Published in final edited form as:

J Am Geriatr Soc. 2019 June ; 67(6): 1123–1127. doi:10.1111/jgs.15798.

Medication Appropriateness in Vulnerable Older Adults:

Healthy Skepticism of Appropriate Polypharmacy

Terri R. Fried, MD^{1,2} and Marcia C. Mecca, MD^{1,2}

¹Clinical Epidemiology Research Center and Geriatrics & Extended Care, VA Connecticut Healthcare System

²Department of Medicine, Yale University School of Medicine

Abstract

Older adults are prescribed a growing number of medications. Polypharmacy, commonly considered the receipt of 5 or more medications, is associated with a range of adverse outcomes. There is a debate about the reason(s) why. On one side is the assertion that older persons are being prescribed too many medications, with the number of medications increasing the risk of adverse events. On the other side is the observation that polypharmacy is associated both with overprescribing of inappropriate medications and underprescribing of appropriate medications. This leads to the concept of “inappropriate” versus “appropriate” polypharmacy, with the latter resulting from the prescription of many correct medications to persons with multiple chronic conditions. There are few studies examining the health outcomes associated with adding and/or removing medications to address this debate directly. However, the criteria used to identify underutilized medications are based on results of randomized controlled trials, which may not be generalizable to older adults. Several randomized controlled trials and many more observational studies provide evidence that these criteria overestimate medication benefits and underestimate harms. In addition, evidence suggests that the marginal effects of medications added to an already complex regimen differ from their effects when considered individually. While there are selected circumstances in which adding medications results in benefit to patients, patients with multimorbidity and frailty/disability have susceptibilities that can decrease the likelihood of medication benefit and increase the likelihood of harms. The identification of appropriate polypharmacy requires more robust criteria to evaluate the net effects of complex medication regimens.

Older adults are prescribed a growing number of medications. The term “polypharmacy” is used to characterize the prescription of multiple medications. While there is no consensus about the number of medications constituting polypharmacy, a cut-off of 5 or more medications is commonly used, with large surveys in the US and Europe¹ demonstrating a

Corresponding author: Terri R. Fried, MD. Clinical Epidemiology Research Center, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516. Phone: 203-932-5711 x54112. Fax: 203-937-4932. terri.fried@yale.edu (no Twitter handle).

Marcia Mecca: @LoveCareLearn

Author Contributions: Both authors contributed to the study concept, analysis and interpretation of data, and preparation of the manuscript.

Conflict of Interest: The authors have no conflicts.

high and increasing prevalence of polypharmacy. Concerns about whether all of these medications are being used appropriately encompass an important debate about the correct approach to ensuring that older persons are receiving optimal medical therapy.

The Debate over Polypharmacy in Older Persons

Both sides of the debate agree that polypharmacy is a problem because it is associated with multiple adverse outcomes, including falls, fall related injury, hospitalizations, mortality, impaired function and cognition, and adverse drug effects.² The disagreement surrounds the mechanism(s) by which polypharmacy results in these outcomes. On one side of the debate is the belief that older persons are being prescribed too many medications, regardless of the specific medications prescribed. Aging is associated with changes in pharmacodynamics and pharmacokinetics that increase the risk of several classes of medications, and multiple medications increase the risk of drug-drug and drug-disease interactions. According to this position, the goal for patients with polypharmacy is to reduce the number of medications and eliminate polypharmacy.

On the other side of the debate is the belief that older persons are not being prescribed the right medications, but that number of medications in and of itself is not the problem. Polypharmacy is associated with both the prescription of medications that may be inappropriate for older persons (potentially inappropriate medications, or PIMs) and the *lack* of prescribing appropriate medications (potential prescribing omissions, or PPOs).³ This argument leads to the concept of “appropriate polypharmacy.”⁴ This view places an emphasis on prescribing the right medications, regardless of number.

Little direct evidence is available to address this question. A Cochrane polypharmacy review demonstrates that no studies examining interventions directed at PPOs include clinical outcomes.⁵ Studies utilizing the strategy of identifying and deprescribing PIMs have mixed results, with several demonstrating a reduction in hospital admissions but none showing an effect on health-related quality of life. The review concludes that these studies are ultimately limited by small sample sizes, poor quality, and heterogeneity.⁵

Potential Limitations of Existing Tools to Identify Medication Appropriateness

Indirect lines of evidence suggest that, while substantial progress has been made in developing tools for evaluating the appropriateness of medication regimens for older adults, we may nonetheless still be overestimating benefits and underestimating harms of medications. A recent systematic review of these tools concludes that many require clinical judgment.⁶ The challenge is the limitations of randomized clinical trials (RCTs) in informing this clinical judgment. Commentators have persuasively argued that older persons with multiple conditions may not accrue the same benefits from medications as seen in RCTs because they are not as healthy as the trial participants, with competing mortality risks and risk for adverse effects from the medications themselves.⁷ While the limitations in generalizability of findings from RCTs to older adults are well recognized, these limitations have not been examined among tools used to measure PPOs. These tools include the

