REDUCING INAPPROPRIATE POLYPHARMACY FOR OLDER PATIENTS AT SPECIALIST OUTPATIENT CLINICS: A SYSTEMATIC REVIEW

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Abstract

Aim: Deprescribing interventions may reduce inappropriate polypharmacy and the associated negative clinical consequences. This systematic review examined current research on the effectiveness of deprescribing interventions implemented within specialist outpatient clinics. Methods: This systematic review was informed by a literature search on 18/10/21 of publications from January 1990 in PubMed and Embase. Studies were included if they focused on patients [?]60 years and measured change in medication burden (defined by number of medications or number of inappropriate medications) as result of an intervention conducted within a specialist outpatient clinic. Methodological quality was assessed by 2 authors using the revised Cochrane risk-of-bias tools. Due to significant heterogeneity between trials, a qualitative synthesis was completed. The primary outcome reviewed was change in medication count or potentially inappropriate medication. Secondary outcomes were maintenance of deprescription and clinical benefits. Results: 19 studies were included for review that included 10,914 participants. They included geriatric outpatient clinics, oncology/haematology clinics, haemodialysis clinics and designated polypharmacy/multimorbidity clinics. Seven RCTs were identified. Other studies included retrospective evaluations and prospective/pilot studies. Four RCTs reported statistically significant reduction of medication burden with intervention, however all studies were assessed as having a high risk of bias. The studies could be grouped into those where the deprescribing intervention was physician-led and implemented, delivered from a multidisciplinary team, or pharmacist-led and physician implemented. Conclusion: The evidence for deprescribing interventions in outpatient clinics is very limited and further research is recommended. The addition of a pharmacist and validated medication assessment tools appear to be enablers.

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Short Running Title: Deprescribing at outpatient clinics

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Conclusion: The evidence for deprescribing interventions in outpatient clinics is very limited and further research is recommended. The addition of a pharmacist and validated medication assessment tools appear to be enablers.

INTRODUCTION

Polypharmacy is the use of multiple medications by a single patient (most commonly defined as five or more concomitant regular medications).[1] Individuals over the age of 60 years are commonly seen to be taking several medications. The main contributor to this is multimorbidity, with most adults over 65 years having at least two chronic conditions.[2] From 2009-2016, 37% of patients over 65 years of age attending US Physician offices were found to be taking over 5 medications.[3] Similarly high rates of polypharmacy in have also been found in other countries[4,5] Within residential care, studies have found that there may be as many as 91% of patients taking more than five medications and up to 74% of patients taking in excess of nine medicines.[6]

Polypharmacy itself has been clearly associated with a broad range of negative clinical consequences.[7] These consequences include a decrease in compliance, increased risk of adverse drug events, falls, impaired cognition, decrease in physical function, hospital admission and increased frailty.[8,9] The World Health Organization has highlighted polypharmacy as one of the key areas to prioritize in the mission to reduce medication harm.[10]

Depending on the individual, polypharmacy can be viewed as appropriate (where the clinical benefits from medication outweigh the risk of harm) or inappropriate. Achieving the desired balance between benefit and risk in patients with multimorbidity can often be challenging, given that evidence-based guidelines are usually for single health conditions. A medication that poses a greater risk of harm than benefit (particularly where there are safer or more effective alternatives) is termed a potentially inappropriate medication (PIM). A significant positive association has been described between the number of medications taken by an individual

and the likelihood of a PIM being used.[11] Multimorbidity, compounded by age-related pharmacodynamic and pharmacokinetic changes all increase the use of PIMS in the older population.[12]

Use of potentially inappropriate medications is commonplace. It is estimated that one in five community dwelling individuals older than 65 years are prescribed at least one medication that is considered inappropriate.[13] It has also been estimated that over a 5-year period, a quarter of all older Australians will be hospitalized for an adverse drug reaction.[14]

