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Critical Review

The Use of Inhalation Therapy in the Management of Chronic Obstructive Pulmonary Disease (COPD) in the Community: A Review of Studies

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ARTICLE INFO	ABSTRACT
*Corresponding author. Tel.: +966547003275 E-mail: f_alhomoud83@yahoo.com 	Inhalation therapies are central to the management of chronic obstructive pulmonary disease (COPD). Although, findings from previous studies reveal suboptimal use and a wide range of problems with inhaler handling among COPD patients, very little is known about how and why problems arise. A systematic search of studies related to the topic area was conducted using Scopus and PubMed, from 2000 to 2013. As a result, twenty-two studies were included. Most studies had similar baseline characteristics. This review indicated that adherence to inhalation therapy was of concern. Rates of non-adherence to medication ranged from 29.5% to 80%. This review confirms non-adherence as a problem among patients and identifies factors which were potential contributors to medication non-adherence. The review reveals issues in operating the inhalation devices especially with the pressurised metered dose inhalers (pMDIs), which may lead to sub-optimal therapeutic outcomes and treatment failures.

INTRODUCTION

Global prevalence and burden of COPD

Chronic obstructive pulmonary disease (COPD) is a long term condition characterised by progressive narrowing of the airways and premature ageing of the lungs. As reported by the Quality and Outcomes Framework (QOF) (DH 2010), in England in 2008, 15.4 million people had a long-term condition, including COPD which was the third most common after coronary heart disease and diabetes. By 2020, COPD is estimated to be the third biggest cause of death in the UK, after heart disease and stroke (Mannino 2006; BLF 2008). In addition to what stated earlier, chronic obstructive pulmonary disease (COPD) imposes a large financial burden on health services and is among the most costly diseases in the UK (DH, 2011).

What are the inhalation therapies available for the management of CODP?

Inhalation therapies are central to the management of COPD. They include both oral and inhaled medications (e.g. bronchodilators, corticosteroids and combination therapies) and are delivered by pressurised metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulisers (NICE 2010).

Why review the use of medication among COPD patients?

Different terms were used in the scientific literature to describe patients' medication use one of which is adherence and compliance. These terms are used

interchangeably, despite being different in the meaning which should be noted. Compliance is defined as "the extent to which a person's behaviour (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice" (WHO, 2008). The term adherence is defined similarly, but implies active participant involvement. Therefore, the term adherence was used throughout this review.

Medication non-adherence has been identified as a major public health problem that imposes a considerable financial burden on healthcare services (Vermeire et al., 2001; Bender et al., 2014). This burden has been estimated worldwide to cost $100 billion each year (Vermeire et al., 2001). In 2010, the cost of COPD was projected to be approximately US$50 billion, which includes $20 billion in indirect costs and $30 billion in direct health care expenditures. These costs can be expected to continue to rise with this progressive disease (Guarascio et al., 2013). The WHO estimates that the average non-adherence rate is 50% among those with chronic illnesses including COPD (Chisholm-Burns and Spivey, 2003). Strategies to improve adherence to inhalation therapy among patients (e.g. patient instruction and education) have been shown to work among patients with asthma (Put et al., 2003; Onyirimba et al., 2003), whereas, in COPD patients, these strategies were less successful (Rand, 2005; Restrepo, et al., 2008). Therefore, non-adherence remains an unresolved problem despite decades of research, and is a factor resulting in suboptimal clinical outcomes and poor disease control.

Why review the use of devices among COPD users?

The review of the literature reveals that incorrect use of inhalation devices in regards to the inhalation techniques which means that little or no medicine reaches the lungs, is very common among patients with COPD, leading to suboptimal drug delivery. Therefore, users may receive lower benefits from their treatment, which may result in the prescription of unnecessarily high doses and higher healthcare costs. It has been estimated that $5 to $7 billion in the United States is wasted every year because of inhaler misuse (Fink and Rubin, 2005). The review of the literature reveals suboptimal use and a wide range of problems with inhaler handling. However, very little

is known about how and why problems arise and what practical issues COPD patients faced when using inhalation devices in combination.

What are the objectives of this review?

The objectives were, firstly, to establish the extent to which COPD patients' medication use regarding adherence to inhalation therapy has been studied and review evidence regarding adherence rates and how COPD patients made decisions about the use of these medications; and, secondly, to identify all research evidence relevant to problems patients had with inhalation devices in the preparation and operation of inhaler equipment aiming to identify behaviours which may lead to treatment failures or exacerbations.

MATERIALS AND METHODS

Search strategy

The electronic databases Scopus and PubMed were searched using the following MeSH terms: [Chronic Obstructive Pulmonary Disease OR COPD OR Chronic Obstructive Airway Disease OR Chronic Obstructive Lung Disease OR Airflow Obstruction Chronic OR Chronic Airflow Obstructions] AND [Drug Therapy] AND [Medication Adherence OR Medication Compliance OR Medication Use] AND [Inhalation Technique]. Searches were restricted to English language and human studies and limited by the period from 2000 to 2013, as this period witnessed the introduction of many therapeutic agents and higher technological devices for inhalation therapy, especially with the introduction of the patient-friendly devices DPIs. Additionally, there was a systematic review published in 2001 by Brocklebank, covering almost similar aspects of this review by comparing the medication use and effectiveness in asthma and chronic obstructive airways disease. Therefore, it was decided to take this review further to find out how COPD patients and their behaviours have changed with regard to their use of their medicines or devices since that review (Brocklebank et al., 2001). The reference lists of all included articles and identified reviews were also manually searched to identify any other relevant studies.

Study selection

The criteria for relevant studies were: (1) patients with COPD aged over 18 years old because COPD mainly affects middle-aged or older adults who usually smoke; using inhalation devices; in primary care; (2) studies reported in the English language. Eligible studies were peer-reviewed studies. Studies that examined the timing, dosage, frequency of medication and inhalation technique were included. Articles referring to adherence to oxygen therapy, pulmonary rehabilitation and exercise were excluded. Articles examining medication adherence for other pulmonary diseases such as asthma were excluded. This criterion was applied given that COPD is a progressive disease, and that treatments for COPD differ markedly compared to other respiratory diseases (Rand, 2005). However, studies that examined COPD together with other diseases were included. Whilst, intervention studies which have not covered or assessed patients' adherence during or after the intercession were also excluded because it was not part of this study objectives.

