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Review Article

Deprescribing Medications for Chronic Diseases Management in Primary Care Settings: A Systematic Review of Randomized Controlled Trials

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A B S T R A C T

Objectives: Perform a systematic review to evaluate the outcome of deprescription compared with standard care. The focus was on chronic medical and mental health conditions managed in primary care.
Design: The databases searched include PubMed, Medline, EMBASE, the Cochrane Library, Scopus, and Web of Science. Each study was assessed for bias with the Cochrane Collaboration tool.
Settings and Participants: This review included outpatient, assisted living, nursing home, and acute care settings (if medications for chronic disease were deprescribed). Subjects were non–terminally ill adults 18 years and older.
Measures: Primary outcome was successful deprescription, defined as a statistically significant reduction in medication burden between the intervention group and the standard care or control group, or when more than 50% of intervention subjects were able to tolerate medication discontinuation compared with control by the end of the study.
Results: Fifty-eight articles met the study criteria. Thirty-three (58%) had a high risk of bias. Studies varied in duration from 4 weeks to 5 years and were conducted across a diverse array of primary health care settings. The most successful interventions used pharmacist-led educational interventions and patient-specific drug recommendations. Cardiovascular drugs including antihypertensives/diuretics and nitrates were the most successfully deprescribed class of drugs. Psychotropic medications and proton-pump inhibitors were the classes most resistant to deprescribing, despite intense intervention.
Conclusions/Implications: Deprescription may be successful and effective in select classes of drugs, with collaboration of clinical pharmacists for patient and provider education, and patient-specific drug recommendations, complemented by close clinical follow-up to detect early signs of exacerbation of chronic diseases. This review also suggests that deprescription may (1) require expensive intensive, ongoing interventions by clinical teams; (2) not lead to expected outcomes such as improved falls rate, cognition, and quality of life, or a lower admission rate; and (3) have unexpected adverse outcomes affecting patients' quality of life.
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With the increasing prevalence of multiple chronic medical conditions, there has been a corresponding increase in use of prescription drugs. The percentage of US adults who report taking 5 or more prescription drugs has risen by 12.8% for adults aged 45 to 64 years, and 28.4% for adults aged 65 and older during the past 30 years.[1] Deprescription is the process of withdrawal of an inappropriate medication, supervised by a health care professional, with the goal of

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managing polypharmacy and improving outcomes.[2] Deprescribing may improve adherence and tolerability, reduce medication errors and expenditure, and improve outcomes.[3,4]

Primary care physicians (PCPs) are best equipped to consider patient goals of care, quality of life, and benefit versus burden of medications. However, PCP time constraints, lack of guidelines or evidence for benefit, fear of potentially preventable adverse outcomes, and patient resistance may be barriers to deprescription.[5] Although the prescribing process is usually evidence-based, deprescription efforts typically rely on retrospective studies and clinical judgment. Exceptions are the deprescription of dual antiplatelet therapy for coronary artery disease[6] and antithrombotics for venous thromboembolism,[7] so studies related to these agents were excluded from this review. Iyer et al[4] performed a systematic review of deprescription trials in the 65 and older age group in 2008 and concluded that there was evidence for short-term effectiveness and/or lack of significant harm in deprescription of antihypertensive, benzodiazepine, and psychotropic agents in older people. Since then, there have been more and longer trials. Page et al[8] conducted a systematic review in 2016 of trials involving deprescription and adverse outcomes in the over-65 population. Given that more than 60% of adults in the United States with multiple chronic conditions are under 65,[9] it is important to extend the research to those under 65 years. This systematic review of randomized controlled trials was performed to evaluate the impact of deprescription on reducing medication burden, and on control of chronic medical and mental health conditions commonly managed by primary care physicians, compared with standard care in the non–terminally ill adult population.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in conducting this systematic review.[10]

Data Sources and Searches

A comprehensive, systematic literature search was performed independently by 2 investigators (K.B. and H.D.). The databases searched include PubMed, Medline, Embase, the Cochrane Library, Scopus, and Web of Science (see PRISMA flow diagram [Figure 1]). The dates searched were from the inception of each database to December 2016. The search terms included the following keywords: *deprescribing*, *drug discontinuation*, *drug withdrawal*, *drug taper*, *pharmaceutical preparations*, *medication management*, *medication review*, *polypharmacy*, *randomized controlled trial*. Limiters included humans, English language, and adults. The references of identified articles were manually searched to identify additional randomized controlled trials. The search strategy in PubMed is available in Appendix A (available online).

Selection of studies

The abstract of each identified trial was evaluated for relevance by both primary authors, H.D. and K.S., using a checklist of inclusion criteria (described in the Appendix A, available online). Differences between review authors were resolved by consulting a third review author (Q.S.). All articles identified for inclusion were reviewed by the third reviewer.

Inclusion criteria:

1. Randomized controlled trials involving chronic medical and mental health conditions managed by PCPs

Exclusion criteria:

1. Study population with life expectancy of 6 months or less. We excluded hospice studies and studies including diagnoses such as advanced malignancy, end-stage chronic obstructive pulmonary disease, end-stage renal disease not receiving hemodialysis, severe dementia (Functional Assessment Staging score 7c or higher), and advanced liver or heart failure not eligible for transplantation

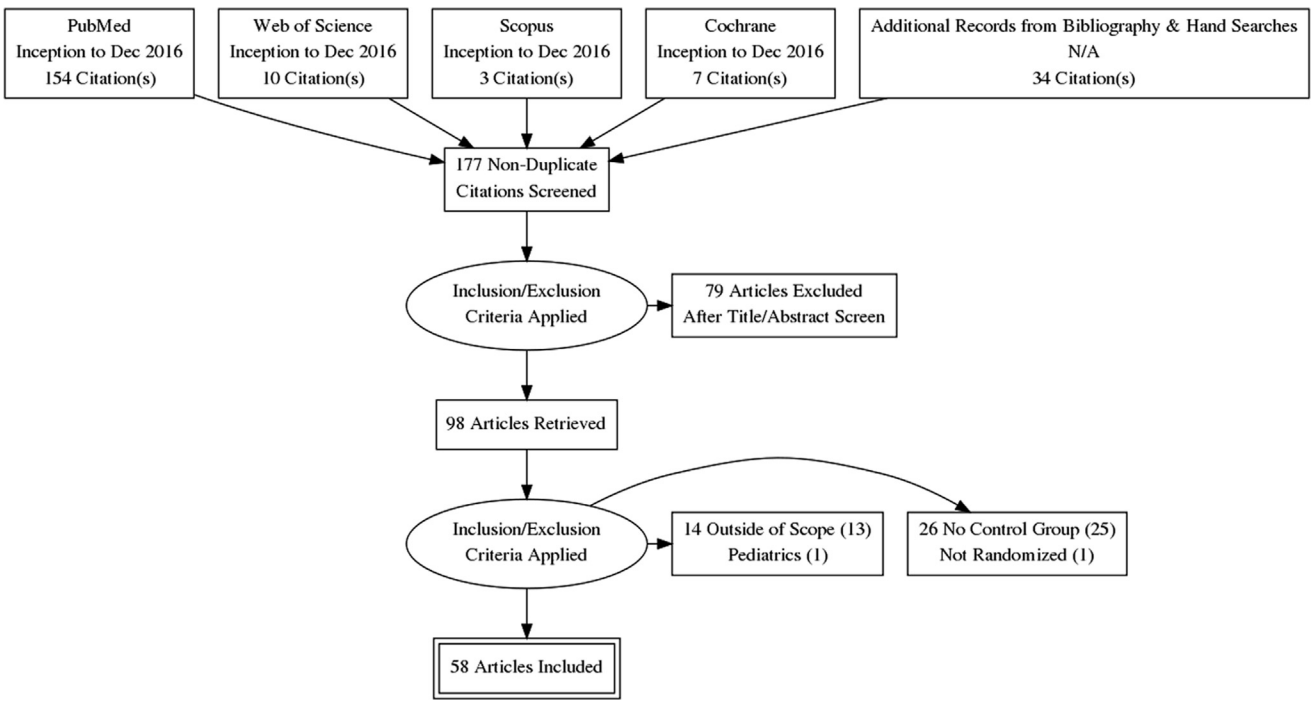

Fig. 1. Flow chart of literature review process. (adapted from PRISMA flow diagram[10]).

2. Opioid deprescribing in opioid dependency, because specialized certifications are often needed for this intervention
3. Acute conditions with planned treatment of less than 3 months

Full inclusion and exclusion criteria are in Appendix A (available online).

Assessment of Risk of Bias

Two reviewers independently assessed the risk of bias. The Cochrane Collaboration's Risk of Bias tool was used to assess the risk of bias for each included study. The detailed risk of bias chart and overall bias grading key is included in Appendix B (available online), and the overall risk of bias for each study is included in Table 1. Risk of bias was graded as high in the domain of "blinding of outcome assessment" if the assessor was using a subjective scale as behavior scale, and was not blinded to allocation of the treatment. Additionally, the domain of "incomplete data" was graded as "high" for studies less than a year in duration and "unclear" for studies a year or longer in duration if more than 20% of subjects dropped out, died, or were lost to follow-up, consistent with the Oxford Centre of Evidence-based Medicine recommendations[69] and the National Nursing Home Survey mortality data.[70] If all domains of bias were low, the study was ranked as having overall low risk of bias. If no domain had a high risk of bias but at least 1 domain was graded unclear, the study was ranked as unclear in risk. Any study with at least 1 domain with high risk of bias was considered to be high risk.

