SYSTEMATIC REVIEW

Evidence of the clinical effectiveness of cognitive pharmaceutical services for aged patients

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Abstract

Background: cognitive pharmaceutical services (CPSs) encompass a variety of pharmacists' interventions to optimise pharmacotherapy. The clinical effectiveness of CPSs for aged patients remains controversial.
Objective: to analyse and describe the evidence of the clinical effectiveness of CPSs in aged patients by means of performing a systematic review of systematic reviews.
Methods: using the recommended methodology by Cochrane, a search was undertaken for systematic reviews of the clinical effectiveness of CPSs in MEDLINE, EMBASE, DOAJ, SCIELO and COCHRANE LIBRARY. Reviews were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) instrument. Quality of the evidence in the reviews was ranked using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
Results: a total of 14 systematic reviews and one meta-analysis were analysed. The overall quality of the reviews was moderate. High and moderate strength of evidence was found for the positive effect of certain CPSs on reducing the number and improving the appropriateness of medicines. There was conflicting evidence of the effect on adherence. There was limited evidence of high and moderate strength on clinical outcomes. No positive evidence was found on mortality, hospitalisations, functional capacity and cognitive function. No systematic reviews reported the effect on the level of control of health problems.
Conclusions: certain types of CPSs reduce the number of medicines and improve the appropriateness of prescriptions. Longer follow-up periods and/or the use of surrogate clinical variables measuring the short-term impact are required to demonstrate the effect on clinical outcomes.

Keywords: *medication therapy management, pharmacists, systematic review, medication review, comparative effectiveness research, cognitive services, aged patients*

Introduction

The world population of persons aged 65 or over [1] is growing rapidly from 600 million in 2000 to an estimated 2000 million in 2050 [2–3]. The physiological changes, co-morbidity and polypharmacy of these patients need to be taken into account when determining pharmacotherapeutic goals [4–5]. People over 65 years have been shown to have a greater risk of presenting medicines related problems [6–9]. Recent studies have shown a high incidence of adverse drug reactions [10], adverse drug effects [11] and poorer control of health problems in this population [12], with a concomitant increase in health care and associated costs [13–14].

A concept, 'cognitive pharmaceutical services' (CPSs) has been used to encompass the variety of pharmacists'

interventions developed to optimise pharmacotherapy. A CPS is 'any activity in which the pharmacists would use their professional knowledge and abilities to improve pharmacotherapy and disease management by means of interacting with the patient or with other health professional' [15].

The number of studies and systematic reviews on CPSs is increasing [16, 17]. Many trials [18, 19] highlight the potential positive effect of pharmacists' interventions on the process of the use of medicines, such as adherence, prescription appropriateness and the number of medicines. However, an important issue in healthcare research and practice is to improve patients' outcomes, understood as the magnitude of change in the patients' health status that interventions achieve [20, 21].

CPSs have been classified into levels of complexity to assist in the evaluation of these complex interventions and to assess of their impact [22, 23]. Pharmacists' interventions range from providing medicines information and improving adherence to more clinically complex ones, such as medication review, disease state management and prescribing interventions [22]. The clinical impact of these interventions needs to be analysed in order to make decisions associated with the optimisation of the available health resources and to identify directions for future research. Performing a 'systematic review of systematic reviews' is a new research strategy recommended for topics on which an important quantity of evidence has been generated yet controversy persists [24, 25]. The objectives of this paper were to critically analyse the evidence from systematic reviews and meta-analysis on the clinical impact of CPS and to determine the effectiveness of these services in aged patients using process and outcome indicators by means of performing a systematic review of systematic reviews.

Methods

A systematic review of systematic reviews and meta-analyses on the clinical impact of CPSs in aged patients was carried out using recommended methodologies defined by Becker and Oxman and Smith *et al.* [24, 25].

Selection criteria

Systematic reviews and meta-analyses were included if they reported the effectiveness of any type of CPS on process or clinical outcome indicators of aged patients, regardless of the setting and length of follow-up. Reviews were considered as systematic according to three criteria from the PRISMA check list [26]: (i) 'State questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design'; (ii) 'Describe all information sources and date last searched'; (iii) 'State studies selection process'. The operational definition of CPS used was that proposed by Cipolle *et al.* [15]. The population in the review would have had a mean age over 65 years or been

specifically identified in the article with any term meaning 'aged patients'. Published articles in the English, Spanish, French, Italian and Portuguese languages were included. Papers assessing the impact of interventions without the involvement of pharmacists and those reporting only economic or humanistic outcomes were excluded.

