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PALLIATIVE CARE (D WU, SECTION EDITOR)

Deprescribing: Right-Sizing Medication Regimens to Optimize Outcomes in Palliative Care

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Abstract

Purpose of Review The purpose of this review is to describe the current state of polypharmacy in older adults and those with an advanced illness, evidence that supports deprescribing, and best practices to implement deprescribing in palliative care.

Recent Findings Practitioners and patients indicate they are interested in reducing the number of medications prescribed, but there are barriers to this practice. Over 90% of Medicare beneficiaries stated they would be willing to stop taking one or more of their medications if endorsed by their doctor. Several tools have become available in recent years to assist practitioners make more consistent decisions about deprescribing.

Summary Deprescribing is a patient-centric, important part of the prescribing process, and it is imperative that providers make this clear in conversations with patients and families. Tools and processes are available to assist providers in having these conversations and making these important decisions in caring for older adults and palliative care patients.

Keywords Deprescribing · Medications · Outcomes · Elderly · Pharmacotherapy · Rationalizing medications

Introduction

Advances in medical science have resulted in an aging population living with multiple comorbid conditions that often necessitate complex medication regimens. Polypharmacy (the concurrent use of 5 or more medications) is steadily increasing. Kantor and colleagues reported that the prevalence of polypharmacy in the USA was approximately 8.2% in 1999–2000 and increased to 15% in 2011–2012 [1]. A systematic review evaluating the prevalence of polypharmacy in long-term care facilities showed 91% of residents taking more than 5 medications, 74% taking more than 9 medications, and 65% taking more than 10 medications [2]. Polypharmacy in older adults is associated with an increased risk of medication-associated adverse events, including frailty, delirium, cognitive decline, disability, hospitalization, and mortality [3, 4]. When the patients in question have a serious or life-limiting illness (e.g., patients receiving palliative or hospice care), the implications are even greater, as more medications are often added to treat pain and non-pain symptoms. This expanded medication load is frequently found to carry a high anticholinergic and sedation burden, which is associated with poor physical and cognitive functioning [5]. The majority of patients with a reduced life expectancy are elderly and are likely to have a higher risk of medication misadventure due to their frailty, beyond age-associated pharmacodynamic and pharmacokinetic changes [6].

If we consider polypharmacy to be a medical condition, what is the treatment? Terms used to describe withdrawing medications where burden is greater than benefit have been referred to as medication "de-intensification," the "geriatrician's salute," and increasingly, "deprescribing" [7]. The term deprescribing was first introduced in the literature in 2003 and is currently defined as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" [8, 9•]. The practice of deprescribing falls within the

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spectrum of the prescribing process, which includes the following: selecting the best medication for a given patient after considering patient- and medication-specific variables, medication dosage titration, monitoring for therapeutic success and toxicity, and deprescribing as appropriate. Deprescribing is a positive, patient-centric intervention that aims to maximize the benefits of medication therapy while minimizing burdens (which may be clinical, financial, tablet burden, etc.). Deprescribing also considers the cumulative risk from all medications in the patient's regimen [4].

Deprescribing: Views and Attitudes, Barriers, and Enablers

What do patients think of deprescribing? A survey of community-dwelling older adults living in Canada responded to a survey offered at their community pharmacy or a community center on this issue [10]. While over 80% strongly agreed or agreed with the statement "I am comfortable with the number of medications that I am taking," about half thought they were taking a large number of medications, and half also stated they would like to reduce the number of medications they were taking. Almost 75% stated they would be willing to stop one or more of their regular medications if their doctor said it was possible, although 80% also said they would take additional medications if necessary. Similarly, residents of aged care facilities in Australia were queried, and about 40% said they wished to stop taking one or more of their medications, which increased to almost 80% of respondents if their doctor said this was appropriate [11]. Older adults admitted to a teaching hospital in Sydney, Australia, were also surveyed, and almost 90% said they would be willing to stop one or more of their medications if their doctor said this was possible [12]. Ninety-five percent were willing to discontinue their statin, and a similar number were concerned about potential side effects from their statin.

