DEVELOPMENT AND EVALUATION OF THE HOME PHARMACY ASTHMA CARE (HOM-PAC) PROGRAMME AMONG ADULT PATIENTS WITH ASTHMA FROM KULIM HOSPITAL, KEDAH, MALAYSIA

JAYA MUNESWARAO A/L RAMADOO@DEVUDU

UNIVERSITI SAINS MALAYSIA

2021

DEVELOPMENT AND EVALUATION OF THE HOME PHARMACY ASTHMA CARE (HOM-PAC) PROGRAMME AMONG ADULT PATIENTS WITH ASTHMA FROM KULIM HOSPITAL, KEDAH, MALAYSIA

by

JAYA MUNESWARAO A/L RAMADOO@DEVUDU

Thesis submitted in fulfilment of the requirements
for the degree of
Doctor of Philosophy

May 2021

ACKNOWLEDGMENT

I would like to express my profound gratitude to Prof. Dr. Mohamed Azmi bin Ahmad Hassali, my main supervisor, whose guidance, support, and insights have contributed to the successful completion of my PhD thesis. His excellent supervision and endless encouragement drove my incredible journey. I'm grateful to my co-supervisors, A/P Dr. Baharudin bin Ibrahim and Prof. Dr. Bandana Saini (University of Sydney, Australia), for their care and aid in assisting me in completing my research. My PhD research would not be possible without my field supervisor, Dr. Irfhan Ali bin Hyder Ali (Penang Hospital, Pulau Pinang), who guided me in this endeavour as a consultant pulmonologist. The clinical prescriptive provided by Dr. Irfhan Ali is highly appreciated.

I would like to acknowledge the staff from Kulim Hospital, Kedah, and Kuala Kubu Bharu Hospital, Selangor, for their endless support, especially Dr. Mohamed Aslam bin Mohamed Micdhadhu and Miss Nur Azimah binti Mohd Rhazi. As an internal medicine specialist, Dr. Mohamed Aslam provided overwhelming clinical insights for my research. I would like to express my appreciation to Universiti Sains Malaysia (USM) for the financial support provided through the Research University Individual (RUI) grant. I want to thank my friends and fellow research mates at the School of Pharmaceutical Sciences (USM) for their friendship throughout my doctorate journey. I owe my sincere thankfulness to my family for their love. To my parents and siblings, thank you for your moral and spiritual backing. Last but not least, to my beautiful wife and twin babies, thank you for sharing the ups and downs of this journey with me.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

ACT	Asthma Control Test
ADR	Adverse drug reactions
AM	Asthma Malaysia
ATS	American Thoracic Society
BM	Bahasa Melayu
BTS/SIGN	British Thoracic Society and Scottish Intercollegiate Guidelines Network
CFI	Comparative fit index
CPG	Clinical practice guideline
CVI	Content validity index
CVR	Content validity ratio
DPI	Dry powder inhaler
ED	Emergency department
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GINA	Global Initiative for Asthma
HCP	Healthcare professional
HMR	Home medication review
HOM-PAC	Home Pharmacy Asthma Care
ICS	Inhaled corticosteroid
IFI	Incremental fit index
IFR	Inspiratory flow rate
IPH	Institute of Public Health

LABA	Long-acting beta$_2$ agonist
MCID	Minimal clinically important difference
MDT	Module development team
MOH	Ministry of Health
MPR	Medication possession ratio
NAEPP	National Asthma Education and Prevention Program
NAHC	National Association of Home Care
NFI	Normed fit index
NHMRC	National Health and Medical Research Council
NRAD	National Review of Asthma Deaths
OCS	Oral corticosteroids
PDC	Proportion of days covered
PIC	Physician in charge
PEFR	Peak expiratory flow rate
pMDI	Pressurised metered-dose inhaler
PSP	Pharmaceutical Services Programme
QoL	Quality of life
RCP	Royal College of Physicians
RCT	Randomised controlled trial
RMSEA	Root mean square error of approximation
RMTAC	Respiratory Medication Therapy Adherence Clinic
SABA	Short-acting beta$_2$ agonists
SMI	Soft Mist Inhaler
TAI	Test of Adherence to Inhalers
TLI	Tucker Lewis index
WAAP	Written asthma action plan
WHO	World Health Organization

LIST OF APPENDICES

PEMBANGUNAN DAN PENILAIAN PROGRAM FARMASI PENJAGAAN ASMA DI RUMAH (HOM-PAC) DALAM KALANGAN PESAKIT ASMA DEWASA DARI HOSPITAL KULIM, KEDAH, MALAYSIA

ABSTRAK

Kawalan penyakit asma di kalangan pesakit dewasa di Malaysia adalah kurang optimum. Beberapa garis panduan mengesyorkan penjagaan di rumah sebagai salah satu strategi pengurusan asma. Strategi penjagaan di rumah terbukti mendatangkan hasil yang berkesan pada populasi pesakit asma pediatrik tetapi terhad di kalangan orang dewasa. Sehingga kini, tiada kajian yang telah menilai keberkesanan intervensi penjagaan rumah yang dipimpin oleh ahli farmasi khususnya untuk pesakit asma dewasa. Program Farmasi Penjagaan Asma di Rumah (HOM-PAC) memberi ruang kepada ahli farmasi untuk memberi penjagaan di rumah yang komprehensif kepada pesakit asma dewasa. Oleh itu, kajian ini bertujuan untuk menilai keberkesanan program HOM-PAC di kalangan pesakit asma. Satu kajian terkawal rawak dua kumpulan telah dijalankan selama 6 bulan dengan label terbuka dan kumpulan selari. Pesakit dengan gejala asma yang tidak terkawal direkrut dari klinik pernafasan, Hospital Kulim, Kedah. Pesakit dimasukkan sama ada dalam kumpulan intervensi (program HOM-PAC) atau kumpulan kawalan (rawatan biasa) berdasarkan senarai rawak. Sebanyak tiga lawatan rumah (setiap 3 bulan) telah dirancang untuk pesakit dalam kumpulan intervensi. Pesakit dalam kumpulan kawalan tidak menerima program HOM-PAC dan meneruskan rawatan biasa di klinik. Lima puluh satu pesakit dalam kumpulan intervensi dan 54 pesakit dalam kumpulan kawalan telah lengkapkan kajian dan dimasukan dalam analisis akhir. Skor gejala berdasarkan Ujian Kawalan