Search methods for identification of reviews

Systematic searches were carried out in MEDLINE, EMBASE, the Cochrane Library, Directory of Open Access Journals (DOAJ) and Scientific Electronic Library Online (SCIELO) following the recommendations published in the scientific literature [27–29]. The retrieved systematic reviews were searched for additional references. The search performed in MEDLINE/Pubmed (1948–2011) was: ('aged'[MH] OR 'health services for the aged'[MH] OR geriatric*[TW] OR 'ageing' [TW] OR elderly [TIAB] OR 'Nursing Homes'[TW] OR polypharmacy[TW]) AND ('community pharmacy services'[MH] OR 'medication therapy management'[MH] OR pharmacist*[TW] OR 'pharmaceutical care'[tiab] OR 'medication review'[tiab] OR 'pharmacy service, hospital'[MH]) OR (pharmacist* [TW] AND ('drug utilisation review'[MH] OR 'cognitive services'[tiab])) AND (systematic review* [tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR systematic 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 pharmaceutical abstracts')) NOT (letter[pt] OR newspaper article[pt] OR comment[pt]) AND has abstract [text]. Search strategies and dates of coverage of the other databases are available from the authors.

Data collection and analysis

The selection process was undertaken by discussion between two experts on CPSs. Abstracts were screened and excluded if they did not meet any of the selection criteria. Duplicated records were removed using Endnote®. The complete text of the remaining references was assessed against the same criteria. Abstracts with insufficient information were assessed in full text. Any differences of opinion between reviewers were resolved by discussion with a third CPS expert. The data-extraction form (Supplementary data are available in *Age and Ageing* online, Appendix S1) was piloted with a sample of three papers. Interventions were categorised using Benrimoj's hierarchical model, which comprises 10 different levels of pharmacists' interventions, according to their complexity of clinical decision making [22]. Indicators of effectiveness were further classified into process and outcome measurements according to the Donabedian definition model of health outcomes [20]. When two or more reviews were found to extract data from the same original study, data were compared to validate reviews' data extraction quality.

The quality of the reviews was assessed using the validated instrument Assessment of Multiple Systematic Reviews (AMSTAR) [30], which comprises 11 criteria. A score of one was given to each of the criteria with a positive judgment. Papers scored from 9 to 11 were considered high quality, 5–8 indicated moderate quality and 0–4 meant a poor quality review [16]. Process and clinical outcome indicators, reported in each systematic review, were assessed for the level of evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [31] was used for this purpose. A researcher ranked the quality of the evidence according to the underlying methodology of the original studies included in the reviews. Based on the judgments provided by the review authors, the upgrading and downgrading factors were identified, and the final quality of the evidence was categorised in high, moderate, low or very low strength.

Results

Review selection and content of the included systematic reviews and meta-analysis

A total of 352 references were retrieved. Fourteen systematic reviews and one meta-analysis were included in the final analysis (Figure 1).

The 15 papers [32–46] contained 110 studies on the effectiveness of CPSs, of which 42 were included in more than one review. The mean length of subject follow-up was 8.25 months (standard deviation = 3.34). The majority of the reviews focused on the impact of interventions on medication adherence [34, 35, 38, 39, 43] and appropriateness of prescriptions [33, 37, 40–42]. Two studies addressed the effect of CPSs on drug-related problems (DRPs) and associated health outcomes [44, 51]. Rollason and Voget [46] assessed the impact in reducing polypharmacy. Holland et al. [32] meta-analysis determined the clinical, economic and humanistic effect of medication review. Most of the research was undertaken in the ambulatory setting [32, 34, 36, 43, 44]. Four reviews [33, 37, 40, 42] focused on nursing home residents, and one [38] included a majority of studies from hospital settings. Two reviews [41, 46] used studies from hospital and residential settings, and one [45] from residential and community. Two articles [35, 39] did not specify the settings of the included studies. Further description of general characteristics of included reviews is provided in Supplementary data available in *Age and Ageing* online, Appendix S2.