Reeve and colleagues surveyed older Medicare beneficiaries in the USA about deprescribing [13••]. Respondents (approximately 2000 individuals) were drawn from round 6 of the National Health and Aging Trends Study (NHATS) for this survey. The main outcomes were responses to two specific questions: "If my doctor said it was possible, I would be willing to stop one or more of my regular medicines" (to which 92% responded strongly agreed or agreed) and "I would like to reduce the number of medicines I am taking" (to which two-thirds strongly agreed/agreed). The authors concluded that this data may reassure clinicians that older patients are open to discussions about deprescribing.

So if the majority of patients are open to deprescribing as directed by their physician, are physicians open to deprescribing? One hundred sixty physicians in Parma were interviewed about deprescribing [14]. Approximately 75% of respondents reported general confidence in their ability to deprescribe, including preventative medications. Fewer were comfortable stopping guideline-recommended medications (53%). Forty percent of physicians were reluctant to discontinue a medication prescribed by another physician, and 45% felt uncomfortable stopping a medication in cases were the patient or caregivers felt the medication was important to continue. General practitioners in Australia reported that they were comfortable with deprescribing and felt they had the skills to communicate this information to their patients [15]. When provided evidence-based deprescribing guidelines, one group of physicians [16] and a group of pharmacists and physicians [17] demonstrated competency (and agreement in the physician/pharmacist group) in deprescribing.

Other surveyed physicians found that in primary care, deprescribing can often be described as "swimming against the tide" caused by several barriers [18], including (1) the medical culture of prescribing (deprescribing is not a skill taught to physicians, and it is often easy to keep adding more and more medications); (2) patient expectations (a medication fixes everything, and medications prevent death); and (3) organizational constraints (lack of time, fragmentation of care, lack of access to expert guidance, etc.). Sixteen general practitioners (GPs) in Denmark were surveyed regarding barriers toward medication reviews in polymedicated multimorbid patients, and three themes were identified in data analysis [19]. These included lack of cross-sectoral professional dialog and collaboration with clinical pharmacologists; patients not embracing the GP's recommendations to deprescribe; and the culture encouraging the continued use of medications and discouraging deprescribing. Anderson et al. evaluated 21 studies of prescriber-reported barriers and enablers to deprescribing and identified four main themes that included awareness (prescribers insight into appropriate prescribing/deprescribing), inertia (deprescribing does not occur despite awareness), self-efficacy (prescribers possessing knowledge, skills, and attitudes that facilitate deprescribing), and feasibility (practical barriers such as time constraints, patient and medical cultural beliefs/practices, and regulatory issues) [20]. Table 1 provides a summary of the most common barriers to deprescribing [18–26].

Evidence Supporting Deprescribing

There are two types of studies that evaluate outcomes associated with deprescribing [23]. The first is more global in approach and evaluates a particular intervention (such as chart review or educational initiative), reporting the number of potentially inappropriate medications identified and/or health outcomes associated with deprescribing. The second type of study is more targeted, such as deprescribing anticholinergic agents, benzodiazepines, and proton pump inhibitors. These results are particularly helpful in developing guidance for practitioners on when to discontinue specific medications.

Table 1 Barriers to deprescribing [18–26]

Providers
General/primary care practitioners (PCPs) vs. specialist providers
PCPs feel isolated from specialist providers
PCPs feel specialists do not see the total picture of the patient; specialists adhere primarily to their guidelines
PCPs are reluctant to discontinue a medication started by a specialist
Difficult to communicate with specialists
PCPs reluctant to risk conflict between prescribers or prescriber/pharmacist
Knowledge, skills, and attitudes of PCPs
Prescribers are awareness of their insight about deprescribing (especially lack of skills), confidence in deprescribing
PCPs feel need for more education about deprescribing (e.g., identifying medications eligible for discontinuation, clinical implications of deprescribing, application of population-based deprescribing guidance to individual patients)
Need for more clinical decision-making support from pharmacology experts
Patients
Hope held that medication will be beneficial/hope for improvement in condition
Taking medication makes patient feel they are being proactive
Insufficient time to fully discuss deprescribing with prescriber
Unclear how to stop taking medication (despite being educated by prescriber or pharmacist)
Difficulty comprehending instructions or communicating with providers
Pressured to continue medication by family members
Prior history of withdrawal syndrome from discontinuing other medications
Fear of stopping medications (negative consequences, worsening disease state, fear of withdrawal)
Lack of decision-making capacity
System level
Lack of reimbursement for prescriber's time
Fragmented transitions in care, including various medical records systems
Lack of computer prompts and alerts, deprescribing guidelines, access to expert advice
Clinical inertia
Perception that stopping a medication is of lower value than continuing medication (fear of unknown consequences of change)
Lack of time on patient visits
Pressure from staff to continue potentially inappropriate medications
Limited availability of non-pharmacologic options

Both types of studies are important to advance the practice of deprescribing.

