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Research Priorities for Optimizing Geriatric Pharmacotherapy: An International Consensus

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A B S T R A C T

Medication management is becoming increasingly challenging for older people, and there is limited evidence to guide medication prescribing and administration for people with multimorbidity, frailty, or at the end of life. Currently, there is a lack of clear research priorities in the field of geriatric pharmacotherapy. To address this issue, international experts from 5 research groups in geriatric pharmacotherapy and pharmacoepidemiology research were invited to attend the inaugural Optimizing Geriatric Pharmacotherapy through Pharmacoepidemiology Network workshop. A modified nominal group technique was used to explore and consolidate the priorities for conducting research in this field. Eight research priorities were elucidated: quality of medication use; vulnerable patient groups; polypharmacy and multimorbidity; person-centered practice and research; deprescribing; methodological development; variability in medication use; and national and international comparative research. The research priorities are discussed in detail in this article with examples of current gaps and future actions presented. These priorities highlight areas for future research in geriatric pharmacotherapy to improve medication outcomes in older people.

The process of prescribing, dispensing, administering, and monitoring medications for older people is becoming increasingly challenging, especially in the presence of multimorbidity and frailty. In the United States, the proportion of community-dwelling older adults who use 5 or more medications has tripled to 39% over a 20-year period.[1] Up to 74% of residents of long-term care facilities use 9 or more medications on a regular basis.[2] As a consequence, the average proportion of residents who use 1 or more potentially inappropriate medications has increased from 30% in studies conducted before 1999 to nearly 50% in studies conducted after 2005.[3]

Advances in pharmacotherapy have brought about considerable improvements in patient care. However, age-related pharmacokinetic and pharmacodynamic changes combined with multimorbidity, decline in cognition, and impaired functional status mean older people are more vulnerable to adverse drug events (ADEs).[4] Frailty may confer additional risk, with ADEs in this population often presenting as geriatric syndromes such as falls and delirium.[5] Medication-related harms continue to be associated with considerable economic, clinical,

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and humanistic costs. Polypharmacy and complex medication regimens are independent predictors of hospitalization for people living in community[6] and residential aged care settings.[7] Direct and indirect harms arising from medication use are implicated in up to 30% of unplanned hospitalizations in those aged 75 years or older, with up to three-quarters of these hospitalizations estimated to be potentially preventable.[8]

There is limited evidence to inform prescribing decisions for older people. Older people who are frail, experience multimorbidity, or have polypharmacy rarely participate in randomized controlled trials (RCTs).[9] Prescribing decisions are often based on evidence extrapolated from RCTs conducted in younger and healthier people. Despite a number of recent initiatives, disease-specific clinical practice guidelines rarely provide recommendations specific to older people with multimorbidity, frailty, or at the end of life. Moreover, there is a lack of clear priorities in the field of geriatric pharmacotherapy research.

The objective of this article is to present research priorities for optimizing geriatric pharmacotherapy formulated at an international multidisciplinary workshop in Stockholm, Sweden, in May 2017.

Methods

The 2-day inaugural Optimizing geriatric Pharmacotherapy through Pharmacoepidemiology Network (OPPEN) workshop was hosted by the Aging Research Center, Karolinska Institutet. Five research groups devoted to geriatric pharmacotherapy and pharmacoepidemiology from Australia, Belgium, Finland, Italy, and Sweden were represented. Participants included 2 geriatricians, 5 pharmacists, 2 social scientists, a clinical pharmacologist, a nurse, and a biostatistician. Using a modified nominal group technique,[10] participants worked in international mixed discipline groups of 2 or 3 participants to produce a list of research priorities. The facilitator then asked each group to volunteer 1 research priority in turn until an exhaustive list of research priorities was discussed, revised, and documented. New research priorities generated in the wider group were also discussed, revised, and documented. All research priorities were thematically combined into a final list of 8 research priorities. The final list of 8 priorities was discussed by all participants until final consensus was reached. Priorities are summarized below and in Table 1.

Priorities

Underuse, Overuse, and Misuse of Medications

The prevalence of inappropriate medication use continues to increase in older people residing in the community and residential aged care settings.[3] It has been reported that the majority of emergency hospitalizations for recognized ADEs in older adults result from relatively few commonly used medications.[11] For example, up to 60% of US emergency department visits for ADEs in older adults (aged ≥65 years) are the result of 3 drug classes (anticoagulants, diabetes agents, and opioid analgesics).[12] Research should, thus, focus on medications that are responsible for the highest burden of morbidity and mortality, including these high-risk medications not deemed potentially inappropriate in commonly applied explicit criteria.[12] The development and validation of indicators predictive of medication-related hospitalizations from different practice settings would be beneficial.