Data extraction and quality assessment

Electronic databases were searched and duplicate articles were removed. All articles were reviewed manually by title, abstract and/or full-text for relevance. The reference lists of retrieved articles were manually examined for further applicable studies. Full text manuscripts were retrieved either electronically or as hard copy for assessment (see Figure 1). Information was extracted into a proforma which included: primary author name and date of publication, country of the study, study settings, sample, methods employed, measures used and results. The characteristics of the studies of medication use of multiple inhalation therapy and the practical aspects of operation of the inhalation devices studies among COPD patients are reported Table 1 and Table 2 respectively.

RESULTS AND DISCUSSION

Search results and study characteristics

The initial search yielded 123 results with an additional thirteen studies identified through manual searches of reference lists. After removing 9 duplicates, 127 unique papers were retained and

assessed against eligibility criteria. Of these, 22 studies have met criteria for inclusion in the review. Of the 22 studies, 11 studies examined patients' medication use regarding adherence (Table 1). Eleven studies examined the aspects of operation of inhalation devices and described the frequency and range of problems experienced by COPD patients when using their inhalation devices (Table 2).

These studies were mostly based in outpatient clinics (N=11) (Lenney et al., 2000; Hesselink et al., 2001; George et al., 2005; Khassawneh et al., 2008; De Moraes Souza et al., 2009; Rootmensen et al., 2010; Melani et al., 2011; Agh et al., 2011 ; Cecere et al., 2012; Huetsch et al., 2012; Khdour et al., 2012), and patients' home (N=5) (Melani et al., 2001; Barta et al., 2002; Boyter and Carter, 2005; George et al., 2006; Sestini et al., 2006). Others were based in community pharmacies (N=3) (Hämmerlein et al., 2011; Mehuys et al., 2010; Trivedi et al., 2012).
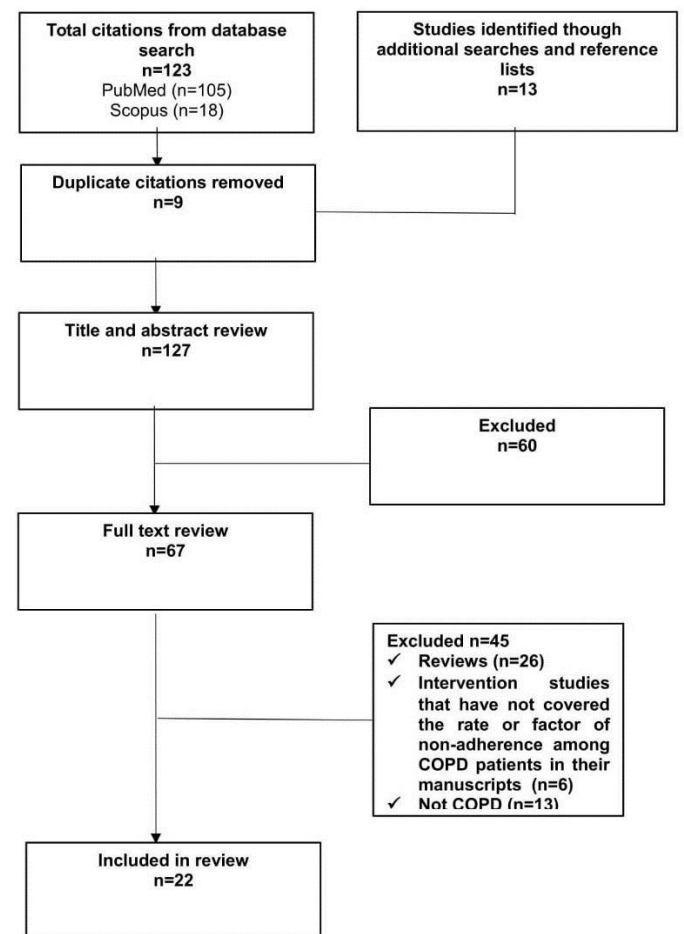

Fig. 1. Flow chart of study selection

Table 1. *Studies of medication non-adherence to COPD medicines worldwide.*

Study, Setting, Country	Sample	Definition of patients' adherence/non adherence	Methods/measures	Study findings and conclusions
Khdour (2012) Outpatient clinics, UK	137 COPD patients	Adherent: patients scoring 3 or above were classified as 'adherent'.	Cross sectional study Adherence to COPD medications was measured using patients' self-reported questionnaire (4-items Morisky)	Adherence was generally good. Rate of non-adherence to COPD medications: 29.5% of the patients. Variables linked to medicine taking: A range of clinical and psychosocial variables such as perceived severity of the disease and benefits of medications.
Cecere (2012) Outpatient clinics, USA	167 COPD patients, prescribed LABA and ICS	Adherent: took 80% of doses as prescribed	Clinical Randomised trial Adherence to COPD medicines was measured using prescription refill rates	Adherence was generally poor. Rate of non-adherence to ICS: 60% of participants. Rate of non-adherence to LABA†: 46% of participants. Variables linked to medicine taking: patient perception of their provider as being an "expert" in diagnosing and managing lung disease.
Huetsch (2012) Outpatient clinics, USA	2,730 COPD patients, prescribed ICS,LABA, and IP	Adherent: took 80% of doses as prescribed	A cohort study Adherence to COPD medicines was measured using prescription refill rates	Adherence was generally poor. Rate of non-adherence to ICS: 80.2% of participants. Rate of non-adherence to IP‡: 74.4% of participants. Rate of non-adherence to LABA†: 69.4% of participants. Variables linked to medicine taking highly variable and dependent on the medication being examined.
Trivedi (2012) Outpatient clinics, USA	374 COPD patients, prescribed LABA	Adherent: took 80% of doses as prescribed	Non-blinded cluster randomised clinical trial. Adherence to COPD medicines was measured using prescription refill rates	Adherence was generally poor. Rate of non-adherence to LABA: 43% of participants. Variables linked to medicine taking: social care.
Agh (2011) Outpatient clinics, Hungary	170 participants with COPD	Adherent: patients scoring 3 or above were classified as 'adherent'.	Cross-sectional observational study. Adherence to COPD medications was measured using patients' self-reported questionnaire (4-items Morisky)	Adherence was generally good. Rate of non-adherence to COPD medicines: 41.8 % of participants. Variables linked to medicine taking: age, smoking status, number of medicines, the number of daily doses and quality of life.
Mehuys (2010) Community pharmacies Belgium	555 patients with stable COPD	No clear classification.	Cross-sectional, observational study. Adherence to COPD medicines was measured using prescription refill rates.	Adherence was generally poor. Rate of non-adherence to COPD medicines: 53% of participants. Variables linked to medicine taking: age and number of drugs.