Outcomes

Primary outcome was successful deprescription, defined for the purpose of this review as a statistically significant reduction in medication burden between the intervention group (IG) and the standard care or control group (CG), or, when more than 50% of the patients in the intervention arm were able to tolerate medication discontinuation compared with control by the end of the study. Secondary outcome was emergence of adverse effects related to drug or underlying chronic condition as a result of deprescription (as reported in the studies). Study investigators defined medication burden in various ways, including change in the total number of medicines or potentially inappropriate medications (PIMs), the Anticholinergic Drug Scale, Medication Appropriateness Index (MAI), and others.

Results

The initial search identified 177 studies. Fifty-eight articles (detailed list in Table 1) met the study criteria, and were included in the analysis. The Cochrane Collaboration tool suggested that 9 studies had low risk of bias; 16 studies had unclear risk of bias, and 33 studies had a high risk of bias. The trials fell into 2 general categories. The first category included studies that compared a method of reducing the medication burden (as defined in the study) to a control, typically usual care, without focusing on a specific drug, class of drug, or chronic disease. The second category included studies that examined withdrawal of a medication or a class of medications for a specific chronic condition, specifically hypertension, diabetes, asthma, chronic obstructive pulmonary disease, gastroesophageal reflux disease, osteoporosis, heart failure, stable angina, Parkinson's disease, depression, and mood disorders.

Deprescription Methods to Improve the Total Medication Burden

Twenty studies[11–30] met the search criteria for comparing a method of deprescription with a control intervention or usual care. Among those studies, 2 studies were classified as educational interventions,[11,12] 12 as patient drug–specific interventions,[13–24] and 6 as mixed interventions[25–30] where there was substantial education but also an opportunity for patient drug-specific interventions. See Table 2 for a detailed analysis of outcomes of the included studies.

An educational intervention was defined for this systematic review as an intervention that intensively trained clinicians (including but not limited to prescribers) in methods and benefits of symptom management and medication deprescribing, without addressing the needs of specific patients. A modest deprescription of up to 0.5 drugs per subject was achieved,[11,12] without any increase in measured adverse outcomes, in a nursing home and assisted living setting, respectively. However, the risk of bias was graded as unclear or high for these studies.

Patient drug-specific interventions were defined for this review as educational interventions directed at individual patients to educate them about chronic disease management and inappropriate medication use. Communication could be direct (face-to-face sessions or telephonic encounters) or indirect (mailed educational material). Twelve such studies were identified, including 5 conducted in the outpatient setting,[13–17] 2 in the inpatient setting,[18,19] and 5 in a long-term care residential setting.[20–24] These interventions identified patients taking "high risk" medications across classes and medical conditions, and brought them to the attention of the clinical care team. The definition of "high risk" varied between studies and included number of medications, frailty, anticholinergic burden, and/or another characteristic(s). The measured outcomes varied as well, and included the number of potentially inappropriate medications, Anticholinergic Drug Scale, MAI, total number of medications, cognition, cost, hospitalization, emergency department visit, fallers, falls, and/or quality of life.

Neither of the patient drug-specific studies in the inpatient setting successfully reduced polypharmacy by utilizing potentially inappropriate medication screening tools.[18,19] Of 5 outpatient patient drug-specific studies, a statistically significant reduction in medication burden (as defined by the study) occurred in 2, and these required intense pharmacist-physician collaboration.[14,17] In one study, the MAI improved in the intervention group (IG), but quality of life and social functioning measures showed a nonclinically significant reduction in IG.[14] In a Comprehensive Geriatric Assessment trial,[15] anxiolytics were more likely to be stopped in the IG, but other hypnotics and sedatives were also started. Half of the drugs started by the Comprehensive Geriatric Assessment team were still in use a year later, and one-fourth of the drugs stopped by the Comprehensive Geriatric Assessment team were restarted by the PCP by the year's end. The risk of bias was graded as unclear or high in each of the successful studies.

Of 5 patient drug-specific studies in the long-term care setting, 4 successfully reduced the medication burden.[20–22,24] However, an improvement in cognition, serum anticholinergic activity, or mouth dryness, or a reduction in number of falls or hospitalizations was not generally achieved. Additionally, the risk of bias was graded as high in all these studies.

The category of mixed interventions was defined for the purposes of this systematic review to have a significant educational component plus patient drug-specific interventions for high-risk patients (as defined in the individual study) in the community. Four of 6 of these studies were successful.[25,28–30] Involvement of the local Alzheimer's Association staff in educating nurses regarding management of dementia-related behaviors led to a statistically significant reduction in benzodiazepine use in the IG.[28] An outpatient clinic pharmacist intervention demonstrated a significant reduction in MAI in the IG.[25] The Tinetti study[29] demonstrated both reduction in polypharmacy and a clinically and statistically significant fall reduction in the community by individualizing nursing, social work, and therapy educational interventions, as well as addressing patient-specific polypharmacy. However, none of the 6 studies demonstrated any statistically significant difference in patient-related outcomes, including readmissions, behaviors in dementia patients, self-

Table 1
Description of all the Studies

Articles Pertaining to Deprescribing Methods							
Study	Learner/Involved Personnel/ Setting	Education/Method	Outcome	Duration	Results	Results/Comment	Risk of Bias
Educational interventions							
Pitkälä, Finland, 2014[11]	Assisted living nurses	IG: total 8 h CG: standard care	Mean no. of PIMs	12 mo	Positive	0.4 fewer drugs/person. Maintained HRQoL, reduced hospitalization	Unclear
Garcia-collarte, Spain, 2014[12]	Nursing home physicians	IG: 10 h + on-demand support CG: standard care	Mean no. of PIMs using STOPP/ START	12 mo	Positive	0.5 fewer PIMs/person based on STOPP criteria	High
Patient drug-specific interventions in the outpatient setting							
Blalock, USA, 2010[13]	PharmD	IG: patient visit with PharmD CG: standard care	Falls	12 mo	Negative	No difference in falls or refill of PIM	High
Bryant, New Zealand, 2011[14]	PharmD	IG: PharmD meeting with patients and PCP CG: v	MAI	12 mo	Positive	MAI improved; nonclinically significant reduction in QoL and social functioning in IG	High
Lampela, Finland, 2010[15]	Comprehensive Geriatric Assessment (CGA) team	IG: CGA consult CG: standard care	Medication changes and persistence	12 mo	Negative	IG: stopped CV drugs and anxiolytics but started new drugs, >50% of these in use at 1 y; one-fourth of the drugs stopped were later resumed; improvement in self-reported health status in IG	High
Allard, Canada, 2001[16]	Intervention Team—MD, PharmD, RN	IG: consult to PCP about specific patients CG: standard care	No. of PIM	12 mo	Negative	No difference in mean no. of PIMs, which declined in both groups	High
Lenander, Sweden, 2014[17]	PharmD	IG: PharmD review of medications, education for patients and PCP. CG: standard care	Drug-related problems (DRPs) and no. of drugs	12 mo	Positive	Reduction of 0.7 drugs/patient in IG ($P < .05$); no decrease in DRP or hospital admissions	Unclear
Patient drug-specific interventions in the inpatient setting							
Dalleur, Belgium, 2014[18]	Inpatient geriatric consultation	IG: STOPP tool CG: standard care	Discontinuation of PIM at discharge	Hospital stay	Positive	Reduction in PIM 40% in IG, 19% in CG, $P = .01$; no difference in percentage of patients with 1 + PIM at discharge	High
Michalek, Germany, 2014[19]	MDs, inpatient geriatric ward	IG: FORTA tool to evaluate PIM CG: standard care	No. of drugs at admission and discharge; falls	Hospital stay	Negative	No difference in no. of medications in the 2 groups at discharge; greater fall rate in the CG	Low
Patient drug-specific interventions in the long-term care setting/nursing homes							
Potter, Australia, 2016[20]	MD, nurse, PharmD	IG: Deprescribing based on patient assessment and caregiver interview CG: standard care	Mean change in no. of routine medications	12 mo	Positive	Mean change in IG −1.9, vs CG +0.1; success in ASA, minerals, bisphosphonate, ARB, statins	High
Crotty, Australia, 2004[21]	PharmD	IG: Medication review, care conference with MD and nurse CG: standard care	MAI	8 wk	Positive	MAI significantly lower (better) in IG; no difference in hospitalization between groups; no difference in behavior scores	High
Frankenthal, Israel, 2014[22]	PharmD, MD	IG: Medication review using STOPP/START criteria CG: standard care	No. of falls, hospitalization, medicine cost	12 mo	Positive	Reduction in %PIM and no. of medicines by average 1; cost saving $29/mo/person; no difference in hospital use and QoL between groups.	High
Furniss, UK, 2000s[23]	PharmD	IG: PharmD recommended medication changes CG: standard care	No. of drugs per person	8 mo	Negative	Drugs declined in each group, no statistical difference	High

