Management of Asthma Patients by Community Pharmacists - A Focus on High-Risk Patients and Inhaled Medication Use

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Management of Asthma Patients by Community Pharmacists - A Focus on High-Risk Patients and Inhaled Medication Use

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Declaration

The research presented within this thesis *"Management of Asthma Patients by Community Pharmacists - A Focus on High-Risk Patients and Inhaled Medication Use"* has been conducted under the supervision of my previous supervisor, Professor Sinthia Bosnic-Anticevich, and my current supervisor, Professor Bandana Saini, within the Sydney Pharmacy School, University of Sydney.

To the best of my knowledge, the research presented within this thesis is original and the product of my own work, except when acknowledged in text. Full acknowledgements have been presented wherever the work of others has been cited or used. The contributions of all authors in publications in this thesis have been declared.

I also declare that I have adhered to the ethical guidelines of research as set forth by the University of Sydney, and have attained all required permissions and approvals for all the research performed. This thesis has not been submitted in part or in whole for any other degree or purpose.

Sarah Barbara

August 2025

Artificial Intelligence Declaration

I declare that no content generated by generative artificial intelligence (AI) tools has been used in the preparation of this thesis.

Sarah Barbara

August 2025

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I would like to express my deepest gratitude to all who have supported me in the preparation and completion of my thesis.

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Abstract

Introduction

The management of asthma in Australia is a significant concern, with many patients experiencing significant burden of disease. [1]. Community pharmacists can improve asthma management in their patients and subsequently reduce the burden, through several interventions, for example by optimising their inhaler technique as part of asthma management programs [2-5] . However, only a limited number of patients receive such services due to barriers associated with program implementation [6].

Identification of patient groups most likely to use inhalers appropriately may assist community pharmacists to identify which groups of patients require their assistance in optimising inhaler use.

Therefore, the overall aim of this thesis is to gain insight into which patient cohorts are most at risk of poor clinical asthma outcomes consequent to suboptimal inhaler technique, with this cohort being most likely to benefit from the skills of community pharmacist. In light of the significant global trend towards an increasingly ageing population [7], this thesis will determine whether older adults are more at risk of poor inhaler technique. A literature review and database study of respiratory patients was conducted to achieve this aim.

Aim 1: *To determine whether older age is a risk factor for inhaled medication misuse, that is, inhaler technique errors*

Methods:

A systematic review of the literature was conducted in Embase *via* Ovid SP, Medline *via* Ovid SP, and PubMed from July 1 to December 31 2016.

The review was performed in compliance with the methodological and reporting standards recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Articles were assessed for relevance through the PRISMA flow diagram for data inclusion, and reviewed by examination of titles and abstracts. Duplicate studies and articles not satisfying the inclusion criteria were omitted via EndNote X7. Articles were augmented by publications otherwise known to the authors.

Following screening for relevance, eligibility, and duplicate titles, a total of fourteen studies were included in the final qualitative synthesis of the outcomes of the systematic review. Fourteen studies examined the impact of age upon the frequency of inhaler technique errors presented as a main outcome, and three investigations explored variations in the nature of inhaler technique error with age with regards to the pressurised metered dose inhaler (pMDI).

Findings of the Review:

Based on the articles reviewed, with regard to the incidence of incorrect technique there is some evidence that increasing age is associated with increasing proportions of incorrect pMDI and dry powder inhalers (DPI) users, with the majority of studies identifying a positive correlation or statistically significant difference in means between older age and inaccurate technique. However, the results were conflicting, with statistical significance unreported in two studies, and conflicting results for the Turbuhaler (TH) and Diskhaler (both DPI type inhalers).

With regards to variations in the nature of inhaler technique error with age, one study identified that older adults (> 65 years) were most likely to actuate pMDI devices at the end of inspiration, manage a breath hold for less than 5 seconds, whilst younger adults were most likely to present with breath-holding for less than 5 seconds, followed by actuating pMDI devices at the end of inspiration. In terms of ranking of inhaler errors, following the above highly ranked errors, both cohorts were equally likely to inhale too rapidly and prematurely actuate the device. Older adults were also likely to actuate the device during expiration, followed by the error of performing multiple actuations, whereas adults <65 years were equally likely to present both errors.

Although identifying variations with age, further studies are required to support these results before applying them to the general population of older aged individuals.

Conclusion:

The systematic review provided initial evidence of age-associated differences in the number and type of inhaler technique errors. Further research is required to assess outcomes in individual DPIs, reproducibility and the effects of confounders, such as cognitive function, physical ability, and differences in the complexity of use of the devices.

__Aim 2:__ To identify risk factors associated with the performance of inhaler technique errors and poor asthma outcomes in patients with asthma prescribed the Turbuhaler (TH), pressurised Metered Dose Inhaler (pMDI), and Accuhaler (AH) device.

Original Article I: *Identifying patients at risk of poor asthma outcomes associated with making inhaler technique errors.*

Methods:

A cross-sectional study exploring demographic variables associated with the performance of a specific subset of inhaler technique errors (to be defined below) was performed using data collected from the international Helping Asthma in Real life Patients, or iHARP, database [8]. This database is an extensive international database containing pertinent information relating to asthma control and characteristics of those with asthma, including patient demographics, symptoms, lung function, and inhaler technique [8].

This study was restricted to the exploration of a subset of patients from the database who were at least eighteen years of age and prescribed the TH, pMDI, or AH devices. Patients were only using type of inhaler device. The subset of inhaler technique errors were those specifically associated with poor asthma outcomes, that is, errors significantly associated with uncontrolled asthma and/or an increased rate of asthma exacerbations (i.e., having at least one exacerbation in the 12 months prior to review). These were identified by reference to the Critikal study, and will be referred to as 'critical inhaler technique errors,' within this thesis [9].

Demographic and clinical factors associated with at least one of these errors were identified using multivariable logistic regression. Variables explored included level of asthma control (as per GINA criteria), self-reported adherence to maintenance therapy, age, gender, body mass index (BMI), smoking status, educational status, patient-reported prior inhaler technique review by a healthcare professional (HCP), patient adherence and self-assessment of inhaler technique.

Statistical analyses were performed using SPSS Statistics version 24. Characteristics of patients who made no inhaler technique errors associated with poor asthma outcomes using each device were compared with those making at least one inhaler technique error associated with poor clinical outcomes. A significance level of $p<0.05$ was used for all statistical procedures. Analyses were carried out within device cohorts.

A total of 4134 adult patients from the iHARP database with asthma were available for inclusion and analysis into this study. Three device cohorts were formed based on the three most common inhaler devices used by patients; with TH used by 2065 (46.2%) patients, pMDI used by 1245 (27.9%) patients, and AH used by 824 (18.4%) patients. Using the GINA-defined criteria, 30.5% had controlled asthma, 43.9% had partly controlled asthma and 25.6% had uncontrolled asthma. There was no significant difference in these proportions across devices.

Findings of the Research:

Factors significantly associated with at least one inhaler technique error and worsening asthma outcomes include the following:

1) For the TH cohort: Female gender and very poor to average self-assessment of inhaler technique.
2) For the pMDI cohort: female gender, secondary education, and current smoking status.
3) For the AH cohort: Very poor to average self-assessment of inhaler technique and lack of inhaler technique review by a trained healthcare professional in the previous twelve months.

Conclusion:

In conclusion, a multitude of demographic factors associated with the performance of these errors were identified. These differed according to the device used. Inhaler technique error associated with poor asthma outcomes is further widespread across devices. Knowledge of these factors and the frequency of their occurrence may assist in optimizing device selection and training.

Authorship Attribution Statement

This thesis contains two original publications completed for the degree of Master of Philosophy.

Notes on the author's contributions and statement of contribution of others.

1. Section 4.3 is published as:

Barbara S, Kritikos V, Bosnic-Anticevich S. Inhaler technique: does age matter? A systematic review. European Respiratory Review. 2017;26(146).

Contributions: *Sarah Barbara and Sinthia Bosnic-Anticevich developed the research aim and review methodology. Sarah Barbara collected, analysed, and interpreted the data. Vicky Kritikos assisted in the quantitative analysis and synthesis of the data. Sinthia Bosnic-Anticevich supervised the data collection process and critically reviewed the interpretation of the data. All authors drafted and critically revised the article, and provided intellectual input into the concepts explored. Sinthia Bosnic-Anticevich gave final approval of the version to be published.*

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In addition to the statements presented above, permission to include any published material where I am not the corresponding author has been provided by the corresponding author.

Sarah Barbara

Date: 12/12/24

Authorship Attribution Statement:

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Bandana Saini

Date: 12/12/24

Presentations of Research Work

Oral Presentations

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List of Tables

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List of Figures

Additional figures have been presented within the text of submitted/published manuscripts.

List of Abbreviations

Full text	Acronym
Abbreviated Mental Test	AMT
Accuhaler	AH
Age-related Macular Degeneration	AMD
Airway Hyper-responsiveness	AHR
Asthma Control Test	ACT
Australian Asthma Handbook	AAH
Body Mass Index	BMI
Chronic Obstructive Pulmonary Disease	COPD
Combination inhaled corticosteroid and long-acting β_2 agonist	ICS/LABA
Disability-Adjusted Life Years	DALYs
Dry Powder Inhaler	DPI
Eighth Community Pharmacy Agreement	8CPA
Forced Expiratory Volume (in one second)	FEV1
Gastro-Oesophageal Reflux Disease	GERD
General Practitioner	GP
Global Burden of Disease	GBD
Global Initiative for Asthma	GINA
Health Care Professional	HCP
Health Related Quality of Life	HRQoL
Inhaled Corticosteroids	ICS
international Helping Asthma in Real life Patients	iHARP
Late Onset Asthma	LOA
Leukotriene Receptor Antagonists	LTRA
Long Acting Muscarinic Antagonist	LAMA
Long Standing Asthma	LSA
Long-acting β_2 Agonist	LABA

Low and Middle Income Countries	LMICs
Mental Status Questionnaire	MSQ
Mini-Mental State Examination	MMSE
National Asthma Council of Australia	NAC
Obstructive Sleep Apnoea	OSA
Over The Counter	OTC
Peak Expiratory Flow	PEF
Peak Inspiratory Flow	PIF
Pharmaceutical Benefit Scheme	PBS
Preferred Reporting Items for Systematic Reviews and Meta-Analyses	PRISMA
Pressurised Metered Dose Inhaler	pMDI
Short-acting β_2 Agonist	SABA
Symbicort Maintenance and Reliever Therapy	SMART
Teach-To-Goal	TTG
Turbuhaler	TH
Written Asthma Action Plan	WAAP
Years Lived with Disability	YLD

Chapter 1

General Management of Asthma in Australia

A Review of the Literature

1.1 Asthma – Clinical Pathophysiology of Asthma and Burden of Disease

1.1.1 Description and Pathophysiology of Asthma

Asthma is a common, chronic respiratory disease typically associated with airway inflammation and hyper-responsiveness to a myriad of direct and indirect stimuli [10]. Exposure to such stimuli results in the release of an array of inflammatory cells, including mast cells, neutrophils, eosinophils, T lymphocytes, macrophages and epithelial cells, resulting in inflammation of the smooth muscle of the bronchi [10]. In turn, this induces bronchoconstriction, airway hyper-responsiveness (AHR), and, in those with persistent disease, mucous hypersecretion, leading to airway oedema [10].

Symptoms are diverse in nature, and may include wheezing, tightness of the chest, cough, and variable expiratory airflow limitation particularly evident at night or in the early morning [2]. They may also vary in frequency, duration, pattern, and intensity, potentially being absent for a period of time or occurring as episodic flare-ups in response to certain stimuli, for example, allergens [11].

Chronic airway inflammation and AHR are further usually present in patients with asthma, even in those not displaying any further symptoms [10]. Whilst treatment may assist in reducing such processes, persistent alterations in the structure of the airways may occur, limiting reversibility of airflow limitation, and thus, the maximal clinical outcomes able to be attained through best practice management [11].

1.1.2 Burden of Disease from Asthma

1.1.2.1 Prevalence of Asthma

Asthma is increasingly gaining recognition as both a global health epidemic and a national health priority. According to the most recent comprehensive analysis of the Global Burden of Disease (GBD) Study 2021, which describes the global distribution and causes of a wide range of health risk factors, injuries and diseases, approximately 262 million people worldwide were affected by asthma [1]. It is estimated that the number of people with asthma will increase to greater than 400 million by 2025, making asthma a major global health concern [12] .

Of concern, prevalence rates in Australia are high by international standards, with Australia being in the highest prevalence brackets for both asthma and wheeze in 13-14 year old adolescents (≥20%) [13], and asthma symptoms in 18-45 year old patients (>25%) [12]. Australia also has the highest rate of people reported to receive an asthma diagnosis, representing 21% of all people ever receiving a diagnosis [14].

Of further concern, the prevalence of asthma in Australia is on the rise, with approximately 2.8 million, or nearly 11% of Australians, identified to have a current diagnosis of asthma in 2022; representing an increase from the 9.8% of Australians reported in 2007-08 [15].

1.1.2.2 Burden of Disease

Internationally, asthma ranks thirty-fourth among the leading causes of burden of disease and twenty-seventh in low- and middle-income countries (LMICs) [16]. Asthma has further been identified to be the sixteenth most significant disorder in the world when examining years lived with disabililty [YLD]), and the twenty-eighth greatest when measured by disability-adjusted life years

(DALYs) [12]. A relatively higher burden of disease has been recorded in Australia, New Zealand, North-Western Europe, and some nations in South America, the Middle East, and Africa [12].

In Australia, 141 621 DALYs, or years of healthy life, were lost due to asthma [17].

1.1.2.3 Quality of Life

Significant impacts on the physical, psychological, and social wellbeing of people with asthma have all been identified [15]. Compared to people without asthma, people with asthma were more likely to describe themselves as having a poor quality of life, with self-assessed health status among people with aged 15 and over described as worse than those without asthma [15].

People with asthma were further more likely to experience moderate (27%), severe (11%) and very severe (2.8%) bodily pain compared with people without asthma (17%, 5.4% and 1.3%, respectively), and very high (11%) and high (15%) levels of psychological distress than those without asthma (3.4% and 8.7%, respectively [15].

1.1.2.4 Impact of Asthma on the Health Economy

The impact of asthma on the Australian health economy is significant. In Australia in 2020–21, the combined total cost of asthma was estimated at $851.7 million of expenditure [17]. This represented 19% of the total expenditure of all respiratory conditions in Australia, and 0.6% of Australia's total health expenditure [17]. Of concern, It has been estimated that there will be a 205% increase in expenditure for respiratory conditions between 2002–03 to 2032–33 from $7,188 million to $21,947 dollars) [18].

Reductions in asthma control may further increase the financial burden on the healthcare system [19]. Research findings have revealed that the costs associated with managing severe asthma are significantly greater than those for less severe asthma [20]. In Australia, patients with poorly controlled asthma were evidenced to work less, retire earlier, experience higher temporary absenteeism rates from paid employment (being absent from work on average 2.1 days more per year than people without the condition), be less productive while at work, or die prematurely relative to those with well-controlled or no asthma [21].

1.1.2.5 Asthma Mortality

According to the National Health Survey 2022, asthma was identified, as an underlying cause for death 467 deaths or 1.8 deaths per 100,000 population, and an associated cause of death for an additional 2005 deaths, in 2022 [17]. This culminated in a total of 2,472 deaths due to, or associated with, asthma, representing 1.3% of all deaths and 4.5% of respiratory deaths [17].

Since the late 1980s, the overall rate of mortality attributed to asthma has decreased markedly, declining by almost 70% to 1.5 deaths per 100000 population in 2003, and remaining stable since that time period [22]. On the international scale, asthma mortality rates in Australia are relatively high, with asthma mortality rates for people 5-34 years of age between 2003-2007 in Australia ranking fourth highest in an international comparison of asthma mortality rates, following the USA, UK and NZ [12].

1.2 Management of Asthma

Although asthma cannot be cured, effective treatment and management plans may assist in minimising and controlling symptoms [10]. Asthma management plans aim to minimise the impact of asthma on quality of life and the healthcare economy by reducing both the number and severity of asthma flare-ups and impairment of pulmonary function, and the corresponding personal and economic costs associated with their management [10]. The long-term goals of asthma management plans are to achieve and maintain good symptom control and minimise the risk of exacerbations, fixed airflow limitation, and adverse effects of treatment [10].

The National Asthma Council of Australia (NAC) guidelines for asthma management aim to attain such outcomes by encouraging optimisation of symptom control with the minimal quantity and dosages of medications required, minimisation of adverse effects from pharmacotherapy, and engagement of the patient in optimal self-management plans [2].

The Australian Asthma Handbook (AAH), first published by the NAC in 1990, and most recently revised and updated in April 2022, presents best-practice evidence-based guidelines and methods of practical application for primary healthcare providers involved in asthma management and diagnosis in the primary care setting [2]. It provides evidence-based approaches for asthma management and diagnosis to primary health care professionals, lists preferred choices for medications for each stage of the condition, and recommends manners of prescribing them for optimal benefit [2].

Asthma management in adults is currently based on a multitude of strategies, to be discussed below.

1.2.1 Diagnosis

Asthma is defined as the combination of both respiratory symptoms (e.g. wheeze, shortness of breath, cough and chest tightness, many of which may be variable in nature), and excessive changes in the functioning of the lungs [2]. It is advised to be considered in those with a history of variable symptoms common in asthma and variable expiratory airflow limitation; and in whom no alternative diagnoses may be considered [2].

Diagnosis currently involves assessment of a patient's medical history, physical examination of the patient (primarily via spirometry, the gold standard lung function test, before and after fast acting β_2 agonist administration), and consideration of other diagnoses, such as COPD, in the patient [2].

1.2.2 Asthma Status/Level of Control

Asthma control explores the extent to which asthma symptoms are apparent in patients, or have been altered by treatment [10]. It may be affected by several factors, including genetics and disease [10]. Asthma control assessment is essential in guiding the treatment options and management strategies provided by practitioners.

Asthma control is divided into two domains: symptom control, and future risk of adverse outcomes [10]. Asthma symptom control refers to the frequency with which patients experience symptoms typical of asthma, and the level to which they are experienced. In contrast, future risk explores any triggers or risk factors a patient may have for future exacerbations. Poor asthma symptom control is strongly associated with an elevated risk of flare-ups, increasing the burden of disease. It is recommended that asthma symptom control be assessed at each opportunity with the patient [10].

It is categorised into the following criteria, by the following clinical features *(Table 1 is a direct excerpt from the Australian Asthma Handbook reproduced with permission from the Australian Asthma Council)*:

Table 1: Criteria for Good, Partial, and Poor Asthma Control [2]

Good control	Partial control	Poor control
All of: • Daytime symptoms ≤2 days per week • Need for SABA reliever ≤2 days per week • No limitation of activities • No symptoms during night or on waking	One or two of: • Daytime symptoms >2 days per week • Need for SABA reliever >2 days per week • Any limitation of activities • Any symptoms during night or on waking	Three or more of: • Daytime symptoms >2 days per week • Need for SABA reliever >2 days per week • Any limitation of activities • Any symptoms during night or on waking

1.2.3 Initial treatment Choice

Treatment of asthma primarily occurs via the delivery of medication directly into the airways [2]. A number of medications have been approved for the management of asthma management, differing primarily in their onset of action and duration of activity. Treatment selection is primarily dependent on the health of the patient, ability to administer a particular medication, severity of their condition, level of asthma control, and any comorbidities or further risk factors for the progression of the condition [10].

The medications employed in the management of asthma are divided into three major classes: controller (preventer) medications, reliever (rescue) medications, and add-on therapies for patients with severe asthma [10].

They are categorised into the following groups:

1. *Controller medications:*

Controller medications are utilised for regular, long-term maintenance treatment [10]. They assist in controlling asthma symptoms and reducing the risk of future exacerbation by reducing airway inflammation [10]. The primary classes of medications employed as controller agents are ICS and long-acting β_2 agonists (LABAs).

The below table lists the classes of controller medications available and their mechanism of action.

Table 2: Controller Medications and their Mechanisms of Action [10]

Controller medication	Mechanism of Action
Inhaled Corticosteroids	Reduces airway hyper-responsiveness by binding to glucocorticoid receptors expressed in bronchial epithelial cells, reducing a number of inflammatory cells in asthmatic airways, including dendritic cells, eosinophils, mast cells, and T-lymphocytes; inhibit inflammatory gene transcription in epithelial cells in the airways.
Long-acting Beta-2 agonists (LABAs, symptom controllers)	Bind to and activate Beta-2 adrenoceptors in pulmonary tissue, inducing cyclic AMP and initiating biochemical processes including the phosphorylation of regulatory proteins in muscles and modification of cellular calcium concentrations. This relaxes smooth muscle in the airways and the induction of bronchodilation for a period of 12-24 hours.
Leukotriene receptor antagonists (LTRA) (Montelukast)	Blocks leukotriene D4 and leukotriene E4 in pulmonary tissue, reducing inflammation and relaxing smooth muscle present in the airways.
Cromones/Mast cell stabilisers – sodium cromoglycate, nedocromil sodium).	Inhibits histamine release from mast cells, reducing inflammatory mediator production; reduces inflammation from eosinophils via direct action.
Methylxanthines - Theophylline	Reduces airways hyper-responsiveness to a number of compounds, including allergens, histamine, adenosine, and methacholine. Relaxes bronchial smooth muscle and smooth muscle in the pulmonary blood vessels.
Anti IgE monoclonal Antibody (Omalizumab)	Prevents IgE from binding to allergens, basophils, and mast-cells.
Anti IL-5 monoclonal Antibodies	Mepolizumab prevents IL-5 from binding to IL-5 receptors on basophils and eosinophils, and inhibiting their signalling. This reduces their production and causes cell apoptosis. Benralizumab binds to the IL-5α receptors expressed on Eosinophils, inhibiting their signalling, reducing their production, and causing cell apoptosis. Dupilumab binds to the IL-4Rα and IL13 receptor alpha subunits, inhibiting their signalling.
Long-acting muscarinic antagonist (LAMA)	Blocks the action of acetylcholine, inhibiting cholinergic bronchomotor tone. This results in bronchodilation of the airway smooth muscle.

2. *Reliever Medications*

Reliever medications assist in the rapid relief of asthma flare-ups [10]. Such medications are supplied to all patients for as-needed relief of breakthrough symptoms, and are also used for short-term prevention of bronchoconstriction induced by exercised [10].

In Australia, reliever medications are advised for use on an 'as required' basis as sole pharmacotherapy in patients experiencing symptoms less than twice per month and no flare-ups requiring oral corticosteroids within the previous year [2].

Table 3: Reliever Medications and their Mechanisms of Action [10]

Reliever Medication	**Mechanism of Action**
Short-acting Beta$_2$ Agonists (SABAs):	Bind to and activate Beta-2 adrenoceptors in pulmonary tissue, inducing cyclic AMP and initiating biochemical processes including the phosphorylation of regulatory proteins in muscles and modification of cellular calcium concentrations.
Long-acting Beta2 Agonists in combination with ICS ***Budesonide/Eformoterol fumarate dehydrate (Symbicort SMART (Symbicort Maintenance and Reliever Therapy) regimen)***	Relaxes bronchial smooth muscle via the cAMP process as described for LABAS, above, dilating the airways; corticosteroids as per 'inhaled corticosteroids' in Table 2, above.
Systemic Corticosteroids	Reduce airway hyper-responsiveness and inhibit the activation of inflammatory cells by blocking the late-phase reaction to allergens.

3. Add-on therapies

Add-on therapies are treatments prescribed to those experiencing symptoms despite the use of regular controller medication and management of modifiable risk factors [10]. They include tiotropium, leukotriene receptor antagonists, low-dose macrolides, and biologic agents for severe allergic or severe type 2 asthma [10].

1.2.4 Delivery of Pharmacotherapy

Asthma pharmacotherapy is primarily delivered directly to the airways via the inhaled route [2]. This enables faster absorption of the medication via the bronchial smooth muscles within the lungs, assisting in the absorption of a higher concentration of medicine at the site of action and reducing the risk of side effects [10].

A diverse range of inhalation devices are currently available in the delivery of asthma pharmacotherapy. These include pMDIs; breath-actuated pMDIs (autohalers); DPIs such as the AH and TH; capsule-containing DPIs, such as the Handihaler™; and respimat devices. Such devices differ in their structure and appearance, medication delivered, method of dispensation (passive or active), number of doses contained, whether the inhaler is disposable, refillable, or contains a reservoir of medication, maintenance, and preparation and technique for proficient use. Thus, selection of an appropriate agent is highly dependent the personal and medical profile of the patient [2].

Certain factors may further affect the extent to which the drugs are delivered effectively to their intended site of action, directly impacting their clinical effect. The predominant number of these factors are non-modifiable, being based on the nature of the medication, the device, and the formulation used [2]. However, the quality of the inhaler technique of the patient can further greatly impact the amount of medication deposited in the airways, and therefore, it is essential that the patient is able to effectively use the delivery device prescribed [2]. Incorrect inhaler technique may result in reduced to negligible drug delivery in the lung, increasing the risk of the adverse effects, and has been associated with poor asthma outcomes [10]. Therefore, caution is required in the selection of inhaler device by the prescriber, and the quality of education and training in its use provided to the patient.

1.2.5 Medication Selection

Judicious medication selection is essential in the attainment of optimal symptom control and quality of life [10]. A stepwise approach to medication selection in asthma patient is currently advised [2]. The medications advised for each stage of asthma control are summarised in the following chart (*Figure 1 is a direct excerpt from the Australian Asthma Handbook reproduced with permission from the Australian Asthma Council)*:

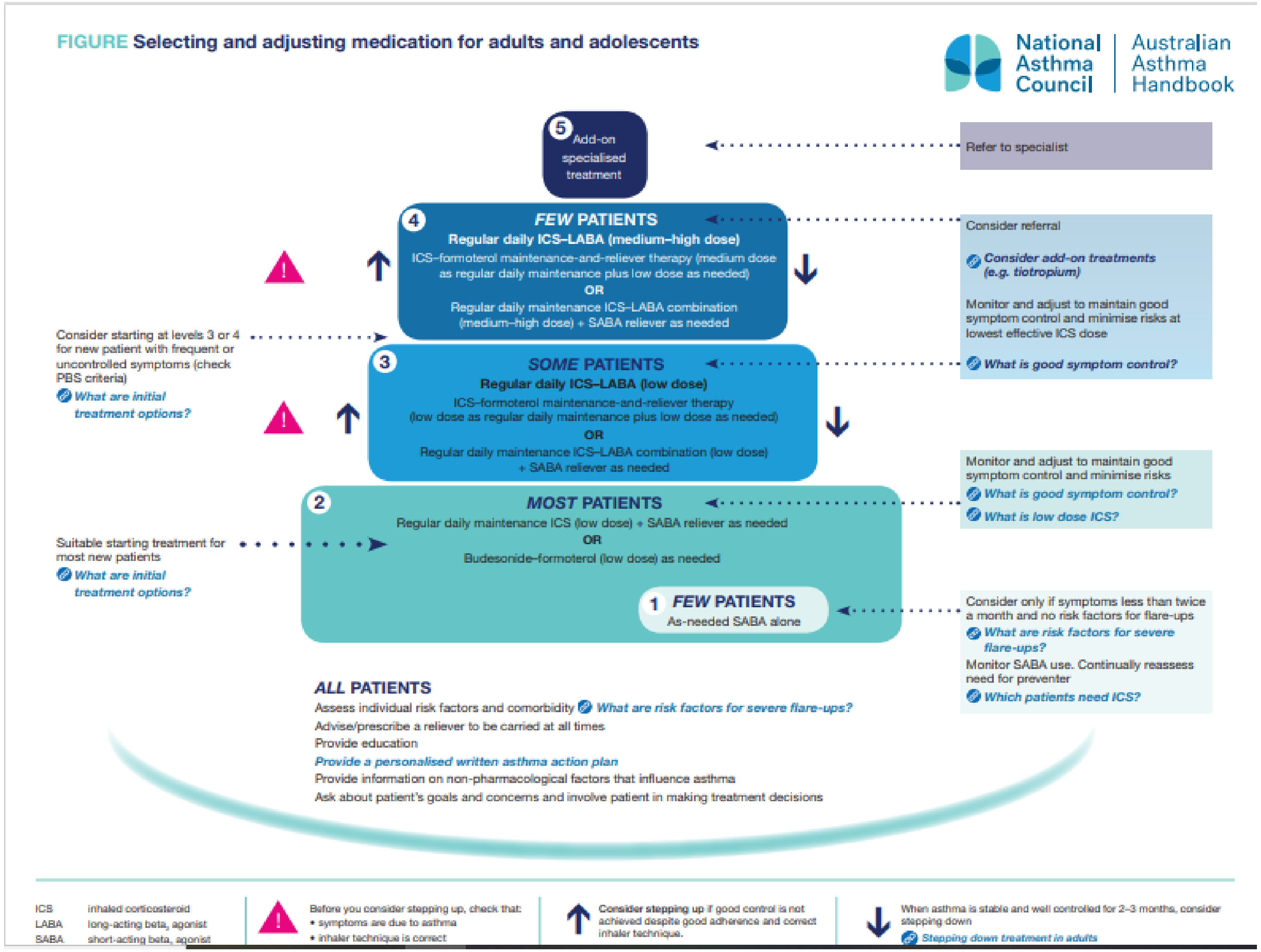

Figure 1: Selection and Adjustment of Asthma Medication for Adults and Adolescents [2]

1.2.6 Patient Review

Due to the variability of the condition, it is advised that all asthma patients be reviewed at every healthcare practitioner visit to monitor symptom control and future risk of exacerbations [2]. Patients should undergo review within 3 months of commencing any medications [2]. After initial review, it is then advised to undergo regular review every 3-12 months [2]. Reviews should include assessment of Inhaler technique, asthma control, future exacerbation risk, and response to any changes in medications. The patient's written asthma action plan (to be discussed, below) is also advised to be reviewed annually [2].

1.2.7 Provision of information, skills and tools for self-management

Guided education and the provision of self-management skills is an essential component of asthma management [2]. This involves the provision of education and skills in asthma self-management by the primary healthcare practitioner to the patient via active collaboration [2, 10], to assist them to acquire the skills required to assume a major role in the management of their condition [10].

A written asthma action plan (WAAP) is essential in the promotion of active patient self-management of asthma [2]. A WAAP is a document devised between the patient and the prescriber containing information about signs of worsening asthma, appropriate use of medications, methods of obtaining medical care, and asthma first aid [2, 10]. They should be individualised to the needs of the patient, and contain information specific to their medical profile [2].

1.2.8 Management of flare-ups/exacerbations

An asthma exacerbation refers to an incident where asthma symptoms are acutely increased, and lung function progressively reduced [23]. They are generally triggered by exposure to external triggers specific to the patient, and require urgent treatment with a bronchodilator stimuli [10].

Currently, it is essential that each patient has a personal WAAP explaining what to do if their reliever is being required on several occasions [2]. It should further detail how to increase or modify their medication regimen to assist in controlling the flare-up, and be reviewed within 1-2 weeks of any exacerbations [2]. Specialist referral is currently advised for patients experiencing more than 1-2 exacerbations per year despite step 4-5 of treatment [10].

1.2.9 Management of comorbidities

Several comorbidities are commonly present in patients with asthma, many of which may contribute to poor asthma control and burden of disease [24]. In particular, patients should be assessed for the presence of obesity; gastro-oesophageal reflux disease (GERD); anxiety and depression; food allergy/anaphylaxis; rhinitis; obstructive sleep apnoea (OSA); psychological disturbances; and chronic infections [10]. Active management of such comorbidities may therefore contribute to reductions in symptom burden and improved quality of life.

1.3 Issues with Asthma Pharmacotherapy Management in Australia - Real-world Evidence

As discussed, Australia has an extensive network of General Practitioners (GPs), pharmacists, nurses, and asthma educators who are primarily responsible for the management of patients with asthma, a condition predominantly managed in primary practice [2]. However, whilst comprehensive clinical guidelines published by GINA [10] and the AAH [2] regarding patient assessment and management are readily available in Australian practice, poor asthma control still remains highly evident in practice [25].

A primary contributor to poor asthma control in practice concerns the suboptimal use of asthma pharmacotherapy in Australia [26]. With regards to asthma medication management, we have a major problem, particularly with regards to the inappropriate use of asthma inhalers [27]. Of concern, numerous issues have been revealed in practice surrounding the field of medication use, varying in nature and potentially impeding patients from achieving their greatest level of asthma control, and increasing the burden of disease.