Asma (ACT) adalah lebih tinggi pada kumpulan intervensi (median 22, IQR 4) berbanding dengan kumpulan kawalan (median 19, IQR 2); p <0.001. Bilangan pesakit yang mencapai perbezaan penting minimum dalam skor ACT juga lebih tinggi dalam kumpulan intervensi (n = 33, 64.7%), berbanding dengan kumpulan kawalan (n = 8, 14.8%); p <0.001. Bilangan pesakit dalam kumpulan intervensi yang membuat sekurang-kurangnya satu kesalahan "keseluruhan" (kritikal dan tidak kritikal) dalam teknik alat sedut adalah lebih rendah (p <0.05). Begitu juga, pesakit yang berada dalam kumpulan intervensi (n = 14, 27.5%) kurang membuat kesalahan teknik alat sedut kritikal (sekurang-kurangnya satu kesalahan) berbanding dengan pesakit dalam kumpulan kawalan (n = 35, 64.8%); p <0.001. Sebilangan besar pesakit dalam kumpulan intervensi mencapai kadar optimum aliran inspirasi untuk alat sedut mereka (p <0.05). Pesakit dalam kumpulan intervensi mempunyai skor kepatuhan ubat yang lebih tinggi (berdasarkan soal selidik kepatuhan) terhadap alat sedut mereka (median 49.0, IQR 5) berbanding dengan kumpulan kawalan (median 45, IQR 7.3); p <0.01. Bilangan pesakit yang patuh pada pengunaan alat sedut mereka adalah lebih tinggi dalam kumpulan intervensi (p <0.05). Pemilikan rancangan tindakan asma bertulis (p <0.01) dan pengetahuan penyakit asma (p <0.05) juga lebih tinggi di kalangan pesakit dalam kumpulan intervensi berbanding kumpulan kawalan. Analisis dalam kumpulan intervensi melaporkan penambahbaikan yang signifikan dalam pengurusan alat sedut di rumah dari segi stok, penyimpanan dan tarikh luput (p <0.05). Walau bagaimanapun, tiada perbezaan yang signifikan dilaporkan dalam serangan asma akut dan kadar aliran ekspirasi puncak di antara kumpulan kajian. Kesimpulannya, program HOM-PAC telah mendatangkan hasil yang positif di kalangan pesakit asma dewasa and mampu berfungsi sebagai intervensi tambahan yang melengkapi sistem penjagaan kesihatan yang sedia ada.

DEVELOPMENT AND EVALUATION OF THE HOME PHARMACY ASTHMA CARE (HOM-PAC) PROGRAMME AMONG ADULT PATIENTS WITH ASTHMA FROM KULIM HOSPITAL, KEDAH, MALAYSIA

ABSTRACT

Asthma control among adult patients in Malaysia is unsatisfactory. Several guidelines have recommended home care interventions as part of asthma management strategies. The evidence of home-based care in improving asthma outcomes is well established in the paediatric population but limited among adults. To date, there are no published studies that evaluated the effectiveness of pharmacist-led home care interventions, specifically in adult asthma patients. The Home Pharmacy Asthma Care (HOM-PAC) programme was developed to enable pharmacists to provide comprehensive home-based care for adult asthma patients. Therefore, the present study aimed to develop and evaluate the effectiveness of the HOM-PAC programme in patients with asthma. A two-arm, 6-month, open-label, parallel-group, randomised controlled trial (RCT) was conducted. Patients with uncontrolled asthma symptoms were recruited from the adult respiratory clinic of Kulim Hospital, Kedah. The patients were assigned to either the intervention (HOM-PAC programme) or control (usual care) groups based on a pre-generated random list. A total of three visits (3 months apart) were planned for patients in the intervention group. The patients in the control group did not receive the HOM-PAC intervention and continued their regular clinic follow-ups. Fifty-one patients in the intervention group and 54 patients in the control group completed the study and were included in the final analysis. The symptom score based on Asthma Control Test (ACT) was significantly higher in the intervention

group (median 22, IQR 4) compared with the control group (median 19, IQR 2); p <0.001. The proportion of patients who achieved minimal important difference in ACT score was significantly higher in the intervention group (n = 33, 64.7%), compared with the control group (n = 8, 14.8%); p <0.001. The proportion of patients in the intervention group that made at least one "overall" (critical and non-critical) inhaler technique error was significantly lower (p <0.05). Similarly, significantly fewer patients in the intervention group (n = 14, 27.5%) made at least one "critical" inhaler technique error compared with the patients in the control group (n = 35, 64.8%); p <0.001. A higher number of patients in the intervention group achieved optimal inspiratory flow rates for their controller inhaler devices (p <0.05). The patients in the intervention group also had significantly higher medication adherence score (based on adherence questionnaire) towards their controller inhalers (median 49.0, IQR 5) compared with the control group (median 45, IQR 7.3); p <0.01. The proportion of patients categorised as adherent to their controller inhalers was significantly higher in the intervention group (p <0.05). The patients in the intervention group also had significantly higher written asthma action plan ownership (p <0.01) and asthma knowledge (p <0.05). The within-group analysis reported that the patients in the intervention group had significant improvements in home inhaler management in terms of inhaler stock, storage, and expiry (p <0.05). However, there were no significant differences in asthma exacerbations and peak expiratory flow rates between the study groups. In conclusion, the HOM-PAC programme can serve as an additional intervention complementing the existing healthcare system to improve outcomes among adult patients with asthma.