AMSTAR assessment showed a majority of the reviews (8 out of 15 papers) to be of moderate quality [36–43]. The main limitations found related to the lack of assessments of both the publication bias and studies' quality. Results from the AMSTAR assessment are further
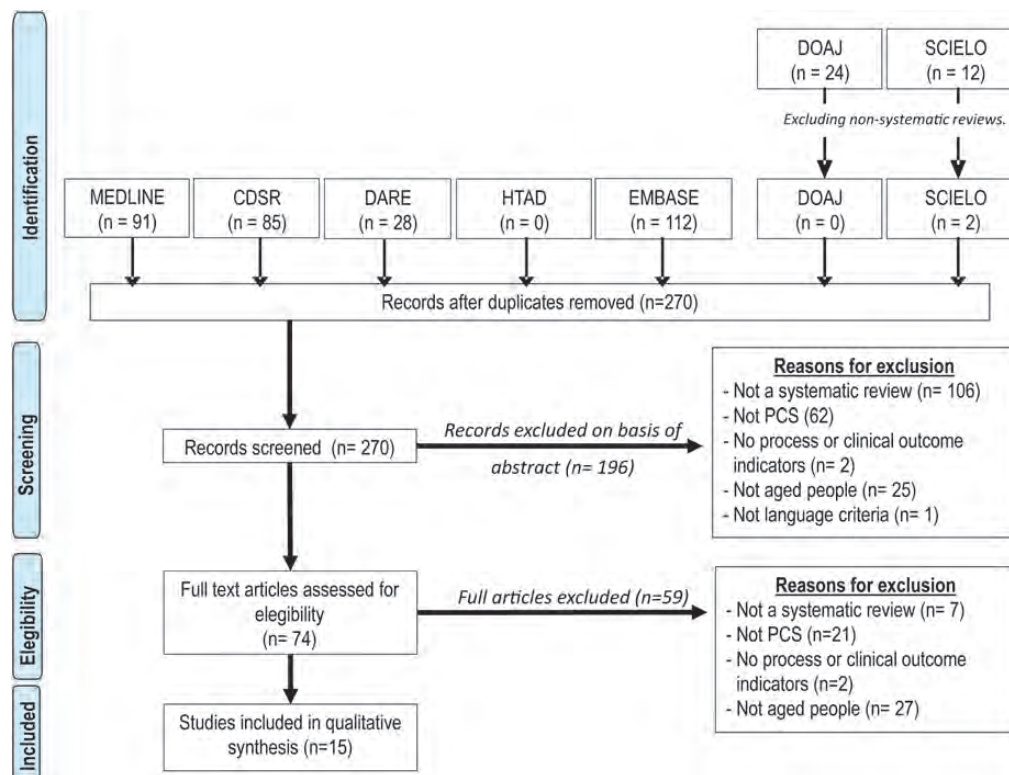

Figure 1. Flow diagram of the screened, assessed for eligibility, included and excluded reviews. CDSR: Cochrane Database of systematic reviews (2005–February 2012); DARE: Database of Abstracts of Reviews of Effects (first quarter of 2012), HTAD: Health Technology Assessment Database (first quarter of 2012).

described in Supplementary data available in *Age and Ageing* online, Appendix S3.

Quality of the evidence on CPSs

Every pharmacists' intervention studied in the reviews could be re-categorised in the 10 levels of Benrimoj's hierarchical model [22] based on the description provided by reviews' authors. Many of the papers included different levels of services without differentiating the effect that each one had on the studied indicators.

Table 1 provides a summary of the indicators of the effectiveness of the systematic reviews, organised according to their methodological quality and the strength of their evidence. An extended version of this table, showing the results of the systematic reviews on the clinical effectiveness of CPSs, is provided in Supplementary data available in *Age and Ageing* online, Appendix S4.

High quality reviews

Holland *et al.* [32] performed a meta-analysis on the effectiveness of pharmacist-led medication review. Based on a subsample, they found a reduction in the number of prescriptions (with very marked heterogeneity) but no effect on mortality (no heterogeneity found) nor in hospital admissions (moderate heterogeneity). They also identified four studies suggesting a reduction in DRPs and some low-strength evidence of non-conclusive results on a variety of process measurements. Re-categorisation of the interventions showed eight different levels of CPSs.

Forsetlund *et al.* [33] studied the effect of medication review and the participation of the pharmacists in therapeutic decisions (case conferences and meetings to discuss patients' medication), finding moderate-strength evidence of an improvement in the appropriateness of medicines and no effect on the reduction of the number of falls.