To address issues of suboptimal medication use, research should be conducted into identifying safer medication and nonmedication alternatives to potentially inappropriate or unnecessary medications.[13] Research should not only focus on strategies to discontinue inappropriate or unnecessary medications, but also on addressing potential underuse of clinically indicated and appropriate medications.[14] In addition, it should be acknowledged that whether or not medications are indicated may depend on each patient's current goals of care, personal preferences, and life expectancy.[15]

Furthermore, research should assess the possible contribution of medications to geriatric syndromes such as frailty, falls, incontinence, and cognitive impairment.[16–18] These geriatric syndromes are seldom comprehensively assessed in RCTs but are important due to their association with negative outcomes including functional decline,[19] hospitalizations,[20] and mortality.[21] Pharmacoepidemiologic research can, thus, have an important role in investigating the interplay between medication use and geriatric syndromes.[22,23]

Medications in Frail and Vulnerable Patient Groups

Particular subsets of the older population require special consideration when prescribing, dispensing, administering, and monitoring medications. These include those who are frail, experience multimorbidity, have cognitive impairment,[24–26] are socially and economically disadvantaged,[27] have renal or hepatic impairment,[28,29] are unable to self-manage their own medication regimen,[30] those that reside in residential aged care, and those at the end of life.[31] These vulnerable patient groups present unique challenges with regards to medication use. People in these population groups are often excluded from RCTs, and RCTs that include people from these population groups may do so in insufficient numbers to conduct sufficiently powered subanalyses. For this reason, prescribing recommendations in disease-specific clinical practice guidelines based on research conducted in adult populations may not be applicable to these vulnerable patient groups.[4] Further research is needed to better understand the benefits and risks of medication treatment specific to each of these groups. This can lead to the development of clinical services that better recognize and respond to ADEs.

Research should also recognize that biological age may be a better predictor of drug response or failure than chronological age. The use of polypharmacy and inappropriate medications have been reported to be associated with frailty,[16,32–34] and frailty may impact on patient medication adherence and response to therapy.[35] For example, frailty-related parameters were more strongly associated with impaired gait performance than the use of psychotropic drugs.[36] Conversely, no evidence was found that frailty modifies the effect of antihypertensive treatment in people aged 80 years and older.[37] Pharmacoepidemiologic research should, thus, assess the potential modifying effects of frailty when studying the benefits and harms of medications.

Understanding and Informing Prescribing in People With Multimorbidity and Polypharmacy

Multimorbidity is associated with reduced quality of life (QoL), higher mortality, polypharmacy, higher rates of ADEs, and greater health service use.[38] The National Institute for Health and Care Excellence guidelines on multimorbidity highlight the importance of addressing this issue.[38] Treatment regimens can become very burdensome for people with multimorbidity, and care can become uncoordinated and fragmented. Polypharmacy in people with multimorbidity is often the result of multiple preventative medications prescribed in relation to disease-specific guidelines. However, the appropriateness for using these medications weakens if life expectancy is reduced by other conditions or frailty. Further research into developing guidelines that are safe and effective in people with multimorbidity is needed.[38,39]

The evidence base for managing chronic diseases is largely drawn from trials of interventions for single conditions and individuals with multimorbidity are often excluded from these trials.[40,41] Older patients with multimorbidity and polypharmacy are, thus, often underrepresented in clinical trials of medications. Age disparities between patients participating in clinical trials and those encountered

Table 1
Priorities, Current Gaps, and Future Actions in Geriatric Pharmacotherapy Research

