

Polypharmacy, inappropriate prescribing, and deprescribing in older people: through a sex and gender lens



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Polypharmacy is very common in older adults and increases the risk of inappropriate and unsafe prescribing for older adults. Older adults, particularly women (who make up the majority of this age group), are at the greatest risk for drug-related harm. Therefore, optimising drug prescribing for older people is very important. Identifying potentially inappropriate medications and opportunities for judicious deprescribing processes are intrinsically linked, complementary, and essential for optimising medication safety. This Review focuses on optimising prescribing for older adults by reducing doses or stopping drugs that are potentially harmful or that are no longer needed. We explore how sex (biological) and gender (sociocultural) factors are important considerations in safe drug prescribing. We conclude by providing a practical approach to optimising medication safety that clinicians can routinely apply to the care of their older patients, highlighting how sex and gender considerations inform medication decision making.

Introduction

The global population is aging rapidly. Many countries are now super-aged societies where more than 20% of their population are older than 65 years.¹ Women comprise the majority of the older population, a percentage that increases with advancing age.² Older adults are at greatest risk for drug-related harm. Older women might be more susceptible to drug-related harm than older men, which is due, in part, to pharmacokinetic and pharmacodynamic changes,³ making medication optimisation for older women particularly important.

If done carefully and systematically, reducing drug doses, stopping inappropriate drug therapies, and choosing alternative safer therapies can improve the quality of life for many older people. Realising the widespread scale of harm arising from polypharmacy, WHO identified Medication Without Harm as the third international Global Patient Safety Challenge.⁴ This initiative, designed to raise global awareness about inappropriate and hazardous prescribing, was launched in 2017 and aims to reduce avoidable medication harm by 50% globally over 5 years. Deprescribing potentially inappropriate medications can minimise drug-related harm for older adults, particularly women. Proper medication management requires attention on an international scale, now more than ever.

This Review focuses on optimising prescribing for older adults by reducing doses of certain drugs or stopping drugs that are no longer needed. Although we focus on high-income countries, what we describe should be relevant worldwide. Throughout this Review, we explore how sex (biological) and gender (sociocultural) factors are important considerations in safe medication prescribing and deprescribing for older adults. We conclude by providing a practical approach to medication review and management that clinicians can routinely apply to the care of individual older patients.

Problems with the way that drug therapies are prescribed

A series of problems with the way that pharmacotherapeutic decisions are made and implemented contribute to polypharmacy, inappropriate medication prescribing, and the need for deprescribing. When making treatment decisions, physicians often do not consider non-pharmacological approaches as a first step. The benefit of implementing good sleep hygiene to improve sleep⁵ instead of prescribing a sleep aid is an example of a non-pharmacological approach, which can be very effective but is under-used.⁶ In a retrospective cohort study done in community-dwelling older adults, one in five participants with a new sleep disorder diagnosis were prescribed a medication for sleep, and a higher proportion were women.⁷ Further, prescribing guidance is generally based on what is appropriate for a single medical condition, without taking into consideration that two-thirds of adults older than 65 years have multiple chronic conditions requiring the use of numerous medications. Following prescribing guidelines for each medical condition separately might result in medications being prescribed that place an older adult at an increased risk for drug interactions and other adverse events.⁸ Additionally, evidence shows that prescribing practices for antibiotic therapy among nursing home residents with advanced dementia do not routinely take into consideration an individual's goals of care or their remaining life expectancy.⁹ Important factors such as an individual's cognitive status and whether they are frail are insufficiently considered when assessing the potential benefit of a medication.¹⁰ Further, drug therapies are often generally added but seldom stopped.¹¹ Drug prescribing texts and online resources do not routinely provide information about judicious stopping of drug therapies. Finally, and perhaps most important, drug prescribing takes a holistic approach that generally does not consider important biological and sociocultural differences between women and men. Given that the majority of older people are women, and

Lancet Healthy Longev 2021; 2: e290-300

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women are more vulnerable than men to drug-related harm, it is important to consider sex and gender differences when striving to optimise drug prescribing.

Applying a sex and gender lens to drug therapy

The importance of considering sex and gender has been highlighted in the recent *Lancet* Series on sex and gender¹² and in a review on sex and gender as modifiers of health and disease and medicine.¹³ Women and men respond to drug therapies differently; therefore, when sex and gender differences are not considered, women are placed at greater risk of medication-related harm.³ Yet, this fundamental information is noteworthy for its absence in the medical literature.¹³ The scarcity of information about differences between older women and men in regards to the effects of drug therapies can be largely traced back to their under-representation in clinical trials. It was not until 1993 that the US National Institutes of Health (NIH) established guidelines for the inclusion of women and minority groups in NIH-funded clinical research through the NIH Revitalization Act of 1993.¹⁴ Notably, this directive focused on women in general. Although it might be assumed that older women should be a key group, considering that they are the largest consumers of medications in most countries, the intersection of sex and age was not highlighted in the NIH Revitalization Act. In 2019, the NIH Inclusion Across the Lifespan policy¹⁵ was implemented to help address the inadequate inclusion of older adults in NIH-funded studies; the policy also required that study enrolment reporting had to be done on the sex, gender, age, and race of participants.¹⁶ When policies focus separately on these characteristics, the identification of older women might be missed.¹³ Additionally, despite these initiatives, older adults continue to be under-represented in clinical trials, due to implicit exclusion based on comorbidities, function, or cognitive status that disproportionately affects older adults.^{17,18}

The drug therapies prescribed to men and women often differ, and these prescribing decisions are not always aligned with evidence. For example, women are more likely to be prescribed medications for the management of conditions, including migraine, thyroid disorders, depression, and sleeping problems.¹⁹ However, men are more likely to be prescribed secondary prevention therapy, particularly for heart disease.^{20,21} There is also evidence that women are at greater risk for adverse drug-related events than men.^{19,22,23} In 2001, the General Accounting Office evaluated the prescription drugs that were withdrawn from the market in the USA.²⁴ Of the 10 drug therapies withdrawn, eight were withdrawn due to greater risks to women than men. Another example is zolpidem, a non-benzodiazepine hypnotic that is widely used for insomnia, which illustrates that women might be more likely than men to need a lower dose of a drug therapy due to sex-based pharmacokinetic and pharmacodynamic differences.²⁵ In 2011, in the USA, about 39 million

prescriptions of zolpidem were dispensed nationally and 63% of these were to women.²⁵ After being on the market for more than 20 years, data showed that the risk of next-morning drowsiness from zolpidem—enough to impair driving ability—was greater in women than in men receiving the same doses.²⁵ There are important pharmacokinetic differences associated with sex; the clearance rate of zolpidem is 40–50% lower in females than males.²⁶ As a result, the Food and Drug Administration recommended that the zolpidem dose for women should be reduced by half.²⁵ Older adults also have lower clearance rates of drugs leading to higher concentrations relative to younger adults. This information is seldom presented in a sex-disaggregated and age-disaggregated manner that would be particularly helpful to guide prescribing for individuals who are women and who are also older. There are also instances in which men might be more affected by a drug therapy than women. This situation has been shown by the presentation of serious events after the use of atypical and typical antipsychotic therapy, in which men had more serious events than women.²⁷