Assessment of Underutilization (AOU), which is based on a review of the patient's chronic conditions and the use of clinical judgment and clinical guidelines to identify missing medications,⁸ and the START criteria, which are consensus recommendations based on review of systematic reviews and RCTs.⁹

Association of PPO Tools with Clinical Outcomes

Observational studies highlight the narrow therapeutic window of medications included in PPO tools. In one study using implicit chart review to determine the contribution of PIMs identified by STOPP and PPOs identified by START with hospitalizations among frail older persons, these medications were assessed to have contributed to 27.1% of admissions. Of these, 2/3 were a result of PIMs and 1/3 of PPOs. Aspirin was implicated both as a PPO and a PIM.¹⁰ In a second observational study using START/STOPP criteria among a cohort of older persons discharged from the hospital, PIMs were associated with an increased risk of hospital readmission and PPOs with increased mortality.¹¹ However, a third cohort study suggests that the association between PPOs and mortality is not causal. Among individuals with cardiovascular disease, the likelihood of a PPO identified by START was associated most strongly with frailty. In analysis adjusted for frailty and comorbidity, there was no association of medication underutilization with cardiovascular deaths, but there was an association with competing deaths from non-cardiovascular causes.¹² The authors suggest that PPOs are withheld among patients at increased risk of competing adverse outcomes who are least likely to benefit from these medications. There is additional evidence for decreased medication benefits and increased harms in studies of individual medications or classes of medications included in criteria identifying PPOs among older persons who are vulnerable because of disability and/or comorbidity.

Overestimation of Medication Benefits

Lipid-lowering and antihypertensive agents were two of the most common medications identified by the AOU in a study of outpatient Veterans age 65 years and older.³ Statins and beta-blockers for ischemic heart disease are included in the START criteria.⁹ However, in the context of multimorbidity and polypharmacy, these medications may fail to demonstrate expected benefits. Although patients with significant comorbidities are frequently excluded from RCTs, two adequately powered RCTs examined statin use in patients with end-stage renal disease (ESRD), and demonstrated no reduction in a composite of cardiovascular outcomes.^{13,14}

Several observational studies also illustrate the reduced benefit of these therapies among vulnerable patients. In a nationally representative cohort age 65 and older, hypertension was not associated with a higher mortality risk among those with slow gait speed, and higher systolic blood pressure was associated with a lower risk of death among participants who did not complete the walk test, suggesting that frail patients might not derive mortality benefit from antihypertensive treatment.¹⁵ In a cohort study of patients with Type II diabetes mellitus (DM), those with high comorbidity did not achieve the reduction in cardiovascular risk with more intensive glucose control that was seen in patients with low-to-moderate comorbidity.¹⁶ In addition, targeting risk factors with multiple medications may not be

necessary. In a study examining the association of adherence with multiple preventative therapies and all-cause mortality following myocardial infarction among Medicare beneficiaries, patients adherent to angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and statins had similar mortality to those adherent to beta-blockers in addition to those therapies, suggesting no additional benefit of the beta-blockers.¹⁷

Underestimation of Medication Harms

Observational studies demonstrate that vulnerable older patients are at increased risk of suffering harm from various medications included in PPO criteria. First, a cohort study utilizing data from a nationally representative sample of community-living Medicare beneficiaries older than 70 years with hypertension found that individuals who received moderate- or high-intensity antihypertensive therapy had an increased risk of serious fall injury compared to antihypertensive nonusers. Subgroup analysis revealed that among those with a previous fall injury in the past year, the use of moderate and high intensity antihypertensive therapy doubled the risk of injury.¹⁸ Second, while inhaled anticholinergic agents were identified as the most commonly underutilized medication using the AOU in a study of frail Veterans at time of hospital discharge,¹⁹ they were associated with a markedly increased risk of acute urinary retention in men with COPD in a large case-control study.²⁰ Finally, a cohort study of individuals with DM enrolled in private and Medicare Advantage plans demonstrated that, among persons receiving intensive treatment, those with high clinical complexity, defined as age >75, dementia or ESRD, or 3 chronic conditions, had nearly double the risk of severe hypoglycemia as compared to patients with low complexity.²¹