Priority	Current Gaps	Future Actions
Underuse, overuse, and misuse of medications	• There is limited research on the drug classes that cause the majority of serious ADEs in older people • It is unknown how best to manage suboptimal medication use including inappropriate, unnecessary or underused medications • Geriatric syndromes are usually not assessed in clinical trials	• Identify medications responsible for the highest burden of morbidity and mortality • Conduct research into safer pharmacological and nonpharmacologic alternatives • Focus research on both discontinuing inappropriate medications but also on potential underuse of adequate medications • Assess the possible contribution of medications to geriatric syndromes
Medications in frail and vulnerable patient groups	• There is limited evidence for medication use in people who are frail, with multimorbidity, have cognitive impairment, are socially and economically disadvantaged, those that reside in residential care, and are at the end of life	• Focus research on these vulnerable patient groups • Recognize that frailty may be a better predictor of drug response than chronological age • Assess the potential modifier effect of frailty when studying the benefits and harms of medications
Understanding and informing prescribing in people with multimorbidity and polypharmacy	• Older people with multimorbidity and polypharmacy are under-represented in clinical trials • Polypharmacy is ill-defined and often perceived as indicative of suboptimal care • There is limited research into how polypharmacy changes over time	• Ensure adequate representation of older people with multimorbidity in research • Investigate the fact that polypharmacy may be a proxy for multimorbidity and disease severity • Investigate how polypharmacy should be defined in different settings • Apply best practice methods to account for the fact that polypharmacy is a dynamic state • Explore variability in the medications that contribute to polypharmacy in different settings
Person-centered practice and research	• Older people are often excluded from the research process	• Engage patients in the research process • Investigate clinical outcomes that are important to older people
Deprescribing and regimen simplification	• There is limited research into the optimal duration of use of long-term medications and the effects of deprescribing them • It is unknown what factors influence deprescribing and how it should be promoted to key stakeholders	• Encourage research into continuation versus discontinuation of long-term medications • Encourage research into optimum treatment duration with long-term medications • Implement strategies to incorporate patient goals of care into decisions regarding medications • Conduct education for patients, caregivers and health professionals regarding the possible need to deprescribe
Methodological development	• Geriatric pharmacoepidemiologic studies are prone to bias and confounding, and medication exposure is difficult to define • Research findings may not be translatable to clinical practice or policy	• Compare and contrast medication exposure defined using different methods • Conduct longitudinal research using methods appropriate for time-varying exposure • Better account for reverse causation when conducting longitudinal studies • Encourage collaboration between researchers in the fundamental and applied sciences • Engage with key stakeholders regarding medications to inform research and policy
Understanding unexplained variability in prescribing and medication use	• Variations in medication use exist, but it is unknown what factors may contribute to this • There is limited research into how medication use changes over time	• Conduct research that explores unexplained variation in medication use within and between health services, including socioeconomic and geographic factors • Conduct longitudinal research into different medication use trajectories
National and international comparative research	• It is often unknown whether research findings are valid or generalizable to other settings outside of the context of the original study	• Replicate observational studies across multiple settings and using multiple methodologies to validate research findings and improve generalizability • Provide clear descriptions of the study setting and context • Use standard definitions and collect data on core outcome measures in geriatrics and gerontology • Explore the opportunity to use existing data to maximize prior investment in data collection

in routine clinical practice varies according to disease, with older patients with hypertension being particularly under-represented in trials used for drug regulatory approval in Japan.[42] Similarly, more than one-third of Australian patients with atrial fibrillation discharged from hospital on direct oral anticoagulants would have been ineligible for participation in any of the 3 pivotal trials of dabigatran, rivaroxaban, and apixaban.[43] Even persons participating in RCTs of antidementia medications are not necessarily representative of real-life users of these medications in clinical practice.[44] To date, few studies have investigated the effectiveness of interventions for specifically addressing health outcomes in people with multimorbidity.[41,45] Clinical and epidemiologic research should thus strive to ensure adequate representation of older people with multimorbidity to improve generalizability of findings to "real world" settings. This issue has been recognized by drug regulatory agencies such as the European Medicines Agency and United States Food and Drug Administration. Both agencies encourage pharmaceutical companies to consider inclusion of an appropriate representation of older patients in drug

development programs, including those with concomitant therapies and comorbidities. Certain specific adverse events and age-related efficacy endpoints should be assessed and pharmacokinetic studies performed in geriatric patients. Where data specific to prescribing for older people are lacking at the time of market authorization, data should be collected postmarketing.[46,47]

Although polypharmacy may be associated with negative outcomes,[48] polypharmacy itself should not necessarily be perceived as indicative of suboptimal care.[49,50] For example, although the number of regular medications has been shown to be strongly associated with unplanned hospitalizations, this effect was reduced in people with multiple health conditions.[51] At the individual patient level, polypharmacy should be considered in the context of the clinical conditions for which medications are prescribed.[38] Studies should also investigate to what extent the apparent harms associated with polypharmacy can be attributed to the fact that polypharmacy may be a proxy for multimorbidity and disease severity. It was recognized that polypharmacy often arises through adherence to prescribing recommendations in clinical practice guidelines, particularly for cardiovascular, cerebrovascular, and endocrine conditions,[52] and efforts to address polypharmacy are closely linked to research on whether or not frail older people realize the same benefits from adherence to these guidelines as younger populations of older people. At a health service level, polypharmacy may be measured as a quality indicator for interpretation at the local level to assist clinicians and policy makers identify possible areas for quality improvement.[53] When used as a quality indicator at the health service level, it should be recognized data on polypharmacy prevalence is unlikely to be able to account for an individual patient's clinical, diagnostic, and treatment situation.[54]

Polypharmacy is often ill-defined, and definitions vary across countries and settings.[2] Research should explore how polypharmacy is best defined in different settings, including differentiating between appropriate and inappropriate polypharmacy. In particular, investigation should be made into the rationale for using particular cut-offs to identify "at risk" patient groups for the purpose of better targeting clinical services.[55,56] It was recognized that the value of a particular "cut-off" for defining polypharmacy is likely to be dependent on the clinical context and patient group. For example, different polypharmacy "cut-offs" may be applied to whether patients are frail or not, or whether or not people reside in the community or residential care.

Polypharmacy should be recognized as a dynamic state impacted by the inclusion or exclusion of acute and as-needed medications.[57] Best practice methods must thus be applied when examining these trends over time. In addition, variability in the medications that contribute to polypharmacy in different settings and countries,[58] and whether prescribing of these medications is clinically appropriate, should be further explored.

