Deprescribing Trials: Methods to Reduce Polypharmacy and the Impact on Prescribing and Clinical Outcomes

Danijela Gnjidic, PhD, MPH[a,b,c,*], David G. Le Couteur, MBBS, PhD[b,c,d], Lisa Kouladjian, BMedSc (Hons), MPharm[a], Sarah N. Hilmer, MBBS, PhD[a,b]

KEYWORDS

- Effectiveness of interventions • Medications • Polypharmacy
- Medication withdrawal • Older adults

THE RISKS OF POLYPHARMACY

There are many challenges to ensuring good outcomes from the pharmacologic management of older adults. With advancing age, the increased prevalence of diseases promotes high use of medications in older adults and of polypharmacy, commonly defined as the use of 5 or more medications. Further, there is a lack of data to guide the use of medications in older adults. This is because older adults are rarely included in randomized, controlled trials (RCT),[1] and most evidence-based clinical guidelines for older people are extrapolated from younger populations.[2] Older adults use medicines extensively, and evidence suggests that polypharmacy may even be increasing.[3] For instance, older people living in the community consume on average 4 medications, whereas older people living in nursing homes use on average 7 medications.[4–6]

Many risk factors for polypharmacy have been identified, commonly grouped as demographic, health status, and access to health care services factors.[7] Of demographic

Disclosures: The authors gratefully acknowledge the funding support from the Geoff and Elaine Penney Ageing Research Unit and the Ageing and Alzheimer's Research Foundation.
[a] Departments of Clinical Pharmacology and Aged Care, 11C Main Building, Royal North Shore Hospital, St Leonards NSW 2065, Australia
[b] Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia
[c] Centre for Education and Research on Ageing, Concord Hospital, C22, Concord NSW 2139, Australia
[d] ANZAC Medical Research Institute, Concord Hospital and University of Sydney, Concord NSW 2139, Australia
* Corresponding author. Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia.
E-mail address: danijela.gnjidic@sydney.edu.au

Clin Geriatr Med 28 (2012) 237–253
doi:10.1016/j.cger.2012.01.006 **geriatric.theclinics.com**
0749-0690/12/$ – see front matter

risk factors, advancing age, female gender, and low education level are associated with increased polypharmacy exposure.[3,7–9] Recent hospitalization, multiple comorbidities, and depression are some of the health status markers associated with higher rates of polypharmacy.[9] The involvement of multiple prescribers and greater health care utilization are important health care characteristics that increase the risk of polypharmacy.[8] A recent study conducted in a sample of older disabled women found that in addition to comorbidity and difficulties with instrumental activities of daily living, frailty was associated with increased polypharmacy.[10]

Although use of multiple medications might generate positive outcomes for some older adults with multiple diseases, there is increasing evidence that it is associated with increased risks of adverse events. The clinical consequences of polypharmacy on health outcomes in older adults have been widely documented. Polypharmacy is associated with increased risks of adverse drug reactions (ADRs), adverse drug events (ADEs), inappropriate prescribing, inappropriate drug use, falls, hospitalization, institutionalization, mortality, and other important negative outcomes in studies of older adults.[6,11] Indeed, polypharmacy is often considered to be among the most important risk factors for ADRs in older people. Therefore, rational withdrawal of medications may be the appropriate clinical decision and may result in significant clinical and functional benefits in some older people with polypharmacy. The feasibility of deprescribing was recently evaluated in a pilot study,[12] where it was found that a RCT of deprescribing is acceptable to participants, and recruitment is feasible. Current evidence suggests that stopping some classes of medications in older patients does not worsen clinical outcomes, is not often associated with withdrawal syndromes, and can improve some outcomes such as falls, behavior, and cognition.[13]

Not surprisingly, withdrawing medications in older people has often been found to be difficult, and requires consideration of a range of factors. To date, interventions to reduce medication exposure in older adults have shown mixed results. Approaches including pharmacist-led medication reviews, prescriber feedback, and multidisciplinary interventions involving a team of health professionals have been trialed to reduce medications, with the aim of improving medication-related outcomes in older adults. The clinical implications of different interventions in older people from care homes,[14] and pharmacist-based interventions to optimize prescribing in older adults,[15] especially for those living in nursing homes[16,17] have been evaluated recently. The aim of this clinical review is to highlight the evidence for the impact of various types of interventions designed to reduce polypharmacy on prescribing and clinical outcomes in older adults from community, nursing home, and hospital settings.

