to examine a different Medicaid population: Maryland. This may alter the population in a variety of ways, including exposure to different asthma risk factors, provider practices for treating asthma, and state Medicaid policy and programs, thereby resulting in a varied distribution of LTRA and ICS use throughout the population. The purpose of this study is to evaluate ED visits and INPHs utilization of recipients

with probable mild to moderate persistent asthma within the Maryland Medicaid population whose initial treatment was either LTRA or ICS (see Appendix A for a glossary of terms).

Methods

Data Source

This study used administrative claims data from the Maryland Medicaid program for state fiscal years (FYs) 2010 through 2015. The retrospective cohort was defined as the Maryland Medicaid population with probable mild to moderate asthma between July 1, 2009, and June 30, 2014 (i.e., FY 2010 through FY 2014) (see Appendix A for the definition of mild to moderate asthma). The population included Maryland Medicaid recipients (hereafter referred to as recipients) from the fee-for-service (FFS) and HealthChoice managed care organization (MCO) programs with at least one month of eligibility during the study period. Both the Maryland Department of Health and the University of Maryland, Baltimore County Institutional Review Boards gave approval to conduct this study. Maryland Medicaid administrative data from July 1, 2010, to June 30, 2015 (FY 2015) were used for assessment of the twelve-month follow-up period for study participants. Data included Medicaid eligibility, recipient demographic information, administrative claims for health care utilization, pharmacy dispensing, provider demographics, and program enrollment (FFS versus MCO enrollment dates during the eligibility period).

Study Population Selection

Recipients were initially eligible for the study if they had a diagnosis of asthma according to the International Classification of Diseases, Ninth Revision (ICD-9; codes included started with 493), on any ED visit or INPH record and filled a prescription for ICS or LTRA. Recipients who had at least four physician visits with an ICD-9 code for asthma and filled a prescription for

ICS or LTRA were also included. A physician visit is defined as a physician FFS claim (claim) or MCO claim (encounter) for a unique service day-provider combination.

The qualifying prescription had to be dated within 90 days of the ED visit, INPH, or fourth physician visit. For the purposes of this study, this 90-day window was considered the initial treatment for asthma. The 90-day window was chosen for several reasons: a recipient may have been seen by a physician up to three times for asthma prior to the qualifying diagnostic event; LTRA is also used for seasonal allergies, resulting in patients already being on the medication; and both ICS and LTRA are considered maintenance medications that may be a 90-day supply rather than the typical 30-day supply. Only recipients with a qualifying visit and a corresponding prescription occurring between July 1, 2009, and June 30, 2014, were included in the study. The follow-up period was identified for each person as the twelve-month period starting with the initial date of entrance (IDE) to the "study date" of qualifying event. If a recipient had multiple qualifying events (e.g., an inpatient hospitalization and four physician visits), then the date of the first qualifying event was used as the IDE. Thus, study dates were unique to each recipient considered for the study.

During FY 2010 through FY 2014, approximately 1.8 million people were identified in the Maryland Medicaid eligibility data. Of the Maryland Medicaid population, 182,877 people (about 10%) had a recorded primary diagnosis for asthma (ICD-9 of 493.xx) from an INPH, ED visit, or physician visit record. Only 83,561 recipients met the diagnostic definition of asthma, which limited those qualifying with a physician visit to have at least four physician visits with an ICD-9 of 493.xx, or 45.69% of the recipients with a primary diagnosis of asthma. During this period, a total of 293,337 people filled a prescription for one or both treatments of interest. Recipients were excluded if they were not placed on monotherapy or if a prescription was filled

for a medication indicating severe asthma. Table 1 represents the flow of recipients through the study population definition.

While many algorithms for identifying severe asthma in administrative claims data exist, this study used the one described by Erickson and Kirkling (2004) (Table 1) as described in Jacob, Haas, Bechtel, Kardos, & Braun, 2016 (pg. 236). The definition is based on an assessment of asthma medications filled, and the person must meet at least one of four possible definitions. This definition was applied across the study period, and recipients were eliminated from the study if they met the criteria for severe asthma prior to IDE. On the other hand, if the definition of severe asthma was met during the follow-up period, then the study recipient was identified as having developed severe asthma at some point during the study.

Table 1

Definition of Severe Asthma Using Administrative Pharmacy Data

To be classified as having severe asthma, a Medicaid recipient must meet the criteria for one of the following four groups.

Group 1:

≥6 prescriptions of any bronchodilator

AND

≥6 prescriptions for ICS or LTRA

Group 2:

≥3 prescriptions in at least three of the different classes:

β-agonist; theophylline, anti-allergic, ipratropium bromide, corticosteroids (inhaled or oral)

Group 3:

≥2 prescriptions for oral corticosteroids

AND

≥6 prescriptions for any other asthma medication

Group 4:

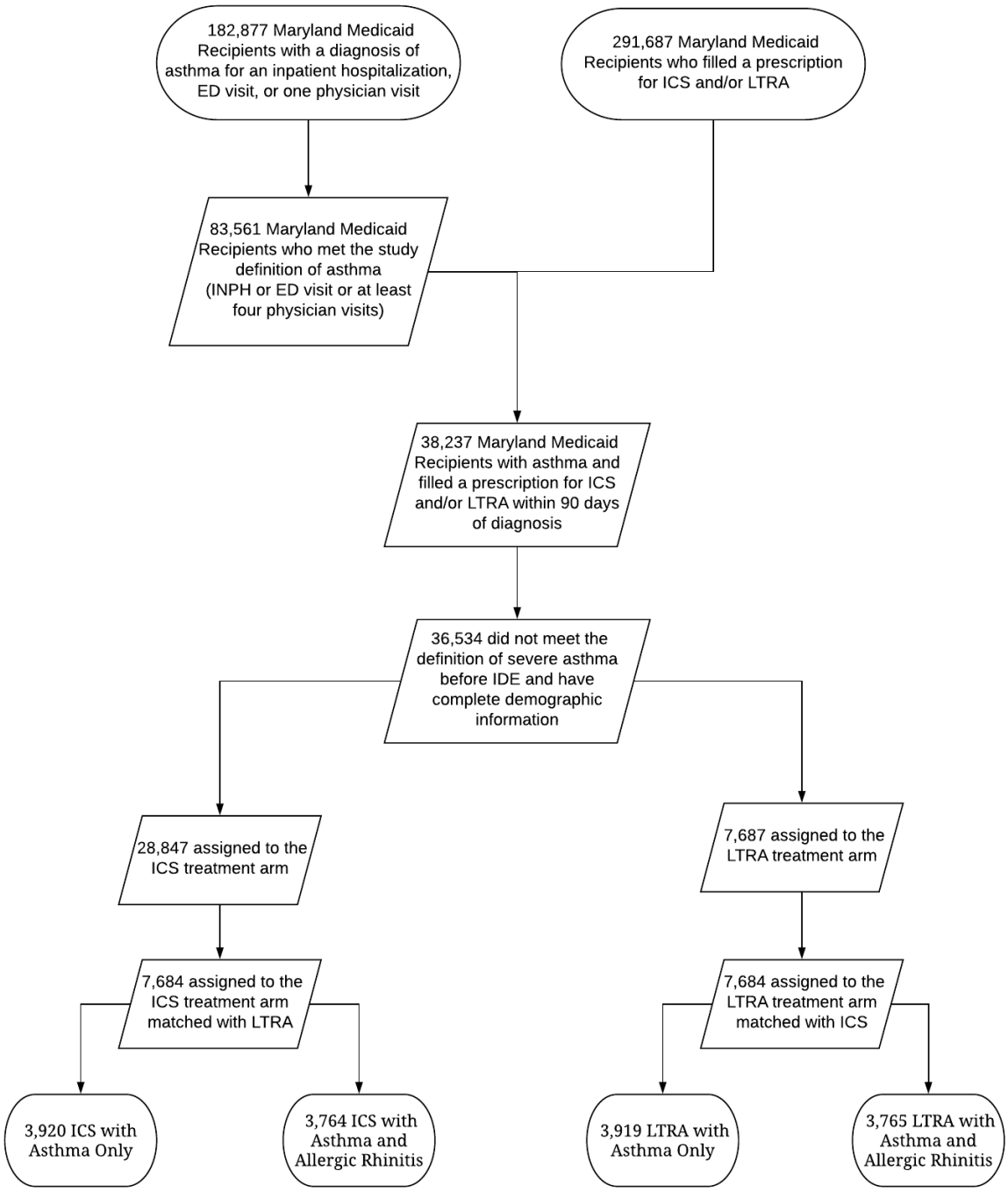
≥25 canisters of a β-agonist bronchodilator

Of those who met the diagnostic definition, a total of 36,534 recipients (43.72%) were eligible for the study because they (1) had a qualifying prescription; (2) had not met the definition of severe asthma prior to the IDE; and (3) had complete demographic data. The study treatment arm assignment was based on the prescription filled, ICS or LTRA, with the closest date to the IDE. Of the 36,534 recipients, a total of 28,847 (78.96%) were assigned to the ICS treatment arm and 7,687 (21.04%) were assigned to the LTRA treatment arm. Propensity score matching (PSM) was performed on this population, matching one ICS-treated recipient with one LTRA-treated recipient, as discussed below. A total of 7,684 LTRA-treated recipients were able to be matched to 7,684 ICS-treated recipients. Thus, a total of 15,368 recipients were the focus of

this study. The PSM model included the co-morbidity allergic rhinitis (AR), so both the ICS and the LTRA arms were split between those with only asthma (51%) and those with asthma and AR (49%). A visual of this process is presented in Table 2.

Table 2

Flow Chart of the Process of Identifying the Multivariate Cohort from Maryland Medicaid Recipients after Each Step of Evaluating the Eligibility Criteria and Propensity Score Matching



Study Measures

This study assessed two outcomes: ED visits and INPHs for asthma exacerbation. The analysis was also stratified by the presence of the co-morbidity AR. Each outcome was a binary indicator reflecting the existence of the outcome event during the 12-month follow-up period versus no event occurring. The outcome indicators were derived from the recipient's inpatient and outpatient claims for the follow-up period. The same definition for an asthma ED visit or INPH that was used in the population definition was applied for the outcome measures.

Statistical Analyses

Propensity Score Matching

As this is an observational study, selection bias for the assigned asthma treatment was of concern. Preliminary analysis of the initial population (36,534 recipients) indicated significant differences between the LTRA and ICS populations. PSM was used to address possible selection bias when selecting the matched study cohort. The SAS 9.4 procedure PSMATCH was used to assess propensity scores and conduct the matching between recipients in the treatment (LTRA) and comparison (ICS) groups. The potential confounders that may affect the outcome were identified *a priori* and used in a logistic regression model to predict assignment to the LTRA treatment. The confounders used in the PSMATCH included IDE location, age group, gender, race, IDE physician type, and presence of AR at IDE. Given that LTRA is commonly used for treatment, AR was included in the PSMATCH model.

Post analysis of the 15,368 recipients identified through PS modeling revealed a balance of confounders. Age groups for this study, as well as for matching in the PSM, were defined as 1 to 5 years, 6 to 12 years, 13 to 18 years, and 19 years and older. The age categories were based on an examination of US Food and Drug Administration-approved usage for each medication for

various age ranges. The decision to group all recipients aged 19 and older into a single category was based on the skewed distribution of the study cohort to younger ages.

The PSM method of greedy nearest-neighbor matching was employed using the PSMATCH procedure in SAS 9.4. This procedure matched the propensity score of each recipient in the LTRA group to the unmatched ICS recipient possessing the nearest propensity score (SAS Institute, Inc., 2017). The caliper was set to restrict the matched propensity scores to be within 0.5 of each other, thereby limiting the distance between the LTRA recipient's propensity score and its ICS-matched nearest neighbor. This ensures a degree of certainty that the matched pair will have similar characteristics (Gant & Crowland, 2017; SAS Institute, Inc., 2017). Analysis of the balance of covariates was performed on the final matched study population, indicating that the two groups resemble one another, thereby increasing the possibility that any identified difference in outcomes between the two groups is related to the treatment.

Morbidity was calculated using the chronic condition warehouse (CCW) categories (Chronic Conditions Data Warehouse, n.d.). Morbidity was determined at IDE based on the information available up until that point in time. All available claims and encounters were used to assess the presence of each CCW condition, including inpatient, outpatient, and physician data. Each recipient has the presence of at least one CCW: asthma. The total number of CCW categories was then summed to result in the level of morbidity for the logistic regression.

Logistic Regression

Multivariate logistic regression analysis was performed for each outcome to determine the association of LTRA initial treatment with either ED visit or INPH, while controlling for known confounders. Due to research indicating that LTRA may be more appropriate for recipients with AR, separate analyses were conducted for the asthma-only group and the asthma-

AR group (Global Initiative for Asthma, 2016). Thus, a total of four models were run: asthma-only ED visit, asthma-only INPH, asthma-AR ED visit, and asthma-AR INPH. All initial covariates were determined *a priori* and entered into a model (see Appendix B). Models were run iteratively to achieve a regression model with the most precise estimates. This method also enhances examination of the relationship between the covariates and the ensuing impact on the outcome, resulting in some variables being dropped during the estimation process. The final model included LTRA, age group, race, region of residence, primary provider specialty, Medicaid coverage group, total number of chronic conditions, FFS, and the development of severe asthma after IDE.

Results

Study Cohort

The identified asthma population was statistically different in composition between the ICS- and LTRA-treated groups prior to PS matching. However, after PS matching, no apparent differences for observable characteristics were detected between the LTRA and ICS groups. Table 3 displays the initial asthma population characteristics, including a stratification by ICS and LTRA prior to PS matching. Table 4 presents the study cohort characteristics by treatment Group. Statistical significance at the 95% confidence level is reported in both tables. Since the initial diagnosis may have occurred in either an INPH, ED visit, or physician office setting, the provider was entered into the model using two distinct methods. “PCP provider” refers to the specialty of the provider the study participant saw most for health care needs during the study period. “Diagnostic provider” is the specialty of the provider listed on the IDE claim or encounter. Based on UMBC’s Health Insurance Portability and Accountability Act (HIPAA) adherence, regional information is not included in the demographic tables.

