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Economic impact of pharmacists' interventions in asthma management: a systematic review

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Abstract

Objective: The purpose of this study was to review in a systematically way the studies that investigated the economic impact of clinical pharmacist services delivered to asthma individuals. **Methods:** A systematic survey was conducted in the PubMed, Scopus, Lilacs and Cochrane databases aiming to grade the economic evaluations published until January 2020. English, Spanish, Portuguese or French language articles were included if they evaluated a pharmaceutical intervention aiming asthma patients and also reported economic data about these interventions. There was no limitation regarding the study design or type of economic analysis. Two independent authors assessed and selected the studies, extracted the data, and measured risk of bias. Risk of bias was measured through the Cochrane's risk of bias tool for randomized controlled trials and the Newcastle-Ottawa quality assessment scale for cohort studies. **Results:** 2,832 references were identified through the search strategy, but only seven studies met the inclusion criteria to be selected into the final analysis. Out of these seven articles, four consisted of cohort studies, and three consisted of randomized controlled trials. Instructional programs and patient counseling were the most usual components of pharmaceutical care interventions. Six articles showed statistically significant positive economic outcomes of pharmaceutical care interventions in asthma management. Moreover, pharmaceutical interventions were found to decrease hospitalizations, emergency visits, symptoms, and increase adherence to pharmacotherapy. **Conclusions:** Studies included showed acceptable and satisfactory cost-saving ratios, demonstrating the potential benefit of inserting the pharmacist into the multidisciplinary team. Nevertheless, long-term studies and randomized clinical trials are needed to establish solid evidence in order to expand the results found in this review to broader and different contexts.

Keywords: health economics; pharmaceutical care; pharmaceutical services; health technology assessment; asthma.

Impacto econômico da intervenção farmacêutica no manejo de pacientes portadores de asma: uma revisão sistemática

Resumo

Objetivos: Conduzir uma revisão sistemática de estudos que avaliam o impacto econômico das intervenções do farmacêutico clínico junto a pacientes asmáticos. **Métodos:** Foi realizada uma revisão sistemática de artigos publicados até janeiro de 2020 no PubMed, Scopus, Lilacs e Cochrane. Para atingir os critérios de elegibilidade o estudo precisava apresentar a intervenção do farmacêutico no manejo de pacientes com asma e ainda relatar os dados econômicos destas intervenções. Não houve restrição quanto ao desenho do estudo ou tipo de análise econômica. Dois revisores fizeram a triagem e selecionaram independentemente os estudos, extraíram os dados e avaliaram o risco de viés. O risco de viés foi avaliado por meio da ferramenta de risco de viés Cochrane para ensaios clínicos randomizados e da escala de avaliação de qualidade do Newcastle-Ottawa para estudos de coorte. **Resultados:** 2.832 referências foram identificadas por meio de nossa estratégia de busca, mas apenas um total de sete estudos preencheram os critérios para serem selecionados para a análise final. Destes sete artigos, quatro consistiam em estudos de coorte e três consistiam em ensaios clínicos randomizados. Programas educacionais e aconselhamento ao paciente foram os componentes mais frequentes das intervenções de assistência farmacêutica. Seis artigos mostraram resultados econômicos positivos estatisticamente significativos de intervenções de assistência farmacêutica no tratamento da asma. Em relação aos desfechos clínicos, as intervenções farmacêuticas diminuíram as hospitalizações, as visitas ao pronto-socorro, os escores dos sintomas e aumentaram a adesão aos medicamentos. **Conclusões:** Os estudos incluídos mostraram satisfatória redução nos custos, demonstrando o potencial benefício da inserção do farmacêutico na equipe multidisciplinar. No entanto, estudos de longa duração e ensaios clínicos randomizados são necessários para estabelecer evidências mais sólidas a fim de expandir os resultados encontrados nesta revisão para contextos mais amplos e distintos.

Palavras-chave: economia da saúde; assistência farmacêutica; avaliação das tecnologias de saúde; asma.



Introduction

One of the most commonly chronic diseases¹ found is asthma and it is estimated to be affecting more than 339 million people worldwide in 2016². It is a heterogeneous disease, usually characterized by chronic airway inflammation³, which varies in severity and frequency from person to person².

The disease cannot be cured³, but it is effectively treated by controlling symptoms. Factors that influence response to asthma treatment include: incorrect diagnosis; lack of adherence; use of drugs that can decrease the response to treatment (non-steroidal anti-inflammatory drugs and β -blockers); environmental exposure (dust or smoke); smoking; and other comorbidities⁴. The treatment's target is to achieve and stabilize control of the disease and avoid future risks (aggravation, inconstancy, accelerated loss of lung function and undesirable effects of treatment)⁴.