Table 1. Continued….

Study, Setting, Country	Sample	Definition of patients' adherence/non adherence	Methods/measures	Study findings and conclusions
George (2006) Patients' homes Australia.	28 patients with moderate to severe COPD	The identified themes for medication adherence were agreed among all the authors (pharmacists)	Randomized controlled trial study. Factors associated with adherence to disease management interventions were explored using in depth semi-structured questionnaire.	Adherence to disease management programs was found to be a complex process driven by 15 major themes such as personal beliefs and experiences which are related to patient, treatment, disease, and health professionals.
George (2005) Ambulatory care, Australia	276 patients with chronic lung diseases (90.6% with COPD, 5.4% with asthma, 2.2% bronchiectasis,and 1.8% others)	Highly adherent: (a score of 25 indicates), while any other score reports suboptimal adherence.	Cross-sectional descriptive study. Adherence was measured using patients' self-reported questionnaire (the Medication Adherence Report Scale MARS). A 30-item Beliefs and Behaviour Questionnaire (BBQ) under three sections: beliefs, experiences, and behaviours were used to determine the factors that are related to medicine taking.	Adherence was generally poor. Rate of non-adherence to COPD medicines: 60% of participants. Variables linked to medicine taking: patients' beliefs, experiences, and behaviors with regards to both disease and treatment.
Boyter (2005) Patients' homes, The United Kingdom	117 patients mainly with COPD, prescribed home nebuliser treatment	Adherent: used home nebulizers at four times a day	A survey study. Adherence to COPD nebulised medications, use and maintenance of equipments were measured and explored by patients' self-reported using anonymous postal questionnaire	Adherence was generally poor. Rate of non-adherence to COPD medicines: 57% of participants.
Barta (2002) Patients' homes, The United Kingdom	75 patients most with COPD, prescribed home nebuliser treatment	Adherent: used home nebulizers at least once a day	A survey study. Adherence to respiratory nebulised medications, use, technical issues, and concerns about side effects were measured and explored using patients' self-reported anonymous postal questionnaire.	Adherence was generally good. Rate of non-adherence to COPD medicines: 40% of participants. Variables linked to medicine taking: feeling worse, less confidence in treatment.
Melani (2001) Patients' homes, Italy	1,257 COPD patients, prescribed home nebuliser treatment	Adherent: used home nebulizers at least once a day	Open, multicentre, cross-sectional, observational study. Adherence to respiratory nebulised medications, use, technical issues, and concerns about side effects were measured and explored using patients' self-reported anonymous postal questionnaire.	Adherence was generally poor. Rate of non-adherence to COPD medicines: 60% of participants. Variables linked to medicine taking: medication forgetfulness.

ICS: inhaled corticosteroids, COPD: Chronic Obstructive Pulmonary Disease, †LABA: long-acting beta-agonists, ‡IP: Ipratropium bromide

Table 2. *Characteristics of studies of inhalation technique assessment among COPD patients worldwide.*

Study, Setting, Country	Sample	Developing check-lists	Definition of incorrect technique	Kind of assessment	Methods/measures	Study findings and conclusions
Hämmerlein (2011), Community pharmacies Germany	757 patients with asthma or COPD using pMDIs and DPIs	21-items checklist was developed to be used for all types of inhalation devices	As a matter of principle, an error probability of less than 5% was demanded (P < 0.05), when using independent sample t-test	Assessment was made based on a personal view of one rater.	Multi-centre intervention study. Each single step was marked as been performed correctly or incorrectly. However, not all steps were relevant for each inhaler system, for example, shaking the inhaler in case of a DPI, non-relevant steps should be marked as correct.	Inhalation technique was judged insufficient in 80% of the patients.
Melani (2011) Outpatient clinics, Italy	1633 patients, most with COPD and asthma, using MDIs and DPIs	Check-lists were adapted from previously published criteria by (Newman, 2005)	If one or more errors were made regarding these essential steps determined by (Newman, 2005)	Assessment was made based on an agreement between multiple raters on set of criteria for the correct use.	Cross-sectional, observational study. Assessment of inhalation technique was done using; a checklist that measures steps required for adequate drug delivery and categorized the steps into 'essential' and 'non-essential' errors and assessed only those 'critical errors or essential steps'.	Inhalation technique was judged insufficient among all DPIs users, ranging from 44% for Turbuhaler, 35% for Diskus and Handihaler. While, the inhalation technique among pMDIs users was generally good (12% of users made errors with the use). Patients committed more errors when using DPIs.
Rootmensen (2010) Outpatient clinics, The Netherlands	156 patients most with COPD and asthma, using MDIs and DPIs	Check-lists adapted from published criteria (van der Palen, et al., 1995; van Beerendonk et al., 1998).	If one or more errors were made regarding these essential steps determined by (van der Palen, et al., 1995)	Assessment was made on an agreement between 3 raters on set of criteria for correct use with the assessment of the total inhalation technique.	Randomized controlled trial. Assessment was done using checklists that measures steps required for adequate drug delivery and categorized the steps into 'essential' and 'non-essential' and only those 'critical errors or essential steps' were measured.	Inhalation technique was judged insufficient in 40% of the patients. Most errors were seen in demonstrations with pMDIs with or without spacer (respectively, 47 and 81%). Essential errors were recorded least in the prefilled Diskus (15%), Turbuhaler (18%), and Diskhaler (21%). Patients committed more errors when using pMDIs than when using DPIs.
De Moraes Souza (2009)	120 patients with COPD and asthma, using MDIs and DPIs	Check-lists were adapted from previously	No clear definition.	Assessment was made based on a	Observational study. Measuring the total inhalation technique for each inhaler	Inhalation technique was judged insufficient in 94.2% of the patients.

