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Medication appropriateness criteria for older adults: a narrative review of criteria and supporting studies

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***Abstract*:** Polypharmacy is common among older adults and is associated with adverse outcomes. Polypharmacy increases the likelihood of receiving a potentially inappropriate medication (PIM). PIMs have traditionally been defined as medications that have either no benefit (e.g. therapeutic duplication) or increased risk (e.g. altered pharmacodynamics/kinetics with aging). A growing literature supports the notion that these represent only a subset of the potential risks of medications prescribed to older adults. Different authors have proposed new sets of criteria for evaluating medication appropriateness. This narrative review had two objectives: 1) to summarize the contents of these criteria in order to obtain preliminary information about where clinical consensus exists regarding appropriateness; 2) The second was to describe studies examining the risks and benefits of medications identified by the criteria to determine the strength of the evidence supporting the derivation of these criteria. We identified 13 articles sharing overlapping criteria for evaluating appropriateness including: (1) delayed time to benefit; (2) altered benefit–harm ratios in the face of competing risks; (3) effects that do not match patients' goals; and (4) nonadherence. The similarities across the articles suggested strong clinical consensus; however, the articles presented little data directly supporting these criteria. Additional studies provide evidence for the proof of concept that average estimates of benefit and harm derived from randomized controlled trials may differ from the benefits and harms experienced by older persons. However, more data are required to characterize the benefits and harms of medications in the context of the regimen as a whole and the individual's health status.

Keywords: medication appropriateness, multimorbidity, polypharmacy

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Introduction

The use of multiple medications, commonly referred to as polypharmacy, is steadily increasing among older adults. While there is no firm consensus regarding the number of medications defining polypharmacy,[1] a cutoff point of ⩾5 medications is commonly used.[2] The proportion of community-dwelling adults in the United States (US) aged ⩾65 years taking more than five medications rose from 24% between 1999 and 2000 to 39% between 2011 and 2012.[2] In a systematic review of observational studies, polypharmacy, defined using different cutoffs, was associated with multiple adverse health outcomes, including falls, fall-related injury, hospitalizations, mortality, impaired function and cognition, and adverse drug reactions.[3]

Polypharmacy is strongly associated with the prescription of potentially inappropriate medications (PIMs).[4] There are several well-established and validated strategies for evaluating the medical regimen and identifying PIMs. One is the Medication

Appropriateness Index, which requires implicit medication review using a set of criteria looking for medications without benefit because, for example, they represent therapeutic duplication, and medications with drug–drug or drug–disease interactions.[5] A second is the use of consensus-based lists of medications that should not[6–11] and should[10] be prescribed to older adults, generally because of altered pharmacokinetics or dynamics or drug–drug/drug–disease interactions.

A growing literature suggests that these established methods for identification of PIMs addresses only a subset of the potential risks imposed by polypharmacy. Clinical practice guidelines do not yet exist for the evaluation of medication appropriateness across an entire medication regimen. Nor are there studies examining the clinical outcomes associated with the use of these expanded criteria. One well-established limitation for the development of guidelines is the lack of data regarding medication outcomes in older adults, who are regularly excluded from randomized controlled trials (RCTs) of the medications they are most likely to be prescribed.[12,13] Even with the inclusion of observational studies, several large systematic reviews also reveal the absence of data.[14,15] For a few individual medications or classes of medications, strong evidence of harms outweighing benefits has supported the development of deprescribing guidelines, including proton-pump inhibitors,[16] benzodiazepine receptor agonists,[17] and psychotropic medications for the treatment of the behavioral symptoms of dementia and insomnia.[18] However, for other medications, such as for antihyperglycemic agents, evidence is not strong, and the guideline developed for deprescribing notes highly variable glycemic targets in different diabetes treatment guidelines.[19] Uncertainty resulting from lack of data is also reflected in the description of the development of STOPPFrail criteria, a consensus-based list of PIMs for frail older adults, and for which consensus could not be achieved for all proposed medications.[20]