These include the following issues:

1.3.1 Overuse of Short-Acting Beta Agonists

Asthma relievers are essential in the rapid management of acute asthma flare-ups, many which have the potential to be life-threatening without timely medication use. As such, they are currently available without a prescription in Australia, provided a pharmacist is available to counsel the patient on their use. Despite the requirement for pharmacist intervention in ensuring the medication is required in the clinical best interest of the patient, a recent real-world study conducted in community pharmacy exploring over-the-counter SABA purchase in Australia identified a significant number of patients to be over-users of the medication; that is, patients using the medication in doses and frequencies greater than that advised in clinical guidelines [28]. Of concern, 70.1% of participants were identified to be SABA over-users, with 73.6% reporting lack of use of a preventer daily and only 81.6% reporting a doctor diagnosis of asthma. Remarkably, almost 20% of SABA purchasers reported that they did not have asthma [28].

Overuse of reliever therapy is associated with poor asthma control [29], increased airway hyper-responsiveness [30], increased asthma-related mortality [31] and increased healthcare utilization due to asthma [32]. In particular, regular or frequent SABA use is associate with adverse events including increased allergic response, β_2-receptor downregulation, and decreased broncho-protection [33].

Excessive use of reliever inhalers has further been associated with increased mortality from asthma, with dispensing of more than 12 reliever inhalers to one individual over a 12 month period associated with increased risk of asthma related death [34]. Associations between over-use of SABAs and uncontrolled asthma, a diagnosis of depression, moderate-to-severe nasal symptoms, requirement for oral corticosteroids to manage worsening asthma, and consultations with a medical practitioner for asthma in the previous 12 months have further been noted [35].

It is therefore critical and a fundamental principle of asthma medication management that, as the guidelines articulate, reliever use be exclusively restricted to use on an ‘as needed’ basis; *ideally, this should be no greater than twice per week in the case of well-controlled asthma* [10]. In addressing this issue, it is critical to engage pharmacy in Australia as reliever inhalers are available over the counter (OTC), without a prescription; thus, only the pharmacist that can comprehensively monitor asthma medication use.

1.3.2 Poor Inhaler Technique

An integral aspect of asthma self-management is the effective training, demonstration and review of patient inhaler technique [2]. As described, the use of inhalers in the delivery of medication in asthma management offers a multitude of advantages relative to systemic delivery of medications. These include the delivery of a higher concentration of medication in the airways, a reduction in the time of onset of action of the medications, particularly relevant in the management of acute asthma flare-ups, and a reduction in the proportion of systemic adverse effects evident relative to that associated with systemic therapy, which may assist in improving adherence to asthma pharmacotherapy [10].

Of concern, although inhalers are the most common type of medication devices used in asthma treatment, they are often used sub-optimally [27]. Current investigations estimate that as many as 70-80% of patients are unable to demonstrate proficiency in inhaler technique [10]. In a review of 21 studies examining proficiency in pMDI technique, poor technique was estimated in up to 90% of cases, with an average of 50% of patients demonstrating incorrect technique (range 14-90%) [36].

Errors may be critical or non-critical in nature, with a critical error referring to one associated with an increased risk of poor asthma outcomes, that is, uncontrolled asthma and/or an increased number of asthma exacerbations, as described above [9]. In consequence of differences in inhaler technique and design, the pattern and nature of errors demonstrated may very across devices; however, a broad array of both critical and non-critical errors may be demonstrated regardless of the device employed [27] . Errors may vary according to the type of device, however, some are non-device dependent in nature, as in the example of not inhaling prior to inhalation for a number of devices [27].

Numerous factors have been proposed to impact upon inhaler technique. Lack of self-awareness of demonstration of incorrect technique by patients may hinder or delay access to self-management and educational programs [37] . In addition, the inability of “many” healthcare providers to correctly demonstrate the technique of the inhalers they prescribed, may potentiate this issue, with only 15-69% of healthcare professionals (across all disciplines) demonstrating the ability to correctly use inhaler devices [37].

Of concern, poor inhaler technique has been associated with a myriad of physiological and economic ramifications, as discussed below:

1.3.2.1 Clinical impact of poor inhaler technique

Clinically, poor inhaler technique has been associated with numerous markers of inferior asthma management. Inefficient use of inhaler devices may result in decreased pulmonary drug deposition and subclinical dosing, promoting suboptimal therapeutic effects.

Numerous well-designed studies have demonstrated explicit effects of improper pMDI usage on the pulmonary deposition of inhaled medications [38-40]. Taken together, these have identified reductions in pulmonary drug deposition of 50-66%, with associated reductions in bronchodilation by 30%. In consequence, symptoms such as dyspnoea, discomfort, coughing, wheezing, and other associated morbidities which could potentially have been avoided may present in the patient, increasing the severity of the condition, and burden of the disease on quality of life, and promoting poor asthma control [38-40]. Reductions in quality of life, limitations in day time activity, and increased night-time awakening have further been associated with poor or improper inhaler technique in asthma [41, 42]. Of further concern, increased hospital visits have further been associated with the clinical ramifications of poor inhaler technique, increasing the burden on patient quality of life and the healthcare system [38].

In a further small investigation, a difference in the mean improvement in forced expiratory volume in 1 second (FEV_1) of approximately 50% after two inhalations of bronchodilator was identified between groups of users demonstrating correct and incorrect technique [43]. An additional 30% improvement in FEV_1 in those demonstrating incorrect technique was further noted following active education in inhaler technique [43].

Strong associations between pMDI misuse, in particular, poor hand-lung coordination, and asthma instability have further been identified in the literature [36]. This implies that patients demonstrating incorrect pMDI technique with regard to ICS devices may experience clinically significant reductions in the efficacy of the dose intended to be delivered, and consequent increases in the risk of exacerbations and impairments in asthma control [36]. Patients demonstrating incorrect inhaler technique have further been identified to be more 50% more likely to be hospitalised, and to experience increased emergency department visits and increased use of oral corticosteroids [44]. Lack of perceived clinical benefit may further contribute to overprescribing by medical practitioners and/or overuse of relievers and preventers by patients, increasing the risk of treatment duplication or omission and its associated increased risk of adverse effects or subclinical outcomes in consequence of increased treatment complexity and cost [27].

1.3.2.2 Economic implications of poor inhaler technique

Misuse of asthma inhalers may further render significant economic impacts on the healthcare system [45, 46]. Internationally, a significant proportion of prescription pharmaceutical costs were attributed to inhaler misuse [45]. In the United States of America, economic analyses have revealed forfeiture of $5-7 billion out of estimated sum of $25 billion spent for inhalers annually [45]. In a hospital-based population, it was further estimated that as much as $900 per month had been forfeited on the purchase of inhalers by twenty-three patients who could not operate them correctly [46].

Poor inhaler technique may therefore increase both the burden of disease and the financial burden to the healthcare system, thus placing the improvement of inhaler technique as a significant focus of research.

1.3.3 Poor adherence to and underuse of preventer medication

Numerous reports have indicated that patient adherence to prescribed regimens of preventer medications are significantly poor [26, 35, 47]. Clinical guidelines currently advise regular daily doses of ICS in patients presenting with symptoms at least twice a month and/or who have risk factors for flare-ups, and regular daily doses of either ICS/LABA combination therapy or ICS only in patients with worse asthma control [10]. Despite these explicit guidelines, a random population survey of Australian adults exhibiting poor symptom control (ACT score <20) elucidated that only 60% of participants (n=1204) were identified to take their preventer daily[35]. A further study of adults with asthma in primary care, with poor symptom control (ACT <20) using electronic inhaler monitoring further reported that patients were only taking 60% of their prescribed dose in the month after initially consulting with their GP regarding their asthma, and that this had fallen to only 29% of the prescribed dose within a 6 month time period [47].

Shockingly, further largescale reports by the Australian Institute of Health and Welfare indicate that only 17% of patients had enough prescriptions of preventer medication dispensed to be taking it at least half of the time (that is, at least 7 prescriptions) [26]. Underuse of preventer medication can result in significantly worse asthma control [10], and is therefore a major issue.

1.3.4 Over-prescription of symptom controllers/high dose ICS

In an analysis of respiratory medication usage in Australia between 2003-13, it was identified that a substantial number of prescriptions for combination ICS/LABA inhalers and for higher potency ICS medications were dispensed to patients for whom a less potent ICS formulation alone would have been effective[26]. Of concern, it was identified that 4.9% of patients aged 65 years and over were dispensed at least 13 prescriptions of ICS, exceeding the prescription frequency of one prescription per month [26]. This implies that older patients were either more likely to be prescribed higher ICS doses than required, or more likely to incorrectly over-use their inhalers.

Reports indicate that older adults are further more likely to overuse combination ICS/LABA therapy [26]. In 2013, 4.8% of people aged 65 and over were identified to have at least 13 prescriptions for combination ICS/LABA therapy, compared to only 0.3% and 2.6% of people 0-4 years and 35-64 years of age, respectively [26].

With a dispensing frequency equating to greater than one prescription per month, this suggests an issue of either the prescription of higher-than-advised doses for such patients, and/or potentially overuse by such patients. With the number of prescriptions for combination inhalers exceeding the number of patients with moderate-to-severe asthma for who they were advised, there is concern that these agents may be used in an inappropriate clinical setting, and not in accordance to guidelines [26]. Such prescription practices may potentially increase the risk of patients of experiencing adverse effects, and lead to a significant and unnecessary economic burden on patients and the government [26].

1.3.5 Patients' beliefs/attitudes/and concerns about Asthma Severity

A further challenge in the management of patients with asthma in Australia pertains to the manner in which patients view the severity of their condition. Numerous studies have revealed discordance between the actual severity of a patient's asthma, and the severity of asthma the patient believes they have [48, 49]. In a study of 2467 patients from eight Asian countries/regions, only 18% of patients who categorised their asthma as being well-controlled actually had well-controlled asthma in practice [48]. Similar results were identified in another study, with 91% of patients with poorly controlled asthma self-reporting that their asthma was well-controlled, and 82% of patients with partially controlled asthma self-reporting that their asthma was well-controlled [49].

This poses an issue to healthcare professionals basing their management of asthma patients on their patients' perceptions of their level of asthma control, in that it can potentially misguide them in their knowledge of the patient's condition, and required treatment options. As such, it is essential that healthcare professionals be aware of the considerable potential for potentially incorrect information to be given on patient asthma severity, and to ensure that they have guidelines in place to assist them to ensure objectivity of information is attained at all times.

1.3.6 Management of Severe Asthma

A further issue in the field of Australian asthma management regards the management of patients with severe asthma, defined as asthma requiring treatment with high-dose ICS, LABAs, or maintenance oral corticosteroids in patients with good adherence and correct inhaler technique, or asthma that is uncontrolled despite this treatment [2].

A major concern is the lack of explicit treatment guidelines for such patients. Whilst treatment options reserved for patients with severe asthma, including LAMAs, LTRAs, low dose azithromycin, and biologic agents for severe allergic or severe Type 2 asthma are available, research regarding which treatments are of greatest effect in patients with differing clinical phenotypes of the condition are still in progress [10]. In addition, prescribers may not always be aware of the need to assess for the particular clinical phenotype of the patient, for example, whether the patient has primarily eosinophilic or neutrophilic asthma, and which medication is most able to assist their unique clinical profile [10]. Hence, further information is required to match the best specialised medication with the unique clinical profile of the particular patient, and time required to train prescribers in the most effective treatment options for such patients.

A further concern is the lack of clear referral pathways for prescribers and other healthcare professionals for such patients [19]. Patients with severe asthma may require assistance from a specialist multidisciplinary healthcare team, including an experienced respiratory physician to confirm the diagnosis and prescribe management strategies, a specialist nurse to provide education, administer add-on therapies, and coordinate disease management; an accredited respiratory scientist to conduct lung function assessment to confirm the disease and determine the disease phenotypes; and a pharmacist to provide inhaler technique training and provide advice about concomitant medications [19]. Comorbidities must also be addressed, and this could involve referring the patient to numerous healthcare specialists, including a psychologist or psychiatrist if the patient is experiencing emotional stress which is contributing to and/or resultant from the condition, and a number of other healthcare professionals, including speech pathologists, dietitians, psychologists, sleep physicians, gastroenterologists, otolaryngologists, and physiotherapists [19].

However, the point at which referral should occur, and by whom, is currently unclear. Current guidelines state that GPs undertake a comprehensive review of the patient, including confirming a diagnosis, investigating symptoms contributing to the patient's symptoms, optimising management through patient education, pharmacological therapy, and trigger avoidance, and reviewing the patient over a 3-6 month period prior to referral [10]. This could potentially lead to a delay in timely referral in the patient if appointment times are not maintained. Other members of the healthcare team such as nurses and pharmacists further may not be aware of the signs of severe asthma, and may miss points at which the patient should be referred to a specialist medical team. Thus, current ambiguity regarding optimal patient management and when and by whom referral should occur are significant issues affecting the real-world management of asthma patients in Australia.

1.4 Role of Pharmacists in Asthma Management

The management of asthma requires intervention across numerous aspects of patient care, including assessment of clinical status, symptom control, and risk factors for future exacerbations; provision of patient education and WAAP; regular review; and numerous other aspects of patient care [2, 10]. As such, the involvement of a multidisciplinary healthcare team with various specific areas of expertise is essential in the management of the asthma patient.

With the clinical management of asthma being highly centred on pharmacotherapy, pharmacists have a vital role to play in the management of asthma patients. Trained to be medication experts, pharmacists are specialists in the use of asthma devices, inhalers, medication use, and adherence to treatment regimens. Furthermore, it is an uncontroversial fact that people with chronic respiratory conditions, whether prescribed regular medication or not, frequent the community pharmacy regularly. When it comes to people with asthma, with the availability of reliever inhalers OTC, our recent research indicates that the opportunity for people with asthma to engage with a pharmacist can be up to 12-fold higher than with a GP [28, 35]. With consultative services further offered free of charge to the patient, pharmacists are one of the most accessible healthcare providers to asthma patients. Therefore, there is great opportunity for pharmacists to become involved in numerous aspects of patient care in patients with asthma.

Currently, a substantial body of evidence indicates that pharmacy interventions have a significant impact on numerous asthma outcomes. In a systematic review of twenty-one studies exploring the influence of pharmacist intervention on asthma outcomes [50], nine out of ten studies revealed a positive impact on asthma control following the provision of pharmacists' interventions. Improvements were also identified in asthma action plan ownership [3], quality of life [3], adherence [3-5], perceived asthma control [3], asthma knowledge [3], and inhalation technique [4, 5]. Further studies have additionally identified improvements in medication adherence, appropriate drug use, asthma knowledge, pulmonary function test, and asthma control following varied pharmacist interventions on asthma patients [51].

These interventions were diverse in nature, and included patient education and counselling on medication use and adherence, knowledge of disease and health beliefs, asthma triggers, use of an asthma action plan, and referral to a primary care physician where indicated [3]; verbal instructions, physical demonstration, and written information regarding inhaler device use and exploration of adherence utilising both the Health Beliefs Model and the Beliefs about Medicines Questionnaire; collaborative goal-setting [52]; and interventions focused on improving inhalation technique and medication adherence, such as inhaler technique demonstration and training [5].

One study involved enrolling patients in an intensive asthma service aiming to improve asthma knowledge over a period of six months [53]. Patients were required to attend three or four visits at their pharmacy, in which the pharmacist would select interventions appropriate to educational needs of the patient, as pre-determined using a protocol-specific checklist. These interventions, the most common of which involve counselling about triggers and the role of controller medications, resulted in improvements in knowledge in patients with asthma. Furthermore, they appeared to slow the rate of knowledge decline, with examination of patient knowledge at a follow-up visit at 6 months indicating a slower rate of knowledge decline after the program [53].

Pharmacist-led patient education conducted over a four month period via four structured asthma education visits was further identified to lead to improvements in patient asthma knowledge, device technique, asthma management, treatment adherence, and attitudes [54].

In a study exploring whether pharmacists could assist in improving asthma control, medication adherence, and device technique, pharmacists provided educational interventions, including verbal instruction on asthma control, inhaler technique demonstrations, and written information on the proper use of inhaler devices to a group of patients [52]. Similarly, these educational interventions were tailored to the patients' individual needs, as based on their unique beliefs, barriers to adherence, and personal goals. They also assisted patients to improve adherence by assessing and exploring reasons for non-adherence utilising the Health Belief Model and the Beliefs about Medicines Questionnaire, and assisted patients to set goals for their next visit. At the end of the six-month study, it was identified that such interventions resulted in significant improvements in patient asthma control, adherence, and patient knowledge [52].

Asthma control has further been identified to be improved in more comprehensive pharmacist interventions involving lung function by spirometry, and an ongoing cycle of assessment, management, and review involving inhaler technique review, adherence assessment, detection of drug-related issues, goal setting and review, targeted counselling and education on asthma, and GP referral where required, conducted over a 6 month period [55]. Interventions further included a series of five one-on-one pharmacist-patient consultations in which patients were educated on asthma pathology, the use of asthma medication, inhalation technique, and self-management skills. In addition, pharmacists were given the opportunity to assess drug use for issues; and implement a six step plan based on guidelines provided by the National Asthma Council of Australia, involving pharmacist assessment of patient's asthma severity, achievement of best lung function, maintenance of best lung function through avoidance of triggers, maintenance of best lung function through optimal medications, provision of a written action plan, and education and regular review.

The interventions resulted in a multitude of improvements in patient asthma control, including improved adherence to preventer medication, a reduction in the mean daily dose of reliever medication, an alteration in prescribed medication from reliever only to a combination of preventer and reliever, and improved scores on risk of non-adherence, quality of life, asthma knowledge, and perceived control of asthma questionnaires were further identified [55]. These led to significant reductions in the percentage of patients with severe asthma and asthma severity scores [55].

Pharmacist-led interventions have further been identified to assist in improvement the appropriateness of drug therapy. In a prospective cohort study in the Netherlands evaluating the impact of an internet-based support tool used to identify drug-related problems and provide pharmaceutical care interventions, the prevalence of drug-related problems was significantly less in the intervention group than in the control group [56].

Significant improvements in asthma-specific quality of life [57], self-efficacy [57], knowledge [57, 58], medication adherence [57], self-reported symptoms [57], perceived asthma control [58], peak expiratory flow [58], inhaler technique [57], the daily dose of SABA dose required [58], and annual cost of medication [58] have further been identified across the literature. A number of studies have further identified significant improvements in clinical outcomes such as PEF and FEV_1 [50]. There is therefore substantial evidence that pharmacists are particularly well-suited healthcare professionals in the assessment and optimisation of asthma medication use and outcomes.

Despite this information, there is still evidence of numerous issues in asthma patient management in the real-world setting, as discussed in part 1.3, above. To understand why this is occurring, it is essential to identify the issues and challenges associated with the implementation of such pharmacist interventions in practice.

1.5 Challenges in the Implementation of Pharmacist Interventions in Asthma Management in Real-World Practice

Despite the presence of a substantial body of evidence indicating that pharmacists can significantly improve a broad array of asthma outcomes in patients, asthma outcomes in patients in the real-world setting have continued to remain poor [17]. This suggests the presence of a significant number of challenges in the implementation of such interventions, preventing their full practice in the real-world setting.

As described, such interventions are highly comprehensive in nature, requiring the pharmacist to participate in a number of asthma care practices, including patient education on the condition, medication, and inhaler technique; liaison with medical practitioners where necessary; assessment of and assistance with patient adherence; clinical assessment of the patient; use of technology; and follow-up as required. In additions, such interventions have generally been studied and conducted over an extended period of time, often over a period of 12 months. As such, significant pharmacist and patient involvement is required in the conduction of these interventions.

In order to be effective, evidence-based practice must be actively implemented into health systems and policies, with passive implementation efforts deemed relatively ineffective. As such, implementation science, which explores the strategies required to transition knowledge into practice, with the recognition that knowledge is contextual and implementation models must satisfy the demands of the population they are being use for, is rapidly becoming required to ensure the outcomes achieved in the research setting are able to be achieved in real world practice [59].

Currently, implementation strategies have been primarily hypothesised to fail mainly due to a lack of systematic approach in their implementation, and a lack of understanding of the organisational contexts and other critical determinants of a successful implementation [59]. As such, it is imperative to understand the limitations placed on such pharmacist intervention in consequence of the nature of the community pharmacy environment, and the abilities and particular skill-set of the pharmacist.

Studies exploring pharmacist perspectives of barriers to optimal patient care have revealed a number of barriers to patient care. An investigation by Nadaira et al. (2009) [6] identified that these could be categorised into three main groups: organisational factors, relational factors, and professional factors [6].

1.5.1 Organisational factors

Organisational factors refer to factors emanating from the structure or workflow of the occupational environment [6]. One such factor is that of time availability. Numerous studies have revealed that a large multitude of pharmacists feel that they do not have enough time in their workday to participate in comprehensive asthma interventions such as peak flow testing or patient education, due to the presence of competing tasks [6, 60, 61]. This includes their perceived need to supply prescriptions quickly, complete administrative tasks, and assist other patients in the pharmacy [6, 60, 61]. Time was further listed as one of the four major barriers impacting ability to provide specific asthma services by over 95% of pharmacists in an investigation exploring community pharmacists' role in asthma management and barriers to pharmacy asthma services in metropolitan and rural NSW, Australia [62]. The time taken to perform specific interventions should therefore be considered in the ability of pharmacists to assist patients with asthma, and may potentially be contributing to the suboptimal outcomes often evident in the Australian asthma population.

A further barrier is that of lack of reimbursement for some cognitive services in asthma in community pharmacy [6, 60, 62]. In Australia, federal community pharmacy agreements enable funding for established, set programs such as MedsChecks [63]; however, these programs often do not enable extensive time to be dedicated purely towards asthma, and the comprehensive interventions associated with improved clinical outcomes, rather requiring exploration of the full range of medical issues in the patient within a set time period. Similarly, there are currently no privately funded programs in Australia dedicated towards asthma services, resulting in a lack of reimbursement for participation in specific asthma interventions associated with improved clinical outcomes. Such lack of funding may potentially affect pharmacists' desires to participate in comprehensive asthma interventions, with lack of financial incentive for participation in such interventions and conflict between professional and commercial interests identified to be barrier by over half of all pharmacists surveyed in the Australia literature [62].

This impact has further been noted to extend to the international audience. In a Canadian study [6], lack of reimbursement was identified to diminish pharmacist intervention in asthma-specific interventions, due to a perceived lack of importance placed on its role by such external bodies [6]. Pharmacists also elicited that a lack of fee for expanded services appears to reduce their importance in the eyes of patients, affecting their sense of morale and confidence in the degree to which their contribution would be considered significant and of relevance in the eyes of the patient [6]. As such, lack of financial incentive or reimbursement may potentially limit the ability of the pharmacist to assists in improving clinical outcomes in patients with asthma in the real-world setting.

In contrast, a study in Norway identified that pharmacies that were reimbursed by the Norwegian Government to implement and conduct an 'Inhaler Technique Assessment Service' (ITAS), were able to achieve significant improvements in inhaler technique and a reduction in the median rate of incorrect inhaler technique steps in their patients [64]. This suggests that the provision of financial assistance to pharmacies or pharmacists to conduct inhaler technique services may potentially aid in improving outcomes in such patients [64]. In the international setting, insufficient support from other team members in the pharmacy (for example, pharmacy assistants and dispensary technicianshas also been identified to limit the ability of the pharmacist to provide comprehensive asthma support to their patients [6]. In a Canadian study, all participants stated that they were more likely to perform interventions for asthma patients if they were surrounded by a sufficient number of competent pharmacists and pharmacy technicians, each with their own distinct roles and tasks [6]. Ensuring that a well-organised workload was maintained was also stated to significantly assist in performing asthma-management interventions [6].

Lack of access to resources has further been identified to be a barrier to the successful participation of pharmacists in comprehensive asthma services [6, 65]. In a Canadian study, pharmacists stated that access to a greater number of asthma management tools, including action plans, peak flow meters, and educational material would assist in improving their motivation to monitor patient asthma control [6]. In addition, lack of access to the diagnosis of the patient was further identified to limit the type and number of interventions that could be performed, a factor considered of concern in that medications used for asthma could also be indicated for other medical conditions [6]. As such, there are a multitude of factors potentially limiting pharmacists from aiding pharmacists to attain the clinical outcomes achieved in the literature in the real-world setting.

Identification of equipment required for participation in such interventions, and provision of the diagnosis by medical practitioners or the patient could therefore assists pharmacists to aid patients in gaining the clinical improvements identified in the literature in the real-world setting.

1.5.2 Relational Factors

Relational factors refer to factors associated with relationship issues between pharmacists, the patient, and further members of their professional healthcare team [6]. A number of relational factors have been identified to potentially affect the extent to which pharmacists can assist patients to improve clinical asthma outcomes in the real-world setting.

In the Australian setting, numerous concerns exist with regards to relationships with patients, and how they perceive the nature of their condition [66]. Of concern, a frequently reported barrier was that patients with asthma did not appear to always understand that they had a disease [66]. Contributors felt that there was a misconception where patients with asthma often did not understand the need to self-manage their condition, or to manage their asthma proactively, particularly in contrast to other medical conditions [66]. Contributors further noted that many patients believed asthma to be a disease of childhood which could be outgrown, and that asthma was often not considered by patients to be a serious or a priority condition [66].

Shockingly, in a further report, 97% of pharmacists reported their patients perception that they were already well cared for by their doctors to be a barrier to their participation in comprehensive asthma interventions, with 96% of pharmacists further identifying a patients' lack of asthma knowledge to be a barrier to their participation in asthma interventions [62]. Patients' health beliefs and their perception that it was not the pharmacist's role to assist in asthma management were further identified to be barriers by 85% and 84% of pharmacists, respectively [62]. Stakeholders in the position statement have suggested that improved training is required to understand the psychology of asthma, to assist patients in improving their ability to self-manage their condition [66].

Lack of knowledge and familiarity within the broader social and environmental context of the patient has further been identified to be a barrier to successful implementation of asthma interventions in the real-world setting [66]. There is growing acknowledgement that asthma increasingly needs to be managed from the perspective of the patients' personal disease experience, and their social and environmental context; that is, it is essential that the individual needs of the patient be identified [66]. There is further an urgent demand to research population groups to better assist them to engage in asthma self-management, and to incorporate their insights and factors assisting them on a personal level into asthma products and self-management plans [66].

The lack of knowledge of a patients' level of health literacy was further identified to be a factor affecting the implementation of such interventions in the real-world setting [66]. The use of complex and inconsistent language between differing healthcare practitioners was identified to be a source of confusion in patients with lower levels of education and health literacy, and a potential barrier to their interest and ability to self-manage their condition [66].

Such issues have further been reflected in the international setting [6]. In Canada, pharmacists stated that medical practitioners were often difficult to gain contact with; however, once in contact, identified to be generally collaborative [6]. As such, methods of improving the ease with which physicians can be contacted may assist in improving results in the real-world setting.

1.5.3 Professional Factors

Professional factors relate to factors associated with the professional training, competence, and knowledge of the pharmacist, in addition to their perception of the requirement to participate in such interventions [6]. A number of professional factors have been identified to be barriers to pharmacist participation in asthma interventions associated with improvements in clinical outcomes in asthma patients in both the Australian and the international setting [66]. One such factor is that of pharmacist confidence in participation in such interventions [6, 60-62, 65]. In a study in Australia, 75% of all respondents lacked confidence or skills in asthma self-management counselling, asthma monitoring, reviewing and counselling on asthma control, counselling on asthma trigger factors, and counselling on asthma adherence [62].

In an exploratory paper of current practices and new approaches to asthma healthcare in Australia, it was further identified that practitioners involved in asthma management, including pharmacists, felt frustrated that they lacked the skills to affect changes in behaviour in asthma patients, particularly with regards to medication adherence [66]. In addition, they felt that they did not always have the knowledge or skills to effectively support self-management practices and were challenged by motivating consumers to self-manage their asthma [66]. Stakeholders felt that there was a need to upskill health professionals in these areas, and that they particularly required more tools to support their interactions with 'disengaged patients' [66].

Of concern, lack of pharmacist knowledge on asthma has been identified to be a barrier in the literature, a major concern considering their clinical training prior to practice [6, 62]. In Canada, a few participants in a study exploring pharmacist barriers to asthma management stated that they lacked knowledge on asthma and its treatment [6]. This was particularly true with regard to the serious consequences associated with asthma, particularly in comparison to other chronic conditions whose consequences have been more significantly reported, such as diabetes [6].

Pharmacist motivation was further reported to be a significant professional factor affecting pharmacist implementation of asthma services in the real-world settings [6]. In Canada, some pharmacy owners state that a few of their salaried pharmacists did not possess motivation with regards to the implementing chronic disease management interventions [6]. Furthermore, salaried pharmacists who had only recently graduated from university further stated that it was sometimes difficult to remain motivated at work [6].

Issues pertaining to healthcare systems and processes were further identified to affect the successful practice of asthma interventions by pharmacists. In a position statement exploring current practices and new approaches in asthma management in Australia, it was identified that incorporation of tools such as an asthma medication review system, greater prescriber access to dispensing data, and pharmacist inhaler technique remuneration could assist in improving uptake of services [66].

1.5.4 Role Definition and the Contribution of the Pharmacist

The lack of professional role and task definition of pharmacists in Australia with regards to participation in asthma interventions has been revealed to be a major barrier to the implementation of such interventions in real-world practice [62]. Of concern, over half of pharmacists surveyed in Australia did not believe it was their role to participate in comprehensive asthma interventions [62]. Further investigation revealed that over three-quarters of pharmacists were concerned they would be 'overstepping' the role of the Doctor, and that nearly 85% of respondents believed that patients did not consider such interventions to be part of the role of the pharmacist [62].

A primary challenge towards the improved and expanded practice of pharmacists in the field of asthma management is the lack of clear, structured guidelines designed ***specifically for pharmacists*** regarding asthma assessment and counselling. In Europe, the EuroPharm Pharmacy-Based Asthma Services Protocol and Guidelines [67], developed by the WHO collaborating centre for drug policy and pharmacy practice development, provide clear guidelines to pharmacists on quality documentation; technical advice giving; outcome-oriented patient counselling; therapeutic outcomes monitoring; self-care, health promotion and ill-health prevention; influencing prescribing and medicine use; and implementation at pharmacy level, in addition to guidelines for implementation of all of the above at pharmacy level [67].

In Australia, both the AAH [2] and the GINA report [10] are accessible for healthcare professionals, and provide overall structured guidelines and recommendations on numerous aspects of asthma best management and practice. However, a key issue with these guidelines and reports is that they are generalised for all groups of healthcare professionals, rather than specifically directed to the needs of pharmacists and their patients; that is, they do not have sections which specifically articulate the roles of each group of healthcare professionals, making it difficult to understand what one's roles are in the field of asthma management.

In addition, they provide very comprehensive information on numerous aspects of asthma management, including diagnosis and physical monitoring, and, as such, can present a burden with regards to finding pharmacy-specific information in a timely manner.

In contrast, there is a scarcity of information on what the specific roles of the pharmacist are; that is, where they can collaborate with GPs and other healthcare professionals on holistic approaches to asthma management; key areas to assess patients on; access to recent research; the importance of teaching correct inhaler technique and monitoring at regular intervals; methods of patient assessment; communication strategies; exploration of the patient, their barriers to learning, and their most effective learning style; and methods of documentation of clinical intervention; to name a few. Thus, it can be difficult for pharmacists to develop a clear understanding and direction of the form, depth, and direction of assessment and counselling to be provided to patients, and the extent and type of clinical information to gather and communication style to use to gain measurable improvements in clinical outcomes.

Beyond this, remuneration pathways, such as those offered through the eighth community pharmacy agreement (8CPA services) [63], which can help to guide practice, are not well developed for asthma management. For example, whilst guidelines are available for the conduct of Home Medications Reviews and MedsChecks and Diabetes MedsChecks [68], which involve pharmacist review of medications and encourage engagement with healthcare professionals, they are not condition specific, and therefore do not directly guide pharmacists in the specific needs of the asthma patient. This may lead to ad hoc and incidental provision of similar services by a range of health professionals, and can potentially limit the quality of care provided and hinder the transition of pharmacists towards being not just counsellors of medication use, but assessors of disease control, medication safety, and medication choice; a shift that will be essential in the changing face of asthma care.