Table 3

Baseline Characteristics of the Eligible Maryland Medicaid Asthma Population

	Medicaid Asthma Population % (n) N = 36,534	LTRA Treatment Arm % (n) 21.04 (7,687)	ICS Comparison Arm % (n) 78.96 (28,847)	p-value
Qualifying Event				
ED Visit	41.73 (15,246)	38.90 (2,990)	42.49 (12,256)	p = 0.0009
Inpatient Hospitalization	9.54 (3,484)	9.85 (757)	9.45 (2,727)	
Physician Visits	48.73 (17,804)	51.25 (3,940)	48.06 (13,864)	
Age Group				
0 – 5 Years of Age	37.40 (13,665)	20.75 (1,595)	41.84 (12,070)	p < 0.0001
6 – 12 Years of Age	33.02 (12,064)	40.74 (3,132)	30.96 (8,932)	
13 – 18 Years of Age	10.84 (3,960)	13.80 (1,061)	10.05 (2,899)	
19+ Years of Age	18.74 (6.845)	24.70 (1,899)	17.15 (4,946)	
Sex				
Female	47.26 (17,265)	50.51 (3,883)	46.39 (13,382)	p < 0.0001
Male	52.74 (19,269)	49.49 (3,804)	53.61 (15,465)	
Race				
Black	48.48 (17,711)	50.62 (3,891)	47.91 (13,820)	p < 0.0001
Caucasian	21.66 (7,912)	25.58 (1,966)	20.61 (5,946)	
All Other Races	29.87 (10,911)	23.81 (1,830)	31.48 (9,081)	
Area Primary Residence				
Baltimore City	N/A	N/A	N/A	p = 0.0274
Baltimore Suburbs				
Washington DC Suburbs				
Eastern Shore MD, Southern/Western MD, Out of State				
Primary Care Provider Specialty				
Pediatrics	55.88 (20,414)	62.13 (13,151)	47.26 (7,263)	p < 0.0001
Primary Care	21.93 (8,013)	17.58 (3,720)	27.93 (4,293)	
All Other Specialties	22.19 (8,107)	20.29 (4,295)	24.80 (3,812)	
Diagnostic Provider Specialty				
Pediatrics	28.05 (10,246)	22.56 (1,734)	29.51 (8,512)	p < 0.0001
Primary Care	8.46 (3,091)	11.84 (910)	7.56 (2,181)	
All Other Specialties	63.49 (23,197)	65.60 (5,043)	62.93 (18,154)	
Presence of AR				
Yes	44.58 (16,288)	48.99 (3,766)	43.41 (12,522)	p < 0.0001
No	55.42 (20,246)	51.01 (3,921)	56.59 (16,325)	

Table 3

Baseline Characteristics of the Eligible Maryland Medicaid Asthma Population, Continued

	Medicaid Asthma Population % (n) N = 36,534	LTRA Treatment Arm % (n) 21.04 (7,687)	ICS Comparison Arm % (n) 78.96 (28,847)	p-value
Medicaid Program				
FT HealthChoice	45.59 (16,665)	47.59 (3,658)	45.05 (12,997)	p = 0.0027
Part-Year HealthChoice / Part-Year FFS	53.05 (19,381)	50.64 (3,893)	53.69 (15,488)	
FT FFS	1.36 (498)	1.77 (136)	1.25 (362)	
Medicaid Coverage Group				
Families and Children	67.49 (5,188)	67.49 (5,188)	74.66 (21,537)	p < 0.0001
MCHP	16.11 (1,238)	16.11 (1,238)	13.98 (4,034)	
Disabled, Medicaid Expansion, Other	16.40 (1,261)	16.40 (1,261)	13.61 (3,276)	
Number of Chronic Condition Categories				
Average Number at Time of IDE	1.45 (range 1 – 15)	1.50 (range 1 – 15)	1.43 (range 1 – 14)	p < 0.0002

Table 4

Baseline Characteristics of Recipients Included in the Multivariate Analysis

	Study Cohort	Study Population		
	% (n) N = 15,368	LTRA % (n) 50 (7,684)	ICS % (n) 50 (7,684)	p-value
Qualifying Event				
ED Visit	38.98 (5,990)	38.90 (2,989)	39.06 (3,001)	p = 0.9611
Inpatient Hospitalization	9.79 (1,504)	9.84 (756)	9.73 (748)	
Physician Visits	51.24 (7,874)	51.26 (3,939)	51.21 (3,935)	
Age Group				
0 – 5 Years of Age	20.72 (3,184)	20.72 (1,592)	20.72 (1,592)	p = 0.9222
6 – 12 Years of Age	40.79 (6,269)	40.76 (3,132)	40.83 (3,137)	
13 – 18 Years of Age	13.83 (2,125)	13.81 (1,061)	13.85 (1,064)	
19+ Years of Age	24.66 (3,790)	24.71 (1,899)	24.61 (1,891)	
Sex				
Female	50.60 (7,776)	50.53 (3,883)	50.66 (3,893)	p = 0.8718
Male	49.40 (7,592)	49.47 (3,801)	49.34 (3,791)	
Race				
Black	50.64 (7,782)	50.61 (3,889)	50.66 (3,893)	p = 0.9922
Caucasian	25.53 (3,923)	25.59 (1,966)	25.47 (1,957)	
All Other Races	23.83 (3,663)	23.80 (1,829)	23.87 (1,834)	
Area Primary Residence				
Baltimore City	N/A	N/A	N/A	p = 0.3906
Baltimore Suburbs				
Washington DC Suburbs				
Eastern Shore MD, Southern/Western MD, Out of State				
Primary Care Provider Specialty				
Pediatrics	47.26 (7,263)	47.18 (3,625)	47.35 (3,638)	p = 0.9137
Primary Care	27.93 (4,293)	28.03 (2,154)	27.84 (2,139)	
All Other Specialties	24.80 (3,812)	24.79 (1,905)	24.82 (1,907)	
Diagnostic Provider Specialty				
Pediatrics	22.57 (3,468)	22.55 (1,733)	22.58 (1,735)	p = 0.9846
Primary Care	11.80 (1,814)	11.84 (910)	11.76 (904)	
All Other Specialties	65.63 (10,086)	65.60 (5,041)	65.66 (5,045)	
Presence of AR				
Yes	48.99 (7,529)	49.00 (3,765)	49.99 (3,764)	p = 0.9871
No	51.01 (7,839)	51.00 (3,919)	51.02 (3,920)	

Table 4

Baseline Characteristics of Recipients Included in the Multivariate Analysis, Continued

	Study Cohort	Study Population		
	% (n) N = 15,368	LTRA % (n) 50 (7,684)	ICS % (n) 50 (7,684)	p-value
Medicaid Program				
FT HealthChoice	45.76 (7,033)	47.59 (3,657)	43.94 (3,376)	p < 0.0001
Part-Year HealthChoice / Part-Year FFS	52.60 (8,084)	50.64 (3,891)	54.57 (4,193)	
FT FFS	1.63 (251)	1.77 (136)	1.50 (115)	
Medicaid Coverage Group				
Families and Children	69.00 (10,604)	67.48 (5,185)	70.52 (5,419)	p = 0.0002
MCHP	15.35 (2,359)	16.11 (1,238)	14.59 (1,121)	
Disabled, Medicaid Expansion, Other	15.65 (2,405)	16.41 (1,261)	14.89 (1,144)	
Number of Chronic Condition Categories				
Average Number at Time of IDE	1.54 (range 1 – 15)	1.50 (range 1 – 15)	1.57 (range 1 – 13)	p = 0.0003

Most people in the PS-matched cohort were identified as probably having mild to moderate asthma through visits to a physician (51.24%) or an ED (38.98%). Less than 10% of the people qualified for the study through an INPH. The cohort was equally divided between males and females (49.40% and 50.60%, respectively). Overall, the cohort—as in the general Maryland Medicaid asthma population—skewed toward younger ages. Less than 25% of the cohort was over the age of 18, with the majority (40.79%) being between the ages of 6 and 12.

Overall, the cohort was Black and urban. Specifically, 50.64% the cohort listed their race as Black; the remainder was split between White (25.53%) and All Other Races (23.83%). Of note, of the recipients in the All Other Races category, 19.31% had a documented race of Unknown, which includes recipients who refused to offer race information, missing data, and other reasons (e.g., those who are mixed race) (see Appendix A for the definition of the

race/ethnicity variable in Maryland Medicaid data). The majority of the cohort resides in Baltimore and surrounding suburbs. Many also reside in the suburbs of Washington D.C.

As most of the cohort are children, almost half (47.26%) of them see a pediatrician as a primary source of health care. Another roughly 28% of the cohort predominantly visits primary care specialists, such as general practitioners, internists, family practitioners, and nurse practitioners. About 25% of the cohort most often visits other specialists for health care needs. This group includes but is not limited to diabetes management clinics, cardiologists, and allergists.

About half of the cohort was enrolled in the HealthChoice program at some point during the study period for which their data was collected, nearly half were in HealthChoice for the entire period, and only 1.63% used only FFS health services during the study period. Around 46% of the cohort was enrolled in an MCO during the entire study period. The cohort was overwhelmingly assigned to the Families and Children coverage category (69.0%), with another 15.35% in the Maryland Children's Health Program (MCHP). The remaining 15.65% of the cohort fell into other coverage categories, including the medically disabled and Medicaid expansion (see Appendix A for the definition of the Medicaid Expansion program in Maryland).

Due to the use of AR within the algorithm for PS matching, the cohort population was evenly split between those who had AR (48.99%) and those who did not have a diagnosis of AR prior to the IDE (51.01%). However, the cohort did have a wide range of co-morbidities. On average, besides having asthma, the cohort met the criteria for 1.54 condition categories. The number of co-morbidities ranged from only meeting the criterion for asthma to a maximum of 15 co-morbidity CCW categories.

The outcomes of ED visit and INPH during the year after IDE were identified for the study population (Table 5). Only 7.21% of recipients initially treated with LTRA had an INPH for asthma exacerbation, compared to 4.58% of those treated with ICS ($p < 0.0001$). A higher percentage of recipients starting on LTRA had an ED visit within the follow-up period than those ICS (20.72% versus 15.67%, $p < 0.0001$). A total of 1,842 LTRA recipients (23.97%) and 1,412 ICS recipients (18.38%) were identified as having one or both outcomes of interest during the years after IDE.

Table 5

Frequency of Outcomes during the year after IDE for the Maryland Medicaid Study Population

	Study Cohort	Study Population		
	% (n) N = 15,368	LTRA % (n) 50 (7,684)	ICS % (n) 50 (7,684)	p-value
Outcome				
ED visit	18.19 (2,796)	20.72 (1,592)	15.67 (1,204)	p < 0.0001
INPH	5.90 (906)	7.21 (554)	4.58 (352)	p < 0.0001
ED visit or INPH	21.17 (8,084)	23.87 (1,842)	18.38 (1,412)	p < 0.0001

Logistical Regression Results

Logistical regression models were run for each outcome (INPHs and ED visits) for both the asthma-only population and the asthma-AR co-morbidity population. The results for the two sub-cohorts were markedly different. Tables 6 to 9 provide the results of the various regression models and include the odds ratios (OR) resulting from the logistic regression.

Asthma-Only Cohort Analysis

Table 6

Multivariate Analysis of ED Visit Outcome for the Asthma-Only Cohort

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA*	0.184	0.0014	1.202	1.073 - 1.346
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.2451	0.0015	0.783	0.673 - 0.911
Ages 13 – 18*	-0.453	<.0001	0.636	0.521 - 0.776
Ages 19+*	-0.3392	0.0007	0.712	0.586 - 0.866
White	Reference			
Black*	0.4315	<.0001	1.54	1.313 - 1.805
All Other Races	0.1702	0.0718	1.186	0.985 - 1.427
Baltimore City	Reference			
Baltimore Suburb	-0.1096	0.1434	0.896	0.774 - 1.038
Washington Suburb*	-0.318	0.0001	0.728	0.618 - 0.857
All Other MD Counties*	-0.3239	0.0003	0.723	0.607 - 0.862
Pediatrician	Reference			
PCP	0.1102	0.1812	1.116	0.950 - 1.312
All Other Specialists*	0.4222	<.0001	1.525	1.323 - 1.758
Families & Children	Reference			
MCHP*	-0.2301	0.0132	0.794	0.662 - 0.953
All Other Coverage	0.0779	0.3482	1.081	0.919 - 1.272
HC Full-time	Reference			
HC Part-time	0.0423	0.4727	1.043	0.929 - 1.171
FFS Only*	-0.6093	0.0118	0.544	0.338 - 0.874
Total CCW* #	-0.262	<.0001	0.77	0.719 - 0.823
Severe Asthma*	1.3478	<.0001	3.849	3.363 - 4.405

* Significant at p = 0.05

Entered into model as continuous variable

Table 7

Multivariate Analysis of INPHs Outcome for the Asthma-Only Cohort

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA*	0.2765	0.0011	1.319	1.116 - 1.558
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.4481	0.0001	0.639	0.508 - 0.804
Ages 13 – 18*	-0.66	<.0001	0.517	0.379 - 0.705
Ages 19+*	-0.4356	0.0021	0.647	0.49 - 0.853
White	Reference			
Black*	0.3319	0.0043	1.394	1.11 - 1.751
All Other Races	0.0996	0.4775	1.105	0.839 - 1.454
Baltimore City	Reference			
Baltimore Suburb	-0.1527	0.1577	0.858	0.695 - 1.061
Washington Suburb	-0.2156	0.074	0.806	0.636 - 1.021
All Other MD Counties	-0.1885	0.1369	0.828	0.646 - 1.062
Pediatrician	Reference			
PCP	0.1916	0.1185	1.211	0.952 - 1.541
All Other Specialists*	0.3557	0.0013	1.427	1.148 - 1.774
Families & Children	Reference			
MCHP	-0.2093	0.1648	0.811	0.604 - 1.09
All Other Coverage*	0.3784	0.0005	1.46	1.18 - 1.806
HC Fulltime	Reference			
HC Part-time	-0.0167	0.8455	0.983	0.832 - 1.163
FFS Only	0.2551	0.2759	1.291	0.816 - 2.042
Total CCW #	-0.00843	0.809	0.992	0.926 - 1.062
Severe Asthma*	1.5124	<.0001	4.538	3.826 - 5.382

* Significant at p = 0.05
# Entered into model as continuous variable

For the recipients who only met the criteria for asthma, the results of the regression models indicate that the initial treatment of LTRA for asthma was associated with both more frequent ED visits and INPHs. Recipients initially placed on LTRA were more likely to be seen in the ED for an asthma exacerbation within the following year, compared to ICS (OR = 1.202, p = 0014). Similarly, recipients taking LTRA were significantly more likely to have an INPH than those taking ICS (OR = 1.319, p = 0011).