Even beyond the challenge of defining the overall benefits and harms of individual medications, is evaluating the potential for medications with demonstrated benefit for certain disease-specific outcomes to nonetheless fail to have benefit or cause harm among selected groups of older adults, particularly those with multimorbidity or frailty and disability. Several investigators have separately proposed criteria for an expanded assessment of medication appropriateness based on this concept. The purpose of this review was to compare these criteria, an effort that can serve as the beginning of a derivation of expert consensus around these criteria. This review also sought to summarize the studies regarding the benefits and harms of medications that would be identified by these criteria, in order to evaluate the strength of the current evidence underlying these criteria and to identify where additional evidence is most needed.

Methods

The authors began with the articles known to them that presented sets of criteria for the evaluation of medication appropriateness among older adults based on the expert opinion of the author(s). A review of the MeSH headings of these articles revealed a lack of common indexing terms, precluding the conduct of a systematic review. Instead, we used a search strategy consisting of a text search of keywords, title, and abstract in *Ovid MEDLINE* for the following terms: 'polypharmacy' and 'drug-related side effects and adverse reactions' and 'inappropriate prescribing' (66 results) or 'deprescri* and polypharmacy' (153 results). The abstracts of the search results were reviewed to identify additional articles presenting sets of criteria, and then the references for these articles were examined for further relevant articles. We included only articles that were written specifically to provide a description of processes for conducting an appropriateness review. We did not include articles addressing medication appropriateness at the end of life or among individuals with a specific condition, such as cancer, or providing general principles regarding appropriateness rather than a set of specific review criteria. A total of 13 articles were identified. In a second round of review, we examined the citations provided by these articles as empirical evidence supporting the criteria. We supplemented these citations with additional studies presenting supporting evidence.

Results

The criteria across the 13 articles are presented in Table 1.[21–33] Virtually all articles include PIMs as traditionally defined and described above. Because the methods for identifying these PIMs are well established, they are not further discussed. We present four additional criteria expanding the dimensions of medications that may be inappropriate for the older patient.

Table 1. Criteria for the evaluation of medication appropriateness included in the frameworks.[a]

Author	PIMs	Time to benefit	Harm *versus* benefit	Goals of care	Adherence
Barnett and colleagues[21]	X	X	X	X	X
Drenth-van Maanen and colleagues[22]	X	X			
Frank and Weir[23]	X	X		X	X
Garfinkel and colleagues[24]	X	X	X	X	
Haque[25]	X		X		
Hilmer and colleagues[26]	X	X	X	X	
Holmes and colleagues[27]		X		X	
Jetha[28]	X	X	X	X	
Lee and colleagues[29]	X				
Scott and colleagues[30]	X	X	X	X	X
Scott and colleagues[31]	X	X	X	X	
Steinman and colleagues[32]	X	X	X	X	
Woodward[33]	X				

[a]The shaded boxes indicate primary literature provided to support the criterion.
PIM, potentially inappropriate medication.

Medications with a delayed time to benefit

A total of nine articles present the criterion of evaluating the time to benefit (TTB). A PIM is defined as one providing benefit in a timeframe exceeding the patient's life expectancy. Only two provide citations to support examples of such medications. Scott and colleagues cite a review article of bisphosphonate therapy concluding that fracture risk reduction requires more than 12 months of therapy;[34] however, the review does not provide primary literature reporting the TTB. This article also cites a review article to support the assertion that the TTB for statins is 12 months.[35] Within this review article is a meta-analysis presenting the TTB for different outcomes ranging from 3 months to 2–3 years.[36] Steinman and colleagues cite the American Geriatrics Society (AGS) Diabetes Guidelines, which state that the TTB for glucose control is approximately 8 years to reduce the risk of microvascular complications and 2–3 years for blood pressure control to reduce the risk of macrovascular changes. It is challenging to verify these statements in the articles cited by the guideline.[37]

Medications whose likelihood of harm outweighs the benefit because of competing risks

In eight articles, there is a description of the criterion of the likelihood of harm outweighing the likelihood of benefit. Most of these articles include a discussion suggesting that patient-specific factors can alter the likelihood of benefit and harm, including frailty/disability, quality of life (QOL), chronic conditions, and age. While each of the articles recommends assessing some combination of these factors and considering the medications in their context, only three provide specific examples of inappropriate medications based on citations of the literature for hypertension (HTN) and diabetes mellitus (DM).

