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REVIEW ARTICLE

Clinical Pharmacy Services in Older Inpatients: An Evidence-Based Review

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Abstract

Background Hospital admissions in older adults are frequently drug related and avoidable. Clinical pharmacy interventions during hospital stay might reduce drug-related harm and reduce hospital visits. Moreover, several recent positive clinical pharmacy investigations incorporated a transitional care component to further improve medication use after discharge. It is currently unclear what the strength of evidence is and what the exact components should be of such clinical pharmacy interventions in older adults.

Objective An evidence-based review was performed to determine the status of the evidence and also to explore whether a clinical pharmacy intervention incorporating transitional care was associated with reduced hospital visits after discharge.

Methods Prospective controlled investigations were included if they contained a clinical pharmacy intervention that was initiated before discharge in older inpatients. Relevant quasi-experimental and randomized controlled trials were searched in MEDLINE. First, an evidence-based review was performed, including a description of the study design, characteristics, and outcomes. Major components of successful clinical pharmacy interventions were described and potential implications for clinical practice and research were determined. Second, the Fisher's exact test was used to explore the association between transitional care and reduced hospital visits. Third, based on these findings, a medication review proposal was developed to improve medication use in older adults.

Results Thirty-five studies were included, with 26 randomized controlled trials. Median patient follow-up after discharge was 90 days (interquartile range 37–180 days) and investigators enrolled a median of 210 (interquartile range 110–498) study participants. On average, patients were aged 77.5 years (interquartile range 73–82.2 years). Nine randomized controlled trials had sufficient power to detect a reduction in hospital visits after discharge; this was reduced in three randomized controlled trials. Post-discharge follow-up was not associated with reduced post-discharge hospital visits (20 randomized controlled trials: follow-up vs. no follow-up: 6/11 vs. 1/9, $p = 0.070$). There was a significant reduction in post-discharge hospital visits in patients aged 75 years or older (12 randomized controlled trials: follow-up vs. no follow-up: 5/7 vs. 0/5, $p = 0.028$). A medication review proposal was developed, consisting of six steps.

Conclusions Three powered randomized controlled trials were identified that found a significant association between a pharmacist-led intervention in older adults and a reduction in post-discharge hospital visits. In clinical practice, an intervention consisting of medication reconciliation, review, counseling, and post-discharge follow-up should be provided to such high-risk inpatients. Regarding research priorities, large, multi-center randomized controlled trials should be performed to generate more evidence on the impact of clinical pharmacy interventions on the patient trajectory and economic outcomes.

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1 Introduction

Improvements in medicine have made a large impact on life expectancy, which has never been higher. This has resulted in a longevity revolution, with a global doubling of the number of older people expected by 2050 [1, 2]. As part of these continuous improvements in healthcare, increasing numbers of patients have been granted access to a plethora of therapies. Not all therapies however are able to positively affect patient outcome. In particular, older adults might incur

Key Points

Older inpatients are regularly (re)admitted to the hospital and medication harm might play an important role herein.

Clinical pharmacists can reduce medication harm, improve overall medication use, and reduce post-discharge hospital visits in older inpatients, in particular when providing their services in a multi-faceted and multi-disciplinary manner.

Post-discharge follow-up is important to extend the clinical pharmacy intervention beyond the hospital stay, to further impact the patient's trajectory.

net harm by experiencing drug-related problems [3]. Drug-related problems can become an important cause of iatrogenic morbidity at a high age, underscoring the persistent importance of the old adage *'first do no harm'* [4]. This burden of this drug-related problem is particularly high in older adults admitted to the hospital [5].

Pharmacists can play an important role in improving outcomes such as hospital admissions in very old adults, mainly through a process of identifying, preventing, and resolving drug-related problems [6, 7]. Patient-directed care provided by pharmacists has been introduced increasingly during the past decades [5, 8–12]. Importantly, several seminal investigations pointed towards improved post-discharge outcomes when the intervention contained a transitional component (e.g., telephone follow-up) [13, 14].

It is difficult to perform a meta-analysis on such investigations in older inpatients, given the broad definition of what constitutes a medical inpatient, but also because of different follow-up times, different definitions used for outcome measures, the actual content of the clinical pharmacy intervention, and whether the meta-analyzed outcome measure was initially a sufficiently powered primary outcome. Several meta-analyses have indeed concluded that it is difficult to draw robust conclusions given the high level of heterogeneity and the overall low quality of evidence [10, 11, 15–18]. As a result, equipoise remains about whether clinical pharmacy services in general can reduce overall healthcare use in older inpatients [14, 19]. Subsequently, there is a need for pragmatic information on *how* to best provide clinical pharmacy services in older inpatients based on the current body of evidence.