CHAPTER 1

INTRODUCTION

1.1 Background

The Global Initiative for Asthma (GINA) guideline defines asthma as a heterogeneous lung disease, usually characterised by chronic airway inflammation (Muneswarao et al., 2019; GINA, 2020). Asthma causes narrowing of the airways and hyperresponsive to triggers such as dust, pollen, viral infections, and others (BTS/SIGN, 2019). The inflammation process is also responsible for mucus production in the respiratory tract (GINA, 2020). Patients with asthma typically present with pulmonary symptoms such as wheeze, shortness of breath, chest tightness, and cough (GINA, 2020). The symptoms vary over time and intensity, together with variable expiratory airflow limitations (BTS/SIGN, 2019; GINA, 2020). Asthma management goals are to achieve good symptom control and reduce future risks such as acute exacerbations, fixed airflow limitation, and adverse drug reactions (ADR) (Papi et al., 2018a; GINA, 2020). Both symptom control and future risk must be assessed to determine patients' overall asthma control. Symptom assessment can be performed using validated tools such as Asthma Control Test (ACT) (Nathan et al., 2004), the GINA symptom control tool (GINA, 2020), and Asthma Control Questionnaire (ACQ) (O'Byrne et al., 2010). Patients are defined as having well-controlled asthma symptoms if they achieve an ACT score ≥ 20 or do not fulfil any of the following criteria (1) daytime asthma symptoms more than twice/week (2) any night waking due to asthma (3) reliever needed for symptoms more than twice/week and (4) any activity limitation due to asthma (GINA, 2020). The second component of assessing asthma control is identifying patients at risk of future adverse asthma

outcomes such as exacerbations. The overall definition of uncontrolled asthma includes one or both of the following (1) poor symptom control (2) frequent exacerbations (≥2/year) requiring systemic corticosteroids, or serious exacerbations (≥1/year) requiring hospitalization (GINA, 2020).

The Global Burden of Diseases (GBD) report estimated that 358 million people worldwide have asthma (GBD, 2017). There are many published reports on the prevalence of asthma, but the lack of standardisations makes the appropriate comparison of reported prevalence from different countries are less reliable (GINA, 2020). There are several methods utilised in asthma prevalence studies to recruit eligible subjects such as doctor-diagnosed asthma, presence of clinical indicators, prescribed with asthma medications, self-reported and others (IPH, 2012; To et al., 2012; Muttalif et al., 2014). However, based on methods such as doctor-diagnosed asthma, it appeared that the global prevalence of asthma was estimated to be 4.3% (To et al., 2012). The prevalence of doctor-diagnosed asthma varied widely among countries, ranging from 0.2% (China) to 21% (Australia) (To et al., 2012). A more recent report documented that overall worldwide asthma prevalence was 3.6% (GBD, 2020). Asthma is estimated to cause 495,000 deaths worldwide annually (GINA, 2020), with a mortality rate of 6.48 per 100,000 population (GBD, 2020). The World Health Survey, which was conducted from 2002 to 2004, reported the prevalence of adult asthma in Malaysia based on three definitions (1) doctor-diagnosed asthma (5.2%), (2) clinical asthma (5.5%), and (3) wheezing symptoms (7.55%) (To et al., 2012). Subsequently, the Institute of Public Health (IPH) published the NHMS III, 2006, which reported asthma prevalence in adults at 4.5% (IPH, 2008). The definition of asthma was based on symptoms such as breathlessness, wheezing, night awakening, or chest tightness in the past 12 months (IPH, 2008). The NHMS, 2011 reported that

the prevalence of adult asthma in Malaysia was 6.3%, and the definition was based on if a doctor ever informed the patients that they had asthma (Chan et al., 2015). The Chinese had the lowest percentage of asthma (4.0%), compared with the Indians (7.6%) and Malays (7.2%) (IPH, 2012). According to a report by the Ministry of Health (MOH) Malaysia, asthma mortality has reached 1642 or 1.29% of total deaths (MOH, 2018). There is an increasing trend in disease prevalence (based on NHMS reports), and asthma-related deaths are still occurring in Malaysia.

Asthma treatment is based on a stepwise approach, and the cornerstone of asthma pharmacotherapy is inhaled corticosteroids (ICS) (Papi et al., 2018a). Other important factors determining optimal patient outcome are (1) correct inhaler technique, (2) good medication adherence, (3) avoidance of asthma triggers, (4) self-management education with written asthma action plan, and (5) comorbidities management (BTS/SIGN, 2019). Inhaler technique errors and unsatisfactory medication adherence are associated with poor clinical outcomes in asthma (Laube et al., 2011; Price et al., 2013; Braido et al., 2016b; ADMIT, 2019; GINA, 2020). One of the challenges faced by healthcare professionals in the assessment of medication adherence is the method of measuring adherence. There are many methods available to measure medication adherence in asthma patients, however, no method is considered a gold standard (Lam and Fresco, 2015). The Test of Adherence to Inhalers (TAI) was developed to provide a new questionnaire that would help healthcare professionals determine medication adherence levels and the barriers related to inhalation therapy in adult patients with obstructive airway diseases such as asthma or chronic obstructive pulmonary disease (COPD) (Plaza et al., 2016). The TAI questionnaire allows for not only identifying patients with poor adherence, but also determining the level of adherence by categorizing patients into adherent,

intermediate adherent, and nonadherent, as well as determining the nonadherence behavioral pattern. The TAI questionnaire is comprised of two versions, 10-item TAI and 12-item TAI (Plaza et al., 2017).

The National Association of Home Care (NAHC) defines home care as the provision of services and equipment in the place of residence of individuals and families who have needs resulting from acute illness, long-term health conditions, permanent disability, or terminal illness (NAHC, 2010). The American Thoracic Society (ATS) identifies asthma as one of the diseases that may benefit from home care services (ATS, 2005). Home care interventions' general aims are to improve survival, decrease morbidity, enhance the quality of life (QoL), promote self-management, and encourage positive health behaviours (ATS, 2005). The National Asthma Education and Prevention Program (NAEPP) and GINA also have incorporated home care approaches in their guidelines (NHLBI, 2007; GINA, 2017).

The Pharmaceutical Services Programme (PSP), Ministry of Health, Malaysia defines pharmacy home care as pharmaceutical care services provided at patients' home or residential care facilities (PSP, 2019). The entire process comprised of medication review and reconciliation, resolving pharmaceutical care issues such as medication adherence, ADR, medication storage at patient's home, patient referrals, and others (PSP, 2019). A home-based pharmacy assessment can reveal many problems with medication management that are not otherwise easily detected (Naunton and Peterson, 2003). These assessments can lead to potentially useful interventions to improve medication utilisation and patients' adherence (Naunton and Peterson, 2003).