Gender-related sociocultural factors might also influence the decision to stop a medication. For example, gender might influence the ability to pay for a medication. Paying for costly drug therapy is a particular issue for people on fixed incomes who might be choosing between buying food and medications.²⁸ Older women are less likely than older men to have pensions or drug benefit plans because they are less likely to have engaged in the formal work force.²⁹ Additionally, older women are more likely to be caregivers and to have responsibility for supervising the medications for a spouse or an older family member.³⁰ These caregivers need to be included in the medication review process. When older women themselves require assistance with their medications, they might be less likely to have a spouse or a partner to help provide that supervision. Further, evidence suggests that, compared with older men, drug therapies are prescribed differently to older women. For example, older men are even more likely than older women to continue receiving drug therapies often designed for secondary prevention at the end of life. This finding is, in part, because men are more likely to receive more aggressive medical care than women.⁹ This more aggressive care might continue even when these therapies are deemed to no longer be helpful and might actually be burdensome.⁹ Finally, although women are more likely than men to visit their health professionals, evidence suggests that women might be less likely to follow preventive guidance and to adhere to therapies.^{21,31,32} This information highlights the importance of exploring sex and gender differences to better understand how interventions can be implemented to stop unnecessary medications and improve medication optimisation.

Figure 1 shows our suggested approach to optimising medication safety that clinicians can follow. This approach starts with the problem of polypharmacy,

identifies inappropriate prescribing, and uses this information to inform deprescribing decisions to stop medications, with sex and gender considered throughout.

Polypharmacy increases the risk for inappropriate and unsafe prescribing to older adults. Identifying potentially inappropriate prescribing practices (by use of tools and frameworks) informs judicious deprescribing and promotes medication safety (figure 1). Some tools and frameworks can help to identify inappropriate prescribing, and these approaches might also provide guidance on which drugs should be prioritised for deprescribing.³³ Although little is known about how sex and gender influence polypharmacy and inappropriate prescribing tools or deprescribing protocols, we present what is known and identify the main knowledge gaps.

Polypharmacy

Polypharmacy is generally defined as the use of five or more prescribed or over-the-counter drug therapies. The terms excessive polypharmacy and hyperpolypharmacy³⁴ have been used for people taking 10 or more prescription or over-the-counter drug therapies. Another less common approach to defining polypharmacy has been to use the terms appropriate polypharmacy or problematic polypharmacy. Appropriate polypharmacy recognises that older people might require multiple drug therapies to manage their complex medical conditions. Problematic polypharmacy³⁵ refers to the use of multiple drug therapies in a way that is not appropriate—ie, the medications are not providing an overall benefit. This approach is further operationalised into hazardous drug combinations, unacceptable pill burden, difficulty with medication adherence, or when medications are being prescribed as part of a prescribing cascade,³⁵ in which drug side-effects are misinterpreted as a new medical condition, leading to additional medications.

The international importance of polypharmacy was highlighted in WHO's report on the Medication Without Harm Challenge.⁴ WHO's 2019 technical statement asks member countries to prioritise their strong commitment to medication safety, identifying polypharmacy as one of the three action areas.³⁶ 22 countries were reported to have created national guidance on polypharmacy management.³⁷

Although most people understand the general sense of the term polypharmacy, poor specificity can lead to confusion. One systematic review estimated that there are 138 different definitions of polypharmacy.³⁸ Further, it is not clear if polypharmacy encompasses prescribed medications only or if over-the-counter drugs and other therapies are also included.

Given that people now live longer with multiple medical conditions, many older adults, particularly women, experience polypharmacy. Polypharmacy is particularly important for older women because women are more at risk for drug-related adverse events due to sex-related and gender-related considerations. Further, polypharmacy is

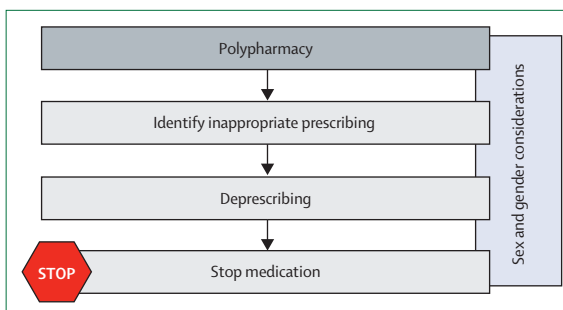


Figure 1: Approach to optimising medication safety for older adults

Polypharmacy increases the risk for inappropriate and unsafe prescribing in older adults. Our suggested approach allows for the identification of potentially inappropriate prescribing (using tools and frameworks) and deprescribing processes (using the information to stop medications). Sex and gender considerations need to be incorporated throughout.

associated with the prescribing of potentially inappropriate medications,^{39–41} which heightens the risk of adverse events. Additionally, another reason polypharmacy is a particular issue for women is because women make up the majority of long-term care residents. In 2012, among older adults living in long-term care homes in Europe and Israel, almost 50% used between five and nine daily drug therapies and almost a quarter used 10 or more drugs.⁴² For older adults living in long-term care homes in Canada, where almost 70% of residents are women,⁴³ close to 50% are being prescribed medications from 10 or more drug classes.⁴⁴

Tools to identify inappropriate prescribing

Numerous tools and frameworks are available to identify inappropriate prescribing and to facilitate deprescribing internationally. To identify inappropriate prescribing tools that are widely known, we selected those to profile by use of the list generated by the International Group for Reducing Inappropriate Medication Use and Polypharmacy (IGRIMUP)⁴⁵ and cross-referenced them with tools included in two recent systematic reviews.^{46,47} Given the large number of these tools, we profiled those with 500 or more citations for inappropriate prescribing tools and 200 or more citations for deprescribing tools by use of Google Scholar as of January 19, 2021. For each tool, we identified whether sex or gender were considered. Lists of tools and frameworks used to identify inappropriate prescribing and deprescribing that met our inclusion criteria are shown (table). Panel 1 briefly describes each of the identified inappropriate prescribing tools. Although none of these inappropriate prescribing tools were developed with the consideration of sex or gender differences, they might have been used by other investigators to explore this issue. We searched Google Scholar for papers, using sex or gender and the name of the inappropriate prescribing tool or deprescribing process as search terms and summarised the relevant information.