The primary aim of this research was hence to perform an evidence-based review on the content of successful clinical pharmacy services in older inpatients and the impact on hospital visits. In addition, we also specifically aimed to further explore the potential value of providing post-discharge follow-up to reduce hospital visits. Finally, based on the review results, the goal was to provide a practical medication review proposal for clinical pharmacists dealing with older inpatients.

2 Methods

2.1 Data Source

An evidence-based review of the literature was performed. The data search was based on search terms previously reported by Kaboli et al. [20]. Studies were retrieved from the bibliographic database MEDLINE using the following search terms: *clinical pharmacy, clinical pharmacists, hospital pharmacists, pharmacy services, pharmaceutical care, outcome, healthcare utilization, hospital utilization, morbidity, readmissions, and hospital visits*. Searches were limited to English articles published from inception to July 2019. Snowball sampling was used to identify additional publications for review.

2.2 Study Selection

One reviewer selected the publications (LVDL). In case of any doubt, consensus was reached with two other researchers (JH and KW) about whether to include the publication for further review.

First, relevance to the research questions was evaluated based on screening the title and abstract. Second, articles were included in the review if the following criteria were met: a prospective controlled study design, with a clinical pharmacy intervention component, that was initiated before discharge. Both randomized controlled trials (RCTs) and quasi-experimental (QE) studies were eligible for inclusion. Only primary study results were included for review, and the average age of study participants had to be at least 65 years, by design or owing to the age of enrolled study participants.

Studies in which children were enrolled or patients were exclusively admitted to intensive care units or surgical wards were excluded. Investigations pertaining to a specific drug treatment (e.g., only warfarin or antimicrobial therapies) were excluded as well.

2.3 Data Extraction and Synthesis

A data collection form was used to extract the following information from the included studies: author, year, country and region, study design (RCT or QE), and study population (sample size and age). Regarding study methods, the following data were retrieved: number of study arms, mono- or multi-centric design, and whether a primary outcome was defined and a prior sample size estimation was performed

for any of the reported outcomes. We also evaluated whether post-discharge hospital visits had been included as one of the study outcomes and whether the study intervention contained a transitional intervention component (i.e., post-discharge follow-up, however provided).

Regarding the study results, we obtained mortality rates and documented whether the study had reached a statistically significant result for its primary outcome. We also documented whether a reduction in admissions, all-cause readmissions, or emergency department visits had been reported. In addition, information on cost benefits or balanced cost savings were retrieved. Balanced cost savings were defined as the costs of hospital care minus the costs of the clinical pharmacy intervention.

We also determined whether hospital visits were reduced after discharge. This was defined as a statistically significant reduction in readmissions and/or emergency department visits and was documented for each study, if applicable. In addition, to provide readers with baseline event rates, data were extracted for these three outcomes for control and intervention groups at 30, 60, 90, 180, and 365 days after discharge, if available. No formal quality assessment of the included studies was performed.

2.4 Data Analysis

Normality of continuous variables was ascertained by visual inspection of the histograms and QQ-plots. Parametric data were shown as mean (± standard deviation) and non-parametric continuous data as median (interquartile range [IQR] = Q1−Q3), as appropriate. Counts were summarized as *n* (%).

In general, smaller studies have been associated with an overestimation of the effect size and are more heterogeneous than larger studies [21]. This might render it more difficult to interpret the strength of evidence of such investigations. To evaluate whether study size changed over the years, a Kruskal–Wallis, one-way analysis of variance was used.

To explore the association of a transitional care component with post-discharge hospital visits, the Fisher's exact test was used. Only data from RCTs were used for this exploratory analysis. First, the impact of a transitional component on post-discharge hospital visits was estimated in all RCTs. Second, the exploratory analysis was repeated in RCTs in which the average age of the study population was at least 75 years.

Results were considered to be statistically significant if the two-tailed *p*-value was < 0.05. Statistical analysis was performed with IBM SPSS Statistics for Windows version 20.0 (IBM Corporation, Armonk, NY, USA).

2.5 Medication Review Proposal

Data from positive RCTs were collected and compiled into a preliminary proposal. Additional information was then retrieved from recent reviews on improving medication use in older adults and was added to the proposal. The following reviews and guidance documents were selected by the authors: detailed information on deprescribing as provided by Scott et al.; step-based information from the Dutch Structured Tool to Reduce Inappropriate Prescribing (STRIP); the comprehensive approach of the Northern Irish Integrated Medicines Management (IMM) model, and the American Geriatrics Society Guiding Principles on multi-morbidity in older adults, all of which were further supplemented by our own experiences [22–28]. Importantly, the American Geriatrics Society guidance document strongly promotes determining patient concerns and defining therapy goals before moving forward to the following steps in the algorithm. Consensus was reached among all authors concerning the final proposal.