Despite the pharmacist is usually the patient's first contact and have therapeutic knowledge, they are still underemployed resources⁵. The role of community pharmacists in patient's instruction, adherence aid, and medication therapy administration was enhanced^{6,7,8,9} and has recently been expanded, particularly in high-income countries. It includes improving patients with chronic conditions, in particular asthma, life quality by providing information to the patient, adequate training on asthma medication, instruction on the correct inhalation technique, solving the patient's worries about possible side effects of inhaled corticosteroids and furthering adherence to the controlling medication¹⁰.

Given that asthma requires lifelong care management this implies a personalized approach, specialized devices, training for using the inhalation device, periodic evaluations, self-monitoring, and a personal therapeutic plan¹⁰. The inclusion of the pharmacist in the asthma care delivery may be particularly beneficial for patients with other chronic conditions, avoiding drug-related morbidities and additional use of health services, and, therefore, reducing costs¹¹. Among the most common drug-related problems are adverse reactions, lack of adherence to pharmacotherapy, intoxications, medication errors, the use of inappropriate or contraindicated drugs, and the abrupt reduction in dose/interruption of treatment¹².

Asthma-related costs are usually labeled into direct medical costs (such as emergency room visits, hospital admissions, cost of medication) and indirect costs (such as number of missed work days)^{13,14}. Previous studies on asthma management costs have found that uncontrolled and severe asthma is associated with increased costs and healthcare utilization, and decreased productivity¹⁵⁻¹⁷.

The cost of asthma care varies substantially among countries. While the mean annual cost per patient in Europe is USD 2,300^{14,17}, in the USA that figure is estimated at USD 7,400^{16,18}.

Considering the potential role of the pharmacist in addressing these avoidable negative outcomes and additional costs of poor care delivery for asthma patients, there is a need to further understand the effectiveness and cost-effectiveness of pharmaceutical assistance in this context. Thus, this review goal was to evaluate the economic impact of the pharmaceutical intervention in studies carried out in the care of patients with asthma.

This study emphasizes the importance of researching the impact of pharmaceutical intervention through an economic lens, in contrast to existing systematic reviews that focus on clinical outcomes.

Methods

This systematic review was guided in accordance with the Brazilian Ministry of Health's methodological guidelines for systematic reviews^{19,20}, which is adequate with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)²¹.

The conversion of the amounts expressed was performed using a tool available on the website of the Central Bank of Brazil²², considering the last day of June of the year in which the articles were published. All original manuscript values were converted to be 2020 US Dollars equivalent and then a discount rate of 3% per year was applied in order to bring the value to the present time.

The review was structured in accordance with the PICO model to build a fully-fledged search strategy. The PICO model and the search strategy are shown in Table 1 and Table 2, respectively. The guiding question of this research was the following: "Which economic impact does the pharmacists' intervention induces on the management of asthma patients?"

Table 1. The PICO model.

Description	Explanation
Population	Asthmatic patients of all ages with or without concomitant morbidities.
Intervention	Pharmaceutical intervention was defined as any action taken by the pharmacist to optimize pharmacotherapy for the management of asthma, such as changing the process of using medications (in relation to the patient or other health professionals). This includes pharmacotherapy review, medication reconciliation, preparation of clinical protocols, education for the correct use of inhaler devices, among others.
Comparator	Usual treatment or the non-intervention.
Outcomes	The primary outcome was defined as the cost reduction (direct or indirect costs were considered) resulting from the pharmacists' intervention, the Cost-Effectiveness Ratio or the Incremental Cost-Effectiveness Ratio. Results from Cost-benefit and Cost-Utility analysis were also observed. The secondary outcomes included the clinical impacts of the professionals' work, such as the reduction of problems related to pharmacotherapy, greater adherence to treatment, improvements in the levels of disease markers, and decreased consumption of medications.

Search Strategy

The strategy was carried out in January 2020 and consisted of analyzing the articles published in the Medline (via PubMed), Scopus, Lilacs and Cochrane databases using combined specific search terms. These databases were searched for the free terms: "pharmaceutical care", "pharmaceutical services", "economic impact", "asthma" in titles, abstracts and keywords. All the possible combinations of these terms were checked and chosen the ones that gathered the largest number of studies. Some of the bases had the option to select the filter of time and/or type of study, so we chose a 10-year coverage and the trial type of study trying to be the most inclusive as possible. There were no



restrictions regarding the study design or type of economic analysis, in an attempt to be inclusive and not miss relevant studies. During the initial construction of the search strategy, the descriptors used without any filter returned an impractical quantity of results. In order to restrict the search and carry out a more up-to-date review, the 10-year filter was placed in Pubmed and Scopus databases. Even so, a large number of articles were analyzed, making it possible to study the objectives proposed in this manuscript. The descriptors were searched in English and Portuguese in order to allow the search for studies carried out in Brazil that were not published in a foreign language. The process of study selection was performed based on all the combinations present in Table 2.

Table 2. The search strategy.