	Name of tool or framework or deprescribing process	Country of lead author	Sex or gender discussed?
Tools to identify inappropriate prescribing			
Beers et al (1991) ⁴⁸	Beers criteria	USA	No
Fick et al (2019) ⁴⁹	Beers criteria	USA	No
Zhan et al (2001) ⁵⁰	Inappropriate Medication Use	USA	No
Bushardt et al (2008) ⁵¹	Hyperpharmacotherapy assessment tool	USA	No
Gallagher et al (2008) ⁵²	STOPP/START criteria	Ireland	No
O'Mahony et al (2015) ⁵³	STOPP/START criteria	Ireland	No
Hanlon et al (1992) ⁵⁴	Medication Appropriateness Index	USA	No
Somers et al (2012) ⁵⁵	Medication Appropriateness Index	Belgium	No
Holt et al (2010) ⁵⁶	Old and venerable (PRISCUS)	Germany	No
McLeod et al (1997) ⁵⁷	Inappropriate prescribing for the elderly	Canada	No
Laroche et al (2007) ⁵⁸	French consensus panel list	France	No
Hilmer et al (2007) ⁵⁹	Drug Burden Index	USA	No
Rudolph et al (2008) ⁶⁰	Anticholinergic Risk Scale	USA	No
Carnahan et al (2006) ⁶¹	Anticholinergic Drug Scale	USA	No
Frameworks to identify inappropriate prescribing			
National Action Plan for Adverse Drug Event Prevention (2014) ⁶²	Good Drugs used in Inappropriate Ways	USA	No
Rochon, Gurwitz (1995) ⁶³	Prescribing cascade	Canada	No
Rochon, Gurwitz (2017) ⁶⁴	Prescribing cascade	USA	No
Deprescribing processes			
Scott et al (2015) ⁶⁵	The Deprescribing Protocol	Australia	No
Scott et al (2015) ⁶⁶	CEASE algorithm	Australia	No
Garfinkel et al (2007) ⁶⁷	Good Palliative-Geriatric Practice algorithm	Israel	No

CEASE=current medicines, elevated risk, assess, sort, and eliminate. START=screening tool to alert doctors to the right treatment. STOPP=screening tool of older persons' prescriptions.

Table: Key tools and frameworks to identify inappropriate prescribing and deprescribing processes

The Beers criteria have been used by investigators from many countries, including Canada,⁷¹ Jordan,⁴⁰ Sweden,⁴¹ Switzerland,⁷² Brazil,³⁹ and the USA,⁷³ to explore how sex and gender might influence inappropriate prescribing. Most of these studies have reported that women are more likely than men to be prescribed medications that are potentially inappropriate. In Canada, Morgan and colleagues⁷¹ reported that 31% of women, compared with 26% of men, filled a prescription for a potentially inappropriate drug therapy. This finding is primarily related to women being dispensed more benzodiazepine prescriptions than men. An earlier study among older veterans in the USA also reported that women were more likely to receive 16 of the 33 drugs on the inappropriate drug list, principally certain analgesics, psychotropic drugs, and anticholinergic agents, whereas men were only more likely to receive three of 33 drugs on the list.⁷³ Faustino and colleagues,³⁹ in Brazil, and Al-Azayzih and colleagues,⁴⁰ in Jordan, also reported that female sex was associated with the prescription of a potentially inappropriate medication.

The screening tool of older persons' prescriptions (STOPP) criteria have been used to evaluate inappropriate prescribing in primary care, in which Nuñez-Montenegro

and colleagues⁷⁴ reported that, in Spain, older women had a higher percentage of inappropriate prescribing than older men (78% vs 66%). Similarly, Wickop and colleagues⁷⁵ reported that more medications on the STOPP list were prescribed to older women than men in Germany.

In Germany, Toepfer and colleagues⁷⁶ reported that, although the use of potentially inappropriate medications was more frequent in women than in men when using the PRISCUS tool, the use of potentially inappropriate medications was associated with greater morbidity in men compared with that in women. Finally, a study by Morin and colleagues⁴¹ reported that, in Sweden, female sex was associated with more inappropriate drug use when applying the Beers criteria, PRISCUS, or the French consensus panel list.

Frameworks to identify inappropriate prescribing

We separately identified several frameworks that were not included in lists of inappropriate prescribing tools but that were deemed as important to inform inappropriate prescribing by the authors. We include the prescribing cascade as an important framework to provide general guidance on drugs to be avoided or stopped. We also include in this category the US National Action Plan for Adverse Drug Event Prevention⁶² as an important reminder for those prescribing to older people that so-called good drugs used in inappropriate ways can become so-called bad drugs and cause the majority of adverse events.

The prescribing cascade is a framework that can be used to help identify an important situation when good drugs are used in potentially inappropriate ways. The prescribing cascade concept was developed by Rochon and Gurwitz, from Canada and the USA, respectively, in 1995⁶³ and updated in 2017.⁶⁴ A prescribing cascade occurs when health-care providers misinterpret the side-effect of a drug as a new medical condition and prescribe a second drug therapy to manage this unrecognised drug-induced side-effect. A series of prescribing cascades have been identified and documented with large population-level data, such as calcium channel blockers leading to ankle oedema and the initiation of loop diuretic therapy.⁷⁷ This framework applies generally to any drug therapy in which a side-effect develops that is mistaken for a new medical condition and the provider responds with new drug treatment. In some cases, over-the-counter medications can be taken by the patient to manage their new medical condition.⁶⁴ Discontinuing or reducing the dose of the initial drug therapy could avoid or reverse these cascades. The prescribing cascade has been incorporated into many deprescribing protocols,^{65,78,79} and process mapping can be used by clinicians to identify prescribing cascades in their patients.⁸⁰ Further, researchers have reported that there are five key factors for physicians to consider

Panel 1: Inappropriate prescribing tools

The Beers criteria⁴⁸ were first created in 1991 by an expert consensus panel led by geriatrician Mark Beers and colleagues in the USA. The Beers criteria have undergone multiple updates, including the most recent (sixth iteration) published in 2019 under the auspices of the American Geriatrics Society.⁴⁹ The criteria were initially designed to assist researchers in identifying the quality of prescribing in long-term care homes, but these criteria have subsequently been applied to all clinical settings.⁶⁸ This tool provides a list of medications that are considered potentially inappropriate, medications to avoid in certain conditions, medications to use with caution, specific drug–drug interactions, and medications that require dose adjustment related to kidney function. Other researchers in the USA have applied the Beers criteria to generate lists of inappropriate medications related to community-dwelling older people⁵⁰ and a hyperpharmacotherapy assessment tool.⁵¹

The screening tool of older persons' prescriptions (STOPP) criteria were developed by O'Mahony and colleagues from Ireland. These criteria were first published in 2008⁵² and were updated in 2015⁵³ to include more recent drug therapies. This tool was created by a group of experts who identified drug therapies that were potentially inappropriate for older people, organised by physiological system. This tool includes drug therapies in which there are drug–drug interactions and duplications of drugs within a class. The screening tool of older persons' prescriptions in frail adults with limited life expectancy (STOPPfrail) criteria,⁵⁹ which are partly based on the STOPP/screening tool to alert doctors to the right treatment (START) criteria,⁵³ were developed in Ireland and first published in 2017. This tool provides a list of potentially inappropriate drug therapies that should be discontinued in older adults who have all of the following characteristics: "end stage irreversible pathology, poor one-year survival prognosis, severe functional impairment or severe cognitive impairment or both, [in whom] symptom control is the priority rather than prevention of disease progression".⁶⁹ This tool has also been assessed for use at end of life among people who are hospitalised. The second iteration of the STOPPfrail criteria was published in 2021.⁷⁰

In 1992, the Medication Appropriateness Index was created by Hanlon and colleagues⁵⁴ in the USA. In 2012, this tool was adapted by Somers and colleagues⁵⁵ in Belgium. The original Medication Appropriateness Index provides a list of 10 questions that must be addressed to identify potential drug-related problems associated with a specific medication.