To date, the only written document identified for use in Australian asthma management practice for pharmacists is that produced by the Pharmaceutical Society of Australia, which provides guidance for provision of salbutamol and terbutaline as Pharmacist-Only, or OTC, items [69]. Whilst providing general considerations of one's professional obligations, suggestions of what to assess when assessing patient's needs, and suggestions of what to include when counselling and when to refer, it does not elaborate on these points. Thus the method in which these are enacted has the potential to vary considerably between pharmacists.

Without explicit knowledge of their role in asthma management and the clinical relevance of their activities and knowledge, pharmacists may experience difficulty in performing asthma-specific interventions in real-world practice. It is therefore essential to develop a clear understanding of what pharmacists currently consider their role to be in the management of their asthma patients in the real-world setting (to be discussed further in Chapter 3, below).

Chapter 2

The Need to Focus on High-Risk Asthma Patients

A Rationale

2.1: The Changing Role of the Pharmacist: Identification of High Risk Asthma Patients

Despite substantial evidence that community pharmacists can assist asthma patients to obtain improvements in numerous clinical outcomes in the research setting (as above), the number of patients presenting with poorly controlled asthma in the real-world setting is high [17]. Poorly controlled asthma is a major issue in Australia[17], placing significant burden on patient health-related quality of life (HRQoL) and the healthcare system [17]. In particular, poorly controlled asthma has been identified to have significant impacts on physical, emotional, mental, and social functioning via effects on ability to complete daily activities (85%) [70],ability to participate in physical activity (69%) [71], productivity at work (73%) [70] or study (64%) [72], and effects on ability to participate in leisure and lifestyle activities (78%) [73, 74].

Financially, the cost of managing poorly controlled asthma is further significant, with hospitalisation costs estimated at $179.9 million, and placing significant burden on tax payer dollars [17]. It is therefore imperative that urgent and significant improvement in the healthcare services provided to poorly controlled asthma patients be achieved in practice.

One strategy to improve asthma care is to identify patients demonstrating a high risk of poor symptom control and future asthma exacerbations, that is, *high-risk asthma patients*. In being high-risk of experiencing poor asthma control, high-risk patients are more likely to experience its associated impacts on HRQoL and the financial system [19]. Identification of high-risk patients in practice by pharmacists is therefore essential in improving asthma management and their level of asthma control, through a variety of manners. Firstly, it can assist pharmacists to manage and overcome barriers affecting their ability to participate in comprehensive asthma interventions with asthma patients, such as lack of time or resource availability, by enabling them to identify patients in urgent need of care and funnel their resources to where they are most urgently required.

Secondly, it can assist in optimising medication selection and management in the asthma patient. With recent updates to the Australian asthma management guidelines now offering the option of selecting between a SABA or a combination ICS-LABA medication for patients presenting with asthma symptoms greater than twice a month [2], there is a demand on pharmacists to be able to assess both their patients' degree of symptom control and level of risk of future exacerbations in assessing medication suitability for their patients; a demand previously unrequired from the pharmacist. Therefore, the ability to assess which patients are high-risk and could benefit from more potent and clinically relevant medications is essential in the assistance of patients at high risk of poor asthma outcomes.

Thirdly, it can enable pharmacists a greater opportunity to explore the factors resulting in these patients being risk-risk, for example, poor adherence to medications or low levels of health literacy and education, in a more comprehensive manner. With pharmacists being experts in the field of medication use, they may also identify problems that no one else can see with regards to medication use. This can enable the pharmacist to provide education targeted to the specific educational and health needs of the patient, improving patient asthma outcomes through the provision of tailored health education. Communication and behavioural interventions tailored to the individual's health literacy level may be an effective strategy to improve knowledge and indicators of disease control in selected clinical settings, and may therefore be of significant benefit in such patients [75]. Therefore, identification of high-risk asthma patients by pharmacists is essential in optimising the management of such patients, and the degree to which they are able to adhere to recommended interventions on a continual basis.

2.2 Identification of High-Risk Asthma Patient Groups in Australia – do we know who they are?

Despite the benefits associated with the identification of high-risk patients, there is concern that they are not being identified and evidence-based interventions are not being delivered. High risk patients present to pharmacy en masse and on a daily basis; in 2019/2020, over 12 million reliever inhalers were dispensed to people with asthma and COPD, providing 12 million opportunities to intervene yet 70% of patients remain high risk experiencing complications associated with medicines use [28, 76], and only 3% receive an intervention [77].

Whilst it has been identified in an Australian study that 70% of patients were at high risk of poor asthma outcomes as based on their frequency of SABA use [28], the specific demographic characteristics of such patients were not identified. Thus, we still do not know if there are any particular demographic characteristics placing them at increased risk of poor inhaler technique and poor asthma outcomes (potentially contributing to an increased frequency of SABA use). Furthermore, these factors are not systematically identified or screened within a community pharmacy setting. With multiple risk factors for poor asthma control being evident in practice, it can be difficult to ascertain whether a particular patient entering the pharmacy is more at risk than any other, rendering difficulty in prioritising care in a busy community environment where it may be difficult to assess each and every patient entering the pharmacy. Australia has an ethnically rich and diverse population, with patients of a multitude of health literacy and educational backgrounds, socioeconomic statuses, locations of residence, health statuses and degrees of mobility, ages, and employment statuses, each of which could potentially affect their exposure to risk factors for poor asthma control. Knowledge of which groups of patients are most at high-risk of adverse asthma outcomes could assist in streamlining resources and patient care in the busy community pharmacy environment, and could therefore assist in optimising clinical care and outcomes.

I therefore aim to identify which groups of asthma patients are currently considered high-risk, to assist in aiding pharmacists and further healthcare professionals to identify such groups in practice. This can assist in ensuring such patients receive timely and targeted care, in the face of current issues affecting the quality of care, such as lack of time and inadequate training.

2.2.1 Potential Populations at Risk

Of concern, a number of specific populations in Australia may potentially be at risk of lower health outcomes with regards to respiratory conditions. These populations include First Nations People (that is, Aboriginal and Torres Strait Islander people) culturally and linguistically diverse (CALD) people, and older adults.

In particular, it has been identified that chronic respiratory conditions such as asthma are a significant cause of poor health and mortality for First Nations People [78]. Currently, there appears to be a major gap between First Nations People and the non-Indigenous Australian population with regards to the burden of respiratory disease. Of concern, the age-standardised burden due to respiratory disease in such populations has been identified to be 2.7 times the rate experienced by non-Indigenous Australians [78]. Furthermore, the mortality rate due to respiratory disease for First Nations People has been reported to be double the rate of non-Indigenous Australians, contributing significantly to the discrepancies evident in life expectancy between Indigenous and non-Indigenous Australians [78]. Factors such as poor living conditions, smoking, and dietary factors such as overconsumption of alcohol and malnutrition identified to exist in such populations have all been associated with the higher burden of respiratory disease in First Nations People, placing demand for greater study in this population [78]. These issues raise significant concern into the impact of respiratory diseases on this population.

Similarly, those from CALD backgrounds may experience unique challenges to the management of chronic respiratory conditions, increasing their risk of poor clinical outcomes [79]. Of concern, asthma mortality rates have been identified to be twice as high in patients from CALD backgrounds [80]. With over one quarter (or 28%) of Australia's population being comprised of people born overseas, it is imperative to be aware of health concerns specific to such populations to assist in ensuring equitable health outcomes are attained with respect to those not from CALD backgrounds [81].

In particular, there are a number of factors which could potentially place CALD patients at greater risk of suboptimal asthma outcomes [79]. Lower English proficiency may potentially limit health literacy levels and the extent to which such patients can access healthcare and communicate with HCPs [79]. In some instances, there has further been evidence that patients from CALD backgrounds may further be hesitant to ask questions about asthma or their asthma treatment [79]. In turn, this could reduce the amount of healthcare information able to be received or understood by the patient, potentially affecting their knowledge of or adherence to medications. Effects on social and emotional well-being such as fears, stress, and concerns about asthma have further been observed by community pharmacists in those from CALD backgrounds experiencing limited English language proficiency [79].

Of further concern, lack of accessibility to translators or medical professionals proficient in the patient's primary or most fluent language has additionally been identified to limit access to healthcare providers by patients from CALD backgrounds [82]. Further cases of 'cultural incompatibilities' between healthcare providers and patients, for example, lack of awareness of cultural practices and/or racism, have further been identified in practice, contributing to a lack of willingness of affected CALD patients to engage with healthcare providers [82].

Socioeconomic factors have additionally been identified to restrict access to healthcare or medications amongst CALD patients diagnosed with chronic disease [82]. In particular, high costs of services and treatment, such as costs associated with specialist services, have been cited to make access to such aspects of healthcare prohibitive in certain populations [82]. Taken together, these concerns illuminate how patients from CALD backgrounds may be at heightened risk of poor asthma outcomes.

Another patient population group potentially at high-risk of poor asthma outcomes is the older adult population [83]. Of concern, there is a significant gap in clinical outcomes between older adults with asthma and the younger population, with women 75 years of age and older being the most highly represented group of patients attending the emergency department for asthma and demonstrating greater hospitalisation rates for asthma than any other age demographic [84].

With the number of older adults in Australia rapidly increasing [85], and older adults potentially being at greater risk of experiencing certain risk factors for poor asthma control (to be discussed below) [83], there is reason to undertake greater exploration of the issues affecting this population group in asthma management, and whether they are at greater risk of experiencing poor asthma outcomes.

As such, this thesis will be exploring older adults in lieu of these other populations, due to a myriad of reasons. Firstly, their presence is rapidly increasing both nationally, and in the global setting [7]. Secondly, by focusing on increasing awareness of issues pertaining to inhaler technique and asthma outcomes in older adults without regard to their ethnicity, the application of these results in pharmacy practice may further be increased to patients of all ethnicities.

Thirdly, improving the pharmaceutical care of older adults is furthermore a current significant focus of the Australian Government, with the Australian Government allocating $333.7 million to support pharmacists employed in the aged care setting [86]. The aim of this program, the Aged Care On-site Pharmacist (ACOP) Program, which commenced in July 2024, is to embed pharmacists into the aged care setting to assist in optimising medication use and minimising harm from inappropriate use of medications, improving medication management and safety in residential aged care homes [87]. Thus, improved knowledge of the impact of age (as opposed to ethnicity), on the performance of critical inhaler technique errors, and thus, asthma outcomes, may greatly assist pharmacists employed in such programs.

Finally, there are a number of social determinants of care which place older adults at higher risk of poor asthma outcomes, including lower levels of health literacy, increased incidence of living alone, and potentially lower socioeconomic status than younger adults. These will be discussed in Section 3.1.5, below.

As such, this thesis will explore the impact of older age on inhaler technique in lieu of other at-risk groups. The aims of this thesis are therefore as follows in Section 2.3, below.

2.3 Aims of Thesis

Thesis Aim:

Overall Aim: This thesis will aim to determine which patient cohorts are most at risk of poor clinical asthma outcomes in consequence of suboptimal inhaler technique.

To do this, we will first aim to determine whether older age is a risk factor for inhaled medication misuse via a narrative and systematic literature review, to assist in providing further clarity into the influence of age on inhaler technique. This will enable analysis of the existing literature to occur, and can further assist to identify gaps in the literature.

Secondly, we will aim to explore the influence of a broad array of other demographic factors on inhaler technique, specifically inhaler technique errors contributing to poor clinical outcomes. This will enable insight to be gained on demographic factors associated with the performance of such inhaler technique errors. This will enable insight to be gained on demographic factors associated with the performance of inhaler technique errors associated with poor clinical outcomes to be determined, assisting in identifying patient groups at risk of poor clinical outcomes.

These aims are defined below.

Aim 1:

To determine whether older age is a risk factor for inhaled medication misuse, that is, inhaler technique errors

Aim 2:

To identify risk factors associated with the performance of inhaler technique errors and poor asthma outcomes in patients with asthma prescribed the Turbuhaler (TH), pressurised Metered Dose Inhaler (pMDI), and Accuhaler (AH) device.

The next part of this thesis will explore the current picture of asthma care in this special population, and the factors which could potentially place them at greater risk of poor asthma control.

Chapter 3

Exploration of Patient Groups at Greater Risk of Poor Asthma Control: Older Adults

A Review of the Literature

3.1 Older Adults and Asthma

3.1.1 Definition

The term 'older adult' will herein refer to persons of at least sixty-five years of age. This concords with definitions applied by the Australian Bureau of Statistics for utilisation in census data collection, reporting and analysis [85].

3.1.2 Population of Older Adults and Projected Growth

Improved management of asthma in older adults is a particular concern in both Australia and the international setting, in consideration that the proportion of older adults is dramatically increasing on the global platform [7]. Internationally, populating ageing is occurring in nearly all the countries of the world, including both developed and developing countries [7].

Currently, the number of older adults (aged at least 60 years of age) is expected to increase to greater than 1.5 billion in 2050 globally, attaining 16% of the global population by 2050, and more than doubling 2020 figures [7]. In the United States of America, the older adult age demographic accounts for the fastest growing segment of the population [88].

In addition, the older population in itself is further ageing, with the global share of older persons aged at least eighty years of age equating to 14% of the older population in 2013, and projected to reach 19% in 2050 [7]. Current estimates project that 392 million persons worldwide will be aged eighty years or over by 2050, exceeding present estimates by a factor of three [7]. By 2047, the number of older adults is furthermore projected to exceed the number of children for the first time in history [7].

In Australia, the proportion of older adults has similarly assumed an upward trend, increasing from 1 million adults over 65 years of age in 1970 to 4.2 million in 2020 [85]. Increases in the proportion of people in the older adult age demographic are similarly projected to continue until at least 2051, reflecting global trends [7, 85].

Sociocultural and medical analyses have attributed these trends to three predominant factors: increases in national life expectancy, declining fertility, and the ageing of the Baby Boomer Generation [7, 85].

In developed countries, significant advancements in medical care have contributed to declining mortality rates from disease over the previous two decades, increasing life expectancy figures for males and females [7, 85]. Baby Boomer generation ageing has also contributed to this population shift. Coupled with the sustained relatively lower fertility rates subsequent to the post-war baby boom, it is predicted that the ageing of the Baby Boomer population will continue to increase the relative proportion of older adults in Australia [85].

3.1.3 Profile of Asthma and Asthma Control in Older Adults

Investigations into the clinical presentation, clinical outcomes and burden of disease of asthma on the healthcare system and patient quality of life have revealed significant discrepancies in older adults relative to their younger counterparts [88, 89]. Relative to their younger counterparts, older adults may be at greater risk of underdiagnosis, undertreatment, elevated morbidity, hospitalisation and mortality rates, and inferior quality of life, increasing the burden of disease on both the healthcare system and patient quality of life [88-91].

Current evidence suggests that older asthmatic patients form an at-risk group for suboptimal clinical outcomes relative to the general adult population, due to variations in the phenotypic presentation, symptoms and ability to adhere to prescribed treatment options relative to younger patients [90]. These may affect rates of diagnosis and the efficacy of prescribed treatment options in this cohort, ultimately affecting clinical outcome and response to therapy. Examination of the literature reveals the following issues in asthma presentation, control and management in older adults:

3.1.3.1 Phenotypic Presentations and Variations with Age.

Examination of the phenotypes and physical manifestations of asthma in older adults have revealed differences relative to those of younger individuals, affecting diagnosis and optimal management of the condition [92]. Two distinct clinical presentations have currently been described for asthma in older adults: late, or new, onset asthma (LOA), and long-standing asthma (LSA). These differ with regards to the onset and duration of the condition [92].

3.3.1.1 Late-Onset Asthma (LOA)

LOA is generally defined as "asthma with onset of symptoms in adult life in a patient with no pre-existing, persistent respiratory symptoms [93]." Patients with LOA generally start experiencing initial asthma symptoms at sixty-five years of age or older, although they may occur in some middle-age individuals [93]. LOA is generally considered the more severe phenotype, and is associated with less symptom-free days, and a greater demand for oral corticosteroids [92].

3.1.3.1.2 Long-Standing Asthma (LSA)

Patients with LSA present with asthma symptoms early in life [94]. Relative to those with LOA, they generally describe a higher incidence of atopic diseases, greater hyper-inflation, and more severe and irreversible or partially reversible airway obstruction [92]. In this age group, the severity and extent of irreversible airflow obstruction typically depends upon the duration of the disease [95].

3.1.3.1.3 Differences in phenotypic presentations to younger cohorts

Examinations of the pathophysiological characteristics of asthma in older adults have further revealed variations in cellular composition and function between ages. In particular, age-associated alterations in immune cell expression and function have been identified in older asthmatic patients [96]. One such alteration involves neutrophils, with an increase in airway neutrophils and neutrophilic inflammation with ageing being evident in asthma patients [97]. As predominantly neutrophilic airway inflammation has been identified as a characteristic of a more severe phenotype of asthma [98], this may be a potential explanation for the greater severity of asthma generally evident in the elderly; however, further investigation is required to endorsing an association.

Immuno-senescence, the decrease in immune cell functioning with age, has further been reported in elderly patients [96]. Currently, the impact of immune-senescence on the production of inflammatory mediators secreted by eosinophils, neutrophils and T-cells (including leukotrienes and cytokines) at baseline or during an exacerbation of symptoms is unknown [96]. However, it suggests that age-related alterations in inflammatory cell function may be pathognomonic in allergic asthma [96]. Immuno-senescence may further decrease the ability of older adults to clear viruses efficiently, contributing to greater and more prolonged inflammation and greater severity of symptoms and rates of comorbidity [96]. However, further research is required to prove an association.

More progressive, irreversible disease processes exhibiting greater degrees of fixed airway obstruction have further been noted in elderly asthma patients in a review exploring 242 asthmatic patients over 65 years of age [99]. This has been suggested to be due to more severe airway remodelling, chronic inflammation and bronchiectasis in the elderly population [99].

Regardless of the particular asthma phenotype expressed by the patient, longitudinal studies of asthmatic populations have revealed that remission from asthma is uncommon in older age groups [100]. In contrast, remission of asthma symptoms may occur in as many as 60-70% of children and adolescents, particularly in their second decade of life [101]. As such, greater consideration into continuity of care and prolonged asthma management support may be required in such populations.

3.1.3.2 Asthma Severity

There is a growing body of evidence that the degree of asthma severity most likely to be demonstrated by a certain population may vary with age, with numerous investigations revealing relatively greater instances of symptom frequency or severity in older adults [102, 103]. The Cardiovascular Health Study, a prospective investigation, examined the prevalence and impact of asthma or wheezing in a cohort of 4581 community-based patients over 65 years of age via provision of an asthma questionnaire [104]. The investigation revealed that respiratory symptoms were more prevalent in older asthmatics. In this cohort, patients over this age threshold demonstrated a two to five-fold increase in the presentation of cough, phlegm, wheezing and dyspnoea [104]. Greater rates of bronchial hyper-responsiveness and hyper-reactivity have further been noted in older adults relative to their younger counterparts [103].

3.1.3.3 Hospitalisations

Variations in hospitalisation rates, separations, and durations of stay have further been apparent with regards to age, displaying evidence of deficits in efficacy in asthma management in older adults with regards to reductions in hospitalisations. In the United States, hospitalisation rates in older adults have been documented to be greater than twice that of persons of 15-34 years of age (25.6 vs 10.0 hospitalisations per 10 000 patients, respectively) [83].

The duration of hospitalisations has further shown a direct proportionality with increasing age [105]. In 2007-08, the average length of stay in hospital in 2007-08 for patients admitted to hospital with a principal diagnosis of asthma was greater in those aged over 45 years of age, documented at 4.3 days relative to 2.2 days for all patients [83]. Continuations of this trend amongst those aged over 45 years of age have further been evident, with the length of stay of hospitalisations amongst those greater than seventy years of year being almost twice that for those aged 45-54 years of age [83].

These trends have partly been attributed to a combination of various physiological and socioeconomic factors. According to Diette et al. (2002) [106], older patients are more likely to demonstrate a greater prevalence of risk factors predicting hospitalisation, including a greater number of respiratory symptoms, inferior general health, and limited education. Increased comorbidities and the delayed pace of recovery with age have further been postulated as contributing factors [107]. In a survey by Hanania et al. (2011) [103], the presence of co-morbid

COPD, a chronic condition predominantly evident in those over 55 years of age, further increased the risk of an asthma-related hospitalisation in Medicare patients by 3.6 times relative to the general population.

Older adults have further been identified to typically experience an inferior rate of recovery from asthma exacerbations relative to their younger counterparts [108], exhibiting a reduced response rate to salbutamol treatments administered in the emergency room [109], and requiring admittance into hospital (see below). The greater incidence of more severe asthma in older adults [110, 111] may further contribute to their relatively greater rates and durations of stay in hospital [106]. As such, there appears to be great discrepancies in both the frequency and length of hospital admissions in older adults with asthma.

3.1.3.4 Mortality

Of concern, investigation of hospital autopsy reports indicate that deaths where the primary cause is documented as 'asthma' do not display an even distribution over the age spectrum, but are highly over-represented by the older adult population. Of concern, in 2022, deaths from asthma were greatest in those 85 years of age and older at 39 per 100,000 population [17].

Of further concern, older adults were further identified to have been more vulnerable to the recent increase in asthma-related mortality rates relative to other age demographics. Examination of national reports indicates that the increase in asthma-related mortalities evident in 2006 which occurred after the sustained decline from 1995-2005 was particularly evident amongst those at least seventy years of age [83]. In particular, reports indicated that female asthma deaths in those at least seventy years of age in 2006-07 approached those prior to 1995 levels, when asthma-related deaths were at their prior peak reading [83]. This is particularly of concern, in that such patients had been evidenced to experience a greater overall decline in asthma-related mortality than other age demographics in the previous decade, and potentially indicates deficits in asthma diagnosis and/or adherence to or efficacy of asthma management guidelines.

Asthma is further acknowledged as a risk factor for mortality from certain medical conditions in older adults. In patients 55-69 years of age, COPD or bronchiectasis were evident in 13.2% of all deaths in 2006, greater than twice the proportions that the two conditions were listed as a cause of death where asthma was not also a cause (4.9%; 95% CI 4.8-5.1) [83]. This suggests that mortality from asthma is more likely to be associated with COPD or bronchiectasis than mortality from other causes.

3.1.4 Asthma Management Issues in Older Adults

3.1.4.1 Diagnosis

There is growing evidence that asthma is widely underdiagnosed in older adults, delaying access to appropriate management. Whilst the prevalence of asthma appears similar in older and younger adults (4% to 9%) [112, 113], recent investigations have revealed that significant proportions of patients aged at least fifty-five years of age have undiagnosed asthma, with estimations of under-diagnosis rates approaching at least 15-50% of patients in such populations [114].

International reports indicate that under-diagnosis of older adults is a global issue. In the United States of America, the Cardiovascular Health Study [115] revealed that, even when smokers and individuals with congestive heart failure were excluded, at least 15% of patients with asthma-like symptoms had not undergone proper investigation. In England, a cross-sectional survey of 6000 residents over 65 years of age not prescribed asthma therapy, further reported an estimated population prevalence for untreated asthma of 1.7%, despite the majority (84%) of participants having moderate or severe disease as per spirometric parameters [116]. It further elucidated that a history of wheeze and breathless or a past history of doctor diagnosed asthma were the most likely predictors of unmanaged asthma [116].

Of concern, underdiagnosis may contribute to significant ramifications with regards to asthma management in older adults. One such aspect includes delayed access to timely and therapeutically appropriate treatments. Lack of awareness of a patient's medical history may further promote underestimation or misrecognition of the severity of an acute exacerbation by medical practitioners, in turn increasing the risk of reference to guidelines not applicable to the particular patient [117].

Omission of a clinically applicable diagnosis of asthma may further increase the risk of patient harm by delaying the implementation of interventions designed to reduce exacerbation risk or progression of the condition. For example, medical practitioners may not be aware of the requirement to avoid the prescription of medications which may increase the risk of bronchoconstriction in such patients, for example, non-steroidal anti-inflammatory drugs (NSAIDs) and non-selective β-blockers such as propranolol, nor may formulate and provide asthma management plans to these patients. Delay of prescription of preventative medications, where indicated, may further increase the risk of more frequent or severe exacerbations, increasing the risk of hospitalisations and the cost of asthma management on the healthcare system. Similarly, patients may not receive the self-management education required to avoid the risk of exacerbations, for example, identification and avoidance of triggers to exacerbations, and appropriate sources of patient care. Underdiagnosis of asthma in the older adult population therefore represents a significant issue potentially delaying access to care, increasing the burden of disease.

A multitude of factors have been postulated to contribute to the high rates of under-diagnosis of asthma in older adults. These include both patient- and physician-attributed factors.

Compared with younger patients, older patients with asthma tend to present for medical care after years of symptoms and with more severe obstructive lung disease [88]. One reason is that older adults may not detect that they are experiencing dyspnea and broncho-restriction as clearly as younger adults [88].

Age-related cognitive impairment may further delay recognition of symptoms due to a reduction in the ability to process new information. Studies further indicate that older adults are less likely to associate symptoms of asthma as part of an active disease process, but are more likely to attribute them to part of the normal ageing process, delaying self-referral to licensed medical practitioners for appropriate investigation and management [103]. The non-specificity of certain symptoms such as wheeze, dyspnea, chest tightness, and cough can further contribute to the delayed diagnosis of asthma in older adults. These symptoms can emulate those characteristic of several other conditions more common in older adults, including Chronic Obstructive Pulmonary Disease (COPD), heart failure, emphysema and chronic bronchitis, chronic aspiration, GERD, tracheobronchial tumours, and obesity [88]. This can lead to greater complexity and ambiguity in the diagnostic process, potentially delaying the diagnosis of asthma in older adults.

Psychosocial and socioeconomic factors in older adults may further contribute to increased rates of underdiagnosis of asthma. Many elderly patients are fearful of having an illness and dying, and may be reluctant to admit they are having symptoms [95]. Underreporting of symptoms in the elderly may have many causes including depression, cognitive impairment, social isolation, and denial [88]. Reduced access to healthcare by older adults with lower socioeconomic status may further result in a delay in reporting symptoms to their GPs [92]. Social isolation and the knowledge and beliefs of older adults may also bar doctors from gauging the severity of an acute asthma flare-up in this population [105].

Under-diagnosis of asthma in older adults may also be resultant from gaps in knowledge in doctors in the differences in asthma between older and younger adults, and the unique care needs of the older adult population [95]. In particular, doctors may not be familiar with the symptoms and risk-factors for the different phenotypes of asthma typically present in older adults; may have difficulty distinguishing between symptoms of asthma and age-related pulmonary decline or other medical conditions, such as COPD; and may underutilise diagnostic tools such as spirometry and lung function testing in the elderly [95, 118]. Therefore, under-diagnosis of asthma in older adults is a significant issue in society.

3.1.4.2 Pharmacotherapy and Treatment

3.1.4.2.1 Suboptimal response to pharmacotherapy

Of concern, there is a growing body of evidence indicating that older adults may exhibit variations in the manner in which they respond to certain types of pharmacotherapy [90]. In particular, alterations in the time required to attain a peak clinical effect, the maximal peak response able to be attained, and the ratio of adverse effects to clinical outcomes demonstrated for certain pharmacological agents may vary in this age demographic [90, 119, 120].

Numerous discrepancies have particularly been identified for β_2-agonist bronchodilator therapy. In a prospective cohort study exploring the responses of 2064 patients presenting to emergency departments in North America with acute asthma, patients at last fifty-five years of age demonstrated the smallest change in PEF after treatment with emergency bronchodilators, with the age difference being unexplained by differences or intensity of therapy [109]. Connolly et al. (1992) [121] further compared the broncho-dilatory effects of salbutamol following methacholine-provoked bronchoconstriction in healthy young (age 20 to 36 years) and elderly (age 60 to 76 years) volunteers. The investigation identified an impaired bronchodilator response to a beta$_2$-adrenergic agonist, and a significant increase in the time course for recovery after salbutamol therapy in elderly subjects to reverse the same degree of methacholine-provoked bronchoconstriction relative to their younger counterparts (ANOVA - F_8,180 equals 41.23, p = 0.004) [121] .

Factors such as the greater degree of airway remodeling and more severe bronchoconstriction typically presented by older asthmatic patients; increased sympathetic system activity, reduction in adenyl cyclase responses, and reduction in β_2-adrenergic receptor number and affinity with ageing; increased use of concurrent medications, such as β-blockers, that could interact with or diminish the response to bronchodilator therapy; and the presence of more comorbid conditions (e.g., COPD), leading to an overall worse clinical status, could all contribute to this effect [121].

With regards to the efficacy of newer agents on the market, there is also concern that some trials actively exclude older people [122] or people with certain comorbidities [123] or asthma severity [124], limiting the information able to be gained from clinical trials with regards to medication efficacy in older adults.

3.1.4.2.2 Adverse effects and Inferior Pharmacodynamic Effect

The pharmaco-therapeutic management of asthma is further complicated in older adults on account of the increased prevalence of a multitude of other medical conditions potentially affected by asthma medications in this age demographic [125]. In particular, asthma drugs may worsen the management of comorbid conditions, on account of their adverse effect profile. Of concern, both long and short-acting β2-adrenoceptor agonists may cause adverse inotropic and chronotropic effects that may increase the risk of arrhythmias and cardiomyopathy, and may worsen or induce myocardial ischaemia or cause electrolyte disturbances that may contribute to arrhythmias [125, 126]. Adverse effects such as arrhythmias, tremor, hypertension and hypokalaemia may further be of increased likelihood in older adults on account of differences in the pharmacokinetic profile of such patients, in particular, the rate at which they eliminate or clear drugs [125].

Theophylline consumption has further been implicated with deteriorations in the management of pre-existing medical conditions more frequently evident in older adults [125]. Of concern, theophylline has a narrow therapeutic index and range of doses in which its clinical benefit to risk profile is considered optimal. This is a significant issue in the older adult population, with reductions in the hepatic and renal clearance of the agent noted in as many as 22-35% in elderly patients being evident in the literature [125]. As such, theophylline may worsen GERD, arrhythmias, tremor and insomnia in older patients [125]. In addition, the risk of drug-drug interactions with theophylline is often heightened in the older adult population, on account that many of the interacting agents, such as calcium channel antagonists, anticonvulsants and histamine H_2 receptor antagonists, are often used in the older adult population. As such, older adults are at greater risk of experiencing drug-drug interactions with theophylline, compromising their safety [127].

Due to reductions in metabolism and drug elimination in older adults, chronic use of anticholinergic drugs, such as ipratropium bromide, may result in numerous side effects increasing the drug burden index in older adults [125, 127]. It may also cause urinary hesitancy and constipation, and potentially exacerbate glaucoma, all of which may significantly affect older adults [127].

Corticosteroids may also exacerbate a broad array of medical conditions which older adults may already exhibit or be prone to, on account of their age. These includes diabetes, osteoporosis, cataracts, hypertensions, osteoporosis, vertebral fractures, skin thinning, and bruising [88] [105]. Inhaled corticosteroids have also been reported to increase the risk of cataract formation, and oral corticosteroids increase the risk of posterior subcapsular cataracts [127].

Variations in the physical structure and functioning activity of pulmonary tissue in older adults may further potentially cause deviations in the maximal therapeutic responses attainable from licensed therapeutic agents in the pharmacological management of asthma. Of concern, evidence indicates that the physiological production, expression and function of β_2-selective adrenoceptor agonist proteins in the pulmonary tissue declines with age. There is a growing body of evidence that lymphocyte membrane receptors, despite exhibiting normal densities in the pulmonary tissue in the elderly, demonstrate reductions in agonistic affinity [120]. Alterations in the pharmacokinetic profiles of older adults due to ageing with regards to drug absorption, distribution and metabolism may further contribute to these inferior clinical outcomes.

3.1.4.3 Under-treatment

3.1.4.3.1 Asthma Action Plans and Self-management of asthma

Of concern, Australian studies indicate that older adults are less likely to be provided with WAAPs by health providers, despite evidence that they are protective against both asthma morbidity and death [92, 105]. Between 2007 and 2010, WAAPs were provided to adults in only 1.9% of asthma encounters with GPs, a proportion less than half that of the 5.4% of encounters with children in which WAAPs were provided [128].

This could lead to specific ramifications in the amount of education and self-management skills a patient may have, as reflected in the international setting [106]. In an investigation by Diette et al. (2002) [106], 40% of older asthma patients reported that they did not feel they had sufficient education on how to manage an acute flare-up, avoid asthma triggers, or adjust their medications according to their current level of asthma severity. In addition, the majority did not own a peak flow meter, and a further 29% of those who did were not aware of how to respond in the case of a low peak flow reading. Furthermore, older patients were less likely to rate knowledge regarding how to manage a severe flare-up as excellent (12% vs 23%, $p<0.001$) [106].