Study, Setting, Country	Sample	Developing check-lists	Definition of incorrect technique	Kind of assessment	Methods/measures	Study findings and conclusions
Outpatient clinics, Brazil		published criteria (Steier, et al., 2003; Molimard, et al., 2003; Muchão, et al., 2008).		personal view of one rater.	individually. The quantity of errors committed by the asthma group patients and by the COPD group patients was compared for each device separately.	Patients committed more errors when using pMDIs than when using DPIs.
Khassawneh (2008) Outpatient clinics, Jordan	500 patients with COPD using pMDIs and DPIs	Not clearly listed	If one or more errors were made regarding these essential steps, leading to indicating little or no delivery of the drug.	No clear assessment.	Cross-sectional observational study. Measuring steps required for adequate drug delivery and categorized the steps into 'essential' and 'non-essential'. When one or more essential steps were made, inhalation technique was defined as incorrect.	Among the DPIs, the Accuhaler device had the lowest rate of incorrect handling, when compared to Turbuhaler and Aerolizer. Patients committed more errors when using pMDIs than when using DPIs.
Wilson (2007) Outpatient clinics, London, United Kingdom	30 patients with COPD with evidence of airflow obstruction (*FEV1/FVC < 70%) and had no previous experience of DPIs	Device-specific checklists were adapted from the package leaflet of each inhaler	If one or more errors were made regarding these essential steps, leading to indicating little or no delivery of the drug.	Assessment was made based on an agreement between two raters on set of criteria for correct use	Randomized controlled trial. Measuring steps required for adequate drug delivery and categorized the steps into 'essential' and 'non-essential'. When one or more essential steps were made, inhalation technique was defined as incorrect.	The numbers of perfect scores were not significantly different between devices, but the number of fatal errors that would result in no drug delivery was significantly more common in Aerolizer, and Handihaler.
Sestini (2006) Outpatient clinics Italy.	1,126 patients with COPD and asthma, using MDIs and DPIs	Device-specific checklists were adapted from the package leaflet of each inhaler.	A sum score was computed separately for each device, in which each item of the checklist considered as minor was scored as 1, and each one considered as major flaws received a score of 3.	Assessment was made based on an agreement between two raters on set of criteria for correct use.	An open, observational study. Measuring steps required for adequate drug delivery and categorized the steps as 'minor' and 'major' errors and only those 'major' errors were measured. When one or more major errors were made, inhalation technique was defined as incorrect.	Inhaler misuse was common and similar for both pMDIs and DPIs.
Ho (2004) Patients' homes United Kingdom	423 patients use MDIs, MDIs with a large volume spacer and bread actuated	Check-lists adapted from previously published criteria (Connolly, 1995).	Major errors were identified using previously published criteria (Connolly, 1995).	Assessment was made based on a personal view of one rater with the assessment of the total inhalation.	Cross-sectional study. Measuring steps required for adequate drug delivery and categorized the steps into acceptable (perfect or minor errors not preventing adequate use of the	Inhalation technique for breath actuated-inhalers was judged insufficient in 27.8% of the patients, compared to 17.9% of patients used p-MDIs alone and 2.9% with large volume spacers.

Study, Setting, Country	Sample	Developing check-lists	Definition of incorrect technique	Kind of assessment	Methods/measures	Study findings and conclusions
					device) or unacceptable (major errors).	
Molimard (2003) Outpatient clinics, France	3811 adult with COPD and asthma, using MDIs and DPIs	Device-specific checklists were adapted from the package leaflet of each inhaler.	If one or more errors were made regarding these essential steps, leading to indicating little or no delivery of the drug.	Assessment was made based on an agreement between multiple raters on set of criteria for correct use.	Randomized control clinical trial. Measuring steps required for adequate drug delivery and categorized the steps into 'critical' and 'non-critical' errors and only those 'critical' errors were measured.	Inhalation technique judged insufficient in 49-55% of the patients use breath actuated devices compared to 76% used p-MDIs. 11-12% of patients treated with Aerolizer, Autohaler, or Diskus made critical errors compared to 28% and 32% of patients treated with p-MDI and Turbuhaler, respectively.
Hesselink (2001) Outpatient clinics The Netherland	588 COPD and asthma patients using pMDIs and DPIs	Using the short version, validated inhaler-specific checklist of the Dutch Asthma Foundation	If one or more errors were made regarding these essential steps, leading to indicating little or no delivery of the drug.	Unspecified	Cross-sectional study. The checklist measures the adequacy of the most essential preparation and breathing manoeuvres necessary for optimal drug delivery.	Inhalation technique was judged sufficient in 75.8% of the patients. Diskhaler device had the lowest rate of incorrect handling (4%), when compared to cyclohaler (11%) and Rotahaler/ Spinhalers (37%).
Lenney (2000) Respiratory Function Laboratory United Kingdom	100 patients with COPD using MDIs and DPIs	Device-specific checklists were adapted from the package leaflet of each inhaler.	If one or more errors were made regarding these essential steps, leading to indicating little or no delivery of the drug.	Assessment was made based on an agreement between multiple raters on set of criteria for correct use.	Cross-sectional observational study. Inhaler technique was graded in the following way; A. good technique indicating good delivery of the drug; B. poor technique indicating partial delivery of the drug; C. very poor technique indicating little or no delivery of the drug.	Inhalation technique was judged sufficient in 91% of the patients using the breath-actuated inhalers (Easi-Breathe and Autohaler), when compared to 79% of patients using pMDIs.