In addition, some medication harms do not receive adequate weight in decision making about appropriateness. Primary or secondary prevention medications, prescribed to decrease the risk of future disease-specific events, may cause immediate non-disease-specific symptoms. These are commonly referred to as “side-effects.” This term reflects the understanding that these symptoms are an unavoidable consequence of and less important than the primary goal of reducing future risk. However, for many older persons, these effects are not to the side of the primary goal, but rather are outcomes as important or more important to avoid than the primary outcome is to achieve. Because of the relegation of these non-disease-specific outcomes as side effects, there is little evidence about their prevalence. One example of the adverse effects of medications on an outcome highly important to older persons is an observational study of community-living men age 65 years and older demonstrating that those who began statin therapy had a steeper rate of decline in physical activity compared to non-users and chronic users.²² In a cohort study of nursing home residents hospitalized for acute myocardial infarction (MI) with propensity matching, the prescription of beta-blockers post-MI was associated with reduced mortality risk but an increased risk of functional decline.²³

Evaluating the Net Benefit of the Medication Regimen

Criteria for identifying both PIMs and PPOs focus on individual medications without considering the benefits and harms of the medication regimen as a whole. While there are

scales to measure the cumulative burden of medications with known adverse effects, such as anticholinergics and sedatives,^{24,25} little evidence exists regarding the marginal benefits and harms of any given n^{th} medication added to a regimen.⁷ However, it is highly likely that the marginal effects of medications are different from their effects when considered individually. The strongest evidence for this comes from the well-established association between number of medications and likelihood of an adverse drug reaction (ADR). In a study of hospitalized persons age 65 years or older, those taking 8 or more medications had four times the odds of an ADR compared to those taking 5 or less.²⁶ Although number of medications is a risk factor for receipt of a PIM, it is unlikely that the large excess risk of ADRs associated with multiple medications is completely accounted for by the individual medications. Instead, this risk more likely reflects the exponentially increased number of drug-drug and drug-disease interactions that can occur when multiple medications are prescribed. In the face of an already narrowed gap between the benefits and harms of many medications for vulnerable older adults, even small excess marginal risks could tip the balance in favor of reducing the number of medications in a regimen.

A second consideration is whether the patient can/will take all prescribed drugs. Medication non-adherence is more common among individuals with cognitive impairment and more complex regimens.²⁷ Even if the regimen has net benefit outweighing harms and acknowledging the existence of tools to simplify complex regimens,²⁸ the patient may nonetheless not be able to manage the regimen. To achieve feasibility, even medications that would otherwise not be considered inappropriate will need to be discontinued. While this principle is controversial, it achieved consensus support in a Delphi panel examining recommendations for deprescribing.²⁹

Conclusions

Figure 1 provides a suggested approach to the evaluation of medication appropriateness, which includes the key step of stratifying patients as “robust” or “vulnerable.” All older persons require evaluation for PIMs that can be easily identified, using established tools such as the Medication Appropriateness Index, Beers, and/or STOPP. Periodic re-evaluation can identify medications that no longer have indications and, if done after a change in health status, identify new risk factors for adverse events. “Robust” older persons can benefit from the identification of PPOs. For example, physicians tend to overestimate fall risks in decisions not to prescribe anticoagulants to patients for whom risk of stroke outweighs their risk of bleeding.³⁰ However, for “vulnerable” patients, clinicians should be wary of adding PPOs and have a high index of suspicion for additional PIMs. Until there are better tools to aid in their identification, clinicians must depend on the limited literature and clinical judgment. In a study of older patients admitted to an acute inpatient geriatric unit, only 34% of START criteria were implemented by a multidisciplinary geriatric team upon discharge as compared to 87% of STOPP criteria. Reasons for not following START criteria included severe disability and high risk of adverse events,³¹ suggesting that seasoned clinicians can use their knowledge and experience to avoid high-risk medications in vulnerable older persons.

ACKNOWLEDGMENTS:

Sponsor's Role: The sponsor had no role in the design, methods, analysis, or preparation of the paper.

Funding sources: The Claude D. Pepper Older Americans Independence Center at Yale University School of Medicine (#P30AG21342 NIH/NIA.) This work was supported with resources and the use of facilities at the VA Connecticut Healthcare System. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

