Published in final edited form as:
J Am Geriatr Soc. 2013 August ; 61(8): . doi:10.1111/jgs.12354.

Update of Studies on Drug-Related Problems in Older Adults

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Medications, when used correctly in older adults, can maintain or improve quality of life. Unfortunately, medications are commonly used incorrectly in older adults, resulting in medication errors, adverse drug events (ADEs), poor quality of life, and mortality. To provide optimal care for older adults, it is necessary to keep abreast of the current literature on drug-related problems. The literature on drug-related problems is challenging to search and discover because these problems do not fit under discrete, easily searchable terms, as specific diseases do. To aid in the task of staying up to date on drug-related problems in older adults, in 2000, a summary of the recent literature was published using multiple techniques to find the most important articles.[1] For the next decade, the editors of the *American Journal of Geriatric Pharmacotherapy* (JTH, KES) continued to publish a

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Drs. Schmader and Semla both wrote an annotation and critique of a study, critically reviewed a draft of the manuscript, and approved the final version. Dr. Hanlon assembled the articles for inclusion in this review and for the Appendix; wrote the first draft of the Introduction, Methods, and Conclusion sections; wrote an annotation and critique of an article; and edited and submitted the final agreed upon version.

summary of this literature each year. Because the last issue of that journal was published in December 2012, the editor of the *Journal of the American Geriatrics Society* has generously agreed to continue this tradition and publish this popular review. We hope that you enjoy it.

METHODS

A search of Medline and Google Scholar restricted to 2012 was conducted on a combination of the terms elderly, aged, drug-related problems, medication related problems, medication errors, suboptimal prescribing, inappropriate prescribing, underutilization, polypharmacy, medication monitoring, medication dispensing, medication administration, medication adherence, adverse drug events, and adverse drug withdrawal events. Preference was given to studies that used rigorous observational or experimental study designs and reliable, valid measures. A manual search for relevant articles from the *New England Journal of Medicine; Annals of Internal Medicine; JAMA; Journal of Gerontology: Medical Sciences, Clinical Pharmacology and Therapeutics*; and *Annals of Pharmacotherapy* was also conducted. Additional articles that the authors identified were also considered. Studies published in the *American Journal of Geriatric Pharmacotherapy, Consultant Pharmacist, Drugs and Aging*, and the *Journal of the American Geriatrics Society* were excluded because they are obvious places for readers to look for relevant articles.

RESULTS

A total of 40 articles were identified and selected (see online Appendix 1). There were 24 selected articles regarding medication errors, with the majority on the topic of suboptimal prescribing, and 18 articles on ADEs, with the majority addressing adverse drug reactions. Three of these articles were thought to be particularly important and are described and critiqued below.[2–4]

Clinical practice guidelines, implicit and explicit criteria, and quality indicators are tools developed to assist healthcare professionals, administrators, and researchers in providing or measuring the use of recognized standards of care. The highest tier of this standard is evidence based, but the evidence is not always clear or complete. Regardless of the volume or quality of the evidence, a consensus is desired by healthcare providers, administrators and researchers on how it is to be applied to patient care. A method to reach consensus known as the Delphi technique has been employed to develop a number of criteria on prescribing for older adults. With this as a background, a critical analysis of 14 sets of criteria on appropriate prescribing for elderly adults was recently published.[2] The authors critique was organized into three domains: review of the scientific literature, formulation of the criteria, and criteria evaluation. Of the 14 sets of criteria identified, none provided strength-of-evidence ratings for the literature reviewed or used to develop or support the criteria, and only a few provided references for the recommendations. Only three of the 14 sets of criteria provided a rational for using the Delphi technique to formulate the criteria. The authors also were concerned about the lack of transparency as to whether the formulation of the explicit criteria sets was based upon a consensus on the scientific literature, expert opinion, or both. The lack of information about panel members' potential conflict of interests was also mentioned. Regarding evaluation, only one set of criteria (Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START)) formally tested interrater reliability. Articles that validated theses sets of criteria were also summarized. Most published studies have applied the various versions of the explicit Beers criteria to determine its predictive validity with health outcomes. They conclude the review by stating that, because of concerns raise above, "widespread use of most criteria may not be justified."

