

Special Communication | LESS IS MORE

Reducing Inappropriate Polypharmacy

The Process of Deprescribing

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Inappropriate polypharmacy, especially in older people, imposes a substantial burden of adverse drug events, ill health, disability, hospitalization, and even death. The single most important predictor of inappropriate prescribing and risk of adverse drug events in older patients is the number of prescribed drugs. Deprescribing is the process of tapering or stopping drugs, aimed at minimizing polypharmacy and improving patient outcomes. Evidence of efficacy for deprescribing is emerging from randomized trials and observational studies. A deprescribing protocol is proposed comprising 5 steps: (1) ascertain all drugs the patient is currently taking and the reasons for each one; (2) consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention; (3) assess each drug in regard to its current or future benefit potential compared with current or future harm or burden potential; (4) prioritize drugs for discontinuation that have the lowest benefit-harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes; and (5) implement a discontinuation regimen and monitor patients closely for improvement in outcomes or onset of adverse effects. Whereas patient and prescriber barriers to deprescribing exist, resources and strategies are available that facilitate deliberate yet judicious deprescribing and deserve wider application.

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← Invited Commentary

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In developed countries, approximately 30% of patients aged 65 years or older are prescribed 5 or more drugs.¹ Whereas many may benefit from such polypharmacy² (defined here as >5 regular prescribed drugs), it comes with increased risk of adverse events in older people³ due to physiological changes of aging that alter pharmacokinetic and pharmacodynamic responses to drugs.⁴ Approximately 1 in 5 drugs commonly used in older people may be inappropriate,⁵ increasing to one-third among those living in aged care facilities.⁶ Among nursing home residents with advanced dementia, more than half receive at least 1 drug with questionable benefit.⁷ Approximately 50% of hospitalized or ambulatory care patients or nursing home residents receive 1 or more unnecessary drugs.⁸ Observational studies have documented adverse drug events in at least 15% of older patients, contributing to ill health,⁹ disability,¹⁰ hospitalization,¹¹ and, in some cases, death.¹² This high level of iatrogenic harm mandates a response from prescribing clinicians. The number of drugs that a patient is taking is the single most important predictor of harm.¹³ In this article, we define the process of deprescribing potentially inappropriate drugs, the evidence supporting the process, and barriers and enablers to its adoption in routine clinical practice. Whereas the focus here is on deprescribing prescription drugs in older people, the same principles can be applied to any patient,

regardless of age, who is prescribed multiple long-term drugs, and to all drugs, be they prescription or nonprescription drugs (alternative or complementary or over the counter).

Defining Deprescribing

We define *deprescribing* as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences. Deprescribing is part of the good prescribing continuum, which spans therapy initiation, dose titration, changing or adding drugs, and switching or ceasing drug therapies. Deprescribing is not about denying effective treatment to eligible patients. It is a positive, patient-centered intervention, with inherent uncertainties, and requires shared decision making, informed patient consent, and close monitoring of effects—the same good prescribing principles that apply when drug therapy is initiated. It involves diagnosing a problem (use of an inappropriate drug), making a therapeutic decision (withdrawing it with close follow-up), and altering the natural history (reducing incidence of drug-related adverse events such as falls, relieving adverse effects, improving func-

tion, preventing premature death). Deprescribing considers not only the risk associated with individual drugs but also the cumulative risk from multiple drugs due to pharmacokinetic and pharmacodynamic interactions.

Evidence of Efficacy of Deprescribing

Considerable observational evidence of the adverse effects of polypharmacy in older patients indirectly supports the need for deprescribing in this population.^{14,15} We obtained an overview of more direct evidence of the efficacy and safety of deprescribing by retrieving articles from Medline, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library using the search terms "deprescribing," "polypharmacy," and "inappropriate medications." Sentinel articles known to us or found by scrutinizing reference lists of retrieved articles were also included. Preference was given to systematic reviews of randomized trials and high-quality observational studies. Studies were grouped according to whether they investigated effects of withdrawing specific drugs or effects of multifaceted interventions aimed at reducing inappropriate polypharmacy across multiple drug classes and clinical settings.