For each question, a rating from 1 to 3 is given, to indicate in some cases the degree to which the medication is indicated or not, or whether the directions are practical or impractical. A strength of this tool is that it assesses a range of issues that are important to consider when evaluating the ongoing need for a medication and it can be used to assess a variety of medications.

The PRISCUS criteria were developed in 2010 by an expert consensus panel through a modified Delphi process, led by Stefanie Holt and colleagues,⁵⁶ in Germany. This list of potentially inappropriate medications was developed for informing safer medication use among the older adult population and was specifically tailored for the German pharmaceutical market. Alongside a list of potentially inappropriate medications, details addressed also included the associated main concerns, possible therapeutic alternatives, and precautions to be taken when these medications cannot be avoided.⁵⁶

The inappropriate prescribing for the elderly tool is a consensus-based list first developed in 1997, led by McLeod and colleagues⁵⁷ in Canada. This list identifies inappropriate practices in prescribing for older people that are included in three categories: drugs generally contraindicated for older people, drug–disease interactions, and drug–drug interactions. Along with the clinical importance of the risk, suggestions for alternative therapies that might be equally or more effective and less risky were included.⁵⁷

The French consensus panel list was developed in 2007 by an expert consensus panel through a two-round Delphi method, led by Marie-Laure Laroche and colleagues⁵⁸ in France. This list of potentially inappropriate medications was developed for safer medication use among the French population aged 75 years and older. The tool provides a list of criteria along with the reasons for concern and possible alternative drugs.⁵⁸

Another tool that has been developed specifically to assess pharmacological risk is the Drug Burden Index, led by Hilmer and colleagues⁵⁹ (from the USA), which is used to assess the burden of anticholinergic and sedative medications. Further tools include the Anticholinergic Risk Scale, developed by Rudolph and colleagues⁶⁰ (from the USA) and the Anticholinergic Drug Scale, developed by Carnahan⁶¹ (from the USA), which are used to assess the burden and risk of adverse events associated with the use of anticholinergic drugs. None of these tools take sex or gender into consideration.

with regard to prescribing cascades.⁸¹ Providing medication history, particularly when a medication is ed, would help clinicians to determine the drug prescribing sequence and facilitate the early recognition of a prescribing cascade. The iKASCADE team is currently studying how sex and gender influences prescribing cascades.⁸²

The US National Action Plan for Adverse Drug Event Prevention⁶² describes an important way of thinking

about medications and safety that recognises that good drugs when used in an unsafe or inappropriate way become bad. This framework builds on the work of Budnitz and colleagues,⁶⁸ who examined emergency department visits for drug-related adverse events among older adults and reported that good drug therapies (eg, anticoagulants and insulin) used in inappropriate ways were responsible for most of these emergency room visits. These individual drug therapies are important

because they each have narrow therapeutic windows. This study identified the essential need for interventions to improve the prescribing of good drugs used in inappropriate ways, to reduce adverse events leading to excess emergency department visits among older adults. For example, to prevent these problems there needs to be timely intervention when a patient's clinical situation changes. These interventions might include dose reduction or discontinuation, even in some cases on a temporary basis, and involve working closely with patients and their care providers.

The deprescribing process: tools and protocols

Deprescribing is defined 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”.⁶⁵ The term “deprescribing” was first used by Michael Woodward in 2003⁸³ and has since gained traction and popularity because it provides a call-to-action to consider when and how to stop a medicine that might be inappropriate for the patient's clinical status and prognosis.

Reducing inappropriate medication use, specifically among older adults, has been linked to decreases in

falls,⁸⁴ confusion,⁸⁵ and emergency room visits.⁶⁸ Although there is a great deal of support for deprescribing by clinicians and patients internationally, a systematic review of the literature has not shown the benefit of deprescribing on hospital admission or mortality.⁸⁶

Given the magnitude of overprescribing in older adults, deprescribing initiatives have been developed at an international level (IGRIMUP)⁴⁵ and national level in several countries, including Canada, the USA, and Australia, as a means to reduce excessive doses or to discontinue inappropriate drug therapy. A narrative review conducted by Reeve⁸⁷ categorises the available types of deprescribing tools, including those that provide general deprescribing guidance, those that are drug-specific, tools for identifying potentially inappropriate medications (table), and those that are designed to engage patient participation. Tools developed to identify inappropriate medications can directly inform deprescribing and the deprescribing processes and often use inappropriate medication tools as one of their steps. Some deprescribing processes have been developed for use in key life stages in which it is important to reconsider the ongoing benefit of medications, such as when an individual's goals of care change because they become frail, develop cognitive impairment, or are approaching the end of their life.⁶⁷ Two of the most widely cited deprescribing protocols are described (panel 2). Neither of these protocols mention sex or gender.

Despite the importance of deprescribing and the evidence that older women experience more drug-related adverse events, to our knowledge, only one study has explored gender differences in the deprescribing process. This study showed that women were more aware of harmful medications and were more likely than men to initiate a deprescribing conversation and to seek out medication-induced harm.⁹⁰

Implications of deprescribing in clinical practice Deprescribing a medication is not always easy

Judicious deprescribing of a medication can be challenging and is not always successful. There are several barriers to stopping medications. Whether justified or not, prescribers might be more concerned about harm caused by stopping a medication than by the potential harm associated with continuing a medication of questionable benefit that is being tolerated.⁹¹ This concern might, in part, be due to the dearth of evidence to support deprescribing of a specific drug in older people. The attitude of older patients themselves towards deprescribing is crucial for success. A population-based survey in the USA reported that older adults are willing to having their medications deprescribed if their provider says this is possible. Further, two-thirds of patients want to take fewer medicines,⁹² indicating that there is support for deprescribing from older people. There are also differences between men and women when considering awareness of harmful medications

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For more on **deprescribing in the USA** see <https://deprescribingresearch.org/>

For more on **deprescribing in Australia** see <https://australiandeprescribingnetwork.com/au/>

Panel 2: Deprescribing tool

The deprescribing protocol is a five-step approach that was published by Scott and colleagues⁶⁵ (from Australia) in 2015. The CEASE algorithm describes the approach used in the following order: current medicines, elevated risk, assess, sort, and eliminate.⁶⁶ Scott has also created an algorithm for deciding the order and the mode in which a drug therapy could be discontinued.⁶⁵ This approach identifies each medication the individual is taking and the reasons for them, considers the overall risk of drug-induced harm, assesses each drug for its eligibility to be discontinued, prioritises the drugs for discontinuation, and implements and monitors the drug discontinuation regimen.⁶⁵