Person-centered Practice and Research

Person-centered care may be defined as "providing care that is respectful and responsive to individual patient needs, preferences and values, and ensuring that patient values guide all clinical decisions."[59] Although such an approach to clinical practice has been associated with higher quality of care and improved patient outcomes,[60,61] a similar philosophy should be adopted when conducting research.

Research into geriatric pharmacotherapy should engage older people at all stages of the research process where possible—from study conception and design to interpretation and dissemination of key research findings. For example, stakeholder consultation and review of study protocols by older people or their representatives should occur prior to study commencement to identify potential barriers and facilitators to implementation.[62] Guidelines published by organizations such as the Alzheimer's Australia Consumer Dementia Research Network are particularly useful for guiding patient participation in research. The types of outcomes that are investigated as endpoints in research studies should be relevant and applicable to older people. This includes investigating clinical and humanistic outcomes that are important to older people such as QoL, pain, cognitive function, ability to undertake activities of daily living, mobility, and sleepiness. It was recognized that these "patient-centered outcomes" are not currently investigated in most clinical trials. Ways to effectively involve older people in geriatric pharmacotherapy research should be further explored.

Deprescribing and Regimen Simplification

Deprescribing has been defined as "the systematic process of identifying and discontinuing medications 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."[63] Regimen simplification refers to the process of "consolidating the number of administration times through strategies such as administering medications at the same time, standardizing routes of administration, using long-acting formulations in preference to shorter-acting agents, and switching from multiple single-ingredient preparations to a combination formulation where possible."[64] Unlike deprescribing, regimen simplification does not alter the therapeutic intent of a patient's medication regimen.

Although there is some evidence for the short-term clinical benefits of drug withdrawal,[65] further research is needed into the effects of continuation vs discontinuation of long-term medications.[66] For example, withdrawal of donepezil in people with moderate-to-severe Alzheimer's disease increased the risk of nursing home placement over a 12-month period.[67] Further studies can provide clinicians with better evidence to inform the possible need to deprescribe and in which situations it is best indicated. Research is underway into the possible benefits of regimen simplification for residents and aged-care provider organizations.[64] Given the uncertainties in this area, the deprescribing and medication regimen simplification processes should be flexible and individualized on patients' needs. Development of implicit tools to guide the deprescribing and regimen simplification process should assist.[68]

In addition, research into optimum treatment durations with long-term medications, and investigations into time-until-benefit and time-until-harm, is needed. Such research should also be placed in the context of specific clinical situations so that practical approaches can be developed and adopted. Deprescribing and regimen simplification strategies should aim to incorporate patient goals of care into decisions regarding initiation and discontinuation of medications.[69]

Research into the best mechanisms to promote and deliver education for patients, their family or caregivers and health professionals regarding the possible need to "deprescribe" medications for which the benefits no longer outweigh the risks should be conducted. Such research should explore the various barriers and facilitators to deprescribing and acknowledge that factors vary between patients, caregivers and health professionals.[70]

Methodological Development

The methodologies used in geriatric pharmacoepidemiology come with a unique set of challenges. Medication exposure can be defined in several ways and derived from different sources.[71] For example, medication exposure defined based on prescriptions, dispensing, or administration is likely to vary because of attrition and non-adherence.[72] Sensitivity analyses using different definitions of medication exposure when addressing the same outcome should be

undertaken and reported where relevant. Validation studies should be conducted to compare and contrast medication exposure defined using different methods, including prescription registers, pharmacy refill data, claims data, and participant self-report.[73–75]

Medication taking is often a dynamic process involving periods of differing doses, formulations, and use and nonuse of medications. This can make it difficult to identify true "new users" of medications, and also complicate the establishment of comparison groups of nonusers for pharmacoepidemiologic studies in older people. Where possible, longitudinal research should employ appropriate methods to take into account this time-varying nature of medication exposure. When this is not possible, the limitations of assessing medication use at single time points should be clearly acknowledged.

Other forms of bias and confounding should be addressed and handled with appropriate methods, including the use of particular study designs and analytic techniques.[71] For example, reverse causation should be taken into better account when conducting longitudinal studies, such as when prodromal symptoms of dementia and Parkinson disease prompt specific prescribing patterns (eg, initiation of an antidepressant or antipsychotic) that precede the diagnosis of these conditions.[76–78] Confounding by indication is another important limitation of geriatric pharmacoepidemiologic studies that can benefit from the employment of appropriate analytic methods.[71] For example, although a study of all people with Alzheimer's disease in Taiwan found that lithium use was associated with increased risk of dementia, this association disappeared when limiting to those with bipolar disorder, suggesting that the initial association may have been driven by confounding by indication.[79]

Collaboration between researchers in the basic and applied sciences should be encouraged to better understand the biological mechanisms underpinning the associations observed in pharmacoepidemiologic research. The importance of translational research, which integrates animal and human data, has been highlighted as a way of moving the field of geriatric pharmacotherapy research forward.[80]

Pharmacoepidemiologic studies in older people can help inform quality improvement interventions and drive sustained improvements in medication use. Key stakeholders, including policy makers, clinicians, healthcare organizations, and consumers and caregivers, should be engaged regarding the prescribing, dispensing, administering, and monitoring of medications to help inform research and facilitate uptake of findings into policy and practice.