2.6 Ongoing Investigations

The online databases MEDLINE and ClinicalTrials.gov were searched using the same search terms as detailed above to identify ongoing relevant investigations. The following data were extracted: authors, country (region), setting, design, participants, inclusion criteria, primary outcome, estimated sample size, usual care, intervention components, expected duration, and recruitment status.

3 Results

3.1 Literature Overview

The literature search resulted in 35 publications ($n = 13{,}003$ participants), with nine studies having a QE design ($n = 3845$) and 26 an RCT design ($n = 9158$). A summary of the main trial components is provided in Table 1.

The sample sizes did not differ significantly over the years (1994–2019) ($p = 0.772$). Most studies were monocentric ($n = 27$) and were performed in Europe ($n = 20$). Median patient follow-up after discharge was 90 days (IQR 37–180 days) and study investigators enrolled a median of 210 (IQR 110–498) study participants. Across all studies, patients were aged on average 77.5 years (IQR 73–82.2 years); 21 studies enrolled participants with an average age of 75 years or older.

Mortality was high in both control and intervention groups in this review. Overall, studies reported similar mortality rates in control and intervention groups (median mortality rate of 16% [IQR 8.6–2.7] and 16% [IQR 8.8–2.2],

Table 1 Literature search results

Year	Author	Continent	Mono (0) or multicentric (1)	QE (0) or RCT (1)	Number of study arms	Transitional intervention component	Post-discharge follow-up (days)	A well-defined primary outcome	HU as part of the primary outcome	Any information on HU provided	Sample estimation	Health economics evaluation	*N*	Age, years	Primary outcome reached	Fewer readmissions	Fewer ED visits	Fewer all-cause readmissions	Reduced post-discharge HU	Balanced cost savings
1994	Lipton [47]	NA	0	1	2	1	90	1	0	1	1	0	706	74.6	1	0	0	0	0	
2001	Nazareth [48]	EU	1	1	2	1	180	1	1	1	1	0	362	84	0	0	0	0	0	
2002	Al-Rashed [49]	EU	0	0	2	0	90	0	0	1	0	0	89	80.7		1	1	1	1	
2003	Naunton [50]	AU	0	1	2	1	90	1	1	1	0	0	121	75.5	1	1	0	1	1	
2004	Crotty [51]	AU	0	1	2	1	56	1	0	1	1	0	110	82.7	1	1	1	1	1	
2006	Lopez Cabezas [29]	EU	0	1	2	1	365	1	1	1	1	1	134	75.7	1	1	1	1	1	1
2007	Spinewine [52]	EU	0	1	2	0	365	1	0	1	1	0	186	82.2	1	0	0	0	0	
2007	Triller [53]	NA	1	1	2	1	180	1	1	1	1	0	154	79.7	0	0	0	0	0	
2007	Scullin [24]	EU	1	1	2	0	365	1	0	1	0	0	762	70	1	1	0	0	1	
2009	Gillespie [14]	EU	0	1	2	1	365	1	1	1	1	1	368	86.8	1	0	1	0	1	1
2009	Makowsky [54]	NA	1	0	2	0	180	1	0	1	1	0	452	74	1	1	0	0	1	
2009	Koehler [55]	NA	0	1	2	1	60	1	1	1	0	0	41	78.2	0	1	0	0	1	
2010	Eggink [56]	EU	0	1	2	0		1	0	0	1	0	85	73	1					
2010	Lisby [57]	EU	0	1	2	0	90	1	0	1	1	0	99	79.2	0	0	0	0	0	
2011	Bladh [58]	EU	0	1	2	0	180	1	0	0	1	0	345	81.5	0					
2011	Hellstrom [33]	EU	0	0	2	0	90	1	0	1	1	0	210	82.4	1	1	0	0	1	
2012	Elliott [59]	AU	1	0	2	0	28	1	0	0	1	0	428	84	1					
2012	Scullin [60]	EU	1	0	2	0	365	0	0	1	0	1	833	70		0	0	0	0	1
2012	Barker [61]	AU	0	1	2	1	180	1	1	1	0	0	120	72.5	0	0	0	0	0	
2013	Marusic [62]	EU	0	1	2	0	30	1	1	1	1	0	120	74	0	0	0	0	0	
2014	Eisenhower [63]	NA	0	0	2	0	30	1	1	1	0	1	25	73		0	0	0	0	

Table 1 (continued)