Scott and colleagues discuss the potentially inappropriate treatment of HTN based on the evidence for an increased risk of mortality among older persons for whom systolic blood pressure control is achieved only with low diastolic readings. This article cites an observational prospective cohort study of persons with a mean age of 72 years, 75% of whom were being treated for HTN,

in which lower diastolic blood pressures were associated with a higher mortality risk.[38] Included in that cohort study is a reference to a review summarizing the findings of multiple observational studies of cohorts of people aged ⩾85 years, demonstrating an association between higher systolic or diastolic blood pressure and lower mortality.[39] This review also presented a subgroup meta-analysis of RCTs of antihypertensive treatment including patients aged ⩾80 years and older, demonstrating that, while treatment was associated with reductions in stroke and heart failure, it was also associated with an increased mortality risk.[40]

Scott and colleagues and Steinman and colleagues discuss the potentially inappropriate treatment of DM. Scott and colleagues cite a decision analysis demonstrating that the benefits of intensive control decline as multimorbidity increases and function decreases.[41] Steinman and colleagues cite an observational cohort study demonstrating that patients with DM and high comorbidity did not achieve a reduction in cardiovascular risk with more intensive glucose control.[42] Steinman and colleagues also cite the 2003 AGS Diabetes Guidelines, which states 'the risks of intensive control…may significantly alter the risk–benefit equation' without providing supporting citations.[37] The AGS subsequently published updated guidelines citing the American Diabetes Association (ADA) 2013 guideline recommending 'a less stringent target such as 8.0%' for 'persons with limited life expectancy or extensive comorbid conditions, and others in whom the risks of intensive glycemic control appear to outweigh the potential benefits.'[43] The ADA guidelines cite expert consensus or clinical experience as the source for this recommendation. Updated ADA 2017 guidelines upgrade the source of evidence to well-conducted observational studies, but do not provide specific citations.[44]

There is additional evidence regarding altered benefits and harms of treatment in HTN, DM, and end-stage renal disease (ESRD) among older persons. An observational study of a nationally representative sample of community-living Medicare beneficiaries aged >70 years with HTN found that individuals who received moderate or high-intensity antihypertensive therapy had an increased risk of serious fall injury compared with antihypertensive nonusers.[45] In a second observational cohort study examining a nationally representative cohort aged ⩾65 years, the association between HTN and mortality varied by gait speed. HTN was not associated with a higher mortality risk among those with a slow gait speed, and a higher systolic blood pressure was associated with a lower risk of death among participants who did not complete the walk test, suggesting that these patients might not derive a mortality benefit from treatment.[46]

A cohort study utilizing a large claims database of individuals enrolled in private and Medicare Advantage plans demonstrated that, among patients receiving intensive treatment, those with high clinical complexity, defined as aged >75 years, dementia or ESRD, or more than three chronic conditions, had nearly double the risk of severe hypoglycemia as compared with patients with low complexity.[47] In a cohort study of nursing home residents with DM, there was no difference in the likelihood of functional decline or death over 24 months across the strata of baseline HbA1c.[48] Among patients with ESRD, in one RCT of patients undergoing hemodialysis and a second RCT of patients with DM undergoing hemodialysis, statins did not decrease the risk of a composite endpoint of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction.[49,50]