Reeve and colleagues reported on several intervention-based studies in a narrative review that used a variety of approaches to deprescribing [23]. Not all studies reported clinical outcomes, and those that did showed conflicting results. Others showed a positive effect at reducing polypharmacy but did not necessarily demonstrate improved mortality or morbidity [23]. Page et al. published a systematic review of 132 papers in 2016, specifically evaluating the feasibility and impact of deprescribing in older adults on mortality and health [27•]. Deprescribing did not reduce mortality in randomized controlled trials; however, nonrandomized data did show a trend toward reduced mortality. Further, patient-specific deprescribing interventions (such as specific medications targeted for deprescribing, or medication regimen reviews resulting in recommendations to a prescriber for an individual patient) also showed mortality was significantly reduced. The authors concluded that deprescribing was feasible and safe.

A more recent systematic review evaluated the outcome of deprescribing medications for chronic diseases in primary care settings [28]. Fifty-eight studies were included in the review; 20 of the 58 compared some method of deprescribing with a control intervention or usual care. The remainder evaluated withdrawal of a specific medication or class of medications (e.g., such as those for hypertension, gastroesophageal reflux disease, heart failure, depression). Results showed that deprescribing could be successful and effective in select classes of drugs, using clinical pharmacists to educate patients and providers. Their conclusions were that deprescribing likely requires intensive ongoing interventions and may not result in expected improved outcomes. Overall, evidence on deprescribing is limited but suggests it is a feasible and safe practice and shows some favorable outcomes.

Polypharmacy at the End of Life

Do patients approaching the end of life take approximately the same number of medications as patients in a similar age bracket, more, or less? As patients approach the end of life, one might expect the addition of medications used to treat pain and other symptoms. However, it would also seem reasonable that practitioners should discontinue medications that are medically futile (e.g., medications that no longer slow disease progression) or preventative in nature. Patients with life-limiting illnesses are likely frailer than the general population, and thus at increased risk of medication-induced toxicities due to declining organ status and age-related changes in medication pharmacodynamics and pharmacokinetics.

Considering the benefits and burdens or potential futility of many medications in the face of advanced or terminal illness, one might presume that the medication regimen for patients in this situation would be of declining number. This does not seem to be the case, however. Morin et al. reconstructed the medication regimens for the previous 12 months of over 500,000 older adults who died in Sweden between 2007 and 2013 [29]. Their results showed that during the year before death, the percentage of patients taking 10 or more different medications increased from 30.3 to 47.2%. Their conclusions were that medications were not only added for pain and symptom management but that long-term preventative medications of questionable value were also continued.

A retrospective cohort study of over 500 older nursing home residents in Sydney, Australia, evaluated changes in the prescribing of symptomatic and preventative medications in the last year of life [30], finding that overall medication use changed little, although symptom management medications increased slightly and disease-prevention medication use decreased slightly. At the time of death, about one-third of the cohort had actively prescribed antithrombotic agents, antihypertensive medications, and osteoporosis medications. The authors concluded that high-quality evidence to guide deprescribing at the end of life is lacking.

Even at the very end of life, we see questionable prescribing. Prescribing practices were assessed in 179 patients in the last week of life in the hospital, hospice, or home setting in the Netherlands [31]. Results showed the mean number of medications used per patient was nine on day 7 before death and six on the day of death. Interestingly, almost 30% of patients were receiving a preventative medication on the day of death.

Why does prescribing continue in this fashion as patients approach death? Interestingly, 321 physicians responded to a survey about prescribing practices at the end of life, and almost three-quarters of respondents agreed that patients in the last phase of life receive too many medications [32]. Given a hypothetical case of a patient with end-stage chronic obstructive pulmonary disease approaching death, there was tremendous interphysician variability regarding deprescribing preventative medications. Clearly, better guidance is needed.