Kersten, Norway, 2013[24]	PharmD, MD	CG: ADS score to deprescribe anticholinergic drug CG: standard care	Cognition, anticholinergic activity (SAA)	8 wk	Positive	Median ADS score reduced by 2 units in IG; no improvement in cognition, SAA, or salivary flow	High
Mixed interventions (education plus patient-specific interventions)							
Hanlon, USA, 1996[25]	PharmD; outpatient	IG: Medication review with patients, PCP CG: standard care	MAI	12 mo	Positive	28% reduction in MAI in IG vs 5% in CG; no difference in QoL or adverse events	Unclear
Bonnet-Zamponi, France, 2013[26]	Transitions of care; inpatient geriatric units	IG: enhanced discharge planning CG: standard care	Chronic medications at discharge, DRP	6 mo	Negative	NSS difference in readmissions; no. of drugs or prescribing patterns	High
Roberts, Australia, 2001[27]	PharmD, nursing staff, MD; nursing home	IG: PharmD educate nursing staff, PCPs CG: standard care	Prescription claims	12 mo	Negative	Reduction in use of antacids, hypnotics, NSAIDs, and laxatives and improved survival in IG on individual level; but not significant difference from CG when adjusted for clustering both for prescriptions and survival	High
Crotty, Australia, 2004[28]	Alzheimer's Association; nursing home	IG: Alzheimer's Association staff educated nurses, attended IDT meetings CG: standard care	MAI	12 wk	Positive	Positive study, driven by reduction in BDZ use. No difference in behavior scores among the two groups.	High
Tinetti, USA, 1994[29]	NP, PT, SW; outpatient	IG: home visits—PT, education, medication review CG: standard care + home visits by SW students.	No. of patients who fell, or incidence of falls	12 mo	Positive	Falls 35% of IG vs 47% of CG ($P = .04$); At 12 mo, 63% of IG had >4 Rx vs 86% of CG ($P = .009$); mean decline in total no. of risk factors for falls in IG	Low
Clyne, Ireland, 2015[30]	PharmD, PCP; outpatient	IG: PharmD 1:1 session with PCP CG: PCP got list of PIM	PIM	6 mo	Positive	PIMs declined in both groups but difference was −0.5, $P = .02$; outcome driven by PPI group; no difference in patients' self-reported well-being scores	High

Articles Pertaining to Specific Agents

Study	Setting/Medication class	Intervention	Outcome	Duration	Results	Comments	
Antipsychotics							
Ballard, UK, 2009[31]	Nursing Home	IG: placebo CG: antipsychotic	Survival at 1 and > 2 y	12 mo	Positive	11% in IG restarted on the drug in 1 year; survival better for IG	Unclear
Ballard, UK, 2004[32]	Nursing home	IG: placebo CG: antipsychotic	NPI and QoL at 1 and 3 mo	3 mo	Positive	85% in CG and 78% in IG completed the trial; NSS difference in behaviors; 13% dropout in IG vs 9% in CG	High
Devanand, USA, 2011[33]	Outpatient	IG: placebo CG: antipsychotic	Worsening behaviors	24 wk	Negative	2× higher rate of relapse and shorter time to relapse in IG	High
Devanand, USA, 2012[34]	Outpatient, assisted living and nursing home	IG 1: antipsychotic × 16 wk, then placebo × 16 wk IG 2: placebo × 32 wk CG: antipsychotic × 32 wk	Relapse of behavior symptoms	32 wk	Negative	Relapse rate 60% in IG 2 vs 33% in CG at 16 wk; 48% in placebo group (IG 1, 2) vs 15% in CG at 32 wk ($P = .02$)	Low
Ruths, Norway, 2004[35]	Nursing home	IG: placebo CG: continue antipsychotic	NPI scores at week 4; actigraphy	6 wk	Positive	Behavior scores stable; reduced sleep efficiency in IG; 1/15 in IG resumed the drug	Low

(*continued on next page*)

Table 1 (*continued*)

Articles Pertaining to Specific Agents							
Study	Setting/Medication class	Intervention	Outcome	Duration	Results	Comments	
Ruths, Norway, 2008[36]	Nursing home	IG: placebo CG: continue antipsychotic	Successful discontinuation, changes in behaviors	3 mo	Positive	85% in IG off antipsychotic by the end of the trial, 46% a month later and 33% 3 mo later; NSS difference in behaviors	Low
van Reekum, Canada, 2002[37]	Nursing home, geriatric chronic care floors	IG: placebo, taper off antipsychotic CG: continue antipsychotic	Cognition, behaviors, use of as-needed drugs	6 mo	Negative	Dropout higher in IG vs CG but NSS; NSS difference in outcomes between groups	High
Ahmed, UK, 2000[38]	Community residential homes	IG: taper off antipsychotic CG: continue antipsychotic	Behaviors, dyskinesia	6 mo	Negative	In IG discontinued 33%; 50% dose reduction 19%, resumed 47%	High
Bridges-Parlet, USA, 1997[39]	Nursing home	IG: placebo CG: continue antipsychotic	Behaviors	4 wk, follow-up to 40 wk	Positive	50% in IG were resumed on antipsychotic by 40 wk	Unclear
Benzodiazepines (BDZ)							
Habraken, Belgium, 1997[40]	Nursing home	IG: taper to placebo over 5 wk CG: continue BDZ	Geriatrics Behavior Observation Scale	12 mo	Positive	Improved function at 6 mo and 1 y; drop out one-third patients in both arms; reduced sleep quality in IG	Unclear
Tannenbaum, Canada, 2014[41]	Outpatient	IG: written tapering protocol, PCP/PharmD visits CG: standard care	Complete sensation at 6 mo	6 mo	Negative	Complete cessation: IG: 27% vs CG: 5% (significant difference); Cessation or dose reduction: IG: 37.8 vs CG: 11% (significant difference)	Low
Cormack, UK, 1994[42]	Outpatient	IG 1: letter from PCP IG 2: letter + info on medication reduction CG: standard care	Complete cessation at 6 mo	6 mo	Negative	BDZ use reduced in both IG and CG: 23% in IG 1, 13% in IG 2, and 6% in CG did not require any treatment during study period	High
Heather, UK, 2004[43]	Outpatient	IG 1: PCP letter and visit, self-help book IG 2: letter from PCP CG: standard care	Change in BDZ use	6 mo	Negative	Reduction in BDZ use: 37% in IG 1, 41% in IG 2, 24% control (statistically significant difference between IG 2 and CG). Complete cessation <10% in all groups	High
Vicens, Spain, 2006[44]	Outpatient	IG: tapering protocol and PCP visits CG: standard care	BDZ use at 6 and 12 mo	12 mo	Negative	BDZ were stopped in 39.7% IG vs 3.1% CG at 6 mo; and 45.2% IG vs 9.1% CG at 1 y	High
Zwar, Australia, 2000[45]	Outpatient	IG: educate PCP on BDZ CG: other clinical topics	Rate of BDZ prescribing	12 mo	Negative	BDZ use dropped in both groups, but no significant difference.	High
SSRIs/SNRIs							
Ulfvarson, Sweden, 2003[46]	Nursing home	IG: gradual tapering CG: continue therapy	Depression, functional scores	6 mo	Positive	No difference in outcomes between the groups; 20% in IG resumed SSRIs because of clinical decline	High
Montgomery, Europe, South Africa, Canada, 2005[47]	Outpatient/anxiety disorder	IG: placebo CG: continue escitalopram	Relapse at 24 wk and time to relapse	24 wk	Negative	41% in IG completed successful withdrawal. Risk of relapse 2.8× in IG vs CG; 50% in IG vs 22% in CG had a relapse; time to relapse—407 d in CG vs 144 in IG	Unclear