CHALLENGES OF DISCONTINUING MEDICATIONS

Before addressing interventions to reduce medications in older adults, it is important to briefly discuss factors that need to be considered during the medication withdrawal process (**Fig. 1**). There are many barriers to successfully stopping medications in older adults. Health professionals may find it difficult to reduce the dose or to stop the medication once a prescription is initiated. Clinicians might feel uncomfortable with changing or discontinuing a medication prescribed by another clinician.[18] The evidence base, marketing, and guidelines for initiating medications are vast, but there is little to support ceasing or reducing medications. Patients' preferences are also important to consider before initiating the process of medication withdrawal. Patients may be psychologically and physically attached to their medications.[19] Stopping a medication may be perceived by the patient or their carer/family as inadequate care. The relationship between the health professionals and patient may hinder the efforts to stop medicines.

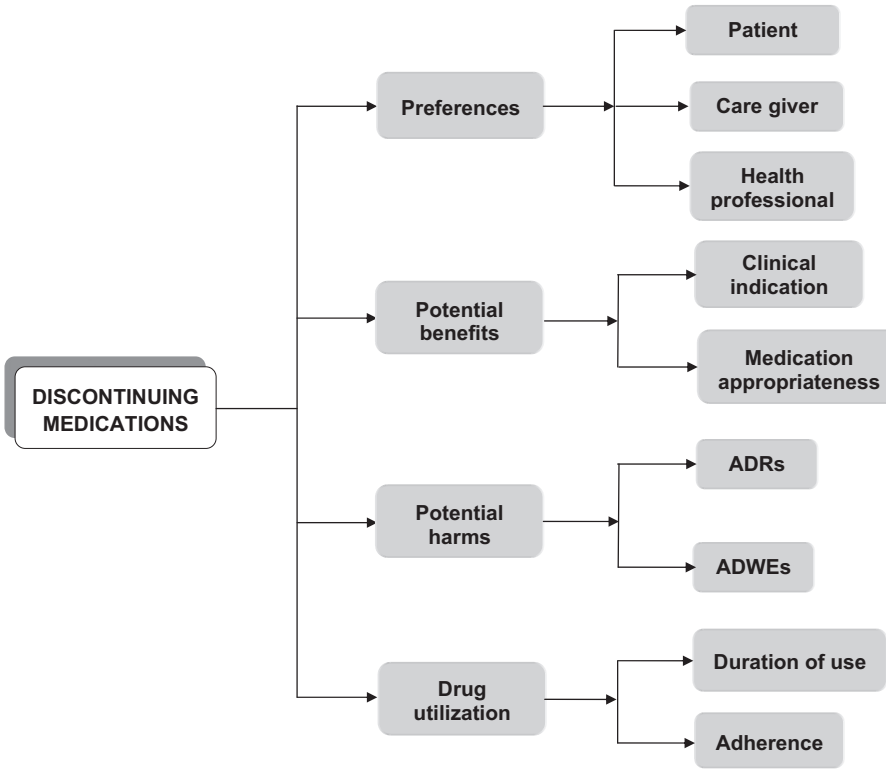

Fig. 1. Factors to consider when discontinuing medications in older adults. ADRs, adverse drug interactions; ADWEs, adverse drug withdrawal events.

The potential harms of discontinuing medications may be a barrier to successful medication withdrawal process. The process of stopping medications can result in ADRs or adverse drug withdrawal events (ADWEs). An ADWE is characterized by a clinically significant set of symptoms or signs caused by the medication cessation.[20] Some medications are more likely to cause ADWEs than others. For example, the cardiovascular and central nervous system drug classes are the most common medications associated with ADWEs.[20,21]

When considering whether to continue or withdraw a patient's medicines, it is important to establish duration of use of each medication, whether there is still an indication for the use of medication, and if so, the use is still consistent with current guidelines.[22] Medication adherence is another important factor that might impact on attempts to withdraw medications.[23] For example, if the patient has remained well without taking the medicine, then it is pointless to continue prescribing the medications. The so-termed prescribing cascade, when additional medicines are initiated to treat adverse effects of other medications, might influence attempts to cease medications, as the adverse effects of remaining drugs will reemerge.[24]

There is very limited evidence to guide the medication withdrawal process in older adults with polypharmacy. An algorithm approach that expands the prescribing stage to include a step for rationally discontinuing medications has been proposed.[19] In clinical practice, a step-wise approach to discontinuing medications is

Table 1
Clinical controlled studies to reduce medication exposure

		Study Results	
Intervention	**Study Setting[a]**	**Impact on Prescribing**	**Impact on Outcomes**
Pharmacist-based interventions			
Clinical pharmacist medication review combined with physician and patient education[26]	Outpatient managed care (n = 195,971)	Significant reduction in the number of prescriptions	Not assessed
Clinical pharmacist consultation and computer-based medication profiles provided to physician[27]	Internal medicine clinic (n = 512)	Significant reduction in the number of medications	Not assessed
Clinical pharmacist patient tailored medication review provided to physician[28]	Outpatient clinic (n = 562)	Significant reduction in the number and costs of medications	Not assessed
Medication review performed by pharmacist and reviewed by the primary care provider[29]	Geriatric outpatient clinic (n = 250)	Significant reduction in the mean number of medications	Neutral or positive in 99.5% of cases
Physician-based interventions			
The Good Palliative–Geriatric Practice algorithm compromised of physician individual review[30]	Community dwelling (n = 75)	Discontinued 311 medications (58%) in 64 participants	Improved cognition and global health
Prompting participants to bring their medications for review by their physician[31]	Managed care organization (n = 37,372)	Significant reduction in the number of medications observed in 20% of patients	Not assessed