Medications inconsistent with patient's goals of care

A total of nine articles present the criterion of a mismatch between the medication and the patient's treatment goals. Among these nine, three refer to patients' goals or preferences without further elaboration, and one discusses goals in terms of cure *versus* palliation. The other five refer to goals in terms of health outcomes including prolonging life, maximizing function and QOL, reducing symptoms, avoiding medication adverse effects, and avoiding disease progression, and one also included minimizing the pill burden and reducing medication costs. The evaluation of medications in the context of patients' goals is closely related to the evaluation of benefits and harms. The articles recognize that the process of weighing the likelihood of benefit *versus* harm requires an assessment of how the patient or family values these outcomes. For example, medications prescribed with the objective of reducing the likelihood of disease-specific outcomes, such as myocardial infarction or stroke, or of mortality, may also have adverse effects on patients' function or QOL, and the patient may more highly value the latter than the former.[51]

Although the articles did not include references providing data on potentially competing outcomes, the authors identified several relevant studies. A narrative review summarized 19 observational and intervention design studies which assessed the relationship between specific medications and functional decline. The review concluded that the use of certain individual medications, specifically benzodiazepines and medications with a higher load of anticholinergic effects, are associated with functional decline.[52] In an observational cohort study of community-living men aged 65 years and older, those who began statin therapy had a steeper rate of decline in physical activity compared with nonusers and chronic users.[53]

Nonadherence to medications

While eight articles state that patients' adherence to their medications should be assessed, only three assert that poor adherence is a criterion for PIMs. These three recommend that medications with poor adherence be evaluated according to the criteria stated elsewhere in the articles, implying that a medication with poor adherence is one with a limited TTB, risk outweighing benefit, or failing to meet patients' goals.

Discussion

The similarities in criteria for evaluation of appropriateness across the articles summarized in this review provide evidence for a strong consensus of expert opinion. Further supporting this consensus are the recommendations provided by several practice guidelines. However, evaluation of the evidence base underlying these recommendations reveals the limited data available to inform the question of how aging alters the benefits and harms of medications beyond the consideration of drug–drug and drug–disease interactions. Even when moving beyond the literature cited by the articles, it is challenging to find evidence regarding how the benefits and harms of medications may be affected by aging and its effects on health status, such as multimorbidity, frailty, and limitations in life expectancy.

Time to benefit

The inclusion of TTB in so many of the criteria attests to the strong clinical belief that many medications prescribed for primary or secondary prevention may not benefit patients with limited life expectancy. However, a recent review points out that the methodology for calculating the TTB is in its infancy.[54] Most RCTs only report cumulative outcomes at the end of the study period, so that the time to a given event is unknown. Even if time to events are measured and reported in a Kaplan–Meier curve, a visual inspection of the separation in curves cannot determine the statistical significance of any differences seen. In addition, the TTB depends upon the sample size of the study, the effect size being examined, and the study outcome (e.g. a single *versus* composite endpoint). One recent innovation to address the methodological issues with calculating the TTB has been the application of the statistical process control method, a statistical method used in healthcare improvement research to identify significant variations in clinical outcomes.[55] However, in addition to these methodological considerations, the TTB, as determined by RCTs, suffers from being a population-level outcome. This has the same limitation as other findings from RCTs when applied to older persons with multiple conditions, since such patients are rarely included in the trials and may have outcomes substantially different from study participants.[56] The ideal TTB would be calculated on an individual level, using patient-specific factors that could modify the TTB.