Drug Withdrawal Trials

A systematic review of 31 withdrawal trials (15 randomized, 16 observational) of specific classes of drugs in people 65 years and older demonstrated that, with appropriate patient selection and education coupled with careful withdrawal and close monitoring, use of antihypertensive agents, psychotropic drugs, and benzodiazepines could be discontinued without harm in between 20% and 100% of patients.¹⁶ Withdrawal of agents in the latter 2 classes of drugs was associated with reduction in falls and improvement in cognitive and psychomotor function, a finding replicated in a more recent review.¹⁷ Another review of 9 randomized trials demonstrated the safety of withdrawing antipsychotic agents that had been used continuously for behavioral and psychological symptoms in more than 80% of participants with dementia.¹⁸ The Australian National Blood Pressure study, although not designed as a deprescribing trial, found that 37% of participants remained normotensive 1 year after drug withdrawal.¹⁹ In another observational study, cessation of inappropriate antihypertensive agents was associated with fewer cardiovascular events and deaths over a 5-year follow-up period.²⁰ In another randomized trial, patient education provided through community pharmacists led to a 77% reduction in benzodiazepine use among long-term users at 6 months with no withdrawal seizures or other ill effects.²¹ In an observational study of older outpatients, 60% had 1 or more drugs successfully discontinued over a 6-month period.²²

Studies of Interventions for Reducing Inappropriate Polypharmacy

Multifaceted interventions for reducing use of inappropriate drugs comprise pharmacist or physician drug review, education programs, audit and feedback, geriatric assessment, and multidisciplinary team approaches. In a 2013 systematic review of 36 studies (including 20 controlled trials) involving 13 906 frail older patients

in various settings, 22 of 26 studies containing quantitative data reported statistically significant reductions in the proportions of drugs deemed unnecessary (defined using various criteria), ranging from 3 to 20 percentage points.⁸ A 2013 Cochrane analysis of 5 randomized trials of inpatient medication reviews led by physicians, pharmacists, or other health professionals involving 1186 participants demonstrated a 36% reduction in emergency department visits from 30 days to 1 year following discharge but no effect on readmissions or mortality.²³ A more recent review of 20 trials of pharmacist-led reviews in both inpatient and outpatient settings involving 9858 participants showed no effects except for reduction in unplanned hospitalizations in patients with heart failure.²⁴ A 2012 review of 10 controlled and 20 randomized studies involving 247 674 older patients revealed statistically significant reductions in the number of drugs in most of the controlled studies, although mixed results in the randomized studies.²⁵ A 2012 Cochrane review of 10 studies of different designs concluded that interventions were beneficial in reducing inappropriate prescribing and drug-related problems.²⁶ Another 2011 review of 20 randomized trials specific to nursing homes and involving 14 416 residents concluded that educational interventions and pharmacist drug review may reduce inappropriate drug use under certain circumstances.²⁷ A later 2013 Cochrane review restricted to 8 randomized trials of various interventions involving 7653 nursing home residents suggested that drug-related problems were more frequently identified and resolved, together with improvement in drug appropriateness.²⁸ In general, studies were highly heterogeneous in their interventions and measures of drug use, analyses of appropriateness did not always separate underuse of effective drugs from overuse of unnecessary drugs, methodological quality was low to moderate, few reported impact on patient outcomes, and follow-up periods were short. However, the evidence overall suggests that deprescribing is feasible, safe, and, in many instances, beneficial.