Principles and Data Informing Deprescribing at the End of Life

What data informs deprescribing at the end of life? Holmes suggests, in a classic paper, four components to guide deprescribing late in life [33••]: remaining life expectancy, time until benefit, goals of care, and treatment targets. Obviously, patients with a short life expectancy have less time to benefit from a medication. She elaborates on this concept by introducing the "time until benefit" factor, which is the amount of time that is required on average to see the clinical benefit of a medication. If the patient's life expectancy is less than the time until benefit, it would be unwise to begin the medication (see Fig. 1) [34]. Goals of care are a shared decision between the patient and provider, likely superseding standards of care, practice guidelines, and other clinical pathways per Holmes. As a patient approaches death, palliative care often takes a more predominant role vs. curative care. A decision to embrace more of a palliative approach has a direct

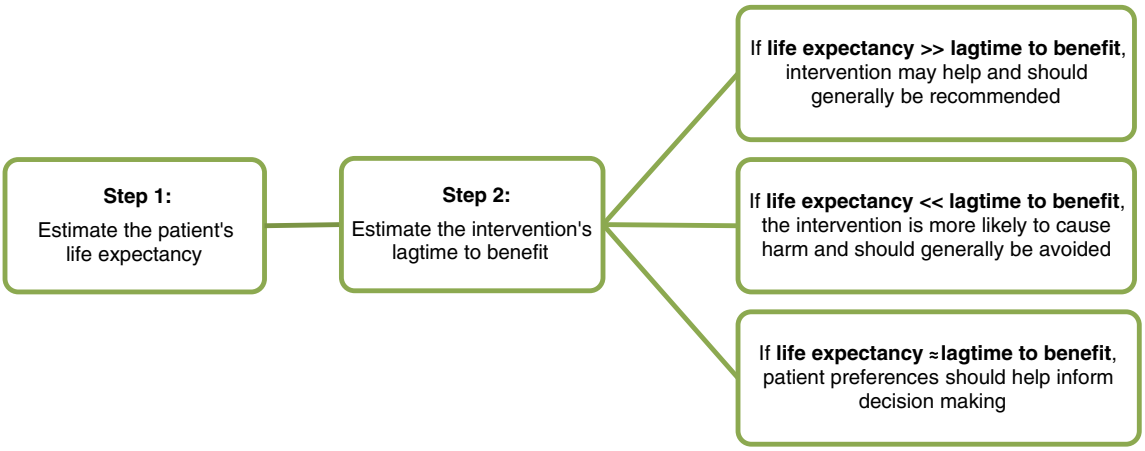

Fig. 1 Life expectancy and time to benefit

impact on the treatment targets, such as comfort care in lieu of life prolongation or preventative measures.

Other data that inform the decision to start, or stop a medication, are the number needed to treat (NNT), number needed to harm (NNH), and persistence of benefit. The NNT translates the absolute risk reduction of an intervention into a concept that is easier to comprehend. It is defined by how many people must be treated with a therapeutic intervention (e.g., a medication) for one person to achieve the desired outcome (over some defined period of time). For example, we may find that if we treat 1000 patients for 10 years with an antihypertensive agent, we can prevent 3 strokes. But if we are using this antihypertensive in a population with only months to live, we would have to treat many fold greater patients to prevent 3 strokes. In other words, the NNT would be enormous because there is insufficient time to accrue the medication benefit. On the flip side, the NNH defines how many people would need to be treated with a therapeutic intervention for one to experience a pre-determined adverse outcome, over some defined period of time. Given the number of comorbidities, increasing frailty, and diminishing functional status, a patient with a life-limiting illness may experience a much lower NNH than the general population. See Sidebar for additional information about NNT and NNH.