Geriatric medicine fellows reviewed each patient's medication list, and recommended the changes to the patients' primary care physician[32]	Nursing homes (n = 74)	Significant reduction in the number of medications	Not assessed
Provision of admission medication list to physician[33]	Hospitalized patients (n = 836)	Significant reduction in the number of medications	Not assessed
Multidisciplinary-based interventions			
Clinical pharmacists prescribed medications under the supervision of a family physician[34]	Nursing homes (n = 139)	Pharmacists prescribed significantly less medications than physicians	Improved survival ($P = .05$); more patients discharged to lower levels of care ($P = .03$)
Case conference involving health professionals including general practitioner, pharmacist, nurses and other health professional[35]	Nursing home (n = 245)	Nonsignificant reduction in the number of medications	No effect on mortality

[a] N refers to number of patient participants.

usually recommended.[22,25] A gradual tapering of a dose, particularly for medications used on a long-term basis and those associated with withdrawal syndromes is often recommended. If the process of medication withdrawal is undertaken slowly and under appropriate supervision, the likelihood of clinically significant ADWEs is low.[13]

INTERVENTIONS TO REDUCE MEDICATIONS: IMPACT ON PRESCRIBING AND OUTCOMES

A number of clinical controlled studies have been performed to assess the effectiveness of various interventions to reduce medication exposure in older adults (**Table 1**). These approaches have commonly included medication reviews delivered by clinical pharmacists, prescriber education programs, academic detailing combined with additional strategies, comprehensive geriatric assessments, and multidisciplinary interventions engaging health professionals such as physicians and pharmacists.

Of 4 clinical studies that involved pharmacist-based interventions, all reduced polypharmacy, but only one assessed the impact of medication reduction on clinical outcomes. One intervention, compromising of a clinical pharmacist medication review combined with physician and patient education, resulted in significant reductions in number of prescriptions and medication costs.[26] Two identical interventions separated by 1 year were administered in the same study sample. The number of prescriptions decreased from 4.6 to 2.2 after the first intervention and from 4.5 to 4.0 six months after the second intervention. Further, adding a computer-based medication profile during the consultation between clinical pharmacists and physicians results in a significant reduction in the number of medications.[27] The provision of a patient-tailored medication review by pharmacist to physician reduces the number and cost of medications.[28] Medication reviews led by a pharmacist and reviewed by the primary care provider have also been found to result in a significant reduction in the mean number of medications, as well as reduced medication costs.[29] Moreover, the same study reported neutral or positive clinical outcomes of medication-related changes in 99.5% of patients.

Four clinical controlled studies employing physician-based interventions were identified[30–33]; similarly, although all reduced polypharmacy, only 1 study reported the impact of medication reduction on outcomes.[30] A recent trial of polypharmacy reduction in older people showed that over half of medicines can be discontinued.[30] The study utilized the good palliative–geriatric practice algorithm, which involved physician-based reviews. Only 2% of medicines had to be restarted because of recurrence of the original indication and overall there was improvement in cognition and global health. This is a very important study, because it showed that not only can polypharmacy reduction be achieved, but that this is associated with long-term adherence and improved patient outcomes. In a study that promoted medication reviews by primary care physicians with their patients, significant changes in physicians' prescribing practices were observed.[31] Of the 42% of the participants who underwent the medication review by the physician, 20% reported having a medication stopped and 29% reported a change in the dose of a medication. The other 2 studies also demonstrated a significant reduction in the number of medications.[32,33]

Two controlled studies utilizing a multidisciplinary intervention assessed the impact of medication reduction on outcomes. One study compared prescribing practices of the clinical pharmacists, under the supervision of a physician, with the usual care in a nursing home setting.[34] The study found that pharmacists prescribed significantly lower numbers of medications than physicians. Moreover, this was associated with a significantly lower number of deaths ($P = .05$) and a significantly higher number of

patients being discharged to lower levels of care ($P = .03$). The other study reported no change in the number of medications or impact on mortality.[35]

DEPRESCRIBING TRIALS TO REDUCE MEDICATIONS: IMPACT ON PRESCRIBING AND OUTCOMES

The studies described in this section represent those which have employed an RCT design to assess the effects of interventions to reduce medicines in older adults. These trials have been conducted in a range of settings, and have yielded mixed results and are summarized in **Table 2**.