Older age had a protective correlation for both an ED visit and INPH. Compared to the youngest age group (aged one to five), the older the person was, the less likely he or she was to have an ED visit or INPH for asthma. Compared to Whites, Blacks were more likely to be seen in the ED for asthma (OR = 1.54, $p < 0.0001$) and have an INPH (OR = 1.39, $p = 0.0043$). Recipients of other races, though, were not statistically different from Whites. Residents living in other areas of Maryland (OR – 0.723, $p = 0.0003$) or the Washington DC suburbs (OR = 0.728, $p = 0.0001$) were less likely to be seen in the ED in the year after IDE. Residential area did not differ significantly for INPH.

Participants who see primarily doctors with specialties rather than a PCP had a higher chance of being seen in the ED (OR = 1.53, $p < 0.001$) or having an INPH (OR = 1.43, $p = 0.0013$) for asthma in the following year than participants who primarily see a pediatrician. Those in MCHP were less likely than those in the Families and Children coverage category (OR = 0.794, $p = 0.132$) to be seen in the ED. Participants in other coverage categories did not differ significantly from those in Families and Children (OR = 1.081, $p = 0.3482$) regarding ED visits, but they were more likely to have an INPH (OR = 1.46; 0.0005). Recipients who were in FFS during the year following IDE were less likely to have an ED visit compared to those in HealthChoice for the entire year (OR = 0.544, $p = 0.0118$). No significant difference was detected in the INPH model.

The number of co-morbidities a recipient has was associated with the likelihood of having an ED visit. That is, the higher the number of co-morbidities, the lower the chance of an ED visit (OR = 0.77, $p < 0.0001$). However, there was no significant difference regarding having an INPH in the twelve months following IDE between recipients with an increased number of co-morbidities and those who only have asthma (OR = 0.992, $p = 0.809$). Recipients who

developed severe asthma were highly likely to have either an ED visit (OR = 3.849, $p < 0.0001$) or an INPH (OR = 4.538, $p < 0.0001$) after IDE.

Asthma-AR Cohort

Table 8

Multivariate Analysis for ED Visit Outcome for the Asthma-AR Group

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA	0.1134	0.1192	1.12	0.971 - 1.292
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.4025	<.0001	0.669	0.564 - 0.793
Ages 13 – 18*	-0.7279	<.0001	0.483	0.377 - 0.618
Ages 19+*	-0.7946	<.0001	0.452	0.343 - 0.596
White	Reference			
Black*	0.4262	<.0001	1.531	1.26 - 1.861
All Other Races	0.1957	0.0835	1.216	0.974 - 1.518
Baltimore City	Reference			
Baltimore Suburb*	-0.2139	0.0369	0.807	0.66 - 0.987
Washington Suburb	-0.2052	0.0548	0.814	0.661 - 1.004
All Other MD Counties*	-0.2252	0.0495	0.798	0.638 - 0.999
Pediatrician	Reference			
PCP	0.0512	0.5884	1.053	0.874 - 1.267
All Other Specialists*	0.5002	<.0001	1.649	1.359 - 2.001
Families & Children	Reference			
MCHP	-0.1161	0.2532	0.89	0.73 - 1.087
All Other Coverage*	0.2891	0.0172	1.335	1.053 - 1.694
HC Fulltime	Reference			
HC Part-time*	0.169	0.0201	1.184	1.027 - 1.366
FFS Only	-0.0956	0.8181	0.909	0.402 - 2.053
Total CCW* #	-0.0946	0.0366	0.91	0.833 - 0.994
Severe Asthma*	1.2752	<.0001	3.579	2.994 - 4.28

* Significant at p = 0.05

Entered into model as continuous variable

Table 9

Multivariate Analysis for INPH Outcome for the Asthma-AR Group

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA	-0.0253	0.8761	0.975	0.709 - 1.34
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.7454	<.0001	0.475	0.328 - 0.686
Ages 13 – 18*	-0.8083	0.0031	0.446	0.261 - 0.761
Ages 19+*	-0.8592	0.0047	0.424	0.233 - 0.768
White	Reference			
Black*	0.4929	0.0264	1.637	1.06 - 2.529
All Other Races	0.3377	0.1776	1.402	0.858 - 2.29
Baltimore City	Reference			
Baltimore Suburb	0.023	0.9174	1.023	0.663 - 1.58
Washington Suburb	-0.2566	0.2959	0.774	0.478 - 1.252
All Other MD Counties	-0.089	0.7236	0.915	0.559 - 1.498
Pediatrician	Reference			
PCP	-0.22	0.3041	0.802	0.527 - 1.221
All Other Specialists	-0.1853	0.4381	0.831	0.52 - 1.327
Families & Children	Reference			
MCHP	-0.2507	0.3082	0.778	0.481 - 1.26
All Other Coverage*	0.663	0.0049	1.941	1.223 - 3.079
HC Full-time	Reference			
HC Part-time	1.768	0.094	1.309	0.955 - 1.793
FFS Only	1.768	0.6093	0.59	0.078 - 4.46
Total CCW#	-0.0148	0.8611	0.985	0.835 - 1.163
Severe Asthma*	1.768	<.0001	5.859	4.198 - 8.177

* Significant at p = 0.05

Entered into model as continuous variable

Allergic Rhinitis Results

LTRA was not correlated with either ED visit or INPH for recipients in the study cohort who had AR as a co-morbidity (OR = 1.12, p = 0.1192 and OR = 0.975, p = 0.8761). Younger asthmatics were more likely to experience both an ED visit and an INPH after IDE. Blacks with AR were more likely than Whites to have an ED visit (OR = 1.531, p < 0.0001) as well as an

INPH (OR = 1.637, p = 0.264). Residents of Baltimore suburbs and "All Other MD Counties" were found to be less likely than those in Baltimore City to have an ED visit (OR = 0.807, p = 0.0369 and OR = 0.798, p = 0.0495, respectively). Recipients primarily seeing a specialist other than a PCP were more likely to have an ED visit after IDE compared to those seeing a pediatrician (OR = 1.649, p < 0.0001). Neither residential area nor physician type were significant for INPH.

Recipients in coverage categories other than MCHP were more likely than recipients in Families and Children to have both an ED visit (OR = 1.335, p = 0.0172) and INPH (OR = 1.941, p = 0.0049). Recipients who were in HealthChoice part of the year following IDE were more likely to have an ED visit than those in HealthChoice for the entire year (OR = 1.184, p = 0.0201). An increased number of co-morbidities was negatively associated with the likelihood of an ED visit (OR = 0.91, p = 0.0366). The number of chronic conditions was not statistically significant for INPH. Recipients who developed severe asthma during follow-up were more likely to have an ED visit or INPH (OR = 3.579, p < 0.0001 and OR = 5.859, p < 0.0001, respectively).

Sensitivity Analysis of Race

Given the substantial proportion of recipients without a defined race, the regression models were also run separating the categories of Other Races and Unknown Races. While the percentages and regression estimates changed in all of the models, the overall outcome in most of the models remained consistent. The two models evaluating asthma-only recipients produced similar outcomes to the original models. Likewise, the model evaluating INPH for asthma-AR recipients did not change significantly. However, for recipients with asthma and AR, LTRA was significantly correlated with ED visits (Table 10).

Table 10

Race Sensitivity Analysis - ED Visits for Asthma-AR Group

	Parameter Estimate	p-value	Odds Ratio	95% CI
LTRA*	0.1867	0.0113	1.205	1.043 - 1.393
Ages 6 – 12*	-0.4012	<.0001	0.67	0.563 - 0.797
Ages 13 – 18*	-0.7238	<.0001	0.485	0.377 - 0.624
Ages 19+*	-0.6605	<.0001	0.517	0.392 - 0.681
Black*	0.5121	<.0001	1.669	1.368 - 2.036
All Other Races	0.0662	0.7464	1.068	0.716 - 1.595
Race Unknown*	0.2489	0.0408	1.283	1.01 - 1.628
Baltimore Suburb*	-0.2317	0.0243	0.793	0.648 - 0.97
Washington Suburb*	-0.2769	0.0102	0.758	0.614 - 0.936
All Other MD Counties	-0.2867	0.0137	0.751	0.598 - 0.943
PCP	0.0911	0.3394	1.095	0.909 - 1.321
All Other Specialists*	0.5069	<.0001	1.66	1.364 - 2.02
MCHP	0.0467	0.6438	1.048	0.86 - 1.277
All Other Coverage	0.272	0.0274	1.313	1.031 - 1.671
HC Part-time*	0.1994	0.0069	1.221	1.056 - 1.411
FFS Only	0.2731	0.4463	1.314	0.651 - 2.653
Total CCW* #	-0.1074	0.0173	0.898	0.822 - 0.981
Severe Asthma*	1.2666	<.0001	3.549	2.966 - 4.246

* Significant at p = 0.05
# Entered into model as continuous variable

The categorization of Unknown Race separately from All Other Races (Asian, Hispanic, Native American, and Hawaiian/Alaskan) for the recipients who had asthma-AR co-morbidity indicates that LTRA was significantly correlated with ED visits. Recipients initially given LTRA were more likely than those given ICS to be seen in the ED (OR = 1.205, p = 0.0113) for an asthma exacerbation within the following year. Compared to the White recipients, both Blacks (OR = 1.669, p < 0.001) and recipients with Unknown Race (OR = 1.283, p = 0.0408) were more likely to visit the ED.

Recipients aged six years and older were less likely to have an ED visit compared to those aged five years and younger. Compared to Baltimore City residents, those living in the

metropolitan suburbs of Baltimore (OR = 0.793, p = 0.0243) or Washington DC (OR = 758, p = 0.0102) were less likely to be seen in the ED in the following year. Asthma-AR recipients seeing a doctor other than a PCP (OR = 1.66, p < 0.0001) were more likely to be seen in the ED for asthma than were recipients seeing a pediatrician. Compared to those in HealthChoice full time, recipients only in the managed care program part-time had an increased chance of being seen in the ED (OR = 1.221, p = 0.0069). Coverage category was not significantly associated with ED visits.

As seen in previous models, recipients with more co-morbidities were less likely to have an ED visit for asthma in the twelve months following IDE (OR = 0.898, p = 0.0173). Also consistent with previous models, recipients who developed severe asthma were more likely to be seen in the ED for asthma after IDE (OR = 3.549, p < 0,0001) than recipients who did not develop severe asthma.

Discussion

This comparative-effectiveness study of LTRA versus ICS within the Maryland Medicaid asthmatic population brought to light three main findings. First, overall, the period prevalence of asthma in the Maryland Medicaid population was similar to previously reported findings in the literature. Second, the distribution of LTRA and ICS for the treatment of asthma resembled rates reported in commercial populations. Third, recipients initially treated with LTRA were more likely to have an ED visit or INPH after diagnosis than recipients initially treated with ICS, except if a co-morbidity of AR was present.

While the focus of this study was not to determine prevalence, the prevalence of asthma in the Maryland Medicaid population was a result of this analysis. The period prevalence for an asthma-related event in the Maryland Medicaid population for FY 2010 to FY 2014 was around

10%. This is a reasonable finding given prevalence reported both nationally and for the state of Maryland. This finding is higher than the average national prevalence for asthma (8.3%) but similar to the reported prevalence for Maryland children (9.7%) (Schrader, 2017). Maryland Medicaid asthma statistics from 2006 data report that 9% had a current diagnosis of asthma, indicating that asthma might be slowly rising (Maryland Department of Health and Mental Hygiene, 2009, pg. 5). Children and non-Hispanic Blacks have higher prevalence rates, both nationally and in Maryland. As such, it is reasonable to hypothesize that the Maryland Medicaid asthma population would have a higher percentage of Blacks and children. This hypothesis is reflected in this study, where more than 80 percent of the initially identified asthma population was younger than 19 years, and almost 50 percent was Black.

The study distribution of residential location, as well as rates of ED visits and INPHs, are also similar to that reported in various Maryland documents. According to the Maryland Asthma Control Plan, "[for] some populations within Baltimore City, the prevalence rate exceeds 20%" (Maryland Department of Health and Mental Hygiene, 2009, pg. 5). This indicates that Baltimore City may have increased numbers of asthmatics for particular sub-populations. Although HIPAA regulations at UMBC prohibit the reporting of descriptive statistics by area of residence, this study found the majority of asthmatics to reside in urban areas, including Baltimore City. Additionally, a legislative report from 2016—based on statewide hospital data from 2014—indicates that there were more ED visits than INPHs for asthma. Furthermore, 18.34% of the population had an ED visit after IDE, and 5.44% experienced an INPH. This difference remained consistent within the study cohort (18.19% and 5.90%, respectively).

While confirming study results with those reported in literature is a preferred practice, it also suggests that issues surrounding asthma remain over time, regardless of various programs

being enacted. Additionally, this study's results reiterates the need for further research in order to aid in formulating appropriate methods for allocating resources to address the impact of asthma on health care utilization. Assessing the distribution and use of LTRA and ICS within this population—as well as closely examining the other findings of this study—may help focus future responses to asthma in the Maryland population.

Unfortunately, much of the research comparing LTRA with ICS for ED visits and INPHs outcomes is conducted on commercial populations. Two 2014 studies stand out as reporting specifically on a Medicaid population: Li et al. and Wu et al. One of the primary study results from Wu and colleagues (2014) showed that "children in the TennCare Medicaid population were more likely to be started on an LTRA rather than an ICS compared with the health plan population" (pg. 611). Specifically, 55 percent of TennCare children but only 8 percent of the health plan children were started on LTRA (pg. 610). The findings from the Maryland data, though, do not reflect the same experience.

Around 21 percent of the Maryland Medicaid population started on LTRA. This is more in line with findings from other studies of LTRA and ICS with mostly commercial populations for the health outcomes of ED visit and INPH (Allen-Ramey et al., 2003; Ducharme et al., 2012; Tan et al., 2009; Lee et al., 2010; O'Connor et al., 2006). One primary difference between this study and the two evaluating TennCare is that the current study also includes an adult population. The TennCare study population reported by Wu et al. consists of only children, whereas over 80 percent of the Maryland asthma population for this study was under the age of 19, with the overwhelming majority being younger than 12. While it is possible that the mixed child/adult population results in the different reported percentage of initially treated with LTRA, other variations between the two populations may also exist. One possible difference between the two

studies may be variation in providers' prescribing practices between the two states. It is unclear, however, whether the differences are related to practicing patterns of doctors in general or whether they are due to differing state Medicaid policies.