Databases	Keywords	Filters	Number of Studies
PubMed	asthma AND pharmaceutical services	10 years	522
PubMed	asthma AND pharmaceutical care	10 years	818
PubMed	asthma AND economic impacts	-	129
Lilacs	asma AND serviço farmacêutico	-	9
Lilacs	asma AND atenção farmacêutica	-	216
Scopus	asthma AND pharmaceutical services AND economic impacts	10 years	1,839
Cochrane Library	asthma AND pharmaceutical services	trials	49
Cochrane Library	asthma AND pharmaceutical care	trials	177

Study Selection

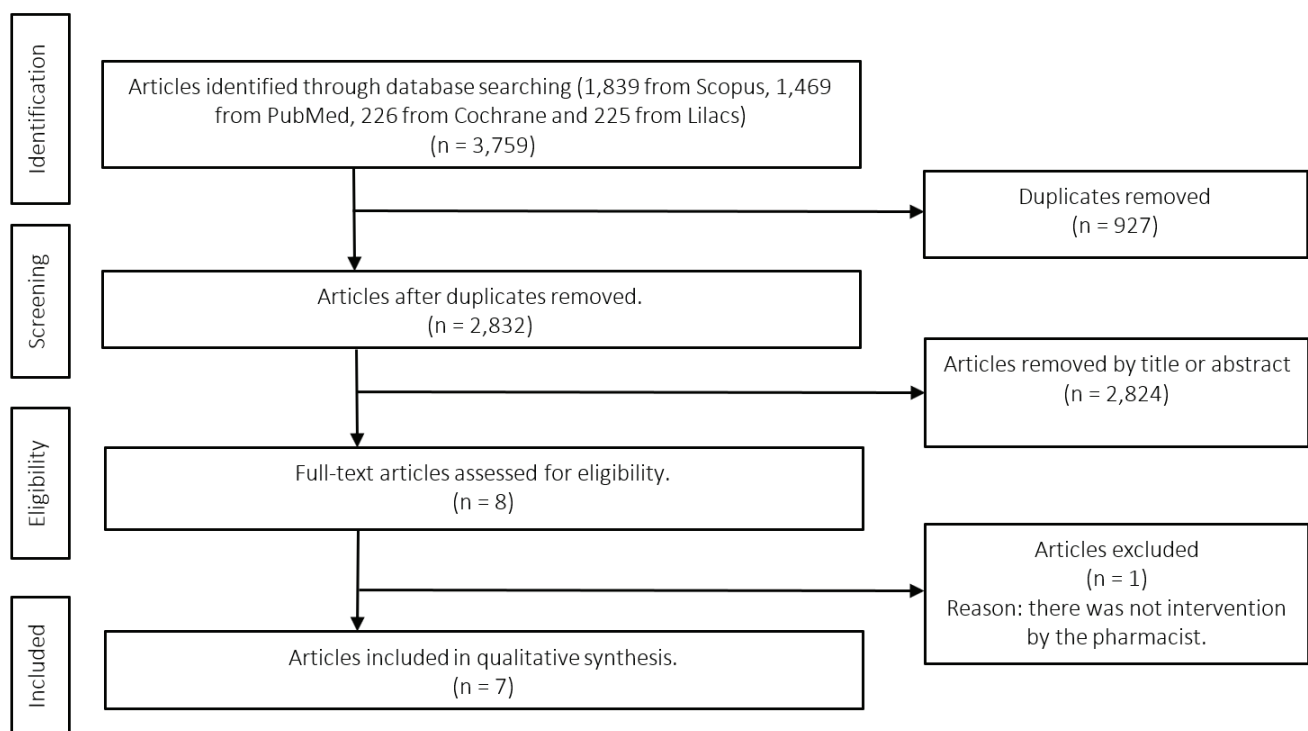
Each article found by the different search strategies (Table 2) was inserted in Rayyan QCRI²³ for later elimination of repeated items. Rayyan QCRI²³ is a tool that helps researchers in selecting studies for systematic reviews, in addition to promoting the elimination of duplicates and being blind to another reviewer's decision.

The inclusion criteria analysis was performed by perusing the abstracts, titles and keywords of the articles. The pre-selected studies were surveyed in full-text to attest the inclusion criteria was achieved. Inclusion criteria: the study describes an intervention aiming asthma patients; the pharmacist must have performed some intervention; report economic data about the pharmaceutical intervention; publications written in English, Spanish, Portuguese or French; the paper should be an original research article (not be a review or protocol). Exclusion criteria: the paper is a systematic review, editorial or commentary piece; the study involves intervention with animals; the study involves practices outside the healthcare realm. All unconformities between the researchers on the inclusion or exclusion of the studies were submitted and sorted out by a third reviewer. The process and the results of the different phases of this review was demonstrated in Figure 1.