Among the small number of studies reporting patient outcomes cited within these reviews, the most notable effects were seen when physician drug review was combined with a palliative care perspective involving discussions with families and primary care teams. In a controlled trial involving 190 patients in aged care facilities, this approach resulted in 63% of patients having a mean of 2.8 drugs per patient discontinued and was associated with a halving in both annual mortality and referrals to acute care hospitals.²⁹ In another prospective uncontrolled study, the same approach applied to a cohort of 70 community-dwelling older patients resulted in a mean of 4.4 drugs prescribed to 64 patients being recommended for discontinuation, of which 81% were successfully discontinued, with 88% of patients reporting global improvements in health.³⁰ In 2 randomized trials conducted in aged care facilities and centered on educational interventions, 1 aimed at prescribers,³¹ the other at nursing staff,³² the number of potentially harmful drugs and days in the hospital was significantly reduced,^{31,32} combined with slower declines in health-related quality of life.³¹

The Process of Deprescribing

In light of evidence supporting prescriber-mediated drug review, we propose a simple 5-step protocol to deprescribing outlined in the Table. An algorithm that guides the order and mode in which po-

Table. The Deprescribing Protocol

Key Step	Detailed Processes
1. Ascertain all drugs the patient is currently taking and the reasons for each one	Ask patients (and carers) to bring all drugs (prescribed, complementary and alternative medicine, and over the counter) and drug delivery aids to consultation or home visit Ask patients (in a nonjudgmental way) about any regularly prescribed drugs not being taken and if so why not (eg, too expensive, adverse effects)
2. Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention	Ascertain and assess risk according to <ul style="list-style-type: none"> • Drug factors: number of drugs (single most important predictor), use of "high-risk" drugs (see text), past or current toxicity • Patient factors: age >80 y, cognitive impairment, multiple comorbidities, substance abuse, multiple prescribers, past or current nonadherence
3. Assess each drug for its eligibility to be discontinued: <ul style="list-style-type: none"> • No valid indication • Part of a prescribing cascade • Actual or potential harm of a drug clearly outweighs any potential benefit • Disease and/or symptom control drug is ineffective or symptoms have completely resolved • Preventive drug is unlikely to confer any patient-important benefit over the patient's remaining lifespan • Drugs are imposing unacceptable treatment burden 	Identify drugs being prescribed <ul style="list-style-type: none"> For a diagnosis that is in doubt, ie, not confirmed; highly atypical presentations; For a confirmed diagnosis but in which evidence of efficacy is nonexistent (eg, ivabradine being prescribed for stable angina despite randomized trials showing no benefit); or That confer no additional benefit after a certain period of continuous use (such as bisphosphonates taken for more than 5 y) or after a certain age (such as hormone therapy in patients older than 70 y) Identify drugs prescribed to counteract adverse effects of other drugs (eg, potassium supplements to counteract effects of diuretics prescribed for ankle swelling secondary to calcium channel blocker use) Reconsider the indications for the initial culprit drug or its substitution by an alternative drug with superior tolerability Identify "drugs to avoid" in older patients (see text) Identify drugs contraindicated in particular patients (eg, β -blockers in an asthmatic patient) Identify drugs causing well-known adverse effects (eg, constipation with calcium antagonists; postural symptoms with α -blockers) Ask patient, "Since you started this medicine, has it made such a difference to how you feel that you would prefer to stay on it?" and consider discontinuing the drug if the response is no or probably not Ask, "Are you still experiencing any troublesome symptoms (cough, headache, dyspepsia, etc)? Do you feel the medicine is still required?" Consider discontinuing use of the drug if the target condition is self-limiting, mild, intermittent, or amenable to nondrug interventions (eg, change in diet, alcohol use) Estimate patient's life expectancy using risk prediction tools or asking "surprise" question (see text) Determine the patient's expectations and preferences—is present-day quality of life more important than prolonging life or preventing future morbid events? Identify drugs unlikely to confer benefit (and that may cause harm) over the patient's remaining lifespan Ask the patient, "Apart from side effects, are there any other concerns you have with your medicines?" Identify drugs that are particularly burdensome (eg, difficulty swallowing large tablets, out-of-pocket expense, monitoring requirements [such as warfarin sodium])
4. Prioritize drugs for discontinuation	Deciding the order of discontinuation of drugs may depend on integrating 3 pragmatic criteria: <ol style="list-style-type: none"> (1) those with the greatest harm and least benefit; (2) those easiest to discontinue, ie, lowest likelihood of withdrawal reactions or disease rebound; (3) those that the patient is most willing to discontinue first (to gain buy-in to deprescribing other drugs) Suggested approach is to rank drugs from high harm/low benefit to low harm/high benefit and discontinue the former in sequential order (Figure)
5. Implement and monitor drug discontinuation regimen	Explain and agree with patient on management plan Cease 1 drug at a time so that harms (withdrawal reactions or return of disease) and benefits (resolution of adverse drug effects) can be attributed to specific drugs and rectified (if necessary) Wean patients off drugs more likely to cause adverse withdrawal effects, instruct patient (or carer) on what to look for and report in the event of such effects occurring, and what actions they can self-initiate if these were to occur Communicate plan and contingencies to all health professionals and other relevant parties (carers, family) involved in patient's care Fully document the reasons for, and outcomes of, deprescribing

