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How Pharmacist–Patient Communication Determines Pharmacy Loyalty? A Review In Effectiveness Of Clinical Pharmacy Services

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Abstract

Background Multiple reviews have evaluated the impact of pharmacist-delivered patient care on health- related outcomes. However, it is unclear which of the pharmacist-delivered interventions in these services are the most effective. Aim of the review To gather the evidence ofthe impact of clinical pharmacy services on the medication use process or on patient outcomes using an overview of systematic reviews. Methods PubMed was searched to re- trieve systematic reviews published between 2000 and 2010that assessed the impact of clinical pharmacy services on the medication use process or patient outc[1]omes. Two indepen- dent reviewers evaluated the study eligibility and one ex- tracted the description and results of the services. The methodological quality of each review was assessed with the R-AMSTAR tool. Results Of the 343 potentially relevant records identified, 49 systematic reviews, comprising a total of 269 randomized controlled trials, met the selection cri- teria. Clinical pharmacy services that focused on specific medical conditions, such as hypertension or diabetes melli-tus, revealed a positive impact of pharmacists' interventions on patient outcomes. For other medical conditions, however,the results were inconclusive (e.g., dyslipidemia or throm- boprophylaxis). Interventions that targeted medication ad- herence and assessed the impact of clinical pharmacy services in prescription appropriateness also produced in- conclusive results because of the variability of methods usedto assess both medication adherence and medication ap- propriateness. Conclusions Systematic reviews that assessed clinical pharmacy services targeting specific conditions were more conclusive given that the intervention was well defined, and the measured outcomes were unequivocal andtangible. Conversely, the results were inconclusive for in- terventions with a broader target and with monitoring pa- rameters that were unclearly established or inconsistently assessed across studies. These findings emphasize the needto better define clinical pharmacy services and standardize methods that assess the impact of these services on patient health outcomes.

Keywords *Clinical pharmacy services · Pharmaceutical care · Pharmacists · Systematic review*

Impacts of findings on practice

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- In order to create robust evidence, a better standard- ization of interventions performed as part of clinical pharmacy services across countries is required.
- Ambiguous terminologies for clinical pharmacy services should be addressed through the creation of glossaries and the achievement of international agreements on the

definition and the components of each clinical pharmacyservice.

- Journal editors play an important role in ensuring the

rigorousness of the description of the interventions performed and the outcomes measured in articles accepted for publication.

Introduction

Over the past five decades, pharmacists have attempted to extend their scope of activity beyond the traditional dis- tributive and dispensing roles [1]. In 2000, the Institute of Medicine recognized the critical role played by pharma- cists in the areas of medication safety and management as well as the value of pharmacist–physician collaboration in patient care [2]. Pharmacists' interventions were shown to help optimize processes of care by improving the quality ofthe medication use process and disease management through effective interactions with both patients and other health professionals [3, 4]. Different terms have been used to define pharmacists' clinical activities; clinical pharmacyservices [5] and pharmaceutical care [6] have been two of the most commonly used.

A vast set of published literature has assessed the impactof clinical pharmacy services in different patient groups. Randomized controlled trials (RCTs) demonstrated that pharmacists have a positive impact on patient health out- comes both in the community and hospital settings [7, 8]. Several systematic reviews and meta-analyses showed that pharmacist care was associated with improvements in health outcomes of patients with heart failure [9], diabetes, hypertension, or hiperlipidemia [10]. However, recent sys- tematic reviews have raised reasonable doubts regarding the actual impact of these pharmacist interventions [11, 12].

