Deprescribing: An intervention to reduce inappropriate polypharmacy

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ABSTRACT

BACKGROUND: Inappropriate polypharmacy (a situation which occurs when a medicine’s risk outweighs its benefit) is on the rise, partly because prescribers tend to follow guidelines for single diseases resulting in multiple medications in co-morbid patients and sometimes failures to consult reference sources to consider possible drug interactions. Inappropriate polypharmacy do cause adverse drug reactions, hospitalisations, medication non-adherence, drug reactions, falls and malnutrition. Deprescribing, the process of withdrawing an inappropriate medicine under the supervision of a health care professional is an intervention which can be used to reduce inappropriate polypharmacy. Although not new, not much deprescribing has been carried out in the UK and the world at large.

OBJECTIVES: To highlight the evidence available to support deprescribing and to determine if it does improve any clinical outcomes.

METHOD: “Deprescribing” was searched in Medline. The search yielded 123 results. Following removal of duplicates, 23 articles were reviewed for eligibility. Of these, 22 were retrieved for full text assessment and 9 were subsequently used for the review. Only trials in English that deprescribed one or more regular medicines with the participants being 65 years or older were included. No limitations were put on the setting.

RESULTS: Our search resulted in 9 studies which included 2 systematic reviews, 5 randomised controlled trials, 1 prospective feasibility and 1 prospective cohort study. Control and intervention groups of trials were similar in characteristics such as age and co-morbidities. The results involved 36,032 elderly adults who were 65 years and above and had 26 different types of drugs targeted for deprescribing. Deprescribing was found to reduce mortality, falls, hospitalisation and improve sleep quality in some of the studies.

CONCLUSION: Deprescribing is possible and does reduce inappropriate polypharmacy. In some of the trials there was a positive effect of deprescribing on mortality, falls and hospitalisation whilst others did not find any such effect. Future research needs to focus on the effect of deprescribing on improving clinical outcomes.

INTRODUCTION

The use of many medicines (polypharmacy) for the elderly is on the rise and has become a global issue. It is prevalent across the various healthcare settings with approximately 20% of all adults taking five or more medications and up to 70% of hospitalised older adults exposed to it (Reeve et al., 2015). Polypharmacy may be appropriate or inappropriate. Inappropriate polypharmacy occurs when the risk associated with a drug exceeds its benefits, or if the intended benefit of a drug is not realised. These untoward effects occur as a result of adverse drug reactions, drug-to-drug interactions and drug disease interactions. Although the adverse effects of polypharmacy and that of co-morbidities targeted for treatment in the elderly are similar, observational data suggests that inappropriate polypharmacy independently increases the risk of frailty, falling and hospital admission (Potter et al., 2016). It is therefore necessary that appropriate interventions are employed to reduce inappropriate polypharmacy. On such intervention is deprescribing. In the absence of an available evidence-based clinical practice guidelines for deprescribing, I aim
to review the applicable evidence which can be used to deprescribe medicines in the elderly if need be, as well as reviewing some of the clinical outcomes which have been measured in deprescribing trials.

**Pharmacokinetic and Pharmacodynamic changes in the elderly**: Older people are at high risk of adverse drug effects and toxicity due to reduced renal and liver function, and age-related changes in physiological reserve, body composition and cellular metabolism (Potter et al., 2016, 2). These pharmacokinetic and pharmacodynamic changes are briefly described below.

**Absorption**: There are several physiologic changes that occur in the gastrointestinal tract as one ages. This includes reduction in intestinal blood flow, decreased gut motility and delayed gastric emptying. Gastric acid production may be reduced, although this may be caused by atrophic gastritis that frequently occurs in old age rather than a natural ageing process. There is evidence that the active diffusion of some nutrients such as iron, calcium, and vitamin B12 is diminished; however, most drugs are absorbed passively and appear not to be affected (Sera and McPherson 2012, 274).