Interventions to reduce polypharmacy and enhance the deprescription of potentially inappropriate medications are the focus of current research. The process of deprescribing can often be complicated and requires individualization. While there are opportunities for intervention that start from the time of prescribing, it is still unclear how best to organize and implement processes to achieve a meaningful reduction in inappropriate polypharmacy. There have been several systematic reviews looking at the efficacy of deprescribing interventions within primary care,[15,16] within residential care,[17,18] and for hospital-inpatients.[19] However, another area that has been less well researched is the impact of interventions delivered within medical specialist outpatient clinics. Specialist clinics, such as general medicine, geriatric, oncology, cardiology, and haematology clinics, are likely to encounter patients with a high medication burden and increased risk of medication-related problems due to advancing age and multimorbidity. In patients reviewed at a heart failure clinic, 72% were taking eleven or more medications.[20] A recent study, found that 41% of people who attended a memory clinic were taking an inappropriate drug choice.[21] Similarly, a study of 248 geriatric oncology patients at an outpatient clinic found PIM use in 51% of individuals.[22] Although the patient may not be referred to a specialist outpatient clinic for a comprehensive assessment of all medications, there may be a possible opportunity here to promote deprescribing. This review aims to examine studies to date on the feasibility and effectiveness of deprescribing interventions implemented within specialist outpatient clinics.

METHODS

This systematic review was informed by a literature search performed by LC on 18th October 2021 of publications from January 1990 until the search date. The search terms included the following: Outpatients [All Fields] OR Geriatric Assessment [All Fields] AND Polypharmacy [All Fields] OR Deprescription [All Fields] in PubMed and Embase, as well as hand searches of reference lists of initially found publications. Studies were included if they were published in English and measured change in medication load as a result of an intervention conducted within the setting of a specialist outpatient clinic. Articles were excluded if the study was based within another medical setting or did not include our target patient group of older patients. Articles examining interventions relating to change in drug-related problems, but did not measure change in medication burden (as defined by number of medications or number of inappropriate medications) were excluded. Where change in number of inappropriate medications were measured, only trials using validated tools (implicit or explicit) were included. Studies using expert opinion or self-developed algorithms were only included if they measured total medication count, rather than number of potentially inappropriate medications. For this review, we focused on patients older than 60 years of age. Studies were included with younger patients if the majority were within the older age group.

Trials were assessed by two authors (LC and LH) for methodological quality according to the revised Cochrane risk-of-bias tools.[23,24] Smaller, pilot and prospective studies were also included in the analysis, given the limited research available and novel area under review.

The search resulted in 4,362 publications. After exclusion of 4,324 publications based on title and abstract and excluding 19 publications after full-text review, 19 were deemed to be eligible for inclusion in the review (Supplement 1).

The key characteristics of the eligible publications are summarized in Supplement 2. Due to substantial heterogeneity between studies, a qualitative synthesis of the literature was completed. The primary outcome reviewed was change in medication load as measured by a decrease in medication count or decrease in potentially inappropriate medication. Secondary outcomes reviewed included maintenance of deprescription and clinical benefits from deprescription.

RESULTS

All studies identified were assessed to have at least a moderate risk of bias and most had a critical risk of bias. Five RCTs and 2 pilot RCTs were identified. Four of these studies reported a statistically significant reduction of medications or PIMS in the control group. However, many studies were of small size, completed at a single centre, and were pilot studies or prospective in design.

The identified studies span a range of specialist outpatient clinics. The majority of interventions have been evaluated within geriatric outpatient clinics.[25-32] Two studies measured deprescribing interventions in oncology/haematology clinics,[33,34] and 2 studies examined outpatient haemodialysis patients.[35,36] Other locations included a memory clinic,[37] heart failure clinic,[38] and geriatric preoperative clinic[39] and pilot studies looking at designated polypharmacy/multimorbidity review clinics.[40-43]

The included studies ranged from no follow-up post-intervention, to 2-years of follow-up. They have used a range of screening instruments to identify PIMs and to review, optimize, and assess deprescription of medications. The well validated Beers criteria[44] and STOPP/START criteria[45] were the most often used explicit tools applied to identify PIMS. The Medicines Appropriateness Index (MAI) was also used in some instances as an implicit tool to assess the appropriateness of all medication by looking at indication, efficacy, dose, directions, interactions, duration, duplication, and cost.[46] Less well published tools adopted include the Individualised Medication Assessment and Planning (iMAP) tool that has been more recently developed specifically for assessing and resolving medication-related problems in outpatients[47] and the FORTA (Fit for the Aged) list and scoring system, which evaluates patients medication for undertreatment, overtreatment, and mistreatment.[48] Several other studies have used their own algorithms and grouped medication related issues into a set of 'drug-related problems'.[33,38] Within specialized settings, such as oncology, palliative care, and haemodialysis, the need for additional screening tools has been identified as essential to address condition-specific considerations, such as specific drug-interactions or intolerances and treatment goals.[36,49]