Data extraction

Applying a standardized extraction tool, the following elements were consistently obtained from each full-text reviews of eligible study: first author and year of the publication; study design; number of subjects; pharmaceutical intervention; result of pharmaceutical intervention; type of economic analysis and outcomes. Data variances were decided by a third reviewer consulting the original articles.

Figure 1. Flow diagram of study selection.



Quality Assessment

The risk of bias in the randomized controlled trials was conducted according to the Cochrane tool for assessing risk of bias²⁴, a reference in RCT analysis. The studies were assessed through five main domains: selection bias; realization bias; attrition bias; detection bias and notification bias. As per risk of bias domains, the studies were rated using low, high and unclear risk. Any other bias found was also reported. Risk of bias visualization web app²⁵ was used to illustrate the analysis as shown in Figure 2.

The risk of bias in the cohort studies was assessed through the Newcastle Ottawa scale²⁶, reasoned on three categories: selection; comparability and outcome. The scale consists of eight items, and the total maximum score of these three subsets is 9. We considered a study which scored ≥ 7 a high-quality study.

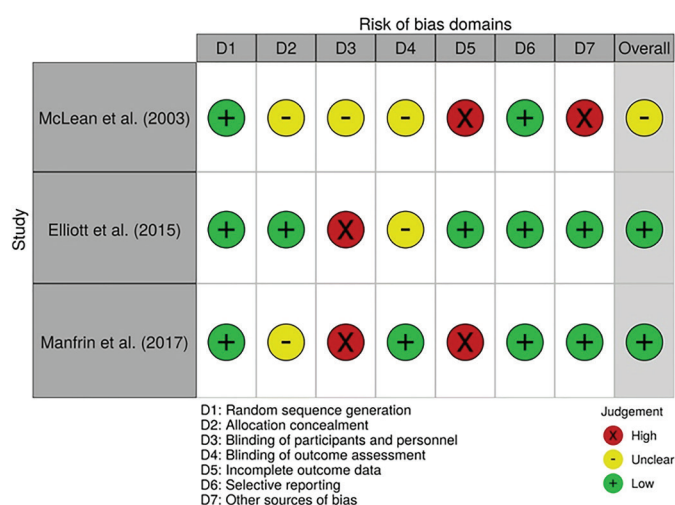
The studies were also assessed in terms of their methodological quality by the instrument ISPOR Consolidated Health Economic Evaluation Reporting Standards (CHEERS), which consists of a 24-item checklist²⁷. The results measured by the CHEERS checklist are shown in Table 6.

All discrepancies were solved by a third reviewer. No study was excluded from this review, based on the risk of bias assessed.

Synthesis of the results

The results were extracted and synthesized based on the economic and clinical outcomes. Individual qualitative analyses were made in terms of cost reduction, cost-effectiveness ratio or the incremental cost-effectiveness ratio and other economic indexes deriving from pharmacoeconomic analysis resulting from the pharmacists' intervention. The qualitative results presented in Tables 3 and 4 of clinical and economic improvements refer only to asthmatic patients, and not to all patients followed in the studies that presented pharmaceutical care to patients with chronic diseases other than asthma. A meta-analysis was not possible to conduct due to the enormous heterogeneity found among the economic results obtained in the included studies.

Figure 2. RCT risk of bias analysis.



Results

The selection process is shown in the flow diagram of Figure 1. After duplicates removal, we obtained 2,832 entries for initial screening. From these, 8 studies were selected for full-text review. Seven studies were deemed eligible for further data analysis. The study remaining was not eligible because there was no intervention by the pharmacist, but an evaluation, through a discrete choice experiment, on the preference of the patients, as well as their willingness to pay for specialized asthma services supplied by the community pharmacy. The most frequent motive for the exclusion of articles throughout the selection process was that they did not evaluate economic impact.

Tables 3 and 4 resume the technical features and results of the included studies. There were four cohort studies²⁷⁻³⁰ and three randomized control trials³¹⁻³³. The analytic methods of the cost analysis were one cost-benefit²⁹, three cost-effectiveness presented by the authors as cost-saving analysis^{28,30,32} and three cost-effectiveness analysis^{27,31,33}. The studies were performed in five different countries (Canada, England, Finland, Italy and United States) between 1997 and 2018. In all studies, clinical services were supplied by the pharmacist during a visit to a medical office or over the phone, with follow-up. In four studies²⁸⁻³¹, not only patients with asthma were evaluated, but also with other chronic diseases such as hypertension and diabetes.

Among the three included studies reporting randomized control trials³¹⁻³³, one conducted by Elliot and colleagues (2015)³¹ evaluated the cost-effectiveness of a program called New Medicine Service (NMS), implemented in 46 community pharmacies in England. It begins when the patient fills an application for an intervention in a community pharmacy and encompasses two elements: intervention and follow-up, with objective of identification of any issue with the treatment (including adverse drug reactions) and support required. NMS significantly increased adherence to the new medicine by 10% compared to normal practice. Adherence ratio was calculated on an intention-to-treat (ITT) basis returning an odds ratio (OR) of 1.62 (95% CI: 1.04-2.53, $p = 0.032$) in favor of NMS, in the full sample. The study has shown economic outcomes with no relevant statistical distinction in the intervention group when compared to the control group.