Table 1. Summary of findings extracted on the clinical effectiveness of each intervention (abbreviated version)

Study	AMASTAR score[a]	Strength of evidence (GRADE) of effectiveness		
		GRADE: high	GRADE: moderate	GRADE: low (or very low[a])
Holland *et al.* [32]	10	Number of drugs prescribed; mortality; hospital admissions	Drug-related problems	Knowledge; adverse drug events; storage problems; unnecessary drugs
Forsetlund *et al.* [33]	9	None	Appropriateness of medicines; falls	Number of drugs; number of drug changes; hospitalisation; mortality
George *et al.* [34]	9	None	Medication adherence	None
Van Eijken *et al.* [35]	9	None	Medication adherence	None
Lau and Dolovich [36]	8	None	None	Medication adherence; medication knowledge; no of prescriptions/patient; patients with DRP; mean DRPs per patient; DRP resolution
Loganathan *et al.* [37]	8	Appropriateness of medicines; number of medicines	Hospital admissions; mortality	Adverse drug events; number of drug changes; behaviour; falls
Higgins and Regan [38]	7	None	Medication adherence	None
Russell *et al.* [39]	6	None	Medication adherence	None
Verrue *et al.* [40]	6	None	Appropriateness of medicines; Mortality; Cognitive function; Patient function.	Number of medicines; ADEs; drug change; behaviour: outpatient consultations; depression; worsening pain; hospitalisations
Castelino *et al.* [41]	5	None	Appropriateness of medicines	Number of medicines; DRPs
Marcum *et al.* [42]	5	Appropriateness of medicines	Number of medicines; mortality; cognitive function; functional capacity	Hospitalisations; ADE; drug changes; behaviour; falls; outpatient visits; depression; worsening pain; morbidity; level of care
Schlenk *et al.* [43]	5	None	Adherence	None
Hanlon *et al.* [44]	4	Hospital admissions; appropriateness of medicines; number of medicines	Medication adherence; medication knowledge; outpatient physician visits	Adverse drug events (ADE); level of care; disruptive behaviour; heart failure events; drug-related problems (DRPs); complex regimens; deterioration of health and falls; general well-being; attitude and practice; duration of home health care; mortality; drug changes; functional capacity
Kaur *et al.* [45]	4	None	Appropriateness of medicines	None
Rollason and Vogt [46]	4	None	Number of medicines	Inappropriate medicines

[a]High quality reviews = AMSTAR score from 9 to 11; Moderate quality reviews = AMSTAR score from 5 to 8; Poor quality reviews = AMSTAR score from 0 to 4.

George *et al.* [34] and Van Eijken *et al.*'s reviews [35] did not show clear conclusions for the effectiveness of medication reviews with follow-up and adherence interventions on actual patients' medication adherence.

Moderate quality reviews

Lau and Dolovich [36] reported a positive effect of 'pharmaceutical care' on the identification and resolution of DRPs as well as non-significant results on the number of prescriptions and on patients' knowledge and adherence. Nevertheless, evidence provided by this systematic review was considered as low-strength of evidence and was not included in further analysis.

Loganathan *et al.* [37], Verrue *et al.* [40] and Marcum *et al.* [42] studied the effectiveness of interventions aimed to improve prescribing. Overall, results showed a consistent improvement of appropriateness of medicines. High and moderate evidence of results, with no statistical significance, was found on the effect on the number of medications and a variety of outcome indicators in these reviews. Castelino *et al.'s* review [41] also found moderate evidence of CPSs effectiveness for reducing inappropriate prescriptions.

Russell *et al.* [39], Schlenk *et al.* [43] and Higgins and Regan [38] identified 33, 19 and 5 studies, respectively, of pharmacists' interventions to improve patient adherence, providing inconclusive results. Interventions from these systematic reviews were re-categorised into three different types of CPSs, adherence interventions and medication review, with and without follow-up.

Low quality reviews according to AMSTAR assessment

Hanlon *et al.*'s review [44] included a wide variety of CPSs and indicators of effectiveness. The authors found an improvement in the appropriateness of medicines and patient adherence but mostly negative results were found for hospitalisations, outpatient visits and patient knowledge.

Kaur *et al.* [45] identified 11 out of 14 studies presenting moderate evidence on the effectiveness of CPSs to reduce inappropriate prescriptions. Interventions were re-categorised into several levels of CPSs (i.e. clinical interventions, medication review and participation of the pharmacists in therapeutic decisions).