In a prospective cohort study of 6590 adults with asthma in 15 managed care organisations in the United States [106], older patients were more likely to report having been told all they needed to know about what to do during a severe flare-up (61% vs 49%, $p<0.001$), but were less likely to rate this knowledge as excellent (12% vs 23%, $p<0.001$) [106].

Of concern, Australian interventions recognising the value of more regular GP review of patients with asthma have been unable to achieve substantial utilisation in the Australian healthcare system, predominantly because patients do not attend sufficient sessions for education to be completed [129].

A further concern regards the strength of the evidence with regards to how effective current educational strategies in this particular age group may be [130]. Of concern, limited educational programs have been conducted in solely the older adult population [130]. Therefore, it is unknown how effective these strategies are in improving asthma outcomes in older adult populations [130]. Thus, further investigation of the constituents of an effective educational strategy in older patients with asthma is required to improve asthma outcomes in this population [90, 130].

3.1.4.3.2 Quality of the consultation

In an investigation by Bauer et al. (1997) [131] examining the use and characteristics of health services used by a cohort of 102 elderly patients with asthma, the quality of care provided within the consultations was further considered suboptimal. Diagnostic efforts were documented to be performed with lower intensity than that recommended, and the efficacy of treatments, for example with serial peak flowmeters of other pulmonary tests, was also documented to be low [131]. The number of pulmonary function tests reports available was also observed to decline from age from 39% (24/61) in patients aged 65 to 74 years, to 23% (7/30) in patients aged 75 to 84 years, to 0% (0/7) in patients aged 85 years or older, and were only available in less than one third of older adult patients overall [131].

3.1.4.4 Adherence to prescribed asthma management plans

Poor adherence to asthma medication management plans is gaining increasing significance as a reason for suboptimal clinical outcomes in older adults. Of concern, low adherence to anti-asthmatic treatment is considered common in elderly patients, with investigations estimating that only 9-21% of such patients demonstrate high adherence to therapy [132]. A number of investigations further indicate that elderly patients are more likely to experience physiological or cognitive barriers to adherence than their younger counterparts.

A review of the literature has revealed numerous factors affecting adherence to asthma management plans. These include:

3.1.4.4.1 Self-perceptions of Asthma Severity

A number of studies have shown evidence of a direct relationship between the severity to which they perceive their condition to be, and the degree to which they are adherent to their asthma management plan [133, 134].

In an investigation by Adams et al. (2003) [134], it was suggested that one's perception of how severe their condition was could influence the extent to which they were adherent to their preventer therapy.

Ulrik et al. (2006) [133], in an exploration of patient factors affecting adherence to ICS controller therapy in adult asthma patients further identified a lack of perceived symptoms to be the predominant predictor of non-adherence. In a further investigation, it was identified that lower levels of both intentional and accidental non-adherence to ICS therapy were apparent in patients who graded their asthma to be severe, as opposed to mild or moderate ($p < 0.005$). Having a fixed daily routine was identified to be the predominant reason for patients with severe asthma, unlike in those with mild asthma, for whom this was evident for only 41% of patients ($p < 0.01$) [133].

In the Asthma Beliefs and Literacy in the Elderly (ABLE) cohort study [135], 57.0% of the older adult patients with asthma further exhibited poor adherence to daily controller therapy, with a *"no symptoms, no asthma"* mindset being demonstrated by 58.7% of the poorly adherent group [135] .

3.1.4.4.2 Asthma Medication Regimen Complexity and Cost of Medications

A multitude of studies across a range of chronic health conditions have identified associations between patient adherence and certain characteristics of their prescribed treatment regimen [136, 137]. Generally, poorer adherence has been associated with extended or complicated treatment regimens, with medication regimens placing greater interference on a patient's lifestyle typically being less likely to be adhered to [136, 137]. In an investigation by Gray et al. (2001) [138], polypharmacy and higher medication use were further significantly associated with poorer levels of adherence, with the likelihood of non-adherence increasing by 16% for each one-unit increase in medications that a person was taking [138].

Polypharmacy and elevated treatment complexity is a particular issue in older adults [139]. In consequence of the more severe phenotypes of asthma often evident in older adults, older patients may be more likely to be prescribed greater quantities of pharmacotherapy, as per the advice of international guidelines [10] to consider use of add-on therapies for the management of more severe symptoms. In addition, the prevalence of certain comorbidities or other medical conditions, such as COPD [140], further tend to be more commonly evident in older adults, leading to the use of greater quantities of medications. This is on account that the treatment of multiple conditions may require medications to be taken multiple times per day, presenting both pharmacological and adherence risks. In an investigation by Stoehr et al. (2008) [141] , use of a higher total number of prescription drugs (at least 5), was significantly negatively associated with adherence (AOR 0.45; 95% CI, 0.21-0.99, p=0.04) [141]. Further literature has identified clear associations between more complex dosing regimens and poorer adherence [142].

In addition, the increased financial burden of such treatment plans may further increase the risk of non-adherence in elderly patients. Throughout the literature, strong associations have been identified between the cost of prescribed medications and their underuse in society [105]. In an exploration of medication adherence in 380 low-income elderly patients in Chicago, only 18% were identified to be adherence to their medications; of concern, this low level was predominantly due to the expense associated with their purchase [143]. Stevens et al. (2003) [144] further revealed that patients who lacked medical insurance and had to pay for medications themselves were more likely to report delaying or failing to fill a prescription, and to take less medication than that prescribed to ensure the longevity of the medication. The methods used, including intentional underuse of inhaled corticosteroid therapy, have further been identified in financially developed countries such as Australia where substantial government financial support for medication exists [105, 144].

Of further concern, financial status and the increased financial burden of treatment in the elderly has further been elucidated to impact clinical outcomes and asthma severity. In an investigation by He et al. (2021) [145], it was identified that the risk of hospitalisation from non-adherence was greatly increased (OR 8.3) in older adults aged at least 65 years of age who had a middle income level ($10000-$15000) (p=0.02), relative to those with a high income level ($150000-$20000) (OR = 0.002) (p=0.02) [145]. On account that older adults typically demonstrate a lower socioeconomic status than their younger counterparts, as based on employment levels, there is significant concern of impacts on asthma outcomes in this age group.

In Australia, the financial cost of asthma medications may further be a factor affecting adherence to asthma pharmacotherapy, with evidence that 52.9% of adults are under-using asthma treatment due to cost [146]. In 2009, it was further identified that ICS prescriptions were dispensed to concession-card holders (i.e., those paying a lower copayment for their medication), than general patients [147], additionally implying that cost could be a barrier to the purchase of ICS in those with obstructive lung disease (independent of socioeconomic status).

Whilst there is currently no direct evidence that older adults cannot afford ICS in Australia, considerations inclusive of a potential reduction in income in this age group warrant further study of the impact of older age on one’s ability to afford ICS. Further research could explore the impact of older age on the ability to afford asthma medication, taking into consideration complex factors such as accumulated net wealth, concession or health card status, and employment status.

3.1.4.4.3 Physical Status and Comorbidities

The increased prevalence of specific medical conditions in older adults may further increase their risk of non-adherence to asthma medications. One issue is that of vision loss and cognitive impairment. In a report by van Eijken et al. (2003) [148], adherence levels have been claimed to vary from 26-59% in the older adult population, due to the impact of vision loss and cognitive impairment on their ability to use medications and devices correctly. Older patients may further be more vulnerable to incorrect use of medication resultant from vision loss and cognitive impairment, as these may affect their ability to select the appropriate medication, read the directions for us and any further supplementary written material, and assemble and use their inhaler devices correctly [105].

Age-associated cognitive impairment may further increase the risk of older adults displaying non-adherent behaviours. Difficulties with learning new information regarding the purpose, directions of use and technique with a device or particular asthma management regime may cause older adults with cognitive impairment to experience issues with the use of any inhaler or device that requires multiple separate steps. In an examination by Gray et al. (2001), underadherence, defined as the demonstration of less than 70% compliance for at least one medication, was significantly associated with poor cognition (Mini-Mental State Examination score <24, AOR 2.5, 95% CI 1.02-6.10) [138]. Similarly, an observational cross-sectional survey assessing medication adherence and self-reported management of medication in 343 patients at least 65 years of age identified significant associations with higher levels of adherence and superior executive function (AOR 3.25; 95% CI 1.13-9.33, p=0.03) [141].

Fluid ability, or the ability to gain and apply new skills, has further been significantly associated with adherence (OR, 1.89; 95% CI, 1.30-2.75), DPI technique (OR, 2.52; 95% CI, 1.59-3.98), and MDI technique (OR, 1.57; 95% CI, 1.15-2.14) in multivariable models. In contrast, crystallized ability, or the ability to draw upon previous knowledge, has been identified to be a significant independent predictor of controller medication adherence (OR, 1.05; 95% CI, 1.00-1.10) and DPI technique (OR, 1.17; 95% CI, 1.08-1.26) but not MDI technique (OR, 1.03; 95% CI, 0.99-1.07), in such models [149].

Poor recollection of instructions has further been identified to be a major contributor to non-compliance, as was identified in a study of 70- to 97-year-old patients discharged after a hospital admission for heart failure, in which 27% were noncompliant after 30 days despite having received written instruction on account of this issue [150]. Reduced cognitive function has further been partly associated with poor medication behaviours and lower levels of health literacy, or ability to understand and apply health directions [149].

Finally, issues pertaining to deteriorating mental health status, depression, and social isolation may further reduce access to medical care and medication supplies, affecting one’s ability to access medication supplies, and therefore, their level of adherence [142].

3.1.4.4.4 Patient beliefs about asthma medications

Whilst most patients with asthma take their reliever and controller medications when symptomatic, due to the immediate connection drawn between taking medication and symptom relief, continued adherence generally becomes difficult for the majority of people with asthma once symptoms have resolved [151].

Patients who are concerned about using corticosteroids may under-dose or discontinue long term use in an effort to be steroid-sparing [92]. Of concern, there is a substantial fear of corticosteroid side effects in the older adult population [92]. This fear is further greater in those with asthma than those without, and may the risk of non-adherence [92]. These fears are emphasised by the increasing frequency of cataracts and osteoporosis in this age-group [117, 130].

In an investigation by Chambers et al. (1999) [152], the most frequently cited reasons for discontinuation or erratic use of ICS were concerns about adverse effects and perceived lack of efficacy about treatment. Using pharmacy records, they identified an association between non-adherence and a patient's perceived need for their ICS relative to their concerns about potential adverse effects. In addition, a significant negative association was further identified between adherence to therapy and concerns about adverse effects of medications [152]. This suggests that these can have a major influence on patient attitudes and behaviours with regards to taking asthma medications, and should be a particular focus during asthma consultations [153].

3.1.4.4.5 Family support

Adherence to asthma medications may further be affected by one's access to social and family support [154]. In a study exploring the impact of family support on medication taking, it was identified that patients who actively solicited family support were more likely to adhere to psychiatric medications than those living alone [155]. This has been reflected in the asthma setting, with an 8-week pilot study conducted on older adults (mean age 81.6 years) with poorly controlled asthma and comorbidities identifying improvements in lung function in patients who were given assistance by caregivers in using ICS therapy effectively [156]. As older adults may be more likely to live alone, they may be at increased risk of poor asthma outcomes consequent from non-adherence, suggesting that they are an 'at-risk' group.

3.1.4.4.6 Health Literacy and Education

Of concern, the level of patient health literacy may influence numerous aspects of patient care. Health literacy is defined as "the degree to which individuals have the capacity to obtain, process and understand basic health information and services to make appropriate health decisions [157]." In particular, inaccurate beliefs, poor adherence, and incorrect inhaler technique have been identified to occur more frequently in those with poor health literacy [157-159].

In multivariable models, adequate health literacy has been identified to be significant independent predictor of adherence to controller medication (OR, 2.30; 95% CI, 1.29-4.08), correct DPI technique (OR, 3.51; 95% CI, 1.81-6.83), and correct MDI technique (OR, 1.64; 95% CI, 1.01-2.65) [149]. In further studies, lower levels of health literacy have been associated with poor adherence in unadjusted analyses, suggesting that an adequate level of functional health literacy is required to achieve successful medication adherence [160].

To date, there is currently concern that many information and instruction leaflets are prepared in language that is too difficult for the majority of patients to understand. As such, it is essential to be cognizant of the patient's level of education, cultural background, and literacy skills when providing information, to ensure their adherence to their asthma medications is not compromised [161].

3.1.5 Social Determinants of Health and Older Australians

Of concern, there are a number of social determinants of care which place older adults at higher risk of poor asthma outcomes. These include the following issues:

3.1.5.1 Health literacy

Currently, there is evidence that the majority of Australians with inadequate health literacy are aged 65-74 years of age [162]. Of concern, this may increase their risk of experiencing poor asthma outcomes by potentially reducing their adherence to their asthma medication regimen (see section 3.1.4.4.6)

3.1.5.2 Reduced Social Support

Recent data from the Australian Bureau of Statistics indicates that older adults aged 85 years and older being more likely to live alone (35%) than other age groups [163]. This may potentially result in reduced levels of social support if they do not have access to adequate care arrangements (for example, visits from family or carers), potentially reducing their access to healthcare providers in the event where they cannot transport themselves to medical appointments or pharmacies.

It may further result in reductions in support with medication use for those with poor health literacy or physical issues affecting hearing, sight, and cognition, in the event where they are unable to gain support from carers. In turn, this may affect medication adherence, as discussed in Section 3.1.4.4.5.

3.1.5.3 Socioeconomic status

As will be discussed in Section 3.2.3.2, below, older adults in Australia typically demonstrate lower levels of household income than younger adults, and are more likely to be in the lowest 40% of income distribution [164]. This could potentially contribute to a greater risk of not being able to adhere to medication regimens due to affordability concerns (see Section 3.1.4.4.2) or attend training sessions on inhaler device use (see Section 3.2.3.2).

3.1.6 Concluding Remarks

In light of all this information, there is sufficient reason to believe older adults with Australia are significantly likely to be at high risk of poor asthma outcomes. The next part of this chapter will explore a significant factor associated with poor asthma outcomes, the demonstration of correct inhaler technique, and the current information available regarding the level of risk older adults demonstrate with regards to using their asthma inhalers correctly.

3.2 Older Adults and Asthma - Inhaler Technique

Accurate inhaler device technique is essential to the attainment of optimal clinical outcomes by asthma patients [10]. The practice of accurate inhaler technique requires the integration of several aspects of patient care, being patient education, ongoing retraining and re-assessment of inhaler technique by trained healthcare professionals, regular use of the device, the ability to coordinate breathing manoeuvres with hand coordination in the use of the device, and the ability to retain information and/or access and understand information provided to the patient, such as written instructions, for future information [2].

Of concern, older age is increasingly gaining recognition as a potential risk factor in the demonstration of inferior inhaler technique [165, 166]. A significant body of literature comparing the frequency of errors in inhaler technique in older adults and the general adult population has suggested that the incidences of errors in elderly patients across a range of inhaler devices may be statistically greater than that evident in younger patients [167]. These devices include both the more frequently prescribed pMDIs [36, 167, 168], and the more recently developed DPIs [165, 169]. Thus, the impact of this could affect a significant proportion of patients, or potentially remain unrecognised.

A number of physical, cognitive, and social, and socioeconomic factors unique to or more highly evident in the older adult population could potentially place them at greater risk of poor inhaler technique relative to the younger adult population, to be discussed below.

Whilst these may be more predominant in the older adult population, as to be discussed below, a key concern is that older age in itself may not necessarily be the sole cause of such issues(i.e., in the event where an older adult is experiencing optimal health, mobility, high health literacy levels, a strong financial position, and optimal access to healthcare). Rather, and particularly in the case of those who have had asthma for an extended period of time (for example, since childhood), loss of inhaler technique skills in older adults is considered to be most likely a consequence of loss of maintenance, assessment, and re-training of inhaler technique over time, as opposed to older age in itself [27, 170]. However, older adults may exhibit a number of risk factors not experienced in the younger population which may increase their risk of poor inhaler technique and suboptimal clinical outcomes with regards to their asthma. This next stage of the literature review will explore such risk factors.

In particular, a review of the literature reveals that older adults may be at greater risk of the following aspects of poor inhaler technique:

3.2.1 Increased frequency of inhaler technique errors

Older adults exhibit a number of biophysical differences in their anatomy and physiology relative to younger adults (to be discussed below), which may potentially increase their risk of performing a greater number of inhaler technique errors. These include the following:

3.2.1.1 Age-related reductions in muscle strength

Older adults may experience a range of age-associated declines in physical functioning and muscle strength in consequence of reduce anabolic activity, muscle tone, and mass [171], affecting the ability to use pMDI devices appropriately [166]. A primary consideration is that of hand strength. In an investigation by Armitage and Williams (1988) [166] of the ability of 45 elderly patients to generate the minimum force required to fire an inhaler, 36% of patients could not generate the minimum force required to fire any inhaler, and only 29% could generate the hand force required to actuate all MDI inhalers [166]. This correlated with their ability to activate an MDI, suggesting that inadequate hand strength may contribute to non-activation of the device.

Gray et al. (1996) further identified hand strength to be a predictor of correct MDI technique in patients with sufficient strength for actuation of the pMDI canister [172]. Although the mechanism by which decreased hand strength may interfere with the ability to use an MDI correctly was not identified, it was postulated that it could interfere with the coordination of inhalation with device activation. For example, the patient may be preoccupied with canister activation rather than on inhalation coordination, contributing to the delayed activation of the device. As such, inadequate hand strength may be a contributing factor to the two errors for which elderly patients were most likely to present with errors relative to the adult population, delayed and non-activation of the pMDI device.

Patients with arthritis or medical conditions affecting fine motor movement may further experience more difficulty with timely actuation of pMDI devices, as opposed to issues such as breath-holding, thus affecting the results [173], whilst those with neuromuscular disease affecting signalling from the brain to the muscles, for example, dyspraxia, may further experience handling or inhalation problems. [174]. In consideration that these conditions are overrepresented in the older adult population [175, 176], this could potentially contribute to the increased likelihood of older adults presenting these errors.

3.2.1.2 Age-related reductions in peak inspiratory flow (PIF)

Advanced age has further been elucidated to be an independent predictor of the ability to generate the PIFs required for optimal clinical outcomes from certain DPI devices [177], potentially adversely affecting disease severity and management in this cohort [177]. In an investigation by Jarvis et al. (2007) [177] in a cohort of older adults of mean age 73.5 years (range 65-89 years) with varying severities of COPD, a significant negative correlation between advancing age and the PIF rate able to be attained when using an In-Check Dial set to the resistance setting of a TH was identified (r=0.84m p<0.0001) [177]. Stepwise, multivariate linear regression further confirmed that age in itself was an independent predictor of PIF, with decreased PIF rates observed with increasing age independent of the disease state of the patient [177].

The group was further able to develop a formula for estimation of the PIF of a patient of a particular age, with estimated PIF (PIF_{est}) equating to: PIF_{est} = 66.8 – 1.498(age)(for mild COPD), -13.4 (for moderate COPD) and -21.24 (for severe COPD) [177]. This translated to concerning clinical implications, with only one quarter of the study participants demonstrating the ability to generate the minimum recommended PIF of 30L/min for minimal clinical response from the TH device. Of further concern, only one patient could generate the recommended minimum PIF of 60L/min required for optimal clinical outcomes, indicating that older age could be an inhibitory factor in the attainment of optimal clinical outcomes from the TH device [177].

A number of studies have further provided evidentiary support of a negative correlation between PIF and age culminating in clinical impacts with the TH device [178, 179]. Nsour et al. (2001) [178], in an exploration of the PIF of seventy-four older adults of mean age 79.7 years with COPD and prescribed a TH, similarly reported that the majority of participants could not generate the optimal inhalation rate of greater than 60L/min required for optimal inhalation and attainment of the nominal dose. Of concern, only 6 out of 74, or 8% of patients, demonstrated the ability to inhale through the TH at a rate of > 60L/min [178].

Similarly, in an investigation examining PIF rates in a cohort of 40 elderly subjects 70-87 years of age, Janssens et al. (2008) [179] revealed that the PIF able to be attained by a patient using an In-Check Meter set to the resistance levels of the Aerolizer, Diskus and TH devices significantly correlated with age (r=-0.5, p<0.005). Whilst this did not lead to variations in the ability to attain a therapeutic outcome from the Aerolizer and Diskus devices, it did identify a clinical impact with the TH device [179]. In particular, 12.5% (n=5) of the TH users were not able to generate the minimal required flow for therapeutic activity, and only 70% (n=28) of patients able to generate the PIF of at least 45L/min arbitrarily set by the investigators as the threshold for net, rather than maximal, therapeutic flow through the device [179].

In contrast to Janssens et al. (2008) [179], Kamin et al. (2003) [180] further identified that as many as 31.5% of older patients (60-99 years) could not obtain the required airflow required for attainment of a therapeutic effect from the Diskus [180]. Although variations in the study design (sample size, etc), and assessment of inhaler technique could have contributed to these variations, it provides initial insight that further investigation of the PIF of older adults may be required prior to prescribing the Diskus. They further identified that this may be an age-dependent effect, in that the figures approached twice that evident in the 16.7% of patients 18-59 years of age [180].

Examination of age-associated alterations in physiological status, functioning, and prevalence of certain conditions provide support for the inferiority of PIF in older adults, indicating that general age-associated declines in muscle strength, and comorbidities potentially at greater incidence in the older adult population, including malnourishment, chronic heart failure and certain respiratory conditions with significantly greater prevalence rates in the older adult population, such as COPD, may contribute to this occurrence and affect the maximal PIF rate able to obtained [181, 182]

3.2.2 Reduced ability to be successfully trained on inhaler technique

The ability to demonstrate correct inhaler technique is an integral predictor of successful inhaler use and attainment of optimal clinical effects [10]. Although the depth of research examining the ability of older adults to be successfully trained in inhaler technique is limited, reports that this may be inferior to that apparent in the general adult population have emerged in the literature [166, 167]. Of concern, Armitage and Williams (1988) [166] identified that whilst 32% of patients at least sixty-five years of age were unable to develop proficiency in pMDI technique, only 15% of the adult population demonstrated these deficiencies. This difference was further determined to be of statistical significance (p<0.001), despite control of the site of attendance and the training provided by the respiratory physicians [166].

Horsley and Bailey (1988) [167] further noted similar trends when examining pMDI technique in patients seventeen to eighty-three years of age subsequent to instruction by trained investigators [167]. Despite concordance of the trainers to a standardised educational procedure, the inhaler technique scores obtained by older adult patients subsequent to education were identified to be significantly inferior to those of their adult counterparts (p=0.012). Of further concern, the investigators elucidated that older patients became more recalcitrant to instruction than their adult counterparts (p=0.012) [167].

In consideration that the study design of both examinations involved maintenance of consistent educational procedures, including use of standardised procedures, inhaler technique checklists, assessors, assessor training programs and conditions of assessment, these suggest that the educational needs of patients of elderly patients may significantly differ to that of adults. Implementation of educational sessions individualised according to the type of inhaler prescribed, rather than the age of the patient, may bar the maximal improvement in inhaler technique able to be attained. This thus establishes a demand for the development and implementation of individualised training programs able to satisfy the particular learning requirements of these differing age groups in the education of inhaler technique.

This may be due to a myriad of age-related cognitive, physical, and socio-economic barriers to learning particularly evident in the elderly population, including the following:

3.2.2.1 Cognitive Function

A primary concern in the literature is that of cognitive function. Cognitive functioning may be defined as "the performance of the mental processes of perception, learning, memory, understanding, awareness, reasoning, judgment, intuition, and language [183]." Thus, a certain degree of cognitive function is essential in not only the accurate determination of the correct sequence of steps for inhaler use, praxis in device use, and judgement to determine which inhaler to use when multiple therapy is indicated, but in the active intake and recall of new skills [184].

This aspect of cognitive function, referred to as fluid intelligence, assists in the active processing and analysis of new information in which prior knowledge is of limited assistance, as may occur in an educational session for a new inhaler device. It may further affect processing speed, working memory, and executive functioning and global cognitive function, required in the planning and sequencing of steps in inhaler use, and thus, the implementation of acquired skills [185]. In contrast, crystallised intelligence refers to the ability to recall information generally stored in long-term memory over childhood and early adulthood [185].

Of concern, in contrast to crystallised intelligence, fluid intelligence and abilities generally decrease with advancing age [185]. This may result in reductions in short-term memory, concentration, attentiveness, pace and the ability to successfully learn information provided in educational sessions [185].

Numerous studies have reported an association with suboptimal cognitive function and inferior acquisition of inhaler technique skills subsequent to education [186, 187]. In an examination by Allen and Prior (1986) [186] in a cohort of patients 74-89 years of age, it was revealed that only patients demonstrating full cognitive function could successfully acquire the skills required for proficiency in MDI use subsequent to training [186]. Cognitive function had been assessed by an examiner-developed mental status questionnaire (MSQ), a brief, objective, quantitative measurement of cognitive functioning of elderly people in which scores less than seven out of ten were indicative of cognitive impairment. A condensed, ten-point adaptation of the Royal College of Physicians questionnaire, or abbreviated mental test (AMT) (by Hodkinson), the MSQ was selected on account of its extensive use by the department of study, and its consequent acknowledgement as a useful means of detecting impaired intellectual function in elderly patients.

More recent research further supports cognitive function as a significant determinant of the ability to successfully learn proficient inhaler technique subsequent to instruction by trained assessors. Allen (1997) [187] identified the existence of not only an inverse proportionality between the ability to learn inhaler technique and cognitive status, but explicit threshold levels at which nil, half or all patients in a population could be trained in the use of a specific inhaler device, referred to as the 0% (T_0), 50% (T_{50}) and 100% (T_{100}) threshold levels [187]. These were directly proportional to the degree of complexity of the instruction provided, in turn proportional to the complexity of use of the inhaler.

Employing the use of the AMT as a test of cognitive function, the investigators elucidated that the T_0, T_{50} and T_{100} levels associated with successful education in the three-stage technique employed for the inspiration-triggered inhaler (Aerolin Autohaler) were 4, 5 and 7; 5, 6 and 8 for the four-stage technique employed for MDIs with large-volume spacers; and 6, 7 and 8 for the five-stage technique utilised for the standard MDI [187]. With mini-mental test scores of 8-10 being indicative of full cognitive function, 7 and 6 indicative of borderline or mild dementia, respectively, and 5 and 4 indicative of moderate dementia, it provides preliminary evidence that certain levels of cognitive function are required to be successfully trained in the use of certain devices according to established training protocols.

Whilst providing useful guidelines in the assessment of inhaler technique, not all patients with these AMT scores may necessarily display these levels of learning ability. In an investigation by Jones et al. (1999) [188], it was identified that some patients, despite demonstrating normal AMT scores of at least 8, the T_{100} score for MDI technique, were unable to demonstrate proficiency in inhaler technique, despite training and reinforcement. Of concern, these patients were also neurologically intact upon clinical examination, not suffering from any diagnosed neurological conditions. However, when their mental functioning was assessed according to the more sensitive Mini-Mental State Examination (MMSE)/(MMT), which examines global cognitive status, such patients were observed to demonstrate signs of cognitive impairment [189].

On account of its greater power in detecting cognitive impairment in elderly patients, Allen and Ragab (2002) [190] examined the ability of the MMSE to predict the ability of patients to successfully acquire proficiency in MDI technique subsequent to education according to national guidelines. Similarly to the results of Allen (1997) [187], explicit thresholds were apparent at which patients could be successfully trained in adequate MDI technique, with patients demonstrating an adequate inhalation technique (score of at least 6/10) displaying an MMSE score of 23/30 [190]. Gray and Sirgo (1996) [191] similarly identified that patients with an MMSE score less than 24, a score regarded as evidence of probably cognitive impairment, were 3.7 times more likely to demonstrate incorrect technique subsequent to education ($p=0.002$).

Allen et al. (2003) [192] further confirmed the relevance of the MMSE as a surrogate predictor of the ability to learn inhaler technique, and its greater power relative to the AMT. Despite possessing stable, reproducible AMT scores of 8-10 when examined 3-9 days apart, the T_{100} threshold described by Allen (1997) [187], above, 10 out of 29 subjects were unable to demonstrate competence in MDI technique subsequent to teaching. Of these, 9 subjects exhibited an MMSE score less than 24. The examiners further noted that 18/19 of the patients displaying competency in MDI technique demonstrated an MMSE score of at least 24, as opposed to the remaining 1 of the 9 incompetent patients. This difference was of statistical significance ($p<0.01$), thus indicating that the MMSE score of the patient could be used as a predictor of one’s ability to attain successful MDI technique subsequent to teaching when unsuccessful despite being deemed competent according to the AMT [192].

The investigators further identified that the MMSE had greater power than the AMT in predicting one’s ability to successfully attain proficiency in TH upon education [192]. Despite demonstrating stable, reproducible AMT scores of 8-10, as described above, only 9 out of 30 patients were unable to demonstrate competency with regards to TH technique. Of these, 6 patients demonstrated an MMSE score less than or equal to 23, a marker of cognitive impairment. In contrast, all 21 of the competent subjects had an MMSE score of at least 24, as opposed to only three of the incompetent patients. This difference was of statistical significance, signifying the ability of the MMSE to also predict the ability of patients to successfully attain proficiency in TH use ($p<0.001$).

Preliminary evidence has further been provided that MMSE thresholds may further exist with regards to the Handihaler and Aerolizer [193]. In an investigation by Quinet et al. (2010) [193] in 25 COPD patients at least 65 years of age, patients with an MMSE score below 25 were more likely to demonstrate inadequate inhaler technique scores upon education relative to those with scores greater than 25 ($p<0.001$). Whilst providing insight into the impact of cognitive impairment on the ability to learn adequate inhaler technique with regards to the TH, Handihaler and Aerolizer devices, further research is required to assess if these results are reproducible and can be extrapolated to the broader population.

In addition to tests of global cognitive status, the role of frontal cortex, or executive, brain functioning in the acquisition of skills required for successful inhaler technique has further been investigated [192]. Good executive functioning is rapidly gaining acknowledgement as essential in the planning, understanding and correct sequencing of steps required for MDI dosing [192]. It has further been correlated with overall functional performance and other task competencies, including the ability to manage medications, finances, and engage in appropriate self-care behaviours [194, 195].

Investigations examining executive function have similarly identified associations between cognitive impairment and the ability to successfully learn pMDI and TH technique [192]. In an examination by Allen et al. (2003) [192], the EXIT25, a test of executive function validated for use in frail elderly subjects [196], was used to measure executive cognitive function in a cohort of 30 inhaler naïve inpatients with COPD of 75-94 years of age (mean age 85 years). The EXIT 25 classifies patients with scores less than 15 as being of normal cognitive status, and those with scores greater than 15 of being of moderate to severe cognitively impairment [197].

Similarly to the MMSE test, clear threshold levels were apparent for both devices. In particular, all 19 of the competent patients, and none of the 11 incompetent patients, possessed an EXIT25 score less than 15. This difference was statistically significant ($p<0.01$), thus signifying that an EXIT25 score of 15 could accurately be used as a predictor of a patient’s ability to successfully be trained in MDI technique according to the guidelines of the UK National Asthma Campaign.

A similar effect was further apparent with regard to TH technique, with all competent patients and nil incompetent patients demonstrating an EXIT25 score less than 15 ($p<0.01$). This indicates that patients with moderate to severe cognitive impairment according to the EXIT 25 test are unlikely to be successfully instructed in TH technique, despite evidence of full cognitive function according to the AMT test.

Whilst both the MMSE and EXIT25 score may assist in predicting one’s ability to be successfully trained in pMDI and TH use, there is evidence that the EXIT25 may be of greater power in predicting technique. According to Allen et al. (2003) [192], a significant correlation is evident between the MDI technique score of a patient and both the MMSE (r 0.540, $p<0.002$), and the EXIT25 score (r -0.703, $p<.0001$); however, the stronger level of statistical significance associated with the EXIT25 score places it as the more accurate predictor of ability to learn pMDI technique.