1.2 Problem statement

The Global Asthma Network (GAN) report highlighted that Malaysian patients have adequate access to asthma medications (especially in the government sector) and patient support groups (GAN, 2018). Asthma management guidelines such as the clinical practice guidelines (CPG) are freely accessible, and pharmacists have been managing asthma patients in the Respiratory Medication Therapy Adherence Clinic (RMTAC) at the government facilities (the first RMTAC services was started in 2007 at Melaka Hospital) (PSD, 2015; MOH, 2017). However, on the contrary, asthma control in Malaysia is still unsatisfactory. Two major surveys reported that the highest percentage of well-controlled asthma among adult patients in Malaysia was only 28% (Thompson et al., 2013; Muttalif et al., 2014). A study conducted at a local tertiary hospital documented that only 23 % of the patients had well-controlled asthma (Kuan et al., 2015). A recent prospective study conducted at 14 health clinics in Malaysia highlighted that 41% of the patients had well-controlled asthma (Isa et al., 2020). Although asthma control was better than other studies, more than 50% of the patients still had uncontrolled (Isa et al., 2020). Asthma exacerbations are also common, affecting 24% to 50% of the patients (Zainudin et al., 2005; IPH, 2008; Thompson et al., 2013; Muttalif et al., 2014) and with an average annual exacerbation rate of 4.4 (SD 11.8) (Isa et al., 2020). The exacerbation rates were higher than in other regions, such as the UK and the USA (Suruki et al., 2017; Bloom et al., 2019). It is also important to note that several studies have highlighted that more than 50% of the patients were unable to achieve well-controlled asthma albeit treated with controller inhalers such as ICS (Kuan et al., 2015; Wong et al., 2017; Vampanan, 2018; Isa et al., 2020). Achieving optimal asthma control is crucial to prevent the disease's long-term

complications, such as fixed airflow limitations or even death, and reduce the economic burden (GINA, 2017; Yaghoubi et al., 2019).

Several guidelines have incorporated home care strategies for asthma patients (ATS, 2005; NHLBI, 2007; GINA, 2017). The effectiveness of home care interventions is well established among paediatric asthma patients but limited in adults (Krieger et al., 2009; Crocker et al., 2011). A systematic review that evaluated the effectiveness of home care intervention (children and adults) was unable to determine the impact in the adult population; however, the review only included a small number of studies with adult participants (Crocker et al., 2011). Since the publication of the above-mentioned systematic review, several home-based randomised controlled trials (RCT) have been published and reported improvements in clinical outcomes among adult asthma patients (Krieger et al., 2015; Apter et al., 2019; Federman et al., 2019). The home care interventions in the RCTs were delivered by respiratory therapists, nurses, asthma care coaches, and community health workers, but no pharmacist-led studies were identified (Crocker et al., 2011; Krieger et al., 2015; Apter et al., 2019; Federman et al., 2019). Pharmacists' interventions in the hospital and community pharmacy settings have been proven to improve clinical outcomes among patients with asthma (Garcia-Cardenas et al., 2016). Pharmacists also have been conducting home visits in the form of general home medication review (HMR) programmes (Mackeigan and Nissen, 2008; Flanagan and Barns, 2018). However, no studies have investigated the effectiveness of pharmacist-led home care interventions specifically in adult asthma populations (Crespo-Gonzalez et al., 2018; Flanagan and Barns, 2018; Abbott et al., 2020).

1.3 Rationale of the study

Literature highlights that there is a limited number of RCTs evaluated the impact (clinical outcomes) of home care intervention among adult patients with asthma (Vojta et al., 1999; Smith et al., 2005; Brown et al., 2006; Galbreath et al., 2008; Martin et al., 2009; Shelledy et al., 2009; Krieger et al., 2015; Apter et al., 2019; Federman et al., 2019). It is challenging to summarise the findings of the reported RCTs as there were variations in terms of home care personnel (e.g., nurses, respiratory therapists), patient populations, outcome measures, nature of home care interventions, biases, study durations, and power of the studies. A systematic review to evaluate home care interventions' effectiveness is expected to provide a greater understanding of the issue.

The 10th Malaysia Plan highlighted home care services as one of the eight health goals in Malaysia's healthcare system (IPH, 2020). The National Health and Morbidity Survey (NHMS) 2019 reported that 1.7% of Malaysians received home-based care and recommended that the scope of services provided by healthcare agencies or individuals in the country should be broadened (IPH, 2020). The delivered home care services were child healthcare (43.8%), antenatal or postnatal care (40.7%), health check (33.2%), medication reviews (16.8%), medical treatment (wound care, tube feeding, and pressure ulcer prevention) (10.4%), rehabilitation (7.4%) and others (11.4%) (IPH, 2020). However, there were no home-based programmes or modules available for adult asthma patients. Guidelines suggest that asthma patients may benefit from home care interventions by healthcare professionals or community health workers (ATS, 2005; NHLBI, 2007; GINA, 2020). There are no studies that evaluated the effectiveness of pharmacist-led home care interventions in adult patients with asthma (Crespo-Gonzalez et al., 2018; Flanagan and Barns, 2018; Abbott et al., 2020). Developing a specific programme for pharmacists to provide home-based care to

patients with asthma and testing the programme's effectiveness will deliver answers to the knowledge gaps. Hence, the Home Pharmacy Asthma Care (HOM-PAC) programme is to be developed, validated, and tested in an RCT to determine the impact in improving asthma outcomes. The HOM-PAC module provides a comprehensive disease management guide for pharmacists. One of the outcomes to be measured in the RCT is patients' adherence to their inhalers, but there are no validated adherence questionnaires (specific to inhalers) available in Malaysia. The Test of Adherence to Inhalers (TAI) questionnaire was designed and developed to measure patients' medication adherence specific to inhalers (Plaza et al., 2016). The translation of the TAI questionnaire into Bahasa Melayu (BM) and validation in the Malaysian asthmatic population is a prerequisite before it can be used in the RCT.

1.4 Research objectives

The objectives of the present research are as follows:

i. To evaluate the effectiveness of home care interventions among adult patients with asthma through a systematic review
ii. To translate (into BM) and validate (psychometric properties) the TAI questionnaire among adult patients with asthma in Malaysia.
iii. To develop and validate the HOM-PAC module for pharmacists.
iv. To evaluate the effectiveness of the HOM-PAC programme among adult patients with asthma from Kulim Hospital, Kedah, Malaysia.

