Title page

Final proposed title:

Impact of community pharmacists in COPD management: Inhalation technique and medication adherence.

Running title:

Community pharmacists and COPD management: a review

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Summary

Background: Inhalation technique and medication adherence are highly important for the management of chronic obstructive pulmonary disease (COPD) since they are essential pre-requisites for achieving full therapeutic effect in patients**.** Community pharmacists are in the best position to deliver services in these two areas.

Methods: This is a ten-year period review of studies looking into the impact of community pharmacists in the management of COPD in relation to: inhalation technique and medication adherence in the period from 2005 to 2015.

Results: Ten studies are included in the review. The studies show that community pharmacists' interventions had a positive impact on improving patients' inhalation technique and adherence to inhaled medications. This was shown in some studies to be cost-effective in terms of reducing hospitalisation and severe exacerbation rate. Scarcity of studies in this domain is noted through this review.

Conclusions: This review showed that community pharmacists can have a positive impact in the management of COPD especially on inhaler technique education and medication adherence. Nevertheless, their role is still not fully recognised in this area, thus there is a need for more research. There is also a need for more research to identify the optimal frequency for inhaler technique re-checking and education as a pre-emptive measure against technique deterioration in patients. The results highlight the need for healthcare systems to recognise more the role of community pharmacists in COPD management in two critical areas that are still challenging in real practice.

Key words

Community pharmacists; inhaler technique; inhalation technique; Chronic Obstructive Pulmonary Disease/ COPD; COPD management; medication adherence.

Introduction and background

Chronic Obstructive Pulmonary disease (COPD) is a chronic condition characterised by airflow limitation that is progressive in nature and partially reversible [1]. Tobacco smoking, indoor and outdoor pollution are all risk factors for COPD development [2].

One of the main objectives of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is to increase awareness of this condition [2]. This is particularly important due to the high economic and social burden of COPD on healthcare systems worldwide [1, 2]. In the European Union, the estimated cost of COPD to healthcare systems (as direct costs only) is 38.6 billion Euros (equivalent to $42.3 billion); whereas in USA this was found to account to a budget of $29.5 billion as direct costs and $20.4 billion as indirect costs [2].

Inhalation technique (IT) and medication adherence (MA) are two key areas that should be looked upon with serious consideration when addressing management of COPD patients. IT is the process through which the patient correctly performs a number of steps in certain order to obtain the adequate dose out of the inhaler device [3]. The importance of IT stems from the fact that inhalation therapy represents the main pillar in COPD treatment [4-8]. It is the best treatment strategy to ensure delivery of adequate concentrations of the administered drug directly to the lungs [3-5, 9-11]. Adherence is defined as the degree by which a patient follows a mutually agreed plan including medication and life style changes [12]. According to the World Health Organisation (WHO), adherence to therapy in chronic conditions is estimated to be only 50% in developed countries and lower in developing countries [12].

Incorrect IT may lead to poor disease control [6]. Some authors argue for poor IT to be a form of poor adherence [13], whereas others see that poor adherence can be triggered by poor IT, as the latter can result in patient's dissatisfaction with the treatment [3]. This can lead to medication wastage due to prescribing higher doses or even additional medications thus increasing the financial burden of the disease on healthcare systems [7, 10]. In some studies, around 60% of COPD patients had poor adherence to their inhalation therapy [14, 15]. A recent review reported a wide variation in adherence rates for asthma and COPD patients ranging from 22% to 78% [16]. Regarding IT, evidence from Europe shows that up to 50% of patients fail to use their inhalers correctly [17]. Whereas, another review highlighted that nearly 100% of patients perform mistakes in their IT that consequently result in delivering an inadequate dose of the inhaled medication [18]. Poor adherence and suboptimal

IT can lead to increased healthcare costs and poor health outcomes. Thus, there is a need for interventions to improve these two areas.

The aim of this paper is to provide a review of studies evaluating the impact of community pharmacists' interventions on COPD management focusing mainly on IT and MA.

Materials and Methods:

Search Strategy

The search strategy included primary and secondary sources. The following databases were searched: Medline, Scopus, PubMed, Google scholar, Science direct. Key words used in the primary search were: community pharmacy, community pharmacists, inhaler technique, inhalation technique, COPD management, COPD, medication adherence, respiratory patients. The search was limited to articles written in English language and published in the period from January 2005 – February 2015. A manual search of reference lists of primary sources was done to identify any additional studies meeting the inclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria for this review were: studies in English language and studies with interventions done by community pharmacists (CPs) on COPD patients focusing on IT and MA. Studies including COPD and asthma patients together, and observational studies involving CPs or those conducted in community pharmacy settings were also included. As the last decade has witnessed the implementation of community pharmacy medication management services, in many countries, that targets patients with LTCs [19-21], this review included only studies published after 2005.