The Good Palliative–Geriatric Practice algorithm was developed in 2007 by Garfinkel and colleagues⁶⁷ in Israel, and is designed to address the problem of polypharmacy. This approach requires a discussion with the patient or their caregiver. Further, the approach uses a series of questions to guide the process of stopping a drug therapy, decreasing the dose, or shifting to an alternative drug therapy, as appropriate. This approach can lead to discontinuing multiple non-lifesaving drugs in older people and incorporates an individual's circumstances, their goals of care, and ongoing monitoring. In relation to deprescribing, Garfinkel places particular emphasis on the need to focus on patients described as being of VOCODFLEX status (ie, very old age, the extent of comorbidity, dementia, frailty and limited life expectancy).⁸⁸ This deprescribing process has been evaluated in geriatric nursing departments and nursing homes,⁶⁷ and among older people in the community.^{67,89} The tool was used to inform deprescribing and evaluated in disabled patients in a nursing home setting.⁶⁷ On average, approximately 3 drugs were discontinued per individual resident. The discontinuation of medications reduced mortality and improved quality of life. In the study of community-dwelling older adults, among those medications discontinued using the deprescribing algorithm, only 6 (2%) of the 256 discontinued medications in 64 patients were restarted due to the reoccurrence of the original indication, with 56 (88%) of the 64 patients reporting overall improved health.⁸⁹

and willingness to initiate deprescribing conversations.⁹⁰ Stopping medications requires time that might not be readily available to prescribers in the current health system. Clinic visits are generally short and, given that these visits often last only 15–20 min, it is easier for physicians to continue medicines that appear to be tolerated rather than stopping them.⁹³ When deciding whether to discontinue a medication, it is important to understand when and why it was started. Yet, this information might be difficult or sometimes impossible to obtain from existing medical records. These problems might be increased for older people, given that some drugs might have been started many years ago and medical records might not be readily available. Additionally, when older adults are admitted to hospital, chronic care facilities, and long-term care settings, medical records across the health-care system might not be coordinated. Thus, information about why new drugs were initiated might not be provided back to the primary care provider.⁹³ Moreover, primary care providers might be reluctant to modify drugs prescribed by a different specialist.

Despite the challenges, the benefits of deprescribing could be considerable, as shown with antipsychotic drug therapy. Antipsychotic therapy has long been associated with serious adverse events, including death.⁹⁴ Initiatives have reduced the use of antipsychotic therapy for dementia management in long-term care homes by leveraging non-pharmacological approaches⁹⁵ without increasing behavioural or psychotic symptoms. Among people with Alzheimer's dementia receiving risperidone, for every four patients whose risperidone was withdrawn, one relapsed with the symptoms of psychosis or agitation,^{93,96} showing that deprescribing is an iterative process and will not be successful for all. Recognising the challenges with deprescribing, the deprescribing algorithm created by Scott acknowledges that this process might not be successful and that there might be a need to restart treatment with the drug in question.⁶⁵

Practical approach to deprescribing that clinicians can apply to the patient in front of them

Because many older adults, particularly women, are in need of deprescribing, we propose that older adults experiencing polypharmacy (defined as the use of five or more concurrent drug therapies) should be initially screened for judicious deprescribing. In older patients with polypharmacy, it is important to identify potentially inappropriate medications with the use of established tools. Then, the deprescribing process can be initiated. Deprescribing protocols generally consider the key conditions that influence the need for deprescribing decisions for older people, specifically frailty, declining cognitive function, and limited remaining life.⁹⁷ Accordingly, we have created the DRUGS guide to optimising medication safety for older adults, which stands for DISCUSS goals of care and

	DRUGS guide to optimising medication safety for older adults	Sex and gender considerations
D	DISCUSS goals of care and what matters most to the patient <ul style="list-style-type: none"> • Include patients and caregivers in deprescribing discussions to ensure decisions focus on goals of care 	Women are more likely than men to be caregivers, and might not have a caregiver to advocate for them
R	REVIEW medications <ul style="list-style-type: none"> • Encourage patients to bring all prescribed and over-the-counter medications to their appointment • Review medications on an ongoing basis and when clinical conditions or goals of care change • Discontinue potentially unnecessary drugs • Consider drug side-effects as a potential cause for a new symptom • Consider non-pharmacological options • Change for safer alternatives • Lower the dose • To identify possible prescribing cascades, determine when the medication was started and why 	Women use more prescribed and over-the-counter medications than men
U	USE tools and frameworks <ul style="list-style-type: none"> • Identify drugs from the inappropriate prescribing tools, including Beers criteria or STOPP criteria • Use the STOPPFrail list when the individual is extremely frail and approaching the end of life • Consider whether the new or existing medical condition could be the result of a prescribing cascade and ask: <ul style="list-style-type: none"> • Is a new drug being prescribed to manage a side-effect from another prescribed drug? • Could the initial drug be replaced with a safer drug or could the dose be reduced? • Does the patient need the first drug or could this drug be stopped? • Pay attention to older people who are receiving so-called good drugs with narrow therapeutic windows that might no longer be needed or for whom dose reduction might be beneficial 	Women are more often prescribed psychoactive drugs, whereas men are more often prescribed secondary prevention drugs; women might require lower doses; men receive more aggressive medical therapy
G	GERIATRIC medicine approach <ul style="list-style-type: none"> • Geriatricians carefully consider how multiple medical problems, frailty, cognitive impairment, and limited life expectancy reduce medication benefit, increase adverse events, or interfere with medication adherence 	Women are more likely than men to have multiple medical problems, frailty, and adverse drug events; men are more likely than women to adhere to drug therapies; women might be less able than men to pay for medicines, decreasing adherence
S	STOP the medications <ul style="list-style-type: none"> • Consider the algorithm created by Scott⁶⁵ or the Good Palliative–Geriatric Practice algorithm to guide deprescribing 	Women are more likely to discuss deprescribing with providers than men

Figure 2: DRUGS guide to optimising medication safety for older adults

Five DRUGS steps created by eight geriatricians to guide the optimisation of medication safety are outlined: (1) DISCUSS goals of care and what matters most, (2) REVIEW medications, (3) USE tools and frameworks, (4) GERIATRIC medicine approach, and (5) STOP the medications. Each of the five steps are shown with examples of sex and gender considerations. STOPP=screening tool of older persons' prescriptions. STOPPFrail=screening tool of older persons' prescriptions in frail adults with limited life expectancy.

what matters most, REVIEW medications, USE tools and frameworks, GERIATRIC medicine approach, and STOP the medications where appropriate (figure 2). For each of the five steps, we provide sex and gender considerations. This approach was based on our collective expertise as eight geriatricians and researchers with a background in geriatric pharmacology from six countries (Belgium, Canada, Ireland, Israel, Italy, and the USA) working together on iKASCADE, an international initiative designed to improve prescribing for older women and men.⁸² This guide is based on the approach generally used by geriatricians, is consistent with the recommendations outlined in our previous publications on optimising prescribing for older adults,^{33,98,99} and aligned with the approach described by Scott.⁶⁵

Search strategy and selection criteria

To identify inappropriate prescribing tools and deprescribing processes, we used the International Reducing Inappropriate Medication Use and Polypharmacy position statement to identify key papers. This was supplemented by systematic reviews on these two topics. To identify inappropriate prescribing tools and deprescribing processes that are most known, we restricted the list to those that were the most highly cited as of January 19, 2021, using Google Scholar. Only those papers focusing on older adults were included. We searched Google Scholar in January, 2021, for papers published in English, using “sex” or “gender” and the name of the inappropriate prescribing tool or deprescribing process as search terms.