This article is important because it specifies steps that are necessary before it is appropriate to use explicit criteria for potentially inappropriate criteria for judging quality of care in elderly adults.[2] One step the authors did not discuss was identifying the drugs or drug-related problems to be considered for inclusion and literature search terms. Searching the literature and formulating criteria are not mutually independent, and both have to be revised and repeated before criteria are ready to be rated by a panel of experts. The importance of interrater reliability was perhaps overstated because applying explicit criteria to computerized health administration data is expected to have high agreement, whereas applying explicit criteria that require an evaluation of individual patient characteristics might have lower agreement between different raters. Finally, it would have been helpful to state that perhaps the most important health outcome to be measured in predictive validity testing is adverse drug events. The STOPP/START criteria were found to be associated with ADEs in only one study, whereas the Beers criteria have been tested in more than a half a dozen studies, with mixed results. This review was published before the publication of the 2012 American Geriatrics Society Beers criteria, which should fare well and avoid many of the faults of their predecessors.[5] First, each criterion is evidence based, with the quality and strength of the evidence provided along with evidence tables. Second, panelists provided conflict of interest statements. Third, as in previous versions, a modified Delphi technique was used requiring each panelist to rate each proposed criterion independently before full panel discussion for clarification and reaching consensus (unanimous). Finally, in accordance with the Institute of Medicine 2001 report, the draft criteria were available for public comment before being finalized.[6]

In summary, the article[2] reminds those who develop criteria and those who use them for patient care or as a quality indicator of the limitations in their development. Although efforts to establish internal validity are needed, this will continue to be challenging given limited research funding and the constant changes in practice based on new evidence.

Investigations of drug-related hospitalizations in older adults usually focus on adverse drug reactions, but therapeutic failures (a failure to accomplish the goals of treatment resulting from inadequate or inappropriate drug therapy and not related to the natural progression of disease) and adverse drug withdrawal events (a clinical set of symptoms or signs related to removal of a drug) are important but less-studied causes of drug-related hospitalizations. This study aimed to describe the prevalence of any and potentially preventable unplanned hospitalizations caused by therapeutic failure and adverse drug withdrawal events in a nationally representative sample of older adults and to examine the factors associated with these events.[3]

The investigators employed a retrospective cohort design using data from all Veterans Affairs (VA) Medical Centers (VAMCs) nationwide. The authors randomly selected 1,000 hospitalizations of veterans who received regular outpatient care and were hospitalized at a VAMC at least once between December 1, 2003, and November 9, 2006 (n=328,166). From the 1,000 hospitalizations, the study included only individuals hospitalized directly from an ambulatory care setting for an unplanned hospital admission (N=678). Comprehensive clinical data were collected from the VA electronic health record. Using these data, paired pharmacist reviewers applied the Therapeutic Failure Questionnaire and Naranjo Adverse Drug Withdrawal Event algorithm to determine the main outcomes of hospitalizations caused by therapeutic failure and adverse drug withdrawal events.[7,8] The reviewers also assessed preventability (e.g., medication error) of the hospital admissions. Interrater reliability for therapeutic failure and adverse drug withdrawal events and preventability was adequate (kappa statistic = 0.81 and 0.73, respectively). Discordances were resolved by consensus with a separate clinical pharmacist and a geriatrician. The study population had a mean age of 76 and was 98.5% male and 75.5% white, and 44.8% took nine or more

medications. The results showed that therapeutic failure (n = 34) caused 5% of hospitalizations and that adverse drug withdrawal events (n = 8) caused 1%. The hospitalizations involved 54 drugs. (More than one drug was involved in causing the hospitalization in some instances.) Of these admissions, 90% (36/40) were rated as potentially preventable, mostly because of medication nonadherence and suboptimal prescribing. The most common events involving therapeutic failure were heart failure exacerbations, coronary heart disease symptoms, tachyarrhythmias, and chronic obstructive pulmonary disease exacerbations. Multivariable logistic regression modeling indicated that black veterans (adjusted odds ratio=2.92, 95% confidence interval=1.25–6.80) were significantly more likely to experience a therapeutic failure-related admission than white veterans.

This study is valuable because it is a reminder of the importance of therapeutic failure and adverse drug withdrawal events as a cause of hospitalizations in older adults, in addition to adverse drug reactions. The study adds to the small literature in this area by use of reliable and valid algorithms to detect these events and their potential preventability concurrently in a nationally representative sample of older veterans. Medication nonadherence and suboptimal prescribing were the main reasons for the therapeutic failures and adverse drug withdrawal events. If anything, the figures in the study are an underestimate because electronic health records may miss key data related to adherence or other clinical variables, therapeutic failures and adverse drug withdrawal event-related hospitalizations that occurred outside the VA healthcare system were not captured, and objective measures of medication nonadherence were not available. The generalizability of the study is limited to male veterans. Although the study results may differ in magnitude in non-VA populations, these problems exist in any healthcare system. Furthermore, hospitalizations related to therapeutic failures are another example of healthcare disparity between black and white individuals. [9]

Future quality improvement efforts, research investigations, and clinical demonstration programs should pay attention to improving underuse of evidence-based pharmacotherapy equal to what has been given to reducing potentially inappropriate medications in older adults. The study is a reminder of the considerable challenges of finding the “sweet spot” for optimal drug prescribing in which harmful or useless drugs are avoided while employing truly beneficial ones.