COPD: Chronic Obstructive Pulmonary Disease, MDIs: Metered Dose Inhalers, DPIs: Dry Powder Inhalers
*FEV1/ FVC: The ratio of forced expiratory volume in one second to forced vital capacity.

Most of these studies were conducted in Europe, especially the UK (N=6) (Lenney et al., 2000; Barta et al., 2002; Ho et al., 2004; Boyter and Carter, 2005; Wilson et al., 2007; Khdour et al., 2012), followed by Italy (N=3) (Melani et al., 2001; Sestini et al., 2006; Melani et al., 2011), and the Netherlands (N=1) (Rootmensen et al., 2010), Belgium (N=1) (Mehuys et al., 2010), Hungary (N=1) (Agh et al., 2011), France (N=1) (Hesselink et al., 2001), Germany (N=1) (Hämmerlein et al., 2011), the USA (N=3) (Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012), Australia (N=2) (George et al., 2005; George et al., 2006), Brazil (N=1) (De Moraes Souza et al., 2009) and Jordan (N=1) (Khassawneh et al., 2008).

Study design and methods employed

Most studies employed a cross-sectional study deign as the study participants were approached on one occasion (Lenney et al., 2000; Hesselink et al., 2001; Melani et al., 2001; Ho et al., 2004; George et al., 2005; Sestini et al., 2006; Khassawneh et al., 2008; De Moraes Souza et al., 2009; Mehuys et al., 2010; Agh et al., 2011; Hämmerlein et al., 2011; Melani et al., 2011; Huetsch et al., 2012; Khdour et al., 2012). Except for six studies which were conducted on a large national scale (Molimard et al., 2003; George et al., 2006; Wilson et al., 2007; Cecere et al., 2012; Rootmensen et al., 2010; Trivedi et al., 2012), and two were survey studies (Barta et al., 2002; Boyter and Carter, 2005). The sample size in these studies ranged from 28 to 2,730 COPD patients (George et al., 2006; Huetsch et al., 2012).

The majority of studies that has investigated medication use (adherence) among COPD patients have employed quantitative approaches (N=10) (Melani et al., 2001; Barta et al., 2002; Boyter and Carter, 2005; George et al., 2005; Mehuys et al., 2010; Agh et al., 2011; Cecere et al., 2012; Huetsch et al., 2012; Khdour et al., 2012; Trivedi et al., 2012), by measuring the amount of medicine taken over a given time period. There is a paucity of qualitative studies (N=1) that have investigated patients' medication use or adherence to their COPD medications; they have done so by considering variables such as adherence decisions which were influenced by patients' beliefs about inhalation therapies and concerns of side effects (George et al., 2006). The importance of a qualitative research is to

illustrate the way people act and think. For example, how COPD patients use their medications and what their perceptions about these medication are and whether this affect their use. In addition, it explores patterns and barriers in people's thoughts and behaviours. This sharply contrasts with quantitative research which only include numbers and statistical figures to test a hypothesis, or explaining phenomena.

There are a number of ways to measure adherence among patients with COPD. Each method has its strengths and limitations. Most studies focused on assessing medication adherence using self-report questionnaires on medication utilisation (Melani et al., 2001; George et al., 2005; Agh et al., 2011; Khdour et al., 2012). The most commonly used self-report methods were Morisky Medication Adherence Scale (MMAS) (Agh et al., 2011; Khdour et al., 2012), and the Medication Adherence Rating Scale (MARS) (George et al., 2005), which are well-validated tools used widely for all chronic conditions including COPD. Using patient self-report method does not guarantee the accuracy of the result because some patients may want to please the healthcare professionals or the researchers by giving them incorrect information about medication use maybe deliberately or in-accidentally. Therefore, they may have introduced research bias. Self-report method when combined with other means of data collection such as a review of clinical records or medication count maybe more desirable for providing reliable findings by means of triangulation.

Other studies used prescription refill rate by reference to pharmacy records of dispensed prescription or manual recording of collected prescriptions (Mehuys et al., 2010; Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012). Two studies were by means of postal questionnaires (Barta et al., 2002; Boyter and Carter, 2005), which were filled by patients. However, it cannot be ascertained whether the patient was the one who filled the survey. Although the use of postal questionnaires is very common in health and social research and findings can be generalizable to a wider population given that all other aspects of research such as sample size, randomisation, response rate, reliability and validity have been considered, this was rarely the studies described.

Findings of the studies

Type of the used inhaled medication
Bronchodilators were used more often than inhaled steroids in all reviewed studies on medication use (Barta et al., 2002 ; Boyter and Carter, 2005; Mehuys et al., 2010 ; Agh et al., 2011; Cecere et al., 2012; Huetsch et al., 2012 ; Khdour et al., 2012 ; Trivedi et al., 2012). Most frequently used bronchodilators were short-acting β2-agonists (SABA) and short-acting anticholinergic. Salbutamol was the most commonly used bronchodilator in these studies (Barta et al., 2002; Boyter and Carter, 2005; Agh et al., 2011; Khdour et al., 2012; Huetsch et al., 2012). Whilst the least were ipratropium bromide (IP) (Barta et al., 2002; Boyter and Carter, 2005; Huetsch et al., 2012), and theophylline (Mehuys et al., 2010; Agh et al., 2011). In some studies combination drugs were used least often than single drugs (Mehuys et al., 2010; Cecere et al., 2012). Although, current trend include up to 3 combinations because a growing body of evidence suggests that triple therapy with an anti-muscarinic agent, LABA and ICS is efficacious in the management of COPD, the majority of studies which were included in this review suggested that salbutamol/ipratropium bromide were the commonly used combination therapies by patients and are shown to be effective (Barta et al., 2002; Boyter and Carter, 2005). This drug mixture raises concerns about the safety and compatibility of different drug combinations. However, this physical and chemical incompatibility were not noted in any study which used combination therapies (Barta et al., 2002; Boyter and Carter, 2005).