Systematic reviews are usually performed to gather the available evidence and develop guidelines for professional practice. To ensure robust evidence, the quality of sys- tematic reviews is required to be thoroughly evaluated. Previous authors have assessed the methodological quality of systematic reviews and meta-analyses addressing phar- macist-led health interventions and demonstrated that the quality of most reviews ranged from poor to moderate, which could result in misinterpretations of results [13]. Additionally, few systematic reviews with meta-analyses have been published on this topic due to the high hetero- geneity of outcomes reported across primary studies [13]. Heterogeneity is not only an issue when including differentservices in the review, but also when the meta-analysis targets only one specific pharmacist service such as Medication Therapy Management [14]. To analyze the origin of this heterogeneity, a robust subgroup analysis should be performed in systematic reviews [15]. However, a limiting aspect of many systematic reviews and meta- analyses is the poor and inconsistent description of the pharmacist intervention across primary studies [16, 17]. Asa means of addressing this issue a tool to characterize the components of clinical pharmacy services—DEPICT (De- scriptive Elements of Pharmacist Intervention Charac- terization Tool)—was developed in 2013 and recently refined as part of a larger project (http://depictproject.org) [18, 19]. This tool was designed so as each item reflects a component of pharmacists' interventions. This tool has been successfully used to identify reproducible clinical pharmacy services in the area of chronic kidney disease based on the accuracy of the intervention description in these studies [20]. Broader scope systematic reviews could be used to identify the common components

among dif- ferent successful clinical pharmacy services.

Aim of the review

The aim of this study was to assess the impact of sub- stantially different clinical pharmacy services on the medication use process or on patient outcomes using an overview of systematic reviews published in the first dec- ade of the 2000s and to find common elements among theseservices.

Methods

An overview of published systematic reviews was con-ducted following the Cochrane Collaboration recommen- dations and the PRISMA statement [21, 22]. To identifythe articles published between 2000 and 2010, Medline(PubMed) was searched in December 2012 employing the following search strategy: systematic review*[TIAB] OR meta-analysis[PT] OR meta-analysis[TIAB] OR sys- tematic literature review[TIAB] OR ''cochrane database syst rev''[JOURNAL] OR [search*[TIAB] AND (medline OR embase OR peer-review* OR literature OR ''evidence- based'' OR pubmed OR ipa or ''international pharmaceu- tical abstracts'')] NOT [letter(PT) OR ''newspaper arti-cle''(PT) OR comment(PT)] AND hasabstract AND [pharmacist*(TIAB) OR pharmacists(MH)] . In addition, reference lists of the systematic reviews ultimately in-cluded were searched manually to retrieve any further references.

Initially, two reviewers (I.R. and C.J.C.) independently selected studies based on their title and abstract (screening phase), with disagreement being adjudicated by a thirdreviewer (F.F-L.). Articles that appeared to be potentially relevant were fully analyzed by the same reviewers who considered the following inclusion criteria: systematic re- views assessing the impact of a clinical pharmacy service using either measures of the medication use process or patient outcomes. Clinical pharmacy services were defined as those where pharmacists provide patient care that opti- mizes medication therapy and promotes health, wellness, and disease prevention in all health care settings [5]. A study was considered to be a systematic review if it satis- factorily fulfilled the following three items of the PRISMA Statement checklist: (1) item 4: a clear description of the clinical question to be answered by the systematic review, including participants, interventions, controls, outcomes and study design (PICOS); (2) item 7: a description of all data sources used to retrieve the literature and the search period considered; and (3) item 9: a detailed description of the studies' selection process (number of articles included and excluded in each step) [23].

The exclusion criteria used for our study included the following: (1) systematic reviews in which the health in- terventions involved pharmacists but their contributions to the healthcare team were indistinguishable; (2) studies re- viewing guidelines or other overviews of systematic re- views; (3) systematic reviews analyzing non-clinical activities, such as: drug compounding, storage, adminis- tration (including vaccines) or other logistic activities; (4) studies published in a language other than English, Span- ish, Portuguese, French or German; and (5) reviews not including at least one RCT. For systematic reviews pub- lished in duplicate or updated versions of Cochrane re- views, only the most recent publication was considered.

The quality of all systematic reviews was assessed using the Revised Assessment of Multiple Systematic Reviews (R- AMSTAR) checklist [24], which is a revised version of the AMSTAR [25]. R-AMSTAR comprises 11 domains. Prior to the start of the assessment, the items composing the checklistwere thoroughly discussed (I.R. and F.F-L.), and a manual to guide the interpretation of R-AMSTAR items was created to ensure consistency in the analysis.