The exclusion criteria were; studies not in English language, those published before 2005, studies involving interventions done by other healthcare professionals (HCPs) including clinical pharmacists, studies done by CPs or other HCPs on asthma

patients only, studies done by CPs whereby the intervention was not related to IT or MA, reviews, meta-analyses and grey literature.

The excluded studies were as follow: three studies with interventions conducted by clinical/ hospital pharmacists on COPD patients, nine studies including both asthma and COPD patients where by the interventions were not done by CPs, two documents that constituted grey literature, one study in Dutch language, and one study with pharmacist-led intervention but focusing on COPD exacerbation management with systemic corticosteroids. A study with intervention done by CPs was excluded to avoid duplication of data since the data was once published jointly with asthma patients and once on COPD patients only. The study pertaining to COPD patients exclusively was included in the review. In addition, 69 studies that were conducted on asthma patients only either by CPs or other HCPs were excluded (Figure 1).

Results

The search of primary sources identified nine articles that met the inclusion criteria; four studies involved COPD and asthma patients and five studies involved COPD patients only. Search of secondary sources identified one additional study including asthma and COPD patients which was included in the review. Thus ten studies were included in this review. Only one study had an intervention involving IT and MA, three studies focused on IT specifically, four studies had an intervention which partly focused on either IT and/or MA and two studies were non-interventional. The steps of the research process for the identification of relevant articles are provided in Figure 1.

The summary of the studies reviewed in this paper is presented in **Table 1**.