Understanding Unexplained Variability in Prescribing and Medication Use

Variations exist in the way that medications are prescribed, dispensed, administered, and monitored within and between health services and patient groups. These differences may result from the interplay of socioeconomic, geographic, and cultural factors. For example, previous research has indicated that sex differences may exist in the way psychotropic medications are prescribed in people with Alzheimer's disease.[81] Research conducted using the Swedish Prescribed Drug Register has demonstrated that access to specialized prescribing of psychotropics is unequally distributed between socioeconomic groups,[27] and that more highly educated people are less likely to be prescribed antipsychotics in dementia.[82] A recent Finnish study found that long-term use of transdermal opioids was more than 2-fold among opioid users with Alzheimer's disease than among opioid users without Alzheimer's disease.[83] Research that explores these unexplained variations should be prioritized to determine whether these differences reflect potential health inequities. Unexplained variation in healthcare may reflect suboptimal practices and an opportunity to target prescribing interventions.[84]

Variations in medication use may also occur temporally, and may be reflective of changes in the patient, healthcare practitioner, or health system over time. Thus, longitudinal research into different medication use trajectories and the factors that influence these trajectories, such as patient life-course events or changes in diagnoses, prescribers, or practices, should be conducted. For example, it has been reported that after patients were placed on a multidose drug dispensing system, they had an increased number of drugs, more often potentially harmful drug treatment, and fewer changes in drug treatment.[85]

National and International Comparative Research

Conducting research that is comparative and translatable to other settings is needed. By doing so, generalizability of findings would be improved across countries and settings. For example, the Services and Health for Elderly in Long-Term Care (SHELTER) project collects data on residents admitted to 57 nursing homes in 8 countries to investigate a range of clinical questions.[86,87] It is proposed that observational studies be replicated across multiple settings, and employ multiple methodologies to validate and strengthen research findings. This includes validation in specific target populations, such as those who are frail or with cognitive impairment.

When conducting research, it is imperative that clear descriptions of the study setting and context are provided so that clinicians and researchers can better understand the generalizability of research findings. This can facilitate the way in which research findings are adopted into health policy and clinical practice. In addition, cross-national comparisons may allow for investigation of the impact of national legislation, therapeutic practices, and clinical guidelines that can potentially explain some of the differences that exist between countries. Reporting guidelines such as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) statements should be employed to ensure transparency.

Where possible, standard definitions should be used and data collected on core outcome measures in geriatrics and gerontology, such as for activities of daily living, QoL, and other variables. This can facilitate comparisons between studies and possible pooling of data in meta-analyses. When planning new research, researchers should explore the opportunity to use existing data to maximize prior investment in data collection and minimize burden to patients and possible wastage of resources.

Conclusions

Geriatric pharmacotherapy is understudied and treatment recommendations are often based on studies of younger, healthier populations. A range of research priorities were identified for the field of geriatric pharmacotherapy. Issues related to clinical care, health service delivery, research methodologies, and generalizability and application of findings were elucidated. Future studies should aim to address these current gaps and needs to improve medication and health outcomes in older people.

References

1. Charlesworth CJ, Smit E, Lee DS, et al. Polypharmacy among adults aged 65 years and older in the United States: 1988–2010. J Gerontol A Biol Sci Med Sci 2015;70:989–995.
2. Jokanovic N, Tan EC, Dooley MJ, et al. Prevalence and factors associated with polypharmacy in long-term care facilities: A systematic review. J Am Med Dir Assoc 2015;16:535.e1–535.e12.
3. Morin L, Laroche ML, Texier G, et al. Prevalence of potentially inappropriate medication use in older adults living in nursing homes: A systematic review. J Am Med Dir Assoc 2016;17:862.e1–862.e9.