tentially inappropriate drug use can be ceased is depicted in the Figure. This protocol was iteratively developed by us on the basis of research conducted by various members within our group.^{33,34} An earlier version of the protocol was shown to have face validity among a cohort of prescribers and pharmacists.³⁵ Certain steps deserve special mention.

Deciding Which Drug Therapies Can Be Discontinued

What Are Current Indications for Each Drug?

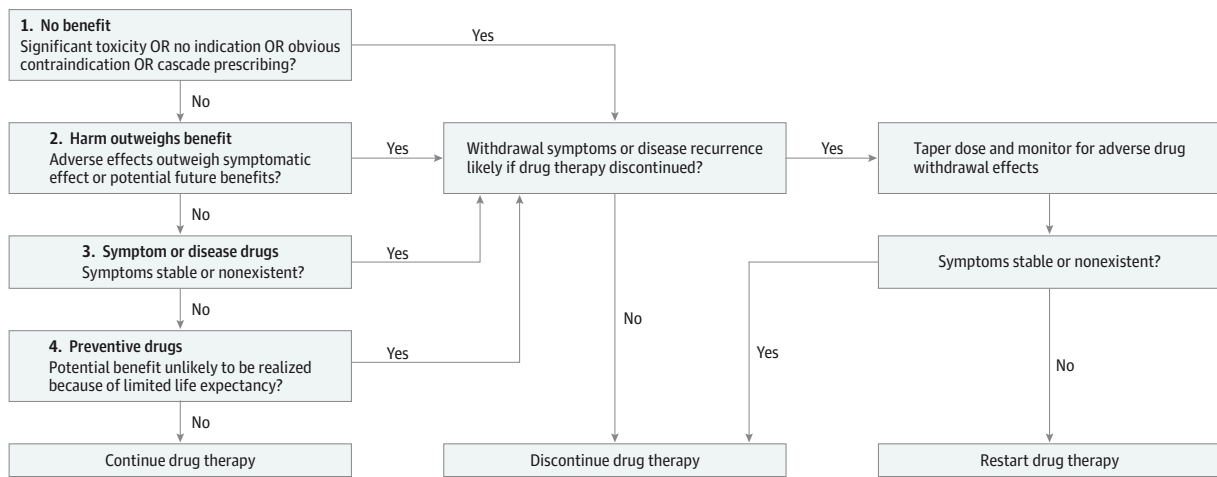
Prescribers and pharmacists must collaborate in collecting as much information as possible in answering the following questions: why and when was a therapy initiated; was the diagnosis substantiated; was the drug prescribed to counter adverse effects of another drug (the prescribing cascade); is the drug continuing to confer evident patient benefit; are there alternative, equally effective nonpharmacological therapies available? Some drugs, being well tolerated, are continued for years on the assumption that they are serving a useful purpose. Drug regimens should come with an expiry or "best before" date prompting reappraisal, with earlier reviews conditional on substantial change in a patient's clinical status.