Kocsis, USA, 2002[48]	Outpatient/depression	IG: placebo CG: continue sertraline	Depression, function	18 mo	Negative	26% in IG completed successful withdrawal. Relapse of depression: 26% in CG vs 50% in IG, $P = .001$. High dropout.	High
Diabetes Medications							
Landstedt-Hallin, Sweden, 1999[49]	Outpatient	IG: insulin + placebo CG: insulin + sulfonylurea	Glycemic control and body weight	18 wk	Negative	79% in IG had >10% rise in blood glucose at 3-4 wk, but less hypoglycemia in IG vs CG; hemoglobin A1c increase by 1%-1.5% in IG; high dropout rate in IG.	Unclear
Asthma Treatment							
Reddel, Australia, 2010[50]	Outpatient	IG: on ICS, withdrawal of salmeterol CG: Salmeterol and ICS Both groups underwent down-titration of ICS	Mean daily ICS dose including ICS for exacerbations	52 wk	Negative	Moderate exacerbations higher in IG vs CG (annualized mean rate 3.7 vs 2.1, $P < .001$)	High
COPD Treatment							
Wouters, Netherlands, 2005[51]	Outpatient	IG: on salmeterol only, withdrawal of ICS CG: Salmeterol and ICS	% rescue medication-free days, change in PFTs	12 mo	Negative	Higher annual incidence rate for mild exacerbations and decline in PFTs in IG vs CG	Low
PPI							
Krol, Netherlands, 2004[52]	Outpatient; PCP	IG: written instructions to reduce or stop PPI CG: standard care	No. of patients deprescribed; dyspepsia	20 wk	Negative	At 12 wk, 24% in IG stopped or reduced PPI, vs 7% in CG; no difference at 20 wk; no difference in symptoms	Unclear
Lampen-Smith, New Zealand, 2012[53]	Inpatient	IG: discharge summary with instructions for PCP CG: standard care	Documentation of review of PPI indication	6 mo	Negative	19% in CG and 24% in IG had documented review of PPI; PPI stopped in 12% of IG, 7% of CG	Unclear
Curtain, Australia, 2011[54]	Outpatient pharmacies	IG: patient education prompt for PharmD CG: standard care	PPI intervention rates	12 wk	Negative	330 PPI interventions, most in IG; 28/34 dose reductions in IG; of 76 surveys, 6 stopped PPI	High
Zwisler, Denmark, 2015[55]	Outpatient	IG: placebo CG: PPI or H2 antagonist	Treatment failure of trial medicine	12 mo	Negative	Treatment failure of trial drug—73% in IG vs 21% in CG; 27% in IG off the drug at 1 y	Low
Clyne, Ireland 2015[30]	Outpatient	IG: PharmD 1:1 session with PCP CG: PCP got list of PIM	PIM	6 mo	Positive	PIMs declined in both groups but difference was −0.5, $P = .02$; outcome driven by PPI	High
Bisphosphonates							
Black, USA, 2006[56]	Outpatient	IG: placebo CG: alendronate 5 mg/day or 10 mg/day	DEXA, bone markers, fractures	5 y	Negative	CG had better hip and lumbar BMD outcomes, lower risk of clinical vertebral fracture	Unclear
Antihypertensives/diuretics							
Burr, UK, 1977[57]	Inpatient long stay geriatric ward	IG: placebo CG: continue diuretic	Signs of CHF, electrolytes, blood pressure	12 wk	Positive	14% in IG resumed diuretics due to edema/signs of CHF. Mean 10 mmHg rise in sBP in IG	High
De Jonge, Netherlands, 1994[58]	Outpatient	IG: stop diuretic CG: continue diuretic	Edema index, clinical follow-up	6 wk	Positive	Diuretics resumed in 23% of IG due to edema or CHF	High
Myers, 1982, Canada[59]	Long-term care	IG: placebo CG: continue diuretic	Hypertension, CHF, mean BP	12 mo	Positive	No difference in outcomes; dropout 15% in IG due to CHF	Unclear
Walma, 1997, Netherlands[60]	Outpatient	IG: placebo CG: continue diuretic	Successful withdrawal of diuretic; BP	6 mo	Positive	50% in IG resumed diuretics during 6 mo (vs 13% in CG), 50% due to CHF; mean rise in SBP was 13 mmHg	Unclear

(*continued on next page*)

Table 1 (*continued*)

Articles Pertaining to Specific Agents							
Study	Setting/Medication class	Intervention	Outcome	Duration	Results	Comments	
Moonen, 2016, Netherlands[61]	Outpatient	IG: discontinue antihypertensives to 20 mmHg increase in SBP CG: continue antihypertensives	Absence of OH; death, MI, stroke, TIA, hospitalization	4 mo	Positive	53% in IG had full withdrawal, 24% had partial withdrawal; 11% required antihypertensives to be resumed/added; recovery from OH positive only for ARBs	Unclear
Nitrates							
George, Israel, 2003[62]	Outpatient	IG: nitrate withdrawal CG: continue nitrate	Recurrence of angina	3 mo	Positive	Drug resumed in 10% in IG, outcome NSS	High
Lemos, Brazil, 2014[63]	Outpatient	IG: nitrate withdrawal CG: continue nitrate	HRQoL, adherence	4 mo	Positive	Lower adherence but better HRQoL in CG, small effect size	Unclear
Anti-Parkinson's Medicines							
Tse, USA, 2008[64]	Nursing home	IG: Levodopa taper (over 1-2 wk) CG: continue levodopa	Cognitive, behavior, motor scores	1 mo	Positive	Successful withdrawal of the drug in IG; no differences in outcomes	Low
Multiple Classes							
Beer, Australia, 2011[65]	Outpatient; CV drugs, analgesics	IG: withdrawal of 1 drug with side effects CG: continue all drugs	QoL, sleep, cognition	2 mo	Positive	73% of patients in IG were able to completely discontinue the target medicine	High
Campbell, New Zealand, 1999[66]	Outpatient; benzodiazepine, hypnotic, antidepressant, tranquilizer	IG 1: drug withdrawal + exercise IG 2: drug withdrawal IG 3: exercise only CG: continue medications	No. of falls	44 wk	Positive	Fall 30% in IG vs 70% in CG; 45% of patients resumed psychotropes a month later, due to insomnia	High
Cohen-Mansfield, USA, 1999[67]	Nursing home; antipsychotics, benzodiazepines	IG: drug withdrawal CG: continue medications	Agitation, MMSE, sleep	14 wk	Positive	High drop-out; no difference in behavior	High
Patterson, UK, 2010[68]	Nursing home; anxiolytic, hypnotic, antipsychotic	IG: pharmacist medication review CG: standard care	Prescription for $\geq$1 psychoactive medication; falls	12 mo	Positive	20% IG vs 50% CG nursing homes taking psychotropes at 12 mo ($P < .001$); no difference in falls among the 2 groups	Unclear

ADS, Anticholinergic Drug Scale; ARB, angiotensin receptor blocker; BMD, bone mineral density; COPD, chronic obstructive pulmonary disease; DRP, drug-related problems; HRQoL, health-related quality of life; IDT, interdisciplinary team; MD, general physician; NPI, neuropsychiatric inventory; NSS, not statistically significant; OH, orthostatic hypotension; PFTs, pulmonary function tests; PharmD, clinical pharmacist; PIM, potentially inappropriate medications; PPI, proton pump inhibitor; QoL, quality of life; sBP, systolic blood pressure; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 2
Success of Deprescription Interventions Based on Methods of Deprescription

Deprescription Methods to Improve Medication Burden		
Type of Intervention	No. of Successful Studies	Results
Educational interventions	2/2	Instruction of nurses in an assisted living,[11] and education with on-demand support of doctors primarily practicing in nursing homes[12] resulted in a small, but statistically significant, reduction in PIM per person (0.4 to 0.5).[11,12] The IG did not have any increase in measured adverse outcomes compared to CG.
Patient-specific interventions (inpatient setting)	0/2	Use of the STOPP criteria demonstrated decline in overall PIM usage though the proportion of patients taking at least 1 PIM at discharge was similar among the 2 groups.[18] Use of the FORTA tool (Fit for the Aged) did not demonstrate a reduction in polypharmacy, but there may have been a higher prescribing quality and a lower rate of falls in the IG.
Patient-specific interventions (outpatient setting)	2/5	Two studies[14,17] demonstrate feasibility of deprescribing via an intense pharmacist-physician collaboration. The CGA[15] resulted in medications both added to and removed from the intervention group. The team of physicians, nurse, and pharmacist sending recommendations to the physician did not result in deprescription.[16] The 2 patient drug-specific studies in the inpatient setting used PIM screening tools to reduce PIMs.
Patient-specific interventions (long-term care setting)	4/5	Three of the 4 successful studies[21,22,24] required strong pharmacist-physician collaboration. The fourth successful study[20] followed an algorithm in a population with high baseline polypharmacy (mean number of medications more than 9 per person) and reduced medication burden by 2 medications per person. Medications withdrawn included bisphosphonates, aspirin, angiotensin receptor blockers (ARB), vitamins/minerals, and statins; medications with the lowest success rate in withdrawal included psychotropic medications and proton pump inhibitors (PPIs).
Mixed (education and patient-specific) method to improve overall medication burden	4/6	These studies[25,28–30] were all multidisciplinary in nature. Of the 2 negative studies, one was an intense added value intervention in elders hospitalized in acute geriatric units to address readmissions by educating patients and families about their medications and condition, and helping patients and families identify patient-specific goals of care.[26] Results may have been attenuated because of the high level of care already offered in the French geriatric care units. The second negative study randomized pharmacists to educate nursing staff in Australian nursing homes as well as make patient-specific drug recommendations to the attending physicians,[27] essentially mirroring the role of the consulting pharmacist in most US nursing homes. However, when adjusted for clustering, neither prescription claims nor survival were improved in the IG compared with the CG (usual care).

CGA, Comprehensive Geriatric Assessment; PIM, Potentially Inappropriate Medication.
Successful deprescribing is defined above in the Outcomes section, medication burden is defined in each study.

perceived quality of life, or any increase in patient-related adverse outcomes as a result of the intervention. The risk of bias was rated low in only 1[29] of the successful studies.

Psychotropic Drug Deprescription

See Table 3 for details of studies pertaining to deprescription of psychotropic medications including analysis of outcomes.