1.5 Overview of the thesis

The present thesis is comprised of eight chapters. **Chapter 1** provides a general introduction to the thesis. The chapter provides basic information on asthma and management principles. The chapter also provides a general definition of home care services. The chapter further elaborates on the problem statement of the research and the rationale of the study. The main objectives of the thesis are also outlined in this chapter.

Chapter 2 consists of the literature review starting with asthma prevalence. The chapter describes asthma control assessment and the level of asthma control in Malaysia. Asthma diagnosis and pharmacotherapy are also discussed, including the recent major updates in the guidelines. Discussions on other essential aspects of asthma management such as inhaler technique, medication adherence, patient education with self-management, asthma triggers, and relevant health models were included. The chapter provides information and the rationale for asthma home care. The role of pharmacists in asthma management is also discussed in the chapter.

Chapter 3 presents the details of the methodologies used in the research. The chapter describes the methods used in conducting a systematic review evaluating the effectiveness of home care interventions among adult asthma patients. The chapter also includes the methodologies used to translate and validate the TAI questionnaire in Malaysian patients with asthma, followed by a description of the methods used to develop and validate the HOM-PAC module. Finally, the chapter describes the RCT's details in evaluating the HOM-PAC programme among adult patients with asthma.

Chapter 4 outlines the results, discussion, limitations, and conclusion of the systematic review that evaluated home care interventions' effectiveness among adult patients with asthma. **Chapter 5** focuses on the findings of the translation and validation of the TAI questionnaire among adult patients with asthma. **Chapter 6** describes in detail the HOM-PAC module development and validation process. **Chapter 7** delineated the findings of the RCT that evaluated the effectiveness of the HOM-PAC among adult asthma patients. Finally, **chapter 8** draws an overall thesis conclusion and recommendations for future studies.

CHAPTER 2

LITERATURE REVIEW

2.1 Diagnosis of Asthma

An accurate asthma diagnosis is crucial for optimal and comprehensive patient management (Brigham and West, 2015; Löwhagen, 2015; Saglani and Menzie-Gow, 2019). Since there is no single 'gold standard' diagnostic test to diagnose asthma, the guidelines recommend that the diagnosis is based on a structured clinical history, physical examination, and variability expiratory airflow limitations (MOH, 2017; BTS/SIGN, 2019; GINA, 2020). Typical asthma symptoms are wheezing, cough, shortness of breath, and chest tightness (Levy et al., 2009). The probability of an asthma diagnosis is considered as "high" if the symptoms are variable over time (and intensity), worsening in the early morning or night, and influenced by trigger factors (Levy et al., 2009). A positive response to corticosteroids or bronchodilators may support the diagnosis, but a lack of response may not exclude the asthma diagnosis (MOH, 2017). Methods to demonstrate the airflow limitation, the variability, and detection of eosinophilic inflammation are summarised in Table 2.1 (MOH, 2017; GINA, 2020)

Table 2.1: Diagnostic tests for airflow limitation, variability, and detection of eosinophilic inflammation

Demonstration of airflow limitation	
Spirometry	FEV_1/FVC ratio of <70% is a positive test for obstructive airway disease
Demonstration of variability in airflow limitation	
Bronchodilator reversibility	An improvement in FEV_1 of ≥12% AND ≥200 ml is a positive bronchodilator reversibility test
Other methods	An increase in FEV_1 >12% and >200 ml (or PEFR >20%) from baseline after four weeks on ICS is a positive test. The patient must not have respiratory infections
PEFR charting	PEFR monitoring over 2 to 4 weeks. Variability ≥20% or diurnal variation >15% on >3 days/week indicates a positive test
Challenge tests	Methacholine challenge: • A value of ≤8 mg/ml is a positive test Mannitol challenge: • Fall in FEV_1 of ≥15% at a cumulative dose of ≤635 mg is a positive test Exercise challenge test: • Fall in FEV_1 of 10% and 200ml from the baseline
Detection of eosinophilic inflammation or atopy	
Blood eosinophils	Threshold for blood eosinophils is >4 %
IgE	Any allergen-specific IgE >0.35 kU/L in adults. Total IgE in adults >100 kU/L
FeNO	A level of ≥40 ppb is a positive test

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, PEFR = peak expiratory flow rate, FeNO = fractional exhaled nitric oxide, IgE = immunoglobulin E, ppb = parts per billion.

2.2 Asthma control assessment

Uncontrolled asthma symptoms have been linked to increased risk of exacerbations, higher healthcare utilisations, and poor QoL (Braido et al., 2016a; Ilmarinen et al., 2019; Sears, 2019; Larsson et al., 2020). Asthma exacerbation contributes to airway remodelling, lung function decline, and mortality (BTS/SIGN, 2019; GINA, 2020). In addition to inadequate symptom control, other significant predictors of asthma exacerbations are past exacerbations history, higher treatment steps, not prescribed with an ICS, low lung function, suboptimal medication adherence, and poor inhaler technique (Bateman et al., 2015; Papaioannou et al., 2016; Tanaka et al., 2017; Sears, 2019; GINA, 2020). Asthma accounts for an economic burden of €72 billion annually in 28 countries of the European Union (ERS, 2017). The burden includes annual costs of health care (€20 billion), loss of productivity for patients (€14 billion), and disability-adjusted life year (DALYs) loss of €38 billion (ERS, 2017). The cost of uncontrolled asthma in the next 20 years is projected to be USD 963.5 billion in the US (Yaghoubi et al., 2019). A Malaysian study reported that the cost of a single hospitalisation event due to acute asthma was approximately RM1800 (Yong and Shafie, 2018a).