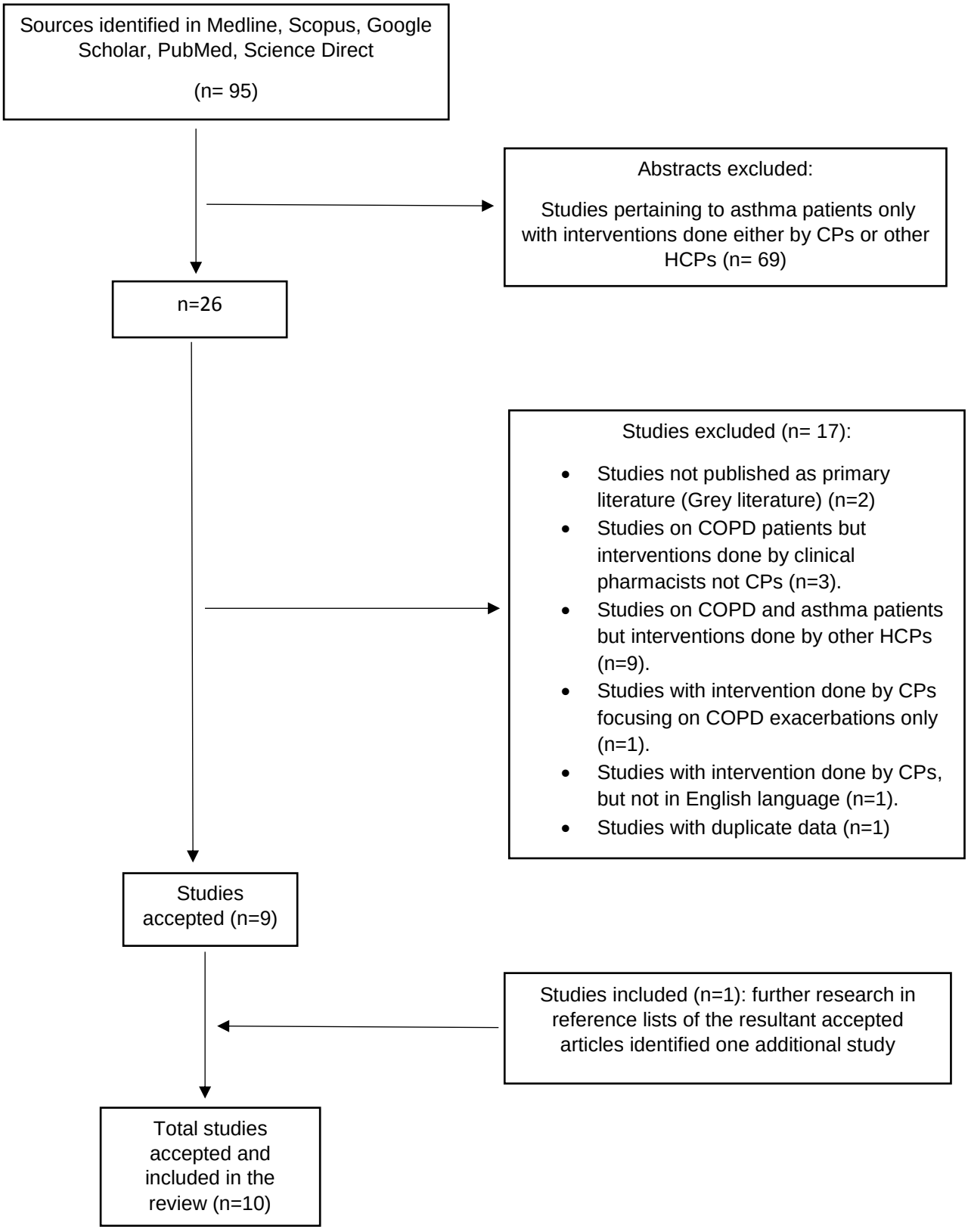

FIGURE 1. Selection of the relevant studies included in the review.

Impact of community pharmacists on the management of COPD: review of evidence from Europe

In England, a recent study has shown that a CP-Led COPD service can have a positive, cost effective impact on patients' outcomes. The study evaluated the effect of COPD support service by CPs over six months in 34 pharmacies from four pharmacy chains. CPs were provided with a one-day training course about service delivery along with distance learning materials before the start of the study. The provided service was comprehensive including smoking cessation, education and advice about IT and inhaler checking, provision of support and awareness of symptoms in case of exacerbations and general life-style advice. Initial consultation involved getting baseline data regarding self-reported MA, clinical outcomes, National Health Services (NHS) resource utilisation and quality of life (QoL). All participants (n=306) had an initial consultation. However, the follow-up frequency was not equivalent for all patients. Monthly consultations for all participants should equate to 1836 consultations over six months; however only 742 consultations were completed. This variation in follow-up cannot be explained by the dropout rate reported as 107 patients. Furthermore, usable data for comparison at baseline and six months was only available for 137 patients. Several improvements were reported in this study but the only improvement that was statistically significant was MA ($P < 0.001$). There was a reduction by 0.869 in COPD assessment test (CAT) score over the six-month study period but that was not statistically significant ($P = 0.078$). Likewise, a 4.1% reduction in the percentage of smokers in the final sample (n=137) was observed which was not statistically significant ($P = 0.219$). As for QoL, the mean change in EQ-5D score was 0.029 between baseline and follow-up (for EQ-5D, 0.03 is regarded as the minimal important difference [22]). The EQ-5D was used to estimate the QALY (quality-adjusted life year) change associated with the intervention. Change in QALY was calculated to be 0.008 (95% CI: 0.000 to 0.017) after a follow-up period of 201 days. The intervention was reported by the researchers to be cost-effective with a mean savings of £87.66 per patient for total NHS costs and £94.12 for total societal costs (i.e.: total NHS costs + cost of lost productivity). The mean cost-saving associated with the intervention was mainly due to the reduction in the use of NHS services notably hospital admissions. However, the results should be treated with some caution due to the before-and-after study

design, the lack of a comparison control group (CG), and the fact that the intervention was conducted in winter period when COPD is expected to be worse in comparison to the pre-intervention period [23].

In Netherlands, a large scale study reported that pharmacist-led interventions can improve sub-optimal medication treatment in COPD and asthma patients. The study comprised 3757 patients across 107 pharmacies in the intervention arm and 105,507 patients in the control arm. The intervention consisted of a comprehensive structured pharmacy program focusing on: compliance with maintenance therapy, improving IT and selection of inhaler devices, and reconsidering the treatment regimen with the possibility of stopping any sub-optimal medication. The primary outcome showed an absolute reduction in high dose treatment (HDT) with corticosteroids and antibiotics by 0.54 (95% CI 0.28-0.86). Secondary outcome measures consisted of changes in a list of 19 potential problems indicating sub-optimal treatment that were defined and set according to prevailing treatment guidelines. The results indicated that 14 out of 19 problems were reduced to a higher extent in the intervention group (IG) compared with CG. However, only three problems were significantly reduced; the 35% (95% CI 6-54%) reduction in the use of obsolete medication (acetylcysteine, cromoglicic acid or nedocromil), the 61% (95% CI 38-75%) reduction in the use of contra-indicated medication (selective beta-blockers) and the 29% (95% CI 13-42%) reduction in the use of powder inhalers for patients over 75 due to their insufficient inspiratory flow rate. A limitation for this study is self-selection bias for CPs in the intervention arm for those pharmacists who were more interested and had better communication skills as there was no randomisation strategy employed. Another possible bias would be that of patient selection since they were selected by the CPs for the IG [24].