Antipsychotic drugs used for behavior

Nine studies[31–39] met the criteria, and 5 of them[31,32,35,36,39] were successful. Eight studies enrolled subjects with dementia, and 1 study enrolled subjects with intellectual and developmental disabilities.[38] The duration of the longest trial was 12 months,[31] with the remaining ranging from 4 to 40 weeks. In most studies, antipsychotic use was longstanding prior to withdrawal, other than 2 studies[33,34] where antipsychotics had been started up to 6 months earlier. Studies were typically small and had substantial dropouts in both the CG (continued antipsychotics) and IG (discontinued antipsychotics) as a result of decline in health and death. Emergence such as dyskinesia or worsening behavior was not cited in the longest, most successful antipsychotic deprescription study,[31] but was often a reason to reinstitute antipsychotics in the smaller studies. Additionally, the longest trial did show a survival benefit of deprescribing antipsychotics.[31] The risk of bias in this study was unclear because of the high dropout rate.

Benzodiazepines

Out of the 6 studies meeting study criteria,[40–45] only 1,[40] a nursing home study, was successful in benzodiazepine withdrawal for more than half of the participants in the trial. However, the risk of bias was graded as unclear.

Antidepressants

Three studies were identified that met the study criteria.[46–48] Deprescription of selective serotonin reuptake inhibitors among nursing home residents without a known diagnosis of dementia or major depression was successful, with only 20% of the IG requiring resumption of the medication.[46] However, the risk of bias was high because of dropout rate and methodological limitations. In the remaining 2 studies of community-dwelling adults, the mean age was between 30 and 50 years, and subjects had a diagnosis of major depression and generalized anxiety disorder, respectively.

Table 3
Success of Deprescribing Psychotropic Drugs

Deprescription of Psychotropic Drugs		
Medication Type	No. of Successful Studies	Results
Antipsychotics for behavior	5/9	Although antipsychotics were successfully withdrawn without need for resumption in 50% of the participants in 5[31,32,35,36,39] of the 9 studies, 2 of the studies[35,36] had a duration of only 4 wk. Actigraphy was measured in Ruths et al,[35] and it revealed that the average sleep efficacy was less (by 54 minutes) in IG. There was notably more physical aggression in the withdrawal group in a study,[37] and preintervention antipsychotic dose was predictive of worsening of behaviors. In the DART-AD,[31] which followed patients for over a year, only 9% of those in IG had to resume an antipsychotic, and there was reduced mortality in the withdrawal group. Only one-third of subjects with intellectual and developmental disabilities (IDD) taking antipsychotics for behavior problems were successfully weaned from the antipsychotic, but another fifth tolerated a 50% dose reduction.[38] Overall, the withdrawal group did better in terms of higher activity engagement, without increase in maladaptive behavior. Individuals with IDD living in hospitals or settings with a specialist mental health orientation or lower staff-to-resident ratios, and those receiving neuroleptic medication for more than 5 y were more likely to be successful in withdrawal of the medication. Greater restrictiveness of the setting, absence of written policy, and poorer staff training on use of physical restraints were associated with higher rates of drug reinstatement.
Benzodiazepines	1/6	Successful withdrawal of benzodiazepines was achieved in a small group of nursing home residents who completed the study (though one-third drop out in both arms) with improved functional scores at 6 mo and 1 y, but there was a decline in sleep quality in IG.[40] Four community-based trials[41–44] used self-tapering protocols in deprescribing benzodiazepines among chronic users who were cognitively intact. Although none met the definition of feasibility, 1 came close, with 45% discontinuation in the intervention group.[44] In all 4 of these trials, there were substantial dose reductions in many who were unable to discontinue the drug. The sixth trial[45] studied "academic detailing." This process involved a 20-min primary care visit with a specially trained general practitioner who advised the physician on management of chronic benzodiazepine users. The prescribing rates dropped in both the intervention group and the control group, but the intervention did not result in a difference in prescribing between 2 groups by the end of the study.
Antidepressants	1/3	Deprescribing in nursing home residents without a diagnosis of major depression or dementia was feasible in 80% of the residents.[46] However, in community-dwellers with major depression or general anxiety disorder, deprescribing is associated with a high risk of relapse.[47,48]

Successful deprescribing is defined above in the Outcomes section.

Antidepressant deprescription was unsuccessful overall because of high rates of relapse.[47,48]

Specific Medication Classes and Chronic Diseases

See Table 4 for details of studies involving deprescription of chronic disease medications including analysis of outcomes.

Oral Hypoglycemics/diabetes

One study met the criteria.[49] Withdrawal of sulfonylureas (SUs) in patients with uncontrolled diabetes on insulin and SUs resulted in more than half of the subjects having a 40% increase in fasting blood glucose and a 1% to 1.5% increase in hemoglobin A1c compared with control. However, the withdrawal group had significantly fewer hypoglycemic events compared to the control.

Asthma

One study met the criteria.[50] Adults with asthma controlled on long-acting beta agonists and inhaled corticosteroids (ICS) were randomized to either withdraw (IG) or continue the long-acting beta agonists (CG). Periodic down-titration of ICS occurred in both groups. The CG tolerated the 50% and 80% dose reductions in ICS more successfully than the IG, with fewer frequent moderate exacerbations.

Chronic obstructive pulmonary disease

One study met the criteria,[51] which evaluated the effect of withdrawal of inhaled corticosteroids in patients with chronic obstructive pulmonary disease stable on both long-acting beta agonists and ICS. The study demonstrated a sustained and statistically significant decline in the pulmonary function test results, and an increase in mild exacerbations requiring rescue inhalers.

Proton pump inhibitors

Five studies met the study criteria.[30,52–55] Four of these studies included substantial educational interventions. Among all studies, the highest rate of discontinuation of proton pump inhibitors at the end of the study period in IG was 27%.[55] Clyne et al[30] demonstrated successful dose reduction to maintenance dose in 50% of the patients by a mixed educational drug-specific intervention related to potentially inappropriate medicines targeting general practitioners.

Bisphosphonates

One trial met the study criteria.[56] More than a thousand postmenopausal women taking bisphosphonates for osteoporosis for a mean of 5 years were randomized to withdrawal (IG), continuation at half, or full strength. The IG demonstrated reduced bone density, increased bone turnover markers, and higher risk of vertebral fractures at 5 years compared to the active treatment group, but there was no difference in nonvertebral fractures.

Diuretics and antihypertensives

Five studies met the criteria and all were successful in antihypertensive and diuretic drug withdrawal. Four studies involved diuretics only,[57–60] and 2 of these studies were conducted in long-term and long-term acute care settings. Moonen et al[61] addressed the broad category of antihypertensives and was able to successfully discontinue antihypertensives in the IG, with a need to resume the medicine in only 12% of the participants. Also, discontinuation of angiotensin II receptor blockers (ARBs) was associated with improvement in orthostatic hypotension. Approximately 15% to 50%[57–60] of the participants in the diuretic trials required resuming of the diuretic during the study period, with heart failure symptoms being the most common reason. Mean blood pressure was higher in the discontinuation group at the end of these studies. The risk of bias was unclear or high in these studies because of the dropout rate and methodological limitations.

Table 4
Success of Deprescribing Drugs With Medical Indications

Medications for Chronic Medical Conditions		
Disease/Medication Class	No. of Successful Studies	Results
Oral hypoglycemic in diabetes	0/1	Postintervention A1c higher by 1%-1.5%, but less hypoglycemia in the IG.[49]
Inhaled corticosteroids in asthma	0/1	Withdrawal of long-acting beta-agonist is associated with more moderate exacerbations when weaning off inhaled corticosteroids.[50]
Inhaled corticosteroids in COPD	0/1	Withdrawal of ICS resulted in sustained and statistically significant decline in PFTs, and increase in mild exacerbations requiring rescue inhalers.[51]
PPI for gastric issues (GERD, dyspepsia, prevention)	1/5	The one successful PPI deprescription required intense efforts directed at both the patient and prescriber.[30]
Bisphosphonates in osteoporosis	0/1	A drug holiday may be considered for some postmenopausal women while understanding the increased risk for clinical vertebral fractures.[56]
Antihypertensives/diuretics	5/5	Antihypertensives and diuretics may be withdrawn while following BP closely. BP may rise above 160 mm Hg (in 15% of the patients). In some (approximately 20%), withdrawal of a diuretic can unmask edema or heart failure, requiring the drug to be restarted.
Nitrates	2/2	Most (approximately 90%) of the persons with chronic stable angina will tolerate withdrawal of long-acting nitrate
Dopaminergic agents for Parkinson's disease	1/1	Frail, dependent elders may tolerate dopaminergic withdrawal to reduce polypharmacy and medication-related adverse effects.
Multiple drug withdrawal	4/4	Beer et al[65] demonstrated gradual withdrawal of 1 target medication related to a stable chronic disease with a negative symptom, with successful discontinuation of the target medicine in 73% of participants in the IG. Among the 3 studies related to psychotropic medicines, a pharmacist-led intervention in nursing homes[68] led to a 0.4 reduction in psychotropic prescriptions and the total number of residents taking psychotropics in IG nursing homes compared to the CG. Attempt at a withdrawal of psychotropics was successful in nursing home residents without diagnoses of major depression or schizophrenia,[67] without any statistically significant increase in agitation or behaviors. Deprescribing of psychotropic medications in outpatient setting[66] demonstrated fall reduction but there was high dropout (45%) and drug resumption by the end of the study (47%) in the IG; insomnia was a frequent complaint.

BP, blood pressure; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; PFTs, pulmonary function tests; PPI, proton pump inhibitor.
Successful deprescribing is defined above in the Outcomes section.