Finally, the data were extracted from the systematic re- views by one of the authors (I.R.), using a previously dis- cussed table for extraction that included the following items:year of publication, number of RCTs included in each re- view, scope of the research, components of the clinical pharmacy services described, and all the results reported including economic, clinical and humanistic outcomes (ECHO model) [26] and medication use process

indicators.

Results

Of the 343 potentially relevant records initially identified, 228 were excluded after screening the title/abstract, and 69 were excluded after full-text analysis. Therefore, 46 systematic reviews were initially included, while three others were identified through a manual search, resulting ina total of 49 systematic reviews analyzed. An outline of the selection process is presented in Fig. 1. These reviews comprised a pool of 269 RCTs published between 1973and 2009. The percentage of reviews who satisfactorily meteach R-AMSTAR criterion is described on Table 1. Ad- ditionally, a detailed analysis of the quality of each review is presented in Online Appendix 1.

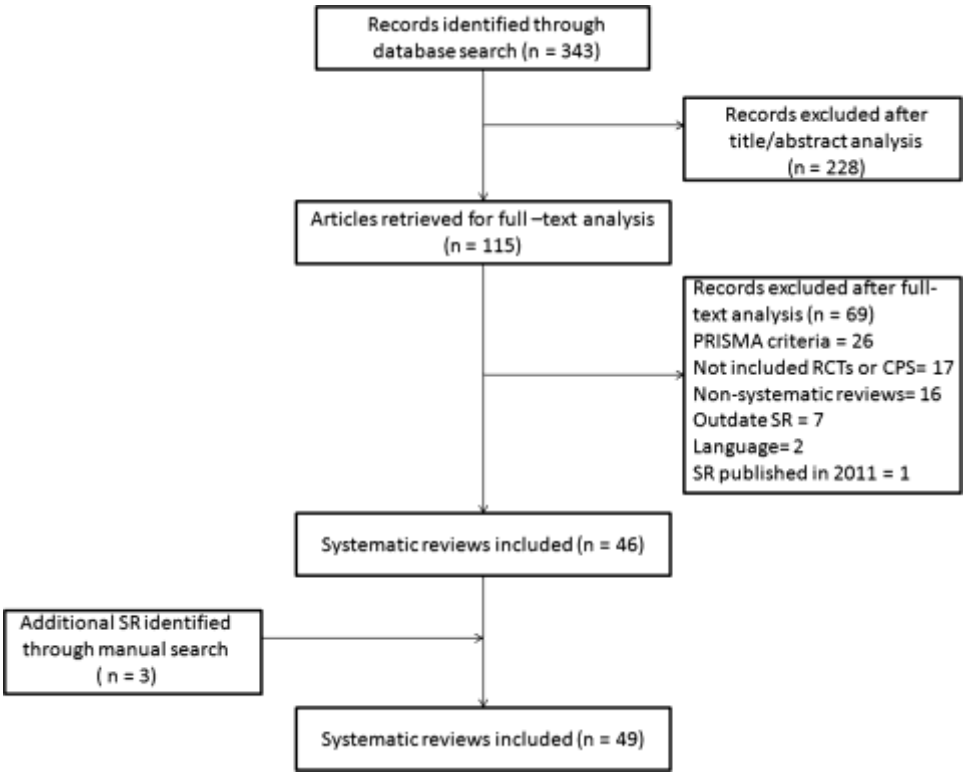
The Online Appendix 2 shows the components and the main findings of clinical pharmacy services reported insystematic reviews. Based on these reports, clinical pharmacy services were grouped into seven categories, which are presented in Table 2. The main research questions ad- dressed by systematic reviews could be grouped as follows: interventions to improve disease or condition management [3, 27–39], patient adherence [9, 40–52], appropriateness of prescriptions [53–68] and miscellaneous interventions [4, 10, 69–71].