In addition, the EXIT25 threshold of 15 apparent for both the pMDI and TH was considered to be more robust in nature than the corresponding MMSE score. This indicates that EXIT25 test may be more reliable test than the MMSE in predicting the adequate acquisition of inhaler technique, particularly in patients demonstrating scores indicative of full cognitive function according to the AMT or subclinical dyspraxia, who are unable to successfully be trained in appropriate inhaler technique. Of concern, executive dysfunction has been identified to be frequently evident in frail older adults with mild cognitive impairment [198], and thus, this test could potentially assist in the selection of appropriate inhaler devices for older adults.

Taken together, these examinations demonstrate a clear impact of cognitive function on the ability to acquire new skills subsequent to education in both pMDI and TH technique. This represents a significant concern with regard to examining the ability of older adults to be successfully trained in inhaler technique relative to adults, on account of the significantly greater incidence of disorders of cognitive impairment, or neurocognitive disorders, in their specific age demographic.

Dementia, the most prevalent neurocognitive disorder both in Australia and worldwide, is particularly a significant concern. Nationally, 8.4% of older Australians have been identified to have dementia [199]. Of concern, it is predicated that, due to an ageing and expanding population, the number of Australians with dementia will exceed more than double its current estimate by 2058 to 859 300 patients [199].

Cognitive impairment is also considered a common comorbidity of COPD [200], which has a greater prevalence in older adults relative to the general adult population [140]. This may thus place older adults at greater risk of experiencing poor inhaler technique due to the reduced ability to acquire and retain new skills relative to the general adult population [190, 201]

Thus, relative to the adult population, older adults may be at increased risk of suffering the impacts of cognitive impairment on inhaler technique, and may benefit from screening and targeted interventions prior to device selection and educational intervention.

3.2.2.2 Vision impairment:

In addition to experiencing greater rates of cognitive impairment that adults, older adults are also more likely to suffer from medical conditions contributing to vision impairment [202]. Visual impairment may adversely affect the ability to acquire inhaler technique skills subsequent to education through a variety of manners. Current guidelines regarding education on inhaler device by the NAC and GINA [10] place considerable emphasis on incorporating visual modalities of teaching in education sessions, including visual demonstrations of device use, and written instructions, diagrams and checklists for patient reference. These have been founded on accounts that interventions such as counselling sessions which have incorporated visual information and device demonstration have been effective in improving inhalation technique and patient respiratory symptoms [203-205]. In particular, visual cues may assist in decreasing learning time, improving comprehension, enhancing retrieval of information, and increasing retention of knowledge [206].

Numerous studies support the theory that the inclusion of visual interventions in inhaler technique educational sessions may result in superior outcomes compared to non-visual sessions. In an investigation by Basheti et al. (2005) [207] examining patients counselled in TH use in a community pharmacy, 7 out of 9 patients who received a combination of verbal counselling and physical demonstration displayed optimal inhaler technique subsequent to education, as opposed to 0 out of 7 patients who received standard verbal counselling (Fisher's exact test, p<0.006). Patients who received the combination counselling were also statistically more likely to demonstrate satisfactory inhaler technique, defined as the attainment of 4 essential steps, relative to those who received verbal counselling alone. (1/9-9/9 vs 3/8-4/7, respectively) [207].

Similarly, in a randomized controlled parallel-group study [203], the inclusion of physical demonstrations of technique to an education program consisting of written and verbal instruction was further elucidated to hasten the time required to achieve significant improvements in inhaler technique. This resulted in improvements being observed at 4, 8 and 16 weeks subsequent to teaching (p<0.05), as opposed to at 16 weeks only (p<0.05), respectively [203].

Visual support cues, such as inhaler-specific checklists of required tasks for appropriate use, may further be of assistance in improving outcomes in inhaler technique [204]. In a primarily visual education session by Fukuda et al., (2009) [204], statistically significant improvements in inhalation technique were evident in a group of 28 asthmatic outpatients trained by pharmacists via a skill-check with inhalers, a checklist of inhalation technique steps, a self-evaluation checklist, and visual information for the patients. A statistically significant improvement in the ACT scores (from 19.1-21.4) of 19 patients receiving this instruction was further evident [204]. Thus, the incorporation of visual educational methodologies into inhaler technique training sessions may assist in significantly improving outcomes in inhaler technique subsequent to education.

Whilst guidelines for educational programs in inhaler technique also recommend the use of other modalities of teaching, including verbal instruction and patient demonstration of the technique to the instructor [10], patients with visual disabilities may be at risk of not gaining the benefits of this aspect of the teaching program. This could potentially result in the attainment of statistically inferior results with regards to the ability to acquire the require skills for optimal technique.

An examination by Press et al. (2011) [208] provided evidence for this potential risk, in examining inhaler technique in a group of patients with varying degrees of visual function. Employing the standardised 'Teach-To-Goal' (TTG) educational intervention [209], the investigators screened the inhaler technique of patients prescribed a pMDI or Diskus DPI, and provided verbal instruction and a visual demonstration of proper technique in those who did demonstrate initially correct technique. Patients were then asked to demonstrate their inhaler technique, and a second round of education provided if necessary. The study revealed that patients with insufficient vision were statistically significantly less likely to achieve mastery of MDI technique following one round of TTG compared to those with sufficient vision, with 58% as opposed to 97% demonstrating correct technique (p=0.05). Similar trends were observed in patients prescribed the Diskus, though statistical significance was not demonstrated (83% vs 67%, p=0.41) (mean age 51.7yrs, patients all greater than or equal to 18 yrs old) [208].

This is of particular concern, in considering that the TTG technique is often used in patient safety, and has been successful among hospitalised patients with asthmatics [210]. As such, this indicates that patients with visual impairment who have been hospitalised with asthma may require an educational plan which has been modified in some manner to dilute the impact of their visual condition on their ability to acquire new skills.

In other instances, patients may be at risk of not being able to accurately emulate steps reliant on a high degree of visual acuity. This could include learning when to determine a device with a counter, such as a TH, is empty, and assembling a canister into the plastic casing of a pMDI, or an pMDI into a spacer [184]. Thus, the greater prevalence of visual impairment conditions in elderly patients relative to their adult counterparts may act as a barrier to the delivery of effective educational interventions.

Of concern, the prevalence of major eye diseases attributing to visual impairment and blindness in Australia, being uncorrected refractive error,, cataracts, age-related macular degeneration, cataracts, diabetic retinopathy, and glaucoma, is significantly greater in older Australians [202]. The number of older adults affected is further prospected to increase over future decades with the ageing of the population, if prevalence rates remain constant [202]. Thus, this remains a concern with regards to the ability of older adults to successfully acquire skills in inhaler technique upon education according to current guidelines.

3.2.2.3 Auditory Impairment

Auditory impairment may further impact upon the ability of older adults to successfully be trained in inhaler technique in sessions conducted as per standardised guidance, decreasing the amount of verbal information from training sessions able to be heard and processed relative to the adult population. Of concern, the prevalence of auditory impairment is greater in older adults, and increases with age [211].

In addition to established hearing impairments from younger ages, for example, from genetic conditions, prior trauma, or as an impact of neurological conditions such as stroke, older adults may further experience age-related losses in hearing, or presbycusis [211, 212]. Abnormalities of the outer or middle ear, including impaired or lowered function of the tympanic membrane or the auditory ossicles, may also contribute to the incidence of presbycusis, though on a less frequent basis [212]. These may reduce the ability to discriminate pitch, elevate the threshold required for hearing high-pitched voices, and reduce hearing acuity [212]. In turn, this may limit their access to and understanding of verbal instruction. In consideration that verbal instruction is recommended for inclusion in inhaler technique demonstrations, the degree to which healthcare outcomes can be maximised may be limited in this population [213].

Older adults may further be at elevated risk of experiencing declines in verbal memory, the retrieval of the meaning of particular words once heard [201]. This is primarily on account of the higher prevalence of medical conditions promoting this issue in the geriatric population, for example, COPD [201]. Impairment of both active recall and passive recognition of learned material in COPD patients may contribute to declines in verbal memory, potentially affecting their ability to interpret instructions and learn new skills [201]. This illuminates the demand to implement appropriate interventions for hearing-impaired individuals, to minimise discrepancies in learning abilities [201].

Interventions employed in other healthcare settings specially designed to facilitate the demands of patients with difficulty hearing, including those who are deaf or hard-of-hearing, have assisted in improving healthcare outcomes in these groups [214-216]. Telemedicine, including the use of internet and webcams have improved access of patients to interpreters when physical or financial constraints prevent physical access to these services [214, 215]. The incorporation of text telephones, in which messages are able to be typed between users, have further assisted patients with hearing impairments to participate in phone conversations, improving their access to health information [216].

Currently, the impact of hearing impairment on the ability to acquire inhaler technique skills according to guidelines has not been investigated. Further examination of any statistically significant impacts, in addition to development and examination of the influence of educational interventions for patients with hearing impairment on their ability to learn adequate inhaler technique may assist in improving outcomes in this population. Thus, consideration of the auditory demands of patients may assist in improving their ability to improve inhaler technique subsequent to education.

3.2.2.4 Physical mobility

By their nature, inhaler devices require a certain degree of manual dexterity and hand strength to be appropriately assembled, primed, and triggered. Numerous stages in the preparation and use of various inhalers, including loading and preparation of devices containing multiple-doses, require fine motor coordination. In the case of DPIs, physical manipulation of movable inhaler parts is often required to effectively prime the device, such as twisting of the base in the TH, and physical movement of a lever in the AH. Preparation of devices such as the Handihaler further require removal of a capsule from an external blister and placement into the appropriate compartment in the inhaler, which may be difficult to perform by patient's with limited manual dexterity.

Other devices may require a degree of assembly prior to use. For example, the pMDI requires placement of a canister into a plastic sheath, and use of a spacer requires assembly of the pMDI into the appropriate location. In addition, a certain degree of hand strength is also required for the appropriate use of such devices. Activation of certain devices, such as the MDI, and priming of devices such as the Handihaler require depression of a button to pierce the capsule, thus requiring a certain degree of hand strength. Thus, patients diagnosed with medical conditions affecting joint mobility, such as osteoarthritis or rheumatoid arthritis, muscle movement, such as dyspraxia and Parkinson's disease, or who have limited hand strength may therefore experience difficulties emulating such skills, despite mentally understanding the process.

Of concern, a broad array of such conditions are markedly more evident in the elderly population. In Australia, the prevalence of arthritis is acknowledged to increase with age, with 49% of people at least 75 years of arthritis suffering from the condition [217]. Hand strength has also been identified as an independent predictor of correct pMDI technique, as described above [191]. According to Armitage and Williams (1988) [166], up to one third of older patients may have the hand strength required to generate the minimum force required to activate any inhaler.

Reduced degrees of lung and intercostal muscle strength in older adults may further affect their ability to use certain inhaler devices. In an investigation by Nsour et al. (2001) [178], only 6 out of 74 patients could inhale through a TH device at a rate of at least 60L/min, being that required for optimal use of the device. As such, this could result in subclinical outcomes in this patient cohort, increasing their risk of experiencing poor asthma outcomes [178]. As such, these factors may place elderly patients at relatively greater risk of poor inhaler technique than adults, despite education.

3.2.3 Reduced ability to retain education information on inhaler technique

In order to attain optimal control of asthma symptoms, regular treatment with appropriate preventative agents is currently advised in all patients experiencing symptoms at least twice per month, or who have experience a flare-up requiring oral corticosteroids within the previous 12 months [2]. Thus, the ability to retain adequate inhaler technique is essential in the continual delivery of inhaled medications over the long-term, and attainment of maximal therapeutic effect. A number of studies have elucidated that older adults may be confronted with numerous challenges to the retention of acquired skills unique to their population. These include the following:

3.2.3.1 Cognitive function

A number of investigations have identified an association between cognitive impairment and the ability to retain proficiency in inhaler technique [186, 218]. In an examination by Allen and Prior (1986) [186] in a cohort of patients 74-89 years of age (mean age 79.9 years) with a range of levels of cognitive function, only 50% of those initially competent in pMDI technique still demonstrated competence four weeks subsequent to training. In addition, only those with full cognitive function as defined by a MSQ score greater than 7 were able to demonstrate the ability to retain technique after this period [186].

Connolly (1995) [218] further supports the notion that cognitive impairment may be an influencing factor in the ability to retain adequate inhaler technique. In contrast to Allen (1986) [186], the investigation, performed in a sample of older adults 70-92 years of age with newly diagnosed stable chronic obstructive airways disease, including asthma, prior to and subsequent to education, revealed that 80% of patients prescribed a pMDI device were able to demonstrate adequate technique one month subsequent to instruction, as opposed to the more conservative figure of 50% identified by Allen (1986) [186]. Higher levels of retentive ability were further evident in those prescribed a pMDI with a large volume spacer, with 97% of patients initially demonstrating proficient inhaler technique also demonstrating proficiency one month subsequent to education [218]. The sample of patients had not received formalised training between assessment sessions, thus providing a more accurate representation of the retentive abilities of the patient.

However, whilst limited information regarding the nature of the training sessions and the tools and modalities of teaching employed by the instructors was presented, the authors did draw attention to the cognitive status of the participants of the study. Unlike Allen and Prior (1986) [186] , Connolly (1995) [218] excluded patients with AMT scores less than 8 out of 10, the threshold level for full cognitive function. Whilst further information is required to assess whether the style and nature of the educational sessions differed between studies, these results suggest that cognitive function in older adults may significantly impact their ability to retain adequate inhaler technique. On account that disorders of cognitive function and age-associated declines in cognitive impairment are generally greater in older adults [219], this may increase their risk of experiencing inferior retention rates with regards to inhaler technique than the general adult population.

3.2.3.2 Access to retraining and re-education

Reports indicate that proficiency in inhaler technique may decrease proportionally from the time of initial instruction in both the general and older adult populations if retraining is not conducted [10]. Currently, both GINA [10] and national guidelines [2] advise that inhaler technique be reassessed and regular training performed to assist in maintaining correct inhaler technique as, after initial training, errors may recur within as little as 4–6 weeks [220].

In cohorts of older adults with varying degrees of cognitive function, assessments of pMDI technique performed 4-6 weeks since initial instruction have reported rates of proficiency as low as 50% [186]. These contrast substantially to rates of 80% described in a cognitively-similar older adult population 50-87 years of age at assessments performed one week from initial instruction [191].

Although differences in the criteria used for assessing correct inhaler technique and the effectiveness of educational tools used could have contributed to the discrepancies between these results, the relatively lower rate of correct inhaler technique in the prior study suggests that the ability to retain correct inhaler technique may decline over time. De Blaquiere et al. (1989) [221] further support these findings, identifying reductions in proficiency in inhaler technique from 80% six weeks subsequent to education to 55% two months after initial instruction in a cohort of older patients with chronic airflow obstruction.

Similar trends have further been apparent in patients without cognitive impairment. In an investigation exploring pMDI and DPI technique in patients 55-86 years demonstrating cognitive competence with regard to understanding instructions, less than half of patients (48%) were able to demonstrate proficient technique 3 months subsequent to instruction, despite training according to an age-specific protocol [222]. Of concern, this proportion was considerably lower than the values of 80-95% quoted by Connolly et al. (1995) [218] four weeks subsequent to training. Although these results could be influenced by factors pertaining to ease of use of the device and potential differences in assessment methodology, they provide initial evidence that cognitive function may not necessarily be a confounding variable in the ability to retain proficiency in inhaler technique. Thus, inhaler technique skills may decline over time even in those without cognitive impairment.

Despite such concerns, continual reinforcement of inhaler technique may assist patients to retain accuracy in inhaler technique once successfully trained. Following re-education of patients with incorrect technique at the 3 month reassessment, Goeman et al. (2014) [222] indicated that the statistically significant improvements in device technique evident at the 3 month reassessment were able to be maintained at a period 12 months from the initial training ($p<0.001$) Similarly, Buist et al. (2006) [223] revealed that patients between 50-92 years of age who underwent individual coaching and assessment in MDI technique at six monthly intervals for a period of two years were able to demonstrate and retain statistically significantly improvements at each point of assessment.

Although repetition of training sessions may assist in maintaining accuracy in inhaler technique in both the general and older adult and populations, older adults may be confronted by specific age-related barriers to re-education. A particular concern is that of physical accessibility to training destinations. The increased prevalence of vision-impairment disorders in the elderly may restrict transportation options to such venues, by causing driving restrictions or issues accessing public transportation. Older adults experiencing social isolation and living alone may further experience difficulty obtaining private transport compared to those with close social networks of family or friends. Similarly, medical conditions affecting physical mobility, many of which are more prevalent in older adults, as discussed above, such as arthritis, stroke, or Parkinson's disease, may restrict the ability to drive or attend training sessions.

Discrepancies in socioeconomic status between age groups may further affect their ability to attend training sessions. In particular, patients of lower socioeconomic status may experience difficulties with the costs associated with attending training sessions, for example, transportation costs. This is of particular concern in the older adult population in Australia, with national statistical measures of income indicating that the average annual household incomes rank lowest in those over 75 years of age ($54 340), and second lowest in those 65-74 years of age [224].

The ability to self-educate and manage inhaler technique may further be restricted, limiting patient access to the complete facets of the program. For example, to assist in reinforcing information and aiding memory, visual information such as inhaler technique checklists and product information may be provided for at home reinforcement. Patients with visual impairment disorders may be at increased risk of being unable to read and refer to such materials, thus placing them at greater risk of losing acquired skills in inhaler technique. Patients with inferior fine motor function may further experience difficulty repeating and practising trained steps in device use requiring the physical assembly or manipulation of movable parts.

In light of the significant issues affecting asthma management in older adults, there is concern that they may be at high-risk with regards to the experience of poor asthma outcomes and increased asthma severity.

As discussed above, correct inhaler technique can significant improve one's clinical outcomes, decreasing their risk of being at high-risk of poor asthma outcomes. One of the aims of this thesis is therefore to assess the literature to determine if there is an association between suboptimal inhaler technique and older adulthood, to assist in determining whether older adults represent a high-risk group with regards to asthma management.

3.3: Systematic Literature Review

Inhaler technique: does age matter? A systematic review

Barbara, S., V. Kritikos, and S. Bosnic-Anticevich, *Inhaler technique: does age matter? A systematic review.* European Respiratory Review, 2017. **26**(146).

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Inhaler technique: does age matter? A systematic review

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The number and type of inhaler errors differs in the elderly http:/ow.ly/9VNH30fFl5 Z

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ABSTRACT Poor inhaler technique and inferior asthma outcomes are evident in older adults. Reviews comparing metered dose inhaler (MDI) and dry powder inhaler (DPI) techniques across older adults and younger cohorts are scarce. This systematic review aimed to determine whether differences exist between such cohorts with regards to the number and type of MDI and DPI errors made. A systematic literature search was conducted in Embase, Medline and PubMed from July 1 to December 31, 2016. Studies were selected in accordance with preset inclusion criteria, relevant data were extracted, and quality was assessed with validated checklists. 14 studies were identified. Evidence suggests a negative correlation between advancing age and correct technique across MDI and varying DPI devices when examined collectively. Differences appear to exist between older adult and younger cohorts prescribed MDIs in error types. There is evidence of age-associated differences in the number and type of inhaler technique errors. Further research is required to assess outcomes in individual DPIs, reproducibility and the effects of confounders.

INTRODUCTION

Proficiency in inhaler technique is critical to the attainment of optimal asthma outcomes. Globally, the centrality of inhaler technique maintenance in asthma management is heavily emphasised by numerous respiratory authorities, and referred to more than 50 times in key asthma management documents [1]. However, although healthcare professional-coordinated inhaler technique training can improve asthma control [2, 3], inhaler technique remains a significant problem. From the currently available data, across all ages, as many as 90% of patients are estimated to demonstrate incorrect technique [4], contributing to increased hospitalisations [5] and forfeiture of billions of dollars in pharmaceutical expenditure [6]. An otherwise vulnerable population, the elderly, are particularly at risk, on account of increased evidence of cognitive and physical disorders affecting their ability to emulate and retain required skills [7, 8].

The need to address any needs of the elderly is a global trend and there is recognition that, with asthma mortalities and management costs being greater in the elderly, it is essential that the ability of guidelines to optimise their technique be urgently reassessed and any issues rectified [9]. Addressing the concern that costs will continue to surge due to ageing of the population, the European Innovation Partnership on Active and Healthy Ageing has advised the implementation of evidence-based innovative healthcare services to enhance healthcare-system outcomes and efficiency [10]. Globally, geriatric-specific education programmes in other chronic disease states, such as arthritis, have elevated outcomes, lending support for their application in practice [11]. However, their application in respiratory management has been underdeveloped and, consequently, inhaler technique education guidelines remain generic, failing to specifically address the way in which training can be delivered effectively and within an age-individualised approach. The development of age-appropriate inhaler technique training able to overcome the unique challenges to skill acquisition in the elderly, including increased rates of cognitive impairment, is an important strategy to enhance healthcare outcomes for the elderly.

To develop education better addressing geriatric needs, we first need to review the evidence behind the differences between the elderly and the general population in terms of their current inhaler use, and their ability to achieve and retain mastery of technique. Reviews have explored factors predisposing elderly patients to inferior technique [12–14], but a comparison of the number and types of errors made with different inhalers across a range of adult ages has not been performed. This is critical in order to determine the specific areas to address in the formulation of age-appropriate training.

This review therefore aims to determine whether there is evidence to support the hypothesis that a difference exists in the 1) frequency and 2) nature of inhaler technique errors made by older adults and younger patients.

MATERIALS AND METHODS

Data sources and searches

An electronic search of the literature was performed between July 1 and December 31, 2016, until data reached saturation. Searches were conducted in Embase via OvidSP, Medline via OvidSP, and PubMed. The full search, including search strategy queries, is presented in supplementary table S1.

Study selection

Titles were independently screened to include relevant articles. Included studies consisted of original research in English comparing at least one of the following: differences in numbers or types of errors with age across older adults and younger patient cohorts with asthma and/or chronic obstructive pulmonary disease (COPD). Interventions were required to include assessment of inhaler technique through observation of unaided or investigator-trained practice. Publication date filters were not applied. Articles were excluded if the full publication was unavailable.

Data synthesis

A systematic review was undertaken in compliance with the methodological and reporting standards recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. Articles were assessed for relevance according to the PRISMA flow diagram for data inclusion, as presented in figure 1, and reviewed by examination of titles and abstracts. Duplicate studies and articles not satisfying the inclusion criteria were omitted via EndNote X7. Articles were augmented by publications otherwise known to the authors.

Data extraction occurred independently according to the University of Wisconsin Health Sciences Data Extraction protocol [16]. Data included reference details, including author, year and citation; eligibility criteria, including sample characteristics and outcomes measured; method of inhaler technique assessment and interventions; and main outcomes results.

Variables for which data were sought included outcomes as above. The results were investigated, quality-assessed and compared to others exploring the same outcomes. The principal summary measure was variation in mean outcomes with age.

Due to the marked diversity in the thresholds applied in the definition of older adulthood, the heterogeneity in the scoring systems and methodologies used, the methods of results presentation, lack of disclosure of potential moderators, and the limited number of studies available for certain outcomes, further meta-analyses and statistical analyses, including sensitivity/subgroup analyses and meta-regression, were not performed.

Quality assessment

To assess quality and the risk of bias, the National Heart, Lung and Blood Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [17] and the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Research for interventional studies [18] were used to assist in selecting investigations of low risk of bias.

Factors potentially affecting the results, including assessment technique, interventions, sample size and potential confounders, such as medical and socioeconomic profile, were considered. Critical appraisal and risk

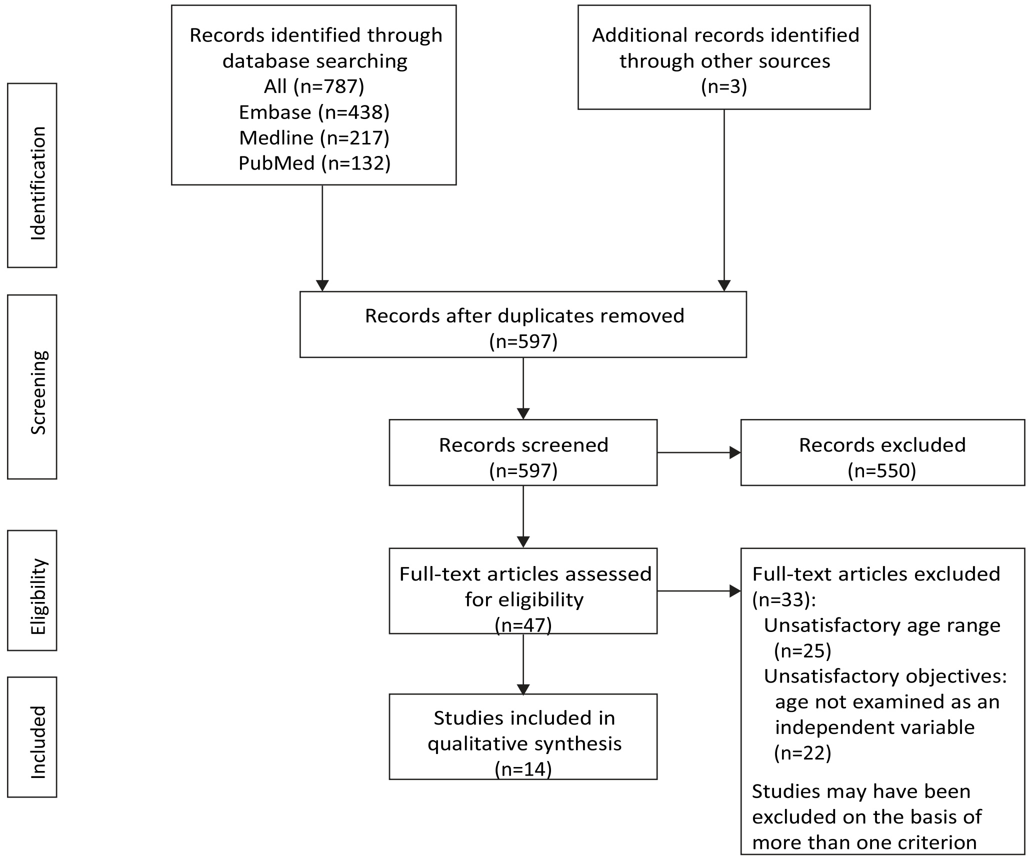


FIGURE 1 Flow diagram of studies included in the systematic review.

of selection, performance, detection, attrition and reporting bias within and across studies on account of methodology, lack of participant or investigator blinding, and potential funding were assessed independently by two reviewers, and papers were included if deemed by both to be of sufficient quality and objectivity.

RESULTS

The search identified 787 investigations, composed of 438 results from Embase via OvidSP, 217 from Medline via OvidSP and 132 from PubMed. Three additional records were sourced through investigations known to the authors. Following duplicate removal, 597 records were retained. After screening by title, abstract and eligibility criteria, 47 articles remained. Full texts were read, and 32 articles excluded, with 25 excluded due to lack of satisfaction regarding the age requirements, 22 due to lack of examination of age as an independent variable, and others due to both (supplementary table S2). A total of 14 studies satisfied the final inclusion criteria and were included in the final qualitative synthesis of the outcomes of the systematic review (figure 1).

Studies differed according to methodology, with 10 employing an observational, cross-sectional methodology [4, 5, 7, 19–25], one an observational, comparative, cohort methodology spanning 18 months [26], one a comparative, cross-sectional methodology employing a community intervention [27], one a comparative, cohort study employing a community intervention spanning 4 weeks [28], and one employing a randomised-controlled-trial cohort design spanning 6–10 weeks (supplementary table S2) [29].

The included studies were published between 1979 [20] and 2015 [25], with samples ranging from 59 [7] to 3995 [4] participants, and ages ranging from 6.1 years [24] to older adulthood. Age thresholds for older adults varied between investigations. The study populations, including the number of patients recruited in each age demographic, and outcomes are reported in supplementary table S2.

Investigation of the literature identified outcomes that will be discussed in the following sections of this article.

Frequency of inhaler technique errors

14 studies examined the impact of age upon the frequency of inhaler technique errors presented as a main outcome. Of these, six explored the impact of age on inhaler technique in general (combining the use of all inhalers, including the metered dose inhaler (MDI) technique), five examined varying dry powder inhaler (DPI) and MDI devices [5, 21–24], and three examined the impact on specific device inhaler technique (four DPIs and an MDI) [19, 25, 28]. Graphical representations of the results for which sufficient data were available for studies exploring age categorically are presented in figures 2 and 3.

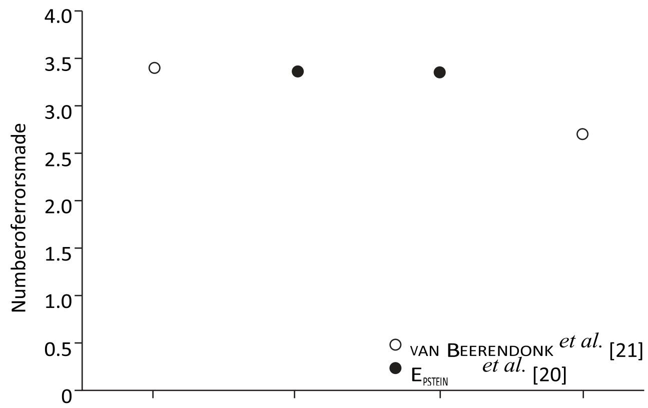
MDI devices

Examinations yielded mixed outcomes. Six studies were observational, with five applying a cross-sectional approach [4, 7, 19–21] and one applying a cohort approach, reassessing participants over 18 months [26]. One employed a community training intervention prior to assessment, examining patients at that point in time [27], and one employed a cohort randomised controlled trial approach, randomising patients into two separate training interventions and assessing patients at baseline and 6–10 weeks afterwards [29]. The final study applied a comparative cohort approach utilising a community training intervention, assessing patients at baseline and 4 weeks afterwards [28].

Inhaler technique was assessed by trained assessors or healthcare professionals, including respiratory technicians [20, 26] and general practitioners (GPs) [4, 19]. Error frequencies were compared on the basis of age using standardised assessment procedures and investigator-developed inhaler technique checklists. Of the eight studies, five identified a positive association between age and MDI technique [4, 19, 26–28], with statistical significance reported in three [4, 26, 27].

In three studies, variations in technique with age were identified in cohorts in which age was expressed categorically. Armitage and Williams [26] divided 326 patients into groups aged <65 years (n=225) and ⩾65 years (n=101) for training and assessment over 18 months according to standardised procedures. Statistical analysis determined that only 29% of older adults, as opposed to 45% of younger patients, were able to demonstrate correct technique (p<0.01, 95% CI 5–28%). Giraud and Roche [4] examined the frequencies of MDI technique errors in patients who had been prescribed regular inhaled corticosteroids for at least 3 months, as per GP assessment, identifying a significant increase in misuse with age. Error frequencies ranged from 61% to 70%, 77% and 86% in patients aged 15–30 years, 30–60 years, 60–75 years and >75 years, respectively (p<0.00001).

Molimard et al. [19] compared the frequency of critical MDI technique errors by device, in a cohort of 552 patients divided into three categories (aged ⩽30 years, 31–64 years and ⩾65 years). Critical errors increased with age, with frequencies of 22%, 24% and 40% in patients aged ⩽30 years, 31–64 years and ⩾65 years, respectively. Dahl et al. [28] employed a 12-point inhaler technique checklist in a cohort of 151 patients, identifying an increase in the percentage of patients demonstrating errors from 50% to 55% and 63% in patients aged 43–65 years, 66–71 years and 72–85 years, respectively; however, statistical significance was unreported.