In Germany, a prospective multi-centre intervention study demonstrated the effectiveness of a single intervention done by CPs in improving the quality of IT in COPD and asthma patients. The study was conducted on a pre-post comparison basis. CPs did not receive any training before the start of the study, but it was mandatory for all recruited CPs to already have the certified continuing education programme in pharmaceutical care for COPD and asthma patients in Germany. The study was based in 55 community pharmacies over three months. 757 patients

received a one-time intervention focusing on IT education through providing demonstration of the correct steps, practical exercises and verbal instructions at baseline according to individual performance. Patients were then required to demonstrate the technique again at a follow-up appointment after 4-6 weeks. At baseline, 78.9% of study sample had at least one error, however this percentage has significantly dropped to 28.3% after the intervention (P <0.001). There was also a significant drop in the average number of errors per patient from 2.5 to 0.5 (P < 0.001). Despite the significance of results, the authors questioned the sustainability of this one-time intervention on the long run and argued for the necessity of performing such educational interventions on a regular basis. They also highlighted that CPs are in the best position to deliver these services. Study limitations were related to its short duration and the possibility of selection bias. In addition, the authors had no information regarding any possible outside training on IT that might have been taken by the patients during the study period [5].

In Belgium, the study of Mehuys et al.[9] was the first cross-sectional, observational study on COPD treatment to be conducted in the community pharmacy setting. The study was based in 93 pharmacies and involved 555 COPD patients. Data regarding COPD medication, smoking history and vaccination status were collected from participants by questionnaires. IT was assessed by checking against device specific checklists, whereas adherence was assessed by retrospective analysis of prescription refill rates for 12 months. Results showed that management of COPD patients in primary care is sub-optimal. Almost half (48%) of the patients had poor MA, 40% were smokers, 21% and 3.5% made errors in IT for rescue and control medications respectively, and only 65% of patients under 65 had flu vaccination. The researchers concluded that CPs can have a potential impact on improving COPD management by focusing more on the following four areas: smoking cessation, influenza vaccination, MA and IT and proposed this as a hypothesis for future testing.

Interestingly, the study of Tommelein et al.[25] evaluated the hypothesis stated above. It was the first randomised controlled trial (RCT) to address the impact of CPs' intervention on IT and MA as primary outcomes in COPD patients in Belgium.

This large-scale trial involved 734 COPD patients who were blinded with respect to group allocation. The trial lasted for three months; patients were followed up at one and three months across 170 community pharmacies. CPs received training about COPD pathophysiology and treatment according to GOLD guidelines before the start of the trial. The intervention offered by CPs was educational in nature based on GOLD guidelines in the form of structured patient education adapted according to patients' needs. The education was offered in written and oral format focusing on MA, information about COPD and its treatment, self-management, smoking cessation and physical demonstration of IT using a placebo inhaler. The education was delivered as one-to-one counselling sessions. Patients in the control arm received usual pharmacist care; IT was evaluated using device-specific IT checklists designed by the researchers. The study reported a significantly greater improvement in IT and MA scores in the IG compared to the CG at the end of the trial [the mean estimated difference was 13.5% for IT (95%CI: 10.8-16.1%; P < 0.0001) and 8.51% for MA (95%CI: 10.8-16.1%; P < 0.0001)]. The number of patients who made major errors in IT (for Metered Dose Inhaler (MDI): failure to remove cap and/or shake the MDI; for Dry Powder Inhaler (DPI): failure to load device correctly and/or inhale quickly and deeply through device) dropped from 15.6% at baseline to 1.2% after three months in the IG, whereas in the CG the drop was from 11.6% to 4.6% (P= 0.002). Another interesting result in this study was the significant likelihood to obtain a 100% inhalation score as a result of the intervention (odds ratio 3.03, 95%CI: 2.12-4.34; P <0.0001) in comparison to no intervention. Likewise, a significant likelihood to obtain more than 80% Medication refill adherence (MRA) scores in the IG in comparison to CG (odds ratio: 2.15, 95%CI: 1.46-3.14; P<0.0001). There was also a significant reduction in annual hospitalisation rate (P= 0.003) and decrease in the annual severe exacerbation rate (P < 0.007) in comparison to the CG. However, there was no significant improvement in health status (at three months, P values for CAT score and EQ-5D were 0.832 and 0.19 respectively) or smoking status (P= 0.33) which was attributed to the short study duration. Other limitations include selection bias since participation is more likely to involve motivated patients. Another source of bias would be that CPs in the study were both doing the educational intervention and measuring their own performance. Furthermore, MRA and IT scores were only calculated for the principal maintenance drug even if the patient is taking more than one inhaled medication [25]. The cost effectiveness analysis of this

intervention in the Belgian Healthcare system showed a cost savings of €227 per patient (95%CI: €58-€403) in the IG for a one-year time period. Savings were mainly generated due to the reduction in exacerbation treatment expenses in the IG compared to CG. QALY gain was minimal in this study (<0.001 QALYs) which was attributed mainly to reduction in exacerbations [26].