Polypharmacy, or multiple drug use, is a major quality-of-care concern for older adults, as a recent issue of clinics of geriatric medicine devoted to the topic evidences.[10] Recently, the Cochrane Collaboration released a review entitled “Interventions to Improve the Appropriate Use of Polypharmacy for Older Adults.” [4] Polypharmacy was defined as the administration of more medicines than are clinically indicated, representing unnecessary use. Thus this definition includes problems with inappropriate prescribing and underprescribing. A comprehensive review of the literature, using a standardized approach, was conducted to identify studies of controlled trials and quasi-experimental design. Data were extracted from studies of older patients (≥65) taking four or more medications. Studies focusing on single diseases or short-term polypharmacy were excluded. Primary outcome measures were inappropriate prescribing, underprescribing, and hospital admissions. Secondary outcome measures included adverse drug events, medication errors other than prescribing, and quality of life as measured by a valid instrument. Two authors independently screened titles and abstracts of studies identified in the literature search, and three authors extracted data from the studies, including those data supplied directly from the first authors. Overall, 2,657 citations were identified, from which 10 studies were included. Data from more than 21,000 individuals were included. The mean age of the participants was nearly 75. Five studies focused on older adults in the community, three on nursing home care, one on hospital care, and one on hospitalized older adults transitioning from the

hospital to a nursing home. Nine studies used pharmaceutical care interventions, and one used a computerized decision support intervention. The data from five studies that used a structured implicit method to assess inappropriate prescribing quality including polypharmacy (the Medication Appropriateness Index (MAI)) were pooled for a meta-analysis that found on average nearly 4-point greater improvement in the MAI summated score in intervention than control patients. Two studies' data were pooled for inappropriate prescribing as measured using the Beers explicit criteria, and the meta-analysis revealed on average a 0.10 greater reduction in potentially inappropriate medications in intervention than in control patients. Four studies measured hospitalization, three measured ADEs, one measured medication adherence, two measured underprescribing, and two included health-related quality of life as measured using the Medical Outcomes Study 36-item Short-Form Survey. Meta-analyses of these primary or secondary outcome measures were not possible for a variety of reasons. In summary, although the interventions in these studies were mostly successful in improving the quality of prescribing, the effect on clinically important outcomes and patient-centered outcomes is unclear.

This Cochrane review improved upon previous publications that summarized this literature on optimal medication use and associated health outcomes by collecting raw data from study authors and conducting meta- analyses when possible. However, the use of the word "polypharmacy" in the title of this publication appears to be a misnomer because the effect of interventions on the use of multiple necessary drugs or any unnecessary drugs was not evaluated. This may have led to the omission of a number of studies focused on these outcome measures. For example a recent review identified at least two additional eligible studies that the literature search did not pick up.[11] Another review identified at least one additional eligible study published after the March 2011 cutoff for this Cochrane review.[12] This further emphasizes the comment above regarding how challenging the literature on drug-related problems is to search. It is also not clear why data from nonrandomized controlled trials were included because this is not customary for clinical drug trials. Moreover, one study was included that focused on a single disease (heart failure), which a priori was deemed as an exclusion criteria. Finally, future efforts should categorize process measure as secondary outcomes (e.g., medication errors) and have primary outcomes focused on health outcomes (e.g., ADEs). This will probably require multicenter studies with large samples to have sufficient power. Health outcomes such as hospitalizations, health-related quality of life, and death are unsuitable for being primary outcomes given that they are caused by multifactorial factors and are probably affected only in part by reducing medication errors.

CONCLUSIONS

These studies highlight that medication errors and ADEs continue to be important concerns for healthcare professionals caring for older adults. In addition to the need for future research in this area, more attention to educating healthcare professionals still in training about these important concerns should be considered.[13]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Semla serves on the Omnicare Pharmacy and Therapeutics Committee (long-term care). He is an author and editor for LexiComp, Inc; his spouse is an employee of Abbott Labs.

Dr. Hanlon is supported by Agency for Healthcare Research and Quality Grants R01 HS018721, and K12 HS019461 and National Institute of Aging Grants P30AG024827, T32 AG021885, K07AG033174, R01AG027017, and R01 AG037451.

Sponsor's Role: This manuscript was not sponsored by any entity.

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