In terms of state policy, Maryland has been aggressive in treating asthma. In 2002, the State Legislature passed legislation to establish the Maryland Asthma Control Program (MACP) "to address asthma through surveillance, planning and interventions" (Maryland Department of Health and Mental Hygiene, 2009, pg. 2). The MACP builds many aspects of the various interventions directly from the United States' version of the best-practice guidelines for the diagnosis, treatment, and management of asthma (National Heart, Lung, and Blood Institute, 2007). As these guidelines have not been updated since 2007, they do not include the suggestion of LTRA for primary treatment of mild to moderate asthma for individuals with AR or those who smoke. Rather, these guidelines promote the use of ICS as the preferred treatment for asthma.

Given Maryland's statewide asthma program, the distribution of medication for initial treatment of asthma may reflect the preference for adhering to national guidelines to ensure quality of care. Assessment of state policies, along with resulting asthma treatment distribution, especially with neighboring states, may provide further insight to this finding. Even so, the study findings indicate the Maryland Medicaid recipients obtain treatment in line with current best-practice guidelines for asthma. The difference between the outcomes of this study and those reported from the TennCare population might also be due to other factors, such as recipient compliance or environmental risk factors.

The initial models indicate that cohort recipients initially treated with LTRA and who also had AR were as likely to experience ED visits or INPHs after IDE than those starting on ICS. This is the opposite finding from recipients without an AR co-morbidity. This finding is

also supported in the literature (Haughney et al., 2008; Li et al., 2014; Wu et al., 2014) and found in the recently updated Global Initiative for Asthma (GINA) guidelines, which state that LTRA "may be appropriate … for patients with allergic rhinitis" (2016, pg. 33). As such, medical professionals and health care policy makers might consider assessing for a co-morbidity of AR in order to determine initial treatment of mild to moderate asthma.

One population that might significantly benefit from such an assessment is younger Black children with asthma. Recipients under the age of six are more likely to have ED visits and INPHs, and being Black (compared to White) is correlated with ED visits and INPHs. Young Black children under the age of six with a co-morbidity of AR might see a decrease in ED visits and/or INPHs for asthma exacerbation after initial treatment of LTRA. One of the reasons this might occur is due to the various delivery modes for LTRA. As opposed to ICS, which is not approved until the age of four, LTRA is approved for individuals aged one year and older. Due to the approved use in young children, LTRA comes in a variety of forms especially made for children (both granular form and chewable tablets are available). Thus, it might be easier to give the medication to a child rather than using a nebulizer or inhaler, thereby increasing adherence with the medication. Consistency with treatment is important in minimizing exacerbation and related ED visits and INPHs.

However, it ought to be noted the AR models did not suggest whether LTRA does better or worse than ICS; rather, they suggested that the differences between the two were not significant treatments for ED visits and INPHs. Further investigation of the results shows that the two medications, while not significantly different, had different ED visits and INPHs outcomes. Recipients who started on LTRA were slightly more likely to be seen in the ED (Table 8: OR = 1.12, CI = [0.971 – 1.292]), while those starting on ICS were slightly less likely to have an INPH

(Table 9: OR = 0.975, CI = [0.709 – 1.34]). Although these differences are present, initial use of LTRA and ICS for mild to moderate asthma did not result in these differences being statistically significant for the asthmatic study population.

Finally, one of the most interesting findings of this study is that those with more co-morbidities were less likely to have ED visits. This seems counter-intuitive, as one would expect people with more co-morbidities to use the ED more often. However, what this finding suggests is that those with an increased number of morbidities are less likely than others to have an ED visit *for asthma* within the year following IDE; it does not indicate whether they are more or less likely to have an ED visit *for any reason*. In fact, they may be more likely to be seen in an ED overall, but the primary reason for the visit might not be asthma-related. Furthermore, it cannot be assumed that they did not receive treatment for asthma during an ED visit—only that it was not the primary reason for the visit.

Another rationale for a higher number of co-morbidities being negatively associated with ED visits is that those with more chronic conditions may be more fastidious about adhering to treatment guidelines. Recipients with an increased number of co-morbidities may also be more apt to seeing a physician regularly and altering lifestyle and environmental factors to reduce illness exacerbation.

Relevance for Medicaid Policy

The findings of this study add to the overall literature on ICS and LTRA comparative effectiveness for asthmatic populations and have direct implication for reducing asthma-related INPH and ED visits for the Maryland Medicaid asthmatic population. The Maryland Asthma Control Plan states "[i]nformation…is critical to planning, implementing, and evaluating activities aimed at reducing the personal and public

health burden of asthma for Maryland residents" (Maryland Department of Health and Mental Hygiene, 2009, pg. 57). Furthermore, "the monetary costs of asthma hospitalizations and emergency department visits is substantial and is largely borne by public insurers, Medicare and Medicaid" (pg. 57). The results of this study provide Maryland Medicaid policymakers and asthma program coordinators a means to adjust policy directives that may significantly affect the Maryland Medicaid asthma population and associated costs.

Recipients initially treated with LTRA, and with a co-morbidity of AR, were equally as likely to have an ED visit or INPH for asthma exacerbation as those initially treated with ICS. However, only 23% of those with AR in the study population were initially placed on LTRA. The disparity in treatment distribution presents a significant opportunity for mitigating INPH and ED visits for asthma. Two options that are available to Maryland Medicaid for accurately estimating the effectiveness of LTRA for reducing ED visits and INPH include conducting a pragmatic trial within the asthmatic population and offering financial incentives for LTRA treatment.

A pragmatic trial comparing LTRA and ICS within the population might illuminate more precise differences in the effectiveness, compared to this analysis. Using Maryland Medicaid's established asthma program, designing a pragmatic trial is feasible. A pragmatic trial is similar to an RCT; however, its focus is on health care innovation—including effective treatment assessment (Ford & Norrie, 2016). The National Institutes of Health (NIH) use pragmatic trials to "address questions that are important to patient, their care providers, as well as researchers" (Boineau, 2017). Therefore, as a significant provider of health care in Maryland, a pragmatic trial to assess the magnitude LTRA treatment for asthma AR-co-morbid population in INPH and ED visits is reasonable.

Another option for Maryland Medicaid is to offer payment incentives to providers to increase the use of LTRA within the asthma-AR population. An incentive could be incorporated into a pragmatic trial setting or accomplished through a more traditional programmatic evaluation. Medicaid programs use various payment incentives to increase the quality of care for multiple populations. Pay-for-performance (P4P) "initiatives [are] aimed at improving quality, efficiency, and overall value of health care….to achieve optimal outcomes for patients" (James, 2012). Using P4P to alter the way providers treat asthma-AR with the purpose of evaluating the reduction of ED visits and INPH falls within current Medicaid practices, thus providing specific evidence to any realized effectiveness of LTRA on overall the costs and burden Maryland Medicaid incurs for asthma.

Conclusion

Treatment for mild to moderate asthma in Maryland Medicaid recipients is similar to previously reported asthma findings. Initial treatment with LTRA for Maryland Medicaid recipients with asthma was found to be positively associated with more ED visits and INPHs. This finding remained after controlling for age, race, residential area, provider type, coverage group, number of co-morbidities, Medicaid program, and development of severe asthma after initial treatment. However, LTRA was not associated with ED visits or INPHs for asthmatic recipients who also had AR. Thus, for Medicaid asthma recipients with AR, LTRA may be an appropriate asthma treatment for controlling exacerbations.

Appendix A

Glossary of Terms

Chronic Condition Warehouse (CCW): The Chronic Condition Warehouse was created by the Centers for Medicare and Medicaid (CMS) as a result of the Medicare Modernization Act of 2003. While this warehouse provides information for many research interests, it also provides a standard algorithm for identifying chronic conditions within administrative data. There are 27 main categories of chronic conditions. An additional 39 categorical definitions are available for more specific conditions related to mental health, substance abuse and disabling conditions. This study used the primary 27 categories in the analysis. One of the categories is asthma.

Emergency Department (ED) Visit: A recipient is identified as having an ED visit for asthma if a record exists within the outpatient file of the Maryland Medicaid data with a primary ICD-9 diagnosis code for asthma and a revenue code of 0450 or 0981. Records for ED visits associated with an INPH are within the inpatient file and, therefore, are not identified as an ED visit.

Fee-For-Service (FFS): This is the traditional payment method for Maryland Medicaid. Under this payment program, providers submit a claim for a service and Maryland Medicaid pays the provider for the service based on contractual agreements. The following are typical populations which participate in the fee-for-service program: recipients dually eligible for Medicare and Medicaid, recipients with rare and expensive diseases/conditions, recipients using mental health services, and recipients using substance use services.

HealthChoice Program (HealthChoice): This is a payment program under the 1115 waiver authorized by CMS. This waiver allows Maryland Medicaid to pay providers through a

managed care organization structure. Currently, the majority of Maryland Medicaid recipients receive care from providers within the HealthChoice program.

Health Insurance Portability and Accountability Act of 1996 (HIPAA): The purpose of this act is to protect the privacy of individuals, specifically related to healthcare information. Furthermore, it defines security measures for the handling of personal healthcare information. This act applies to all providers, researchers, organizations, and agencies that come into contact with healthcare information.

Inhaled Corticosteroid (ICS): This is an inhaled, oral medication used to treat the symptoms of asthma. This treatment is effective only after reaching the lungs.

Inpatient Hospitalization (INPH): A recipient is identified as having an inpatient hospitalization for asthma if a record exists within the inpatient file of the Maryland Medicaid data with a primary ICD-9 diagnostic code for asthma.

Leukotriene Receptor Antagonist (LTRA): This is an oral medication in pill form. This medication works to inhibit the leukotrienes produced by the body which are related to asthma-related symptoms.

Medicaid Expansion: The Patient Protection and Affordable Care Act of 2010 (ACA) allows for states to expand their Medicaid programs to include people previously ineligible for benefits and allows for increased federal funding. Maryland opted to authorize expansion of its Medicaid program effective January 1, 2014. The new policy expanded Medicaid coverage to those under the age of 65 with a household income of up to 138% of the Federal Poverty Guideline (FPG) and former foster care children up to age 26. In Maryland Medicaid, recipients aged 18 and older will have a coverage group indicating Medicaid expansion. Children, however, will have a coverage group of Maryland Children's Health Program (MCHP). The coverage

group indicates the Medicaid benefits the recipient is entitled to receive. A coverage group of Medicaid Expansion indicates that the recipient may receive the benefits outlined through Maryland's Medicaid expansion program.

Mild to Moderate Asthma: Assessment of the severity of asthma is determined from initial diagnosis. The severity level is based on both spirometry and self-reported symptoms over the past month (National Heart, Lung, and Blood Institute, pg. 49). Neither lab results nor self-reported health information is captured within the managed care administrative data for Maryland Medicaid recipients. Thus, asthma severity is assessed based on the type and amount of medication used to treat and control the symptoms of asthma. This study will consider a recipient to have met the definition of mild to moderate asthma if they met the following criteria:

(1) Had an emergency visit, inpatient hospitalization, or at least four physician visits with a primary diagnosis of asthma

(2) Did not meet the criteria of severe asthma as defined in Table 1 on page 7.

Physician Visit: A recipient is identified as having a physician visit for asthma if a record exists within the physician or outpatient file in the Maryland Medicaid data with a primary ICD-9 diagnosis code for asthma. Outpatient records must have a revenue code other than 0450 or 0981.

Propensity Score Matching (PSM): This is a statistical method to minimize the bias found in observational studies. This method uses multivariate regression in order to systematically match similar participants in treatment and control groups. PSM only uses observed characteristics, which is a primary limitation of this method.

Race/Ethnicity: The Maryland Medicaid program combines race and ethnicity into one field. The variable has the following values: Black, White, Hispanic, Asian, Native American,

Hawaiian/Alaskan, and Unknown. The Unknown category includes refusal to provide race, missing, those who do not associate with one of the other categories, and racially mixed. This is considered a “catch all” option.

Appendix B

Variables Initially Entered into the Multivariate Model

INP/ED:	An indicator of the presence of asthma related inpatient hospitalization or ED visit during the year following the initial date of diagnosis. INP/ED is the dependent variable.
LTRA:	An indicator of LTRA treatment. This variable will be coded 1 for LTRA and 0 for ICS. The initial prescription given determines the coding for the variable.
AGEGRP:	Age group is defined as of January 1st of the FY of the initial date of diagnosis. Age group was determined based on the distribution of ages for the cohort eligible for the study. The groups include 0 – 5 years, 6-12 years, 13 – 18 years, and Older than 18 years.
RACE:	Race as recorded as of the initial date of diagnosis. If the initial date of diagnosis is in FY 2014 or FY 2015, race will be assigned as of FY 2013, if available. A substantial change occurred in the collection of race in FY 2014, thus making this variable inconsistent across all years of this study. Per standard analysis protocol used by Medicaid, race is used as of FY 2013, if available.
SEX:	Sex as recorded in the FY of the initial date of diagnosis.

REGION: The Medicaid recipient's region of residence. Due to UMBC's Health Insurance Portability and Accountability Act (HIPAA) adherence, several steps were taken to categorize region to larger areas. Baltimore City is a standard region used within Maryland Medicaid analysis. The following regions were added to Baltimore City for this analysis: Baltimore suburbs, Washington D.C. suburbs, and the rest of Maryland. The "rest of Maryland" include the Eastern Shore, Southern Maryland, Western Maryland, Other, and Out of State. Out of State is included due to the fact that the recipient is still in the HealthChoice program for Maryland Medicaid. However, due to UMBC's HIPAA adherence, regional information is not included in the demographic tables.

COVGRP: The Medicaid coverage group as of the FY of the initial date of diagnosis. Coverage group will be defined as Families/Children, , MCHP, and Disabled/ Expansion/Other.

PROVSPEC: The specialty of the provider prescribing the initial dose of medication. This is a nominal variable that has the categories of primary care physician (PCP), pediatrician, and other specialties.