Year	Author	Continent	Mono (0) or multicentric (1)	QE (0) or RCT (1)	Number of study arms	Transitional intervention component	Post-discharge follow-up (days)	A well-defined primary outcome	HU as part of the primary outcome	Any information on HU provided	Sample estimation	Health economics evaluation	*N*	Age, years	Primary outcome reached	Fewer readmissions	Fewer ED visits	Fewer all-cause readmissions	Reduced post-discharge HU	Balanced cost savings
2015	Basger [64]	AU	0	1	2	0	90	1	0	0	1	0	216	81.5	0					
2016	Khalil [65]	AU	0	1	2	0		1	0	0	1	0	110	70	1					
2016	O'Sullivan [66]	EU	0	1	2	0	7	1	0	0	1	0	737	77.5	1					
2016	Tong [67]	AU	0	1	2	0	2	1	0	0	1	0	881	73.3	1					
2016	Roblek [68]	EU	0	1	2	0	180	1	0	1	1	0	51	79	1	0	0	0	0	
2017	Van der Linden [28]	EU	0	0	2	0	90	1	0	1	1	0	172	84.5	1	0	1	0	1	
2017	Cossette [69]	NA	0	1	2	0	30	1	0	1	1	0	321	81	1	0	0	0	0	
2017	Gustafsson [70]	EU	1	1	2	0	180	1	1	1	1	0	460	83.1	0	0	0	0	0	
2017	Nielsen [71]	EU	0	1	2	0	365	1	0	1	1	0	498	73	0	0	0	0	0	
2018	Van der Linden [27]	EU	0	0	2	0		1	0	0	1	0	59	83	1	0	0	0	0	
2018	Bonetti [72]	SA	0	1	2	1	30	1	1	1	1	0	104	65	0	0	0	0	0	
2018	Rottman-Sagebiel [73]	NA	0	0	2	1	30	0	0	1	0	0	1577	75.1	1	1	0	0	1	
2018	Ravn-Nielsen [13]	EU	1	1	3	1	180	1	1	1	1	1	1467	72	1	1	1	1	1	1
2019	Graabaek [74]	EU	0	1	3	0	180	1	1	1	1	0	600	74	0	0	0	0	0	

ED emergency department, *EU* European Union, *HU* hospital use, defined as ED visits and/or hospital admissions, *NA* North America, *QE* quasi-experimental, *RCT* randomized controlled trial, *SA* South America

respectively). Approximately half of all patients were readmitted to the hospital at 1 year after discharge (control 53.2% [IQR 48.6–57.9]; intervention 49.4% [IQR 34.9–58.8]). A summary of hospital visits and mortality rates is provided in Table 2.

Three studies did not have a clearly defined primary outcome. In 20 of the 32 remaining studies, a statistically significant result for the primary outcome measure was reached (QE 6; RCT 14). Hospital visits after discharge were evaluated in 27 investigations (QE 7; RCT 20), and in 14 as part of the primary outcome (QE 2; RCT 12). A positive effect of a clinical pharmacy intervention on post-discharge hospital visits was reported in 12 individual investigations (QE 5; RCT 7).

Out of 26 RCTs, 22 had sufficient power to detect an impact of the clinical pharmacy intervention on the reported primary outcome. In nine of these 22 studies, the primary endpoint also contained a clinical outcome pertaining to hospital visits after discharge, which was reduced in the RCTs of Ravn-Nielsen et al., Gillespie et al., and López Cabezas et al. [13, 14, 29]. The same positive RCTs also showed balanced cost savings [14, 29, 30].

Post-discharge follow-up was not associated with reduced post-discharge hospital visits in a total of 20 RCTs (follow-up vs. no follow-up: 6/11 vs. 1/9, $p = 0.070$). However, there was a reduction in post-discharge hospital visits when selecting the 12 RCTs, where the average study participants' age was at least 75 years (follow-up vs. no follow-up: 5/7 vs. 0/5, $p = 0.028$).

3.2 Medication Review Proposal

Commonly, clinical pharmacy interventions in complex older inpatients followed a multi-faceted approach, consisting of multiple single components [24]. The Lund IMM model deserves more attention in this regard [24, 31–34]. It entails the systematic provision of pharmaceutical care during hospital stay and was explicitly provided in the investigation by Gillespie et al. and by default, also in the investigations of Ravn-Nielsen et al. and López Cabezas et al. [13, 14, 29]. According to the Lund IMM model, pharmacists are expected to promote a correct medication reconciliation and to perform a medication review using the best possible medication list. A motivational interview technique can be applied to elicit desired changes in patients (and caretakers) to further strengthen the effect of the clinical pharmacy intervention regarding appropriate medication use [13, 32]. Importantly, to increase the persistence of the intervention after hospital discharge, a post-discharge follow-up can be provided. Such a transitional component was shown by Ravn-Nielsen et al. to be essential in reducing the number of readmissions, when compared to a clinical pharmacy intervention without follow-up after discharge [13]. Clinical pharmacists can use a simple phone call to evaluate the