RCTs involving medication review performed by pharmacists have been utilized in a few studies.[36–39] Although clinical pharmacist-based interventions have resulted in substantial changes in medication regimens in 2 studies,[36,38] reduced medication use did not seem to cause significant differences in practice consultation rates, outpatient consultations, hospitalization, or mortality. However, a significant reduction in the number of falls over 6 months was reported in 1 study.[38] In a RCT study of pharmacist medication reviews conducted across 14 nursing homes in the UK, reduction in the number of medicines and costs was observed, but was not significant.[39] Further, the number of accidents, falls, or deaths was not different between the groups.

Studies employing physician-based interventions have mostly reported a significant reduction in medication use; however, the impact on clinical outcomes is unclear.[40–43] In 1 study, provision of a comprehensive medication review with recommended modifications of patient's medication regimen to physicians' resulted in a significant reduction in the number of medications and costs, but it did not improve functional outcomes.[40] In 2 studies, the primary outcome was reduction in medication use.[41,42] The application of inpatient or outpatient geriatric evaluation and management seems to be successful in reducing primarily inappropriate drug use and, consequently, the number of medications, with implications in reducing serious ADRs.[43]

A number of studies utilizing multidisciplinary-based interventions across a range of settings have been conducted.[44–54] Two studies implementing multidisciplinary teams of physicians, pharmacists, and nurses reported no difference in the mean number of medications.[44,45] Both studies had a same duration of follow-up and were conducted in older people living in the community. In contrast, a study of hospitalized patients who underwent multidisciplinary expert panel medication review showed that, although the total number of medications per patient per day fell slightly from 11.64 to 11.09 in the intervention group ($P = .04$), there was no difference in mortality or frequency of acute hospital transfers.[52] Two studies involving a team of physicians, pharmacists, and nurses were conducted in older people living in nursing homes.[53,54] Both studies reported a significant decrease in number of medications over 1 year of follow-up[53,54]; however, only 1 assessed the impact on outcomes.[53] Although medication use was reduced by 14.8% in intervention compared with the control group, the study found no change in morbidity or mortality outcomes.[53]

More recently, an electronic medical records-based intervention was trialed to reduce overall medication use, psychoactive medication use, and occurrence of falls in older community-dwelling people.[55] Although the intervention did not result in a reduction in the total number of medications, a significant negative relationship between the intervention and the total number of medications started during the intervention period ($P<.01$), and the total number of psychoactive medications ($P<.05$) was observed. The impact on falls was unclear. Although the use of computerized physician order entry and clinical decision support systems seems to improve medication safety,[56] future research is warranted to assess the feasibility of

Table 2
Randomized clinical trials to reduce medication exposure

			Study Results	
Intervention Type	**Study Setting[a]**	**Duration of Follow-Up**	**Impact on Prescribing**	**Impact on Outcomes**
Pharmacist-based interventions				
Pharmacist performed medication review, with recommendations made to physician in the case of major changes[36]	Community dwelling (n = 1131)	1 year	The increase in the mean number of repeat medications was significantly lower for intervention (mean difference = 0.2) compared with control group (mean difference = 0.4)	No effect on practice consultation rates, outpatient consultations, hospital admissions, or death rate
Clinical pharmacist intervention involving the patient, with recommendations made to physician[37]	General medicine clinic (n = 208)	1 year	Nonsignificant difference in the mean number of medications	No effect on health-related quality of life
Pharmacist performed medication review and consulted with the patient and carer[38]	Nursing homes (n = 661)	6 months	Significant reduction in the number of repeat medications: 3.1 for intervention compared with 2.4 for control group	Reduction in falls; No effect on consultations rates, hospitalizations, deaths, functional status or cognitive performance
Medication review performed by a pharmacist, with recommendations and follow-up[39]	Nursing homes (n = 330)	8 months	Nonsignificant reduction in the number of medications	Minimal effect on morbidity and mortality

Physician-based interventions				
Patient-tailored information recommending medication reduction to primary care physician[40]	Community dwelling (n = 140)	2 months	Significant reduction in the number of medications	No differences in functioning
Patient tailored information recommending medication reduction to primary care physician[41]	Outpatient clinic (n = 272)	6 months	Significant reduction in the mean number of medications	Not assessed
Group 1: Patient-tailored letter recommending medication reduction to primary care physician Group 2: A chart review, calculation of patient compliance, and individualized suggestions for medication reduction to primary care physician[42]	Outpatient clinic (n = 292)	6 months	Significant reduction in the number of medications No significant difference between the type of intervention	Not assessed
Inpatient or outpatient geriatric evaluation and management (GEM)[43]	Inpatient and outpatient veterans care (n = 834)	1 year	Significant reduction in unnecessary and inappropriate drug use, and consequent reduction in number of medications was observed in patients receiving GEM	Reduction in serious ADRs

(*continued on next page*)