Impact of clinical pharmacy services on diseaseor condition management

The impact of clinical pharmacy services on hypertension and diabetes management was assessed in six [3, 29–33] and four [27, 34, 36, 39] systematic reviews, respectively. All the studies included patient education and counseling regarding disease, therapy and lifestyle modifications, and all of them showed positive results. The reduction in sys- tolic blood pressure ranged from 8 to 11 mmHg, and the reduction in HbA1c ranged from 0.9 to 2.1 %. Drug ther- apy adjustments performed after medication review and medication follow-up were also reported in six of the re- views [3, 31–34, 39]. Three reviews also described other healthcare professionals' education performed by pharma- cists [29, 30, 36]. Wubben et al. [39] noted that there was agreater effect of the pharmacist intervention when the pharmacists were granted prescription autonomy.

Hyperlipidemia management by pharmacists was assessed in two [28, 35] systematic reviews. One of the reviews included a meta-analysis and showed that totalcholesterol significantly improved after pharmacist inter- vention [mean (SD) 22.0 (10.4) mg/dL, P = 0.034], but LDL-C, HDL-C, or triglycerides did not improve [35].Despite the results not being statistically significant, the other review showed that more patients in the intervention group reached the total cholesterol goal, reduced their LDL-C and triglycerides and improved their HDL-C [28]. Additionally, more patients in the intervention group (57 vs. 31 %) had a cholesterol panel ordered and changes in the dose of their cholesterol-lowering medication [OR 3.0; 95 % confidence interval (CI) 2.2–4.1; P ⟍ 0.001] [28].

Fig. 1 Flowchart illustrating the selection process of systematic reviews. RCTs randomized controlled trials, CPS clinical pharmacy services, SR systematic reviews



Anticoagulation management was assessed in one sys- tematic review [37]. Pharmacists' interventions consisted of warfarin dose adjustment, identifying potential drug– drug interactions and educating patients or health profes- sionals. These activities were shown to significantly im- prove the prevention of total bleeding (RR 0.51; 95 % CI 0.28–0.94; P = 0.019). Other warfarin-related complica- tions, such as major bleeding, thromboembolic events, all- cause mortality and warfarin-related mortality, did not improve after pharmacists' intervention [37].

Smoking cessation programs led by pharmacists were the focus of two reviews [28, 38]. Both these studies pro- duced inconclusive results, possibly because both reviews included only two RCTs that had contradictory findings with regards to the prevalence of abstinence during the follow-up period.

Impact of clinical pharmacy services on medication adherence

Fourteen systematic reviews addressed clinical pharmacy services that aimed to enhance patient medication adher- ence [9, 40–52]. In all 14 reviews, the pharmacist inter- vention consisted of providing patient counseling. Adherence rates improved when counseling was ad- dressed to both the patient and the physician, but the rates

did not change when the target was the physician only[47]. Providing medication follow-up in addition to pa- tient counseling [9, 43, 49], self-monitoring blood pres- sure devices [48] or both [42] produced mixed results.Supplementing patient counseling with medication rec- onciliation [40] or giving the pharmacists prescription autonomy [46] did not improve results. Eight of the 14 adherence reviews that presented inconclusive findings included a medication review, [40, 41, 44–46, 50–52] and
in six of them [40, 41, 45, 50–52] the pharmacy service also comprised a comprehensive medication therapy management program with different follow-up duration.

Three of these reviews concluded that the variability in the adherence rates found across studies was due to the variety of methods used to assess medication adherence [9,44, 52]. Additionally, another review pointed out that studies in this area were heterogeneous in terms of quality, patient population, duration, outcomes measured, and lengths of follow-up [40].

The most successful pharmacist interventions included the use of electronic devices [42], a system of reminders and blister packs combined with [50] or without [46] education and pharmacist follow-up, providing concurrent oral and written information [43], and regular scheduled consultations with the pharmacist at the time of prescrip- tion refill [44].