2.3 Asthma control in Malaysia

The Asthma Insights and Reality in Asia-Pacific (AIRAP) survey reported that 32.6% of adult asthma patients visited the emergency department (ED), hospitalised, or had other unscheduled urgent care (Zainudin et al., 2005). The study also reported that 31.4% of the patients experienced productivity losses (Zainudin et al., 2005). The NHMS III reported that more than 50% of adult asthma patients experienced exacerbation in the preceding 12 months, and of these, 10% were hospitalised (IPH,

2008). The survey also reported that 21% of the patients had asthma-related sleeping difficulties, 16.9% had breathing difficulties during physical exertions, and 15.6% had limitations in daily activities (IPH, 2008). The Asthma Insight and Management (AIM) study was conducted to characterise patients' insights, attitudes, and perceptions about their asthma and the treatments (Thompson et al., 2013). The AIM study delineated that only 6% of the Malaysian patients had well-controlled asthma (assessed based on GINA tool) (Thompson et al., 2013). Twenty-two per cent of the patients had daytime symptoms, and 24% reported nocturnal symptoms either every day or most of the days (Thompson et al., 2013). The report also highlighted that 32% of the patients experienced at least one exacerbation in the past 12 months (Thompson et al., 2013). The Recognize Asthma and Link to Symptoms and Experience (REALISE) Asia survey was conducted among adult patients with at least two asthma prescriptions in the last 2 years (Muttalif et al., 2014). The study reported that 28% of Malaysian patients had well-controlled asthma (assessed based on the GINA tool) (Muttalif et al., 2014). Forty per cent of the patients had an ED visit; meanwhile, 24% were hospitalised for acute asthma exacerbation (Muttalif et al., 2014).

A cross-sectional study in a Malaysian tertiary hospital, which was conducted from 2009 to 2011, documented that only 23.2% of the patients had well-controlled asthma (assessed based on ACT score) despite the majority (90%) of the patients were treated with ICS (Kuan et al., 2015). Isa and colleagues conducted a prospective multicenter study, Assessment of Asthma Control Level in Primary Care Setting in Malaysia (ASCOPE), that recruited 1011 adult asthma patients from 14 health clinics (Isa et al., 2020). The ASCOPE study reported that 41% of the patients had well-controlled asthma and the mean exacerbation rate in the past 12 months was 4.4 (Isa et al., 2020). The exacerbation rate was higher than in other parts of the world (Suruki

et al., 2017; Bloom et al., 2019). Similar to the study by Kuan et al. (2015), most of the patients (90%) in the ASCOPE study were also treated with ICS (Isa et al., 2020). However, more than 50% of the patients still experienced inadequate asthma control (Isa et al., 2020). The findings of poor asthma control among patients treated with controller inhalers were also reported in two other studies. Wong et al. (2017) recruited patients who had been prescribed controller inhalers from two health clinics in Malaysia and documented that only 30% of the subjects had well-controlled asthma at the baseline (measured by ACT). A study conducted at two major respiratory centres in Malaysia reported that 93% of the subjects were treated with controller inhalers (Vampanan, 2018). However, the study delineated that merely 30% of them had well-controlled asthma (measured by GINA symptom tool) (Vampanan, 2018). The studies mentioned above summarised that the overall asthma control among Malaysian patients remains unsatisfactory. There are several factors crucial for asthma control and need to be addressed effectively such as (1) pharmacotherapy (including co-morbidities management) (2) medication adherence (3) inhaler technique (4) asthma education, self-management and written asthma action plan (WAAP) (5) asthma triggers, and (6) behavioural change (Papi et al., 2018a; BTS/SIGN, 2019; GINA, 2020; Papi et al., 2020).

2.4 Asthma pharmacotherapy

The inhalation route is the most effective drug administration modality in asthma management (Borghardt et al., 2018). The approach delivers drugs directly into the lungs, producing higher concentrations in the airways and significantly less risk of systemic ADRs (Borghardt et al., 2018). The pharmacological strategies in asthma management are based on stepwise approaches (Chipps et al., 2017; McCracken et al.,

2017; MOH, 2017; Quirt et al., 2018; BTS/SIGN, 2019; Chipps et al., 2019; GINA, 2020). The treatment regimen is intensified if patients' asthma is uncontrolled (stepped-up) and if the patients' asthma has been successfully controlled (for 3 to 6 months), the treatment regimen can be stepped down (Chipps et al., 2017; Chipps et al., 2019). The general rule of thumb of this approach is to treat the patient with the lowest dose or least number of medications, which can provide optimal asthma control (McCracken et al., 2017). The treatment is adjusted in a continuous cycle involving assessment, treatment modifications, and reviewing the response (GINA, 2020).

Optimal asthma management also involves addressing the comorbidities such as allergic rhinitis, obstructive sleep apnea (OSA), rhinosinusitis, nasal polyps, obesity, mental health, and gastroesophageal reflux disease (GERD) (Papi et al., 2018a). For example, symptoms (e.g., dry cough) and diagnosis of GERD are common among patients with asthma and require specific treatment such as proton pump inhibitors (GINA, 2020). Appropriate management of the comorbidities is recommended because they have proven to lead to poor asthma control and QoL (Papi et al., 2018a).

Asthma medications are divided into:

a) Controllers

The controller medications are used to stabilise patients' asthma control (McCracken et al., 2017; Papi et al., 2018a; Quirt et al., 2018; GINA, 2020). Inhaled corticosteroids (anti-inflammatory) are the most effective controller medications, and their efficacy is proven in reducing asthma symptoms, preventing exacerbations, reducing mortality, improving lung function and QoL (Suissa et al., 2000; Reddel et al., 2017; Papi et al., 2018a; Ora et al., 2020). Other controller options are long-acting

beta$_2$ agonist (LABA), long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist, allergen-specific immunotherapies, and methylxanthines (BTS/SIGN, 2019; GINA, 2020). Patients with severe asthma can be treated with add-on medications such as biological agents (e.g., omalizumab), long-term macrolides, and oral corticosteroids (OCS) (NHMRC, 2019; Holguin et al., 2020). Important to note that LABAs are always to be used in combination with ICS (Belhassen et al., 2016; Busse et al., 2018). To date, the only LAMA approved for asthma is tiotropium, delivered through Soft Mist Inhaler (SMI) device (Halpin, 2016; Sobieraj et al., 2018; BTS/SIGN, 2019), because of the solid evidence from the clinical trial programme which involved 5342 patients (Cazzola et al., 2020). However, studies investigating other LAMAs (fixed combination) in adult asthma are also ongoing/ completed and may receive authorities' approval in the near future (Cazzola et al., 2020).

b) Relievers

Relievers such as short-acting beta$_2$ agonists (SABAs) are used "as needed" for relief of breakthrough symptoms (Martin and Harrison, 2019; Muneswarao et al., 2019; Papi et al., 2020). Relievers are also important during exacerbations (Martin and Harrison, 2019; Muneswarao et al., 2019) and exercise-induced bronchoconstriction (Aggarwal et al., 2018; GINA, 2020). Patients with well-controlled asthma are less dependent on reliever treatment in their daily life (Larsson et al., 2020; Papi et al., 2020). In general, the need to use relievers more than twice a week indicates uncontrolled asthma (Larsson et al., 2020; Papi et al., 2020).