Table 2
(*continued*)

Intervention Type	Study Setting[a]	Duration of Follow-Up	Study Results	
			Impact on Prescribing	Impact on Outcomes
Multidisciplinary-based interventions				
Multidisciplinary team comprising a physician, pharmacist and nurse reviewed the list of medications in a case conference[44]	Community dwelling (n = 266)	1 year	Nonsignificant reduction in the mean number of medications	Not assessed
Evaluation performed by a nurse and physician[45]	Community dwelling (n = 174)	2.5 months 1 year	Nonsignificant reduction in the number of medications	Not assessed
Personal educational visits by clinical pharmacist to primary care physician[46]	Prescription database[b]	9 months	Reduced prescribing of the target medications by 14%	Not assessed
Pharmacist educated the patient/carer about their medicines, and subsequently met with the general practitioner to reinforce changes[47]	Community dwelling (n = 136)	6 months	Decreased number of medications	No difference in hospital admissions, care home admissions, or deaths
Clinical pharmacists visited physicians; second group were given data comparing their individual prescribing costs to those of their colleagues[48]	General medicine clinic[b]	7 months	Significant reduction in physicians' prescribing costs but no decrease in the number of prescriptions	Not assessed
Clinical pharmacist medication review involving the patient, with recommendations made to physician to reduce medications after discharge[49]	Hospitalized patients (n = 706)	3 months 20 months	Significant difference in the mean number of medications observed at 20 months only	No effect on service use

Clinical pharmacist medication review involving the patient, with recommendations made to interdisciplinary team (social worker, dietician, physical therapist, geriatric physician and nurse) to reduce medications after admission to a hospital[50]	Hospitalized patients (n = 436)	3 days 3 months	Increase in number of medications in the intervention groups was lower compared with control at 3 days No difference in the number of medications observed at 3 months	Not assessed
Interdisciplinary geriatric evaluation involving the assessment of patient's medical, functional and psychosocial status[51]	Hospitalized patients (n = 123)	2.5 years	No difference in the mean number of medications	Unclear
Medical assessment by a geriatrician and medication review by a multidisciplinary expert panel (geriatricians, specialist registrars in geriatric medicine, hospital pharmacists and senior nurse practitioners)[52]	Hospitalized patients (n = 225)	6 months	Total number of medications reduced in intervention compared with control group	No effect on mortality or frequency of acute hospital transfers
Medication reviews prepared by the pharmacist; educating nurses on common issues in geriatric pharmacotherapy; geriatrician also considered the medication review[53]	Nursing homes (n = 3230)	1 year	Significant reduction in total number of medications when clustering effect was not accounted for	No effect on morbidity or survival

(*continued on next page*)

Table 2
(*continued*)

Intervention Type	Study Setting[a]	Duration of Follow-Up	Study Results	
			Impact on Prescribing	Impact on Outcomes
Case conference involving health professionals including physician, pharmacist, nurses and nursing assistant[54]	Nursing homes (n = 1854)	1 year	Significant reduction in the prescribing of antipsychotics, benzodiazepine hypnotics, and antidepressant medications	Not assessed
Computer feedback-based interventions				
A standardized medication review was conducted and recommendations made to the primary physician via the electronic medical record[55]	Community dwelling (n = 620)	1 year	Nonsignificant reduction in the number of medications	Nonsignificant reduction in falls

Abbreviations: ADRs, adverse drug reactions; GEM, geriatric evaluation and management.
[a] N refers to number of patient participants.
[b] Sample size for patient participants not available.

using electronic medical records-based interventions to reduce medication exposure, and the impact on prescribing and outcomes in older adults.

EFFECTIVENESS OF TRIALS TO REDUCE MEDICATION EXPOSURE

Assessing the effectiveness of a range of interventions on prescribing and clinical benefits is challenging because of the range of outcomes measured across studies, as well as differences in the study designs, settings, and types of interventions (**Fig. 2**). While in some studies the main outcome measure was the surrogate outcome of the change in number of medications, other studies selected more clinically relevant outcomes such as hospitalizations, falls, or mortality. Selecting appropriate clinical outcome measures may be the key to significant changes in medication-related outcomes.[57] Associations between medication exposure and clinical outcomes may differ between older people from different settings, with significant differences even observed between studies in different residential aged care facilities.[58] A reduction in number of medications may not be the most appropriate outcome, because this reflects the quantity not the quality of prescribing and does not reflect the need for clinically indicated medications.[6] The lack of effect of interventions may be due to the methods used to collect outcome data and duration of follow-up. For example, recording outcome data from nursing home records may result in misclassification of outcomes, because it may be difficult to establish the causal relationship between medications and these outcomes.[39,53] Two or 3 months of follow-up may not provide evidence on the long-term impact of the interventions.[40,50]