**Distribution**: The distribution of a drug is primarily dependent on its volume of distribution and the extent of protein binding both of which may be affected by the ageing process. Two major proteins, albumin and 1-acid glycoprotein do bind to drugs determining the amount of free molecules of the drug available to exert a pharmacologic action. Increases in 1-acid glycoprotein are seen in many age-related disorders such as cancer and inflammatory disease, and may decrease the pharmacologically active free fraction of lidocaine, propranolol, and other basic drugs. The level of albumin also tends to be low in the elderly. This results in high levels of acidic drugs such as warfarin, phenytoin and naproxen. (Sera and McPherson, 2012, 275)

**Excretion**: Drugs are excreted mainly through the bile, urine, the lungs and the kidney. Reduction in kidney function alters the excretion of drugs, although this has been found to be a function of morbidity rather than increasing age. Reductions in renal function significantly affect the elimination of drugs such as diuretics, digoxin, lithium, and other water-soluble drugs. (Sera and McPherson, 2012, 277)

**Metabolism**: The metabolism of drugs via phase II reactions appears unchanged with ageing. The activity of cytochrome P450 enzymes has been studied in both in vitro and in vivo investigations and does not appear to change in old age, but there is still some question regarding age-related changes in phase I metabolism. There appears to be age-dependent differences in metabolic clearance of many drugs, including benzodiazepines, theophylline, imipramine, propranolol and indomethacin. Alprazolam and diazepam are bio-transformed by phase I enzymes to active metabolites, which may have a longer duration of action in elderly patients, whereas lorazepam and oxazepam undergo conjugation to inactive metabolites and are not affected by aging. It is important to keep in mind that polypharmacy may have a significant effect on hepatic metabolism, because aside from being substrates for phase I enzymes, many drugs either inhibit or induce their activity. (Sera and McPherson, 2012, 277)

**Deprescribing, what is it?**: Although a universally approved definition of deprescribing is not available, definitions from various literature suggest that deprescribing is a systematic process that involves withdrawing or reducing the dose of an inappropriate medication (one whose risk outweighs the benefit) under the supervision of a healthcare professional to improve patient outcomes. For example, Reeves and colleagues have defined it as the process of withdrawal of an inappropriate medication supervised by a healthcare practitioner with the goal of managing polypharmacy and improving patient outcomes (Reeves., et al 2015 13). whilst Scott and colleagues have defined it as the systematic process of identifying and discontinuing drugs in which existing or potential harm outweigh the potential benefit within the context of
an individual patient’s goals, current level of functioning, life expectancy, values and preferences (Scott et al., 2015 827). The effectiveness and safety of drugs may change with an increase in the age of an individual. The changes in pharmacokinetic and pharmacodynamics properties discussed earlier do account for this. Likewise there are drugs which may be useful in the short term but their long term use is questionable. For example, the long term use of high doses of statins and the use of beta blockers in preventing death and recurrent infarction has been questioned (Julian and Pocock, 2015, 325). Shorter life expectancy, cognitive impairment, pill burden and frailty often presented in the elderly do mean that deprescribing must be considered when deemed necessary. To deprescribe effectively, all medicine taken by an individual must be established and reviewed to determine inappropriate ones and the order in which they are to be stopped with adequate monitoring and follow up. Also, deprescribing has to adopt a patient-centred approach, elements of which include shared decision making, fostering a positive relationship between prescriber and the patient, and involvement of the patient’s general practitioner as they are perceived to have an existing relationship with their clients (Scott et al., 2015, 832). Hence the withdrawal programme must be actively managed by the doctor with the pharmacist, but owned by the patient. Preventative medicines are usually the target for deprescribing. Emerging evidence has shown that deprescribing strategies targeting individual or multiple drug classes are effective and may improve outcomes for patients. In literature, various medicines such as simvastatin, clopidogrel, aspirin, antidepressants and antihypertensive have been deprescribed.

RESULTS
Our search yielded 9 studies of which 2 were systematic reviews, 5 were randomised controlled trials, 1 prospective cohort study and 1 prospective feasibility study. For the randomised controlled trials, the intervention group was similar to the control group in terms of age, co-morbid conditions, number of medications they were taking, gender, cognitive function, etc. Patients were assessed by their physicians to determine their eligibility for the study. Medicines were withdrawn gradually under the supervision of a research nurse. Patients were seen regularly for monitoring either at the hospital, nursing homes, or their homes. For example, Nelson and colleagues monitored participant’s blood pressure weekly for the first two weeks and then monthly. The clinical notes of all the participants were reviewed 6 and 12 months after withdrawal of treatment (Nelson et al., 2002 2). Where necessary some of the studies carried out serum level analysis. For example, Garfinkle and colleagues did measure serum potassium and iron of participants who were being withdrawn their potassium and iron supplements (Garfinkle et al 1 2007). The results are summarised in Table 1.