PROVREGION: The first prescribing provider's practive region. Due to UMBC's Health Insurance Portability and Accountability Act (HIPAA) adherence, several steps were taken to categorize region to larger areas. Baltimore City is a standard region used within Maryland Medicaid analysis. The following regions were added to Baltimore

City for this analysis: Baltimore suburbs, Washington D.C. suburbs, and the rest of Maryland. The "rest of Maryland" include the Eastern Shore, Southern Maryland, Western Maryland, Other, and Out of State. Out of State is included due to the fact that the recipient is still in the HealthChoice program for Maryland Medicaid, and therefore Maryland Medicaid will pay for the encounter/service provided. However, due to UMBC's HIPAA adherence, regional information is not included in the demographic tables.

CCW: The number of chronic conditions the recipient has, as defined by the CCW algorithm. This variable is continuous. By CCW definition, every person in this study ought to have at least one CCW – asthma.

Severe Asthma: An indicator of the presence of medications and utilization correlated with severe asthma. Often, a diagnosis of severe asthma is made after examining lab results and evaluating self-reported symptoms. However, Maryland Medicaid administrative data does not include lab results nor recipient reported symptoms. Thus, severe asthma was identified through the presence of various medications used specifically for severe asthma or an increase in utilization for asthma during the follow-up period.

HC: A categorical variable indicating whether, during the study period, the recipient was only in the HealthChoice program, in the HealthChoice program at some point, or only participated in the fee-for-service program.

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Assessing the Impact of Adherence on Health Care Outcomes for Inhaled Corticosteroids Compared to Leukotriene Receptor Antagonists: Analysis of Maryland Medicaid Data

Introduction

Asthma is recognized as having a substantial burden on the United States population not only in terms of health care utilization, but also in general economic terms such as days missed from work or school (U.S. Health and Human Services, Centers for Disease Control and Prevention, n.d.; Akinbami, Moorman, & Liu, 2011; Bankoski, Hess-Mutinda, McEachern, & De Pinto, 2011; Thorpe, Ogden, & Galactionova, 2010). Rising prevalence rates of asthma over the past 20 years only increase concern for controlling the impact of asthma on the overall population (Akinbami et al., 2011; Bankoski et al., 2011). To combat the effects of asthma, guidelines for best treatment practices, education programs for both providers and patients, and community intervention programs to address risk factors have been deployed all over the country, all with varying success (U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion, n.d.). Specifically, a primary focus is on increasing and sustaining adherence to maintenance medications for asthma. Understanding the best methods to treat asthma is only part of the solution; achieving adherence with the treatment is essential to the success of any asthma program, whether individual- or community-based, in controlling the effects of the disease.

Research has continued to prove the low rate of adherence with several asthma treatments, specifically inhaled corticosteroids (ICS) (Ducharme et al., 2012; Haughney et al., 2008; Price et al., 2011). Examining levels of adherence is essential in understanding the real-world effectiveness of the medication, in spite of clinical efficacy. Two of the primary medications studied are ICS and leukotriene receptor antagonists (LTRA). ICS is generally

acknowledged as the most clinically efficacious treatment for asthma. Randomized control trials (RCTs) over multiple decades have repeatedly demonstrated the superiority of this medication to all others. However, it has also been established that the general population does not adhere to daily prescriptive use, rendering the medication ineffective for controlling asthma (Mahr & Mumm, 2011; Sadatsafavi, Lynd, Marra, Bedouch, & Fitzgerald, 2013; Zeiger et al., 2005). LTRA is a less clinically efficacious medication that is generally well-received, and patients adhere to it better as it comes in a pill form rather than an inhaler.

This study builds on previous research assessing ICS and LTRA within the Maryland Medicaid population (Smith, 2018). The purpose of this analysis is to determine how adherence to the initial treatment prescribed for asthma during the year following initial diagnosis affects the health care outcomes of an asthma-related emergency department (ED) visit or inpatient hospitalization (INPH).

Methods

Data Source

This retrospective study used administrative claims data from the Maryland Medicaid Management Information System II (MMIS2) for state fiscal years (FYs) 2010 through 2015. The cohort consists of Maryland Medicaid recipients (hereafter referred to simply as recipients) with a probable mild to moderate asthma diagnosis during FY 2010 to FY 2014 (July 1, 2009, through June 30, 2014) (see Appendix A for the definition of mild to moderate asthma). Recipients were eligible for this study if they had at least one month of eligibility, had a claim containing an asthma diagnosis, and were enrolled in either fee-for-service (FFS) or the HealthChoice managed care organization (MCO) program. Both the Maryland Department of Health and the University of Maryland, Baltimore County Institutional Review Boards gave

approval to conduct this study. Outcomes during the 12-month follow-up period included MMIS2 data from FY 2010 through FY 2015 (July 1, 2010, to June 30, 2015). MMIS2 data used for this study are composed of Maryland Medicaid eligibility, recipient demographic information, administrative claims for health care utilization, pharmacy dispensing, provider demographics, and program enrollment dates for the FFS and MCO programs.

Study Population Selection

Recipients were initially eligible for the study if a primary diagnosis of asthma according to the International Classification of Diseases, Ninth Revision (ICD-9; codes included started with 493) was present on any ED or INPH FFS claim (claim) or MCO encounter (encounter) and there was record of a filled prescription for ICS or LTRA. Eligibility for the study also included recipients with at least four physician visits having an ICD-9 code for asthma and who filled a prescription for ICS or LTRA. A physician visit is defined as a physician FFS claim or MCO encounter for a unique service day-provider combination.

Qualifying prescriptions had to occur within 90 days of the ED visit, INPH, or fourth physician visit. Since a recipient could be seen by a physician up to three times prior to qualifying for the study, asthma medication may have been started prior to the qualifying diagnostic event. Furthermore, maintenance medication may be prescribed for a 90-day period. Thus, the qualifying medication was the prescription with a fill date closest to the diagnostic event that occurred within 90 days. This is considered the recipient's initial treatment for asthma. The prescriptions had to also occur within the eligibility period (FY 2010 to FY 2014). The follow-up period was identified for each person as the 12-month period starting with the initial date of the qualifying event (IDE), thereby resulting in study dates being unique to each recipient in the study.

There were 1.8 million people with eligibility during FY 2010 to FY 2014 identified in the Maryland Medicaid eligibility data. Of those Maryland Medicaid recipients, 182,877 people had an FFS claim or HealthChoice encounter with a primary diagnosis starting with 493 (ICD-9 of 493.xx) for an INPH, ED visit, or physician visit. Of these 182,877 recipients, 83,561 (46%) met this study's definition of asthma, which required those with only physician visits to have at least four visits for asthma within the study period. Also, during the study period, 293,337 recipients filled a prescription for at least one of the two treatments of interest. Recipients were excluded from the study if they were not placed on monotherapy (i.e., if they filled a prescription for both treatments) or if they met the criteria for severe asthma (see Appendix B).

A total of 36,534 recipients made up the final population for this study because they met all of the following criteria: (1) had a diagnosis of asthma during an INPH, ED visit, or four physician visits, (2) had complete demographic data, (3) filled a qualifying prescription within 90 days of IDE, and (4) did not meet the criteria for severe asthma prior to IDE. Each recipient was assigned to a treatment group (ICS or LTRA) based on the prescription filled with a date closest to the IDE. A total of 28,847 recipients were assigned to the ICS reference group, and 7,687 recipients were assigned to the LTRA treatment Group. Propensity score matching was performed to identify the study population for multivariate analysis, resulting in a final cohort of 15,368 recipients included in the multivariate analysis—7,684 LTRA-treated and 7,684 ICS-treated recipients (see Appendix C for flow chart of cohort selection). See Table 1 for a description of the study cohort baseline characteristics.

Table 1

Baseline Characteristics of Recipients Included in the Multivariate Analysis

	Study Cohort	Study Population		
	% (n) N = 15,368	LTRA % (n) 50 (7,684)	ICS % (n) 50 (7,684)	p-value
Qualifying Event				
ED Visit	38.98 (5,990)	38.90 (2,989)	39.06 (3,001)	p = 0.9611
Inpatient Hospitalization	9.79 (1,504)	9.84 (756)	9.73 (748)	
Physician Visits	51.24 (7,874)	51.26 (3,939)	51.21 (3,935)	
Age Group				
0 – 5 Years of Age	20.72 (3,184)	20.72 (1,592)	20.72 (1,592)	p = 0.9222
6 – 12 Years of Age	40.79 (6,269)	40.76 (3,132)	40.83 (3,137)	
13 – 18 Years of Age	13.83 (2,125)	13.81 (1,061)	13.85 (1,064)	
19+ Years of Age	24.66 (3,790)	24.71 (1,899)	24.61 (1,891)	
Sex				
Female	50.60 (7,776)	50.53 (3,883)	50.66 (3,893)	p = 0.8718
Male	49.40 (7,592)	49.47 (3,801)	49.34 (3,791)	
Race				
Black	50.64 (7,782)	50.61 (3,889)	50.66 (3,893)	p = 0.9922
Caucasian	25.53 (3,923)	25.59 (1,966)	25.47 (1,957)	
All Other Races	23.83 (3,663)	23.80 (1,829)	23.87 (1,834)	
Area Primary Residence				
Baltimore City	N/A	N/A	N/A	p = 0.3906
Baltimore Suburbs				
Washington DC Suburbs				
Eastern Shore MD, Southern/Western MD, Out of State				
Primary Care Provider Specialty				
Pediatrics	47.26 (7,263)	47.18 (3,625)	47.35 (3,638)	p = 0.9137
Primary Care	27.93 (4,293)	28.03 (2,154)	27.84 (2,139)	
All Other Specialties	24.80 (3,812)	24.79 (1,905)	24.82 (1,907)	
Diagnostic Provider Specialty				
Pediatrics	22.57 (3,468)	22.55 (1,733)	22.58 (1,735)	p = 0.9846
Primary Care	11.80 (1,814)	11.84 (910)	11.76 (904)	
All Other Specialties	65.63 (10,086)	65.60 (5,041)	65.66 (5,045)	
Presence of AR				
Yes	48.99 (7,529)	49.00 (3,765)	49.99 (3,764)	p = 0.9871
No	51.01 (7,839)	51.00 (3,919)	51.02 (3,920)	

Table 1

Baseline Characteristics of Recipients Included in the Multivariate Analysis, Continued

	Study Cohort	Study Population		
	% (n) N = 15,368	LTRA % (n) 50 (7,684)	ICS % (n) 50 (7,684)	p-value
Medicaid Program				
FT HealthChoice	45.76 (7,033)	47.59 (3,657)	43.94 (3,376)	p < 0.0001
Part-Year HealthChoice / Part-Year FFS	52.60 (8,084)	50.64 (3,891)	54.57 (4,193)	
FT FFS	1.63 (251)	1.77 (136)	1.50 (115)	
Medicaid Coverage Group				
Families and Children	69.00 (10,604)	67.48 (5,185)	70.52 (5,419)	p = 0.0002
MCHP	15.35 (2,359)	16.11 (1,238)	14.59 (1,121)	
Disabled, Medicaid Expansion, Other	15.65 (2,405)	16.41 (1,261)	14.89 (1,144)	
Number of Chronic Condition Categories				
Average Number at Time of IDE	1.54 (range 1 – 15)	1.50 (range 1 – 15)	1.57 (range 1 – 13)	p = 0.0003

Adherence Calculation

This study defined medication adherence using the proportion of days covered (PDC), which is defined as the total number of days of medication coverage divided by the total days in the follow-up period. Employing the PDC method allows for the adjustment of prescription date ranges based on the date of initial diagnosis as well as the end of the follow-up period (Nau, 2011). Since the qualifying asthma prescription may occur prior to the qualifying diagnostic event, the total number of days of medication coverage within the follow-up year may be less than the total number of days for which the prescription was filled. Furthermore, prescription date ranges were adjusted so as to cap the last prescription period if it extended beyond the end of follow-upg.

Due to the transitory nature of the Medicaid population, not all study recipients were eligible for Medicaid throughout the study period. Thus, the denominator was calculated as the total number of days within the follow-up period during which the recipient was eligible for Medicaid. If a recipient was eligible for Medicaid throughout the entire year, then the total days eligible would equal to the total days in the follow-up period. Otherwise, the denominator was adjusted accordingly.

Evaluating the effect adherence has on outcomes related to asthma exacerbation is not consistent within the literature. First, some studies use the PDC method of calculating adherence, while other studies use the medication possession ratio (MPR) (Blais et al., 2011; Ducharme et al., 2012; Lee et al., 2010; Li et al., 2014; Tan et al., 2009; Wu et al., 2014). Additionally, adherence has been used within various analyses as either a continuous variable or as a binary indicator denoting that the patient has achieved a certain level of adherence. In this study, adherence was used both as a binary indicator for the descriptive statistics and as a continuous variable in the multivariate analysis. The use of a continuous variable was done to ensure that information is not lost within the multivariate analysis, as can happen when dichotomizing a continuous variable. For the binary indicator, adherence to medication was defined as 0.70 or higher (Williams et al., 2011) (See Appendix D).

Study Measures

ED visit and INPH for asthma exacerbation were the outcomes evaluated for this study. Outcomes were identified using the available MMIS2 data of each study recipient for the 12 months following IDE. Outcome variables are binary indicators identifying the presence of an ED visit or INPH during the follow-up period. The definition for an asthma-related ED visit and

INPH outcome was the same as used in the defining the initial asthma population. Analysis was stratified by the presence of the co-morbidity of allergic rhinitis (AR).

Statistical Analyses

Propensity score matching. Selection bias for the assigned initial asthma treatment was of concern due to the inherent nature of observational studies. Propensity score matching (PSM) was used to address the possible selection bias. PSM between the LTRA- and ICS-identified groups was conducted via the SAS 9.4 procedure PSMATCH (SAS Institute, Inc., 2017). All potential confounders were identified *a priori* and included IDE location, age group, gender, race, IDE physician, and presence of AR at IDE. The PSMATCH procedure applied logistic regression to predict the assignment of LTRA.

Matching each recipient in the LTRA group to an unmatched ICS recipient possessing the nearest propensity score was done per the greedy nearest-neighbor method. To ensure that the matches were similar within a defined degree, the caliper was set to 0.5 (Gant & Crowland, 2017; SAS Institute, Inc., 2017). Thus, the maximum difference between the propensity scores of each matched pair had to be within 0.5. Balance of covariates analysis performed on the matched study cohort revealed that the ICS and LTRA groups were not statistically different based on observed characteristics. While this does not eliminate the possibility of bias, it does improve the likelihood that any identified difference in outcomes between the two groups is related to the treatment.