Examples of unnecessary continuation of drugs include patients receiving long-acting nitrates for a past episode of chest pain labeled as angina but in whom no objective evidence of coronary artery disease exists, gastroprotective proton-pump inhibitors following cessation of nonsteroidal anti-inflammatory drug therapy, antidepressants for a previous but resolved episode of reactive depression, antihypertensives in patients now normotensive in response to lifestyle modifications, and risperidone for distant episodes of excessive agitation complicating dementia.

Is the Patient Actually Taking the Drug?

Older patients avoid using drugs that they sense could make, or are making, them feel unwell, especially prophylactic drugs aimed at reducing risk of future illness rather than treating currently symptomatic disease.³⁶ In other cases, patients are confused by conflicting advice on benefit and harm from different health care professionals. Personal costs of buying drugs and associated burdens of monitoring are additional disincentives. By eliminating unnecessary drugs, deprescribing may improve overall adherence to essential drugs while reducing costs and inconvenience.³⁷

Figure. Algorithm for Deciding Order and Mode in Which Drug Use Could Be Discontinued



Does the Drug Fit With the Patient’s Life Circumstances?

Drugs are rarely indicated if they do not confer a patient-important benefit within the context of one’s life circumstances. Patients with severe dementia, end-stage organ failure, or metastatic cancer would derive little benefit from preventive drugs such as bisphosphonates and statins in the relatively short time prior to death.

Does the Likely Benefit of the Drug Outweigh Its Potential for Harm?

Older patients are particularly vulnerable to adverse effects from certain classes of drugs. These “high-risk” drugs include opioids, benzodiazepines, psychotropic drugs, nonsteroidal anti-inflammatory drugs, anticoagulants, digoxin, cardiovascular drugs, hypoglycemic agents, and drugs with anticholinergic effects. “High-risk” drug combinations are those in which each individual drug augments the level of toxicity, such as the “triple whammy” of nonsteroidal agent, diuretic, and angiotensin-converting enzyme inhibitor in people with chronic kidney disease.

When considering deprescribing, it helps to group drugs into 2 categories, while acknowledging that some drugs may appear in both:

Disease and/or symptom control drugs: those that control active disease and symptoms and maintain quality of life (eg, analgesics, anti-anginals, anti-heart failure drugs, levothyroxine sodium). In many instances, if treatment with these drugs is ceased, patients are likely to quickly become symptomatic or lose function from worsening disease. This is not to suggest that these drugs could not be ceased entirely if proving to be ineffective, or reduced in dose or used as required if disease manifestations are mild or intermittent. Aggressive use of drugs aimed at controlling hypertension or diabetes mellitus should be avoided in older patients because they may do little to alter symptoms or change the natural history of the disease, while exposing patients to more immediate threats of hypotension or hypoglycemia.

Preventive drugs: those that prevent future morbid events (eg, statins, warfarin sodium, bisphosphonates). Deciding to discontinue prescribing these drugs involves consideration of the absolute risks and

benefits of treatment for individual patients, the length of time required for benefit to manifest (time to benefit)³⁸ in cases in which therapy has been recently commenced (or is being considered), and patient preferences and estimated lifespan. Estimating life expectancy can be difficult, although the simple “surprise” question, “knowing all that I know about this patient, would I be surprised if he or she were to die in the next 12 months?” is reasonably predictive.³⁹

Instances in Which Deprescribing Should Be Considered

- Deprescribing should be especially considered in any older patient
- presenting with a new symptom or clinical syndrome suggestive of adverse drug effects;
 - manifesting advanced or end-stage disease, terminal illness, dementia, extreme frailty, or full dependence on others for all care;
 - receiving high-risk drugs or combinations;
 - receiving preventive drugs for scenarios associated with no increased disease risk despite drug cessation (eg, discontinuing alendronate sodium therapy after 5 years of treatment results in no increase in osteoporotic fracture risk over the ensuing 5 years⁴⁰; ceasing use of statins for primary prevention after some years results in no increase in cardiovascular events 8 years after discontinuation⁴¹).