Rollason and Voget [46] did not find a significant effect of pharmacists' interventions on the number of medicines. The authors of this review included a broad variety of CPSs, which ranged from clinical interventions to prescribing services, without differentiating between them.

Effectiveness of CPSs on process and outcome indicators

The clinical effectiveness of each type of CPSs in process and outcome indicators is presented in Table 2. The positive effect of CPS was clearly demonstrated in the improvement of the appropriateness of medicines. CPSs that gave this positive effect were clinical interventions, medication reviews (with and without follow-up), disease state management and prescription services. The number of drugs was also reduced by CPSs such as interventions to improve adherence, clinical interventions and prescription services. However, medication review services and participation of the pharmacist in therapeutic decisions provided inconsistent results.

Most CPSs showed conflicting results on patient adherence. Negative conclusions were reported in one review for disease state management and prescribing services. Some high and moderate evidence of the effectiveness of CPSs in clinical outcome measurements was found. Negative conclusions were found for the effect of adherence interventions, medication review, prescription services and participation of the pharmacists in therapeutic decisions on mortality. Negative conclusions were also found for the effect of medication review and prescription services on hospitalisations. Medication reviews without follow-up showed no consistent effect on functional capacity and cognitive function. However, there was evidence for the reduction on hospitalisations and outpatient visits for adherence interventions undertaken at discharge. No systematic reviews reported high or moderate evidence of the effect of CPSs on health outcomes.

Discussion

This review identified 14 systematic reviews and one meta-analysis on the clinical impact of pharmacists' interventions for aged patients, indicating the growing importance that this topic has for both researchers and practitioners [16]. The methodology 'overview of systematic reviews' is considered an aid for evidence-based clinical decision-making [17]. However, this design has inherent limitations in that papers reviewed are systematic reviews instead of the original studies. In the present overview, 42 of the 110 original studies were included in more than one review. 'Double counting' is not an issue addressed by Cochrane [24], therefore care needs to be undertaken when interpreting the results of this type of methodology. Most of the reviews showed a moderate quality based on AMSTAR [30] which is consistent with recent work on the quality of systematic reviews on pharmacists' interventions [16]. We found no reviews which addressed the impact of CPSs on the level of control of health problems. Just two reviews studied the impact on cognitive function and functional capacity which are major areas of concern in aged patients. There was a wide variability in the strength of the evidence and a lack of high and moderate evidence for the effectiveness of CPSs on clinical outcomes, suggesting a direction for future research. The necessity of focusing on clinical outcomes as indicators of the effectiveness of interventions has been widely discussed in pharmaceutical services research [47–51]. However, inconsistent terminology

Table 2. Clinical effectiveness of CPSs on process and outcome indicators

	Types of CPSs							
	Medicines information	Adherence intervention	Clinical intervention	Medication review	Medication review with follow-up	Disease state management	Participation in therapeutic decisions	Prescriptions
Process indicators								
Adherence	[+] [43], [−] [39]	[+] [34, 41, 44], [+ −] [35, 38 ,39], [−] [43]	[+] [43], [−] [39]	[+] [35, 38, 41], [−+] [39, 43], [−] [34, 44]	[+] [41], [+−] [39, 43], [−] [35, 38]	[−] [39,43]	[+ −] [41]	[−] [43]
Appropriateness	NHME	NHME	[+] [41]	[+] [33, 40, 41 42, 44, 45], [−] [37]	[+] [41, 44]	[+] [44]	[+] [33, 44], [+−] [40, 41, 42]	[+] [37]
Knowledge	NHME	[+] [44]	NHME	[−] [44]	[−] [44]	NHME	NHME	NHME
Number of drugs	NHME	[+] [40]	[+] [54]	[+] [40], [+ −] [52, 54], [−] [45, 50]	[+] [40], [+ −] [52, 54]	NHME	[+ −] [54], [−] [45, 50]	[+] [50, 54]
Outcome indicators								
Hospitalisation	NHME	[+] [44]	NHME	[−] [32, 37, 44]	[−] [32,44]	NHME	NHME	[−] [32]
Mortality	NHME	[−] [32]	NHME	[+ −] [37, 40, 42], [−] [32]	[−] [32]	NHME	[−] [32,37,40,42]	[−] [32,42]
Outpatient visits	NHME	[+] 44	NHME	[− +] [44]	[−] [44]	NHME	NHME	NHME
Functional capacity	NHME	NHME	NHME	[−] [42]	NHME	NHME	NHME	NHME
Cognitive function	NHME	NHME	NHME	[−] [40,42]	NHME	NHME	[+ −] [42]	NHME
Control of health problems	NHME	NHME	NHME	NHME	NHME	NHME	NHME	NHME