McLean and colleagues (2003)³² embraced a care protocol with the important pieces of asthma guideline and self-monitoring to be carried out by pharmacists specially informed in asthma care within the context of community pharmacy in the Canadian province of British Columbia. The authors found positive results, as manifested in improved variations between first and final visits of peak expiratory flow readings, symptoms scores and asthma knowledge. In addition, the study suggests that, although the pharmacist intervention in asthma care leads to increase drug costs (due to increased use of anti-inflammatory drugs), these costs are offset by savings in medical costs (ER visits, medical visits, hospitalizations). Cost analysis fortify the enhanced care model, which is more cost-effective in 57% than usual care.

The study conducted at the national level in Italy found a very positive impact of the tested intervention. The study demonstrated that community pharmacists supplied interventions more cost-effective than usual care; and the probability of being cost-effective increased from 51.5% at 3 months to 100% at 9 months. In addition, median asthma control test score increased, leading the number of patients with controlled asthma also to increase. In this research, Manfrin and researchers (2017)³³ mentioned that the study has maintained a substantial cultural shift in Italian community pharmacy practice, leading to the change from a mostly logistic to a more patient-centered and clinically oriented role of the community pharmacist to foment the health care.

Two of the cohort retrospective studies^{28,29}, which evaluated 12 months before and after the intervention period, obtained significant results in reducing the number of hospitalizations of patients who underwent the intervention by trained clinical pharmacist and also significant economic results. In the study conducted by Moore and colleagues (2013)²⁹, a Medication Therapy Management (MTM) program was implemented, focusing on reconciling drug therapies, preventing adverse effects, identifying relevant medication interactions and improving adherence through consultations with specially trained clinical pharmacists and follow-up by phone. The intervention resulted in decrease in emergency visits and decrease in health insurance costs by 10.3% or USD 1,352, compared with the control group increase of USD85. This is one of the largest studies reporting MTM (2,250 patients receiving interventions) showing that pharmacist guidance can be effective in promoting medication therapy and adherence, meanwhile lowering total health care costs. The MTM had a return on investment (ROI) of 2.0.

Matzke et al (2018)²⁸ showed that a collaborative care model between the pharmacist and the physician promoted noticeable improvements in clinical outcomes while reducing hospitalizations for patients with multiple chronic diseases including asthma. The resultant financial savings suggest that this care model has the potential to improve population health and reduce healthcare costs. There was an annual reduction of USD 2,860 per patient in collaborative care compared to a reduction of USD 269 per patient in patients in usual care.

The work by Munroe et al (1997)³⁰ relied on insurance claims data to monitor healthcare costs in two populations of patients, one receiving disease management services and the other receiving traditional pharmacy services. Unadjusted comparisons show no statistically significant difference between intervention and control group. Yet, after controlling for age, comorbid conditions, and disease severity, the point estimates for total monthly costs were significantly smaller in the intervention group.

Haahtela and other researchers (2006)²⁷ assessed changes in asthma management during a 10-year program in Finland²⁶. In 1993, pharmacies' asthma coordinators had no actively organized role in asthma care and the total direct costs from asthma were around USD410 million (3,028 per patient). In 2004, there was an active orientation on the use of preventers and relievers, orientation on inhalation technique, networking with local health care in parallel with costs reduction at 2% (USD 400 million) and costs per patient had decreased as much as 36% (1,938). The authors expressed concern about the annual cost increase in medication per patient with persistent asthma, that is, who needs regular treatment due to the increasing use of drug combinations.

In summary, was observed the costs saved per patient ranged significantly from USD301³⁰ to USD2,860²⁸, values belonging to the studies by Munroe and Matzke respectively. This finding reflects the economic impact of the pharmaceutical care intervention and contribute the development of health planning and policies.

Table 3 – Description of data extracted from RCT studies.