Persistence of benefit is important information for practitioners to share with patients when discussing deprescribing. This refers to continued therapeutic benefit despite stopping a medication. For example, bisphosphonate therapy for osteoporosis treatment has been shown to provide continued benefit in many patients even subsequent to stopping the medications after several years of treatment, particularly with alendronate and zoledronate [35]. The Diabetes Control and Complications Trial (DCCT) evaluated the impact of intensive treatment vs. usual treatment of patients with type 1 diabetes. The study ended in 1993 (1 year early) after demonstrating that patients with blood glucose values closer to euglycemia clearly showed a reduction of risk of diabetes-related complications. The Epidemiology of Diabetes Interventions and Complications (EDIC) study continued to follow these patients for 20-plus years. Their results showed that those patients who received intensive therapy years earlier were still reaping benefits (despite having similar blood glucose control at the time of assessment): the risk of cardiovascular disease and cardiovascular-related deaths was reduced by 57%, renal disease and failure by 50%, neuropathy by 30%, and need for eye surgery by 48% [36]. When discussing the possibility of "loosening the reins" a bit in a seriously ill patient with diabetes (e.g., discontinue rigorous blood glucose monitoring, liberalize the diet), we recommend emphasizing the hard work the patient spent in earlier years assuring the best glucose control possible, which will continue to pay off despite liberalizing blood glucose control at this point. One last unexpected example is the persistent benefit associated with discontinuing prostaglandin therapy for glaucoma [37•]. Researchers in Canada evaluated 214 patients with primary open-angle glaucoma who received a prostaglandin analog for at least 6 months. Half the group was randomized to discontinue the prostaglandin analog, and intraocular pressure was compared with the control group at 1, 3, and 6 weeks later. In the group who discontinued therapy, their intraocular pressure increased somewhat but was significantly lower than their baseline pressure. This effect was seen in some patients for up to a year. This data may reassure patients with a prognosis of a few months that a prostaglandin analog may be safely discontinued without causing harm.

Very little research on outcomes of deprescribing at the end of life exists in the literature. One study by Garfinkel and Mangin used the Good Palliative-Geriatric practice algorithm to evaluate the medication management of 70 community-dwelling older patients [38]. For 64 of the 70 patients, at least one medication was discontinued after applying the algorithm, with a total of 311 medications discontinued for the cohort. The medications recommended for discontinuation were considered not essential for life relative to the time to benefit for the medication over a mean follow-up of 19 months. Patients with a life expectancy of less than 3 months were excluded from the study. Only 2% of discontinued medications required restarting due to recurrence of the original indication. The authors concluded that it is feasible to successfully deprescribe in multimorbid community-dwelling older adults.

Tools to Aid Deprescribing at the End of Life

Thompson and colleagues provide a summary of available tools that can assist clinicians in identifying and deprescribing potentially inappropriate medications in frail older people and those with limited life expectancy [39••]. They categorized the identified tools into three main categories:

1. Tools that describe a model or framework for approaching deprescribing. One example is the Holmes model described above [33••].
2. Tools used to evaluate the entire medication list. Examples include the Geriatric-Palliative algorithm described above [38] and the Screening Tool of Older Persons Prescriptions in Frail adults with limited expectancy (STOPPFrail) [40••].
3. Medication-specific guidelines such as guidance for deprescribing in specific medical conditions and targeting specific medications/class including antihyperglycemics,

proton pump inhibitors, antipsychotics, benzodiazepine receptor agonists, cholinesterase inhibitors, and memantine (www.deprescribing.org).

One important point to make about available deprescribing tools is that they aim to identify potentially inappropriate medications (PIMs) in older adults primarily, but may not be 100% generalizable to the palliative care population (such as those facing death within the year). If a medication is deemed inappropriate by one of the tools above, there is a good chance it would also be a PIM in a terminally ill patient. However, the reverse may not be true. For example, Todd and Holmes point out the application of these tools when considering statin therapy [41•]. When used for the primary or secondary prevention of cardiovascular disease, the Beer's criteria (the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults [42]) or the STOPP/START criteria (a set of inappropriate combinations of medicines and disease [STOPP] and a set of recommended treatments for given conditions [START] [43]) would consider statin therapy to be appropriate. However, evidence presented by Kutner in patients with a prognosis of 1–12 months suggests no difference in mortality between those who continued vs. discontinued the statin at 60 days [44]. Further, those who discontinued statin therapy showed better quality of life. Based on this data, statins may be appropriately discontinued for patients late in life.