Nitrates

Two studies of deprescription of nitrate therapy in patients with stable angina met the criteria, and both were successful.[62,63] Both studies excluded patients with uncontrolled hypertension, significant angina symptoms, and heart failure. The studies did not demonstrate any statistically significant increase in recurrence of angina[62] or any other adverse outcomes.[63] However, the risk of bias was graded as unclear or high for both of these studies.

Parkinson's Disease Medications

One study met the criteria.[64] In a small study of 11 nursing home residents with advanced Parkinsonism and dementia, who were minimally to nonambulatory, discontinuation of dopaminergic medications in the IG did not demonstrate any significant change in cognitive, behavioral, and motor function compared to the CG.

Multiple Classes

Four studies[65–68] assessed patient-specific deprescribing of multiple classes of medications and all were positive. Three of these trials included psychotropic medicines (including selective serotonin reuptake inhibitors, antipsychotics, benzodiazepines, hypnotics, etc), whereas 1 study[65] included cardiovascular and nonopioid analgesic medicines. The risk of bias in all these studies was affected by a high dropout rate.

Discussion

Interventions with the most success in reducing polypharmacy included intense pharmacist intervention, providing both clinician education as well as patient-specific drug recommendations. Gaining buy-in for recommendations was easier with provider agreement to opt *out* rather than opt *in* to medication recommendations by a geriatrics team. Educational interventions in the long-term care setting may have more impact than in the community, perhaps because standardization of care may be more acceptable among facility prescribers than among community providers. For the chronic conditions studied, cardiovascular medicines including antihypertensives, diuretics, and nitrates for stable angina may be deprescribed with clinical follow-up to detect signs of exacerbation of chronic disease. Also dopaminergic medicines in advanced Parkinson's disease may be reduced without any serious adverse outcomes in most persons. Withdrawal of sulfonylureas in patients on insulin therapy for diabetes is feasible in cases of tightly controlled diabetes and frequent episodes of hypoglycemia.

Successful outcomes beyond reducing polypharmacy, such as reduction in mortality by withdrawing antipsychotics in dementia[31] or falls reduction,[29] may be possible. Such outcomes, however, involve consistent and intense education, involvement of multiple disciplines, and multiple visits with the patients and/or clinicians. There were 4 classes of drugs resistant to deprescription, even with intensive intervention. These were chronic antipsychotics, antidepressants, PPIs, and benzodiazepines[20] despite widespread agreement that these medications are likely overprescribed. Additionally, the apparent success of some of the short studies may be misleading. Longer studies that continue for a year or longer may identify drugs that are restarted because of withdrawal or symptom recurrence and may be revealed as less successful.

This review finds that lowering the medication burden may have adverse effects. These include unmasking of heart failure with diuretic withdrawal[59,60] and increase in clinical vertebral fracture with bisphosphonate withdrawal.[56] Polypharmacy reduction may also lead

to a decline in cognition and/or worsening of behavior.[23] Even withdrawal of an antipsychotic in dementia to reduce the impact on mortality can lead to diminished quality of life due to emergence of dyskinesia. This review also finds some potential adverse outcomes when a medication list is scrutinized by a consultant (geriatrics) team for appropriateness because the team may add medications,[15] potentially leading to a higher medication burden.

Limitations

Our systematic review was limited by a number of factors. Although our search was fairly comprehensive, it may have overlooked relevant studies held in databases not used for this review, or studies in which the key or MeSH words did not match our search strategy (see Appendix A [available online] for our search strategy). This review is also limited by the heterogeneity of the included studies. The definitions of polypharmacy and high-risk patients varied across many of the studies included in the review. The reviewed studies included differences in settings, nationality, degree of functional impairment of the population, range of defined outcomes, and other differences. High dropout rate and methodologic deficiencies led to an unclear or high risk of bias in more than half of these studies. Additionally, studies included in this review have been published across more than 20 years, during which time polypharmacy has increased and reducing it has become more challenging. Evolution of guidelines for chronic disease management over the past 20 years as well as the increased prevalence of aging persons with multiple chronic diseases may have driven increased medication prescription. Health insurers have quality measures that include inappropriate prescribing in the United States, and regulations now require pharmacists to review medications in nursing homes. It is also difficult to compare studies across countries because of the differences in the structure of care and in quality monitoring between nations (eg, the acute geriatric units often found in the European Union are rare in the United States; not all countries have pharmacist overview in the nursing home). However, the complexity of chronic disease management, the high prevalence of cognitive impairment with associated behavioral problems in the older population, and the difficulty in helping patients and families establish and communicate goals of care are common to all settings and countries.

Conclusion/Relevance

This systematic review suggests that deprescription may be successful and effective in select classes of drugs, in combination with the collaboration of clinical pharmacists to assist with patient and provider education and patient-specific drug recommendations, and a close clinical follow-up to detect early signs of exacerbation of chronic diseases.

This review also highlights that deprescription may (1) require expensive, intensive, ongoing interventions by clinical teams; (2) not lead to expected outcomes such as improved fall rate, cognition, quality of life, or admission rate; and (3) have unexpected adverse outcomes that affect quality of life. For deprescription to be acceptable to patients, it needs to be part of a multimodal intervention and have well-defined, individualized outcomes for patient-centered care.

This systematic review also highlights the difficulty in reducing bias within deprescription studies, particularly studies of psychotropic medications using subjective assessment tools.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jamda.2018.06.021.

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Appendix B

Cochrane Collaboration's Risk of Bias Chart

References	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Dropout >20% if Length <1 y	Final Bias Rating	Other Sources of Bias
1. Ahmed et al 2000	Unclear	Unclear	High	Unclear	Low	Low		H	None identified
2. Allard et al 2001	Unclear	Unclear	High	Low	Low	Low		H	High (the authors acknowledge that the main author knew most of the patients' physicians, which may have affected the results)
3. Ballard et al 2009	Low	Low	Low	Low	Unclear	Low		U	None identified
4. Ballard et al 2004	Unclear	Unclear	Low	High	High	Low	Y	H	Unclear (method of recruitment not described)
5. Beer et al 2011	Low	High	High	High	High	Low	Y	H	None identified
6. Black et al 2006	Low	Unclear	Low	Low	Low	Low		U	Pharmaceutical funded
7. Blalock et al 2010	Unclear	High	High	Low	Low	Low		H	None identified
8. Bonnett-Zamponi et al 2013	Low	High	High	Low	Low	Low		H	High (authors note possible contamination bias; ie, physicians may have integrated and implemented parts of the intervention in the control group)
9. Bridges-Parlet et al 1997	Low	Unclear	Low	Low	Low	Low		U	None identified
10. Bryant et al 2011	Unclear	High	High	Low	Low	Low		H	None identified
11. Burr et al 1977	Unclear	Unclear	Low	Low	High	Unknown		H	None identified
12. Campbell et al 1999	Low	Low	Low	Low	High	Low	Y	H	None identified
13. Clyne et al 2015	Low	High	High	Low	Low	Low		H	None identified
14. Cohen-Mansfield et al 1999	Unclear	Unclear	Low	Unclear	High	Low	Y	H	None identified
15. Cormack et al 1994	Unclear	Unclear	High	High	Low	Low		H	None identified
16. Crotty et al 2004 (*Age Ageing*)	Low	Unclear	High	High	High	Low	Y	H	None identified
17. Crotty et al 2004 (*Am J Geriatr Pharm*)	Low	Unclear	High	High	High	Low	Y	H	None identified
18. Curtain et al 2011	Unclear	Unclear	High	Unclear	Low	Low		H	None identified
19. Dalleur et al 2014	High	Unclear	Low	Low	Low	High		H	High risk (potential confounding bias)
20. deJonge et al 1994	Low	Unclear	High	High	High	Low	Y	H	None identified
21. Devanand et al 2012	Low	Low	Low	Low	Low	Low		L	None identified
22. Devanand et al 2011	Unclear	Unclear	Low	Unclear	High	Low		H	Low
23. Frankenthal et al 2014	Low	Low	High	Low	Low	Low		H	High (lack of validity step to measure agreement between assessor nurses)
24. Furniss et al 2000	Low	Unclear	High	Unclear	Low	Low		H	Low
25. Garcia-Gollarte et al 2014	Low	Unclear	Low	Unclear	Low	High		H	Authors acknowledge they did not use systematic registry of falls and delirium, so some episodes may have gone unnoticed
26. George et al 2003	Unclear	High	High	Low	Low	Low		H	Unclear (recruitment method not described)
27. Habraken et al 1997	Unclear	Unclear	Low	Unclear	Low	Low		U	None identified
28. Hanlon et al 1996	Low	Unclear	Low	Low	Low	Low		U	None identified
29. Heather et al 2004	Unknown	Unclear	Unclear	Unclear	High	Low	Y	H	None identified
30. Kersten et al 2013	Low	Unclear	High	Low	High	Low	Y	H	None identified
31. Kocsis et al 2002	Low	Unclear	Low	Low	High	Low	Y	H	High (authors acknowledge significant degree of attrition during the treatment, with possibility of some unspecified bias)
32. Krol et al 2004	Unknown	Unknown	Unknown	Unknown	Low	Low		U	None identified
33. Lampela et al 2010	Low	Unknown	High	Unknown	High	Low		H	Unable to record data on short-term medication changes
34. Lampen-Smith et al 2012	Unknown	Unknown	Low	Unknown	Low	Low		U	None identified
35. Landstedt-Hallin et al, 1999	Unknown	Unknown	Unknown	Unknown	Low	Low		U	High (recruitment process not described)
36. Lemos et al 2014	Low	Unclear	Low	Low	Low	Low		U	None identified
37. Lenander et al 2014	Unknown	Unclear	Unclear	Unclear	Low	Low		U	None identified
38. Michalek et al 2014	Low	Low	Low	Low	Low	Low		L	High (2 wards were compared, so heterogeneity in patient and health provider sample may affect results)
39. Montgomery et al 2005	Low	Unclear	Low	Low	Low	Low		U	None identified