Article (year)	Type of Study	Number of Subjects	Duration of Intervention (months)	Pharmaceutical Intervention	Result of Pharmaceutical Intervention	Type of Economic Analysis	Economic Impact
McLean et al. (2003) ²⁷	Randomized controlled trial	631 (191 from enhanced care, 214 from usual care and 226 from control group)	12	Education about the disease; help to identify triggers; development of an action plan; asthma self-management every two to three weeks for at least three appointments; follow-up consultations at least every three months	Increased: overall quality of life by 19%; difference between first and final visits PEFr (peak expiratory flow rates) of enhanced care patients. Decreased: use of inhaled beta-agonists; emergency room visits by 75%; medical visits by 75%	Cost-saving	The usual care had total direct or indirect health costs per month per patient of USD 672 while the enhanced care group only USD 288
Elliott et al. (2015) ²⁶	Randomized controlled trial	58 patients in normal practice with asthma of 253 and 59 patients of the new medicine service with asthma of 251	2,5	Individual consultation 7-14 days after the presentation of the prescription; 14 to 21-day follow-up to discuss compliance, drug experiences and the patient-centered identification of any problems with treatment including adverse reactions	Increased: proportion of patients adhering to their new medicine by about 10%	Cost-effectiveness	The NMS intervention incurred lower cost, statistically non-significant, for USD 30
Manfrin et al. (2017) ²⁸	Randomized controlled trial	816 patients	9	Consultation conducted in a private room covering asthma symptoms, medicines used, attitudes towards medicines and adherence every three months	Increased: patient adherence to medications; change from not controlled/partially controlled to controlled asthma. Decreased: number actives ingredients by 340 or 7,90% (p<0,01)	Cost-effectiveness	Cost-effectiveness of I-MUR asthma service compared with usual care measured in terms of cost per QALY; The probability of the intervention being more cost-effective than usual care was 100% at 9 months

Table 4 – Description of data extracted from cohort studies.

Article (year)	Type of Study	Number of Subjects	Duration of Intervention (months)	Pharmaceutical Intervention	Result of Pharmaceutical Intervention	Type of Economic Analysis	Economic Impact
Munroe et al. (1997) ²⁵	Retrospective cohort study	42 patients with asthma of 188 from intervention and 117 patients with asthma of 401 from control group	17	Evaluation of patients' adherence to medications and non-medicated therapies; disease management services in private pharmaceutical consultations; systematic patient monitoring and feedbacks	Increased: patient adherence to medications	Cost-saving	Total health care cost savings range from a conservative estimate of USD 301 per patient per month to USD 613 per patient per month; Higher monthly prescription cost for patients with asthma in the intervention group; Reduction of overall healthcare expenses
Haahtela et al. (2006) ²²	Retrospective cohort study	-	120	Written or oral information on "preventers" and "relievers"; instructions on inhalation technique	Decreased: the absolute number of deaths; emergency visits due to asthma in adults by 24% and by 61% in children; daily allowances paid by sickness insurance for asthma by 27%; the number of hospitalization days was 54%, and 69% in relation to the number of asthmatics	Cost-effectiveness	In 1993, the year before the launch of the programme, the total direct costs from asthma and work disability were around USD 410 million. Ten years later the total costs were USD 400 million had decreased 2%; Costs per patient have decreased 36% (from USD 3,028 to 1,938)
Moore et al. (2013) ²⁴	Retrospective cohort study	424 patients with asthma in intervention e 420 patients with asthma in control group	12	Review of drug therapy, medical conditions, allergies and adverse drug reactions; individualized care plan that includes drug therapy issues discussed and specific recommendations	Decreased: emergency consultations; Inpatient visits in the medication therapy management group by 18.6%; 15% in inpatient utilization	Cost-benefit	Program costs per patient in 2009 were estimated to be USD 660. The plan-paid health care savings per patient due to program impact but not reduced by program costs was estimated to be USD 1,352. The program had a return on investment (ROI) of 2.0 in 2009
Matzke et al. (2018) ²³	Retrospective cohort study	4,960 (2,480 from collaborative care and 2,480 from usual care)	12	Medication review; follow up by a clinical pharmacist	Increased: patients medication related clinical health outcomes. Decreased: hospitalizations by 31.2%	Cost-saving	The cost reduction in the usual care group was USD 519,122, or 269 per patient while the collaborative care patients had a cost reduction of USD 5,634,838 or 2,860 per patient; The return on investment (net savings divided by program cost) was 504%

Table 5 - Cohort studies risk of bias analysis by the Newcastle-Ottawa scale.

	Selection			Comparability		Outcome		
	representativeness of the exposed cohort	selection of the nonexposed cohort	ascertainment of exposure	demonstration that outcome of interest was not present at start of study	comparability of cohorts	assessment of outcome	follow-up long enough for outcomes to occur	adequacy of follow-up of cohorts
Munroe et al. (1997)	*	*	*	*	*	*	*	*
Haahtela et al. (2006)	*		*	*			*	*
Moore et al. (2013)	*	*		*	*		*	
Matzke et al. (2018)	*		*	*	*	*	*	*

According to the guidelines of the Cochrane risk of bias tool, the randomized control trials studies have a good quality. In two of three of the RCT studies, little information on the allocation^{32,33} and blinding of the evaluators of the study result^{31,32} was available. The most usual bias present was the blinding of participants and personnel. The evaluation of the methodological quality of the included cohort studies is shown in Table 5. Newcastle-Ottawa scale scores for studies ranged from 5 to 7.

In six of the seven studies^{27-30,32,33}, pharmacists received training – that was not described how it occurred, just how long it lasted – to carry out the respective interventions.