In Bulgaria, a RCT was done to assess the effect of educational intervention on QoL for COPD patients, forced expiratory volume in one second (FEV1) rate and IT. The study involved 30 COPD patients with 15 patients in each group. The intervention was delivered by the researchers and five pharmacy students across the 24 private community pharmacies that have the highest number of COPD patients. The content of education included the following topics: COPD as a disease, medication use, IT, adverse drug reactions, symptoms recognition in case of exacerbations and smoking cessation. All information was developed by the authors depending on several asthma and COPD guidelines. Patients in the IG received the educational programme in the form of sessions over a four-month period (one session each month). Patients were also given information leaflets after each session. The level of knowledge gained throughout the study was assessed at the beginning of the second, third and final sessions by conducting direct interviews with patients. Patients in the CG were not provided with any information and received usual care (i.e.: routine dispensing services). Results showed that only improvement in FEV_1 rate was statistically significant for IG compared to CG (after four months, $p< 0.05$). There was improvement in QoL and IT within the IG itself between baseline and the end of the study, but this was not statistically significant when compared to the CG. However, the researchers attributed these results to the short duration of the study. They also highlighted that such results cannot be generalised in the country due to the small sample size [27].

Impact of community pharmacists on the management of COPD: review of evidence from other developed countries

In other developed countries such as Canada, a small pilot study was conducted to shed the light on the impact of CPs in COPD management. 21 CPs participated in the assessment of 59 COPD and 23 asthma patients. All CPs completed a brief continuing educational session about COPD and asthma management prior to the study. The service offered by CPs included: smoking cessation advice, assessment of the patients' medical condition (medications problems, adherence and disease control), checking and rectifying IT and provision of appropriate individualised action plan when needed. The results, due to the nature of the study being pilot, were in the form of recommendations. 59 recommendations were made by pharmacists to the prescribing physicians, including: implementation of patient-customised action plan (n=17), change in pharmacotherapy (n= 12), inhaler device change (n= 9) and reconsideration of adherence to medications (n=7). Interestingly, the majority of the treating physicians reported that the recommendations made were very useful. Approximate time required to deliver this service was 30 minutes per patient and hence lack of time was identified by CPs as a potential barrier for service delivery [28].

In New Zealand, a recent study assessed IT among 103 patients (86 with asthma and 17 with COPD) in 26 community pharmacies. Prior assessment, the researchers received training about the correct IT for all devices available in the country. Almost half (around 47%) of the assessments done indicated poor IT. The study also included a patient survey about previous IT education and re-assessment. Most of the patients (76%) received this education from the doctor, followed by 11% from a nurse, 9% from others (parents, internet, leaflets) and only 4% from the pharmacist. As for technique re-assessment, 44% of patients had their IT rechecked with only 1% of them having this done by a pharmacist. This showed that the role of CPs was not prominent in IT education and re-assessment. Consequently, the authors emphasised the need to reinforce IT education and re-assessment through an interdisciplinary approach [4].

In Australia, a study by Bosnic-Anticevich et al.[29] was the first one investigating the effect of two educational interventions regarding IT in community pharmacy setting.

The study included 52 asthma and COPD patients. Unlike other studies, this one focused mainly on one type of inhaler which is the pressurised Metered Dose Inhaler (pMDI). The two pharmacy student researchers who conducted the assessments and interventions were trained about the use of pMDI and the technique assessment. The two interventions were randomised as follows: standard instruction group (SIG) with patients provided with verbal and written instructions on the pMDI technique, and extended instruction group (EIG) where patients received verbal and written instructions besides physical demonstration using placebo inhaler. Patients were assessed and followed up at baseline and 4, 8 and 16 weeks. In each visit, the IT was firstly assessed then the intervention delivered according to the group and then re-assessed again, this was repetitive up to three times or until the patient showed a correct technique. The study reported improvement in pMDI technique for both groups over the study period and showed that the addition of physical demonstration to written and verbal instructions is a more effective approach to improve IT than written and verbal instructions alone. The SIG showed statistically significant increase in IT score from baseline ($P < 0.05$) at the last follow-up visit only; whereas this was statistically significant in the EIG at all the follow-up visits ($P<0.05$ for each visit). In this study, 86% (45/52) of patients had previous IT education and most of them (62%) had it only at the time of first prescription with a mean of 13 years ago. In a similar manner to the previous study in New Zealand; the role of the pharmacist was not prominent since 33% of patients had their IT education by GP, 29 % by a GP and a pharmacist and only 2% by a pharmacist alone. Among those who had previous IT education (n=45): 69% (31/45) had no IT rechecking, 21% (9/45) had their IT rechecked by a GP, 6% (3/45) rechecked by a specialist and only 4% (2/45) rechecked by a pharmacist. This study also highlighted the issue of IT deterioration over time. Patients showed continuous improvement in IT in the follow-up visits that were separated by one-month interval. However, there was a decline in IT in the last follow-up visit which was two months after the third visit indicating the necessity of repeating instructions in order for patients to maintain the technique. The study emphasised the role of CPs in helping patients with correcting and maintaining IT over time especially when dispensing the medication. Limitations in the study include; the small sample size, interventions and assessments being done by the same researchers and the possibility of patients having outside advice about IT during the study [29].