Table 2 Mortality and hospital use after discharge

	Number of studies	Control (%, event rate)			Intervention (%, event rate)		
		Median	Q1	Q3	Median	Q1	Q3
Total mortality	13	16.0	8.6	27.0	16.0	8.8	22.0
30d readmissions	8	20.0	16.8	22.1	15.0	12.7	15.7
30d ED visits	3	9.4	6.8	18.5	5.9	4.6	11.7
30d hospital use	2	35.9	34.9	37.0	17.5	13.8	21.3
60d readmissions	1	25.0			11.4		
60d ED visits	0						
60d hospital use	2	36.2	32.8	39.5	20.7	16.1	25.4
90d readmissions	3	45.0	42.1	45.3	36.2	32.1	37.6
90d ED visits	1	39.2			28.7		
90d hospital use	1	39.2			34.5		
180d readmissions	7	42.2	40.7	52.6	39.7	32.5	51.6
180d ED visits	1	51.3			48.8		
180d hospital use	0						
365d readmissions	6	53.2	48.6	57.9	49.4	34.9	58.8
365d ED visits	0						
365d hospital use	1	49.3			40.8		

Hospital use was defined as the sum of the ED visits and readmissions

d day, *ED* emergency department, *Q* quartile

drug regimen and resolve any outstanding issues or confusion regarding the patient's therapy.

This holistic Lund IMM approach was used as a template upon which the medication review proposal was based. The medication review proposal in older adults consists of the following six steps: ascertaining patient concerns and defining therapy goals, medication (and medical history) reconciliation, actual medication review, patient education, promoting safe transition, and post-discharge follow-up. The detailed proposal is summarized in Table 3.

3.3 Ongoing Investigations

Five RCTs were identified, all of which take place in Europe. In total, 6840 study participants will be randomized. Relevant data are summarized in Table 4.

4 Discussion

In our evidence-based review, we found that multiple investigations established a role for clinical pharmacists in improving medication use and reducing hospital visits after discharge. The average study population of the included studies largely corresponded with a complex and multi-morbid patient profile, who regularly experience a high burden of amenable drug-related problems [35–37]. Importantly, the number of sufficiently powered investigations, which were dedicated to improving *clinical outcome* in older inpatients, was limited. Our evidence-based review also showed that setting up an RCT is feasible, in complex older inpatients even when aiming for an improvement in clinical outcome. Clinical outcome in this specific setting was mostly defined as a reduction in post-discharge hospital visits. The clinical relevance of fewer hospital contacts is largely related to its association with the patient's clinical condition (e.g., management of heart failure) and has also been used as an indirect metric of the quality of care [38]. We found a positive association between providing post-discharge follow-up and a reduction in hospital visits in RCTs that enrolled participants aged on average 75 years or older.

Only the three following studies, out of 35 investigations, concerned RCTs that had sufficient power to detect a statistically significant difference concerning their clinical endpoints. First, the work of Gillespie et al. should be highlighted as their RCT ($n = 386$) was one of the first that was powered to detect the impact of a clinical pharmacy intervention in octogenarian Swedish inpatients [14]. The authors detected a moderate reduction of 16% in hospital visits during a 12-month follow-up using a Poisson regression analysis (relative risk 0.84, 95% confidence interval 0.72–0.99), driven in part by the reduction in emergency department visits and drug-related readmissions. Second, their Danish counterparts Ravn-Nielsen et al. showed afterwards that a multi-faceted intervention during a hospital stay significantly reduced the same composite primary endpoint at 180 days after discharge in a Danish patient sample (usual care vs. extended intervention 48.8% vs. 39.7%; hazard ratio 0.75, 95% confidence interval 0.62–0.90), which corresponded to a number needed to treat of 12 [13]. Theirs was the largest RCT to date ($n = 1467$). Third, in their RCT ($n = 134$), Lopez Cabezas et al. found that a comparable intervention, aiming to improve medication use during hospital stay while also providing active telephone follow-up after hospital discharge, was significantly associated with fewer readmissions (hazard ratio 0.56, 95% confidence interval 0.32–0.97) [29]. These positive RCTs convincingly showed that outcome can indeed be improved and furthermore that the costs of the clinical pharmacy interventions were at least balanced.

Taken together, these reports add weight to the hypothesis that a ward-based comprehensive intervention improves outcome when performed in acutely admitted older adults, with post-discharge follow-up provided by phone. A medication review algorithm was subsequently derived and we hypothesize that using such an approach would be of value to healthcare professionals when providing standardized comprehensive medication reviews.