The main interventions applied by pharmacists were to ensure better adherence and maintenance of treatments through patient monitoring, early intervention and behavior modification³⁰. There were systems of routine consultations with the pharmacists in which they evaluated patients' adherence to pharmacological and non-pharmacological therapies, in addition to educating them about their particular condition, technique for using different pharmaceutical forms, treatment goal and expected outcomes, nondrug therapy, self-monitoring and adverse effects. In all studies, the pharmacists provided education on disease and on the use of inhalation devices, helped to identify triggers and worked with the patients to develop action plans. The pharmacists also promoted evidence-based care.

The average reporting quality score of the studies based on the CHEERS³⁴ checklist was 75,59%, with standard deviation as: 13,44% (Table 6).

Table 6 – Results of the CHEERS checklist.

Author	CHEERS score ^a
Manfrin, 2017	91
Matzke, 2018	87
Moore, 2013	83
McLean, 2003	83
Elliott, 2015	79
Studies below average	
Munroe, 1997	70
Haahtela, 2006	33

^aCHEERS score represents the percentage of "yes" answers.

and promote regular monitoring of asthmatic patients. Our findings highlighted and established the fact that pharmaceutical intervention in asthma management is promising and it may be applicable to different care environments around the world and too other chronic diseases. The worthwhile experiences of this review and similar reviews should be taken as a guide for health policy makers to provide more opportunities for the development of the clinical role of the pharmacist.

Our findings also show a favorable impact of pharmacist interventions on clinical outcomes as well as symptom scores. Pharmacists recorded symptom scores at the beginning and end of the study period in the McLean and colleagues study³². The analysis was performed only on the most frequent symptoms (dyspnea, cough, wheezing, chest tightness, phlegm production and nasal symptoms). The improvement of all symptoms was significantly higher in the pharmaceutical care group. More severe symptoms were also reduced. Previous study has reported improvement in night or daytime wheeze³⁸, night-time cough³⁸, increased mucus excretion and allergic symptoms³⁸, which are all common symptoms of asthma attacks².

Analyzing the economic and clinical results of the studies included in this systematic review, the wide variety of approaches taken is remarkable. Nonetheless, the number of existing studies is limited and heterogeneous in several aspects, such as how the intervention was implemented how long it lasted and the primary outcomes.

Management programs focusing on reducing hospital admissions represented a cost-effective strategy for the management of asthma. It was observed that from a wider understanding of the disease, through the patient education and review of his drug therapy, there was a strong reduction in the number of hospitalizations and emergency room visits²⁷⁻³⁰. Emergency department (ED) visits made by asthma patients in the general population could increase total costs the health system by 33% according to Sadatsafavi and investigators³⁹. Other authors estimated per patient average annual hospitalization expense of almost USD1,300 per person and 3,600 for the patients with severe disease and/or poorly controlled disease⁴⁰.

These findings are in accordance with other pieces from the literature suggesting that patients value specific pharmaceutical care. In fact, patients in Australia showed great interest and willingness to pay for specialized asthma services, such as the availability of a private area, provision of pulmonary function tests, pharmaceutical consultations and provision of comprehensive advice on asthma and medications⁴¹. In other countries is also noted that the pharmacist is not used as he should in the health system. For example, we can mention Brazil, where there is an average of 350,000 hospitalizations annually of patients in asthma crisis¹. Asthma is the third or fourth cause of hospitalizations by the Unified Health System (SUS, Brazilian healthcare system), corresponding to 2.3% of the total, according to the age group considered¹. Pharmacists working in thousands of community pharmacies in the country could provide these services.

Another major component of costs for asthmatic patients is medications. The rational and proper use of asthma medication has been highlighted in the literature⁴²⁻⁴⁴ and in the studies included in this review^{28,30,31,33}. It is an essential strategy to improve asthma control, especially in primary care. Greater control over asthma reduces total costs. Good adherence is a critical factor in chronic asthma disease control and prognosis⁴⁵ and improves the effectiveness of interventions. In developed countries,

Discussion

This is the very first systematic to focus on the economic impacts related to pharmaceutical intervention on asthma care. Other systematic reviews only approach the clinical impact of pharmacists' intervention on asthma management³⁵⁻³⁷. Our findings suggest that structured educational programs and patient counseling appear to be the most common components of pharmaceutical care interventions. It points out that more data are required to discern what kind of training pharmacists should receive, length and frequency of the intervention and components of the intervention that will ensure the best patient outcomes. Overall, the analysis indicates that a pharmacist with basic training in asthma care can provide a simple educational program resulting in improvements of asthma control³⁷. There is a consensus on the need for this training of pharmaceutical professionals and community pharmacies or primary care to improve accessibility



the adherence rate of patients with chronic diseases is poor, representing only 50%⁴⁶. There is evidence that inappropriate inhalation technique is linked with unsatisfactory asthma control⁴⁷⁻⁴⁹. A Brazilian study elucidates that the main difficulties faced by pharmacists to perform their duties are directly linked to the execution of clinical services⁵⁰.