(*continued on next page*)

(*continued*)

Cochrane Collaboration's Risk of Bias Chart									
References	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Dropout >20% if Length <1 y	Final Bias Rating	Other Sources of Bias
40. Moonen et al 2016	Unclear	Unclear	Unclear	Unclear	Low	Low		U	Unclear (recruitment process not described)
41. Myers et al 1982	Unclear	Unclear	Low	Low	Unclear	Low		U	None identified
42. Patterson et al 2010	Low	Low	Low	Low	Unclear	Low		U	None identified
43. Pitkala et al 2014	Low	Low	Low	Unclear	Low	Low		U	Staff cross-over different wards
44. Potter et al 2016	Low	Low	High	Low	Unclear	Low		H	None identified
45. Reddel et al 2010	Low	Low	High	Low	Unclear	Low		H	None identified
46. Roberts et al 2001	Low	Low	High	Low	Unclear	Low		H	None identified
47. Ruths et al 2008	Low	Low	Low	Low	Low	Low		L	None identified
48. Ruths et al 2004	Low	Low	Low	Low	Low	Low		L	None identified
49. Tannenbaum et al 2014	Low	Low	Low	Low	Low	Low		L	None identified
50. Tinetti et al 1994	Low	Low	Low	Low	Low	Low		L	None identified
51. Tse et al 2008	Low	Low	Low	Low	Low	Low		L	None identified
52. Ulfvarson et al 2003	Unclear	Unclear	High	Unclear	High	High	Y	H	Nonvalidated scale for symptoms and adverse effects
53. Van Reekum et al 2002	Low	Unclear	Low	Unclear	High	High	Y	H	None identified
54. Vicens et al 2006	Unclear	Low	High	High	Low	Low		H	None identified
55. Walma et al 1997	Unclear	Low	Low	Low	Low	Low		U	None identified
56. Wouters et al 2005	Low	Low	Low	Low	Low	Low		L	None identified
57. Zwar et al 2000	Unclear	Low	High	Unclear	Low	Low		H	None identified
58. Zwisler et al 2015	Low	Low	Low	Low	Low	Low		L	None identified

Key:

Risk of Bias	Interpretation	Within the Trial
Low risk of bias (L)	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all domains
Unclear risk of bias (U)	A risk of bias that raises some doubt about the results	At least 1 domain with unclear risk, but no high risk in any domain
High risk of bias (H)	Bias may alter the results seriously	High risk of bias for 1 or more domains

The risk of bias in 2 key domains is rated "high" if:
1. Incomplete outcome data when attrition >20% for a study <1 year, or
2. Lack of blinding when outcome is subjective.

SCOTT ENDSLEY, MD

CME

Deprescribing Unnecessary Medications: A Four-Part Process

With too many patients taking too many unnecessary medications, deprescribing has become a required skill for primary care physicians. Here's how to go about it.

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Ms. Horatio is a 76-year-old patient who has been coming to your practice for more than 10 years. She has Type 2 diabetes with stage-3 chronic renal disease and painful diabetic neuropathy of bilateral lower extremities, chronic obstructive pulmonary disease, stable coronary artery disease, and hypertension. She has seen a cardiologist, pulmonologist, and neurologist for additional care. At today's visit with you, her family physician, she has brought a brown paper bag filled with all her medications per your request. Her medications include amitriptyline, atenolol, atorvastatin, low-dose aspirin, diphenhydramine hydrochloride, clopidogrel, conjugated estrogen tablets, ferrous sulfate, glyburide, isosorbide dinitrate, lisinopril, nifedipine extended release, omeprazole, paroxetine, pregabalin, tolterodine, tiotropium inhaler, and zolpidem. Where do you begin?

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WHAT IS POLYPHARMACY?

Polypharmacy is typically defined as the prescription of five or more medications. However, it also refers to the prescription of medications that do not have a specific current indication, that duplicate other medications, or that are known to be ineffective for the condition being treated. In other words, polypharmacy is the use of multiple medications that are unnecessary and have the potential to do more harm than good.

Polypharmacy is highly prevalent, especially among older adults. A 2016 study found that 36 percent of community dwelling adults age 62 to 85 were taking five or more medications.[1] This is up from 31 percent in 2005. At this rate of increase, almost half of the older population could be affected by polypharmacy by 2030.

Patients at risk for polypharmacy are older than age 62, have comorbidities, have multiple prescribers or pharmacies, self-treat with over-the-counter medications, and have a history of hospitalizations.[1,2,3] They also likely go to practices with poor medication tracking processes, including medication lists that are not updated or are inaccurate. Poor medication tracking processes are more prevalent than physicians might think. For example, an internal study at my previous organization found that only 19 percent of office visits to general internists included a medication review.

Polypharmacy has multiple adverse consequences. These include adverse drug events and other safety events such as falls, medication nonadherence, increased mortality, increased cost, and functional impairment. Polypharmacy often begins when a medication causes an adverse drug event, leading to additional treatment, which causes an additional reaction, and so on.[4] The probability of harm increases exponentially with each medication.

All medications have potential negative consequences. For instance, delirium and worsening of dementia are common with anticholinergics, benzodiazepines, and proton-pump inhibitors; falls are more common with patients on antihypertensives, antipsychotics, benzodiazepines, and opioids; constipation is common with opioids and calcium channel blockers; and orthostasis is common with anticholinergics, antihypertensives, and sulfonylureas.

To avoid polypharmacy and the risks of medication-related harm in their patient populations, family physicians should implement effective medication management practices, including the strategy known as deprescribing.

> Deprescribing is a set of interventions to identify inappropriate or unnecessary medications and discontinue them.

THE DEPRESCRIBING PROCESS

Deprescribing is a set of interventions to identify inappropriate or unnecessary medications and discontinue them. (See "A deprescribing algorithm," page 30.) In essence, it is backing off of care for the safety of the patient, like taking your foot off the accelerator of medical therapy. Studies have suggested that deprescribing leads to improvement in cognition, fewer falls, and improved survival.5

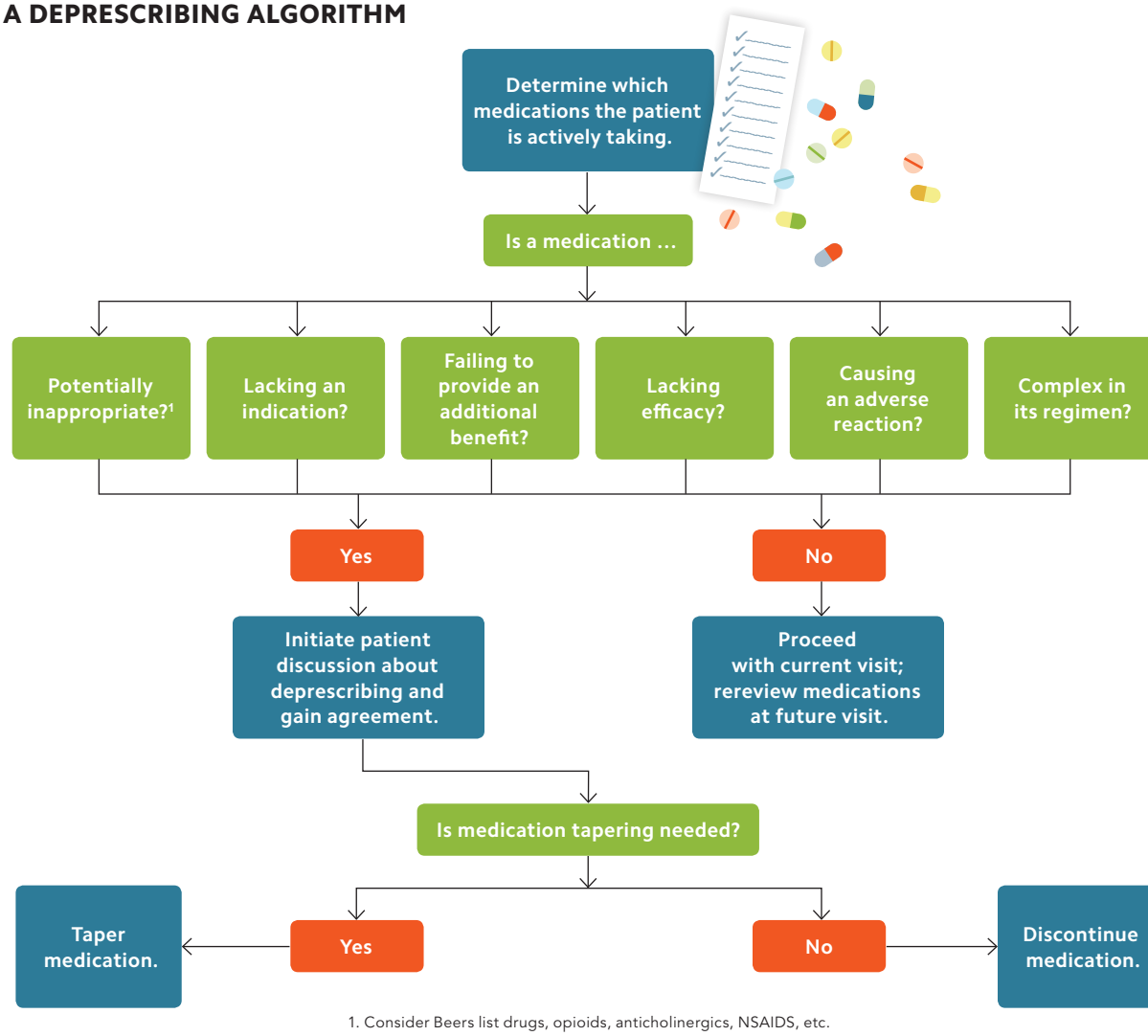
The deprescribing process is generally described as having four key parts:[2,6,7]