The type of the intervention appears to affect the outcome in some studies. For instance, multidisciplinary interventions,[47,52] personal contact, or academic detailing with the physician[46] seem to demonstrate more significant impact on reducing prescribing than providing educational material alone. However, multidisciplinary interventions may be resource intensive, and it may be difficult to implement such interventions at the population level. To make these interventions more applicable and generalizable between health professionals and across different settings, the risk assessment tools based on the drugs or drug classes known to increase the risk of adverse events could be used to identify medicines to stop in older adults.[18,59] The inclusion of such risk assessment tools may improve the process of identifying those patients most at risk of the adverse effects of polypharmacy.[60]

SUMMARY

Different styles of interventions can reduce medication exposure in older adults. However, the evidence for their clinical effectiveness and sustainability is conflicting and lacking. There are some data to guide clinicians on which medicines are more likely to be inappropriate in older people, which medicines are more likely to cause ADWEs, and which medicines should be tapered slowly rather than stopped. To reduce the likelihood of clinically significant adverse events, clinicians should undertake a step-wise approach to discontinuing medications and do so under appropriate supervision. Further research to determine the most effective ways to discontinue medications, and to provide a better understanding of the clinical benefits of various interventions is required. Large RCTs evaluating multidisciplinary interventions and clinical outcomes of changes in medicines regimen across different settings are required to confirm the findings of the studies performed so far.

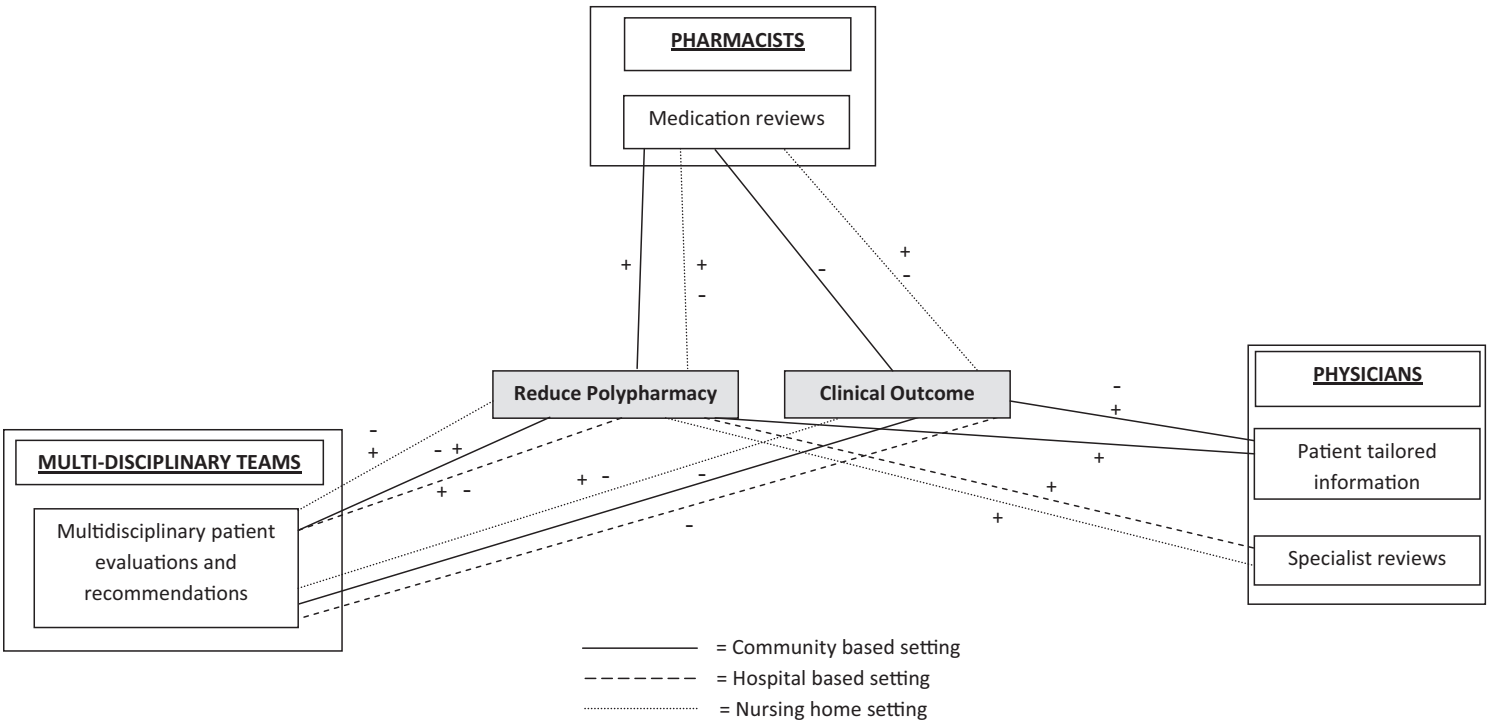

Fig. 2. The impact of methods to reduce medications on polypharmacy exposure and clinical outcomes in older adults. Different line patterns correspond to different study settings. Community based setting includes studies conducted in outpatient clinics. Symbols + (significant reduction in number of medications and/or improved outcomes) or – (non significant effect on number of medications or on outcomes) indicate the impact of methods on polypharmacy and clinical outcomes.