Table 1 Percentage of reviews that satisfactorily met each R-AMSTAR criterion

Criterion	Description	Yes (%)
Q 1.a	‘‘A priori’’ design established	100
Q 1.b	Statement of inclusion criteria	100
Q 1.c	PICO/PIPO research question (population, intervention, comparison, prediction, outcome)	35
Q 2.a	There were at least 2 independent studies selectors and data extractors as stated or implied	61
Q 2.b	Statement of recognition or awareness of consensus procedure for disagreements	59
Q 2.c	Disagreements among extractors resolved properly as stated or implied	8
Q 3.a	At least 2 electronic sources were searched	90
Q 3.b	The report includes years and databases searched	100
Q 3.c	Key words and/or MESH terms are stated and the search strategy is provided	39
Q 3.d	ı addition to the electronic databases, the search was supplemented by consulting current contents such as reviews, textbooks, specialised registers, or experts in the field of study and by reviewing the references in the studies found	55
Q 3.e	ɔurnals were ‘‘hand searched’’ or ‘‘manual searched’’ (i.e., identifying highly relevant journals and conducting a manual, page-by-page search of their entire contents looking for potentially eligible studies)	16
Q 4.a	The authors stated that they searched for reports regardless of publication type	4
Q 4.b	The authors state whether or not they excluded any reports (from the SR), based on their publication status or language	80
Q 4.c	‘‘Non-English’’ papers were translated or readers sufficiently trained in foreign language	39
Q 4.d	No language restriction or recognition of non-English articles	31
Q 5.a	Table/list/or figure of included studies was provided; a reference list does not suffice	100
Q 5.b	'able/list/or figure of excluded studies was provided either in the article or in a supplemental source (i.e., online). (Excluded studies refers to those studies seriously considered on the basis of title and/or abstract, but rejected after reading the body of the text)	29
Q 5.c	Author satisfactorily/sufficiently stated the reason for exclusion of the seriously considered studies	71
Q 5.d	Reader is able to retrace the included and the excluded studies anywhere in the article bibliography, reference, or supplemental source	27
Q 6.a	In an aggregated form such as a table, data from the original studies are provided on the participants, interventions AND outcomes	88
Q 6.b	Provide the ranges of relevant characteristics in the studies analysed (e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases are reported)	24
Q 6.c	The information provided appears to be complete and accurate (i.e., there is a tolerable range of subjectivity here. Is the reader left wondering? If so, state the needed information and the reasoning)	98
Q 7.a	‘‘A priori’’ methods of assessment were provided (e.g., for effectiveness	

	studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant	76
Q 7.b	The scientific quality of the included studies appears to be meaningful	69
Q 7.c	Discussion/recognition/awareness of level of evidence	69
Q 7.d	Quality of evidence was rated/ranked based on characterised instruments which is a created instrument that ranks the level of evidence (e.g., GRADE)	4
Q 8.a	The results of the methodological rigor and scientific quality were considered in the conclusions of the systematic review	65
Q 8.b	The results of the methodological rigor and scientific quality were explicitly stated in formulating recommendations	8
Q 8.c	To have conclusions integrated/drives towards a clinical consensus statement	0
Q 8.d	This clinical consensus statement drives toward revision or confirmation of clinical practice guidelines	0
Q 9.a	Statement of criteria that were used to decide that the studies analysed were similar enough to be pooled	3
Q 9.b	For the pooled results, a test was performed to ensure the studies were combinable, to assess their homogeneity (i.e., Chi square test for homogeneity, I^2)	27
Q 9.c	There was a recognition of heterogeneity or lack of thereof	27
Q 9.d	If heterogeneity existed a ‘‘random effects model’’ was used and/or the rationale (i.e., clinical appropriateness) of combining was taken into consideration (i.e., was it sensible to combine), or stated explicitly	18
Q 9.e	If homogeneity existed, the authors stated a rationale or a statistical test	27
Q 10.a	Recognition of publication bias or file-drawer effect	16*
Q 10.b	Assessment of publication bias included graphical aids (e.g., funnel plot, other available tests)	16*