1. Review all current medications. The first step in deprescribing is medication reconciliation, often centered around a "brown bag" review. Instruct the patient to bring all of his or her medications (including prescription drugs, over-the-counter medications, and supplements such as vitamins and minerals) to a visit, and have your nurse or medical assistant take a

KEY POINTS

- Polypharmacy is the use of multiple medications that are unnecessary and have the potential to do more harm than good.
- Patients at risk for polypharmacy are older than age 60, have comorbidities, have multiple prescribers or pharmacies, self-treat with over-the-counter medications, have a history of hospitalizations, and go to medical practices with poor medication tracking processes.
- Medication reconciliation often begins with a "brown bag" review of the patient's medications.
- To help patients buy into the deprescribing process, consider discontinuing one medication at a time or tapering medications.

A DEPRESCRIBING ALGORITHM



1. Consider Beers list drugs, opioids, anticholinergics, NSAIDS, etc.

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Related article: https://www.aafp.org/fpm/2018/0500/p28.html.

medication history. The information collected, including which medications the patient is actively taking, what regimen is being followed, and whether the patient has experienced any side effects, should be documented in the patient's medication list in the electronic health record (EHR). By the end of the visit, your nurse should be able to generate a patient "medication card," which can empower the patient to maintain his or her own medication list going forward and share the information with his or her providers across all settings. (For additional information on medication reconciliation, see "Resources," page 31.)

2. Identify any inappropriate, unnecessary, or harmful medications. Together with the patient, review all medications listed in the updated medication list and consider which ones are offering benefit and which are causing harm. Look for medications that are potentially inappropriate (per the Beers list, discussed below), lack efficacy, lack an indication, don't provide additional benefit, or require a long duration for effect.[7] Also consider whether the patient would like to stop any medications because of negative

side effects or whether any medications have complex dosing regimens that could be avoided.[7] Drug classes such as antipsychotics, statins, antihypertensives, benzodiazepines, proton-pump inhibitors, and nonsteroidal anti-inflammatory drugs/COX-2 inhibitors/acetylsalicylic acid are common targets of deprescribing.[7]

To aid busy physicians in deprescribing, a number of helpful tools are available:

• The Anticholinergic Burden Calculator (http://anticholinergicscales.es/calculate) can help you evaluate a patient's potential for serious anticholinergic effects. In the geriatric population, this is a great tool to start with, as reducing or eliminating medications with high anticholinergic burdens can often improve patients' overall function and quality of life. Start with deprescribing those medications in the highest (level 3) category.

• The Beers List from the American Geriatric Society lists medications that pose the highest risk to older patients, along with alternatives. There are numerous versions of this list, but one of the better configured lists is found here: https://bit.ly/2GQhM2Y.

• Deprescribing.org, developed by a team of physicians and pharmacists, provides deprescribing guidelines and algorithms, patient decision aids, and an up-to-date resource list of evidence and research.

• MedStopper (http://medstopper.com/) is an online tool that allows you to enter a drug list for a specific patient and receive recommendations regarding which medications might be discontinued or switched.

3. Plan deprescribing with the patient. Many patients will resist stopping medications, especially those they have been taking for a long time. They may be concerned about their conditions worsening or about contradicting the original prescriber. To help patients buy into the deprescribing process, consider discontinuing one medication at a time or tapering medications if necessary, and assure your patients that you will monitor them for worsening conditions or withdrawal effects. Also, discuss the potential or real adverse effects of their medications; the potential benefits of deprescribing, such as reduced risk of hospitalization, cognitive or functional gains, and improved quality of life; and the minimal (if any) impact deprescribing would have on their conditions. This latter point is especially true for medications prescribed without a clear indication or with no significant clinical benefit. These benefits of deprescribing are also critical to consider in patients who are receiving palliative or end-of-life care.

4. Regularly rereview medications. Because deprescribing may require tapering of medications or may involve withdrawal symptoms, the process needs to be monitored closely. Additionally, on at least an annual basis (if not at every visit), look closely at all medications again. Many patients see multiple providers and can quickly accumulate medications across conditions. As much as you are able, actively engage your specialist colleagues in discussions of benefits and harms of new medications, as well as other options. One way to facilitate this is by using electronic or paper consultation reports that clearly list new or modified medications.

Collaborative arrangements with pharmacists may also be helpful.[8] Depending on the practice setting, collaboration between pharmacists and family physicians can occur during medication history taking and medication reconciliation, drug

RESOURCES

Medication reconciliation

- *How-to Guide: Prevent Adverse Drug Events (Medication Reconciliation).* Boston: Institute for Healthcare Improvement; 2011. http://www.ihi.org/resources/Pages/Tools/HowtoGuidePreventAdverseDrugEvents.aspx.
- *Medications at Transitions and Clinical Handoffs (MATCH) Toolkit for Medication Reconciliation.* Rockville, MD: Agency for Healthcare Research and Quality; 2012. https://www.nm.org/-/media/Northwestern/Resources/for-medical-professionals/northwestern-medicine-match-toolkit.pdf.
- *Ontario Primary Care Medication Reconciliation Guide.* Ontario: Institute for Safe Medication Practices Canada; 2015. https://www.ismp-canada.org/download/PrimaryCareMedRecGuide_EN.pdf.

Deprescribing

- The Anticholinergic Burden Calculator: http://anticholinergicscales.es/calculate
- The Beers List: https://bit.ly/2GQhM2Y
- Deprescribing.org: https://deprescribing.org/
- MedStopper: http://medstopper.com/

therapy recommendation and deprescribing, or the management of adverse drug reactions. The IMPACT program in Ontario has had success with this collaborative model for some time using a variety of strategies including separate pharmacist visits, collaborative visits with the physician, and pharmacist-patient follow-up.[9]

The first step in deprescribing is medication reconciliation, often centered around a "brown bag" review.

CASE STUDY CONTINUED

Before you enter the exam room to see Ms. Horatio, your nurse Lois sits with her and reviews the medications she has brought from home in a brown bag. One by one, Lois examines each medication, including the refill date. She asks Ms. Horatio if she is currently taking the medication, when her last dose was, and if she has had any bad reactions to it. For medications Ms. Horatio is not taking currently, Lois asks, "When did you stop taking this medication?" and "What was going on that made you stop taking it?" Lois records this information in the EHR. At the end of the discussion, she asks Ms. Horatio, "Are there any other medications you might be taking, such as vitamins, supplements, or over-the-counter medications?" Ms. Horatio mentions that she takes some ginseng tablets in the morning that her daughter suggested would increase her energy. Lois records that information in the EHR as well. She will later generate a "medication card" for Ms. Horatio to keep in her purse, share with other doctors at other offices or the hospital, and add to or modify when her medications are changed.

A few minutes later, when you enter the exam room, you sit with Ms. Horatio and review the updated medication list. You explain why she doesn't need to continue a number of medications, including the estrogen, iron supplements, and proton-pump inhibitor. You note that her gynecologic history and last hematogram don't indicate a need for therapy at this time and explain that her proton-pump inhibitor may be contributing to her mild cognitive impairment. You also recommend tapering and stopping the zolpidem over several weeks and, in its place, beginning a regimen for sleep hygiene. Based on the results of an anticholinergic burden analysis (http://anticholinergicscales.es/calculate), you determine that Ms. Horatio has a high anticholinergic burden, and you recommend tapering and eliminating the amitriptyline and paroxetine, as well as discontinuing the diphenhydramine hydrochloride. If symptoms confirm her need for an antidepressant, you will prescribe a newer, less anticholinergic medication at that time. You make a plan to follow up with her in two weeks.

Send comments to **fpmedit@aafp.org,** or add your comments to the article online.

A KEY ROLE FOR FAMILY PHYSICIANS

Deprescribing is a necessary process in today's practice environment where patients often take multiple drugs prescribed by multiple physicians who are not in direct communication with one another. Primary care physicians are well positioned to manage this critical process. FPM

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