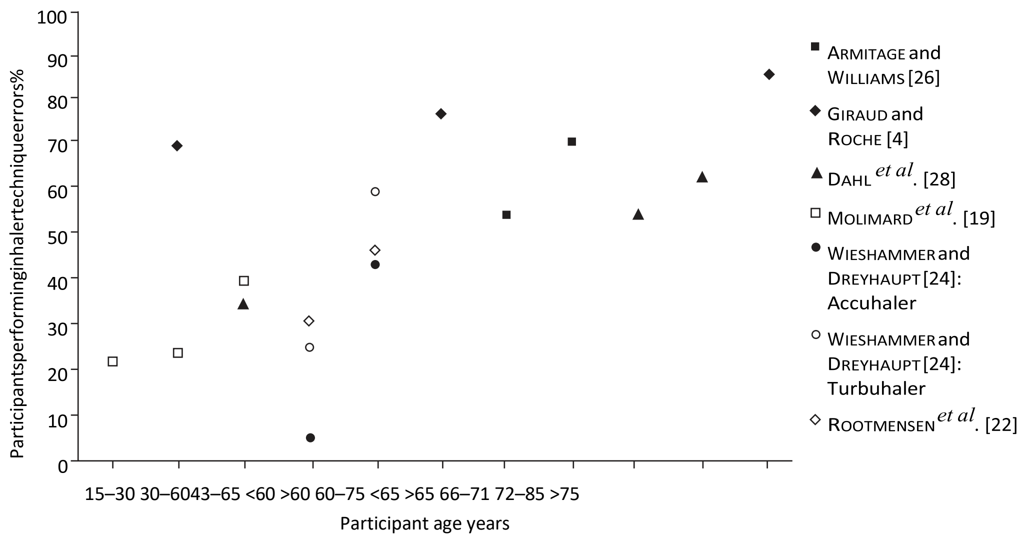


FIGURE 2 Graphical representation of percentage of participants performing inhaler technique errors according to age.
FIGURE 3 Graphical representation of number of inhaler technique errors made (standardised to a
score out of a maximum of 10 20–61 ≤55 ≥56 62–90 errors). Participant age years

Positive associations between advancing age (presented as a continuous variable) and MDI misuse were further identified by Horsley and Bailie [27], who assessed MDI technique in 86 patients aged 17–83 years with reference to a set checklist for inhaler technique prior to community instruction (p=0.019).

Three studies did not identify positive associations between age and error frequency [7, 20, 29]. Epstein et al. [20] performed a single-blinded observational investigation to assess MDI technique in 130 patients aged 18–83 years, identifying that age was not significantly predictive of inferior technique when a cut-off of 56 years was chosen to describe age as a dichotomous variable. Specifically, the mean number of errors made by people <56 and ⩾56 years of age was 7.3±2.8 and 7.3±2.4 errors, respectively (p=0.94).

De Blaquiere et al. [29] compared 100 correct and incorrect MDI users, identifying that the mean age of incorrect users of 60.3±10.9 years was lower than that of correct users, at 63.0±8.7 years; however, this was not statistically significant.

Goodman et al. [7] explored inhaler technique in subjects aged <25 years, 25–39 years, 40–54 years and ⩾55 years, using an MDI adapter and microcomputer to assess inhaler technique. An association between age and inhaler technique failed to be identified.

Sadowski et al. [25] assessed MDI technique via observation in 161 patients with asthma or COPD with a mean age of 56.9±18.59 years according to checklists founded upon national respiratory authorities. Nonsignificant negative correlations of −0.136 and −0.070 were found between age and inhaler technique scores for the MDI and MDI with a spacer, thus indicating a lack of significant association between age and proficiency in technique.

DPI devices

Eight studies explored the impact of age on proficiency in inhaler technique across a range of DPI devices [5, 19, 21–25, 28]. Seven employed a cross-sectional, observational methodology [5, 19, 21–25], and one a cohort community intervention conducted over 4 weeks [28]. A range of DPI devices were analysed collectively in four studies [5, 21–23], and individually in three investigations [19, 25, 28].

Inhaler technique was assessed by investigators [5, 22, 23, 28], research assistants [25], a trained pulmonary technician, or either a GP [19] or GP assistant [21] via reference to standardised investigator-formulated or national [21] inhaler technique checklists employing direct observation or triplicate referral of a video-recording of technique. A positive association between error frequency and age was identified in six studies, with statistical significance identified in five, unreported in one, and unidentified in the latter study [25].

Positive associations were identified in examinations exploring age both categorically and continuously. van Beerendonk et al. [21] explored age categorically in 316 patients aged 20–90 years who were prescribed a Diskhaler, Rotahaler, Ingelheim inhaler (HandiHaler) or MDI. A comparison was undertaken of the number and nature of errors made between age cohorts. Analyses with ANOVA and t-tests revealed a statistically significant elevation in the mean number of errors in patients aged 62–90 years relative to those aged 20–61 years (2.73 versus 2.16 errors, t(314)=−3.15, p<0.01). Rootmensen et al. [22] further performed univariate analysis of a number of potential predictors of inhaler technique in 156 patients prescribed a Turbuhaler, Aerolizer and pressurised MDI (pMDI). A statistically significant difference in error frequency was identified with age, with 47% of patients ⩾60 years demonstrating errors, as opposed to 31% of patients aged 18–60 years (p=0.05).

Dahl et al. [28] identified similar associations with the HandiHaler, identifying proficiency in approximately 65%, 50% and 45% of patients aged 45–65 years, 66–71 years and 72–85 years. Molimard et al. [19] explored the relationship between age and the Diskus and Turbuhaler, similarly identifying increasing trends. The authors found the percentages of patients with errors were 6%, 25% and 10% for the Diskus, and 32%, 25% and 40% for the Turbuhaler for the categories of ⩽30 years, 31–64 years and ⩾65 years, respectively; however, for both investigations, the level of significance was unreported.

Sestini et al. [23] explored the impact of age (as a continuous variable) on inhaler technique and identified a strong negative association between technique proficiency across both pMDI and DPIs and advancing age (n=1305; adjusted regression coefficient 0.09, 95% CI 0.01–0.08; p<0.01). A further two studies identified a significant negative correlation between technique and age (as a continuous variable) in 224 outpatients with a mean age of 55.1±20 years prescribed a Diskus, Aerolizer, HandiHaler or Turbuhaler (p<0.01) [24] and in 1664 patients of mean age 62 years prescribed an MDI, Aerolizer, Diskus, HandiHaler or Turbuhaler [5].

Sadowski et al. [25] assessed Diskus, HandiHaler and Turbuhaler technique as discussed for the pMDI above, and identified a nonsignificant negative correlation of −0.248 between age and inhaler technique scores for the Diskus, and nonsignificant positive correlations of 0.205 and 0.182 between age and the HandiHaler and Turbuhaler, respectively. Thus, a significant association between age and proficiency in technique was not identified.

Nature of inhaler technique errors

Three investigations explored variations in the nature of inhaler technique error with age with regards to the MDI [21, 26, 27]. Armitage and Williams [26] directly compared the percentages of patients aged <65 years and ⩾65 years making seven different types of error, and identified differences in the frequencies with which different errors were made. Older adults were most likely to actuate MDI devices at the end of inspiration and breath-hold for <5 s, and patients <65 years were also most likely to present these errors, although in reverse frequency. Both cohorts were equally next likely to inhale too rapidly and prematurely actuate the device. Older adults were next likely to actuate the device during expiration, then perform multiple actuations, whereas adults <65 years were equally likely to present both errors. Investigation further revealed that the likelihood of one cohort presenting an error differed with the error, with a greater level of statistical difference identified for delayed or failed actuation of the device ($p<0.001$) than for late activation and rapid inhalation ($p<0.01$), and inspiration and breath-holding for <5 s ($p<0.05$) [26]. Horsley and Bailie [27] identified similar trends with regard to activating MDIs during inhalation ($p=0.056$) and failing to assemble the MDI correctly ($p=0.059$) in patients aged 17–83 years; however, these were not statistically significant.

No investigations directly comparing the types of DPI errors with age were identified. However, van Beerendonk et al. [21] identified a statistically significant increase in the number of both skills-related errors (those requiring information and training prior to execution, e.g. simultaneous MDI actuation/ inhalation) and non-skill errors (those requiring information only, e.g. removal of cap), made by patients aged 62–90 years relative to those aged 20–61 years prescribed a Diskhaler, Rotahaler, Ingelheim inhaler/ HandiHaler or MDI device when analysed collectively.

DISCUSSION

Main findings

This systematic review identified 14 comparative studies addressing the study aims. However, although providing initial insight into potential variations in all outcomes with age, the results of such studies were inconsistent in nature or unsupported by further studies, so further study is required to gain a clearer insight into the influence of age on inhaler technique.

With regard to the incidence of incorrect technique there is some evidence that increasing age is associated with increasing proportions of incorrect MDI and DPI users, with the majority identifying a positive correlation or statistically significant difference in means between older adulthood and inaccurate technique. However, the results were conflicting, with statistical significance unreported in two studies [19, 28] and conflicting for the Turbuhaler and Diskhaler [24, 25].

Only one study, restricted to the pMDI, explored variations in the types of errors made between the elderly and the general adult population [26]. Although it identified variations with age, further studies are required to support these results before applying them to the general population, to account for any possible flaws in the study design potentially affecting the accuracy and applicability of their findings.

Result validity

In considering these results, it is difficult to generalise, and several considerations need to be made. One consideration is the external (in particular, ecological) and internal validity of the studies; that is, the extent to which the sampling procedures, methodologies and method of exploring correlations can be applied to the real-world population. Each of these aspects and their implications for the applicability of the findings to the real-world population will be discussed.

One consideration involves the inconsistency of cohort categorisation, with different ages being considered “elderly” in different studies. As sociodemographic factors such as employment status may be affected by highly specific age thresholds, this may limit their generalisabilty to the real-world setting.

Another consideration is lack of participant characterisation, particularly with regards to their medical and socioeconomic profiles. Some studies reported diagnosis of COPD and educational status [29], but their potential relationship with inhaler technique as a subset of age was not explored. This is particularly relevant, as conditions such as cognitive impairment disorders and arthritis can have an impact on mental processes and physical ability, thus becoming confounders. Socioeconomic factors such as lower education and health literacy levels, many of which are more evident in older adults, also remained uncharacterised in the majority of studies, potentially affecting patient aptitude and ability to learn, and compromising both the internal and external validity of the studies.

In exploring the older population with regard to respiratory illness, it is important to consider the condition and the generalisability of its control on outcomes. The majority of studies recruited asthma patients primarily from medical clinics, so there could be bias resulting from recruitment of a more severe cohort or a subgroup who may have an overlap of more than one respiratory illness, e.g. asthma–COPD overlap. This could further contribute to the contradictory findings of certain studies. Recruitment of newly referred outpatients in the earlier study [24], as opposed to those attending community facilities [25], may have falsely elevated error frequencies; however, whether this is the case or whether it would affect the results is inconclusive, limiting the applicability of the results.

The ecological validity of the investigations, that is, the extent to which they can be applied to the real-world setting on account of the study methods employed, may further be constrained by the assessment process. Of concern, most of the studies did not assume a real-life approach, with participant blinding being limited to two investigations [20, 28], potentially resulting in falsely elevated performance scores and affecting statistical outcomes. Further investigations involving recruitment of a more randomised sample with a matched control group or examination of confounders, in addition to technology-enhanced devices that could monitor inhaler technique in real life, could assist in improving their applicability to the real world.

Another important consideration is the lack of power of some studies. Given the potential heterogeneity and importance of identifying and accounting for confounders, only a limited number of studies were powered to a high enough sample size to determine the true relationship between age and inhaler technique. This could explain the failure to reach statistical significance in some of the studies identifying trends.

Of further concern, information pertaining to certain devices and outcomes is scarce. With regard to error frequencies, only one investigation was identified reporting significance with the HandiHaler [25], and examining the Aerolizer and Autohaler [19]. In addition, there is little knowledge of whether a specific age threshold exists at which technique may decline, or if factors associated with technique maintenance, such as regular referral to take-home resources, are under-utilised in older adults.

Similarly, information regarding the impact of age on the nature of errors is also limited, constraining applicability to the broader population. However, investigations performed purely within each age population (for example, in adults aged 18–65 years or ⩾65 years of age) for the MDI similarly suggest that variations may exist, supporting Armitage and Williams [26].

Comparisons of these studies suggest that the forms of errors made by patients of varying ages may differ depending on whether they are more reliant on physical or cognitive function. van der Palen et al. [30] identified that failure to exhale prior to inhalation was the most frequently presented error in patients aged 18–65 years, implying that knowledge deficits as opposed to physical functioning may be of greater influence. This contrasted with errors identified in older adults [31–34], in which tasks dependent more on physical abilities, such as failure to breath-hold and lack of inhalation/actuation coordination [31, 33] occurred more frequently. However, due to the lack of heterogeneity between studies with regard to recruitment, methodology and analysis, further study involving direct comparison within a controlled environment is required to assess result reproducibility.

In considering these results, it is important to explore the basis on which age may be a factor in poor inhaler technique. This necessitates an exploration of the factors that change with age and how they may interact with device use, in particular physical strength and dexterity, lung function and cognitive function.

A primary consideration is that of physical strength and dexterity. Numerous movement disorders, for example, arthritis, are more prevalent in older adults, and may potentially increase the risk of poor inhaler technique. Armitage and Williams [26] revealed that 36% of older patients could not generate the minimum force required to actuate any MDI, correlating with their ability to activate an MDI [35]. With only 29% able to generate the minimum force required to actuate all MDIs, this implies that hand strength may be a particularly relevant consideration in device selection in older adults.

Advanced age may also independently affect lung function and predict the ability to generate the peak inspiratory flow (PIF) rate required for optimal outcomes from certain DPIs, particularly the Turbuhaler, potentially affecting the type of error made [36, 37]. As many as 75% of older adults may be unable to generate the minimum recommended PIF of 30 $L \cdot min^{-1}$ for a clinical response from the Turbuhaler [36], potentially leading to an inferior clinical response [38]. This may be difficult to rectify in practice, with changes subsequent to counselling considered too minor to be cost-effective [39]. The effectiveness of training also appears to be superior with the MDI relative to the DPI [40], demanding a greater consideration of PIF rate in elderly patients prior to device selection.

Age-associated reductions in working memory and executive planning, and the increased prevalence of numerous neurocognitive disorders in older adults, may further contribute to discrepancies in the ability to learn and retain correct technique, potentially increasing the likelihood of error performance in older demographics [41]. There is substantial evidence of significant inverse proportionalities between cognitive status and the ability to successfully learn technique [8, 42, 43]. Allen and Prior [31] identified that only individuals with full cognitive function could be trained successfully in accurate technique. Explicit abbreviated mental test score (AMT), mini-mental test score and EXIT25 score threshold levels have also been identified at which patients can be trained in the use of certain devices [8, 35, 42–44], providing support for such an association. In the case of the AMT, the thresholds increased with the complexity of the device, suggesting that certain devices may be more appropriate for older adults than others, and a potentially increased demand for cognitive screening in elderly patients.

Taken together, these findings indicate that there are numerous physical and cognitive issues unique to or more likely to be evident in the elderly population, potentially increasing their risk of inhaler technique misuse. Knowledge of whether they are contributing to statistically significant differences in the number and types of inhaler technique errors made in real-life practice is therefore essential in the development of innovative and necessary inhaler technique training and monitoring sessions.

Limitations and strengths

Certain limitations of this review may restrict the applicability of these results to practice. The restriction of articles to those available in English or to which full access was obtainable could further minimise the scope of knowledge collected. In addition, the limited number of studies and lack of inter-study homogeneity further limited the extent of result comparison, necessitating further research. Despite this, the use of multiple databases and standardised quality assessment tools to analyse the quality of the studies assisted in improving the strength of the findings by ensuring a consistent and comprehensive analysis of the quality of each investigation, maximising the accuracy of conclusions drawn.

Conclusions and implications for future research, policy and practice

A systematic review of the literature has provided initial evidence of age-associated differences in the number and type of inhaler technique errors. Based on current findings, further study is required to explore the influence of confounders in a controlled setting. Investigations characterising the medical and socioeconomic profiles of participants and any potential confounders may further assist in defining the relationship between age and technique. We still do not understand whether it is age-, cognition-, physical ability- or device-related. There are logical reasons for us to believe that there should be an association, but a well-controlled, sufficiently powered longitudinal study characterising the population and accounting for confounders needs to be undertaken. In addition, it is unknown whether there are any variations with age regarding the ability to be trained in and retain correct inhaler technique and, if so, which factors, if any, may contribute to this. This may assist in profoundly engaging healthcare professionals and policy groups in the clinical urgency of recognising the impact of age on current inhaler technique training outcomes, driving the development of age-appropriate guidelines to be delivered sustainably across health systems. Through the delivery of such pharmacovigilance, a path towards improved clinical outcomes among the elderly can be forged.

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Chapter 4

Exploration of Patient Groups at High Risk of Poorly Controlled Asthma

Original Research Paper 1

Identifying patients at risk of poor asthma outcomes associated with making inhaler technique errors

Barbara, S.A., et al., *Identifying patients at risk of poor asthma outcomes associated with making inhaler technique errors.* Journal of Asthma, 2020: p. 1-12.

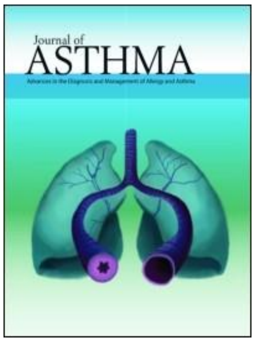
Rationale for Original Research Paper 1:

The study conducted in Chapter 4 provides initial evidence that older age can increase one's risk of performing inhaler technique errors, one of the factors contributing to a higher risk of poor asthma outcomes.

However, as discussed, there are some limitations in the study design which minimise the amount of information able to be obtained. In particular, a well-controlled, sufficiently powered longitudinal study more explicitly defining this population and accounting for any potential confounders is still required to more accurately determine if older patients are at high risk of poor asthma outcomes.

In addition, the limitation of the type of inhaler technique errors to those specifically associated with poor asthma outcomes could further assist in assessing whether older adults are at greater risk of experiencing poor asthma outcomes.

In consideration of these limitations, the study below aims to determine patient demographic factors associated with the performance of inhaler technique errors associated with poor asthma outcomes, that is, 'critical' inhaler technique errors, using a much larger data-set than explored in prior investigations. It is anticipated that knowledge of these patient factors may assist in device optimisation and training, and assisting pharmacists to identify patients at high-risk of poor asthma outcomes within the confines of a busy work environment.



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Identifying patients at risk of poor asthma outcomes associated with making inhaler technique errors

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Identifying patients at risk of poor asthma outcomes associated with making inhaler technique errors

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ABSTRACT

Objectives: Correct inhaler technique is essential to optimal clinical outcomes in asthma patients. The study aim was to use real-life data from the iHARP database to determine patient factors associated with the performance of inhaler technique errors associated with poor asthma outcomes (as identified in the Critikal study) in patients with asthma prescribed the Turbuhaler (TH), Metered Dose Inhaler (MDI), and Accuhaler (AH) device. Methods: This was a retrospective cross-sectional study using the iHARP database, a multinational initiative including questionnaires and technique review. Identification of inhaler technique errors specifically associated with poor asthma outcomes was performed by reference to the Critikal study. Multivariable logistic regression was used to identify demographic and clinical factors associated with 1 of these errors.

Results: Factors significantly associated with 1 inhaler technique error and worsening asthma outcomes for the TH cohort include female gender, very poor to average self-assessment of inhaler technique; for the MDI cohort, female gender, secondary education, and current smoking status; and, in the AH cohort, lack of inhaler technique review by a trained healthcare professional in the previous twelve months and very poor to average self-assessment of inhaler technique.

Conclusions: Numerous specific patient demographic and clinical factors associated with the performance of these errors have been identified, differing according to device. Inhaler technique error associated with poor asthma outcomes is further widespread across devices. Knowledge of these factors and the frequency of their occurence may assist in optimizing device selection and training.

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Introduction

Asthma, an escalating health epidemic, is one of the leading contributors to the global burden of disease, placing significant costs on both the healthcare system and patient quality of life. Despite evidence that it can be effectively managed via appropriate inhaled pharmacotherapy, both hospitalizations and impacts on quality of life remain high.

Of concern is the burden of asthma associated with incorrect medication/inhaler use. Numerous studies have described the high prevalence of sub-optimal inhaler technique of asthma patients (1–4). Additional studies have further identified risk factors associated with the performance of inhaler technique errors (including female gender (5,6) older age (7–12), inferior education (13), lack of healthcare professional (HCP)-led inhaler technique education (5,8,10,14), and diagnosis of chronic obstructive pulmonary disease (COPD) (15)).

However, a key limitation of these studies is that they have not focused on inhaler technique errors which are specifically linked to poor asthma outcomes, that is, uncontrolled asthma and/or increased exacerbations. Recently, ground-breaking research has identified that not all inhaler technique errors lead to clinically relevant effects, with only specific errors being directly related to poor asthma outcomes. This study, the CritiKal (16) study, specifically identified which errors a associated with these poor asthma outcomesin the turbuhaler (TH), metered dose inhaler (MDI), and accuhaler (AH) devices (listed in Table 1, below).

The importance of these errors, iethose supported by evidence, cannot be underestimated, as, whilst it is important that patients are taught to perform all steps

Table 1. Inhaler technique errors associated with poor asthma outcomes.

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Device	Error
TH	Does not remove cap
	Shakes device during preparation
	Device not held upright after the base is twisted until inhalation (within 45 degrees)
	Shakes after dose preparation
	Does not breathe out slowly to empty lungs
	Fails to put in mouth and seal lips around mouthpiece
	Inhalation is not as fast as you can (defined as a very fast suck)
	Inhalation is not forceful from the start
	Inhalation is not as long as you can
MDI	Does not breathe out x
	Exhalation into the inhaler x
	Does not hold inhaler upright
	Does not have head tilted such that chin is slightly upwards x
	Actuation not corresponding to inhalation (actuation before inhalation)
AH	Does not breathe out slowly to empty lungs
	Inhalation is not as fast as you can (defined as a very fast suck)
	Inhalation is not forceful from the start
	Inhalation is not as long as you can

Legend for Tables 1–4: TH: Turbuhaler.
MDI: Metered Dose Inhaler. AH: Accuhaler.

associated with inhaler device use, the steps that truly need to be performed correctly are those that are associated with poor asthma outcomes. However, this information is not enough. In particular, it is essential to determine which patient cohorts are particularly at risk of making these specific errors, to enable the development of personalized interventions specifically targeted to patient's unique educational needs.

To better identify these patient cohorts, it is imperative that the factors associated with making these specific inhaler technique errors be identified. Therefore the aim of this research is to focus only on errors specifically associated with poor asthma outcomes, and to identify factors associated with making these errors.

Methods

Data source

The study was a retrospective cross-sectional study using data from the international Helping Asthma in Real life Patients (iHARP) database. iHARP data was collected prospectively between June 2011 and December 2014, from participating primary care practices in Australia, the United Kingdom, Italy, Spain, the Netherlands, France, Norway, and Sweden. Each practice received an identical face-to-face iHARP review using questionnaire and practitioner-led assessments to collect information about the patient's demographics, symptoms, lung function, and inhaler technique. A copy of the questionnaire is available from the following website: http://iharp.org/questionnaire.aspx (17).

Appropriate ethics approval for the iHARP service was obtained for each practice as per nation requirements. The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee gave approval for the Woolcock Institute of Medical Research to use the iHARP database (ADEPT0617).

Cohort definition

To be eligible for iHARP review, patients had to be diagnosed with asthma, prescribed fixed-dose combination inhaled corticosteroid and long-acting b_2 agonist (ICS/LABA) therapy, and have received at least two prescriptions for such therapy in the twelve months prior to the review via a TH, MDI, or AH.

Patients were excluded if they had received a diagnosis of chronic respiratory disease other than asthma, were at least 40 years of age with a history of smoking and no COPD exclusion, or been prescribed a separate ICS, long-term systemic treatment for asthma, or course of oral corticosteroids and/or antibiotics for a lower respiratory condition in the two weeks prior to review.

Our study cohort was restricted to the subset of patients from the database who were at least eighteen years of age and prescribed the TH, MDI, or AH devices. Patients were only using type of inhaler device. Analyses were carried out within device cohorts.

Study data

Patient demographic and clinical characteristics, including asthma control status and patient-selfassessment of inhaler technique [assessed using a Likert scale with scores ranging from 1 ("I think my inhaler technique is very poor,") to 6 ("I think my inhaler technique is excellent,")] were obtained via questionnaires completed online or in hard-copy on the review day.

Asthma control was assessed using the four Global Initiative for Asthma (GINA) criteria at the time (18), which asked patients if the experienced during the week preceding the review: daytime symptoms (more than twice per week); any night wakening due to asthma; need for reliever more than twice per week; and any limitation in daytime activity. Asthma control was defined as controlled (none of the above); partially controlled (1 or 2 of the above); or uncontrolled (3 or 4 of the above).

Self-reported adherence to maintenance therapy was assessed for patients from countries other than the Netherlands using the Medication Adherence Rating Scale (MARS). For patients from the Netherlands, adherence to maintenance therapy was assessed with the question, "Do you ever forget your prevention inhalation medication?" Adherence was categorized as poor for responses of 'very often,' or 'always;' borderline for responses of 'now and then' or 'regularly' and good for responses of 'never' or 'rarely.'

Other variables recorded during the iHARP interview explored in this study included age, gender, body mass index (BMI), and smoking status, which were shown in the CritiKal study (16) to be associated with significant differences in asthma control when varied. Educational status was further assessed, as recent research (19) had found an association between inferior educational levels and inhaler technique in patients with COPD, and we wanted to identify if this was also an issue in patients with asthma. Associations with patient-reported prior inhaler technique review by a HCP (20), and patient adherence (21) with poor inhaler technique have further been identified in the literature, and have thus been included as variables in this study. Finally, self-assessment of inhaler technique was further included as a variable, as prior research (22,23) has indicated there may be a discordance between patient perceptions of their accuracy in technique, and their actual accuracy. We therefore wanted to investigate if such a variable could possibly be associated with the performance of inhaler technique errors associated with poor asthma outcomes in practice.

Measurement of inhaler technique errors associated with poor asthma outcomes

Inhaler technique errors associated with poor asthma outcomes were defined as errors significantly associated with uncontrolled asthma and/or an increased rate of asthma exacerbations (iehaving at least one exacerbation in the 12 months prior to review) (16). The list of such errors for all 3 inhaler devices is shown in Table 1. We only considered these errors, as these are the only ones shown in the literature to be associated with poor asthma outcomes (16). HCPs were trained to identify inhaler technique errors by watching standardized instructional videos. Observational evaluation of each participant was then conducted via reference to standardized, device-specific checklists developed by clinical experts in the iHARP steering committee. Whilst inhaler use was observed once or twice as per the number of doses required, the data used in this study is restricted to the errors only made on first inhalation through the device.

Statistical analyses

Statistical analyses were performed using SPSS Statistics version 24. Characteristics of patients who made no inhaler technique errors associated with poor asthma outcomes using each device were compared with those making one or more (1) inhaler technique errors associated with poor clinical outcomes. Continuous variables that were normally distributed were compared using the Student's t-test and the Mann-Whitney U-test was used for continuous variables that were not normally distributed. Categorical variables were compared using the v^2 test.

Characteristics associated with making errors associated with poor asthma outcomes were initially identified using univariate logistic regression models with a dichotomous indicator variable for errors associated with poor clinical outcomes made (yes/no) as the dependent variable, and the patient characteristics as independent variables.

Multivariate logistic regression analysis was then performed on the univariate predictors, with $p <$ 0.05 used as the threshold for entry into the model. The goodness of fit of the logistic regression model was confirmed by the Hosmer-Lemeshow test. A significance level of $p <$ 0.05 was used for all statistical procedures.

Results

Patients

After applying inclusion and exclusion criteria, the data from 4134 adult patients from the iHARP database with asthma were available for inclusion and analysis into this study. Three device cohorts were formed based on the three most common inhaler devices used by patients; with TH used by 2065 (46.2%) patients, MDI used by 1245 (27.9%) patients, and AH used by 824 (18.4%) patients. Using the GINA-defined criteria, 30.5% had controlled asthma, 43.9% had partly controlled asthma and 25.6% had uncontrolled asthma. There was no significant difference in these proportions across devices.

1) Turbuhaler cohort

a. Patient characteristics:. There were 2065 (46.2%) patients, with patients present from the UK (1035 [50.1%]), France (7, [0.3%]), Holland (498, [24.1%]), Italy (104, [5.0%]), Norway (14, [0.7%]), Spain (273, [13.2]), Sweden (55, [2.7]), and Australia (79, [3.8%]). The final study cohort comprised 61% females, had a

Table 2a. Patient characteristics part 1 - TH.

Characteristic	Total (n ¼ 2065)	0 errors (n ¼ 817)	1 errors (n ¼ 1248)	p value
Age, mean (SD)	50 (15)	50 (15)	50 (14)	0.97
18-30 years, n (%)	270 (13)	106 (13)	164 (13)	0.013
31-50 years, n (%)	703 (34)	290 (36)	413 (33)	
51-70 years, n (%)	1016 (49)	379 (46)	637 (51)	
> 70 years, n (%)	76 (4)	42 (5)	34 (3)	
Sexn(%)				0.001
Female	1250 (61)	459 (56)	791 (63)	
Male	815 (39)	358 (44)	457 (37)	
Body mass index, n (%)	0.27			
Underweight	20 (1)	5 (1)	15 (1)	
Normal	622 (30)	251 (31)	371 (30)	
Overweight	751 (36)	442 (38)	309 (35)	
Obese	672 (33)	252 (15)	420 (34)	
Smoking status, n (%)	0.322			

Current smoker	281 (14)	102 (13)	179 (14)	
Ex-smoker	686 (33)	284 (35)	402 (32)	
Non-smoker	1098 (53)	431 (53)	667 (54)	
Education, known status, n (%)	1400 (68)	527 (38)	873 (62)	0.054
Post-graduate or professional degree	49 (4)	18 (3)	31 (4)	
University degree	466 (33)	187 (36)	279 (32)	
Secondary education	704 (50)	272 (52)	432 (50)	
Primary education	155 (11)	43 (8)	112 (13)	
None	26 (2)	7 (1)	19 (2)	
Patient-reported prior inhaler review by HCP	1019 (49)	431(35)	588 (38)	0.012
Patient self-assessment of inhaler technique, n(%), known	1728 (84)	645 (37	1083 (63)	0.001
Very poor to poor	54 (3)	12 (2)	42 (4)	
Fair to average	286 (17)	85 (13)	201 (19)	
Good to excellent	1388 (80)	548 (85)	840 (78)	
Adherence to therapy, n(%)	2029 (98)	803 (65)	1226 (79)	0.021
Poor	491 (24)	171 (21)	320 (26)	
Borderline	84 (4)	29 (4)	55 (4)	
Good	1454 (72)	603 (75)	851 (69)	
Adherence to therapy in the Netherlands, n(%), known	498 (24)	248 (50)	250 (50)	0.643
Poor	42(8)	18 (7)	24 (10)	
Borderline	101 (20)	51 (20)	50 (20)	
Good	355 (71)	179 (72)	176 (70)	

mean (SD) age of 50 (15) years, and 281 (14%) were current smokers (Table 2a).

b. Patient characteristics associated with making THtechnique errors associated with poor asthma outcomes:. Sixty percent (60.4%) of patients made from 1 to 6 errors associated with poor clinical outcomes, most commonly one (605 [29.3%]), two (310 [15.0%]), and three (183 [8.9%]) errors; 150 patients (7.2%) made at least four errors. The most frequently made errors were not exhaling slowly to empty the lungs (26.3%), not holding the device upright (within 45) after the base is twisted until inhalation (19.6%), and not inhaling forcefully from the start of inhalation (18.8%) (Figure 1).

Patients making at least one error associated with poor asthma outcomes were significantly more likely to be female, not have undertaken an inhaler review within the twelve months prior to the iHARP assessment, have 'poor-to-borderline' adherence to therapy as opposed to 'good' adherence, and self-assess their inhaler technique as 'very poor to average' as opposed to 'good-to-excellent.' Whilst age appeared to be a factor, subsequent univariate logistic regression did not reveal any significant relationship between age and critical error performance. Body mass index, smoking status, and educational status were not significantly associated with making at least oneerror associated with poor asthma outcomes (Table 2a).

c. Risk factors for making inhaler technique errorsassociated with poor asthma outcomes: multivariable model. The univariable logistic regression results for the risk of making 1 error associated with poor asthma outcomes are reported in Table 2b. There were no correlations between the univariate predictors.

A multivariable logistic regression was performed to determine the effects of gender, inhaler technique review by a trained healthcare professional, MARS adherence, age, and self-assessment of inhaler technique on the risk of performing at least one error associated with poor asthma outcomes.

The multivariable logistic regression model contained 4 independent variables, and was statistically significant (v2 ¼ 32.990, df ¼ 5, p< 0.001) (Table 2c).