DISCUSSION
From the results of this study, it is clear that both preventative and curative drugs can be depre- scribed in those over 65 years old without any, or much, negative consequences. The outcomes measured in the retrieved studies were number of drugs withdrawn, quality of life, mortality rate, adverse drug events, adverse drug withdrawal events, neuro psychiatric symptoms and cognitive function. Some of the randomised controlled trials reported significant difference in mortality, falls and hospitalisation between the intervention and the control group. Other trials did not show any difference in the cognitive function, quality of life and mortality in the intervention and control groups. Given that the control and
intervention groups were homogenous, we could explain that for those outcomes which did not change significantly between the groups, their effect was not just determined or affected by the number of drugs one takes. This review looked at active deprescribing rather than relying on indirect deprescribing methods such as recommendations to prescribers. Most of the papers retrieved for this study were randomised control trials, so the level of bias introduced into the study will be small. Only articles published in English were used. As such useful articles available in other languages will be missed. Sample sizes for some randomised control trials were small thus making it impossible to relate the results to the entire population.

CONCLUSION
There is evidence available in support of deprescribing various classes of medicines with little or no adverse consequences. In some of the trials there was a positive effect of deprescribing on mortality, falls and hospitalisation, whilst other trials did not find any such effect. Future research needs to focus on the effect of deprescribing on improving clinical outcomes.