We believe the findings of our evidence-based review are valid because of the broad inclusion criteria, the explicit documentation of trial design, and the additional analysis regarding transitional care. Importantly, this was however not a systematic review and the quality of the included investigations was not ascertained explicitly, which is a limitation. We cannot exclude that potentially eligible investigations might have been missed. This however fell beyond the scope of performing an evidence-based review. Furthermore, owing to the heterogeneity in designs, settings, interventions, and outcomes, no meta-analysis was performed, hence the preclusion of broad statements on the impact of clinical pharmacy services on clinical outcomes. Some additional considerations for clinical practice and research are proposed below.

4.1 Implications for Clinical Practice

As described in a majority of the included investigations in this review, clinical pharmacists regularly worked in a team setting. Pharmacists should hence proactively participate in ward-based services in older inpatients as members of a multi-disciplinary team [5, 39]. In the case of high-risk patient groups such as geriatric inpatients, pharmacists can perform structured medication reviews and provide recommendations to the prescriber, who remains in charge of coordinating the clinical assessment and therapy plan as was the case in the three positive RCTs. Importantly, working outside of a multi-disciplinary team might lead to failure

Table 3 Medication review proposal: six steps

Medication review steps	Content	Supporting information
1. Ascertaining patient concerns and defining therapy goals	In geriatric patients, a **comprehensive geriatric assessment** should be performed systematically [5, 75]. This concerns a multidisciplinary process consisting of assessing and managing the needs in mostly older inpatients	Patients should be actively asked about their concerns and preferences regarding their medication therapies
2. Medication (and medical history) reconciliation	This should consist of more than merely **compiling drug lists**. More information should for example be collected on previous (potential) adverse drug events, patient preferences, and therapy compliance. It might also be useful to already screen for common drug-related symptoms and signs during reconciliation [45]	To retrieve the best possible medication list, it is suggested to use two sources of information at least. Furthermore, motivational interview techniques might be preferred to evaluate patient motivation and compliance [13]
3. Actual medication review	This step can be surmised as the process of **only** prescribing those **indicated drug therapies** that have an important benefit for the patients in terms of the desired health outcomes	Healthcare providers should take into account the overall therapy goals and whether they are still feasible, the estimated life expectancy, and patient preferences but also the comorbidity burden [25]
	Undertreatment has been associated with adverse outcomes [76]. Polypharmacy might lead to undertreatment. When reviewing drug therapies in older adults, healthcare providers should refrain from solely focusing on deprescribing. It is equally important to initiate therapies that can still be of benefit to patients (e.g., angiotensin-converting enzyme inhibitor in systolic HF; antihypertensive agent in selected older patients). We propose to identify and manage under-treatment first	Healthcare providers should be aware that not all preventive therapies work equally fast. The time to benefit should be ascertained whenever new drug therapies are initiated [77] When prescribing drugs that are commonly used for a specific duration, it is important to explicitly define the end of the prescription or to schedule a visit for further follow-up
	Unwanted polypharmacy is prevalent and should be evaluated systematically, i.e., upon admission to the hospital, during hospital stay, and prior to discharge	Several approaches can be followed: implicit and/or explicit tools can be used and healthcare providers might be supported by the CDSS. We actively promote the framework as promoted by Scott et al. in their 2015 review on deprescribing, which has been built upon several major questions that healthcare providers have to run by their patients [22]: (1) Is there a valid indication? (e.g., ivabradine is not useful in systolic HF with AF) (2) Part of a prescribing cascade? (e.g., proton-pump inhibitor for dyspepsia caused by a non-steroidal anti-inflammatory drug) (3) Actual or potential harm outweighs any potential benefit? (e.g., aspirin in stable anticoagulated AF patients is not needed) (4) Disease and/or symptom control drug is ineffective or symptoms have completely resolved? (e.g., opioid therapies, hypnotics, antipsychotics) (5) Preventive drug is unlikely to confer any patient-important benefit over the patient's remaining lifespan? (e.g., statin initiation in severe HF) (6) Drugs are imposing an unacceptable treatment burden? (e.g., triple therapy in conservatively treated patients with ACS, also experiencing AF and a high bleeding risk)
	This step should end in a **clearly defined pharmaceutical plan**	The complexity of the medication regimen should be reduced as much as possible [78]
4. Patient education, counseling	**Patient/caregiver/family counseling**, as part of extended inpatient interventions, has been shown to be an important add-on to step 3, mostly to ensure that the proposed therapy changes can effectively be implemented after discharge	Motivational interview techniques might be preferred to promote medication adherence

Table 3 (continued)