In Japan, a long term study significantly demonstrated higher adherence to inhaled medications in patients receiving repeated instructions on IT from CPs. The study evaluated the four-year effect of a network system which was implemented in 81 community pharmacies. The system was designed in the form of an educational programme to provide correct and consistent IT to COPD patients. Through this programme, CPs were trained about COPD, IT for all inhaler devices available and adherence to inhaled medications, and were registered as IT instructors upon training completion. The service consisted of providing instructions in correct IT via lectures, demonstrations and role play. This was offered every six months. Despite the small sample size of the study, it demonstrated significant improvement in adherence to inhalation therapy (P= 0.024) as well as significant reduction in the frequency of exacerbations (P= 0.017) after four years in comparison to baseline data. However, there was no significant change with respect to health related quality of life (HRQoL) (P= 0.99). The authors attributed the improvement in clinical outcomes to the improvement in IT and stressed on the need to provide patients with repeated instructions on proper IT at least every six months. The long term design of this study gave strength to the results. However, the small sample size, the lack of a CG and the fact that the participants at study start and after four years were not equivalent because of difficulty of follow-up over a long period constitute the limitations of this study. Usable information was only obtained from 55 patients (out of 88) at baseline and from 51 patients (out of 82) after four years [8].

TABLE 1. Summary of studies included in this review

Study	Type of the Study	Study location	Study Population	Type of Intervention provided by CPs	Findings / Results	Remarks
Wright et al (2015) [23]	Pre-post study (Before-and-after study with no CG)	England	306 initial COPD patients, final cohort is 137 (with usable information)	Comprehensive COPD support service: Smoking cessation, Symptoms recognition in case of exacerbations, General life style advice, Advice on IT and choice of inhaler.	Improvement in MA (P<0.001). Reduction of CAT scores. Estimated cost savings of £87.66 for total NHS costs and £94.12 for total societal costs per patient. Estimated QALY gain of 0.008.	The high dropout rate and the lack of usable information (complete data) for certain patients resulted in having 137 patients in the final sample out of the 306 patients initially recruited.
Ottenbros et al (2014)[24]	Prospective cohort study with IG and CG	Netherlands	3757 COPD and asthma patients in the IG, 105,507 patients in the CG.	Comprehensive care through structured pharmacy care program focusing on areas like compliance with maintenance therapy, improving IT and selection of inhaler devices and reconsideration of the treatment regimen with the possibility of stopping any sub-optimal medication.	Reduction in the need of oral corticosteroids and antibiotics. Reduction in medication wastage by 35 % for obsolete medication and 61% for contra-indicated medication. 29% reduction in the use of DPIs for elderly patients (>75 years)	Additional research is needed to estimate cost-savings due to implementation of such beneficial interventions.

Hammerlein et al (2011)[5]	Prospective multi-centre intervention study (No CG)	Germany	757 COPD and asthma patients: 380 asthma, 184 COPD and 193 other respiratory diseases.	Educational: IT education through providing demonstration of the correct steps in the technique, practical exercises and verbal instructions.	Reduction in the number of patients making errors in IT from 78.6% at baseline to 28.3% after the intervention ($P < 0.001$). Drop in average number of errors from 2.5 to 0.5/ patient ($P < 0.001$).	25% dropout among recruited CPs in the study due to lack of time, staff shortage, illness or difficulties in recruiting patients.
Mehuys et al (2010)[9]	Cross-sectional observational study (No CG)	Belgium	555 COPD patients	Assessment: via administered questionnaire to elicit personal characteristics, influenza vaccination, smoking history, COPD medication and health status.	Sub-optimal management in COPD patients: 48% of patients with poor MA. Low flu vaccination status in patients under 65 (65%). 40% of patients were smokers. 21% had IT errors for rescue medications 3.5% had IT errors for control medications	This was the first observational study on COPD treatment to be conducted in the community pharmacy setting in Belgium.
Tommelein et al (2014) and van Boven et al (2014) [25, 26]	Prospective RCT	Belgium	734 COPD patients : 363 patients in CG and 371 patients in IG	Educational: structured patient education in written and oral format focusing on MA, information about COPD and its treatment, self-management, smoking cessation and physical demonstration of IT using a placebo inhaler.	Significant improvement in IT score ($P < 0.0001$) and MA ($P < 0.0001$). Drop in the number of patients making major errors in IT by 14.4%. Significant reduction in hospitalisation rate ($P=0.003$) and decrease in the annual severe exacerbation rate (P<	Long term trials are needed to confirm other outcome measures like smoking status and health status. This is the first and largest RCT to address the impact of CPs' intervention on