Both gender and self-assessment of inhaler technique were significantly associated with the likelihood

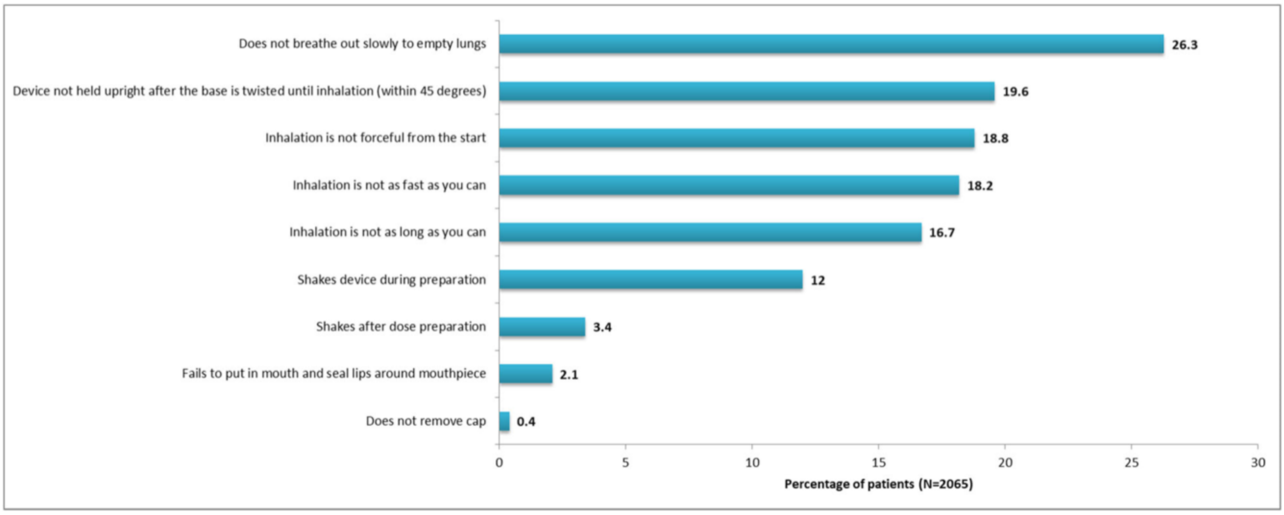

Figure 1. Incidence of TH errors associated with poor asthma outcomes.

Table 2b. Univariate and multivariate logistic regression - TH.

Analysis	Predictors	Reference Category (0)	Category (1)	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B) Lower	Upper
Univariate	Gender	Male	Female	0.300	0.092	10.69	1	0.001	1.35	1.128	1.616
	Inhaler Technique Reviewed	Reviewed	Not reviewed	0.226	0.090	6.273	1	0.012	1.253	1.05	1.496
	MARS adherence	Good	Poor/Borderline	0.284	0.102	7.688	1	0.006	1.329	1.087	1.624
	Age - Group 1	> 51 years	18-30 years	0.030	0.139	0.046	1	0.831	0.971	0.739	1.275
	Age - Group 2	> 51 years	31-50 years	0.113	0.099	1.302	1	0.254	0.894	0.736	1.084
	Age- Group 3	> 51 years	18-50 years		0.090	0.991	1	0.320	0.914	0.766	1.091
	Self-assessment of inhaler technique	Good to excellent	Very poor to average	0.4910.090	0.132	13.836	1	0.000	1.634	1.262	2.117

Multivariate (no interaction)	Gender	Male	Female	0.383	0.102	14.083	1	<0.001	1.467	1.201	1.793
	Self-assessment of inhaler technique	Good to excellent	Very poor to average	0.474	0.133	12.649	1	<0.001	1.607	1.237	2.086
	MARS adherence	Poor/Borderline	Good	0.121	0.109	1.237	1	0.266	0.886	0.716	1.096
	Inhaler Technique Reviewed	Not reviewed	Reviewed	0.147	0.102	2.097	1	0.148	0.863	0.707	1.053

TH

of making an error associated with poor asthma outcomes. In particular, females were almost 1.5 times more likely than males to make an error associated with poor asthma outcomes (OR ¼ 1.467, 95%

CI:1.201–1.793, p< 0.001), and those who self-assessed their inhaler technique to be "very-poor-to-average" were almost twice as likely to make an error associated with poor asthma outcomes to those who selfassessed their inhaler technique as "good-toexcellent"(OR ¼ 1.607, 95% CI:1.237–2.086, p< 0.001). There were no interactions between the variables.

2) MDI Cohort

a. Patient characteristics:. There were 1245 (27.9%) patients, with patients present from the UK (917 [73.1%]), Italy (149 [12.0%]), Spain (88 [7.1%]), Australia (57 [4.6%], Holland (27 [2.2%]), Norway (5 [0.4%]), and France (2 [0.2%]). The final study cohort comprised 60% females, had a mean (SD) age of 50

(14) years, and 167 (13) were current smokers

(Table 3).

b. Patient characteristics associated with makingMDI technique errors associated with poor asthma outcomes:. Fifty seven percent (57.3%) of patients made from 1 to 5 errors associated with poor asthma outcomes, most commonly one (421 [33.8%]), two (176 [14.1%]), and three (63 [5.1%]) errors; 53 patients (4.3%) made at least four errors. The most frequently made errors were not tilting the head such that the chin is slightly upwards during inhalation (31.3%), not exhaling prior to inhalation (24.1%), and actuating the inhaler device prior to inhalation (23.5%) (Figure 2).

Patients making at least one error associated with poor asthma outcomes were significantly more likely to be female, have no greater than a secondary education, and rate their inhaler technique as 'very poor to average' (Table 3a). Whilst smoking status appeared

Table 3a. Patient characteristics, part 1 - MDI.

Characteristic	Total (n ¼ 1245)	0 errors (n ¼ 532)	1 errors (n ¼ 713)	p value
Age, mean (SD)	50 (14)	51 (15)	51 (15)	0.301
18-30 years, n (%)	139 (11)	56 (11)	83 (12)	0.240
31-50 years, n (%)	456 (37)	212 (40)	244 (34)	
51-70 years, n (%)	609 (49)	248 (47)	361 (51)	
> 70 years, n (%)	41 (3)	16 (3)	25 (4)	
Sex, , n (%)				0.003
Female	743 (60)	292 (55)	451 (63)	
Male	502 (40)	240 (45)	262 (37)	
Body mass index, n (%)		0.242		
Underweight	26 (2)	16 (3)	10 (1)	
Normal	363 (29)	155 (29)	208 (29)	
Overweight	429 (35)	185 (35)	244 (34)	
Obese	427 (34)	176 (33)	251 (35)	
Smoking status, n (%)	0.032			
Current smoker	167 (13)	56 (11)	111 (16)	
Ex-smoker	373 (30)	161 (30)	212 (30)	
Non-smoker	705 (57)	315 (59)	390 (55)	
Education, known status, n (%)	1023 (82)	436 (43)	587 (57)	0.009
Post-graduate or professional degree	59 (6)	30 (7)	29 (5)	
University degree	318 (31)	157 (36)	161 (27)	
Secondary education	517 (51)	201 (46)	316 (54)	
Primary education	109 (11)	43 (10)	66 (11)	
None	20 (2)	5 (1)	15(3)	
Patient-reported prior inhaler review by HCP	639 (51)	277 (53)	362	0.596
Patient self-assessment of inhaler technique, n(%), known	1178 (95)	501 (43)	677 (57)	0.01
Very poor to poor	65 (5)	24 (5)	41 (6)	
Fair to average	232 (20)	80 (16)	152 (23)	
Good to excellent	881 (75)	397 (79)	484 (71)	
Adherence to therapy, n(%)	1196 (96)	509 (43)	687 (57)	0.881
Poor	448 (38)	188 (37)	260 (38)	
Borderline	64 (5)	26 (5)	38 (6)	

Good	684 (57)	295 (58)	389 (57)	
Adherence to therapy in the Netherlands, n(%), known	27 (2)	14 (52)	13 (48)	0.754
Poor	5 (19)	2 (14)	3 (23)	
Borderline	10 (37)	6 (43)	4 (31)	
Good	12 (44)	6 (43)	6 (46)	

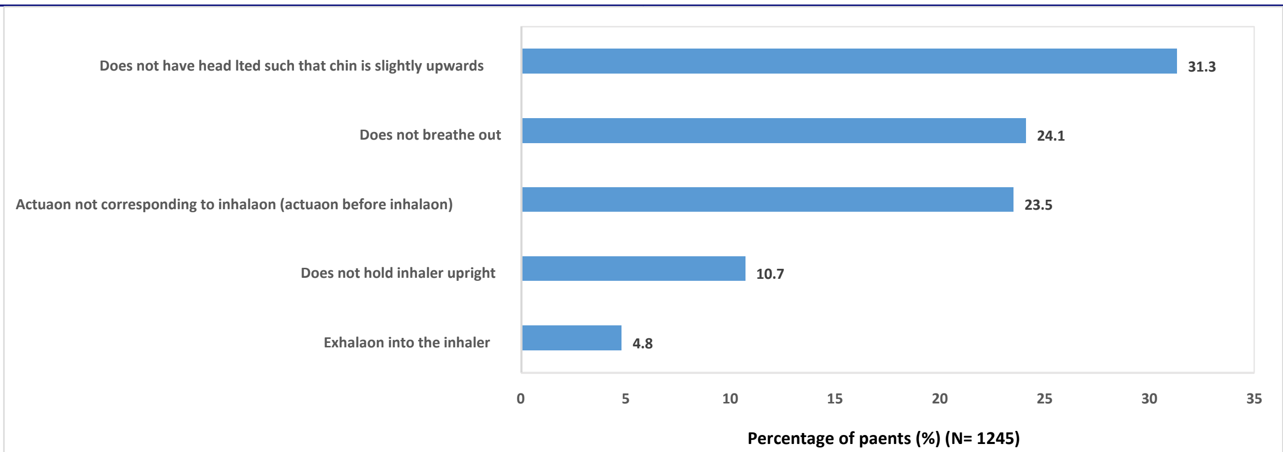

Figure 2. Incidence of MDI errors associated with poor asthma outcomes.

to be a factor, subsequent univariate logistic regression did not reveal any significant relationship between smoking status and performance of inhaler technique errors associated with poor asthma outcomes (Table 3b). Age, body mass index, patient-reported prior inhaler technique review by a trained healthcare professional, and adherence to therapy were not identified associated with making such errors. (Table 3a).

c. Risk factors for making inhaler technique errorsassociated with poor asthma outcomes: multivariable model. The univariable logistic regression results for the risk of making 1 error associated with poor asthma outcomes are reported in Table 3b. There were no correlations between the univariate predictors.

A multivariable binomial logistic regression was performed to determine the effects of gender,

Table 3b. Univarate and multivariate logistic regression - MDI.

Analysis	Predictors	Reference Category (0)	Category (1)	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B) Lower	Upper
Univariate	Gender	Female	Male	0.347	0.117	8.837	1	0.003	0.707	0.562	0.888
	Education	Postgrad/prof/uni degree	Secondary education	0.437	0.137	10.163	1	0.001	1.547	1.183	2.024
	Self-assessment of Inhaler Technique	Good to excellent	Very poor to average	0.420	0.139	9.108	1	0.003	1.522	1.159	2.000
	Smoking Status	Current Smoker	Non-smoker	0.471	0.181	6.793	1	0.009	0.625	0.438	0.89
Multivarite	Gender	Male	Female	0.453	0.169	7.221	1	0.007	1.574	1.131	2.191
	Education	Secondary education	Postgrad/prof/uni degree	0.355	0.168	4.453	1	0.035	0.701	0.504	0.975
	Self-assessment of Inhaler Technique	Very poor to average	Good to excellent	0.494	0.283	0.2	1	0.157	0.753	0.509	1.115
	Smoking Status	Non-smoker	Current smoker	0.462	0.218	4.475	1	0.034	1.587	1.035	2.436

educational status, self-assessment of inhaler technique, and smoking status on the odds of performing at least one inhaler technique error associated with poor asthma outcomes.

The multivariable logistic regression model contained 4 independent variables, and was statistically significant (v2 ¼ 20.153, df ¼ 4, p< 0.001) (Table 3b).

Gender, educational status, self-assessment of inhaler technique, and smoking status were significantly associated with an increased risk of making errors associated with poor asthma outcomes. The study identified that females were 1.6 times more likely to make an error associated with poor asthma outcomes, (OR ¼ 1.574, 95% CI:1.131–2.191, p< 0.05), patients with a secondary education 1.4 times more likely to make an error associated with poor asthma outcomes compared to those with a university degree (OR ¼ 1.427, 95% CI:1.026–1.984, p< 0.001), and current smokers almost 1.6 times more likely to make an error associated with poor asthma outcomes than nonsmokers (OR ¼ 1.587, 95% CI:1.035–2.436, p< 0.05) (Table 3c). There were no interactions between the variables.

3) Ah cohort

a. Patient characteristics:. There were 824 (18.4%) patients, with patients present from England (328 [39.8%]), Italy (148 [18.0%], Spain (140 [17.0%]), Holland (127[15.4%]), Australia (46[5.6%]), France (11[1.3%]), Norway (17[2.1%]), and Sweden (7[0.8%]).
The final study cohort comprised 61% females and had a mean (SD) age of 51 (15) years. 105 (13) were current smokers (Table 4a).

b. Characteristics associated with making AH tech-nique errors associated with poor asthma outcomes:. Fifty one percent (51.6%) of patients made from 1 to 4 errors associated with poor asthma outcomes, most commonly one (216 [26.2%]), two (112 [13.6%]), and three (58 [7.0%]) errors; 39 patients (4.7%) made four errors. The most frequently performed errors were not exhaling slowly to empty the lungs prior to inhalation (32.5%), not inhaling forcefully from the start (21.1%), and not inhaling as fast as one can (20.8%) (Figure 3).

Patients making 1 error associated with poor asthma outcomes were significantly more likely to have a secondary as opposed to tertiary education, have not had had their inhaler technique reviewed by a trained HCP in the previous 12 months, and selfassess their inhaler technique as being 'very poor to average' as opposed to 'good to excellent' (Table 4a).

Age, gender, body mass index, smoking status, MARS adherence were not significantly associated with making at least one error associated with poor asthma outcomes (Table 4a).

c. Risk factors for making AH technique errors asso-ciated with poor asthma outcomes: multivariable model. The univariable logistic regression results for the risk of making 1 inhaler technique error associated with poor asthma outcomes are reported in Table 4b. There were no correlations between the univariate predictors. The multivariable logistic regression model contained 2 independent variables and was statistically significant (v2¼ 18.115, df ¼ 12, p< 0.001). Patients who made 1 error associated with poor asthma outcomes were almost twice as likely to not have had their inhaler technique reviewed in the previous 12months (OR ¼ 1.654, 95% CI:1.225–2.235, p¼ 0.001), and were 1.5 times as likely to have self-assessed their inhaler technique as being 'very poor to average' as opposed to 'good to excellent" (OR ¼ 1.500, 95% CI:1.053–2.137, p< 0.05) (Table 4c). There were no interactions between the variables.

Discussion

This research, to our knowledge, is the first to identify patient factors associated with making inhaler technique errors specifically associated with poor asthma outcomes for people with asthma in primary care.

Table 4a. Patient characteristics part 1 - AH.

Characteristic	Total N (%) (n ¼ 824)	0 errors (n ¼ 399)	1 errors (n ¼ 425)	p value
Age, mean (SD)	51 (15)	51 (14)	51 (15)	0.59
18-30 years, n (%)	91 (11)	46 (12)	45 (11)	0.24
31-50 years, n (%)	283 (34)	137 (34)	146 (34)	
51-70 years, n (%)	408 (50)	202 (51)	206 (48)	
> 70 years, n (%)	42 (5)	14 (4)	28 (7)	
Sex, n (%)				0.128
female,	495 (61)	229 (57)	266 (63)	
Male	329 (40)	170 (43)	159 (37)	
Body mass index, n (%)	0.944			
Underweight	9 (1)	5 (1)	4 (1)	
Normal	275 (33)	135 (34)	140 (33)	
Overweight	288 (35)	140 (35)	148 (35)	
Obese	252 (31)	119 (30)	133 (32)	
Smoking status, n (%)	0.554			
Current smoker	105(13)	47 (12)	58 (14)	
Ex-smoker	260 (32)	132 (33)	128 (31)	
Non-smoker	459 (56)	220 (55)	239 (56)	
Education, known status, n (%)	641 (78%)	302 (47)	339 (53)	0.011
Post-graduate or professional degree	15 (2)	11 (4)	4 (1)	
University degree	187 (30)	99 (33)	88 (26)	
Secondary education	281 (44)	130 (43)	151 (45)	
Primary education	128 (20)	55 (18)	74 (22)	
None	30 (5)	8 (3)	22 (6)	
Patient-reported prior inhaler review by HCP	352 (43)	197 (49)	155 (37) (out of 423)	<0.001
Patient self-assessment of inhaler technique, n(%), known	716 (87)	346 (48)	370 (52)	0.026
Very poor to poor	27 (4)	12 (3)	15 (4)	
Fair to average	145 (20)	56 (16)	89 (24)	
Good to excellent	544 (76)	278 (80)	266 (72)	
Adherence to therapy, n(%)	790 (96)	388 (49)	402 (51)	0.072
Poor	263 (33)	114 (29)	149 (37)	
Borderline	51 (6)	26 (7)	25 (6)	

Good	476 (58)	248 (64)	228 (57)	
Adherence to therapy in the Netherlands, n(%), known	127 (15)	71 (56)	56 (44)	0.299
Poor	13 (10)	9 (13)	4 (7)	
Borderline	23 (18)	15 (21)	8 (14)	
Good	91 (71)	47 (66)	44 (79)	

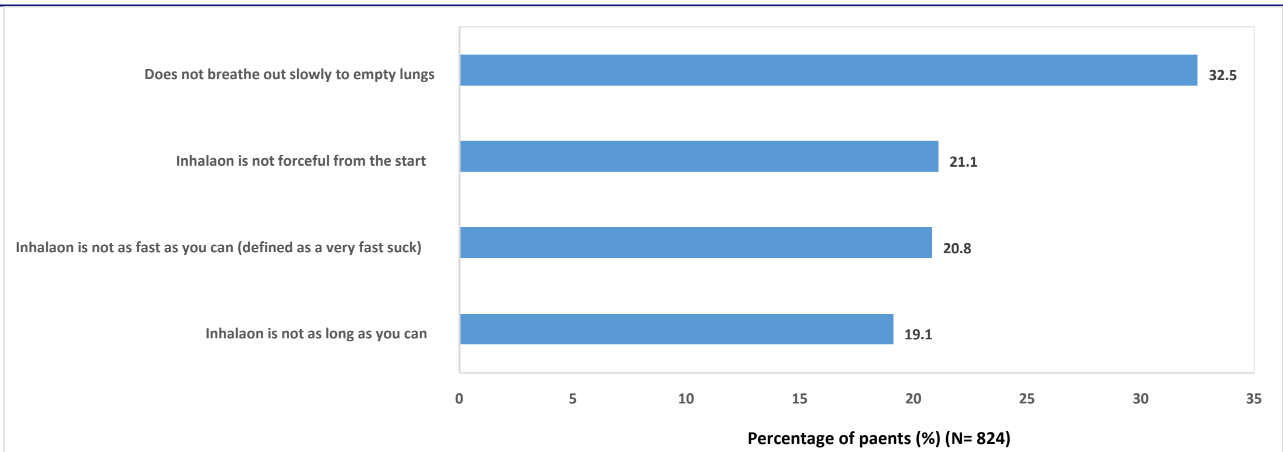

Figure 3. Incidence of AH errors associated with poor asthma outcomes.

The risk factors for making inhaler technique errors which are associated with poor asthma outcomes were not identical across the different devices. For the TH, risk factors for performing 1 error associated with poor asthma outcomes were being female and being aware of sub-optimal inhaler technique (based on selfassessment of inhaler technique as “very-poor-to-average” relative to “good-to-excellent”). For the MDI, risk factors

for performing 1 error associated with poor asthma outcomes were being female, secondary as opposed to a postgrad/prof/or university education, and being a current smoker. For the AH, risk factors for performing 1 error associated with poor asthma outcomes were lack of inhaler technique review by a trained healthcare professional in the previous twelve months and being aware of sub-optimal inhaler technique (based on self-

Table 4b. Univariate and multivariate logistic regression - AH.

Analysis	Predictors	Reference Category (0)	Category (1)	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B) Lower	Upper
Univariate	Patient Reported Inhaler Review	Reviewed	Not reviewed	0.522	0.142	13.509	1	<0.001	1.686	1.276	2.228
	Self Assessment of Inhaler Technique	Good to excellent	Very poor to average	0.469	0.178	6.944	1	0.008	1.598	1.128	2.266
	Education (Group 1)	Post-graduate/ prof/uni degreed	Secondary Education	0.328	0.185	3.147	1	0.076	1.389	0.966	1.996
	Education Level (Group 2)	Secondary	None/Primary	0.287	0.202	2.022	1	0.155	1.333	0.897	1.981
Multivariate	Patient Reported Inhaler Review	Reviewed	Not reviewed	0.503	0.153		1	0.001	1.654	1.225	2.235
(no interaction)	Self-Assessment of Inhaler Technique	Very poor to average	10.774 Good to excellent 5.042	0.405	0.18		1	0.025	0.667	0.468	0.950

assessment of inhaler technique as “very poor to average” as opposed to “good for excellent”).

This study is important to this field of knowledge, research and practice as it, for the first time, focuses only on errors which have been proven to be associated with poor clinical outcomes in real life/daily practice (16), and focuses on determining predictors of errors associated with poor asthma outcomes. In the complex field of asthma management, this is particularly important as there are many facets to asthma management and the challenges associated with managing them all simultaneously can be overwhelming. This enables HCPs to target resources toward implementation of interventions specifically able to reduce the errors that really matter (those more likely to contribute to increased hospitalizations and healthcare expenditure). Identifying these factors can also enable a HCP to predict which patients are more likely to perform an error associated with poor asthma outcomes for at least three commonly prescribed devices. Ultimately, this new knowledge is able to assist HCPs to identify patients at risk of poor asthma outcomes, based on risk factors for poor medication use.

The study further identified that the performance of specific inhaler technique errors associated with poor asthma outcomes is common in practice, with over half of the cohort of patients using each device making at least one of these asthma-outcome-related errors. Overall, the most frequent errors associated with poor clinical outcomes for the dry powder inhalers (DPIs, being the TH and AH) were related to breathing maneuvers ienot exhaling prior to inhaling for the TH and AH, and positioning (not having the head tilted such that the chin is pointing slightly upwards) for the MDI device. In addition, whilst these were the most common errors associated with poor clinical outcomes, it is important to note that a majority of patients also made multiple errors associated with poor clinical outcomes.

These results correlate with prior studies indicating that incorrect technique when using inhaled medicines is very common among patients with asthma or COPD (1,14,24), with some indicating that as few as 10% of patients use correct technique (4,5). Whilst varying from results from previous investigations identifying not holding the inhaler upright (9,25), not inhaling forcefully enough through the device (26) for DPIs, and continuing to inhale after device actuation (11) not coordinating actuation with inspiration (25), and incorrect preparation of the device (2,26) for the MDI to be more common errors, a number of factors could have contributed to these discrepancies. This includes limitation of analysis to errors associated with poor asthma outcomes only, and study design variations. This further highlights the advance made to this field of research with regards to identifying errors that truly matter with regards to clinical outcomes.

It was interesting to note that our study did not identity smoking status as a predictor for higher frequency of inhaler technique errors associated with poor clinical outcomes for any of the DPI devices. Smoking triples the risk of airflow obstruction in nonatopic asthmatics (27), potentially influencing the risk of not inhaling as fast as you can or as forcefully, inhaler technique errors determined to be associated with poor asthma outcomes in the TH and AH devices. However, as it is not known which phenotype of asthma our study cohort had, it is not known if this is potentially a predictor of making such errors. Future research could therefore aim to investigate this in patients with known non-atopic asthma.

In contrast to previous investigations, age was not associated with increased incidence of inhaler technique errors associated with poor asthma outcomes (5,7,8,10–13). However, this difference could be due to the influence of multiple factors potentially affecting inhaler technique also associated with age, such as declining muscle strength and inspiratory flow, which were potentially not accounted for in previous studies.

The results for gender correlated with results by Goodman et al. (6), and Capanoglu et al. (2) but contrasted with Van Beernendonk et al. (11) Hesselink et al. (25), Sadowski et al. (28) who did not identify any relationship between gender and device use. Chafin et al. (29) further did not note a relationship between MDI device technique and gender when patients were inhaling at rates less than 18L/min. However, it should be noted that they examined the MDI when used with a spacer, which assists in holding the medication particles for a longer period and such, facilitates the ease with which a slower, inspiratory breath can be taken. In our study, we did investigate any patients using a spacer or similar holding aid, and thus, gender still appears to be an issue in the real-world setting when only an MDI (without a spacer). It further contrasts with Westerik et al. (20), who identified a significant association between female gender and increased rates of serious errors in patients prescribed the AH; however, ours was the only study to explore only errors associated with poor asthma outcomes. In addition, we used an intercontinental database with a significantly greater sample size, improving accuracy.

Variations in the results regarding age in the MDI sample could further be due to explicit exclusion of patients with COPD in this study, a further factor associated with increased error rates in MDI users (15). In addition, it did not differentiate between patients with late- or early-onset asthma. This could affect the results by affecting their level of experience using their inhaler device and recency of training.

BMI was further identified not to be a risk factor for the performance of inhaler technique errors associated with poor asthma outcomes. This is important, as obesity doubles the odds of developing asthma (30), and with obesity becoming a growing health concern, it is essential that any further risks it may have on the management of asthma be identified and addressed as early as possible.

Lack of comprehensive training in device technique was further significant for the AH. Currently, there is explicit evidence that patients of any age are unlikely to use inhalers correctly unless they are given an effective educational intervention/instruction, including a physical demonstration, and have their inhaler technique checked regularly (1,3). The results of this study once again highlight the need for repeated intensive instruction in inhaler technique by trained healthcare professionals (at least in the previous 12months), and the need to consider personalized prescribing. For example, a female patients may be more suited to the use of an AH device, whereas patients who are unable to attend regular review sessions on inhaler technique may be better suited to the use of a MDI or TH device.

Personalized prescribing could therefore safely and effectively reduce exacerbations, hospitalizations admissions, and ultimately, healthcare costs.

This study calls for a shift in the current paradigm as it relates to inhaler technique/use. Whilst historically, research and practice around inhaler technique has not been based on a specific understanding or knowledge about the inhaler technique errors that impact on asthma outcomes; we now have evidence that some

(and not all) inhaler technique errors are directly associated with poor asthma outcomes. It is these specific evidence-based errors that therefore need to be 'named' and used in reference to all matters relating to inhaler technique in the future. Moving forward, there seems little value in obsessing over all errors but rather a precision approach which focuses on individuals and their ability to perform the 'critical' steps correctly is essential.

It further illuminates a demand to develop standardized terms to identify which errors are evidence-based in practice being linked to poor asthma outcomes. Whilst use of the words 'non-serious', 'potentially serious,' and 'serious' are often used in practice to describe the impact of an inhaler technique error on patient clinical asthma outcomes, there is no term present to describe an error shown by evidence to contribute to poor asthma outcomes. Development of a standardized internationally and inter-professionally recognized terminology can assist HCPs and patients to rapidly identify their risk of poor outcomes and discuss patient care and education in a manner explicitly understood by all parties.

This study is the first of its kind to identify the characteristics of the patients performing TH, MDI, and AH errors associated with poor asthma outcomes. Further investigations could assist in improving data by including objective inhaler technique with devices such as the InCheck ™ Dial or the Aerosol Inhalation Monitor, accessing medical records from healthcare facilities rather than relying on patient recall, and further exploring the nature of certain patient characteristics (e.g.how often inhaler technique review had been performed in the previous 12months, and which style of training).

Limitations of the study

The use of real-life datasets presents a set of limitations for which adjustments are not always possible, particularly the issue of missing data, which in the required anonymised form was not feasible to retrieve. In addition, variabilities in the abilities of the assessor to objectively evaluate particular inhaler technique errors may also have been evident, for example, with inhaler technique errors such as 'inhalation as fast as you can,' which may be interpreted differently between assessors.

A further limitation is that the study only explored patients who had been prescribed one type of inhaler device. In the real-world setting, patients may be prescribed more than one type of inhaler device if they are on multiple respiratory medications. This could lead to confusion and difficulty remembering the steps for appropriate use of each device, which could potentially lead to a greater number of errors than what has been presented in the iHARP database. Investigation in a set of patients using multiple types of inhalers could assist in improving the external validity of the study.

Conclusion

This study indicates that inhaler technique errors associated with poor asthma outcomes differ according to particular patient characteristics. These patient characteristics should be used to predict those patients who are likely to experience poorer asthma outcomes, as a result of poor inhaler technique and should be used to guide more appropriate prescribing of inhaler devices.

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Declaration of interest

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting the following conflicts of interest.

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Board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva (Sanofi Generics); payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Skyepharma, Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, Zentiva (Sanofi Generics); stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment.

I have disclosed those interests fully to Taylor & Francis, and I have in place an approved plan for managing any potential conflicts arising from these involvements.

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Chapter 5

Discussions and Conclusions

5.1: Discussion of Results

The aim of this thesis was to identify the patient groups most at risk of poor clinical asthma outcomes in consequence of inadequate inhaler technique, that is, those patients most likely to benefit from the skills of community pharmacist with regards to asthma management and inhaler technique training. In light of the global trend towards an ageing population [7], this thesis further aimed to identify the existence of any associations between older age and the performance of inhaler technique errors, both critical and non-critical in nature, across a range of pMDI and DPI devices, to determine if any broader associations were evident in practice.

The results of my systematic literature review (Section 4.3) revealed an absence of any clear positive associations between older age and the performance of a greater number of inhaler technique errors. However, a broad array of factors should be considered when exploring both the accuracy and ecological validity of these results. These include variations in the age threshold for 'older age' across studies, inconsistences in the lists of inhaler technique errors between studies, and a lack of exploration of the impact of age on the performance of inhaler technique errors with specific DPI devices, for example, the AH and TH devices, as opposed to the broader class of DPI devices.

Thus, a further aim of this thesis was to determine patient factors associated with the performance of critical inhaler technique errors in patients prescribed the TH, MDI, and AH device. By restricting the subset of inhaler technique errors to those solely associated with poor asthma outcomes, this study was able to address the aim of identifying which patient groups were most at risk of poor clinical asthma outcomes, utilising inhaler technique as a marker, to better assist community pharmacists to identify high risk patients in practice. To determine this, a retrospective cross-sectional study using the iHARP database [225] was performed, using multivariable logistic regression to identify factors associated with the performance of at least one critical inhaler technique error.

Of importance, this study identified that these factors varied with the type of inhaler device prescribed. For the TH cohort, factors associated with the performance of critical inhaler technique errors were *female gender* and '*very poor to average' self-assessment of inhaler technique;* for the AH cohort, factors associated with the performance of critical inhaler technique errors were *lack of inhaler technique review by a trained healthcare professional in the previous twelve months* and '*very poor to average' self-assessment of inhaler technique*, and for the MDI cohort, factors associated with the performance of such errors were *female gender, secondary education* and *current smoking status*.

The fact that these patient demographic variables altered with the type of device indicates a stringent need for healthcare professionals to consider the type of device that would be most appropriate for the patient when prescribing inhaled asthma pharmacotherapy, as based on their demographic characteristics. This is further applicable to the broader class of device, with both the TH and AH devices presenting with differing factors, despite being both categorised as DPI devices. The broad range of factors present further indicates that a significant number of patients in both the national and international setting are at high risk of poor asthma outcomes purely based on their inhaler technique. This raises an urgent case for assessment of the suitability of a particular inhaler device to be conducted by the pharmacist, regular re-assessment of such devices to be conducted in case of any changes in the cognitive or physical status of the patient, and, in the case where a specific type of inhaler device cannot be avoided in the patient, comprehensive inhaler technique training be provided.

Of particular interest, older age was not determined to be associated with the performance of critical inhaler technique errors for any of the devices, contrasting significantly to results obtained from prior studies [166, 167, 169, 226, 227]. Whilst the findings of the systematic literature review in section 4.3, above, were inconclusive with regards to older age being a risk factor for poor inhaler technique, there were a number of reasons, as per the narrative literature review in section 4.2, above, why it was hypothesised that older age would be associated with inferior inhaler technique. These were inclusive of an increased frequency of inhaler technique errors [167], age-related reductions in muscle strength [166], age-related reductions in PIF [177], and a reduction in the ability to be successfully trained in inhaler technique [167]. Although disproving this hypothesis, it should be considered that a multitude of factors may have contributed to such results.