DISCUSSION

The participants in all included studies had a high prevalence of polypharmacy (mean number of medications ranged from 4.6 to 23.2 [SD 4.7]), multimorbidity, and use of PIMS. The studies were heterogenous with regards to how medication count was captured. Some studies incorporated 'when required (*pro re nata, PRN)* ' medications or self-prescribed (over-the-counter) medications. Pill burden (as assessed by a living with medicines questionnaire) and tablet count was examined in one study.[36] The definition of polypharmacy was consistent between studies with five or more medicines classified as polypharmacy. The mean number of medications for study participants varied between settings, with medication load being highest for individuals attending the heart-failure clinic and renal dialysis units.[35,38] Polypharmacy and increase in pill burden has previously been associated with reduced compliance and quality of life scores in dialysis patients[50] and negative medication interactions in heart-failure patients.[51] A high medication burden was also notable for oncology patients [?]65 years, where polypharmacy and use of PIM is associated with an increased risk of postoperative complications, lower adherence to medication, and increased chemotherapy toxicity.[52]

The prevalence of PIM use between settings varied from 55% to 100% of patients depending on the assessment tools used.[26,34]It is known that the sole use of explicit tools such as Beers or STOPP is insufficient to address all medication concerns. Use of a combination of three validated instruments (STOPP, Beers, and MAI) was found to be superior and identified significantly more PIMS than a single instrument alone when reviewed in the oncology setting.[34] Another recent study in an oncology unit noted that while 46% of patients were identified as taking a PIM using Beers criteria, the number of patients identified with 'drug-related problems' was 95%.[53]'Drug related problems' not revealed using explicit tools may include under treatment, dosing concerns, lack of monitoring, and compliance with therapy. It should be noted that adverse drug-reactions may also occur with so called 'appropriate medications'; anticoagulants, antiplatelets, and antidiabetics (both oral and insulin) have been found to be more frequently implicated in hospital admissions, than the usual 'medications to avoid' lists.[54] Thus, accurately assessing the medication burden and appropriateness of medication for each individual is a complicated process.

The identified studies could be grouped into those where the deprescribing intervention was physician-led and implemented, delivered from a multidisciplinary team with pharmacist support, or pharmacist-led, physician implemented.

Physician-led interventions

There were 3 RCTs that looked at Physician-led medication changes occurring as a result of a comprehensive geriatric assessment (CGA).[26,32,39] All showed an improvement in appropriateness of medication as demonstrated by a decrease in use of PIMS or improvement in MAI. However, a reduction in total medication count was not achieved in the retrospective study completed by Lampela et al. with the overall medication burden increasing by a mean of 0.5 medications at 12 months.[26] Another retrospective evaluation of CGA medication changes also noted an increase in medications.[27] The increase in medications noted in the retrospective studies suggested that deprescribing may not be a main priority during routine assessments. A more recently completed performance improvement project at an outpatient geriatric clinic demonstrated that deprescribing was possible by geriatricians at routine patient encounters with integration of a deprescribing algorithm.[25] This study was physician-led and implemented, but concluded that deprescribing would be more positively influenced by systematic multidisciplinary medication review. Another study reviewed the challenges of physician-led deprescribing of inappropriate medications within geriatric outpatient clinics. The data collected from this pilot study had notable limitations; however, it was interesting to note that the major barrier cited was establishing an accurate medication history – a challenge that may be overcome by pharmacist inclusion.[55]

Multi-disciplinary interventions including pharmacy support

The inclusion of a pharmacist into an outpatient clinic may be an enabler to improve deprescribing. The benefit of clinical pharmacists for successful deprescription has been highlighted in a number of studies in different clinical settings.[15,56]Additionally, studies looking at integrating clinical pharmacy services within outpatient clinics have already demonstrated benefits in terms of improving medication management and drug-related problems.[57-59]

A retrospective case-controlled study was identified that included a pharmacist in the multidisciplinary team of a geriatric outpatient clinic. This found the mean number of medications in the intervention group was able to be reduced by approximately eight medications (from 23 to a mean of 15 medications), with no change in the control group.[28] However, it was noted that the intervention group had a higher number of medications at baseline, which may have given greater opportunity to deprescribe.