Medication review steps	Content	Supporting information
5. Promoting safe transition	A **discharge summary**, detailing all drug therapies and (the rationale of) drug changes, should be provided direct to both the general practitioner and the community pharmacist. Additionally, post-discharge visits should be planned pre-discharge and communicated clearly	If possible, discharge information should be shared directly with primary care healthcare providers electronically
6. Post-discharge follow-up	Patients should receive **personalized information and guidance** after discharge to ensure correct medication use	After hospital discharge, patients are confronted with the consequences of the many therapy alterations. Patients are furthermore at increased risk of drug-related harm, owing to the transition of care itself, but also as the medical condition (which was the primary cause of the index acute admission) might not be fully resolved yet. Furthermore, patients might experience (prolonged) medical deconditioning, which might further increase their susceptibility to adverse drug events

ACS acute coronary syndrome, *AF* atrial fibrillation, *CDSS* clinical decision support system, *HF* heart failure

of a pharmacist approach in medical inpatients, as recently discussed by Petrovic et al. [5]. Moreover, the integration of multiple healthcare providers, including pharmacists but also physical therapists, nurses, and psychologists, with complementary skills, seems warranted to fully impact outcome of the older inpatient [40].

Hospital-wide implementation of clinical pharmacy services, while potentially useful, is not common in Europe. This is currently not feasible in many hospitals because of insufficient staffing or funding, but also because of other priorities of the hospital pharmacy management and hospital boards [41]. Hence, it may then be reasonable to target a high-risk population, such as older adults acutely admitted to the hospital, who are more likely to derive a meaningful and clinical benefit from a clinical pharmacy service. Most commonly, this will pertain to adults, aged at least 65 years, who have been acutely admitted to an internal medicine or geriatric care ward, as was the case in the majority of studies included in this review.

In larger hospitals, it might be easier to find the necessary resources. In the case of limited resources, it could be efficient to divert scarce means to the period directly prior to discharge to promote appropriate medication use in the high-risk period after hospital discharge [13, 17].

4.2 Implications for Research

Several pertinent questions remain regarding the clinical benefits of clinical pharmacy services in daily clinical practice. Most investigations in our review were monocentric, were not powered for clinical outcomes, did not ascertain patient-reported quality of life, and did not enroll the oldest old. It is furthermore unclear how study findings should be implemented into clinical practice as academic investigations might be limited in their external validity, e.g., regarding staff allocation and time investment per patient [42]. For example, in Belgium, there is one hospital pharmacist available per 150 beds, with additional governmental funding to support clinical pharmacy services (0.25 full-time equivalent per 250 beds) [43]. In contrast, the clinical pharmacy intervention as described by Ravn-Nielsen et al. required on average 2 h per patient [13]. Their intervention was however proven to be cost effective; a significant reduction in readmissions was not associated with an increase in cost. In contrast, a trend toward a total cost reduction of €1657 ($p = 0.1083$) was found per patient in their cost-consequence analysis in favor of the extended clinical pharmacy intervention [30].

In the reviewed studies, patient's family members or caretakers were rarely engaged, which can be considered to be a missed opportunity. In a 2017 meta-analysis, Rodakowski et al. showed the importance of actively drawing upon their presence and influence in the care trajectory of

Table 4 Ongoing investigations

Title and ClinicalTrials.gov identifier	Country	Setting	Design	Study participants: inclusion criteria	Primary outcome	Sample size	Usual care	Intervention	Expected duration	Recruitment status
Optimising therapy to prevent avoidable hospital admissions in the multimorbid older people (OPERAM); NCT02986425	Belgium, Ireland, the Netherlands, Switzerland	Inpatient and outpatient setting	European multicenter, cluster randomized, controlled trial	People 70 years of age or older; multimorbidity and polypharmacy	Patients with confirmed drug-related admission during a 12-month follow-up	2000	Medication review by the prescribing physicians in accordance with usual care	Systematic drug review and pharmacotherapy optimization by a physician and a pharmacist using STRIP [23], including the STRIPA software	12 months	Ongoing
Impact of a Medication Review on Hospital Readmission (CONCREHOSP); NCT02734017	France	1 hospital	RCT	Age ≤ 18 or ≥ 65 years + hospitalized in the multi-disciplinary pediatric service or internal medicine ward + after ED department visit	Rate of readmission at 30 days post-discharge	1400	Not receiving medication review	(1) Medical and pharmaceutical admission medication reconciliation and treatment review, (2) medical and pharmaceutical medication reconciliation at discharge and treatment review, and (3) medication liaison service	30 days post-discharge	Unknown
Impact of Collaborative Pharmaceutical Care on Hospital Admission Drug Prescriptions for Patients 65 Years of Age and Older (MEDREV); NCT02598115	France	6 hospitals	Cluster-randomized study with a stepped-wedge design	Admitted as in-patient to one of the participating hospitals + available for 3 months of follow-up	Number of patients with at least one preventable medication error	630	No intervention: before collaborative pharmaceutical care. All clusters start in this arm for 15 days. Following the start of the study, 1 randomly chosen cluster will switch to the experimental arm every 15 days	Collaborative pharmaceutical care: medication reconciliation revision of drug prescriptions indicated on the admission drug prescription. In addition, recommendations are then discussed during a collaborative interview	90 days post-discharge	Completed