REFERENCES

1. Van Spall HG, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 2007;297:1233–40.
2. Hilmer SN, Gnjidic D, Abernethy DR. Pharmacoepidemiology in the postmarketing assessment of the efficacy and safety of drugs in older people. J Gerontol A Biol Sci Med Sci 2012;67:181–8.
3. Linjakumpu T, Hartikainen S, Klaukka T, et al. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol 2002;55:809–17.
4. Gnjidic D, Cumming RG, Le Couteur DG, et al. Drug Burden Index and physical function in older Australian men. Br J Clin Pharmacol 2009;68:97–105.
5. Wilson NM, Hilmer SN, March LM, et al. Associations between Drug Burden Index and falls in older people in residential aged care. J Am Geriatr Soc 2011;59:875–80.
6. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther 2009;85:86–8.
7. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother 2007;5:345–51.
8. Jorgensen T, Johansson S, Kennerfalk A, et al. Prescription drug use, diagnoses, and healthcare utilization among the elderly. Ann Pharmacother 2001;35:1004–9.
9. Bjerrum L, Sogaard J, Hallas J, et al. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. Eur J Clin Pharmacol 1998;54:197–202.
10. Crentsil V, Ricks MO, Xue QL, et al. A pharmacoepidemiologic study of community-dwelling, disabled older women: factors associated with medication use. J Am Geriatr Soc 2010;8:215–24.
11. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet 2007;370:185–91.
12. Beer C, Loh PK, Peng YG, et al. A pilot randomized controlled trial of deprescribing. Ther Adva Drug Saf 2011;2:37–43.
13. Iyer S, Naganathan V, McLachlan AJ, et al. Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs Aging 2008;25:1021–31.
14. Loganathan M, Singh S, Franklin BD, et al. Interventions to optimise prescribing in care homes: systematic review. Age Ageing 2011;40:150–62.
15. 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.
16. Verrue CL, Petrovic M, Mehuys E, et al. Pharmacists' interventions for optimization of medication use in nursing homes: a systematic review. Drugs Aging 2009;26:37–49.
17. Hughes CM, Lapane KL. Pharmacy interventions on prescribing in nursing homes: from evidence to practice. Ther Adva Drug Saf 2011;1–10.
18. Gnjidic D, Le Couteur DG, Abernethy DR, et al. A pilot randomized clinical trial utilizing the drug burden index to reduce exposure to anticholinergic and sedative medications in older people. Ann Pharmacother 2010;44:1725–32.
19. Bain KT, Holmes HM, Beers MH, et al. Discontinuing medications: a novel approach for revising the prescribing stage of the medication-use process. J Am Geriatr Soc 2008;56:1946–52.
20. Graves T, Hanlon JT, Schmader KE, et al. Adverse events after discontinuing medications in elderly outpatients. Arch Intern Med 1997;157:2205–10.
21. Gerety MB, Cornell JE, Plichta DT, et al. Adverse events related to drugs and drug withdrawal in nursing home residents. J Am Geriatr Soc 1993;41:1326–32.