The idea of a designated outpatient polypharmacy clinic has been explored in a few small pilot studies and most included a pharmacist in the team.[40-43,60] All studies demonstrated benefits, but had a high risk of bias. One study noted that the attendance of both a clinical pharmacologist and pharmacist throughout the intervention was unnecessary and recommended that a pharmacist-led service would be more time and cost efficient.[40]

One study was identified that examined the impact of a computer decision support tool containing both implicit guidelines and STOPP/START criteria to a multidisciplinary team at a preoperative review clinic.[39] This study found that the number of PIMS decreased significantly. Some of the known barriers to successful deprescribing include time constraints, self-efficacy, and availability of resources.[61] The availability of easy access to structured deprescribing tools has been highlighted as an enabler to deprescribing.

Pharmacist-led, Physician-implemented interventions

Several small pilot studies in different outpatient clinic settings have explored pharmacist-led deprescribing interventions with positive outcomes.[33,34,37,38,42] However, one RCT did not find reduction of medication with addition of a pharmacist consult to a geriatric outpatient clinic.[31] A notable difference with this study is that the patient was directed to the pharmacist consult clinic after (rather than prior) to geriatrician consultation and no formal deprescribing tool or process was described. The way in which the pharmacist is incorporated into the team may have an effect on efficacy.

Within an oncology outpatient unit, two small prospective studies examined the benefit of pharmacist-led real time deprescribing.[33,34] Both demonstrated a significant decrease in the prevalence of PIMS use based on validated tools and a reduction in mean number of medications per patient. However, both studies had considerable confounding factors and potential for bias. It was noted that updating the medication list to remove medications no longer taken by the patient was also considered as a deprescribing intervention in one study.[34] Similar pharmacist-led studies have looked at identifying and reducing 'drug-related problems in oncology outpatients'.[53,62] These did not meet the criteria to be included in the systematic review, but it was noted that that the most commonly identified drug-related problem was unnecessary drug therapy and the most frequent recommendation was discontinuation of a drug.

The feasibility of a pharmacist-led deprescribing intervention was also examined in a small study completed within the setting of a memory clinic. In this trial, a home medication review and polypharmacy assessment was completed prior to the clinic visit and communicated to the physician via a written report. Thirty of the 46 patients had medications ceased; however, there was no overall significant change in number of medications or PIMs noted 6-months after intervention.[37]

A novel subacute medical outpatient unit was able to demonstrate sustainable deprescribing with a pharmacist-led collaborative intervention in a recent feasibility study.[42] Another study concluded that the addition of a pharmacist-led medication review to usual care in an outpatient heart failure clinic may improve drug-related problems and trend towards a reduction in medication burden.[38] Although unable to meet the criteria for this systematic review, preliminary studies have also suggested benefits from pharmacist led medication optimization for older patients within diabetes clinics, HIV clinics, cardiology, palliative care, and neurology clinics.[59,63-66]

Use of a pharmacist to complete a medication reconciliation and polypharmacy assessment has notable advantages in terms of reducing physician time and workload. Medication assessments are time consuming; medication reviews of geriatric patients are documented to take between 20 and 140 minutes.[53,62,67]

In the reviewed studies, pharmacist medication assessments were either completed remotely by review of electronic patient records,[38] face-to-face in the clinic,[31,33,34,42,60] or at a home visit.[37] Information sharing between the pharmacist and patient is necessary to establish understanding of medications, expectations they may have from treatment and previous (negative) experiences, thus patient-record only reviews have significant limitations.[39] A medication review performed in the home requires a longer duration, but the accuracy of the medication history could be increased; Cross et al. noted that 76% of patients had discrepancies between actual medication used (as obtained by the pharmacist at the home visit) compared to the documented medication history. A home medication review has previously been identified as a positive way to improve prescribing and determine medication related problems unknown to other healthcare providers.[68,69]

The ability of pharmacists to identify meaningful recommendations was highlighted by an acceptance rate from the physician of 40% to 69%.[37,38,42,53,62] Further research is needed to identify the best methods of communicating recommendations, such as verbal communication versus patient-physician written communication.