The STOPPFrail tool seems particularly promising for deprescribing in frail older adults with limited life expectancy [40••]. This instrument was validated using a Delphi consensus survey of experts. The inter-rater reliability was 75% among 12 physicians (6 geriatricians, 3 palliative care, and 3 general practitioners) who reviewed 18 cases using the STOPPFrail criteria [45]. The STOPPFrail was shown to be superior in identifying potentially inappropriate medications in multimorbid older people with polypharmacy than geriatrician-led deprescribing [46]. The STOPPFrail instrument was used to identify PIMs in 410 hospitalized patients deemed to be in their last year of life [47]. Results showed over 80% of patients were prescribed at least one PIM and about a third were receiving 3 or more. Almost 60% of PIMs were accounted for by lipid-lowering medications, proton pump inhibitors, anti-psychotics, and calcium supplements. This is an easy-to-use tool that can quickly identify PIMs in frail older adults with a life-limiting illness.

One last set of "rules of thumb" for deprescribing comes from Todd and Holmes [41•]. These five recommendations for rationalizing medication use may be incorporated into the care of patients late in life and used by all professionals on the team:

1. Shared decision-making is also about prescribing medications – prescribers and other practitioners have a responsibility to discuss the pros and cons of medication therapy with patients, their families, and caregivers. To effectively have these conversations, providers must be familiar with the literature on deprescribing and be able to explain the consequences in layman's terms. Examples as discussed earlier include the continued use of statins and the relevance of continued tight blood glucose control.
2. Not prescribing a medication should be presented as a reasonable alternative for patients late in life, when appropriate – this option may be particularly important in cases where the data about continuing or stopping a medication is not as clear-cut. The patient's goals of care and personal preferences may clarify the situation.
3. Deprescribing is part of prescribing – as discussed earlier, when a provider starts a medication, it does not come with an iron-clad guarantee that it will be appropriate for the rest of the patient's life. We must always assess the benefits and burdens of any therapeutic intervention, both those newly introduced and continuing interventions. Inappropriate prescribing should not just continue due to clinical inertia.
4. Prescribers have to embrace uncertainty – we all try to provide the best possible care for our patients and often invoke the expression "evidence based medicine." Evidence-based medicine (EBM) "is the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients. EBM integrates clinical experience and patient values with the best available research information" [48]. Many times, when evaluating the medication regimen of a patient late in life, we do not have definitive research information, and we must rely on clinical experience and patient preferences to help guide decision-making in the midst of uncertainty.
5. Difficult discussions now will simplify difficult decisions in the future – this speaks to the old axiom "begin with the end in mind." The provider should discuss expected benefits of a medication and how we will know when these have diminished or ceased. Discussing potential toxicities is also important, along with when it would be appropriate to discontinue the medication. When stopping a potentially inappropriate medication, remember to taper corticosteroids of 2 weeks therapy or longer, medications affecting the central nervous system (benzodiazepines, antidepressants, antipsychotics, etc.) and most cardiovascular medications (e.g., alpha-blockers, beta-blockers, nitrates).

As discussed by Thompson et al. [39••], there are three categories of deprescribing tools. The first is a model or framework, a way of thinking. The second model evaluates the patient's entire medication list and takes into consideration medication- and patient-specific variables to make informed

decisions about the medication regimen. The last model includes medication-specific guidance on deprescribing, targeting specific medications or classes of medications (e.g., benzodiazepines, proton pump inhibitors). Skilled practitioners seem to draw from all three models when caring for patients with serious illness. Todd and Holmes [41•], above, provide guidance consistent with Thompson's first model (a way of thinking); this seems to be a "common sense" approach that incorporates the principles of time to benefit, latency effect, patient's clinical status, and life expectancy. The STOPPFrail is a very useful tool when assessing the entire medication regimen, likely more sensitive than the Beers criteria or the original STOPP/START criteria. And last, it is useful for practitioners to keep in mind the "frequent flyer" offender medications/medication classes that are ripe for deprescribing (e.g., statins, vitamins/supplements, acetylcholinesterase inhibitors). Of course, as with all aspects of patient care, tools are helpful but we must interpret in a patient-specific fashion.