Past versions of GINA guidelines suggested that mild asthma in adults can be well managed with either reliever medications, for example, SABA alone, or with the additional use of controllers such as regular ICS (GINA, 2017). Given the low

frequency or non-bothersome nature of symptoms in mild asthma, patients' adherence towards their regular controller medications is not satisfactory (Beasley et al., 2014; Barnes and Ulrik, 2015; Bateman et al., 2018). Such patients often rely on SABA alone to relieve symptoms, contributing to SABA over-reliance (O'Byrne et al., 2017; Bateman et al., 2018). The overuse of SABAs has been associated with poor asthma outcomes, such as exacerbations and even deaths (Suissa et al., 1994; Stanford et al., 2012; Levy et al., 2014). A recent retrospective, population-based cohort study, SABINA (SABA use IN Asthma), which analysed 365,324 asthma patients, also supported the findings (Nwaru et al., 2020). The study reported that the use of three or more canisters of SABAs in a year increased the risk of exacerbation and death (Nwaru et al., 2020). The GINA 2019 asthma treatment recommendations represent significant shifts in asthma management at Steps 1 and 2 of the treatment ladders (Muneswarao et al., 2019; Papi et al., 2020). The guideline acknowledges an emerging body of evidence suggesting the non-safety of SABAs overuse in the absence of concomitant controller medications; therefore, it does not support SABA-only therapy in mild asthma (Muneswarao et al., 2019). The GINA 2019 has included new recommendations such as symptom-driven (as-needed) low dose ICS-formoterol combination (Bateman et al., 2018; O'Byrne et al., 2018) and "low dose ICS taken whenever SABA is taken" (Martinez et al., 2011; Calhoun et al., 2012; Muneswarao et al., 2019; Kuprys-Lipinska et al., 2020; Papi et al., 2020). These changes can be thought of as revolutionising mild asthma management, and the recommendations are maintained in the latest GINA 2020 as well (GINA, 2020; Kuprys-Lipinska et al., 2020).

2.5 Medication adherence

Medication adherence is defined as the extent to which a patient's behaviour corresponds with the prescribed medication dosing regime, including time, dosing, and interval of medication intake (Cramer et al., 2008; Gast and Mathes, 2019). The World Health Organization (WHO) panel positioned importance on the need to differentiate "compliance" from "adherence." It was agreed that the term "adherence" requires the patient's agreement (as active partners) to the recommendations (WHO, 2003). Reviews conducted in developed countries have documented that only 50% of the patients suffering from chronic illness were adherent to their treatment regimen. The scenario is expected to be worst in developing countries, given the scarcity of health resources and limited access to healthcare facilities (Sackett et al., 1978; Haynes et al., 2002; WHO, 2003).

2.5.1 Methods to measure medication adherence

Medication adherence can be divided into three stages; initiation, implementation, and discontinuation of the treatment (Vrijens et al., 2012). Unsatisfactory adherence to medication may be due to specific cause/s that need to be highlighted before the remedial actions can be formulated (Brown and Bussell, 2011). Inaccurate medication adherence measurements will lead to imprecise therapy decisions, and these can potentially inflate the cost as well (Lam and Fresco, 2015).

Several tools are available to measure medication adherence, which can be divided into direct and indirect methods (Osterberg and Blaschke, 2005). Direct measures include measurement of the medication or its specific metabolite concentration/biological markers in body fluids and direct observation of the patient's

medication-taking behaviour by health care professionals (Anghel et al., 2019). Indirect methods include prescription records, electronic medication monitors, pill counts, patient self-reporting questionnaires, patient diaries, and clinical response or physiologic markers (Osterberg and Blaschke, 2005; Jimmy and Jose, 2011; Lam and Fresco, 2015). Two common indirect methods to assess medication adherence are the proportion of days covered (PDC) and medication possession ratio (MPR), which measure prescription fill records (Raebel et al., 2013). Each method to assess medication adherence has its advantages and disadvantages, and no method is considered the gold standard (Jimmy and Jose, 2011; Lehmann et al., 2014; Lam and Fresco, 2015). The summary of the advantages and disadvantages of different types of medication adherence assessment methods is presented in Table 2.2 (Osterberg and Blaschke, 2005; Gillisen, 2007; Hawkshead and Krousel-Wood, 2007; Lam and Fresco, 2015). Literature also recommends to use more than one measures to increase the reliability and accuracy of the results as this strategy allows the strengths of one method to compensate for the recognised weakness of another method (Lam and Fresco, 2015; López-Viña et al., 2017; Papi et al., 2018b; Plaza et al., 2019).

Table 2.2: Advantages and disadvantages of different types of adherence measuring methods

Test	Advantages	Disadvantages
Direct		
Direct observation	Most precise	Can be manipulated by the patients, not practical
Drug or metabolite levels (e.g., theophylline)	Objective	Variability in drug metabolism may result in an inaccurate level of adherence, costly
Biological markers (e.g., fractional exhaled nitric oxide)	Objective	Costly, not practised in clinical practice
In direct		
Questionnaires and self-reports	Simple, economical, the most practical tool in clinical settings, validated tools are available	Erroneous results are more likely with an increase in time between reviews (recall bias), patients can distort the results easily, may overestimate medication adherence, variation in the questionnaire domains
Pill counts (e.g., tablet theophylline, prednisolone and montelukast)	Objective, simple, economical	Unable to confirm medication consumption, prone to alteration by the patient (medication dumping) which can lead to overestimation, requires accurate prescription data
Prescription refills	Objective, timelines, highlights the gaps, easy to perform	Unable to confirm medication consumption, requires pharmacy database, data not immediately available
Clinical responses	Simple, relatively easy	Clinical response is not only dependent on medication adherence