Numbers are coincident with references. [+] Positive conclusions (consistently effective)/[+ −] Neutral conclusions (effectiveness uncertain)/[−] Negative conclusions/NHME No systematic data available with high and moderate quality of evidence.

and definitions about what is a process indicator versus an outcome indicator have been previously reported [52]. This is important since many of the reviews are more concerned about improvements in the process of the use of medicines rather than the amelioration of clinical outcomes. Results support most of the findings of the meta-analysis by Holland et al. [32]. A majority of studies provided negative conclusions on patient clinical outcomes (hospitalisations, mortality, falls, adverse drug events, outpatient visits, functional capacity and cognitive function). Insufficient duration of follow-up could probably be one of the main reasons for these negative conclusions. Most of the indicators (e.g. mortality, hospitalisations etc.) may need longer periods of follow-up in the intervention to show a potential effect. Alternatively, intermediate or surrogate outcomes could be used as proxy indicators of services effectiveness, though this would also require a demonstrated association between such variables and the endpoint outcomes [53]. The main question that arises is, why systematic reviews on aged patients do not use surrogate clinical outcomes as primary variables, such as the level of control of diseases, so that the short-term effect of interventions can be measured? Recent reviews [54, 55] performed on broader populations, have shown evidence of the clinical impact of pharmacists' interventions on indicators of the control of health problems. Systematic reviews on the clinical effectiveness of CPSs in aged people could be missing a potential effect on such outcome indicators.

Moreover, studies included in these systematic reviews usually comprised of pharmacist services at different hierarchical levels of complexity [22] and reviews generally did not draw their conclusions taking into account the differences present in the methodologies of the services. The use of Benrimoj's hierarchical model [22] contributed to an understanding of the effect of the different CPSs. As an example, the number of medicines was reduced by adherence interventions, clinical interventions and prescription services, but medication review services and the participation of the pharmacist in therapeutic decisions showed inconsistent effectiveness. Ignoring this heterogeneity may invalidate the conclusions of these reviews. The selection of outcomes used to test the effectiveness of CPSs should have a robust theoretical basis [56, 57].

Finally, the implementation issues of CPSs should also be considered with process indicators for the intervention itself. Some of the reviews [32, 33, 34, 35, 36, 38, 39] explained the variability of results due to the variable degree of service provision by pharmacists. Some authors [57] also suggest the need to include an operational description of the intervention, so that they may be reproduced in other studies [57].

Authors' conclusions

The systematic reviews were of a moderate quality according to AMSTAR and composed of a heterogeneous strength of evidence. The evidence generated so far indicates that several CPSs constitute effective strategies to improve the appropriateness of medicines and reduce the number of medicines in aged patients. High and moderate strength evidence on the effectiveness of CPSs on clinical outcomes is scarce. No effect has been reported for CPSs on hospitalisations, mortality, functional capacity and cognitive function.

Practical implications

- Indicators of the effectiveness of the intervention should be chosen according to the level of complexity of the CPS that is being assessed.
- Certain clinical outcome indicators may be not appropriate to detect the short-term impact of CPSs in aged patients.
- Surrogate clinical outcome measures should be used to detect the short-term impact of CPSs in aged patients.

Key points

- High and moderate levels of evidence were found for the effectiveness of cognitive pharmaceutical services, such as 'clinical interventions' and 'prescription services', to reduce the number of medicines and improve their appropriateness.
- There was high and moderate evidence for improving patient adherence using cognitive pharmaceutical services.
- There was no evidence found of the impact of cognitive pharmaceutical services on aged patients' outcomes such as mortality, hospitalisations and cognitive function.
- Many systematic reviews searching for the evidence of the cognitive pharmaceutical services' effectiveness do not take into account, state nor define the different levels of services.
- Longer periods of follow-up and the use of appropriate surrogate outcome indicators sensitive to each cognitive pharmaceutical service should be considered in the studies with aged patients.

Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

References

The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available in Supplementary data in *Age and Ageing* online, Appendix S5.

4. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "there's got to be a happy medium". JAMA 2010; 304: 1592–601.

