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Pills and Ills: Methodologic Issues in Pharmacologic Research

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To The Editor: Medications are the most frequently used form of therapy employed in the care of older adults. Unfortunately, the frequent exclusion of these patients from premarketing clinical trials of new medications has limited our knowledge regarding the safety and efficacy of individual medications in our aging population.¹ Moreover, the most

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common chronic condition that older adults experience is multimorbidity, with two of every three older adults having multiple chronic conditions. Multiple chronic conditions account for 66% of the country's overall health expenditures and more than 95% of Medicare expenditures.² Therefore, it is critical to understand the risks and benefits of medications in the presence of multimorbidity.

Despite this, a recent study showed that of 190 clinical trials that explicitly considered multiple chronic conditions in the selection process, 94% excluded older patients – i.e., the very patients who have the most to benefit from therapy and in whom we know the least about medication safety.³ Because of this gap, the role of observational data and pharmacoepidemiologic research in older adults is critical. In this letter, we summarize key points from a Methodology Workshop of the same title presented at the 2013 American Geriatrics Society Annual Scientific Meeting.

MEASURING MEDICATION ERRORS

As noted in the Institute of Medicine 2007 report, a medication error can be defined as “any error occurring in the medication-use process.”⁴ Two of the most important medication errors in older adults are potentially inappropriate medication use and medication non-adherence.

Potentially inappropriate medication use

Potentially inappropriate medication use can be measured by two approaches – implicit or explicit criteria. The most common implicit approach is using the Medication Appropriateness Index, which has been previously described.⁵ It has been shown to have good reliability and predictive validity with important outcomes, including adverse drug events ([ADEs] defined as injury due to a drug), in numerous studies.⁵

The other approach to measuring potentially inappropriate medication use is with explicit criteria. The most common explicit approach is using the Beers criteria in the US or STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria in Europe.^{6,7} Advantages of this approach include the fact that explicit criteria do not require a medical record review by a skilled practitioner, and they can be measured on large populations. The main disadvantage is that they require continuous updating based on new evidence. Future work is needed to further elucidate the association between these explicit criteria and important health outcomes in older adults.

Medication adherence

Medication adherence can be measured using a variety of methods. The two most common ways are via self-report and pharmacy claims. Self-reported methods of medication non-adherence offer advantages in that they are inexpensive, easy-to-administer, and capture actual patient medication-taking behavior and/or beliefs. The main potential disadvantage of self-reported methods is social desirability bias (i.e., some patients report what they think the prescriber wants to hear rather than their actual medication-taking behavior). For pharmacy claims-based adherence, researchers and health systems are able to measure and monitor adherence on large groups of patients (population-level estimates) using objective

methods.⁸ However, pharmacy claims are inherently limited by the use of multiple pharmacies or health plans over time, the fact that medication-filling does not equal medication-taking, and the wide variety of definitions used in the literature.⁸ For example, different studies use various operational definitions for claims-based medication adherence, including the Medication Possession Ratio (MPR), the Proportion of Days Covered (PDC), and the Cumulative Medication Gap (CMG), among others. In addition, some studies assess primary non-adherence (i.e., when a drug is prescribed but the patient fails to pick up the prescription from the pharmacy) and medication persistence (i.e., the duration of time from initiation to discontinuation of therapy).⁹ Despite these limitations, pharmacy claims-based measures of medication adherence are becoming increasingly important in health policy initiatives, including the CMS 5-Star Ratings. In addition, the International Society of Pharmacoeconomics and Outcomes Research has published a checklist to be considered when conducting pharmacy claims-based adherence research.¹⁰ Future research is needed to examine more sophisticated approaches to understanding and measuring medication adherence to complex medication regimens. Taken together, potentially inappropriate medication use and medication non-adherence represent two of the highest priority areas in geriatric pharmacoepidemiological research.

CONCLUSION

Pharmacoepidemiologic research continues to have a vital role in advancing our understanding of the medication use process in older adults given their frequent exclusion from clinical trials. Potentially inappropriate medication use and medication adherence are two components of the medication use process needing the greatest attention from clinical and health policy perspectives.

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REFERENCES

1. Gurwitz JH. The Exclusion of Older People from Participation in Cardiovascular Trials. *AMA J Ethics*. 2014; 16:365–368.
2. Tinetti ME, McAvay GJ, Chang SS, et al. Contribution of multiple chronic conditions to universal health outcomes. *J Am Geriatr Soc*. 2011; 59:1686–1691. [PubMed: 21883118]
3. Jadad AR, To MJ, Emara M, et al. Consideration of multiple chronic diseases in randomized controlled trials. *JAMA*. 2011; 306:2670–2672. [PubMed: 22203536]
4. Institute of Medicine. Preventing Medication Errors. Washington, DC: National Academies Press; 2007.
5. Hanlon JT, Schmader KE. The Medication Appropriateness Index at 20: where it started, where it has been and where it may be going. *Drugs Aging*. 2013; 30:893–900. [PubMed: 24062215]

6. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. AGS Updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012; 60:616–631. [PubMed: 22376048]
7. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther.* 2008; 46:72–83. [PubMed: 18218287]
8. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health.* 2008; 11:44–47. [PubMed: 18237359]
9. Fischer MA, Stedman MR, Lii J, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *J Gen Intern Med.* 2010; 25:284–290. [PubMed: 20131023]
10. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health.* 2007; 10:3–12. [PubMed: 17261111]