Logistic regression. Multivariate logistic regression analysis was used to determine the association of initial LTRA treatment (as compared to ICS) with ED visit or INPH outcomes while controlling for known confounders. Research has suggested that LTRA may be a more effective treatment for asthma in people with the co-morbidity of AR. As such, the analysis was

stratified by AR (Global Initiative for Asthma, 2016). The four logistic regression models run for this study include asthma-only ED visit, asthma-only INPH, asthma-AR ED visit, and asthma-AR INPH. All covariates were determined *a priori*. In each analysis, an iterative process was used to determine the regression model with the most precise estimates. As a result, the estimation process required some covariates to be dropped. The final model included LTRA, age group, race, region of residence, primary provider specialty, Medicaid coverage group, total number of chronic conditions, Medicaid plan, severity of asthma, and adherence to treatment.

Results

Study Cohort Adherence to Treatment

Overall, the mean rate of adherence to treatment for the PSM study cohort was 31.34%. This represents the average PDC for recipients during individual follow-up periods; on average, recipients had enough medication to cover 31.34% of Medicaid days during the year after IDE. Recipients taking LTRA had a higher average PDC than those taking ICS (38.2% versus 24.5%). This means that recipients initially started on LTRA had a higher percentage of days during the follow-up period during which they had medication than those initially started on ICS. Considering the 10% most adherent in both treatment arms (the 90th percentile), the most adherent LTRA recipients had a PDC higher than 75% compared to a PDC higher than only 53% for the most adherent ICS recipients. Table 2 shows the distribution of PDC for the multivariate analysis cohort. Table 3 shows descriptive statistics for the adherent group and non-adherent Group. Due to UMBC HIPAA requirements, descriptive statistics for region of residence are not listed. However, statistical significance is still indicated.

Table 2

Distribution of PDC for Recipients Included in the Multivariate Analysis

	Percent of Medicaid Days Covered		
	Total Cohort	Treatment Groups	
		LTRA	ICS
Percentiles for PDC			
10th	8%	8%	7%
25th	10%	16%	8%
50th	25%	33%	16%
75th	49%	58%	33%
90th	69%	76%	53%
99th	96%	97%	94%
Mean PDC			
Average	31.34%	38.20%	24.50%

Table 3

Descriptive Statistics for Study Cohort by Adherence to Treatment during Follow-Up

	Adherent to Treatment % (n) 7.14 (1,098)	Non-Adherent to Treatment % (n) 92.86 (14,270)	P-value
Qualifying Event			
ED Visit	31.15 (342)	39.58 (5,648)	p < 0.0001
Inpatient Hospitalization	9.74 (107)	9.79 (1,397)	
Physician Visits	59.11 (649)	50.63 (7,225)	
Initial Treatment			
LTRA	75.96 (834)	48.00 (6,850)	p < 0.0001
ICS	24.04 (264)	52.00 (7,420)	
Age Group			
0 – 5 Years of Age	18.12 (199)	20.92 (2,985)	p < 0.0001
6 – 12 Years of Age	33.88 (372)	41.32 (5,897)	
13 – 18 Years of Age	8.20 (90)	14.26 (2,035)	
19+ Years of Age	39.80 (437)	23.50 (3,353)	
Sex			
Female	55.46 (609)	50.22 (7,167)	p = 0.0008
Male	44.54 (489)	49.78 (7,103)	
Race			
Black	43.99 (483)	51.15 (7,299)	p = 0.2177
Caucasian	35.88 (394)	24.73 3,529)	
All Other Races	20.13 (221)	24.12 (3,442)	
Area Primary Residence			
Baltimore City	N/A	N/A	p < 0.0001
Baltimore Suburbs			
Washington DC Suburbs			
Eastern Shore MD, Southern/Western MD, Out of State			
Primary Care Provider Specialty			
Pediatrics	40.16 (441)	47.81 (6,822)	p = 0.2273
Primary Care	39.25 (431)	27.06 (3,862)	
All Other Specialties	20.58 (226)	25.13 (3,586)	
Diagnostic Provider Specialty			
Pediatrics	18.31 (201)	22.89 (3,267)	p = 0.2275
Primary Care	17.40 (191)	11.37 (1,623)	
All Other Specialties	64.30 (706)	65.73 (9,380)	

Table 3

Descriptive Statistics for Study Cohort by Adherence to Treatment during Follow-Up, Continued

	Adherent to Treatment % (n) 7.14 (1,098)	Non-Adherent to Treatment % (n) 92.86 (14,270)	P-value
Presence of Allergic Rhinitis			
Yes	51.55 (566)	48.45 (6,963)	p = 0.0786
No	48.79 (532)	51.21 (7,307)	
Medicaid Program			
FT HealthChoice	50.91 (559)	45.37 (6,474)	p = 0.1315
Part-Year HealthChoice/ Part-Year FFS	44.63 (490)	53.22 (7,594)	
FT FFS	4.46 (49)	1.42 (202)	
Medicaid Coverage Group			
Families and Children	56.47 (620)	69.86 (9,984)	p < 0.0001
MCHP	14.30 (157)	15.43 (2,202)	
Disabled, Medicaid Expansion, Other	29.23 (321)	14.60 (2,084)	
Number of Chronic Condition Categories (CCW)[#]			
Average Number at Time of IDE	1.91 (range 1 – 11)	1.51 (range 1 – 15)	p < 0.0001
Adherence to Treatment in Follow-up Period			
Average Percent of Medicaid Days Covered	86.33%	27.11%	p < 0.0001

[#] Chronic Condition Categories were defined using the Chronic Condition Warehouse definition (Chronic Conditions Data Warehouse, n.d.)

The outcomes of ED visit and INPH for adherent and non-adherent groups are listed in Table 4. The percent of people having an INPH during the follow-up period did not differ significantly between the adherent and non-adherent groups (p = 0.5703). However, the percent of people having an ED visit in the adherent group (13.93%) versus the non-adherent group (18.52%) was significantly different (p = 0.0001).

Table 4

Frequency of Outcomes for the Study Cohort by Adherence to Treatment during Follow-Up

	Adherent to Treatment % (n) 7.14 (1,098)	Non-Adherent to Treatment % (n) 92.86 (14,270)	P-value
ED visit	13.93 (153)	18.52 (2,643)	p = 0.0001
INPH	6.28 (69)	5.87 (837)	p = 0.5703
ED visit or INPH	17.49 (192)	21.46 (3,062)	p = 0.0019

As Table 2 shows, on average, recipients had medication for 33% of the days during the study's follow-up period. Stratifying the sample by treatment group reveals that recipients initially started on LTRA had more days covered than those started on ICS (38.2% versus 24.5%, respectively). This difference in PDC is statistically significant ($p < 0.0001$). Table 1 reveals the median in both treatment arms was lower than the average listed in Table 2, suggesting that more recipients in each group had a PDC that was less than the respective averages. Hence, over half of the recipients in each group have medication for less than a third of the days in the follow-up period.

As Table 3 shows, differences in location of qualifying diagnostic event was significantly different between the adherent and non-adherent groups ($p < 0.0001$). While 10 percent of both groups were identified through INPH, more recipients were identified by physician visits in the adherent group than the non-adherent Group. Like in Table 1, more recipients in the adherent group were initially placed on LTRA than ICS (75.96% versus 24.04%). The adherent group was primarily adults over the age of 19 and children aged 6 to 12 (39.80% and 33.88%, respectively). Teenagers—aged 13 to 18—were the least represented in the adherent Group. The non-adherent group experienced a different distribution: over 40% were children aged 6 to 12. Children aged 0

to 5 and adults over the age of 18 made up about 20 percent of the non-adherent Group. There were more females (55.46%) than males (44.54%) in the adherent group, but both sexes were equally represented in the non-adherent Group.

The distribution of race was similar when comparing the adherent and non-adherent groups. Within the adherent group, the largest percentage of recipients was Black, followed by Caucasians and All Other Races (43.99%, 35.88%, and 20.13%, respectively). Similarly, over 50% of the non-adherent group was Black. The distribution of residential area, on the other hand, was significantly different for the adherent and non-adherent groups.

The adherent and non-adherent groups had comparable distributions for primary care specialty. Only about 20% of recipients adherent to treatment have an "All Other Specialties" as the primary provider. The remaining 80% of adherent recipients are divided between primarily seeing a pediatrician or primary care specialist. In the non-adherent group, though, nearly 50% saw a pediatrician as their primary care provider. Roughly 25% of non-adherent recipients see either a primary care provider (27.06%) or other specialist (25.13%). The majority of the recipients in both the adherent and non-adherent groups had the qualifying diagnostic event diagnosed by All Other Specialist (64.30% and 65.73%, respectively).

While the majority of both of the groups were enrolled in HealthChoice at some point during the study period, 4.46% of adherent recipients and 1.42% of non-adherent recipients only used FFS during the study period. More adherent recipients were in HealthChoice full-time than part-time (50.91% versus 44.63%), while the opposite distribution occurred for non-adherent recipients (45.37% full-time versus 53.22% part-time). Overall, the difference in distribution between the adherent and non-adherent groups was not significantly different ($p = 0.1315$).

Coverage group was significantly different between the adherent and non-adherent groups. Slightly over half (56.47%) of the adherent recipients but nearly 70% of the non-adherent recipients were in the Families and Children coverage Group. Around 15% of recipients in each group were in MCHPG. Almost 30% of adherent recipients were in the Disabled/Medicaid Expansion/Other coverage group, whereas less than 15% of non-adherent recipients were in this coverage Group. This difference between the adherent and non-adherent groups was statistically significant ($p < 0.0001$).

Due to findings previously reported, the presence of AR was used within the algorithm for PSM (Smith, 2018). As such, the cohort population was evenly split between those who had AR (48.99%) prior to the IDE and those who did not (51.01%). A similar distribution was seen in both the adherent and non-adherent groups, where half of each group had AR.

More chronic conditions, on average, were present within the adherent group than the non-adherent group (1.91 and 1.51, respectively). This difference between the two groups was statistically significant. Likewise—and as would be expected due to the fact that one group was deemed "adherent" and the other "non-adherent"—the average adherence rate, as defined by PDC, was significantly different between the adherent (86.33%) and non-adherent (27.11%) groups.

Logistic Regression Results

Logistic regression models were run for both the ED visit and INPH outcomes for each AR stratum. Adherence was entered as a continuous variable; PDC ranges from 0% of days covered to 100% of days covered. After controlling for adherence, LTRA did not significantly differ from ICS for the INPH in recipients with the co-morbidity of AR. While LTRA was statistically significant in all other models, adherence was only significant in the models for the

outcome of ED visit after IDE. Tables 5 through 8 provide the results of the various regression models, which contained the covariates adherence, age group, recorded race, region of residence, primary care provider specialty, Medicaid coverage group, total number of co-morbidities, Medicaid program, and indication of development of severe asthma within 12 months after IDE.

Asthma-Only

Table 5

ED Visits for Recipients with Asthma

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA*	0.2477	<.0001	1.281	1.141 - 1.439
Adherence* #	-0.6503	<.0001	0.522	0.4 - 0.682
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.253	0.0011	0.776	0.667 - 0.904
Ages 13 – 18*	-0.4917	<.0001	0.612	0.501 - 0.747
Ages 19+*	-0.364	0.0003	0.695	0.571 - 0.845
White	Reference			
Black*	0.4152	<.0001	1.515	1.292 - 1.776
All Other Races	0.1541	0.1035	1.167	0.969 - 1.405
Baltimore City	Reference			
Baltimore Suburb	-0.1082	0.1491	0.897	0.775 - 1.04
Washington Suburb*	-0.32	0.0001	0.726	0.617 - 0.855
All Other MD Counties*	-0.3202	0.0004	0.726	0.609 - 0.865
Pediatrician	Reference			
PCP	0.1133	0.1696	1.12	0.953 - 1.317
All Other Specialists*	0.4136	<.0001	1.512	1.312 - 1.744
Families and Children	Reference			
MCHP*	-0.2229	0.0168	0.8	0.667 - 0.961
All Other Coverage	0.1013	0.2234	1.107	0.94 - 1.303
HC Full-time	Reference			
HC Part-time	0.0351	0.5518	1.036	0.923 - 1.163
FFS Only*	-0.5692	0.0188	0.566	0.352 - 0.91
Total CCW* #	-0.2553	<.0001	0.775	0.724 - 0.829
Severe Asthma*	1.4897	<.0001	4.436	3.825 - 5.144

* Statistically Significant at 95% confidence level
# Entered into model as a continuous variable

Table 6

Inpatient Hospitalization for Recipients with Asthma

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA*	0.308	0.0004	1.361	1.147 - 1.614
Adherence #	-0.3097	0.0964	0.734	0.509 - 1.057
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.4507	0.0001	0.637	0.506 - 0.802
Ages 13 – 18*	-0.677	<.0001	0.508	0.372 - 0.694
Ages 19+*	-0.4441	0.0017	0.641	0.486 - 0.846
White	Reference			
Black*	0.3228	0.0056	1.381	1.099 - 1.735
All Other Races	0.0909	0.5174	1.095	0.832 - 1.442
Baltimore City	Reference			
Baltimore Suburb	-0.1513	0.1616	0.86	0.695 - 1.062
Washington Suburb	-0.2137	0.0766	0.808	0.637 - 1.023
All Other MD Counties	-0.1855	0.1434	0.831	0.648 - 1.065
Pediatrician	Reference			
PCP	0.1933	0.1153	1.213	0.954 - 1.543
All Other Specialists*	0.3504	0.0016	1.42	1.142 - 1.765
Families and Children	Reference			
MCHP	-0.2081	0.1676	0.812	0.604 - 1.091
All Other Coverage*	0.3915	0.0003	1.479	1.195 - 1.83
HC Full-time	Reference			
HC Part-time	-0.0218	0.7992	0.978	0.827 - 1.157
FFS Only	0.2705	0.2486	1.311	0.828 - 2.075
Total CCW #	-0.00597	0.8638	0.994	0.928 - 1.064
Severe Asthma*	-0.4507	<.0001	4.848	4.017 - 5.851

***** Statistically Significant at 95% confidence level
# Entered into model as a continuous variable

Findings from the regression models for recipients without the co-morbidity of AR suggest that an initial treatment of LTRA for asthma, when controlling for adherence rate, was correlated with both asthma-related ED visit and INPH during the following 12 months. Initial placement on LTRA for asthma, for this sub-cohort, was more likely for both an asthma-related ED visit and INPH during the follow-up period (OR = 1.281 and OR = 1.361, respectively).