4. Sluggett JK, Ilomaki J, Seaman KL, et al. Medication management policy, practice and research in Australian residential aged care: Current and future directions. Pharmacol Res 2017;116:20–28.
5. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther 2009;85:86–88.
6. Wimmer BC, Bell JS, Fastbom J, et al. Medication regimen complexity and number of medications as factors associated with unplanned hospitalizations in older people: A population-based cohort study. J Gerontol A Biol Sci Med Sci 2016;71:831–837.
7. Lalic S, Sluggett JK, Ilomaki J, et al. Polypharmacy and medication regimen complexity as risk factors for hospitalization among residents of long-term care facilities: A prospective cohort study. J Am Med Dir Assoc 2016;17:1067.e1–1067.e6.
8. Runciman WB, Roughead EE, Semple SJ, et al. Adverse drug events and medication errors in Australia. Int J Qual Health Care 2003;15:i49–i59.
9. Hilmer SN, Gnjidic D, Abernethy DR. Pharmacoepidemiology in the post-marketing assessment of the safety and efficacy of drugs in older adults. J Gerontol A Biol Sci Med Sci 2012;67:181–188.
10. Harvey N, Holmes CA. Nominal group technique: An effective method for obtaining group consensus. Int J Nurs Pract 2012;18:188–194.
11. Budnitz DS, Lovegrove MC, Shehab N, et al. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011;365:2002–2012.
12. Shehab N, Lovegrove MC, Geller AI, et al. US emergency department visits for outpatient adverse drug events, 2013–2014. JAMA 2016;316:2115–2125.
13. Hanlon JT, Semla TP, Schmader KE. Alternative medications for medications in the use of high-risk medications in the elderly and potentially harmful drug-disease interactions in the elderly quality measures. J Am Geriatr Soc 2015;63:e8–e18.
14. Wauters M, Elseviers M, Vaes B, et al. Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalization in a cohort of community-dwelling oldest old. Br J Clin Pharmacol 2016;82:1382–1392.
15. Meid AD, Quinzler R, Groll A, et al. Longitudinal evaluation of medication underuse in older outpatients and its association with quality of life. Eur J Clin Pharmacol 2016;72:877–885.
16. Veronese N, Stubbs B, Noale M, et al. Polypharmacy is associated with higher frailty risk in older people: An 8-year longitudinal cohort study. J Am Med Dir Assoc 2017;18:624–628.
17. Park H, Satoh H, Miki A, et al. Medications associated with falls in older people: Systematic review of publications from a recent 5-year period. Eur J Clin Pharmacol 2015;71:1429–1440.
18. Obermann KR, Morris JC, Roe CM. Exploration of 100 commonly used drugs and supplements on cognition in older adults. Alzheimers Dement 2013;9:724–732.
19. Lakhan P, Jones M, Wilson A, et al. A prospective cohort study of geriatric syndromes among older medical patients admitted to acute care hospitals. J Am Geriatr Soc 2011;59:2001–2008.
20. Wang HH, Sheu JT, Shyu YI, et al. Geriatric conditions as predictors of increased number of hospital admissions and hospital bed days over one year: Findings of a nationwide cohort of older adults from Taiwan. Arch Gerontol Geriatr 2014;59:169–174.
21. Buurman BM, Hoogerduijn JG, de Haan RJ, et al. Geriatric conditions in acutely hospitalized older patients: Prevalence and one-year survival and functional decline. PLoS One 2011;6:e26951.
22. Saraf AA, Petersen AW, Simmons SF, et al. Medications associated with geriatric syndromes and their prevalence in older hospitalized adults discharged to skilled nursing facilities. J Hosp Med 2016;11:694–700.
23. Wierenga PC, Buurman BM, Parlevliet JL, et al. Association between acute geriatric syndromes and medication-related hospital admissions. Drugs Aging 2012;29:691–699.
24. Koponen M, Taipale H, Lavikainen P, et al. Risk of mortality associated with antipsychotic monotherapy and polypharmacy among community-dwelling persons with Alzheimer's disease. J Alzheimers Dis 2017;56:107–118.
25. Taipale H, Koponen M, Tanskanen A, et al. Use of benzodiazepines and related drugs is associated with a risk of stroke among persons with Alzheimer's disease. Int Clin Psychopharmacol 2017;32:135–141.
26. Enache D, Fereshtehnejad SM, Kareholt I, et al. Antidepressants and mortality risk in a dementia cohort: Data from SveDem, the Swedish Dementia Registry. Acta Psychiatr Scand 2016;134:430–440.
27. Wastesson JW, Fastbom J, Ringback Weitoft G, et al. Socioeconomic inequalities in access to specialized psychotropic prescribing among older Swedes: A register-based study. Eur J Public Health 2014;24:991–996.
28. Leendertse AJ, van Dijk EA, De Smet PA, et al. Contribution of renal impairment to potentially preventable medication-related hospital admissions. Ann Pharmacother 2012;46:625–633.
29. Bell JS, Blacker N, Leblanc VT, et al. Prescribing for older people with chronic renal impairment. Aust Fam Physician 2013;42:24–28.
30. Elliott RA, Goeman D, Beanland C, et al. Ability of older people with dementia or cognitive impairment to manage medicine regimens: A narrative review. Curr Clin Pharmacol 2015;10:213–221.