Table 2-2. Continued

Electronic adherence monitoring (e.g., Inhaler Compliance Assessment, INCA device)	Accurate, quantifiable, provides information on routine intake and administration patterns on medication consumption	Costly, malfunctioning device, data download process, return visits required, cumbersome, patient anxiety
Physiological markers	Easy	Marker absentee may be due to other factors
Monitoring medication balance (including canister weighing) and inhaler dose counters	Simple, easy, objective, low cost	Doses may be wasted by patients instead of taking them, no information on the actual dosing schedule, not all devices have dose counters
Asthma diaries	Useful in a patient with poor memory recall	Patients can alter, overestimation, unable to perform if patients do not return the diaries

2.5.2 Medication adherence in asthma

Poor adherence to asthma controller medications has been reported in the scientific literature (BTS/SIGN, 2019; GINA, 2020). A British Columbian study projected adherence rates (measured using PDC) between 16% and 32% (Sadatsafavi et al., 2013). In a survey of 2686 asthma patients in Australia, 43% reported using controller inhalers fewer than 5 days a week, and 31% reported fewer than once a week (Reddel et al., 2015). The scenario was also unsatisfactory in the REALISE Asia study, which documented that only 14% of asthma patients regularly used their controlled inhalers (Price et al., 2015). Based on a systematic review, generally, medication adherence in adult asthma patients ranges from 30 to 70%; however, the prevalence varies by country, gender, and ethnicity (Engelkes et al., 2015). Studies that used electronic inhaler monitoring reported lower adherence rates, between 25% and 50%

of the prescribed doses (Hew and Reddel, 2019). The latest findings of the European Community Respiratory Health Survey (ECRHS III) indicate that although the use of controllers has increased in the last two decades, only 34% of asthma patients have regularly taken their ICS (Janson et al., 2019). Murphy and colleagues published a systematic review and meta-analysis, which delineated that the prevalence of adherence among young adult asthmatics (18 to 30 years) was only 25% (Murphy et al., 2020).

A large multinational observational study (1054 patients), which included Malaysian asthma patients, reported that only 53% of the patients were adherent to their treatment (Chiu et al., 2014). The study used the 8-item Morisky Medication Adherence Scale (MMAS-8) to assess medication adherence (Chiu et al., 2014). The authors also reported that up to 39% of the patients were uncertain about the effectiveness of their inhalers, felt uncomfortable or troublesome using an inhaler, and preferred oral treatment (Chiu et al., 2014). A survey of Malaysian asthma patients by Muttalif et al. (2014) highlighted that only 18% of patients used their controller inhalers daily. Thirty-three per cent of patients admitted taking their controller inhalers only when they have symptoms, and 7% of the survey patients did not use their controller inhalers at all (Muttalif et al., 2014). Moreover, almost half of the survey patients reported that taking their inhalers was troublesome (Muttalif et al., 2014).

Another Malaysian study conducted at a tertiary hospital reported that more than half of asthma patients had unsatisfactory inhaler refills (Ang et al., 2019). The researchers used medication refill adherence (MRA) to assess medication adherence (Ang et al., 2019). However, the study had a small sample size, which was one of the limitations (Ang et al., 2019). The ASCOPE study reported that almost 50% of the patients forgot to take their medication at any point in time, and 32% of the patients

stopped their medication when they felt their disease had improved (Isa et al., 2020). These findings suggest that the overall medication adherence among adult patients with asthma in Malaysia is suboptimal.

2.5.3 Impact of poor medication adherence on asthma outcomes

Poor medication adherence leads to poor asthma control (Williams et al., 2004; GINA, 2020). The National Review of Asthma Deaths (NRAD) report identified poor adherence to treatment as one of the risk factors for asthma-associated deaths (RCP, 2014; Nasser, 2016). Poor adherence was identified in 48% of patients who had died due to asthma (RCP, 2014). In a cohort study of 30,569 patients, the rate of death from asthma decreased by 21 % with each additional canister of ICS, suggesting regular use of ICS is associated with a reduced risk of asthma mortality (Suissa et al., 2000). The systematic review published by Engelkes et al. (2015) indicated that optimal medication adherence was associated with a lower risk of severe exacerbations. The study reported that a 25% increase in medication adherence was associated with an approximately 10% reduction in severe asthma exacerbations (Engelkes et al., 2015). The higher level of medication adherence was also related to improvements in patients' asthma symptoms (Janezic et al., 2017) and QoL (Fitri et al., 2016). Several studies reported that even intermittent use (instead of regular use) of controller inhalers were associated with poor outcomes such as exacerbations (20% to 44% of patients experienced at least one exacerbation in the past 12 months) (Price et al., 2014b; Reddel et al., 2015; Gibbons et al., 2020).

2.5.4 Types of medication non-adherence and contributing factors.

There are different types of non-adherent behaviours to asthma medications with diverse contributing factors, and these must be carefully understood (WHO, 2003). Vigilant clinical investigation can disclose these problems, and remedial strategies can be formulated more effectively (WHO, 2003). In general, medication non-adherence can be divided into intentional and unintentional (Horne, 2006). Unintentional non-adherence is when a patient is prevented from taking the medications as prescribed, by circumstances beyond their control, such as forgetfulness, inadequate understanding about the medication regimens, language barriers, physical inability to administer the medication (e.g., poor inhaler technique), busy lifestyles and cost (Horne, 2006; Pollard et al., 2017; GINA, 2020). Unintentional non-adherents may wish to be more adherent to their medication, but the contributing factors hinder them from making medication-taking part of their lives (Horne, 2006; Pollard et al., 2017). Intentional non-adherence happens when the patients consciously decide to discontinue use (intermittent or total) or modify the medication regimen by themselves (Pollard et al., 2017). The examples are patients who (1) perceive treatment as not necessary, (2) denial of their disease, (3) having inappropriate expectations, (4) concerned about the ADRs, (5) dissatisfied with healthcare professionals, (6) stigmatised, and (7) having cultural/ religion issues (GINA, 2020). The reasons mentioned above are consistent with the REALISE Asia study findings, which analysed physicians' and patients' perspectives on asthma from eight Asian countries (including Malaysia) (Price et al., 2016). Pollard et al. (2017) proposed a theoretical framework (Figure 2.1), which outlined factors associated with a patient's adherence to the prescribed asthma medication. These factors are interrelated and can be categorised as both modifiable and non-modifiable. The framework also recognises