					0.007). Estimated cost savings of €227 per patient (95%CI: €58-€403) in the IG for one-year time horizon. QALY gain was minimal (<0.001 QALYs) and was attributed mainly to reduction in exacerbations.	IT and MA in COPD patients specifically in Belgium.
Andreevska et al (2014) [27]	Prospective RCT	Bulgaria	30 COPD patients : 15 patients in CG and 15 patients in IG	Educational: structured educational programme delivered in form of monthly sessions focusing on appropriate use of medication, adverse drug reactions, information about COPD as a disease, IT training, COPD exacerbations and smoking cessation; combined with provision of leaflets after each session.	Significant improvement in FEV1 rate ($p<0.05$) only. Improvement in IT and QoL were not statistically significant.	The authors highlighted that COPD patients are in constant need for educational programmes in community pharmacy settings.
Beauchesne et al (2012)[28]	Pilot study (No CG)	Canada	59 COPD and 23 asthma patients	Assessment intervention comprising: smoking cessation advice, assessment of the patient's medical condition in relation to medications problems, adherence and disease control, checking and education concerning IT and provision of	59 recommendations were provided from CPs to GPs: implementation of patient-customised action plan (n=17), change in pharmacotherapy (n= 12), inhaler device change (n= 9) and reconsideration of adherence to medications (n=7)	Lack of time was identified as barrier to service delivery for CPs.

				appropriate individualised action plan when needed.		
Bryant et al (2013) [4]	Cross-sectional study (No CG)	New Zealand	103 patients: 17 COPD and 86 asthma patients.	Assessment of IT among patients: via administered questionnaire to elicit personal characteristics and IT education provider; physical demonstration of IT using placebo devices.	47 % of IT assessments indicated poor technique.	Confusion among HCPs about who should be responsible for educating and following up patients concerning IT may result in lack of provision for this service and consequently having high rates of poor technique among patients.
Bosnic-Anticevich et al (2010) [29]	Randomised controlled parallel group study (with SIG and EIG)	Australia	52 patients: 7 COPD, 1 Sleep apnea and 44 asthma patients. 25 patients in SIG , 6 patients remained in the last follow-up; and 27 patients in EIG , 18 patients remained in the last follow-up.	Repeated Assessment and Education: • SIG: receiving verbal and written IT instruction • EIG: receiving verbal and written IT instruction with physical demonstration.	Significant improvement in IT scores in the EIG at the four follow-up visits. Significant improvement in IT scores in the SIG at the last follow-up visit only.	This was the first study addressing the effect of two educational interventions regarding pMDI technique provided repeatedly in community pharmacy setting. Need of repetition of this study with a large sample size and for longer duration in future. Not perceiving any benefits from the

						study was the main reason behind the high dropout rate of patients in the SIG .
Takemura et al (2013)[8]	Pre-post, non-equivalent group study (No CG).	Japan	88 COPD patients initially; usable information obtained from 55 patients at baseline and 51 patients after 4 years.	Educational: providing instructions in correct and consistent ITs via lectures, demonstration and skills training for inhalers use and role playing every six months through an established network system implemented in community pharmacies.	Significant improvement in adherence to inhalation therapy (P= 0.024). Significant reduction in the frequency of exacerbations (P= 0.017).	Further research with large sample size is needed to confirm the validity of this established educational network system in Japan.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; IT, Inhalation Technique ; CPs, community pharmacists; CG, control group; IG, intervention group; MA, Medication adherence; RCT, randomised controlled trial; GPs, general practitioners; FEV1, forced expiratory volume in one second; CAT, COPD Assessment Test; QALY, quality-adjusted life year; DPI, Dry Powder Inhaler; QoL, Quality of Life; HCPs, healthcare professionals; pMDI, pressurised Metered Dose Inhaler; SIG, standard instruction group; EIG, extended instruction group .

Discussion:

This review showed that CPs had a positive impact in relation to IT education and MA of COPD patients. Most of the studies reviewed involved educational interventions. With respect to IT, the offered interventions were found to significantly reduce IT errors or even improve the choice of the inhaler [5, 23-25, 28, 29]. For MA, the review showed that CPs interventions resulted in improving adherence to inhaled medications which was statistically significant in the addressed studies [8, 23, 25]. This is consistent with other studies which show that pharmacist-delivered interventions can lead to significant improvement in medications adherence in other diseases [30, 31]. Two studies [23, 25, 26] in this review showed that the provided interventions were cost-effective in terms of reducing hospitalisation rate and severe exacerbation rate. There was a cost saving of £94.12 per patient (equivalent to €133) for six months in Wright et al.[23] study in the UK and €227 per patient for one year in Tommelein et al. [25, 26] study in Belgium. This highlights that IT and MA interventions provided by CPs are not only beneficial for patients but also for the healthcare system.