22. Le Couteur DG, Banks E, Gnjidic D, et al. Deprescribing. Australian Prescriber 2011; 34:182–5.
23. MacLaughlin EJ, Raehl CL, Treadway AK, et al. Assessing medication adherence in the elderly: which tools to use in clinical practice? Drugs Aging 2005;22:231–55.
24. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ 1997;315:1096–9.
25. Hardy JE, Hilmer SN. Deprescribing in the last year of life. J Pharm Res 2011;41.
26. Zarowitz BJ, Stebelsky LA, Muma BK, et al. Reduction of high-risk polypharmacy drug combinations in patients in a managed care setting. Pharmacotherapy 2005;25: 1636–45.
27. Tamai IY, Rubenstein LZ, Josephson KR, et al. Impact of computerized drug profiles and a consulting pharmacist on outpatient prescribing patterns: a clinical trial. Drug Intell Clin Pharm 1987;21:890–5.
28. Britton ML, Lurvey PL. Impact of medication profile review on prescribing in a general medicine clinic. Am J Hosp Pharm 1991;48:265–70.
29. Blakey SA, Hixson-Wallace JA. Clinical and economic effects of pharmacy services in geriatric ambulatory clinic. Pharmacotherapy 2000;20:1198–203.
30. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. Arch Intern Med 2010;170:1648–54.
31. Fillit HM, Futterman R, Orland BI, et al. Polypharmacy management in Medicare managed care: changes in prescribing by primary care physicians resulting from a program promoting medication reviews. Am J Manag Care 1999;5:587–94.
32. Tamura BK, Bell CL, Lubimir K, et al. Physician intervention for medication reduction in a nursing home: the polypharmacy outcomes project. J Am Med Dir Assoc 2011;12:326–30.
33. Muir AJ, Sanders LL, Wilkinson WE, et al. Reducing medication regimen complexity: a controlled trial. J Gen Intern Med 2001;16:77–82.
34. Thompson JF, McGhan WF, Ruffalo RL, et al. Clinical pharmacists prescribing drug therapy in a geriatric setting: outcome of a trial. J Am Geriatr Soc 1984;32:154–9.
35. King MA, Roberts MS. Multidisciplinary case conference reviews: improving outcomes for nursing home residents, carers and health professionals. Pharm World Sci 2001;23:41–5.
36. Zermansky AG, Petty DR, Raynor DK, et al. Randomised controlled trial of clinical medication review by a pharmacist of elderly patients receiving repeat prescriptions in general practice. BMJ 2001;323:1340–3.
37. Hanlon JT, Weinberger M, Samsa GP, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med 1996;100:428–37.
38. Zermansky AG, Alldred DP, Petty DR, et al. Clinical medication review by a pharmacist of elderly people living in care homes-randomised controlled trial. Age Ageing 2006; 35:586–91.
39. Furniss L, Burns A, Craig SK, et al. Effects of a pharmacist's medication review in nursing homes. Randomised controlled trial. Br J Psychiatry 2000;176:563–7.
40. Williams ME, Pulliam CC, Hunter R, et al. The short-term effect of interdisciplinary medication review on function and cost in ambulatory elderly people. J Am Geriatr Soc 2004;52:93–8.
41. Kroenke K, Pinholt EM. Reducing polypharmacy in the elderly. A controlled trial of physician feedback. J Am Geriatr Soc 1990;38:31–6.
42. Meyer TJ, Van Kooten D, Marsh S, et al. Reduction of polypharmacy by feedback to clinicians. J Gen Intern Med 1991;6:133–6.

43. Schmader KE, Hanlon JT, Pieper CF, et al. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. Am J Med 2004;116:394–401.
44. Allard J, Hebert R, Rioux M, et al. Efficacy of a clinical medication review on the number of potentially inappropriate prescriptions prescribed for community-dwelling elderly people. CMAJ 2001;164:1291–6.
45. Pitkala KH, Strandberg TE, Tilvis RS. Is it possible to reduce polypharmacy in the elderly? A randomised, controlled trial. Drugs Aging 2001;18:143–9.
46. Avorn J, Soumerai SB. Improving drug-therapy decisions through educational outreach. A randomized controlled trial of academically based "detailing". N Engl J Med 1983;308:1457–63.
47. Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care-the POLYMED randomised controlled trial. Age Ageing 2007;36:292–7.
48. Steele MA, Bess DT, Franse VL, et al. Cost effectiveness of two interventions for reducing outpatient prescribing costs. DICP 1989;23:497–500.
49. Lipton HL, Bird JA. The impact of clinical pharmacists' consultations on geriatric patients' compliance and medical care use: a randomized controlled trial. Gerontologist 1994;34:307–15.
50. Owens NJ, Sherburne NJ, Silliman RA, et al. The Senior Care Study. The optimal use of medications in acutely ill older patients. J Am Geriatr Soc 1990;38:1082–7.
51. Rubenstein LZ, Josephson K, Wieland GD, et al. Geriatric assessment on a subacute hospital ward. Clin Geriatr Med 1987;3:131–43.
52. Pope G, Wall N, Peters CM, et al. Specialist medication review does not benefit short-term outcomes and net costs in continuing-care patients. Age Ageing 2011;40: 307–12.
53. Roberts MS, Stokes JA, King MA, et al. Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes. Br J Clin Pharmacol 2001;51: 257–65.
54. Schmidt I, Claesson CB, Westerholm B, et al. The impact of regular multidisciplinary team interventions on psychotropic prescribing in Swedish nursing homes. J Am Geriatr Soc 1998;46:77–82.
55. Weber V, White A, McIlvried R. An electronic medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. J Gen Intern Med 2008;23:399–404.
56. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003;163:1409–16.
57. Majumdar SR, Soumerai SB. Why most interventions to improve physician prescribing do not seem to work. CMAJ 2003;169:30–1.
58. Wilson N, Gnjidic D, March L, et al. Use of PPIs are not associated with mortality in institutionalized older people. Arch Intern Med 2011;171:866.
59. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther 2011;89:845–54.
60. Gnjidic D, Le Couteur DG, Abernethy DR, et al. Reducing drugs in older adults is more. Arch Intern Med 2011;171:868–9.