Barriers to Deprescribing

Systematic reviews of qualitative research^{42,43} suggest that, within prescriber-patient interactions, both participants are challenged by high levels of clinical complexity, limited consultation time, fragmented care among multiple prescribers, incomplete information (on past rationales for, and patient tolerance of, drugs), ambiguous or changing care goals, uncertainty about the benefits and harms of continuing or discontinuing specific drugs, and community and professional attitudes toward more rather than less use of drugs.

Box. System-Level Strategies for Facilitating Deprescribing in Clinical Practice**Professional Societies of Prescribers (Primary Care, Specialists, Pharmacists, Dentists, Nurse Practitioners)**

Develop position statements on high-quality use of drugs in older, multimorbid populations that include and integrate the concept of deprescribing

Provide training, professional development programs, workshops, and seminars that impart knowledge and skills in appropriate initiation, monitoring, evaluation, and cessation of drug use

Universities and Research Bodies

Incorporate appropriately tailored curricula in high-quality use of drugs that integrate deprescribing in all undergraduate, graduate, and post-graduate courses in medicine, pharmacy, nursing, dentistry, and allied health

Require funding and ethics approval for research projects involving drugs to collect, analyze, and report data that relate to frequency of, and reasons for, withdrawal of drug use in trial participants to build the evidence base of drug-related harm

Clinical Guideline Developers

Develop treatment recommendations specific to the needs of older, multimorbid patients that acknowledge the limited evidence base for use of many drugs in such populations

Make explicit reference to commonly encountered clinical scenarios in which use of disease-specific drugs may engender greater risk of harm as a result of drug-drug and drug-disease interactions; include cautionary notes regarding initiation or discontinuation of drug use in high-risk scenarios

Pharmacists and Pharmacy Services

Instruct patients in how to identify drug-induced harm and adverse effects and how to collaborate with their prescribing clinicians in safely discontinuing use of high-risk drugs

Incorporate into practice standards the requirement that pharmacists be assigned to residential care facilities for the purpose of achieving high-quality use of drugs, reviewing drug lists, and highlighting instances amenable to deprescribing

Organizations and Services Responsible for Providing High-Quality Use of Drug Information or Issuing Drug Handbooks, Prescribing Guidelines, and Drug Safety Bulletins

Include information on strategies for therapy cessation in drug handbooks and prescribing guidelines with cross-reference to drug classes and circumstances in which use of specific drugs should be avoided in older, multimorbid populations

Require drug prescribing software vendors to incorporate flags and alerts that prompt prescribers to consider therapy cessation in at-risk patients

Establish websites that provide tools and resources for health care professionals in how to undertake appropriate deprescribing of drugs

Government and Statutory Bodies (Health Departments, Quality and Safety Commissions, Practice Accreditation Services, Health Care Standard-Setting Bodies)

Fund research to develop and evaluate drug safety standards that maximize the potential for reducing inappropriate use of drugs

Identify best practices with regard to the timeliness (when and how often), setting (hospital, primary care, residential aged care facility), and participants (clinical pharmacists, physicians, nurses) of drug review that will enable sustainable interventions supporting therapy cessation

Incorporate formal education and quality measurement systems that support and monitor patients receiving multiple drugs within hospital and primary care accreditation procedures

Issue drug-specific prescribing alerts when pharmacovigilance data suggest higher than expected incidence of drug-related adverse events in older populations