Gaps and needs

Our exploration of polypharmacy, tools, and frameworks to identify inappropriate prescribing and deprescribing processes for older women and men has identified certain gaps in knowledge-based practice. In reviewing the key descriptions of polypharmacy, tools and frameworks to reduce inappropriate prescribing, and deprescribing protocols, it is remarkable that none of these tools and frameworks mention clinically important differences between women and men (table). Although women make up the majority of older people and are more vulnerable than men to drug-related harm, existing research has almost completely neglected this consideration. The solutions offered in this Review will require a consideration of sex and gender, alongside age, in all drug research, from early clinical trials through to postmarketing surveillance.¹³ These considerations will inform the current understanding of polypharmacy, improve the development of future tools and frameworks to identify inappropriate prescribing, and guide geriatric medicine-informed deprescribing protocols.

Conclusion

Improving prescribing for older adults is an international priority for all health-care systems. The approach of geriatric medicine to polypharmacy is one that carefully considers the goals of care of an older person. Although polypharmacy is a major problem, there are tools and frameworks that identify inappropriate prescribing and deprescribing protocols that provide guidance to judiciously decrease doses and stop unnecessary medications. Our DRUGS guide to deprescribing, created by eight geriatricians with a background in geriatric pharmacology, provides five simple steps to stop inappropriate drug therapy. Further research needs to consider the potentially important influence of sex and gender on inappropriate prescribing and deprescribing to optimise medication safety.

Contributors

All authors contributed equally to conceptualising the Review, including the critical analysis of the existing literature, as well as the development of the methodologies described in the Review. PAR and JHG wrote the original draft; all authors reviewed and edited each subsequent draft. All authors approved the final version of the Review.

Declaration of interests

PAR, NMS, GO, SAS, and MP declare no competing interests. DO has a patent (11757950.8-1952) issued from the European Patent Office on Aug 30, 2011, called A Prescription Decision Support System (based on STOPP/START criteria). JHG reports personal fees from United Healthcare, outside of the submitted work. AC reports personal fees from Bristol Myers Squibb for participating in an advisory board on direct anticoagulants and personal fees from MSD for a lecture on aging, outside of the submitted work.

Acknowledgments

We acknowledge the iKASCADE scientists, postdoctoral fellows and trainees, for their insights that guided some of this work; namely, Stephen Byrne (PhD), Barbara Carrieri (PhD candidate), Kieran Dalton (MPharm PhD), Massimiliano Fedecostante (MD), Robin Mason (PhD), Lisa McCarthy (PharmD MSc), Francesco Pegreff (MD), and Rachel Savage (PhD). Additionally, we thank staff members Jennifer Akerman, Peter Anderson, Joyce Li, Andrea Lawson (PhD), Jaimie Roebuck, and Wei Wu for their insights and for their administrative and technical support to the preparation of the Review. The iKASCADE Project is funded by Gender-NET Plus (GNP-1782; Identifying Key Prescribing CASCADEs in the Elderly: A Transnational Initiative on Drug Safety), GENDER-NET Plus ERA-Net Cofund (promoting gender equality in H2020 and the ERA), in partnership with the Canadian Institutes of Health Research–Institutes of Gender and Health and Institute of Aging, the Irish Research Council, Ministero della Salute Italiano, project iKascade RRC-2019-2366768 (Italy), and the Ministry of Science and Technology (Israel). The funding sources had no role in the writing of the Review or in the decision to submit the Review for publication. PAR holds the RTOERO Chair in Geriatric Medicine at the University of Toronto (Toronto, ON, Canada). NMS is supported by the Vanier Canada Graduate Scholarship and the Eliot Phillipson Clinician-Scientist Training Program of the Department of Medicine, University of Toronto (Toronto, ON, Canada).

References

- 1 United Nations Department of Economic and Social Affairs. World population ageing 2019: highlights. 2019. <https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf> (accessed April 21, 2020).
- 2 United Nations Department of Economic and Social Affairs. World population ageing 2017: highlights. 2017. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Highlights.pdf (accessed Oct 5, 2020).
- 3 Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2009; **48**: 143–57.
- 4 WHO. The third WHO Global Patient Safety Challenge: Medication Without Harm. 2019. <https://www.who.int/patientsafety/medication-safety/en/> (accessed Sept 8, 2020).
- 5 Lande RG, Gragnani C. Nonpharmacologic approaches to the management of insomnia. *J Am Osteopath Assoc* 2010; **110**: 695–701.
- 6 Abbraha I, Cruz-Jentoft A, Soiza RL, O'Mahony D, Cherubini A. Evidence of and recommendations for non-pharmacological interventions for common geriatric conditions: the SENATOR-ONTOP systematic review protocol. *BMJ Open* 2015; **5**: e007488.
- 7 Pop P, Bronskill SE, Piggott KL, et al. Management of sleep disorders in community-dwelling older women and men at the time of diagnosis. *J Am Geriatr Soc* 2019; **67**: 2094–101.
- 8 Boyd CM, Darer J, Boulton C, Fried LP, Boulton L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005; **294**: 716–24.
- 9 Stall NM, Fischer HD, Fung K, et al. Sex-specific differences in end-of-life burdensome interventions and antibiotic therapy in nursing home residents with advanced dementia. *JAMA Netw Open* 2019; **2**: e199557.