The RCT studies³¹⁻³³ methodological process is structurally similar. It consists in the patient's education and close monitoring progress. The pharmaceutical intervention contributed to an increase in quality of life, a reduction in emergency room visits and physician visits³², improvement of medication adherence and disease control³³. Other relevant clinical outcomes are the reduction of asthma symptoms, beta-agonist use, hospitalizations and days out of work or school³².

Among the observational studies included, only Moore et al (2013)²⁹ and Munroe et al (1997)³⁰ presented cost analysis as a primary objective, while no RCT did so. According to the results found reduction of the costs was successfully achieved. The total health care savings per patient due to program impact in the 2013 study was estimated to be USD1,352, with program costs per patient of USD 660. While, in the 1997 study savings in the group receiving intervention ranged from a conservative estimation of USD301 per patient per month to as high as USD 613 per patient per month when patient age, comorbid conditions and disease severity were considered.

Regarding the other two cohort studies, in Haahtela et al (2006)²⁷ we see after the 10 years program taking into consideration compensations for disability, drugs, hospital care, and outpatient doctor visits, costs per patient have decreased 36% and, if related to the increase in gross national product, by 50%. While in the study by Matzke et al (2018)²⁸ the return on investment, that consists on net savings divided by the 1-year intervention program cost, was 504%, configuring the intervention as more cost effective.

In regard to the experimental studies embedded in this review, two of them found significant cost reduction associated with the intervention. Manfrin et al (2017)³³ demonstrated that the implementing education patient's services to asthma patients verified that the intervention is more cost-effective than the usual care. Similarly, the intervention tested by McLean et al (2003)³², consisting primarily of pharmacotherapy review, generated savings by decreasing in more than half per-patient cost. Elliot et al (2015)³¹ requires a particular observation because the main outcome was to verify the adherence to the NMS by indicating its lower cost.

Cost analysis of illness is a useful tool for quantifying the economic burden of a disease and for planning cost containment policies. Overall, although the absolute values in cost associated with asthma care vary among studies, the emerging evidence is robust in demonstrating the potential of pharmaceutical care in generating cost-savings. This general message is consistent with other studies^{51,52}.

This study has some strengths that deserve to be highlighted. To our knowledge, it is the first systematic review that evaluates both the economic and clinical outcomes of pharmaceutical intervention in asthma care. Second, six articles of the seven analyzed demonstrated a significant cost reduction in the presence of pharmaceutical intervention. Besides, based on CHEERS checklist, it was observed that most studies have good methodological transparency (only one had a score below 70%) (Table 6).

However, the present work has also few limitations that must be acknowledged. First, heterogeneity was observed among the included studies; therefore, the articles were compared by the type of study performed. It became evident that few studies carry out

economic evaluation and even more infrequently, studies that have it as the main objective of the study.

Lack of specified description of the training of the pharmacists chosen to manage the intervention was noted, and it hindered our analysis of the learning curve.

Given the nature of the intervention, it is not possible to blind patients or pharmacist. Therefore, even in RCT studies, it is not possible to completely rule out some bias associated with the knowledge of being in the intervention group. But it is understandable because occurs an educational intervention to improve knowledge of asthma and the process of using medications.

Lastly the studies that included multiple chronic conditions, there is a lack of specificity and description of the results and cost components. Therefore, it is not possible to state whether asthma patients in these studies had a greater or lesser impact. In addition, the authors do not address indirect costs or savings achieved through pharmaceutical intervention.

Unfortunately, only two studies have the main objective of evaluating the economic impact of the clinical role of the pharmacist in the management of asthma. This fact can also be pointed out as a limitation. Based on the findings found in this systematic review, it is possible to present some recommendations for future studies aimed at evaluating the economic impact of pharmaceutical activities, such as: better standardization of the actions explored and the methodologies used; transparency on the terminology used for pharmaceutical services; conducting controlled clinical trials with the purpose of evaluating economic aspects; specific description of the types of costs (direct medical, direct non-medical, indirect); and, finally, a specific description of the results to be measured.

Conclusion

Despite the relatively low number of articles included in this review, the evidence is coherent and supportive to the role of pharmaceutical care in improving clinical outcomes and reducing costs in asthma care. Studies included showed acceptable and satisfactory cost-saving ratios, demonstrating the potential benefit of inserting the pharmacist into the multidisciplinary team. Policy-makers and healthcare managers, however, also need to take into consideration the contextual and circumstantial factors in developing and implementing pharmaceutical interventions for asthmatic patients. Besides, more research is needed to establish solid evidence, such as long-term studies and randomized clinical trials, in order to expand the results found in this review to broader and different contexts.

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Conflict of interests statement

The authors declare that there are no conflicts of interest regarding this article.



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