Revise national policies and strategies for high-quality use of drugs to ensure that the concept of deprescribing is integrated more clearly into the definition of high-quality use of drugs

Clinical Researchers

Design and conduct clinical trials that recruit older, multimorbid patients, including specific subgroups (eg, patients with dementia) and aim to define drug benefits and harms using patient stratification methods

Adopt the word "deprescribing" in abstract titles as the accepted, universal term for research on prescriber-mediated drug therapy discontinuation so that relevant articles can be more accurately indexed in bibliographic databases and more easily retrieved in literature searches

Medical Journals

Publish prescribing position statements, guides, resources, and clinical vignettes that support appropriate prescribing and integrate deprescribing issues

Residential Aged Care Facilities

Incorporate into practice standards the requirement for training of aged care workers in high-quality use of drugs and pharmacist reviews

Incorporate into accreditation standards the requirement for drug review for every patient newly admitted to an aged care facility and re-turning after recent hospitalization

Both parties fear adverse drug withdrawal effects, even though these occur much less frequently than adverse drug effects.^{22,44}

Another barrier is the pressure to prescribe evoked by recommendations contained within disease-specific clinical guidelines. While intending to optimize care, such recommendations may be less applicable to older, multimorbid patients with polypharmacy,^{45,46} particularly if based on clinical trials that have excluded such patients.

Strategies That Can Assist Deprescribing

Assistive strategies can operate at the level of individual clinical encounters or at the level of whole populations and systems of

care. Within encounters, patients should be empowered to ask their physicians and pharmacists the following questions: what are the treatment options (including nondrug options) for my condition; what are the possible benefits and harms of each treatment (drug); and what might be reasonable grounds for discontinuing use of a drug. In turn, physicians and pharmacists should ask, at every encounter, whether patients are experiencing any adverse effects, unwanted reactions, or administration and monitoring problems in association with any of their drugs. Collaborative prescriber-pharmacist review of drugs that uses validated criteria to identify drugs more likely to be unnecessary or harmful can help initiate and guide deprescribing.^{47,48} In estimating treatment benefit-harm trade-offs in individual patients, prediction tools (<http://>

//www.medal.org/), evidence tables,⁴⁹ and decision aids that estimate absolute disease risk, and absolute treatment benefit and harm for various conditions are increasingly available. Finally, practical guidance in how to safely wean and cease use of particular classes of drugs in older people is now easily accessible.⁵⁰ At the system of care level, deprescribing efforts will be compromised in realizing better population health unless all key stakeholders involved in high-quality use of drugs commit to implementing strategies that recognize deprescribing as an integral part of good clinical care (Box).

Areas Requiring More Research

Future research into the incidence, causes, and remediation of overprescribing of inappropriate drugs in older patients should consider several key questions:

- To what extent does a standardized deprescribing approach affect patient adherence to essential drugs, overall drug costs (to the individual as well as the public purse), patient satisfaction and self-management, and long-term clinical outcomes?
- Under what circumstances could deprescribing confer negative, irreversible effects in both the short and long term?

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- What is the most effective, cost-effective, and practical approach to deprescribing in routine clinical settings?
- What are the absolute estimates of drug-induced benefit and harm, and time until benefit, for specific drug classes of preventive drugs related to specific clinical scenarios?
- How can these benefit-harm estimates be accessed and presented within prescriber-patient encounters in ways that optimally inform deprescribing decisions?

Conclusions

Inappropriate drug use and its associated harm is a growing issue among older patients. It calls for deliberate yet judicious prescribing that includes a systematic approach toward deprescribing applied by all prescribers and supported and reinforced by pharmacists and others responsible for optimizing use of drugs. Widespread adoption of a deprescribing protocol in clinical care has its challenges but also considerable potential to relieve unnecessary suffering and disability in older patients. More high-quality research is needed in defining the circumstances under which deprescribing confers maximal benefit in terms of improved clinical outcomes and should be more widely practiced.

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