REFERENCES


About the Author:
Irene Boateng has been practising as a pharmacist for the past 13 years. Her work as a pharmacist has made her develop great clinical skills. She obtained her Bachelor’s degree from the University of Science and Technology in Ghana, a Postgraduate Diploma in Pharmaceutical sciences from the University of Sunderland and is currently a PhD student at the University of Lincoln. Her research interest is inappropriate polypharmacy in the frail elderly and she hopes to, in her research, estimate the prevalence of the problem in over 75 year olds and identify the risk factors associated with it.
### Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Setting</th>
<th>Drugs Deprescribed</th>
<th>Indications</th>
<th>Participants</th>
<th>Outcome &amp; Results</th>
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| Page et al     | Systematic Review | Community Hospital & Nursing Homes | • Antidiabetics  
• Potassium supplements  
• Anti-hypertensives  
• Anti-platelets  
• Digoxin  
• Statins  
• Diuretics  
• Bisphosphonates  
• Prednisolone  
• Antipsychotics  
• Anti-cholinesterase  
• Nitrites  
• Antihypertensives  
• Salbutamol  
• Alpha blockers  
• Cilostazol  
• Pentoxifylline  | • Diabetes  
• Hypertension  
• Arrhythmias  
• Primary prevention of coronary heart diseases  
• Osteoporosis  
• Asthma  
• Psychosis  
• Depression  
• Enlarged prostate  
• Peripheral vascular diseases  | 34,143 elderly adults  | Main outcome was mortality. Secondary outcomes were adverse drug withdrawal events and adverse drug reactions. 10 studies reported findings on mortality. Across those studies, deprescribing did not significantly modify mortality OR 0.82 (95% CI: 0.61-1.11) (Page et al., 2016 615). However in two studies they indicated significant reduction in mortality OR 0.32, 95% CI 0.17-0.60. Participants were 257 (Page et al., 2016 615). Deprescribing of single medicines in Randomised Controlled trials (RCT) was not associated with a significant difference in mortality e.g. deprescribing antipsychotics didn’t significantly reduce mortality OR 0.59 95% CI 0.33-1.07 participants were 453. The number of studies was 5 (Page et al., 2016 5) Again, deprescribing of single medicines in non-randomised trials was not associated with a reduction in mortality. With regards to secondary outcomes, deprescribing didn’t significantly improve the risk of experiencing at least one fall OR 0.65 95% CI 0.4-1.05 participants were 2173 (Page et al., 2016 615). However participants who did fall had significantly fewer falls overall in the de-prescribing group compared to those in the control group. MD -0.11 95% CI -0.21 -0.02 participants = 844 studies= 3. (Page et al., 2016 615). Deprescribing did not significantly affect the incidence of adverse drug withdrawal events and adverse drug events. It was not associated with significant changes in quality of life except in one study where deprescribing produced a significant yet modest findings that it slows the decline in quality of life. MD 0.03 95% CI 0.01-0.06 participants = 189 (Page et al., 2016 615). |
<p>| Declereq, T et al | Systematic Review | Nursing homes and outpatient settings | • Psychotropic medicines  | Psychiatric diseases | 606 patients | The primary outcome was success of withdrawal and neuropsychiatric symptoms (NPS). 8 out of 9 trials reported no significant difference between groups on the primary outcome although in one pilot study of people with psychosis and agitation who have responded to haloperidol, time to relapse was significantly shorter in the discontinuation group (p value =0.04) (Declereq et al., 2013 3). Also it is worth noting that the 9th trial included people with psychosis or agitation who responded well to risperidone therapy for 4 to 8 months and reported that discontinuation led to increased risk of relapse, P value =0.004 HR 1.94, 95% CI 1.09-3.45 at 4 months (Declereq et al., 2013 3). There was no significant difference in the Neuro psychiatric Indicator (NPI) in two studies between the continuation and withdrawal group. MD -1.49, 95% CI -5.39-2.40 (Declereq et al., 2013 3). |
| Nelson et al   | Prospective cohort design | Community setting | • Antihypertensive agents  | Hypertension | 503 patients | After 12 months of antihypertensive withdrawal, 18/136(35%) were classified as maintaining normotension. 273 (54%) ( Nelson et al., 2002 2) |
| Reeve et al    | Prospective feasibility study | Outpatients clinic | • Proton pump inhibitors  | Gastro Oesophageal reflux disease | 6 patients | Out of the 6, 3 ceased and there was no worsening of GI test score at the end of 6 weeks. At the end of 6 months, 3 remained without the PPI (Reeve et al., 2015 32) |</p>
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| Potter et al   | Randomised control trial | Residential nursing homes   | • Senna  
• Paracetamol  
• Opioid analgesics  
• Aspirin  
• Proton pump inhibitors  
• H2 receptor antagonists  
• Vitamin D and C  
• Antipsychotics  
• Hypnotics  
• Anxiolytics  
• Ticlopidine  
• Fluticasone  
• B2 agonist  
• Calcium channel blockers  
• Bisphosphonates | • Psychosis  
• Anxiety  
• Asthma  
• COPD  
• Blood pressure  
• Osteoporosis | 95           | The main outcome was the number of drugs deprescribed and the effect of deprescribing on falls, fractures, hospital admission and quality of life. At 12 months, the mean change in the number of medicines was -1.9+/−4.1 in the intervention group and +0.1+/−3.5 in the control group. 4.4+/−3.4 regular medicines per participants were successfully deprescribed (Potter et al., 2016 11). At 12 months, there was improved sleep quality but worsening cognitive function in both groups. The general health in the control health was also improved (Potter et al., 2016 11). 4 serious adverse events occurred, 3 in the control group and 1 in the intervention group. In the 12 months after randomisation there was 26% mortality in the intervention group and 40% in the control group. (Potter et al., 2016 11) |
| Kutner et al   | Randomised control trial | Hospital setting. Among elderly with life limiting illnesses | • Statins | • Secondary prevention of cardiovascular disease | 381          | Primary outcome was the proportion of death within 60 days of trial enrolment. Of the 381 patients enrolled, 189 were randomised to discontinue statin therapy and 192 to continue with the statin therapy. The proportion of participants who died within 60 days for discontinuation and continuation group were 23.8% and 20.3% respectively. This was not significantly different between the groups (Kutner et al., 2015 7). |
| Garfinkel et al| Randomised control trial | Nursing homes                | • Nitrates  
• H2 receptor blockers  
• Antihypertensive drugs  
• Potassium and iron supplements | • Angina  
• Peptic ulcer  
• Hypertension  
• Anaemia | 190          | There were 119 participants in the intervention group and 71 people in the control group. Altogether 332 different drugs were discontinued in 119 patients and was not associated with significant adverse events (Garfinkel et al., 2007 1). The overall rate of drug discontinuation failure was 18% for all patients. The one year mortality rate was 45% in the control group and 21% in the study group p < 0.001 (Garfinkel et al., 2017 1). The annual referral rate to acute care facilities was 30% in the control group and 11.8% in the study group. P < 0.002 (Garfinkel et al., 2007 1) |
| Beer C et al   | Pilot randomised control trial | Community and nursing homes | • Diuretics  
• Anti-hypertensives  
• Anti-anginal  
• NSAIDs  
• CCB 2 inhibitors | • Hypertension  
• Angina  
• Arthritis | 15 patients | 11 participants satisfactorily withdrew their medication. 2 withdrew, 1 was referred for clinical review due to hypertension and 1 declined further dose reduction in analgesic therapy (Beer et al., 2011 37) |
| Campbell et al | Randomised control trial | Community setting            | • Psychotropic medications | • Psychiatric diseases | 93           | The main outcome was the number of falls recorded for both groups. After 44 weeks of follow up, there were 57 falls. 17 (30%) in the medication withdrawal group versus 40 (70%) in the continuation group. The overall rate of fall was lower in the medication withdrawal group. 0.32 vs 1.16 falls per year (Campbell et al., 1999 851) |