Competing risks and patients' goals

The limited existing studies summarized in this review provide proof of concept that the average estimates of benefit and harm derived from standard RCTs may be very different from the benefits and harms that individual older persons, with different combinations of impairments, conditions, and other risk factors, will obtain from a given medication or combination of medications.[57] They also demonstrate that medications which improve one outcome may worsen another. While the evidence base is small, and, particularly in the case of diabetes treatment, does not seem to provide direct support for guidelines, it provides strong justification for additional investigation. Observational studies with adequate control of confounding variables can yield data regarding the benefits and harms of medications as prescribed in diverse patient cohorts according to different sets of risk factors. Such studies can generate the information necessary to calculate patient-specific outcomes and the TTB rather than the population average results resulting from RCTs that frequently exclude patients at a highest risk for adverse events or the lowest likelihood of benefit. This limitation in RCTs can be

addressed by enrolling more diverse samples combined with multivariable risk-stratified analysis to identify patient subgroups at a higher or lower likelihood of a given outcome.[58]

Consideration of global benefit versus *harm*

While the articles included in this review expand the criteria to assess the appropriateness of medications, these criteria are all based on a process of evaluating the benefits and harms of individual medications. This approach does not address the most challenging issue related to polypharmacy; namely, evaluating the appropriateness of a medication regimen considered as a whole. In a landmark study, Boyd and colleagues demonstrated the potential harms associated with the application of guideline-directed medication management to an older patient with multiple chronic conditions.[59] In addition to the many drug–drug and drug–disease interactions, the resulting regimen is highly complex and potentially burdensome. In order to address this issue of potentially inappropriate regimens, a comprehensive framework for medication appropriateness will need to include two additional domains: (1) medication regimens that are not feasible for the patient to manage; and (2) medication regimens in which overall harm outweighs the overall benefit.

As acknowledged by the articles in this review, the regimen needs to be evaluated in the context of the patient's ability to adhere. Medication nonadherence is common, and impaired cognitive function is a risk factor for nonadherence.[60] Even among patients without cognitive impairments, there have been few effective interventions to improve adherence.[61,62] Older patients with multiple medical conditions may have indications for more medications than they can feasibly manage given their cognition and available social support. The reviewed articles stipulate that, when nonadherence is detected, medications that meet additional criteria for inappropriateness be discontinued. However, this may not be sufficient. It is possible that, to achieve feasibility, even medications that would otherwise not be considered inappropriate will need to be discontinued. While this principle is likely to be controversial, it achieved consensus support in a Delphi panel examining recommendations for deprescribing.[1]

Perhaps the most important unresolved question regarding polypharmacy is whether the overall medication load confers a risk beyond each medication considered individually. There is not yet an established methodology available to calculate the overall benefits and harms of a given regimen. One approach that begins to address this issue is the use of a utility function to combine the probabilities of benefits and harms across individual medications.[63] While this method provides a prototype for evaluating the medication regimen as a whole, it is limited by the absence of data on the marginal benefits and harms of medications when they are part of a large regimen and potentially interacting with many different other medications and conditions.[64]

Growing the evidence base for deprescribing

It may seem hopelessly complex to try to tease out the 'signal' from the 'noise' of the many possible combinations of conditions, medications, and risk factors that may interact with one another. One approach that may be well suited to this challenge is machine learning, with its ability to look at a large number of predictors and combined them in highly interactive ways.[65] For example, a machine-learning model has been built that identifies treatment response to a specific medication in the treatment of depression.[66] There are also several large trials underway that are developing new algorithms for identifying PIMs and evaluating the effects of deprescribing on clinically meaningful outcomes.[67,68] Ultimately, addressing the question of whether fewer medications are better than more will require RCTs of deprescribing, targeting not only medications with known adverse effects but medications that may have adverse effects as the sixth or seventh medication for a patient whose comorbidities or frailty may increase vulnerability to harms.

Conclusion

There is strong expert consensus that the approach to evaluating appropriateness of medications among older persons needs to incorporate considerations of the TTB for medications prescribed for primary or secondary prevention, the potential for an altered benefit–harm ratio, and a patient's most highly valued outcomes. However, data to inform these considerations are lacking. In addition, even medications that are appropriate when considered individually may be part of regimens that are inappropriate because their complexity makes them unfeasible or changes marginal benefits and harms. Deprescribing trials that include a broad range of outcomes will be

critical to obtaining the data necessary to optimize medication management in older persons.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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