Firstly, in both the narrative and systematic literature review, the potential influence of age on a broad range of inhaler technique errors was explored. In the original research paper in section 5.1 above, however, the range of inhaler technique errors explored was limited to the subset of those evidenced to contribute to poor asthma outcomes, as per the Critikal Study [9]. Whilst this was undertaken purposefully to form a direct link with poor asthma outcomes, it is unknown if exploration of the impact of age on the broader gamut of inhaler technique errors could have resulted in older age being a risk factor for poor inhaler technique. Further investigations exploring the impact of age in a controlled setting on a broader range of inhaler technique errors may potentially result in differing findings.

Secondly, the impact of any potential confounders on the result applicability of this study should further be considered. In particular, it is unknown whether the influence of multiple physical factors potentially affecting inhaler technique had been accounted for in in previous studies, and whether otherwise healthy older adults would also have demonstrated inferior inhaler technique (that is, is it age in itself or the issues that advancing age presents which contributes to such outcomes). However, in considering that older adults would often present with multiple co-morbidities in the real-world setting, the question remains in whether controlling for such health conditions, as occurred in our study, could actually lead to a reduction in the ecological validity of the study.

Whilst it could be considered that a specific medical condition more prevalent in older adults may be the factor contributing to poor inhaler technique as opposed to age in itself, the fact that older adults may be more likely to present with such conditions still may place them at greater risk of poor inhaler technique. It would further be interesting to note whether patients with asthma are more at risk of developing any co-morbidities potentially affecting their inhaler technique as they advance in age relative to younger adults with asthma, further compounding their potential risk of performing critical inhaler technique errors. Further research exploring a broad range of older adults with varying medical conditions without controlling for such factors could assist in identifying whether age is indeed associated with inferior inhaler technique.

Thirdly, factors pertaining to the cohort utilised may also have contributed to these results. One of the strengths of this study was the large sample size of 4134 adult patients. However, the geographical distribution of these patients was limited to eight countries, seven of which were in Europe [228]. This is a significant concern, as it may have potentially excluded regions experiencing numerous issues affecting asthma control, including significant air pollution, a greater proportion of people smoking or lack of strong public health campaigns with regards to smoking cessation, or lack of accessibility to healthcare professionals, as may be evident in those nations with poor infrastructure or a lower percentage of trained healthcare professionals.

Of particular concern, it excluded the ten countries with the greatest number of COPD cases, being China, India, Indonesia, USA, Bangladesh, Japan, Pakistan, Russia, Vietnam, and Germany [229]. Whilst this study explored patients with asthma, older adults are more likely to present with asthma-COPD overlap [230], and, as such, these patients may not have been under-represented in this particular study. As discussed in chapter 4, above, COPD, a condition more greatly represented in in the older adult population [140], can affect the use of proficient use of inhaler devices in a vast myriad of manners, including reducing the PIF able to be obtained by such patients [231], and, therefore, the maximum dosage of drug they are able to inhale. As such, extension of the patient sample to those from nations in which patients are potentially more likely to have asthma-COPD overlap may influence these results.

A further consideration in the potential impact of age on the performance of critical inhaler technique errors is their ability to be trained in correct inhaler technique. As discussed in section 4.2, above, older adults may be at increased risk of not being able to be trained successfully on inhaler technique [166, 167], and/or not retaining inhaler technique instructions [186]. An extensive body of evidence indicates that regular, repeated inhaler technique by trained healthcare professionals may assist in improving inhaler technique and the ability to retain inhaler technique instructions [27], and thus, extension of the study cohort to geographical areas in which healthcare professionals may be less easily accessible (for example, third world countries or those with less roads and infrastructure or a lower percentage of adequately trained healthcare professionals) may further influence the results obtained. Therefore, it is highly advised that future study by performed in a broader range of countries and continents, including those with a greater percentage of patients with COPD, to determine whether older adults may be more at risk of making critical inhaler technique errors.

A further interesting result of this study was that female gender was identified to be a factor associated with the performance of inhaler technique errors associated with poor asthma outcomes for both the TH and the pMDI device (note that this was not a factor for the AH device). Whilst gender had not been hypothesised to be a risk factor for poor inhaler technique in this study, the results correlated with a number of studies which have identified females to be more likely to make inhaler technique errors across a broad array of inhaler devices [174, 232, 233]. In a study by Goodman et al. (1994), of 59 subjects 20-81 years of age prescribed the pMDI device, females of all ages were identified to be more likely to demonstrate improper MDI technique than males [174]. Ocakli et al. (2020) further identified female gender to be predictive of a higher level of inhaler technique errors across a range of pMDI and DPI devices [232]. Similarly, Alotaibi et al. (2023), identified gender to significantly affect the quality of inhaler technique, with men being 2.6 times more likely to exhibit good inhaler technique with pMDI devices relative to women ($p<0.065$) in their multivariate model [233].

Although gender had not been hypothesised to be a risk factor for poor inhaler technique in this investigation, there are certain factors which intuitively may have contributed to these results. Firstly, total muscle mass has been identified to be higher in men than women, varying from 70-89% in men between 20-79 years of age, and 60-75.5% in women of the same age brackets, with the younger age groups exhibiting the greatest percentages of muscle mass [234]. The extent to which this may contribute to a greater proportion of inhaler technique errors associated with poor asthma outcomes, however, is unknown.

In theory, it may be hypothesised that lower levels of muscle mass may potentially place women at greater risk of not obtaining the PIF required for the TH device, the device with the greatest internal resistance, or in actuating the pMDI device. In a systematic scoping review by Leving et al. (2022), nine out of fourteen papers (64%) identified a positive correlation between low PIF and female gender, with a further 7% identifying a correlation between gender and PIF but not specifying which gender had been associated with a lower PIF [235]. This is of concern, as the ability to inhale forcefully from the start of inhalation has been identified as a critical inhaler technique error for the TH device.

However, in a study by Ocakli et al. (2020) [232], the three most commonly self-reported errors or difficulties in using inhaler devices were actually identified to be identical between males and females. Therefore, further study is required to identify whether HCP-identified errors vary in between the genders, and, furthermore, whether physiological differences between the genders (for example, muscle mass), may be of influence. Further research exploring this could assist in broadening our field of knowledge in this domain.

A further consideration with this result could be the influence of potential variations in self-assessment of inhaler technique between males and females. In a study by Ocakli et al. (2020) [232], females were identified to be more likely to self-report difficulties with using a range of inhaler devices than males. Whilst the reasons for this are predominantly unknown, it could potentially influence such results, in that self-assessment of inhaler technique as *'very poor to average'* has been identified to be a factor associated with the performance of critical inhaler technique errors for both the TH and AH devices. As such, this could suggest a potential reason why females may be more likely to make critical inhaler technique errors for the TH device.

Finally, certain sociodemographic and lifestyle factors may further be of impact, particularly in regards to education. Throughout this study, it was identified that holding a maximum of a secondary education in lieu of a tertiary or post-graduate qualification has been associated with the performance of critical inhaler techniques for the pMDI device. This presents a major concern, in that females in low-income nations continue to trail their male peers in lower secondary completion rates, with only 38 percent of girls completing lower secondary school compared to 43 percent of boys [236]. With 10 to 30 percent of females not completing school due to early marriage or pregnancy, and further not completing school due to safety concerns (including those related to sexual harrassment), inadequate menstrual hygiene management accessibility, and physical inaccessibility or long distances to secondary schools, there is concern that this gender gap may continue to occur with regards to the performance of critical inhaler technique errors and inferior asthma outcomes [236]. Furthermore, the decision by some women to delay their education to raise children or engage in housekeeping may further contribute to these results [232]. Whilst it was beyond the scope of this study to explore any differences in the educational levels of the female participants relative to the male participants of this study, further study examining any such variations could assist in identifying whether the results for gender may potentially be influenced by education.

Self-assessment of inhaler technique, or the manner in which one describes their personal ability to use their inhaler device, was further identified to be a patient demographic significantly associated with the performance of critical inhaler technique errors for both the TH and AH device. Whilst appearing logical in nature with regards to the DPIs explored, it is interesting to note that this result did not occur for the pMDI device.

Whilst the exact reasons for this were not examined in this study, there are a number of factors to consider in this result. One such factor is the duration and frequency of use of the device of the patient, and the class of medication delivered by the particular inhaler. The pMDI device is suitable for use from a younger age than the DPI devices are [2], and thus, it is possible that some patients may potentially have been prescribed the pMDI device for a longer time period than those prescribed a DPI device. In addition, reliever medications such as salbutamol are commonly delivered via the pMDI device [2], potentially resulting in such a device being utilised more frequently than the AH and TH devices. Therefore, such patients may potentially feel more experienced in the use of the pMDI device and express a greater level of self-confidence in its use, which, in turn, could potentially translate to a lack of perceived need for regular inhaler technique training and review, even in the instance where they are using the device incorrectly. This could ultimately result in the expression of a similar number of critical inhaler technique errors by those who feel they have good inhaler technique relative to those who feel they have poor inhaler technique.

The type of medication delivered by the inhaler device could further place a potential impact on patient perception of inhaler technique. As reliever medications tend to contribute to more physiologically noticeable effects than preventer medications, it is possible that a patient using a pMDI to deliver a reliever medication may be more likely to perceive they are using their inhaler correctly than a patient using a DPI to deliver a controller medication, even in instances where they may be using their inhaler suboptimally and not receiving a full dose of medication. This could potentially result in a false elevation of the self-perception of one's inhaler technique in those not receiving actual review and regular monitoring of their inhaler technique by a trained healthcare professional, and, in turn, result in less significant differences in actual inhaler technique than may be occurring in those considering their inhaler technique to be poor.

Further factors may potentially contribute to these results, and thus, there is a place for future research to explore whether an association exists between frequency of use and duration of experience with an inhaler device, and the degree to which one perceives their ability to use their inhaler.

Regardless of such factors, the implications of these findings hold significant ramifications in the care of asthma patients by their healthcare team. In particular, the results of this study suggest an urgent need for healthcare professionals to continually seek initiative in reviewing and asking patients to self-evaluate their inhaler technique, to assist in identifying those patient groups who may be at greater risk of poor asthma outcomes. It further brings to light the need to continually provide inhaler technique to patients prescribed the pMDI device, even in instances where the patient may consider their inhaler technique to be good.

This is particularly imperative with the introduction of '60 day dispensing' in Australia [237]. According to this practice, patients may be supplied with two months of controller asthma medication per pharmacy visit, with prescriptions providing enough medication for one year in lieu of the maximum of six months which was allowed previously [237]. As this practice may result in patients significantly reducing the number of consultations they may hold with their pharmacist and healthcare practitioner, it is further imperative that medical practitioners and pharmacists alike seek initiative in actively engaging with patients and providing inhaler technique review at any opportunity which may present itself. This is in line with guidelines by GINA [10] and the NAC [27] which advise reviewing inhaler technique at every opportunity by healthcare professionals and at every dispensing by the pharmacist, a practice which could potentially be significantly reduced in light of these new prescribing practices.

This holds true not merely for the DPI devices examined, but further for the pMDI device, in which patients may potentially be considering their inhaler technique to be more accurate than may be occurring in the real-world setting. It further holds particularly true for the AH device, in consideration that it exhibits the least number of critical errors, and may therefore present as a less difficult device to use by healthcare prescribers, and the TH device, which may be used to deliver terbutaline and formoterol, both of which are rescue medications and may be more widely prescribed and utilised by patients. Thus, the results of this study indicate a pressing need for pharmacists to maximise their review of their patients' inhaler technique, to ensure patient self-assessment correlates with the objective accuracy of their inhaler technique.

A further factor identified to place patients at greater risk of performing critical inhaler technique errors for the pMDI device is smoking status. In particular, current smokers were significantly more likely to make such errors than those who were non-smokers.

This result contributes to an ever-growing body of evidence demanding exploration of patient smoking status and the development of strategies to reduce or completely eliminate smoke and tobacco exposure when considering one's asthma management plan. Current smoking has long been identified to be a risk factor for not only the development of asthma, but for the exhibition of worse clinical outcomes, including suboptimal asthma control, persistent airflow obstruction, increased exacerbations, accelerated decline in lung function, a greater number of comorbidities (including anxiety and depression, osteoporosis, cardiovascular diseases, lung cancer, and pneumonia), and higher all-cause mortality [238].

There is furthermore a growing body of evidence that cigarette smoking may alter airway eosinophil and neutrophil numbers in asthma, potentially contributing to more severe asthma [238]. In particular, a study of predominantly former smokers identified that those with a 10 pack-year history presented with higher proportions of eosinophilic airway inflammation, autoimmunity toward eosinophils, and reduced sputum eosinophil sensitivity to systemic corticosteroids [239]. This suggests that those with a history of a higher cumulative exposure to cigarette smoke may be more likely to present with a phenotype of severe refractory eosinophilic asthma. A number of further studies have indicated that current smoking may further be associated with neutrophilic airway inflammation [240-242]. This is of concern, in consideration that neutrophilia in the airways has been associated with asthma severity and revealed to correlate with asthma that is refractory to corticosteroid treatment, a cornerstone of asthma treatment [98].

A further concern of cigarette smoking in asthma is that evidence for the effectiveness of drug therapies for asthma recommended by GINA is uncertain in current smokers and those with a heavier smoking history, with clinical trial data only generated amongst those who had never smoked, or former smokers with a very low pack-year history (typically 5 pack-years or less) [10, 238]. Cigarette smoking has further been associated with poor adherence to asthma pharmacotherapy [243]. In contrast, a multitude of studies have identified smoking cessation in asthma patients to be associated with improvements in symptoms [244], asthma-related quality of life [244], lung function [245], and airway hyper-reactivity [244].

Taken together, it is important to consider the potential impact smoking status may have on a patient's lung function when considering their ability to use their inhaler. Whilst any potential links between cigarette smoking and the type of critical inhaler technique errors performed for the pMDI device are not known to be determined, future research could explore any connections between physiological changes from cigarette smoking in asthma patients and their ability to use their inhaler device. This is highly essential, in consideration that smokers are at greater risk of severe asthma due to the physiological changes described above [238], and could therefore benefit from the greater medication dose delivery evident with optimal inhaler technique, to assist in preventing hospitalisations and a greater burden of disease from asthma.

Therefore, this presents a case for healthcare professionals involved in the management of inhaler technique of patients prescribed the pMDI device to ascertain and review the smoking status of their patients, and be cognizant of the impact this may present on their overall asthma outcomes. With rescue medicines such as salbutamol being primarily available in the pMDI device [2], it is essential that this become a core aspect of the management of asthma patients.

Whilst GINA indicates that smoking status be ascertained and addressed as part of the management of asthma patients in regards to identifying one's risk of exacerbations [10], this study is the first to link current smoking with the performance of clinically significant inhaler technique errors. With pharmacists being experts in the field of medication use and management, this places them in a unique position to identify and counsel such patients, and ensure that the training on their inhaler technique is comprehensive and actively and regularly reviewed.

A multitude of studies have indicated that models of pharmacist-delivered asthma care including identification of smokers and assistance in smoking cessation have revealed statistically significant improvements in asthma control [51, 55]. In particular, improvements have been noted in the proportion of patients transitioning from "severe" to "not severe" asthma, adherence to preventer medication, the mean daily dose of reliever medication, a shift in medication profile from reliever only to a combination of preventer, reliever with or without long-acting β agonist,, and improved scores on risk of non-adherence, quality of life), asthma knowledge, and perceived control of asthma questionnaires [55].

In the United States of America, the Asthma-Friendly Pharmacy Model [246] further revealed that pharmacist-led interventions amongst asthma patients in which smoking cessation was advised, and OTC or prescription smoking cessation aids were recommended, could be effectively integrated into everyday practice in situations where the motivators and needs of community pharmacists were accounted for [246]. The study suggested that in such models, brief asthma interventions could be effectively integrated into the daily community pharmacy workflow, leading to increased exchanges between pharmacists and healthcare providers, and an increase in the number of patients receiving pharmacist-led consultations [246]. As such, pharmacist-led interventions assisting in smoking cessation may potentially improve to significant improvements in inhaler technique, and thus, clinical outcomes.

Lack of inhaler technique review in the previous twelve months prior to the inhaler technique assessment performed as part of the iHARP data collection process was further identified to be a significant factor for the AH device. Whilst the requirement for regular inhaler technique review has widely been reported in published clinical asthma management guidelines as essential in the maintenance of correct inhaler technique [10], this result was interesting in nature in that it only presented as a significant factor for the AH device. It was further an interesting result in that the AH device presented with the least number of possible critical errors of all the devices, suggesting a potential ease of use of the device relative to the TH and pMDI.

This holds significant implications in the field of inhaler technique management by the community pharmacist, and furthermore, for practitioners involved in selecting inhaler devices for patients. Firstly, it elucidates the importance of not solely considering the number of steps associated with critical errors when ascertaining the level of difficultly a patient may experience with regards to retaining correct inhaler technique.

Secondly, it conveys the need to consider how frequently a device may be being used when monitoring and assisting patients with appropriate inhaler technique. This is of importance, as the TH and pMDI may be utilised in the delivery of rescue medications in addition to controller medications [2], and thus, may potentially be used by patients on a more frequent basis than the AH device, which is solely used in the delivery of controller medications. Whilst this study did not explore if there were any associations between the frequency of inhaler use and the performance of critical inhaler technique errors, it does suggest that a link may potentially exist. Future studies could therefore explore whether any such associations may exist in the real-world setting.

Thirdly, it elucidates the importance of considering the patient's unique lifestyle and ability to attend inhaler technique training sessions when selecting an inhaler device. For example, a patient who experiences difficulty with physically attending a prescriber or pharmacist for regular inhaler technique training, for example, those with extensive working hours, external family demands, or physical issues resulting in difficultly with attending regular inhaler technique review sessions may potentially be better suited to a TH or pMDI device than an AH device. Thus, it is important to be cognizant of the personal situation of the patient with regards to their ability to attend inhaler technique review sessions when considering which device may be best suited to the particular patient with regards to the attainment of optimal clinical outcomes.

A further consideration is the ability of the patient to retain appropriate inhaler technique skills, for example, patients with cognitive impairment or dementia, as described above. Those who may experience difficultly with retaining any inhaler technique skills taught or re-iterated by trained medical practitioners and pharmacists may potentially perform more critical inhaler technique errors with the AH device than with the TH or pMDI, even if they have attended regular inhaler technique training sessions. There could thus be an opportunity for pharmacists to identify such patients by potentially undertaking brief screenings of cognitive function, and asking the patient to demonstrate their inhaler technique at each visit to assess for issues with skill recall. Pharmacists could further assist by then reporting any issues to the patient's prescriber, to ensure the patient is prescribed the device for which they may potentially be less likely to perform critical inhaler technique errors with. This could assist in improving clinical asthma outcomes, reducing the burden of asthma on the patient and the healthcare system.

A further factor identified to increase the risk of performing critical inhaler technique errors was that of having a maximum level of education of a secondary education in lieu of a postgraduate, professional, or university degree, correlating with research which had identified an association between inferior educational levels and inhaler technique in patients with COPD [247]. However, this was only the case for the pMDI device.

One potential consideration could be the health literacy level of the patient, which refers to one's ability to find, understand, and use health information [248]. Of concern, evidence suggests that patients with lower educational levels tend to demonstrate lower levels of health literacy compared to patients with high educational levels [249].

This is of concern, as low health literacy has been demonstrated to be associated with poor longitudinal asthma outcomes, including emergency department use and quality of life [250]. Thus, the health literacy of the patient could potentially be a factor increasing one's risk of the performance of critical inhaler technique errors in the pMDI device.

As this study did not directly explore whether one's level of health literacy was a factor contributing to the performance of critical inhaler technique errors, further research exploring any direct links between the two factors could assist in expanding our field of knowledge, and assist in the creation of the educational materials and teaching strategies on inhaler technique and broader aspects of asthma management targeted to the particular health literacy level of the patient. Further study could also explore why this was a factor for the pMDI device, and not the AH and TH device, with this information currently being unknown.

Despite the gaps in this knowledge, this result, however, does suggest a pressing demand for pharmacists and healthcare practitioners involved in asthma care to take steps to identify or assess the educational status of those prescribed the pMDI device. This could assist in identifying if the patient is potentially at risk of poorer inhaler technique and the performance of critical inhaler technique errors with the pMDI device, and may benefit from prescription of the TH or AH device instead. With the pMDI device being frequently utilised in the delivery of rescue medications, it is particularly essential that this issue be addressed, to ensure such medications can be effectively delivered to their required site of action, and minimise the risk of patients requiring emergency admission to hospital or general hospital admission due to inadequately treated asthma flare-ups, which could otherwise have been managed with appropriate use of the pMDI device. In consideration that emergency rescue medications may also be delivered with the TH device, it is essential that patients with lower levels of education be identified quickly and undergo further training in their device, or switched to a device which they are able to use appropriately.

Taken together, the results of this study thus indicate that there is a diverse range of patient demographic factors associated with an increased risk of critical errors from inhaler devices, the nature of which varies with the specific inhaler device prescribed.

5.1.1 Limitations of the Studies

Whilst providing extensive insights into populations at higher risk of performing critical inhaler technique errors, and thus, poor asthma outcomes, there are some limitations in the study design which could assist in directing a path for future research.

One such limitation is that, whilst this study identifies associations between patient demographic factors and critical inhaler technique errors, it is unable to establish causality. This is due to the use of cross-sectional data, rather than data from multiple stages in time. Future research could explore data from multiple time points, to assist in determining whether any patient demographic factors may potentially be contributing to the performance of critical inhaler technique errors.

A further limitation of this study is the geographical distribution of the cohort examined. Whilst including a large sample size of 4134 adult patients, the geographical restriction of these patients to seven developed European natures and Australia could potentially have impacted the results. For example, it does not allow for exploration of the impacts that the challenges that patients from less developed nations could experience with regards to asthma patients, in addition to any particular challenges that patients from specific nations may be experiencing with regards to asthma management.

Such factors could include access to medical practitioners, access to regular medications, variations in socioeconomic status to those presented in this cohort, and political barriers to healthcare. As such, this places limitations on the generalisability of these findings to other healthcare systems or cultural contexts. Future research could explore a patient cohort from a broader array of nations from differing regions of the world, differing in such variables, to assist in improving the generalisability of such results.

In addition, whilst exploring a diverse range of factors potentially influencing the results, further factors, such as health literacy, cognitive function, and socioeconomic status, were not directly measured or controlled for in this study. Future studies could investigate the impact of these factors on the study results, to assist in more accurately identifying patient groups at increased risk of poor asthma outcomes from poor inhaler technique.

Finally, one of the limitations of this study was that it did not explore data for those who purchased a SABA without a prescription. Future studies could broaden the data collected to those purchasing SABAs OTC or without a prescription, to assist in increasing the amount of information able to be obtained on those who purchase their SABA without a prescription. This could assist in identifying whether there are any distinct differences in SABA use and potential overuse in older adults with respect to younger adults, by examining how often a prescription is used for their SABA, and in turn, how often a prescriber may be being visited for advice and review.

Despite these limitations, these studies provide information which can assist in shaping the future practice of pharmacists with regards to assisting those with asthma. These will be discussed in Section 5.2, below.

5.2: Implication of Findings on Practice and Future Directions

The results of this study indicate a pressing demand for consideration of the demographics of patients prescribed inhaler devices, when considering their level of risk of performing inhaler technique errors associated with poor asthma outcome. Furthermore, it identifies that such demographics vary with the type of inhaler device, and thus, healthcare professionals should be aware that differing groups of patients may be at varied levels of risk of making critical inhaler technique errors based on the device prescribed. In turn, this indicates an urgent need for healthcare professionals to be judicious in both the choice of inhaler device prescribed for a particular patient based on their likelihood of making critical inhaler technique errors; the degree of intensity, repetition, and follow-up to be provided for particular patient groups based on such demographics; and the need for tailored education on inhaler technique based on the specific learning styles and demands of the patient group.

This is particularly true for community pharmacists. As discussed previously, pharmacists play a pivotal role in the management of patients with asthma, on account of their increased visitation by patients, their unparalleled level of expertise in the optimal use of inhaler devices, and their proven success in improving a broad array of asthma outcomes when participating in asthma education and in intervention programs in the research environment.

As discussed in the GINA guidelines, the first step in the clinical assessment of asthma patients is the assessment of symptom control and risk factors for poor asthma outcomes [10]. Thus, we advise that healthcare professionals initially familiarise themselves on the impact of such patient demographics on the ability to use such inhaler devices correctly, and thus, experience poor asthma outcomes. This can assist in the development of educational interventions tailored specifically at the learning demands of these patients.

Educational interventions tailored specifically at the individual's learning needs are further suggested to lead to greater improvements in clinical outcomes than those that do not. Petty and Cacioppo's "Elaboration Likelihood Model of Persuasion" [251] indicates that patients are more likely to carefully consider the elements of a message and judiciously process and analyse information if they consider it to be relevant to their personal situation, increasing their likelihood of processing the information in a manner more likely to have a positive impact. It may further assist in eliminating superfluous information, improving comprehension, and enhancing modifications in behaviour and attitudes [251].

Such tailored interventions have been successfully implemented in the asthma setting. In the United States of America, the development of the Kansas City Childhood Asthma Program [252] is one such program. Utilising interventions tailored at children and their caregivers, including the use of flip-charts employing health literacy techniques inclusive of pictures, wording at a fifth-through-seventh grade reading level, non-medical terms, teach-back techniques, and open communication between patient/family and educator in a learning environment targeted to a variety of learning styles such as VARK (visual, auditory, reading and kinesthetic) or viewing, listening, reading, and hands-on interactive activities, significant results have been reported [252]. This has included caregivers reporting statistically significant greater comfort in managing asthma at home ($p<0.0001$), belief that they had the right information to know what to do when their child had an asthma attack ($p<0.0001$), and belief that they learned something new about asthma home management ($p<0.0001$) [252].

In providing clear information on patient risk factors for performing critical inhaler technique errors for each separate device (AH, TH, and pMDI), this study assists pharmacists to identify patients entering the pharmacy at risk of inhaler technique errors for each device. However, it does not offer any detailed guidance on how pharmacists may build and develop interventions specific to each device. Future research could explore specific educational strategies tailored to each device to assist in improving outcomes in such patients.

Furthermore, this study does not explore how any strategies developed by pharmacists to assist these specific patient groups could be operationalised in the real-world setting. Future research could explore the impact that the known barriers to pharmacist education and counselling of patients such as lack of time, monetary remuneration, training, and support from colleagues could have on such interventions, and explore methods of managing these to improve patient support in the field of inhaler technique.

Currently, there is a lack of asthma and inhaler technique educational programs tailored at the groups at risk identified in this study. As such, further study is required to determine the specific learning requirements and demands of these particular population groups, and specific interventions which may assist them.

This is not without its challenges, particularly with regards to gender. Current social norms have resulted in gender identification being relatively fluid, with some people opting to describe their gender as 'indeterminate,' or 'undisclosed.' Interventions tailored at assisting smokers to reduce or quit smoking further requires in-depth knowledge of smoking cessation strategies, in addition to behavioural change methodologies and methods of overcoming physical addiction, whilst those tailored at people of a lower educational background require knowledge of strategies of assessing health literacy levels and methods of communicating information effectively to those with lower levels of health literacy.

Future research could further assist in identifying the reasons why such patient groups were at greater risk of making critical inhaler technique errors for each particular device. Knowledge of these factors could assist in the formulation of interventions addressing the source of these variations between patient groups, assisting in reducing the risk of such errors from being performed.

Pharmacist perceptions of their role in identification of high-risk asthma patients

A key question with regards to asthma management in Australia is what community pharmacists currently perceive their role to be with regards to the management of asthma patients, and in particular, the identification of high-risk patients. Of particular concern, it is currently unknown to what level community pharmacists are exploring which patient groups are at high risk of poor asthma outcomes in practice. Furthermore, we have a lack of awareness of their degree of confidence in formulating effective resources for such patients and engaging with them in practice.

As discussed, there are currently no asthma-care guidelines published specifically for pharmacists in Australia; thus, the extent to which pharmacists participate in counselling and pharmaceutical care activities with their asthma patients may vary extensively in practice. Whilst the Australian Asthma Handbook provides comprehensive information regarding risk factors for adverse asthma outcomes and methods of managing these outcomes, it is unknown to what degree pharmacists are accessing this information in assisting to manage their patients, and whether they feel it is part of their role in asthma patient management [2].

Not only do we not know the degree to which community pharmacists are currently identifying high-risk patients in community practice, we do not know how frequently pharmacists are engaging in this practice, and whether they feel it is part of their duty of care and role as a pharmacist. Therefore, there is an urgent demand to explore the extent to which this is occurring in practice, and the degree to which this practice is felt necessary by pharmacists in their professional duty of care to their patients.

With the changing dynamic of asthma care management in Australia and the world, it is essential that pharmacists are not only able to address the common problems with medication use, including inhaler technique and adherence, but are able to demonstrate a proactive stance with regard to identifying and intervening with high-risk patients. In revisiting the issues in pharmacy with patients with asthma, and in considering what pharmacists can do, it is further essential that we take a different approach moving forward, and that pharmacists focus their efforts on identifying high-risk patients, and assisting them with regards to medication use, and improving disease/asthma status.

This is particularly essential in light of the expanded pharmacy scope of practice that pharmacists are able to be involved in Queensland, Australia [253]. As part of this program, pharmacists will be able to prescribe structured asthma chronic disease management programs, assisting in delivering more timely asthma care to patients [253]. As such, knowledge of whether consideration of the identification of high-risk patients has been placed within such a program, and the recommendation of its inclusion if not already considered, could assist in improving the outcomes of such a program [253].

Future studies could further explore whether pharmacists are currently engaging in practices identifying high-risk asthma patients, and whether they feel it is within their scope to do so. This may assist in broadening knowledge with regards to this domain.

Despite the limitations of this study, this study provides pertinent information regarding patient groups at risk of critical inhaler technique errors, and informs medical professionals that these may further differ with the device prescribed. It is anticipated that this may help to assist in improving awareness of these factors and assist healthcare professionals involved in the asthma management of these patients to provide tailored interventions to assist in improving inhaler technique and the broader aspects of asthma care, improving clinical outcomes and reducing the burden of disease of asthma on both the patient and the global healthcare system.

5.3: Overall Conclusion

The research conducted in this thesis elucidates the presence of multiple patient demographic factors contributing to the performance of critical inhaler technique errors. With female gender and *'very poor to average'* self-assessment of inhaler technique being patient factors for the TH device, lack of inhaler technique review in the previous twelve months and *'very poor-to-average'* self-assessment of inhaler technique being patient factors for the AH device, and female gender, secondary education, and being a current smoker being patient factors for the pMDI device, it further illuminates how such factors vary with the type of inhaler device prescribed.

Such research indicates a clear and present need for pharmacist intervention with regards to the identification of high-risk patients. With multiple patients potentially exhibiting such factors, there is high risk of a significant number of patients experiencing inferior clinical outcomes based on their inhaler technique alone, increasing their burden of disease from asthma, risk of hospitalisation, and ultimate impact on the healthcare system. It is therefore imperative that the community pharmacist be aware of which patients are entering the pharmacy at greater risk of performing the inhaler technique errors which may place them at high risk of hospitalisation and inferior clinical outcomes.

These findings can be utilised to not only educate community pharmacists on the patient groups at higher risk of performing critical inhaler technique errors, but can guide them to identify such patients in a more timely manner, develop targeted education programs comprised of the specific interventions that may be required for such patient groups, and refer patients or provide detailed reports to prescribers for whom a change to a more appropriate inhaler device may be deemed necessary. This can thus assist pharmacists to more effectively improve inhaler technique and asthma care in such patients, and reduce the impact of asthma on both patient quality of life and the healthcare system.

Although the reasons behind these factors remain unclear, future research could assist in exploring any links to assist pharmacists to provide more comprehensive and targeted education programs than they could otherwise. Future research could further explore current community pharmacist practices with regards to the identification of high-risk patients, and their current practices in assisting such patients with their asthma medication management. This can assist in identifying the current status of asthma care and inhaler technique training by community pharmacists, to enable one to discern how to best assist in improving current practice and which interventions may be required.

Taken together, the information from this research presents a significant opportunity for community pharmacists to become engaged in identifying patients at high risk of poor asthma outcomes, as based on their likely performance of critical inhaler technique errors. Ultimately, this can assist pharmacists to significantly reduce the impact that poor inhaler technique may manifest on the clinical outcomes of their patients, reducing the burden of disease of asthma on both the patient and the global healthcare system.

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