31. Morin L, Vetrano DL, Rizzuto D, et al. Choosing wisely? Measuring the burden of medications in older adults near the end of life: Nationwide, Longitudinal Cohort Study. Am J Med 2017;130:927–936.e9.
32. Maclagan LC, Maxwell CJ, Gandhi S, et al. Frailty and potentially inappropriate medication use at nursing home transition. J Am Geriatr Soc 2017;65:2205–2212.
33. Herr M, Sirven N, Grondin H, et al. Frailty, polypharmacy, and potentially inappropriate medications in old people: Findings in a representative sample of the French population. Eur J Clin Pharmacol 2017;73:1165–1172.
34. Saum KU, Schottker B, Meid AD, et al. Is polypharmacy associated with frailty in older people? Results From the ESTHER Cohort Study. J Am Geriatr Soc 2017;65:e27–e32.
35. Chudiak A, Jankowska-Polanska B, Uchmanowicz I. Effect of frailty syndrome on treatment compliance in older hypertensive patients. Clin Interv Aging 2017;12:805–814.
36. de Groot MH, van Campen JPCM, Kosse NM, et al. The association of medication-use and frailty-related factors with gait performance in older oatients. PLoS One 2016;11:e0149888.
37. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: An investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med 2015;13:78.
38. National Institute for Health and Care Excellence. Multimorbidity and polypharmacy 2017, https://www.nice.org.uk/guidance/ktt18/resources/multimorbidity-and-polypharmacy-pdf-58757959453381. Accessed January 7, 2018.
39. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. BMJ 2015;350:h1059.
40. Wyatt KD, Stuart LM, Brito JP, et al. Out of context: Clinical practice guidelines and patients with multiple chronic conditions: A systematic review. Med Care 2014;52:S92–S100.
41. Smith SM, Wallace E, O'Dowd T, et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev 2016;3:CD006560.
42. Asahina Y, Sugano H, Sugiyama E, et al. Representation of older patients in clinical trials for drug approval in Japan. J Nutr Health Aging 2014;18:520–523.
43. Fanning L, Ilomaki J, Bell JS, et al. The representativeness of direct oral anticoagulant clinical trials to hospitalized patients with atrial fibrillation. Eur J Clin Pharmacol 2017;73:1427–1436.
44. Leinonen A, Koponen M, Hartikainen S. Systematic review: Representativeness of participants in RCTs of acetylcholinesterase inhibitors. PLoS One 2015;10:e0124500.
45. Tinetti ME, McAvay G, Trentalange M, et al. Association between guideline recommended drugs and death in older adults with multiple chronic conditions: Population-based cohort study. BMJ 2015;351:h4984.
46. Cerreta F, Bowen D. European Medicines Agency (EMA): Regulatory Perspectives on Geriatric Medicines. In: Stegemann S, editor. Developing Drug Products in an Aging Society: From Concept to Prescribing. Cham, Switzerland: Springer International Publishing; 2016.
47. U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry: E7 studies in support of special populations: Geriatrics. Maryland: FDA; 2012.
48. 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;62:2261–2272.
49. Wise J. Polypharmacy: A necessary evil. BMJ 2013;347:f7033.
50. Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation. Making it safe and sound. London: The Kings Fund; 2013.
51. Payne RA, Abel GA, Aver AJ, et al. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol 2014;77:1073–1082.
52. Jokanovic N, Tan EC, Dooley MJ, et al. Why is polypharmacy increasing in aged care facilities? The views of Australian health care professionals. J Eval Clin Pract 2016;22:677–682.
53. Australian Government Department of Health. Ageing and aged care—Quality indicators, https://agedcare.health.gov.au/ensuring-quality/quality-indicators-for-aged-care; 2017. Accessed January 7, 2018.
54. Scobie S, Thomson R, McNeil JJ, et al. Measurement of the safety and quality of health care. Med J Aust 2006;184:S51–S55.
55. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol 2012;65:989–995.
56. Turner JP, Jamsen KM, Shakib S, et al. Polypharmacy cut-points in older people with cancer: How many medications are too many? Support Care Cancer 2016;24:1831–1840.
57. Wastesson JW, Oksuzyan A, von Bornemann Hjelmborg J, et al. Changes in drug use and polypharmacy after the age of 90: A longitudinal study of the Danish 1905 cohort. J Am Geriatr Soc 2017;65:160–164.
58. Beloosesky Y, Nenaydenko O, Gross Nevo RF, et al. Rates, variability, and associated factors of polypharmacy in nursing home patients. Clin Interv Aging 2013;8:1585–1590.
59. Institute of Medicine Committee on Quality of Health Care in, A. In: Crossing the Quality Chasm: A New Health System for the 21st Century. Washington (DC): National Academies Press; 2001.
60. McMillan SS, Kendall E, Sav A, et al. Patient-centered approaches to health care: A systematic review of randomized controlled trials. Med Care Res Rev 2013;70:567–596.
61. Fors A, Swedberg K, Ulin K, et al. Effects of person-centred care after an event of acute coronary syndrome: Two-year follow-up of a randomised controlled trial. Int J Cardiol 2017;249:42–47.