Frequency of use and rates of non-adherence
Inhalation therapy was used by patients in these studies on daily basis; which ranged from one to six times daily (Melani et al., 2001; George et al., 2006; Mehuys et al., 2010; Agh et al., 2011; Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012). However, intermittent or occasional use was described in few studies (George et al., 2005; Boyter and Carter, 2005; Mehuys et al., 2010; Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012), which could result in suboptimal adherence. Adherence among COPD patients has been found to be suboptimal in past studies, which ranged from 29.5% (Khdour et al., 2012) to 80% (Huetsch et al., 2012). However, caution must be taken before drawing conclusions due to the wide variation in the estimated rates of non-adherence reported in previous studies. As a result, treatment failures were a major concern for patients with COPD. However, this variation regarding the rate of non-adherence could be due to the differences in patient populations, definition of non-adherence, methods employed, disease status, or respiratory conditions included in each study, as some studies included a variety of lung diseases such as asthma, COPD and other lung conditions.

Definition of non-adherence
The most commonly used definitions of non-adherence among patients with COPD in past studies were the following: three studies defined adherence to COPD medication as taking 80% of doses as prescribed (Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012). Another three studies used a method which was based on the definition used by previously validated questionnaires such as 4-item Morisky (patients scoring 3 or above were classified as 'adherent') (Agh et al., 2011; Khdour et al., 2012), or the MARS score (a score of 25 indicates perfect adherence) (George et al., 2005).

Factors contributing to medication use among COPD patients
The use of inhalation therapy in some studies was found to be dependent on the class of drug in three study (Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012). For example, adherence to long-acting bronchodilators and ICS was found to be suboptimal among previous studies (Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012). This was justified by the prolonged efficacy provided by long-acting bronchodilators and ICS on the symptoms' relief. Among the LABA and ICS users, it was found that participants adhered more to the LABA than ICS (Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012). However, the adherence was suboptimal for both classes among those with a low-adherence rate. The reason behind being more adherent to the LABA than the ICS is that some participants responded better and quicker to the LABA than the ICS and for this reason preferentially used the LABA, which provides superior relief. In addition, experiencing an actual side effect or fears of side effects with the use of ICS was greater among participants who used different classes. In a recent study conducted by

Davis et al.'s (2016) to evaluate health care costs and utilization among COPD patients newly initiating ICS/LABA combination therapy with budesonide/ formoterol (BFC) or fluticasone/salmeterol (FSC) in a managed care system reported that, no difference was observed in rates of health care utilization among BFC or FSC users. However, COPD patients initiating BFC treatment incurred lower average COPD-related and all-cause costs versus FSC initiators, which was driven by cumulative differences in inpatient, outpatient, and pharmacy costs (Davis et al, 2016).

Other factors were found to influence patients' decision to use the inhalation therapy one of which is actual and perceived efficacy and safety of the inhalation therapy (Barta et al., 2002; Boyter and Carter, 2005; George et al., 2005; Cecere et al., 2012; Huetsch et al., 2012; Khdour et al., 2012). Others include: socio-demographic factors, including age (Mehuys et al., 2010; Agh et al., 2011; Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012), educational level (Cecere et al., 2012), and ethnicity (Cecere et al., 2012), in addition to the complexity of drug regimen (George et al., 2006; Mehuys et al., 2010; Agh et al., 2011; Cecere et al., 2012). All these factors were found to have an influence on patients' decisions on not to use the inhalation therapy, which might put patients with COPD at risk of treatment failures.

Patients' beliefs and experiences regarding the efficacy and safety of inhaled therapy
Only few studies have examined patients' perceptions about the efficacy and safety of inhaled therapy among COPD patients (Barta et al., 2002; George et al., 2005; Boyter and Carter, 2005; Cecere et al., 2012 ; Huetsch et al., 2012 ; Khdour et al., 2012). Among these studies the use of inhalation therapy was highly supported especially by participants who reported high adherence rates (Barta et al., 2002; Cecere et al., 2012; Khdour et al., 2012). The benefit was seen in the immediate relief of COPD symptoms and decreased hospital admissions (Melani et al., 2001; Barta et al., 2002). However, in some of these studies patients were less confidence in LABS and ICS received which had a negative effect on medication use (Huetsch et al., 2012).

In Huetsch et al.'s, study (2012), it was suspected that the higher adherence to ipratropium bromide (IP), but not to LABA and ICS, may be related to the perceived immediate benefit of IP on symptom relief. In addition, although patients were typically instructed to use IP at regular intervals, patients might instead be using IP as a rescue medication whereas clear instructions were typically given that neither ICS nor LABA should be used in this manner (Huetsch et al., 2012). It is hypothesised that, because LABA and ICS have no immediate effect on symptoms (Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012). In addition, each medication class has a unique side effect profile (Huetsch et al., 2012). For instance, inhaled LABAs have been reported to cause tremors (Barta et al., 2002; Boyter and Carter, 2005), dry mouth (Barta et al., 2002; Boyter and Carter, 2005), and less frequently palpitations (Barta et al., 2002). These side effects were reasonable to expect that a patient who experiences such a side effect to these mediations may preferentially adhere to their other inhalers. These concerns or experiencing an actual side effect from treatment affected patients' decisions to use the inhaled medication as suggested which may lead to treatment failures.