Adherence, though, was only associated with an asthma-related ED visit. Adherence was negatively associated with ED visit, indicating the higher the level of adherence to treatment, the less likely the recipient will have an ED visit during the follow-up period. While the covariates found to be significant in the ED visit and INPH models differed, all three age variables, Black, All Other Specialists, and severe asthma remained significant across both models.

Compared to the youngest age group, age greater than 5 years was protective against asthma-related ED visit and INPH. In terms of race, however, Blacks were more likely than Whites to have both ED visit and INPH (OR = 1.515 and OR = 1.381, respectively). Recipients without an AR co-morbidity residing in the Washington DC suburbs were less likely to have an ED visit after IDE (OR = 0.716) compared to recipients living in Baltimore City. Residential location was not significant in the INPH model.

The regression results related to the type of provider most seen and type of coverage group were mixed. Principally seeing other types of specialists leads to an increased chance of having an ED visit (OR = 1.512, $p<0.0001$) as well as an INPH (OR = 1.42, $p = 0.0016$). Those in MCHP are less likely than those in Families and Children to be seen in the ED (OR = 0.8, $p = 0.0168$). All Other Coverage groups were more likely to have an asthma-related INPH than recipients in the Families and Children coverage group (OR = 1.479, $p = 0.0003$). Recipients only using FFS were less likely to visit the ED following IDE (OR = 0.566, $p = 0.0188$), though no difference was found for INPH. As the number of co-morbidities increased, there was a less likely chance of an ED visit (OR = 0.775, $p < 0.0001$), whereas the number of co-morbidities was not associated with INPH ($p = 0.8638$). Not surprisingly, people who would eventually be diagnosed with severe asthma were highly likely to have both ED visit and INPH for asthma after IDE (OR = 4.436 and 4.848, respectively).

Table 7

ED Visits for Recipients with Asthma and the Co-Morbidity of AR

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA*	0.1802	0.016	1.198	1.034 - 1.387
Adherence* #	-0.6216	0.0002	0.878	0.389 - 0.741
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.4076	<.0001	0.665	0.561 - 0.789
Ages 13 – 18*	-0.7617	<.0001	0.467	0.364 - 0.599
Ages 19+*	-0.804	<.0001	0.448	0.339 - 0.59
White	Reference			
Black*	0.4032	<.0001	1.497	1.231 - 1.82
All Other Races	0.1675	0.1394	1.182	0.947 - 1.477
Baltimore City	Reference			
Baltimore Suburb	-0.2002	0.0511	0.819	0.669 - 1.001
Washington Suburb	-0.2021	0.059	0.817	0.662 - 1.008
All Other MD Counties	-0.2168	0.059	0.805	0.643 - 1.008
Pediatrician	Reference			
PCP	0.0617	0.5152	1.064	0.883 - 1.281
All Other Specialists*	0.4942	<.0001	1.639	1.35 - 1.99
Families and Children	Reference			
MCHP	-0.1025	0.314	0.903	0.739 - 1.102
All Other Coverage*	0.3132	0.01	1.368	1.078 - 1.736
HC Full-time	Reference			
HC Part-time*	0.1536	0.0352	1.166	1.011 - 1.345
FFS Only*	-0.0587	0.8881	0.943	0.416 - 2.137
Total CCW* #	-0.0947	0.0367	0.91	0.832 - 0.994
Severe Asthma*	1.3921	<.0001	4.023	3.328 - 4.864

***** Statistically Significant at 95% confidence level
# Entered into model as a continuous variable

Table 8
INPH for Recipients with Asthma and the Co-Morbidity of AR

	Parameter Estimate	p-value	Odds Ratio	95% CI
ICS	Reference			
LTRA	0.0109	0.9477	1.011	0.729 - 1.402
Adherence	-0.329	0.3592	0.72	0.356 - 1.454
Ages 0 – 5	Reference			
Ages 6 – 12*	-0.7494	<.0001	0.473	0.327 - 0.683
Ages 13 – 18*	-0.8261	0.0025	0.438	0.256 - 0.749
Ages 19+*	-0.8569	0.0048	0.424	0.234 - 0.77
White	Reference			
Black*	0.4769	0.032	1.611	1.042 - 2.492
All Other Races	0.3204	0.202	1.378	0.842 - 2.254
Baltimore City	Reference			
Baltimore Suburb	0.0319	0.8857	1.032	0.669 - 1.594
Washington Suburb	-0.2534	0.3021	0.776	0.48 - 1.256
All Other MD Counties	-0.0841	0.7382	0.919	0.561 - 1.506
Pediatrician	Reference			
PCP	-0.2126	0.3213	0.809	0.531 - 1.231
All Other Specialists	-0.1903	0.4262	0.827	0.517 - 1.321
Families and Children	Reference			
MCHP	-0.2435	0.3227	0.784	0.484 - 1.27
All Other Coverage*	0.6714	0.0044	1.957	1.233 - 3.105
HC Full-time	Reference			
HC Part-time	0.2617	0.1039	1.299	0.948 - 1.781
FFS Only	-0.5071	0.6233	0.602	0.08 - 4.557
Total CCW #	-0.016	0.8499	0.984	0.834 - 1.161
Severe Asthma*	1.8277	<.0001	6.22	4.349 - 8.895

***** Statistically Significant at 95% confidence level
# Entered into model as a continuous variable

Asthma with Allergic Rhinitis Co-Morbidity Results

Being initially placed on LTRA was associated with more ED visits (OR = 1.198, p = 0.016) but not INPH when controlling for adherence rate. Similarly, adherence rate was only significant in the model for ED visits, where it has a negative correlation (OR = 0.878, p = 0.0002). Thus, as the adherence rate increased, the likelihood of asthma-related ED visit decreased. There were mixed results for the other independent variables as well. Although, as in

the analysis for recipients without AR, several co-variates were consistent across the two models: all age variables, Black, all other coverage groups, and severe asthma.

Being older than five years was negatively associated with both asthma-related ED visit and INPH. Blacks were more likely than Whites to have both ED visit (OR = 1.497, $p < 0.0001$) and INPH (OR = 1.611, $p = 0.032$). The variable representing all other races was not significant. Residential location was not associated with ED visits or INPHs for recipients with the co-morbidity of AR.

Provider type was not consistent across the two models. Having a primary provider other than a PCP, as compared to a pediatrician, indicated an increased chance of having an ED visit (OR = 1.639, $p<0.0001$) but not an INPH ($p = 0.4262$). Those in a coverage group other than MCHP were more likely than those in the Families and Children coverage category to be seen in the ED and/or have INPH after IDE (OR = 1.368 and OR = 1.957). Being in the MCHP coverage category was not significant in either model.

Being in HealthChoice part-time was associated with increased ED visit after IDE (OR = 1.166, $p = 0.0352$), though it was not associated with INPH. Only being in FFS was not significant in either regression. Likewise, the number of CCW (other than AR) was negatively correlated with an asthma-related ED visit (OR = 0.91, $p = 0.0367$). Thus, as the number of co-morbidities increased, the chance of an ED visit for asthma decreased. The number of co-morbidities, however, was not associated with INPH ($p = 0.8499$). As seen in the analysis for recipients without AR, people who would eventually be diagnosed with severe asthma were highly likely to have both an ED visit and/or INPH for asthma after IDE (OR = 4.023 and 6.22, respectively).

Discussion

Previous studies have illuminated the differences in adherence between ICS and LTRA to treat asthma (Wu et al., 2014; Lee et al., 2010; Tan et al., 2009). The results found within the Maryland Medicaid data provide several important insights into adherence to initially prescribed asthma treatment and health care outcomes for asthma. First, LTRA was associated with more ED visit after IDE for recipients with asthma, as well as INPH for recipients with both asthma and the co-morbidity of AR, even when controlling for adherence rate. Second, although recipients starting on LTRA experienced higher adherence rates for treatment, overall adherence rates for both LTRA and ICS were low. Finally, an increase in adherence to treatment reduced the likelihood of an asthma-related ED visit during the year after initial treatment.

This study found an association between LTRA and asthma-related health outcomes in three of the four models. This finding is in contrast to the majority of evidence in the literature, which indicates that LTRA is not more likely than ICS to be linked to ED visits or INPHs, even after controlling for adherence (Allen-Ramey et al., 2003; Allen-Ramey, Duong, Riedel, Markson, & Weiss, 2004; Blais et al., 2011; Colice et al., 2008; Ducharme et al., 2012; Lee et al., 2010; Li et al., 2014; Tan et al., 2009; O'Connor, Parasuraman, Roberts, & Leibman, 2006; Wu et al., 2014). However, in the cohort of cited studies comparing LTRA with ICS for health care outcomes, the majority do not provide Medicaid-specific results.

Only two of the studies specifically analyzed Medicaid data separately from commercial insurance data (Li et al., 2014; Wu et al., 2014). Furthermore, both of these studies examined Tennessee Medicaid data for similar cohorts. It is reasonable to hypothesize that variations between Maryland and Tennessee Medicaid populations would affect the overall results. Such variations between Maryland and Tennessee Medicaid recipients might include racial

composition, urban versus rural distribution, provider practices, state interventions, barriers to health care services, and number of environmental risk factors. In fact, the racial distribution reported in the Tennessee data for LTRA was 60% White, 31% Black, and 9% Other (Wu et al., 2014, pg. 609). However, the Maryland Medicaid cohort is composed of a mostly Black population (roughly 51% Black, 25% White, and 24% Other) (Table 2). This difference in racial distribution might account for some of the variation found within reported results. Residential area (rural versus urban) was not reported for the Tennessee population, so it is impossible to ascertain any residential differences between the two state cohorts. However, it is apparent that the two cohorts may differ significantly in terms of identifiable asthma risk factors and perhaps even behavioral patterns.

The second result from this current study, though, does reflect findings in the overall literature (Allen-Ramey et al., 2004; Blais et al., 2011; Colice et al., 2008; Cutler & Everett, 2010; Ducharme et al., 2012). An analysis of adherence rates for both LTRA and ICS within Maryland Medicaid demonstrates that recipients, on average, had a higher rate of adherence with LTRA than ICS (38.2% versus 24.5%). The literature has delineated several reasons for this disparity. First, it is a generally accepted fact that people do not like to use the inhaler. Reasons cited range from not liking the taste to personal experience of the medication not working (Haughney et al., 2008). Because reports of the medication not working may be reflective of improper use of the inhaler, education programs and spacers have been established to optimize the chances of the medication sufficiently reaching the lungs as it is intended to do. LTRA, on the other hand, is delivered in granules, chewable tablets, or regular tablet form. Higher adherence rates with LTRA suggest that patients might prefer an oral treatment versus an inhaler.

This preference in medication type is further noted by examining the distribution of adherence rates. As Table 1 shows, half of the recipients who initially started on LTRA had medication to cover 33 percent of Medicaid days. Half of the recipients beginning on ICS, though, only had 16 percent of Medicaid days covered. A similar difference is seen between the two treatment groups—except for those recipients who are almost 100 percent adherent to treatment. Evaluating the group designated as adherent—those having a PDC greater than or equal to 70 percent—reveals an average adherence rate of 86.33% (compared to 27.11% for the non-adherent group) (Table 3). This difference was statistically significant ($p < 0.001$).

For several reasons, it is difficult to compare the adherence rates from this study with those from other studies. One reason is that the level at which adherence is achieved is not firmly established, but rather left up to the researcher to define within the study. Also, multiple methodologies besides PDC exist for the calculation of adherence (Nau, 2011). Furthermore, even when adherence is calculated in a study and incorporated into the predictive model, it is not always reported. Some studies opt to report the percentage of the cohort that does not refill a prescription during the study period. Among the number of studies assessing ED visit and INPH outcomes for LTRA and ICS via comparative analysis, adherence was not reported consistently.

Of the studies that reported adherence, however, several presented findings comparable to this research. One study reported mean PDC rates of 33.3% for LTRA and 15.1% for ICS (Blais et al., 2011). Two studies reported medication possession ratios (MPR): one found an overall rate of adherence at less than 6% for the study, 14.9% for LTRA, and 1.5% for ICS (Lee et al., 2010), while the other reported 16% for the overall adherence rate (MPR > 0.80), 30.2% for LTRA, and 3.4% for ICS (Tan et al., 2009).

In their study using Tennessee Medicaid data, Wu and colleagues (2014) also used the PDC calculation, where adherent was defined as PDC > 0.75. While this is very similar to the methodology employed in this research, the PDC was not reported. Rather, Wu et al. reported the percentage of people who did not refill the prescription. While this does provide some information and, more importantly, can be compared to this Maryland Medicaid study, it must be noted that it does not strictly report on adherence rates.

When comparing the above findings to this study's median adherence rate of 33 percent for LTRA and 16 percent for ICS, it is apparent that Maryland Medicaid recipients are similar to other populations studied. Thus, illuminating the reality that adherence to asthma medication is not easily addressed, as numerous interventions and education programs have been initiated over the past decade. The results of this study also highlight a major area of opportunity within asthma research in general, as well as within Maryland Medicaid asthma programs. Further investigation into correlates and causality to asthma adherence is essential to advancing the understanding of and eventually improving asthma health care outcomes for Maryland Medicaid recipients.

Furthermore, improving adherence to asthma treatment is particularly important in light of the negative correlation between adherence rate and asthma-related ED visits in the results above. Increasing overall adherence rates for both LTRA and ICS may reduce the number of ED visits for asthma for both recipients with and without the co-morbidity of AR. Additionally, a reduction in INPH for asthmatics without the co-morbidity may result. This would not only have a direct impact on health care expenditure for the Medicaid program, but also positively affect Medicaid recipients' lives by increasing health and reducing sick days for both adults and children.

While this study examined all of the Maryland Medicaid data for the identified cohort, it is necessary to address several limitations to using administrative claims data. The use of only paid Medicaid claims requires assumptions to be made *a priori*. First, if a person met the criteria for asthma, as defined in this study, then it was assumed the claim or encounter was the initial diagnosis. In other words, the recipient was not given a diagnosis of asthma by a health care provider prior to entering the Medicaid program.

Also, all medical care received by the recipient during the study period was paid for by Maryland Medicaid. Any health care interactions not paid for by the state would not be recorded in the data and thus not used in the analysis. Similarly, all prescriptions identified in the data were filled prescriptions paid by Medicaid. It is assumed that each prescription filled was taken as prescribed. This assumption is essential to any adherence calculation and interpretation.