62. Alzheimer's Australia. Consumer Involvement in Dementia Research: Alzheimer's Australia's Consumer Dementia Research Network, https://www.dementia.org.au/files/20100906-NAT-NP-Alzheimers-Australia-Consumer-Involvement-in-Dementia-Research-Paper-22-final.pdf; 2010. Accessed November 29, 2017.
63. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Intern Med 2015;175:827–834.
64. Sluggett JK, Chen EYH, Ilomäki J, et al. SImplification of Medications Prescribed to Long tErm care Residents (SIMPLER): study Protocol for a cluster randomised controlled trial. Trials 2018;19:37.
65. Iyer S, Naganathan V, McLachlan AJ, et al. Medication withdrawal trials in people aged 65 years and older: A systematic review. Drugs Aging 2008;25:1021–1031.
66. Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: A randomized clinical trial. JAMA Intern Med 2015;175:691–700.
67. Howard R, McShane R, Lindesay J, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: Secondary and post-hoc analyses. Lancet Neurol 2015;14:1171–1181.
68. Chen EY, Sluggett JK, Ilomäki J, et al. Development and validation of the Medication Regimen Simplification Guide in Residential Aged Care (MRS GRACE)'. Melbourne: Australian Dementia Forum; 2017.
69. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through shared decision making. BMJ (Clinical research ed) 2016;353:i2893.
70. Turner JP, Edwards S, Stanners M, et al. What factors are important for deprescribing in Australian long-term care facilities? Perspectives of residents and health professionals. BMJ Open 2016;6:e009781.
71. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 6). EMA/95098/2010. Available at: http://www.encepp.eu/standards_and_guidances. Accessed January 7, 2018.
72. Pottegard A, Christensen R, Houji A, et al. Primary nonadherence in general practice: A Danish register study. Eur J Clin Pharmacol 2014;70:757–763.
73. Taipale H, Tanskanen A, Koponen M, et al. Agreement between PRE2DUP register data modeling method and comprehensive drug use interview among older persons. Clin Epidemiol 2016;8:363–371.
74. Rikala M, Hartikainen S, Sulkava R, et al. Validity of the Finnish Prescription Register for measuring psychotropic drug exposures among elderly finns: A population-based intervention study. Drugs Aging 2010;27:337–349.
75. Tanskanen A, Taipale H, Koponen M, et al. Drug exposure in register-based research-An expert-opinion based evaluation of methods. PLoS One 2017;12:e0184070.
76. Power MC, Weuve J, Sharrett AR, et al. Statins, cognition, and dementia-systematic review and methodological commentary. Nat Rev Neurol 2015;11:220–229.
77. Koponen M, Tolppanen AM, Taipale H, et al. Incidence of antipsychotic use in relation to diagnosis of Alzheimer's disease among community-dwelling persons. Br J Psychiatry 2015;207:444–449.
78. Puranen A, Taipale H, Koponen M, et al. Incidence of antidepressant use in community-dwelling persons with and without Alzheimer's disease: 13-year follow-up. Int J Geriatr Psychiatry 2017;32:94–101.
79. Cheng C, Zandi P, Stuart E, et al. Association between lithium use and risk of Alzheimer's Disease. J Clin Psychiatry 2017;78:e139–e145.
80. Johnell K. The polypharmacy mouse model: Novel findings and new opportunities. J Gerontol A Biol Sci Med Sci 2016;71:569–570.
81. Moga DC, Taipale H, Tolppanen AM, et al. A comparison of sex differences in psychotropic medication use in older people with Alzheimer's disease in the US and Finland. Drugs Aging 2017;34:55–65.
82. Wastesson JW, Ringback Weitoft G, Johnell K. Educational disparities in antipsychotic drug use among older people with and without dementia in Sweden. Acta Psychiatr Scand 2015;132:20–28.
83. Hamina A, Taipale H, Tanskanen A, et al. Long-term use of opioids for nonmalignant pain among community-dwelling persons with and without Alzheimer disease in Finland: A nationwide register-based study. Pain 2017;158:252–260.
84. Bachmann CJ, Aagaard L, Bernardo M, et al. International trends in clozapine use: A study in 17 countries. Acta Psychiatr Scand 2017;136:37–51.
85. Wallerstedt SM, Fastbom J, Johnell K, et al. Drug treatment in older people before and after the transition to a multi-dose drug dispensing system—A longitudinal analysis. PLoS One 2013;8:e67088.
86. Vetrano DL, Tosato M, Colloca G, et al. Polypharmacy in nursing home residents with severe cognitive impairment: Rresults from the SHELTER Study. Alzheimers Dement 2013;9:587–593.
87. Onder G, Liperoti R, Foebel A, et al. Polypharmacy and mortality among nursing home residents with advanced cognitive impairment: Results from the SHELTER study. J Am Med Dir Assoc 2013;14:450.e7–450.12.