Table 1 continued

Criterion	Description	Yes (%)
Q 10.c	Statistical tests (e.g., Egger regression test)	12*
Q 11.a	Statement of sources of support	88
Q 11.b	No conflict of interest	59
Q 11.c	An awareness/statement of support or conflict of interest in the primary inclusion studies	2

* Calculated only for the 14 meta-analyses

Table 2 Clinical pharmacy services categories identified from the literature

No.	Clinical pharmacy services categories	Study references
1	Patient education and counseling about medication, diseases and non-pharmacological treatment. These services can (or not) be provided along with medication dispensing, with the aim of promoting the correct use of medicines and adherence to treatment. The pharmacist can also provide additional educational support, like printed materials or multimedia and compliance aids, such as pillboxes, pill organisers, dispensers, dosage systems, medication packs, medication diaries, reminder systems, beep-cards, among others.	
2	Structured programs for detection, prevention or control of specific risk factors (e.g. smoking cessation, point-of-care testing, screening services), in which interventions are usually focused on behavioral techniques and individual or group education.	
3	Medication review and drug therapy adjustments, with or without direct contact with the patient. The aim is to identify and correct any failures with the medication use process, issues related to inappropriate prescribing, therapeutic regimen, treatment costs or adverse effects. The pharmacist usually makes recommendations to the patient or physician and can have major or minor autonomy to modify pharmacologic treatment.	
4	Elaboration or refinement of a complete and reliable medication history and therapeutic reconciliation during hospital admission, transference between settings and after discharge. These services can include provision of information to the physician and patient, usually written, with the aim of correcting any discrepancies.	
5	Medication therapy management and medication follow-up targeting health outcomes and continuity of health care, by using several ways of contact with the patient and physician (e.g. face-to-face, telephone, fax, web or email), different duration of follow-up and number of appointments.	
6	Provision of information by the pharmacist to the physician and health care team, without the need of direct patient care. It may include multidisciplinary case discussions, ward rounds, development of clinical protocols, therapeutic formularies and closer relationships with the team. It also includes services of academic detailing, in order to provide scientific information and to promote good practices of prescription, usually focused on specific clinical conditions or medications.	
7	Services in which the pharmacist has the autonomy to manage or prescribe medicines to the patient according to pre-defined clinical protocols or collaborative agreements	

between providers or within ambulatory care settings. It also includes patient referral to thecommunity pharmacist for assessment and management of minor illness.

[3, 4, 9, 10, 27–57, 61, 63, 66, 68–71]

[3, 4, 28, 29, 39, 42, 45, 48, 51, 61]

[3, 4, 10, 31–35, 37, 39–41, 44–46, 50–56, 58–69]

[4, 40, 53, 59]

[3, 4, 9, 10, 27, 28, 31–35, 39–43, 45, 49–58, 60, 61, 65–67, 69, 71]

[29, 30, 36, 37, 47, 50, 59–61, 67–69]

[46, 55, 60, 61]

Impact of clinical pharmacy serviceson appropriateness of prescription

The objective of 16 systematic reviews was to assess the impact of pharmacists on improving medication appropri- ateness [53–68]. Seven of these reviews [56–60, 63, 67] focused on elderly patients and their results were incon- clusive. All but one [57] consisted of a medication review service, and in one review [60] the pharmacist had pre- scription autonomy. Another review, evaluating pharma- cists' interventions on the transition of elderly patients between healthcare settings, reported positive resultsnamely: improvement of prescription appropriateness, successful documentation rates, reduction of omitted medications and a decrease in discrepancy-related adverse drug events [59].

Among the causes of variability in the results across primary studies is the lack of agreement of the definition ofpolypharmacy [63]. The use of different process indicators such as the medication appropriateness index (MAI), the Beer's criteria, or ad hoc-created indicators was also re- ported as a major cause of heterogeneity across studies [58,60]. Even when the rate of inappropriate prescriptions was reduced, no effect was observed in the patients' clinical outcomes such as morbidity, hospitalizations, mortality or healthcare costs [56, 57].