- 10 Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med* 2006; **166**: 605–09.
- 11 Dalton K, O'Mahony D, Cullinan S, Byrne S. Factors affecting prescriber implementation of computer-generated medication recommendations in the SENATOR trial: a qualitative study. *Drugs Aging* 2020; **37**: 703–13.
- 12 Darmstadt GL, Heise L, Gupta GR, et al. Why now for a Series on gender equality, norms, and health? *Lancet* 2019; **393**: 2374–77.
- 13 Rochon PA, Mason R, Gurwitz JH. Increasing the visibility of older women in clinical research. *Lancet* 2020; **395**: 1530–32.
- 14 Institute of Medicine (US) Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. B, NIH Revitalization Act of 1993 103–43. In: Mastroianni AC, Faden R, Federman D, eds. Women and health research: ethical and legal issues of including women in clinical studies, volume 1. Washington DC: National Academies Press, 1994: 233–36.
- 15 National Institutes of Health. Revision: NIH policy and guidelines on the inclusion of individuals across the lifespan as participants in research involving human subjects. Notice number: NOT-OD-18–116. 2017 <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>. (accessed April 12, 2021).
- 16 Bernard MA, Clayton JA, Lauer MS. Inclusion across the lifespan: NIH policy for clinical research. *JAMA* 2018; **320**: 1535–36.
- 17 DeJong C, Covinsky K. Inclusion across the lifespan in cardiovascular trials—a long road ahead. *JAMA Intern Med* 2020; **180**: 1533.
- 18 Nanna MG, Chen ST, Nelson AJ, Navar AM, Peterson ED. Representation of older adults in cardiovascular disease trials since the inclusion across the lifespan policy. *JAMA Intern Med* 2020; **180**: 1531.
- 19 Regitz-Zagrosek V. Sex and gender differences in pharmacology. Heidelberg: Springer, 2012.
- 20 DeWilde S, Carey IM, Richards N, Whincup PH, Cook DG. Trends in secondary prevention of ischaemic heart disease in the UK 1994–2005: use of individual and combination treatment. *Heart* 2008; **94**: 83–88.
- 21 Franconi F, Campesi I. Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women. *Br J Pharmacol* 2014; **171**: 580–94.
- 22 Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin Interv Aging* 2014; **9**: 2079–86.
- 23 Bartz D, Chitnis T, Kaiser UB, et al. Clinical advances in sex- and gender-informed medicine to improve the health of all: a review. *JAMA Intern Med* 2020; **180**: 574–83.
- 24 United States General Accounting Office. Drug safety: most drugs withdrawn in recent years had greater health risks for women. 2001. <https://www.gao.gov/assets/100/90642.pdf> (accessed Sept 8, 2020).
- 25 US Food and Drug Administration. Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). 2013. <https://www.fda.gov/media/84992/download> (accessed Sept 8, 2020).
- 26 Greenblatt DJ, Harmatz JS, Singh NN, et al. Gender differences in pharmacokinetics and pharmacodynamics of zolpidem following sublingual administration. *J Clin Pharmacol* 2014; **54**: 282–90.
- 27 Rochon PA, Gruneir A, Gill SS, et al. Older men with dementia are at greater risk than women of serious events after initiating antipsychotic therapy. *J Am Geriatr Soc* 2013; **61**: 55–61.
- 28 Steinman MA, Sands LP, Covinsky KE. Self-restriction of medications due to cost in seniors without prescription coverage. *J Gen Intern Med* 2001; **16**: 793–99.
- 29 Cheff R, Hill M, Iveniuk J. Who Benefits? Gaps in medication coverage for Ontario workers. Wellesley Institute. 2019. https://www.wellesleyinstitute.com/wp-content/uploads/2019/12/Coverage-Gaps-for-Ontario-Workers-EMBARGO_27.11.19.pdf (accessed Sept 29, 2020).
- 30 Reinhard SC, Levine C, Samis S. AARP Public Policy Institute. Home alone: family caregivers providing complex chronic care. 2012. https://www.aarp.org/content/dam/aarp/research/public_policy_institute/health/home-alone-family-caregivers-providing-complex-chronic-care-rev-AARP-ppi-health.pdf (accessed April 12, 2021).
- 31 Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *J Womens Health (Larchmt)* 2014; **23**: 112–19.
- 32 The Medicines Utilisation Monitoring Centre. National report on medicines use in Italy. Year 2019. Rome: Italian Medicines Agency. 2020. <https://www.aifa.gov.it/documents/20142/1205984/rapporto-osmed-2019.pdf/f41e53a4-710a-7f75-4257-404647d0fe1e> (accessed Oct 9, 2020).
- 33 Petrovic M, Gnjidic D, Tommetein E, Boussery K. Pharmacotherapy. In: Roller-Wirnsberger R, Singler K, Polidori MC, eds. Learning geriatric medicine: a study guide for medical students. Cham: Springer, 2018: 219–235.
- 34 Rochon PA, Stall NM, Holmes HM. Drug therapy and frailty: chicken or the egg? *J Am Geriatr Soc* 2019; **67**: 2441–43.
- 35 Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation: making it safe and sound. 2013. https://www.kingsfund.org.uk/sites/files/kf/field/publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf (accessed Sept 8, 2020).
- 36 WHO. Medication safety in key action areas. 2019. <https://www.who.int/patientsafety/medication-safety/technical-reports/en/> (accessed Sept 8, 2020).
- 37 WHO. Medication safety in polypharmacy. Technical report. 2019. <https://apps.who.int/iris/bitstream/handle/10665/325454/WHO-UHC-SDS-2019.11-eng.pdf?ua=1> (accessed Sept 8, 2020).
- 38 Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; **17**: 230.
- 39 Faustino CG, Martins MA, Jacob Filho W. Potentially inappropriate medication prescribed to elderly outpatients at a general medicine unit. *Einstein (Sao Paulo)* 2011; **9**: 18–23.
- 40 Al-Azayzih A, Alamoori R, Altawalbeh SM. Potentially inappropriate medications prescribing according to Beers criteria among elderly outpatients in Jordan: a cross sectional study. *Pharm Pract (Granada)* 2019; **17**: 1439.
- 41 Morin L, Fastbom J, Laroche ML, Johnell K. Potentially inappropriate drug use in older people: a nationwide comparison of different explicit criteria for population-based estimates. *Br J Clin Pharmacol* 2015; **80**: 315–24.
- 42 Onder G, Liperoti R, Fialova D, et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. *J Gerontol A Biol Sci Med Sci* 2012; **67**: 698–704.
- 43 Statistics Canada. 2016 Census of Population, Statistics Canada Catalogue no. 98-400-X2016018. 2019. <https://www12.statcan.gc.ca/census-recensement/2016/geo/geosearch-georecherche/ips/index.cfm?q=98-400-X2016018&l=en&g=2016A000011124> (accessed Sept 12, 2020).
- 44 Canadian Institute for Health Information. Drug use among seniors in Canada. 2016. <https://www.cihi.ca/sites/default/files/document/drug-use-among-seniors-2016-en-web.pdf> (accessed Sept 8, 2020).
- 45 Mangin D, Bahat G, Golomb BA, et al. International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): position statement and 10 recommendations for action. *Drugs Aging* 2018; **35**: 575–87.
- 46 Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. Tools for assessment of the appropriateness of prescribing and association with patient-related outcomes: a systematic review. *Drugs Aging* 2018; **35**: 43–60.
- 47 Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. *Eur J Clin Pharmacol* 2014; **70**: 1–11.
- 48 Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. *Arch Intern Med* 1991; **151**: 1825–32.
- 49 Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 updated AGS Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019; **67**: 674–94.
- 50 Zhan C, Sangl J, Bierman AS, et al. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. *JAMA* 2001; **286**: 2823–29.
- 51 Bushardt RL, Massey EB, Simpson TW, Arial J, Simpson KN. Polypharmacy: misleading, but manageable. *Clin Interv Aging* 2008; **3**: 383–89.