REFERENCES

1. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother* 2007;5:345–51. [PubMed: 18179993]
2. Fried TR, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261–72. [PubMed: 25516023]
3. Steinman MA, Seth Landefeld C, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006;54:1516–23. [PubMed: 17038068]
4. Hughes CM, Cooper JA, Ryan C. Going beyond the numbers - a call to redefine polypharmacy. *Br J Clin Pharmacol* 2014;77:915–6. [PubMed: 24853404]
5. Cooper JA, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. *BMJ Open* 2015;5.
6. Masnoon N, Shakib S, Kalisch-Ellett L, et al. Tools for assessment of the appropriateness of prescribing and association with patient-related outcomes: A systematic review. *Drugs Aging* 2018;35:43–60. [PubMed: 29350335]
7. Tinetti ME, Bogardus ST Jr., Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med* 2004;351:2870–4. [PubMed: 15625341]
8. Jeffery S, Ruby CM, Twesky J, et al. Effect of an interdisciplinary team on suboptimal prescribing in a long-term care facility. *Consult Pharm* 1999;14:1386–9.
9. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213–8. [PubMed: 25324330]
10. Dalleur O, Spinewine A, Henrard S, et al. Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. *Drugs Aging* 2012;29:829–37. [PubMed: 23044639]
11. Counter D, Millar JWT, McLay JS. Hospital readmissions, mortality and potentially inappropriate prescribing: a retrospective study of older adults discharged from hospital. *Br J Clin Pharmacol* 2018;84:1757–63. [PubMed: 29744901]
12. Meid AD, Quinzler R, Freigofas J, et al. Medication underuse in aging outpatients with cardiovascular disease: Prevalence, determinants, and outcomes in a prospective cohort study. *PLoS One* 2015;10:e0136339. [PubMed: 26288222]
13. Wanner C, Krane V, März W, et al. Atorvastatin in patients with Type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;353:238–48. [PubMed: 16034009]
14. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;360:1395–407. [PubMed: 19332456]
15. Odden MC, Peralta CA, Haan MN, et al. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch Intern Med* 2012;172:1162–8. [PubMed: 22801930]
16. Greenfield S, Billimek J, Pellegrini F, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study. *Ann Intern Med* 2009;151:854–60. [PubMed: 20008761]
17. Korhonen MJ, Robinson JG, Annis IE, et al. Adherence tradeoff to multiple preventive therapies and all-cause mortality after acute myocardial infarction. *J Am Coll Cardiol* 2017;70:1543–54. [PubMed: 28935030]

18. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Intern Med* 2014;174:588–95. [PubMed: 24567036]
19. Wright RM, Sloane R, Pieper CF, et al. Underuse of indicated medications among physically frail older US veterans at the time of hospital discharge: Results of a cross-sectional analysis of data from the Geriatric Evaluation and Management Drug Study. *Am J Geriatr Pharmacother* 2009;7:271–80. [PubMed: 19948303]
20. Stephenson A, Seitz D, Bell CM, et al. Inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease: a population-based study. *Arch Intern Med* 2011;171:914–20. [PubMed: 21606096]
21. McCoy RG, Lipska KJ, Yao X, et al. Intensive treatment and severe hypoglycemia among adults with type 2 diabetes. *JAMA Intern Med* 2016;176:969–78. [PubMed: 27273792]
22. Lee DS, Markwardt S, Goeres L, et al. Statins and physical activity in older men: the osteoporotic fractures in men study. *JAMA Intern Med* 2014;174:1263–70. [PubMed: 24911216]
23. Steinman MA, Zullo AR, Lee Y, et al. Association of β -blockers with functional outcomes, death, and rehospitalization in older nursing home residents after acute myocardial infarction. *JAMA Intern Med* 2017;177:254–62. [PubMed: 27942713]
24. Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol* 2006;46:1481–6. [PubMed: 17101747]
25. Kouladjian L, Gnjdic D, Chen TF, et al. Drug Burden Index in older adults: theoretical and practical issues. *Clin Interv Aging* 2014;9:1503–15. [PubMed: 25246778]
26. Onder G, Petrovic M, Tangiisuran B, et al. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: The gerontonet adr risk score. *Arch Intern Med* 2010;170:1142–8. [PubMed: 20625022]
27. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: Looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother* 2011;9:11–23. [PubMed: 21459305]
28. Chen EY, Sluggett JK, Ilomaki J, et al. Development and validation of the Medication Regimen Simplification Guide for Residential Aged Care (MRS GRACE). *Clin Interv Aging* 2018;13:975–86. [PubMed: 29844664]
29. Fried TR, Niehoff K, Tjia J, et al. A Delphi process to address medication appropriateness for older persons with multiple chronic conditions. *BMC Geriatr* 2016;16:67. [PubMed: 26979576]
30. Anderson N, Fuller R, Dudley N. ‘Rules of thumb’ or reflective practice? Understanding senior physicians’ decision-making about anti-thrombotic usage in atrial fibrillation. *QJM* 2007;100:263–9. [PubMed: 17389657]
31. Lozano-Montoya I, Vélez-Díaz-Pallarés M, Delgado-Silveira E, et al. Potentially inappropriate prescribing detected by STOPP–START criteria: are they really inappropriate? *Age Ageing* 2015;44:861–6. [PubMed: 26175348]

Figure:

Algorithm for evaluation of medication appropriateness in older adults. PIM = potentially inappropriate medication. PPO = potential prescribing omission.