Most of the remaining nine reviews that were not fo- cused on elderly patients showed positive results with re- gards to improving medication appropriateness [54, 55, 61, 62, 65, 68]. Services such as medication review, medica- tion follow-up, patient education and prescribing new medications showed a positive impact on optimizing an- timicrobial prescriptions [65, 68], improving medication use in children [54], enhancing patient safety [62], reduc- ing the number of prescribed medications [61], and im- proving prescribing practices, patient satisfaction and cost avoidance [55]. However, a pharmacist-led medication review was not effective in reducing hospital admissions when clinical outcomes were considered [64]. Even when the medication review was complemented with a follow-upperiod, the results did not demonstrate a consistent im- provement of patients' quality of life or satisfaction nor didit reduce adverse drug reactions or drug procurement costs.These negative findings were attributed to an underlying different research design of the studies included [66].

Other impacts of clinical pharmacy services

Five systematic reviews could not be grouped into thepreviously categories because they described very heteroge- neous outcomes. Stemer et al. [71] assessed the impact of therapeutic drug monitoring and patient education on the management of solid organ transplant recipients and found positive perceptions of patients and healthcare profession- als and high physicians' acceptance rates of pharmacist's recommendations. Chisholm-Burns et al. [10] assessed the integration of a pharmacist within a multidisciplinary team and found favorable results in effectiveness and safety;however, they also found less favorable results in human- istic outcomes, particularly quality of life. Ellit et al. [69] evaluated the pharmacist's role in continuity of patient careand also found positive results for economic, clinical and humanistic outcomes. However, the authors criticized the exclusion criteria used in 19 of the 21 included studies, andthese criteria may have biased their results. Kaboli et al. [4]focused on pharmacists' care to inpatients and found im- provements in care in the reduction of the rate of adverse drug events, medication errors and lengths of hospital stay,even though the authors recognized several limitations to their work. Naik Panvelkar et al. [70] showed high levels ofpatient satisfaction with any type of community pharmacy services, but they referred to the lack of consistent instru- ments to measure this humanistic outcome.

Discussion

The present overview of systematic reviews was purpose- fully conducted broad in scope in order to identify common elements across substantially different clinical pharmacy services. An in-depth analysis of 49 systematic reviews revealed that clinical pharmacy services that focused on specific medical conditions such as hypertension or dia- betes mellitus showed a positive impact on outcomes, the common element being the measurement of unequivocal and tangible outcomes. However, interventions that tar-geted medication adherence or prescription appropriatenessproduced inconsistent results. Due to the small number of systematic reviews addressing hyperlipidemia, warfarin therapy management by pharmacists and smoking cessa- tion programs, we could not draw a conclusion of the im- pact of clinical pharmacy services on these conditions.

After applying the R-AMSTAR to the systematic re- views, we identified that most were insufficiently reported, and many did not employ methodological procedures that are critical to reduce the risk of bias. For example, 30reviews included only studies published in English, which does not account for potential language or publication bias,and study selection and data extraction were not performedby two independent reviewers in 17 other reviews. In ad- dition, for 33 % of the systematic reviews the authors did not assess nor documented the methodological quality of the primary studies included. These findings are in line with those reported in a study that assessed the quality of systematic reviews and meta-analysis on pharmacist health interventions which concluded that the quality of publishedreviews varied from moderate to poor [13]. Additionally, some reviews have only reported the primary studies' re- sults individually without synthesizing the findings, as opposed to what the PRISMA statement advocates: ''au- thors should give a brief and

balanced summary of the nature and findings of the review'' [22]. Although the R-AMSTAR was originally created with a scoring system, we preferred not to use it similarly to what other authors have done [72]. Scoring systems have been criticized for their excessive rigidity in favor of more versatile systemsas it happens with the Cochrane's ''risk of bias'' instrument[21].