As seen from this review, there are only a few studies addressing the impact of CPs in COPD management. Some case studies which involved CPs were found during the literature search but these were not published as primary literature and hence could not be used in this review. The scarcity of research in this area can have two possible explanations. First, COPD is still underdiagnosed in many countries [32-40]. Estimates by the Department of Health in the UK indicate that approximately 2.2 million people are still undiagnosed [1].This has been corroborated by a recent study, which showed that the chances of early diagnosis of COPD by doctors in the UK have been missed in 85% of cases in the five years before the actual diagnosis [41]. In the USA, 12.7 million people have COPD. However, evidence suggests that around 24 million have impaired lung function, indicating that almost half of the cases in the USA remain undiagnosed [42]. Second, the potential role of CPs in the reduction of medical and economical costs of inappropriate medication use is still not well recognised by the public. This can be partly attributed to the top down nature of

the health sector; patients usually perceive doctors of higher authority in the medical hierarchy in comparison to pharmacists [43]. The call for enhancing the agenda for research into the impact of CPs on health has already been raised in the UK [43]. It can be argued that this approach should also be followed by other countries given the economic burden of COPD on healthcare systems all over the world. Nevertheless, it is obvious from the studies reviewed in this paper that evidence regarding impact of CPs on COPD management is growing in the literature, since most of the studies reviewed were published between 2010 and 2015.

There was a clear emphasis from the reviewed studies on the need to provide patients with repeated instructions on correct IT by CPs and not to consider it as a one-time service in order to ensure sustainability [5, 8, 29]. The German study [5] in this review highlighted that patients benefited from IT education intervention irrespective of their previous education. On the other hand, two studies [4, 29] in this review showed how the role of CPs in IT education and re-assessment was not prominent. There are three possible reasons for this issue. The first reason might be the lack of sufficient knowledge and skills by CPs in IT education [44-46]. Several studies have shown that HCPs including pharmacists lack the knowledge needed to educate patients about correct IT [47-51]. The second reason could be that although CPs might be aware of the importance of IT as a concept, yet they might not be fully aware of the importance of sustaining the correct IT in patients and the possibility of technique deterioration, even if patients have been using their inhalers for years. Consequently, CPs overlook the necessity of IT assessment on a routine basis. Thus, despite the obvious importance of inhalation therapy as a treatment strategy in respiratory conditions, the significance of correct IT gets overlooked [9]. The third reason is the lack of clarity within healthcare systems as to which professional has responsibility for IT assessment [4, 52] hence pharmacists do not feel accountable for it. In fact, previous studies emphasised that HCPs should not make assumptions that their patients are being instructed by other colleagues from different disciplines about IT and should assure routine education and re-checking of their patients' IT [52, 53].

Existing evidence suggests that IT decline over time due to patients forgetting the proper instructions [17, 18, 29]. However, there was a disparity between the Japanese and the Australian study reviewed about the optimal frequency for IT re-checking and education. While the Japanese study recommended this to be done every six months as a minimum, the Australian study showed that a two-month gap period is sufficient to cause decline in IT even with patients using their inhalers for years. Interestingly, a previous study has shown the presence of a significant positive relationship between the provision of repeated IT instruction and adherence ($p=0.04$) and HRQoL ($P=0.017$) in COPD patients [54]. However, the frequency of repetition was not clearly specified [54]. COPD guidelines such as GOLD emphasise the importance of IT re-checking at each visit but with no specific frequency [2]. The National Institute for Health and Care Excellence (NICE) guidelines specify the frequency as once yearly [55]. Therefore, more research is needed to determine the optimal frequency of IT assessment and education to avoid deterioration of IT in patients.

Conclusions

This paper aimed at reviewing studies evaluating CPs' interventions and their impact on COPD management. As seen from this review, there is paucity of studies investigating such impact. The reviewed studies revealed that CPs can have a positive and cost-effective impact in the management of COPD in relation to MA and IT education which in turn can decrease medication wastage, hospital admissions and severe COPD exacerbations. However, the role of CPs is still not fully studied or recognised, thus there is a clear need for more research. The review also highlighted the need for more research to achieve a consensus on the frequency of IT re-checking and education to prevent technique deterioration. The results highlight the need for healthcare systems to recognise more the role of CPs in COPD management in two critical areas that are still challenging in real practice.

Conflicts of interest:

None.

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