- 52 Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008; **46**: 72–83.
- 53 O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015; **44**: 213–18.
- 54 Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992; **45**: 1045–51.
- 55 Somers A, Mallet L, van der Cammen T, Robays H, Petrovic M. Applicability of an adapted medication appropriateness index for detection of drug-related problems in geriatric inpatients. *Am J Geriatr Pharmacother* 2012; **10**: 101–09.
- 56 Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int* 2010; **107**: 543–51.
- 57 McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ* 1997; **156**: 385–91.
- 58 Laroche ML, Charnes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. *Eur J Clin Pharmacol* 2007; **63**: 725–31.
- 59 Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. *Arch Intern Med* 2007; **167**: 781–87.
- 60 Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The Anticholinergic Risk Scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008; **168**: 508–13.
- 61 Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol* 2006; **46**: 1481–86.
- 62 US Department of Health and Human Services, Office of Disease Prevention and Health Promotion. National action plan for adverse drug event prevention. 2014. <https://health.gov/sites/default/files/2019-09/ADE-Action-Plan-508c.pdf> (accessed Oct 5, 2020).
- 63 Rochon PA, Gurwitz JH. Drug therapy. *Lancet* 1995; **346**: 32–36.
- 64 Rochon PA, Gurwitz JH. The prescribing cascade revisited. *Lancet* 2017; **389**: 1778–80.
- 65 Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015; **175**: 827–34.
- 66 Scott IA, Le Couteur DG. Physicians need to take the lead in deprescribing. *Intern Med J* 2015; **45**: 352–56.
- 67 Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. *Isr Med Assoc J* 2007; **9**: 430–34.
- 68 Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med* 2007; **147**: 755–65.
- 69 Lavan AH, Gallagher P, Parsons C, O'Mahony D. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. *Age Ageing* 2017; **46**: 600–07.
- 70 Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. *Age Ageing* 2021; **50**: 465–71.
- 71 Morgan SG, Weymann D, Pratt B, et al. Sex differences in the risk of receiving potentially inappropriate prescriptions among older adults. *Age Ageing* 2016; **45**: 535–42.
- 72 Schnegg D, Senn N, Bugnon O, Schwarz J, Mueller Y. Drug prescription in older Swiss men and women followed in family medicine. *Drugs Real World Outcomes* 2020; **7**: 87–95.
- 73 Bierman AS, Pugh MJ, Dhalla I, et al. Sex differences in inappropriate prescribing among elderly veterans. *Am J Geriatr Pharmacother* 2007; **5**: 147–61.
- 74 Nuñez-Montenegro A, Montiel-Luque A, Martin-Aurioles E, Garcia-Dillana F, Krag-Jiménez M, González-Correa JA. Evaluation of inappropriate prescribing in patients older than 65 years in primary health care. *J Clin Med* 2019; **8**: 305.
- 75 Wickop B, Härterich S, Sommer C, Daubmann A, Baehr M, Langebrake C. Potentially inappropriate medication use in multimorbid elderly inpatients: differences between the FORTA, PRISCUS and STOPP ratings. *Drugs Real World Outcomes* 2016; **3**: 317–25.
- 76 Toepfer S, Bolbrinker J, König M, Steinhagen-Thiessen E, Kreutz R, Demuth I. Potentially inappropriate medication in older participants of the Berlin Aging Study II (BASE-II)—sex differences and associations with morbidity and medication use. *PLoS One* 2019; **14**: e0226511.
- 77 Savage RD, Visentin JD, Bronskill SE, et al. Evaluation of a common prescribing cascade of calcium channel blockers and diuretics in older adults with hypertension. *JAMA Intern Med* 2020; **180**: 643–51.
- 78 Scott IA, Gray LC, Martin JH, Mitchell CA. Minimizing inappropriate medications in older populations: a 10-step conceptual framework. *Am J Med* 2012; **125**: 529–37.
- 79 Todd A, Jansen J, Colvin J, McLachlan AJ. The deprescribing rainbow: a conceptual framework highlighting the importance of patient context when stopping medication in older people. *BMC Geriatr* 2018; **18**: 295.
- 80 Piggott KL, Mehta N, Wong CL, Rochon PA. Using a clinical process map to identify prescribing cascades in your patient. *BMJ* 2020; **368**: m261.
- 81 Sternberg SA, Guy-Alfandary S, Rochon PA. Prescribing cascades in older adults. *CMAJ* 2021; **193**: E215.
- 82 Sternberg SA, Petrovic M, Onder G, et al. Identifying key prescribing cascades in older people (iKascade): a transnational initiative on drug safety through a sex and gender lens—rationale and design. *Eur Geriatr Med* 2021; published online April 9. <https://doi.org/10.1007/s41999-021-00480-w>.
- 83 Woodward MC. Deprescribing: achieving better health outcomes for older people through reducing medications. *J Pharm Pract Res* 2003; **33**: 323–28.
- 84 Tinetti ME, Baker DI, King M, et al. Effect of dissemination of evidence in reducing injuries from falls. *N Engl J Med* 2008; **359**: 252–61.
- 85 Palmieri DT. Clearing up the confusion: adverse effects of medications in the elderly. *J Gerontol Nurs* 1991; **17**: 32–35.
- 86 Gnjjidic D, Le Couteur DG, Kouladjian L, Hilmer SN. Deprescribing trials: methods to reduce polypharmacy and the impact on prescribing and clinical outcomes. *Clin Geriatr Med* 2012; **28**: 237–53.
- 87 Reeve E. Deprescribing tools: a review of the types of tools available to aid deprescribing in clinical practice. *J Pharm Pract Res* 2020; **50**: 98–107.
- 88 Garfinkel D, Ilhan B, Bahat G. Routine deprescribing of chronic medications to combat polypharmacy. *Ther Adv Drug Saf* 2015; **6**: 212–33.
- 89 Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med* 2010; **170**: 1648–54.
- 90 Turner JP, Tannenbaum C. Older adults' awareness of deprescribing: a population-based survey. *J Am Geriatr Soc* 2017; **65**: 2691–96.
- 91 Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ Open* 2014; **4**: e006544.
- 92 Reeve E, Wolff JL, Skehan M, Bayliss EA, Hilmer SN, Boyd CM. Assessment of attitudes toward deprescribing in older Medicare beneficiaries in the United States. *JAMA Intern Med* 2018; **178**: 1673–80.
- 93 Gurwitz JH, Kapoor A, Rochon PA. Polypharmacy, the good prescribing continuum, and the ethics of deprescribing. *Public Policy Aging Rep* 2018; **28**: 108–12.
- 94 Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med* 2008; **168**: 1090–96.
- 95 Canadian Foundation for Healthcare Improvement. Appropriate use of antipsychotics. 2020. <https://www.cfhi-fccass.ca/what-we-do/spread-and-scale-proven-innovations/appropriate-use-of-antipsychotics> (accessed Oct 14, 2020).

-
- 96 Devanand DP, Mintzer J, Schultz SK, et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med* 2012; **367**: 1497–507.
- 97 Frank C, Weir E. Deprescribing for older patients. *CMAJ* 2014; **186**: 1369–76.
- 98 Rochon P. Drug prescribing for older adults. 2020. <https://www.uptodate.com/contents/drug-prescribing-for-older-adults/print> (accessed Sept 14, 2020).
- 99 Rochon PA, Gill SS, Gurwitz JH. Chapter 24: General principles of pharmacology and appropriate prescribing. In: Edmonson KG, Davis KJ, eds. *Hazzard's Geriatric Medicine and Gerontology*, 7th edn. New York, NY: McGraw-Hill Education/Medical, 2017.

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