Meta-analyses were only performed in 14 of the 49 re- views due to the heterogeneity of interventions described and the outcomes reported across the primary studies. Poor or inconsistent description of the pharmacists' interventions was one of the main limiting factors to the quality and reproducibility of the studies assessing the impact of clin- ical pharmacy services [13, 16, 73, 74]. Therefore, gener- ating a definitive list of services from the available evidenceis not an easy task.

Among studies describing interventions that targeted medication adherence and which were shown to produce inconclusive results, several factors might have contributedto the heterogeneity of the findings, including the wide variability of methods used to assess medication adherence,such as: self-report tools, pill counts, refill of prescriptions,electronic medication monitors, i.e., MEMS, or medication diaries. Adherence estimates when measured by different methods varied across studies [75–78]. One study con-cluded that pill-count was a superior method of medicationadherence assessment compared to 24-h recall and refill history in both clinical practice and long-term medication studies [10]. Another study, however, drew attention to the fact that a summary measure combining several measures was more strongly related to a clinical response [78]. Pa- tient self-reported adherence and prescription refill records were found to be poorly correlated [76] and patient self- report appeared to overestimate adherence [46, 75, 77]. Other contributing factors to the variety of results could be the selection of patients with different adherence rates at baseline [79, 80] and different cutoff points to classify adherence behavior [46].

Conflicting evidence was also found across systematic re-views that examined the impact of pharmacist interventions onthe quality of prescribing. Similarly to the adherence findings, the multitude of instruments available to assess suboptimal prescribing may be the underlying reason for these discrepan-cies. Some authors reported different ability of different tools, such as the Medication Appropriateness Index (MAI), Beers' criteria 2003, the Improved Prescribing in the Elderly Tool (IPET) and Health Plan Employer Data and Information Set (HEDIS), to assess changes in medication appropriateness [81, 82]. Multidimensional approaches using different tools simul-taneously will likely be necessary to robustly assess the qualityof prescribing [82]. Another important aspect is that the authorsused endpoints such as hospitalization, mortality or outpatientvisits as effectiveness indicators, but these endpoints require longer follow-up periods to show a potential effect. Thus, in-termediate or surrogate outcomes such as level of disease control could be used as proxy indicators of pharmacists' ser-vice effectiveness to appropriately measure an intervention's short-term effect [12].

As practical implications of our study, we highlight the need to better standardize the interventions performed as part of clinical pharmacy services, especially in services involving complex interventions which present a great number of components and therefore more likelihood of variability. This will require a close collaboration between researchers and practitioners, and also more international collaboration among pharmacy practice researchers. Am- biguous terminologies should be eliminated, not only by creating glossaries [83], but also through the achievement of international agreements on the definition and the compo- nents of each clinical pharmacy service [84]. Additionally, journal editors should be very rigorous with regards to the description of the interventions performed and the outcomesmeasured in articles accepted for publication.

The main limitation of our study is the specific time frame used (2000–2010). However, we believe that analyzing the first decade of the 2000s would ensure that the included studies reflect a higher position in the learning curve of clinical pharmacy services development. Only Pubmed was used to search the studies included since this is one of the most comprehensive scientific databases [85] and the overview method allowed for the collection ofsystematic reviews whose primary studies were in turnretrieved from several

other databases.

Conclusions

In conclusion, clinical pharmacy services seem to be more successful when they target specific medical conditions, such as diabetes mellitus or hypertension, and when using objective parameters to assess patient health status, such asblood pressure or glycosylated hemoglobin. The results areinconclusive for the pharmacists' interventions that have a broader target and whose monitoring parameters are not clearly established or have an unstandardized assessment. Although clinical pharmacy services seem to improve patients' health, efforts should be done to prove the added value of these services based on evidence-based practice standards and an intensive analysis of components.

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Conflicts of interest None of the authors has any conflicts of in- terest to disclose that could affect the study results.

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