6. Hanlon JT, Lindblad CI, Hajjar RR, McCarthy TC. Update on drug-related problems in the elderly. Am J Geriatr Pharmacother 2003; 1: 38–43.

15. Cipolle J, Strand LM, Morley PC. A Reimbursement System for Pharmaceutical Care: Pharmaceutical Care Practice. New York: McGraw-Hill, 1998.

16. Melchiors AC, Correr CJ, Venson R, Pontarolo R. An analysis of quality of systematic reviews on pharmacist health interventions. Int J Clin Pharm 2011; 34: 32–42.

20. Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q 1966; 44(Suppl): 166–206.

21. Outcomes Research. Fact Sheet. AHRQ Publication No. 00-P011 [Internet]. Rockville, MD: Agency for Healthcare Research and Quality, 2000 [cited 2011 Dec 27]. Available at: http://www.ahrq.gov/clinic/outfact.htm (accessed 30 April 2013).

22. Benrimoj SI, Feletto E, Gastelurrutia MA, Martinez-Martinez F, Faus MJ. A holistic and integrated approach to implementing cognitive pharmaceutical services. Ars Pharm 2010; 51: 69–87.

24. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org (accessed 30 April 2013).

27. Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009; 62: 944–52.

30. Shea BJ, Hamel C, Wells GA *et al.*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009; 62: 1013–20.

31. Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: interpreting results and drawing conclusions. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org (accessed 30 April 2013).

32. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol 2008; 65: 303–16.

33. Forsetlund L, Eike MC, Gjerberg E, Vist GE. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. BMC Geriatr 2011; 11: 16.

34. George J, Elliott RA, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. Drugs Aging 2008; 25: 307–24.

35. Van Eijken M, Tsang S, Wensing M, de Smet PAGM, Grol RPTM. Interventions to improve medication compliance in older patients living in the community: a systematic review of the literature. Drugs Aging 2003; 20: 229–40.

36. Lau E, Dolovich LR. Drug-related problems in elderly general practice patients receiving pharmaceutical care. Int J Pharm Pract 2005; 13: 165–77.

37. Loganathan M, Singh S, Franklin BD, Bottle A, Majeed A. Interventions to optimise prescribing in care homes: systematic review. Age Ageing 2011; 40: 150–62.

38. Higgins N, Regan C. A systematic review of the effectiveness of interventions to help older people adhere to medication regimes. Age Ageing 2004; 33: 224–9.

39. Russell CL, Conn VS, Jantarakupt P. Older adult medication compliance: integrated review of randomized controlled trials. Am J Health Behav 2006; 30: 636–50.

40. Verrue CLR, Petrovic M, Mehuys E, Remon JP, Vander Stichele R. Pharmacists' interventions for optimization of medication use in nursing homes. Drugs Aging 2009; 26: 37–49.

41. Castelino RL, Bajorek BV, Chen TF. Targeting suboptimal prescribing in the elderly: a review of the impact of pharmacy services. Ann Pharmacother 2009; 43: 1096–106.

42. Marcum ZA, Handler SM, Wright R, Hanlon JT. Interventions to improve suboptimal prescribing in nursing homes: a narrative review. Am J Geriatr Pharmacother 2010; 8: 183–200.

43. Schlenk EA, Bernardo LM, Organist LA, Klem ML, Engberg S. Optimizing medication adherence in older patients: a systematic review. J Clin Outcomes Manag 2008; 15: 595.

44. Hanlon JT, Lindblad CI, Gray SL. Can clinical pharmacy services have a positive impact on drug-related problems and health outcomes in community-based older adults? Am J Geriatr Pharmacother 2004; 2: 3–13.

45. Kaur S, Mitchell G, Vitetta L, Roberts MS. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs Aging 2009; 26: 1013–28.

46. Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. Drugs Aging 2003; 20: 817–32.

47. Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management. Ann Pharmacother 2007; 41: 1569–82.

53. Thompson DF. Surrogate end points, skepticism, and the CAST study. Ann Pharmacother 2002; 36: 170–1.

54. Chisholm-Burns MA, Kim Lee J, Spivey CA *et al.* US pharmacists' effect as team members on patient care: systematic review and meta-analyses. Med Care 2010; 48: 923–33.

56. Mayo NE, Scott S. Evaluating a complex intervention with a single outcome may not be a good idea: an example from a randomized trial of stroke case management. Age Ageing 2011; 40: 718–24.