Problems encountered with the use of inhalation devices in regards to the operation and inhalation techniques
Problems were reported with the inhalation techniques when operating the inhalers including: pMDIs alone or with large-volume spacers (Ho et al., 2004), DPIs alone including Accuhaler, Turbohaler, Handihaler, and Aerolizer (Wilson et al., 2007), or a combination of both pMDIs and DPIs (Hesselink et al., 2001; Sestini et al., 2006; Khassawneh et al., 2008; De Moraes Souza et al., 2009; Rootmensen et al., 2010; Hämmerlein et al., 2011; Melani et al., 2011). In all studies, COPD patients were found to be using a combination of inhalation devices either from the same class (different types of dry powder inhalers together or different types of pMDIs in combination) (Ho et al., 2004; Wilson et al., 2007), or different classes including pMDIs and DPIs (Lenney et al., 2000 ; Hesselink et al., 2001; Sestini et al., 2006; Khassawneh et al., 2008; De Moraes Souza et al., 2009; Rootmensen et al., 2010; Hämmerlein et al., 2011; Melani et al., 2011). These devices were commonly used to deliver mainly the following: salbutamol by pMDIs, salmeterol/fluticasone by Accuhalers;

terbutaline and formoterol/budesonide by Turbohalers; salbutamol, salmeterol/beclometasone or fluticasone by Accuhaler; formoterol by Aerolizer and tiotropium by Handihaler.

Participants using pMDIs and DPIs were found to handle their inhalation devices erroneously as the percentage of participants with COPD who made at least one deviation from the recommended technique ranged from 2.9% (De Moraes Souza et al., 2009) to 94.2% (Ho et al., 2004). The percentage of COPD participants who made at least one deviation from the recommended inhalation technique was greater among pMDIs users than DPIs users (Lenney et al., 2000; Hesselink et al., 2001; Khassawneh et al., 2008; De Moraes Souza et al., 2009; Rootmensen et al., 2010). However, different studies by Melani et al (2011) and Ho et al (2004) reported that pMDIs were correctly used by most patients, especially with large volume spacers (Ho et al., 2004; Melani et al., 2011). Three studies found no significant difference between the pMDIs and DPIs; therefore, they were handled similarly by all patients (Lenney et al., 2000; Ho et al., 2004; Hämmerlein et al., 2011). Examining the inhalation technique among COPD patients with different devices is important, to detect whether users are using them effectively or not, as suboptimal techniques affect the drug delivery and moderate the efficacy of the therapy and are a cause of treatment failures and poor clinical outcomes (Rootmensen et al., 2010).

For the pMDIs, the steps concerning shaking inhaler (the canister) well before use and actuating while inhaling deeply and slowly were the most frequently performed incorrectly, with the inhaler not being shaken (N=7) (Hesselink et al., 2001 ; Molimard et al., 2003 ; Ho et al., 2004 Sestini et al., 2006 Khassawneh et al., 2008 Rootmensen et al., 2010 ; Melani et al., 2011), or the device being fired before start of inhalation or after end of inhalation (N=4) (Ho et al., 2004; Sestini et al., 2006; Khassawneh et al., 2008; Rootmensen et al., 2010). For the DPIs, the most common errors were in not exhaling away from the inhaler before inhalation or exhaling into the mouthpiece (N=5) (Molimard et al., 2003 ; Sestini et al., 2006 ; Rootmensen et al., 2010 Hämmerlein et al., 2011 Melani et al., 2011), and no/short holding of breath for less than five seconds (N=4) (Molimard et

al., 2003; Sestini et al., 2006; Rootmensen et al., 2010; Melani et al., 2011).

Further studies of inhalation technique in DPIs (Accuhaler, Turbohaler, Aerolizer, Handihaler and Diskhaler), reported that the percentage of COPD participants who made at least one deviation from the recommended inhalation technique when using DPIs was more when using single-dose DPIs such as Handihaler (Wilson et al., 2007), and Aerolizer (Wilson et al., 2007; Khassawneh et al., 2008; De Moraes Souza et al., 2009) than when using the multiple-dose DPIs such as Turbohaler and Accuhaler. These findings were contradicted by two other studies documenting that the essential errors which compromise treatment efficacy were made more among Turbohaler users than other DPI users using Aerolizer and Accuhaler (Molimard et al., 2003), or Handihaler and Accuhaler (Melani et al., 2011).

Checklists used for the inhalation technique assessment in previous studies
Most previous studies have adopted checklists for the inhalation technique assessment among COPD patients. They have been based on previously published checklists or by using checklists given by pharmaceutical companies or medical leaflets (Lenney et al., 2000; Molimard et al., 2003; Sestini et al., 2006; Wilson et al., 2007), or previously published criteria by previous raters (Ho et al., 2004; De Moraes Souza et al., 2009; Rootmensen et al., 2010; Melani et al., 2011). Two other studies developed their own checklists, based on information from the drug information centre of the German Association of Pharmacists (Hämmerlein et al., 2011), or the Dutch Asthma Foundation (Hesselink et al., 2001).

Definition of inadequate inhalation technique
The majority of studies defined essential steps for optimal delivery of the active drug into the lungs for each device. When one or more deviations were made regarding these essential steps, the inhalation technique was defined as inadequate or incorrect, potentially resulting in suboptimal drug delivery to the lungs (Lenney et al., 2000; Hesselink et al., 2001; Molimard et al., 2003; Ho et al., 2004; Sestini et al., 2006; Wilson et al., 2007; Khassawneh et al., 2008 Rootmensen et al., 2010; Melani et al., 2011). Despite the importance of defining the adequate inhalation

technique, past studies have not used validated instruments when assessing the inhalation technique. Only one study used a validated scoring method, which involved viewing and assessing a video-recorded inhalation demonstration by participants using device-specific checklists and mutually agreed scoring rules by raters (Rootmensen et al., 2010). However, to maximise the accuracy of the findings, some studies included more than one rater in the assessment process (Lenney et al., 2000; Molimard et al., 2003; Sestini et al., 2006; Wilson et al., 2007; Rootmensen et al., 2010; Melani et al., 2011), whilst others included only one rater (Ho et al., 2004; De Moraes Souza et al., 2009; Hämmerlein et al., 2011).