Table 4 (continued)

Title and ClinicalTrials.gov identifier	Country	Setting	Design	Study participants: inclusion criteria	Primary outcome	Sample size	Usual care	Intervention	Expected duration	Recruitment status
A New Interdisciplinary Collaboration Structure to Improve Medication Safety in the Elderly (IMMENSE); NCT02816086	Norway	2 acute internal medicine wards at the UNN + 1 geriatric internal medicine ward at UNN Tromsø + 1 general acute internal medicine ward at UNN Harstad.	RCT	Age ≥ 70 years + acutely admitted	Rate of 'acute readmissions and ED visits' 12 months after discharge	500	Standard care may include elements such as MedRec, medication review, and patient counseling performed by physicians or nurses during a hospital stay	(1) MedRec at admission, (2) medication review and monitoring during the hospital stay, (3) patient counseling designed to meet the needs of each individual patient, (4) MedRec at discharge together with an updated and structured medication list given to patients and submitted to primary care at discharge, and (5) a follow-up phone call to the patient's GP and nurses in home care service/nursing home to inform about and discuss current medication therapy and recommendations	12 months	Recruiting
Medication Reviews Bridging Healthcare: a cluster-randomised crossover trial (MEDBRIDGE); NCT02999412	Sweden	8 wards with a multidisciplinary team within 4 hospitals in 3 Swedish counties	Multicenter, three-treatment, replicated, cluster-randomized, crossover trial	Aged 65 years or older	Incidence of unplanned hospital visits during a 12-month follow-up period	2310	The control group will receive usual hospital care	Intervention 1: (1) A thorough medication reconciliation, including a patient/caretaker interview, (2) comprehensive medication review, and (3) before discharge, the clinical pharmacist performs another medication reconciliation Intervention 2: The same as Intervention 1 but with the following additions: (1) in the case of any monitoring needs or necessary subsequent actions to be taken after hospital discharge, the clinical pharmacist and the ward physician will send an electronic medication review referral to the patient's primary care physician upon discharge; (2) a first phone call to the patient or caretaker is made by the clinical pharmacist 2–7 days after the patient is discharged; and (3) s second phone call will be made 30 days after hospital discharge	12 months	Recruiting

ED emergency department, *GP* general practitioner, *MedRec* medication reconciliation, *RCT* randomized controlled trial, *STRIP* Systematic Tool to Reduce Inappropriate Prescribing, *UNN* University Hospital of North Norway

older inpatients after hospital discharge [44]. They found a 25% reduction in hospital readmissions at 90 days. In particular in very old inpatients, we propose to involve family members and caretakers to increase the impact of a clinical pharmacy intervention.

Five relevant ongoing RCTs have been identified. These investigations can be expected to shed more light on the impact of clinical pharmacy services in older inpatients. In particular, MEDBRIDGE and IMMENSE could be expected to provide robust information [32, 45]. Both studies will enroll exclusively older adults and apply a comprehensive clinical pharmacy intervention, which will include post-discharge follow-up. Importantly, both are also sufficiently powered to detect an impact on hospital visits after discharge.

In sum, more data should be collected on the impact of clinical pharmacy services on the older patient's trajectory after a hospital stay. Although several quasi-experimental study designs were retrieved in our literature search, the majority of results were still derived from RCTs. We propose that new investigations should maximally apply the RCT design and primarily aim to improve clinical outcome, including drug-related, disease-specific (e.g., heart failure-related hospitalizations), and all-cause readmissions. This proposal corresponds largely to the research priorities as proposed recently by an international consortium of experts [46].

5 Conclusions

A literature review was performed and 35 studies were identified. Three sufficiently powered RCTs found a significant association between a pharmacist-led intervention performed in older, acutely admitted medical inpatients and a reduction in post-discharge hospital visits. In clinical practice, a comprehensive pharmacist intervention consisting of medication reconciliation, review, counseling, and post-discharge follow-up should be provided to high-risk inpatients. Regarding research priorities, large multi-center RCTs should be performed to collect information on the impact of clinical pharmacy interventions on the patient trajectory and economic outcomes in very old inpatients.

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Compliance with Ethical Standards

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