Medication changes after review

Medications most commonly deprescribed successfully and consistently in the reviewed studies included multivitamins, proton pump inhibitors, antihypertensives, and analgesics. Statins were also able to be easily deprescribed in patients with limited life expectancy.[25,34] Antidementia drugs and antipsychotics were reduced after CGA[29]; however, another study noted that antipsychotics were often psychiatrist managed and this was a barrier to deprescribing attempts.[25] Another perceived barrier to deprescribing cited by doctors was a lack of information regarding the indication of medications. This was highlighted as a significant reason why proton pump inhibitors are continued.[35] (A particular concern given the possible long-term effects of proton-pump inhibitors, including an increased risk of gastric cancers).[70] It was noted that the medications identified as inappropriate in these outpatient clinics are similar to those highlighted in other

clinical settings.[13,71]

In the haemodialysis outpatient unit, targeted deprescribing of quinine, diuretics, statins, α1-blockers, and proton pump inhibitors was effective using a medication algorithm.[35] In the memory clinic, medications affecting cognition were a focus and they were able to deprescribe benzodiazepines and tricyclic antidepressants.[37] It was suggested that deprescription may be most successful when targeting select classes of drugs and following patient-specific drug recommendations.[15]

Secondary outcomes

There was minimal data on secondary outcomes from deprescription interventions in outpatient settings. One study followed patients receiving regular CGA over 2 years and concluded a significant reduction in primary care utilization, in addition to a reduction in medication burden.[28] In three pilot studies a reduction in medication related side-effects was reported[34,37,40]and reduction in blood pressure was evident after 2 weeks at the heart failure clinic in a pilot study.[38] At the perioperative clinic no difference in postoperative mortality was noted 3-months after deprescribing intervention[39] and after pharmacist-led deprescribing at the memory clinic, participants did not appear to experience any change in health outcomes or quality of life at 6-months.[37] It is noted that the benefit from deprescribing interventions on clinical outcomes is not strongly evidenced from any clinical setting at this stage. Some systematic reviews have failed to demonstrate any significant benefits from deprescribing on clinical outcomes.[72] A recent review cited benefits for deprescribing interventions on mental health, functional status and frailty, but results for cognition and falls were mixed.[73]

Strengths and limitations

This is the first systematic review to investigate deprescribing interventions within specialist outpatient clinics. However, this review was limited to studies in English and those published after 1990. The broad search strategy needed to capture all relevant trials yielded a high number of initial results.

Due to significant heterogeneity between trials, a meta-analysis could not be completed. Conclusions on the efficacy of interventions conducted within this setting could not be made due to the few studies identified and the low quality of many of the trials. Only 7 randomized controlled trials were identified[26,28,31,32,38,39,42] and randomization was adequate in only 1 study.[32] There was a moderate-critical risk of bias identified in all included studies that should be considered when interpreting results.

Conclusion

A specialist outpatient clinic provides an additional setting to review for inappropriate medication use, especially for older patients who are often co-morbid and at significant risk of polypharmacy. Deprescribing for hospital inpatients may not be a focus during an acute admission, and in primary care general practitioners might be reluctant to cease medications prescribed elsewhere. A specialist outpatient clinic provides a setting for experts to appraise medical conditions that might change the risk-benefit profile of existing medications. While the evidence for deprescribing interventions in outpatient clinics is very limited, the addition of a pharmacist and use of validated medication assessment tools appear to be significant enablers. The most effective way to incorporate the deprescribing intervention has not been established and requires more research, but it might involve a multidisciplinary clinic that includes a pharmacist or a targeted pharmacist-led, physician-implemented intervention. It is also possible that the existence of a specific polypharmacy service could help to break the lack of intervention for patients with high medication burdens. Further research is recommended to confirm if this approach is effective, if the changes can be maintained, and if this approach translates to clinical benefit.

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Conflicts of interest

The Authors declare no conflict of interest.

Authors' contributions

LC conceived the research question and designed the study; undertook the literature review and data extraction; conducted the risk of bias assessment and interpreted the data; drafted the article and prepared the manuscript after review and critique. LH conducted the risk of bias assessment; provided critical assessment of the paper for important intellectual content; and provided final approval. TK and AL provided guidance, review and critical assessment of the manuscript and approved the final version.

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