Many past studies have assessed inhalation technique among patients with a number of lung diseases including asthma and COPD (Hesselink et al., 2001; Ho et al., 2004; De Moraes Souza et al., 2009 ; Rootmensen et al., 2010 ; Hämmerlein et al., 2011; Melani et al., 2011). Two of those have shown that COPD patients made or were more likely to make more deviations from the recommended inhalation technique when using their inhalers than those with asthma (De Moraes Souza et al., 2009; Melani et al., 2011). Some other past studies have included only one class of device in the assessment process, such as pMDIs only (Ho et al., 2004), or DPIs only (Wilson et al., 2007). No previous study assessed the inhalation technique using all three classes of inhalation devices to examine what device was associated with more errors or deviations when assessing the technique. Therefore, there is a need for more studies to examine how patients practically use a combination of inhalation devices and what are the frequency and range of problems experienced by patients that may lead to suboptimal use or treatment failure.

Discussion

With regards to the findings reported in these studies on medication use, careful attention must be paid before coming to such a conclusion because of the wide discrepancy reported in the rates of non-adherence to COPD medication, which ranges from 29.5% (Khdour et al., 2012) to 80% (Trivedi et al., 2012). This variation can be explained by the dissimilarities in COPD population (e.g. age, disease severity, smoking history, etc.), the differences in

adherence/non-adherence definition and the variation of methods employed. The results are also limited by the duration of some studies, which ranged from two weeks (Boyter and Carter, 2005) to 12 months (Mehuys et al., 2010).

Although a number of instruments and methods have been used to measure adherence, there was no gold standard method for measuring medicine taking due to the advantages and disadvantages of each method. For example, the easiest and most feasible way for most settings to measure medicine taking is to collect information from the patients themselves through questionnaires which were used in most reported studies (Melani et al., 2001; George et al., 2005; Agh et al., 2011; Khdour et al., 2012). However, a direct self-report method such as a questionnaire may overestimate adherence and may be subject to memory biases. In two studies adherence was not assessed using validated tools (e.g. surveys); in these studies when optimal adherence was noted by the authors, this might be biased as patients were received instructions prior to their adherence assessments (Barta et al., 2002; Boyter and Carter, 2005).

The use of inhalation therapy was found to be influenced by patients' decisions, which in turn were guided by many factors. However, the most frequently reported factor was actual and perceived efficacy and safety of the inhalation therapy. Despite the perceived effectiveness reported by most patients using inhalation therapy in studies that examined patients' believes about inhaled therapy (Melani et al., 2001 Barta et al., 2002; Khdour et al., 2012), these studies did not mention whether their outcome was measured by means of validated questionnaires, except for one study which used a validated questionnaire (e.g. Health Belief Model questionnaire) (Khdour et al., 2012). Two studies described the instruments used to assess the subjective benefits, however, no details were gives about their validity and reliability (Melani et al., 2001 Barta et al., 2002). In one of these two studies no measure of objective validity was obtained for the responses, and no information was collected on non-respondents (Melani et al., 2001).

There were some contradictory results among these studies examining the factors affecting the

medication use. For example, in four studies, it was found that, as complexity of the medical regimen increases (e.g. the number of medications, frequency of dosage, etc.), medicine taking decreases (George et al., 2005; Mehuys et al., 2010; Agh et al., 2011; Cecere et al., 2012), whereas the same factor was not a significant predictor of non-adherence in George et al.'s, study (2005) (George et al., 2005). Other studies have shown that disease severity or the decline in the FEV1% may be either not (Agh et al., 2011), or negatively related to medicine taking (Cecere et al., 2012; Khdour et al., 2012). Others have shown that adherence is related to age: some authors found that, among adults, older age had a positive association with medicine taking (Mehuys et al., 2010; Agh et al., 2011), while others found that older age had a negative association with medicine taking due to risk of memory loss and cognitive impairment, which are associated with age and may adversely affect adherence (Cecere et al., 2012; Huetsch et al., 2012; Trivedi et al., 2012).

Studies which examined how patients operate their inhalers were also at risk of selection bias as some studies included only one class of device in the assessment process, such as pMDIs only (Ho et al., 2004) or DPIs only (Wilson et al., 2007). No previous study assessed the inhalation technique using all three classes of inhalation devices to examine what device was associated with more errors or deviations when assessing the technique. In addition, the inhalation technique, breathing pattern and drug administration were not examined in previous studies. Among the devices examined in previous studies including pMDIs and DPIs, incorrect use was very common among patients with COPD and was more frequently associated with the use of pMDIs than DPIs.

The reviewed studies on the medication use had several limitations which might affect exploring findings from these studies to other population or settings. One of the limitation was the inclusion criteria which was a particular issue in the reviewed studies; some studies included patients who were carefully selected and received instructions prior to the study enrolment (Barta et al., 2002; Boyter and Carter, 2005). A minimum duration of use, for a six months or more was a part of the inclusion criteria in some studies (Melani et al., 2011; Huetsch et al.,

2012). Other studies excluded any COPD patient who had a history of asthma or other respiratory disease, or had a heart failure, moderate to severe learning difficulties or severe mobility problems or had attended a pulmonary rehabilitation programme (Agh et al., 2011; Khdour et al., 2012; Trivedi et al., 2012). In one study selection was biased and only patients with stable COPD (defined as "no prescription for systemic corticosteroids") and a smoking history of at least 10 pack-years were included in the study (Mehuys et al., 2010). Another limitation is that this review was a part of a big study conducted in four years among patients with COPD who are using only a combination of classic old devices in their homes including pMDIs, DPIs (Turbuhaler, Handihaler, Accuhaler, Diskhaler, Aerolizer and Clickhaler) and nebulisers. The newest inhaler products to the market such as soft mist inhalers (e.g. Respimat®) were not part of this study because patients were not using them at home. Therefore, they were not included in the review. However, future work can be done to compare the new devices with the old ones and see how patients are using them and whether they prefer the old classic devices or the new ones. In addition, searches were limited to the period from 2000 to 2013 and all other studies conducted from 2014 and to date is the subject to future works.

CONCLUSION

Treatment failures were a major concern for COPD patients due to suboptimal use of medication and a wide range of problems with inhaler handling among COPD patients which were revealed by this review. Therefore, there is a need for studies that examine how patients make decisions regarding the use of inhalation therapies especially when a combination of inhalation devices is used at home, and how those decisions and difficulties may contribute to suboptimal outcomes and treatment failures.

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