Conclusion

Polypharmacy is very common in older adults and patients living with an advanced illness, often leading to medication-related adverse outcomes. It is critically important that providers recognize that deprescribing is part of the prescribing process, and it is imperative that we remain vigilant in continuously reviewing the patient's medication regimen and identifying medications that are too burdensome or have outlived their usefulness. Patients indicate that they are interested in reducing the number of medications they are taking, particularly if endorsed by their prescriber. Many tools and resources are available to assist practitioners in the deprescribing process, including guidance for shared decision-making with patients and families.

Sidebar: Number Needed to Treat and Number Needed to Harm

Number Needed to Treat

The *number needed to treat* (*NNT*) can be defined as the expected number of people that must be treated with one therapy versus another for one person to derive benefit over a specified time period. In other words, how many people would we have to give an intervention to before one has the desired outcome [49, 50]?

If the NNT is not explicitly provided, it can easily be calculated using the following formulas:

$$\mathrm{NNT} = \frac{1}{\text{Absolute Risk Reduction (ARR)}}$$

$$\mathrm{ARR} = \text{Event rate}_{\text{control group}} - \text{Event rate}_{\text{treatment group}}$$

Let us consider a (fictitious) study of 100 patients randomized 1:1 to receive BetterBlocker (treatment group) or placebo (control group) for the secondary prevention of acute myocardial infarction (MI). During a follow-up period of 5 years, 30% of patients in the BetterBlocker group had an acute MI vs. 40% in the placebo group. Therefore, the ARR = 40–30% = 10%, and the NNT = 1/0.10 = 10. In other words, if we treat 10 patients for 5 years with BetterBlocker, one patient will avoid an acute MI.

Ideally, the NNT would always equal 1. This means that every person treated with a given intervention will benefit. Unfortunately, that is rarely the case, and NNTs are often much larger. This is especially true when considering the NNT of preventative interventions.

Let us consider the use of aspirin for primary prevention in patients with diabetes mellitus to better illustrate this concept. The ASCEND trial, which randomized 15,480 patients with diabetes to aspirin or placebo and assessed for serious vascular events, reported an NNT of 91 (ARR = 1.1%) during a mean follow-up of 7.4 years [51]. That is, it is expected that 1 less person will experience a serious vascular event for every 91 people receiving aspirin rather than placebo over the course of 7.4 years.

There are several key questions to consider when it comes to NNT.

1. The first question is *what is the comparator*? This is important because NNT is a comparative measure of effect, and the NNT will differ based on whether you are comparing a given drug to placebo or another active therapy.
2. The second question is *what is the time frame*? If the NNT is calculated on a 5- or 10-year study period or longer, the NNT may not be accurately applied to a patient who is at the end of life. In this case, the NNT would likely be substantially higher.
3. The final question is *what is the baseline risk*? Knowing the baseline risk in the population studied is important in assessing the applicability of the results to the patient at hand [52]. Because patients in clinical trials are much less likely to have multimorbidity, the NNT in a real-world patient population is likely much higher and the number needed to harm (NNH) may be much lower.

While the NNT is certainly a useful tool for quantifying magnitude of effect, it fails to tell the entire story. We must also consider other factors such as the side

effects or harm associated with a given intervention, cost effectiveness of therapy, and alignment with patient preference and/or goals of care.

Number Needed to Harm

The *number needed to harm* (*NNH*) is a complementary measure that can be defined as the expected number of people that must be treated with one therapy versus another for one person to experience a specific negative outcome over a given time period. The equation for calculating NNH is the same as that for NNT, but unlike NNT, we want the NNH to be as high as possible [53].

Using the earlier example from the ASCEND trial, the NNH (major bleeding) was 112 (absolute risk increase = 0.9%) [51]. In other words, it is expected that 1 additional person will experience a major bleed for every 112 people receiving aspirin rather than placebo over the course of 7.4 years. In this case, the NNT (91) and NNH (112) are of similar magnitude. Basically, the odds of a good outcome are about equal to the odds of a bad outcome. But if the patient in question has an advanced illness, this may tip the scales in favor of an undesirable outcome.

Compliance with Ethical Standards

Conflict of Interest Alexandra McPherson and Mary Lynn McPherson declare no conflict of interest.

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- • Of importance
- •• Of major importance

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