Finally, as this is an observational study, there exist limitations due to selection bias. Although PSM was employed to address bias concerns, it does not eliminate the possibility of bias remaining. Furthermore, the cohort of recipients within the Medicaid eligibility data were only those who have gone through the eligibility determination process and been found to be eligible for the program. Although Medicaid expansion has made people more aware of being eligible for Medicaid benefits, there may be inherent bias within the eligibility process in that certain groups may be more likely to apply for Medicaid than others.

Relevance for Maryland Medicaid

The most significant finding of this analysis, as it pertains to Maryland Medicaid, is the difference in adherence between LTRA and ICS. Increasing adherence to asthma medication is a crucial factor in decreasing ED visits and INPH for asthma. The Agency for Healthcare Research and Quality (AHRQ) reports explicitly on avoidable ED visits as they are expensive and could

save millions of dollars annually (U.S. Health and Human Service, Agency for Healthcare Research and Quality, n.d.). Asthma is one of the primary areas of avoidable admissions reported on by AHRQ. ED visits for asthma are viewed as a "failure of prevention-oriented care since most asthma exacerbations are preventable with high-quality long-term management" (U.S. Health and Human Service, Agency for Healthcare Research and Quality, n.d.).

Historically, increasing adherence for ICS has been difficult, regardless of the population. However, higher levels of adherence to LTRA is evident both in the literature and this study. While LTRA is associated with increased ED visits for both the asthma-only and asthma-AR populations, given the negative association between adherence and ED visits there may be policy related gains. Increasing the use of LTRA within the Maryland Medicaid asthmatic population could result in a decrease of ED visits due to the adherence to medication; even a relatively small reduction in ED visits may result in substantial cost savings.

Estimating the effectiveness of a policy change impacting preferred treatment can be accomplished through further research. A pragmatic trial within the Maryland Medicaid population, as discussed by Smith (2018), would allow for a more accurate estimate of the impact adherence has on Medicaid ED visits than the one provided in this study. Pragmatic trials are often used within a healthcare policy setting to assess innovation in treatment. The National Institutes of Health provides funding for health care providers interested in evaluating interventions related to medication adherence and related outcomes (Boineau, 2017). While increasing both LTRA and ICS adherence ought to be considered, there are two reasons beginning with LTRA adherence within the Maryland Medicaid population is preferred. First, the disparity of adherence levels in the study population between the two treatments suggest adherence to LTRA might be more easily attained than adherence to ICS. Second, LTRA

provides multiple treatment options for recipients under the age of four, allowing Maryland Medicaid to focus on a population more at risk for ED visits.

As stated above, while there is a positive association between LTRA and ED visits in both the asthma-only and asthma-AR population, any reduction in ED visits could translate to noticeable cost-savings for the state. In both models with an outcome of ED visit, the OR is just over 1.0. While the OR indicates a statistically significant positive association exists, the small increased risk may be less of a concern for real-life policy decisions. If adherence levels are more significant in predicting ED visits than treatment, a reduction in ED visits will result. The parameter estimates for adherence indicate a decrease in the likelihood of ED visits for each incremental increase in a percentage point of PDC. Increasing adherence level in the Maryland Medicaid asthmatic may result in a substantial practical reduction of adverse health outcomes such as ED visit.

The opportunity exists within Maryland Medicaid to explore this possibility. Less than one-fourth of the identified asthma study population identified as having an initial treatment of LTRA. Focusing on expanding the use of LTRA in the asthmatic population, while also seeking to increase adherence to the medication has significant potential to reduce costs associated with avoidable asthma-related ED visits and its related costs for Maryland.

Conclusion

In conclusion, increased adherence to asthma medication is negatively correlated with ED visit and/or INPH for asthma during the year after initial treatment. Asthmatic Medicaid recipients initially started on LTRA treatment were more likely to have an ED visit than those initially treated with ICS, even after controlling for adherence. Likewise, LTRA was also associated with INPH in the year following initial treatment with LTRA, but only for recipients

without the co-morbidity of AR. Although the median adherence rates are low for both LTRA and ICS, adherence to LTRA was twice that of ICS (33% versus 16%, respectively). However, while ICS may have a lower adherence rate, recipients starting on ICS were less likely to have an ED visit or INPH due to asthma exacerbation. Increasing adherence to ICS may bring improved health outcomes and a reduction of health care utilization associated with asthma.

Appendix A

Glossary of Terms

Chronic Condition Warehouse (CCW): The Chronic Condition Warehouse was created by the Centers for Medicare and Medicaid (CMS) as a result of the Medicare Modernization Act of 2003. While this warehouse provides information for many research interests, it also provides a standard algorithm for identifying chronic conditions within administrative data. There are 27 main categories of chronic conditions. An additional 39 categorical definitions are available for more specific conditions related to mental health, substance abuse and disabling conditions. This study used the primary 27 categories in the analysis. One of the categories is asthma.

Emergency Department (ED) Visit: A recipient is identified as having an ED visit for asthma if a record exists within the outpatient file of the Maryland Medicaid data with a primary ICD-9 diagnosis code for asthma and a revenue code of 0450 or 0981. Records for ED visits associated with an INPH are within the inpatient file and, therefore, are not identified as an ED visit.

Fee-For-Service (FFS): This is the traditional payment method for Maryland Medicaid. Under this payment program, providers submit a claim for a service and Maryland Medicaid pays the provider for the service based on contractual agreements. The following are typical populations which participate in the fee-for-service program: recipients dually eligible for Medicare and Medicaid, recipients with rare and expensive diseases/conditions, recipients using mental health services, recipients using substance use services.

HealthChoice Program (HealthChoice): This is a payment program under the 1115 waiver authorized by CMS. This waiver allows Maryland Medicaid to pay providers through a

managed care organization structure. Currently, the majority of Maryland Medicaid recipients receive care from providers within the HealthChoice program.

Health Insurance Portability and Accountability Act of 1996 (HIPAA): The purpose of this act is to protect the privacy of individuals, specifically related to healthcare information. Furthermore, it defines security measures for the handling of personal healthcare information. This act applies to all providers, researchers, organizations, and agencies that come into contact with healthcare information.

Inhaled Corticosteroid (ICS): This is an inhaled, oral medication used to treat the symptoms of asthma. This is treatment is effective only after reaching the lungs.

Inpatient Hospitalization (INPH): A recipient is identified as having an inpatient hospitalization for asthma if a record exists within the inpatient file of the Maryland Medicaid data with a primary ICD-9 diagnostic code for asthma.

Leukotriene Receptor Antagonist (LTRA): This is an oral medication in pill form. This medication works to inhibit the leukotrienes produced by the body which are related to asthma-related symptoms.

Medicaid Expansion: The Patient Protection and Affordable Care Act of 2010 (ACA) allows for states to expand their Medicaid programs to include people previously ineligible for benefits and allows for increased federal funding. Maryland opted to authorize expansion of its Medicaid program effective January 1, 2014. The new policy expanded Medicaid coverage to those under the age of 65 with a household income of up to 138% of the Federal Poverty Guideline (FPG) and former foster care children up to age 26. In Maryland Medicaid, recipients aged 18 and older will have a coverage group indicating Medicaid expansion. Children, however, will have a coverage group of Maryland Children's Health Program (MCHP). The coverage

group indicates the Medicaid benefits the recipient is entitled to receive. A coverage group of Medicaid Expansion indicates that the recipient may receive the benefits outlined through Maryland's Medicaid expansion program.

Mild to Moderate Asthma: Assessment of the severity of asthma is initially made upon initial diagnosis. The severity level is based on both spirometry and self-reported symptoms over the past month (National Heart, Lung, and Blood Institute, pg. 49). Neither lab results nor self-reported health information is captured within the managed care administrative data for Maryland Medicaid recipients. Thus, asthma severity is assessed based on the type and amount of medication used to treat and control the symptoms of asthma. This study will consider a recipient to have met the definition of mild to moderate asthma if they met the following criteria:

(3) Had an emergency visit, inpatient hospitalization, or at least four physician visits with a primary diagnosis of asthma

(4) Did not meet the criteria of severe asthma as defined in Table 1 on page 7.

Physician Visit: A recipient is identified as having a physician visit for asthma if a record exists within the physician or outpatient file in the Maryland Medicaid data with a primary ICD-9 diagnosis code for asthma. Outpatient records must have a revenue code other than 0450 or 0981.

Propensity Score Matching (PSM): This is a statistical method to minimize the bias found in observational studies. This method uses multivariate regression in order to systematically match similar participants in treatment and control groups. PSM only uses observed characteristics, which is a primary limitation of this method.

Race/Ethnicity: The Maryland Medicaid program combines race and ethnicity into one field. The variable has the following values: Black, White, Hispanic, Asian, Native American,

Hawaiian/Alaskan, and Unknown. The Unknown category includes refusal to provide race, missing, those who do not associate with one of the other categories, and racially mixed. This is considered a “catch all” option.

Appendix B

Severe Asthma Algorithm

To be classified as having severe asthma, a Medicaid recipient must meet the criteria for one of the following four groups.

Group 1

≥6 prescriptions of any bronchodilator

AND

≥6 prescriptions for ICS or LTRA

Group 2

≥3 prescriptions in at least three of the different classes:

β-agonist; theophylline, anti-allergic, ipratropium bromide,

corticosteroids (inhaled or oral)

Group 3

≥2 prescriptions for oral corticosteroids

AND

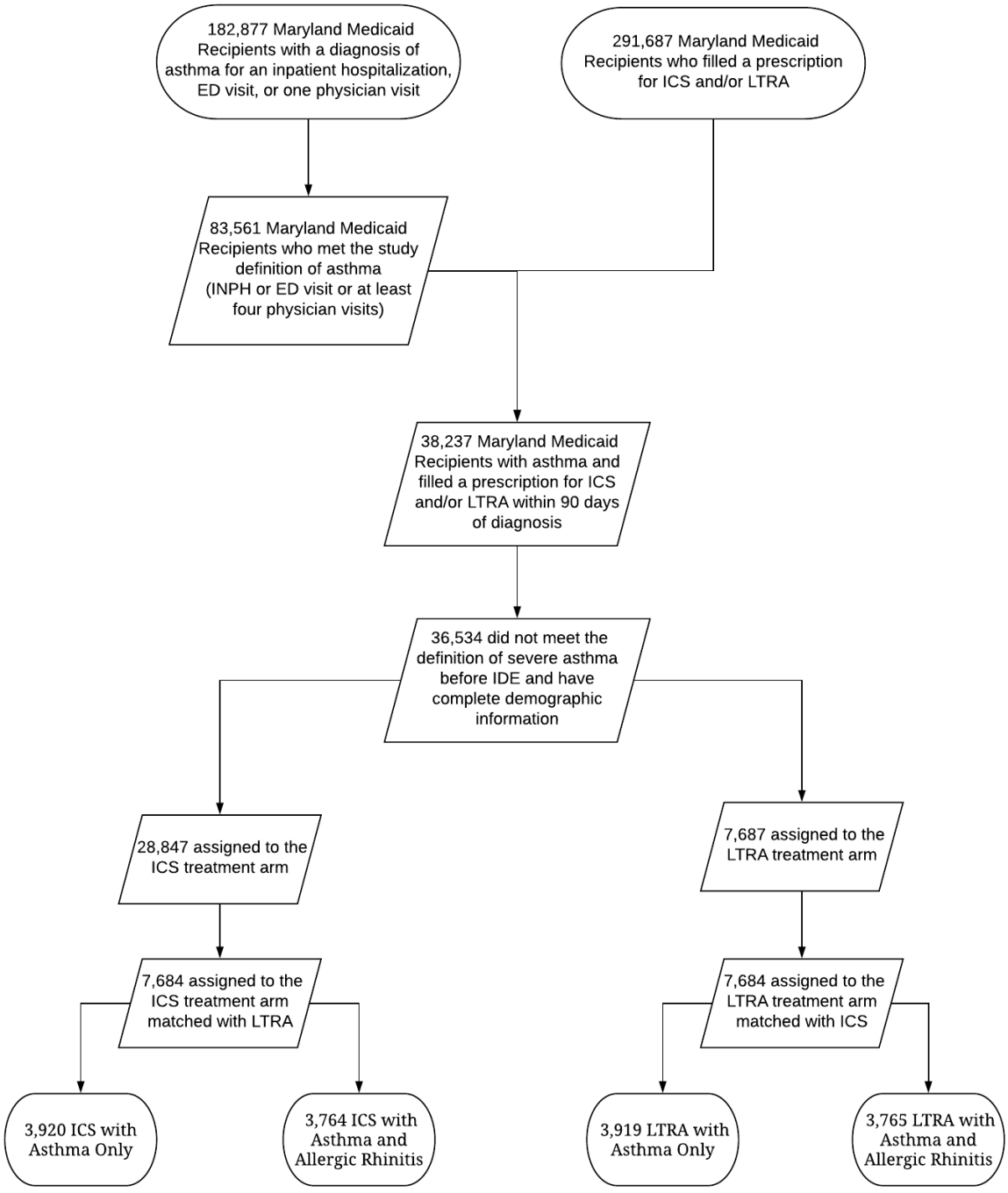
≥6 prescriptions for any other asthma medication

Group 4

≥25 canisters of a β-agonist bronchodilator

Appendix C

Flow Chart of the Process of Identifying the Multivariate Cohort from Maryland Medicaid Recipients after Each Step of Evaluating the Eligibility Criteria and Propensity Score Matching



Appendix D

Definition of Adherence Level

Defining the point at which a patient becomes adherent to medication has been considered arbitrary. Realistically, no patient is 100% adherent to medication. A variety of factors, including illness, may prevent a patient from taking the prescribed medication as directed. As a result, researchers must define the level at which a patient is considered adherent to treatment.

This study defined the level of adherence rate of 70% and higher to indicate adherence to treatment. Several factors contributed to this decision. First, comparable literature was examined to identify the various methods adherence was measured. For studies that dichotomized adherence, the threshold was established between 75% and 80%. Second, an evaluation of the literature surrounding the determination and comparison of adherent algorithms was undertaken. The study by Williams et al. (2011), cited above, found that the "thresholds between 70% and 80% often used to describe the level above which a patient is considered adherent might actually have clinical relevance" (pg. 1188). Finally, analysis of adherence rate distribution within this population was conducted. Based on the low adherence rates within this population, and the analysis provided by Williams et al., a level of 70% was set for a Maryland Medicaid recipient to be considered adherent to treatment.

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