COMMENTARY

Adverse Drug Events in the Elderly: An Ongoing Problem

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By the year 2030, nearly 1 in 5 U.S. residents is expected to be aged 65 years or older; this age group is projected to more than double in number from 38.7 million in 2008 to more than 88.5 million in 2050.[1,2] Likewise, the population aged 85 years or older is expected to increase almost 4-fold, from 5.4 million to 19 million between 2008 and 2050.[1] As the elderly population continues to grow, the number of older adults who present with multiple medical conditions for which several medications are prescribed continues to increase, resulting in polypharmacy.

In a manuscript that we reviewed recently for possible publication in *JMCP*, the authors examined the prevalence of concomitant drug-drug interactions (DDIs) and potentially inappropriate medications (PIMs) in 6 health plans and concluded that 2 factors, polypharmacy and polyprescribers, appear to be strongly associated with the increased exposure of elderly patients to DDIs and PIMs.

Polypharmacy can be appropriate when multiple drug regimens are necessary for the treatment of conditions and are carefully monitored by clinicians for achieving a therapeutic goal and for drug-related problems. Illnesses such as cardiovascular disease, arthritis, gastrointestinal disorders, and bladder dysfunction are common in the elderly. A patient who has congestive heart failure requires multiple agents such as digoxin, a diuretic, and angiotensin-converting enzyme (ACE) inhibitor for management. Even with specialized attention, balancing the multiple medications and their potential related side effects can be challenging for clinicians and patients. The key question is how to address the overall care needs of these patients, while ensuring appropriate medication use. In this commentary, we review "best practices" used at Kaiser Permanente (KP) to address these challenges, and address specific concerns about the implications of research into potentially inappropriate drug use in the elderly for routine care.

Multidisciplinary Approach to Promotion of Appropriate Medication Use

KP, through its Care Management Institute and interregional pharmacy program, has developed initiatives to address inappropriate use of medications in the elderly. KP's interregional "High Risk Medications in the Elderly" focus group, composed of clinicians, pharmacists and senior care program managers from KP regions across the country, meets regularly via teleconference. Meetings include discussions of best practices and review of monthly data on use of specific high-risk medications. These discussions inform the development, implementation, or retooling of strategies to reduce the utilization of high-risk medications. KP regions use a variety of provider education strategies, including formal continuing medical education (CME) programs, pocket cards listing high-risk medications, messaging in the electronic medical record suggesting therapeutic alternatives to high-risk medications, focused therapeutic interchange initiatives, and dissemination of "frequently asked questions" documents. These tools are designed to explain, teach, and reinforce the message that many drugs adversely affect older patients by leading to falls, fractures, and functional and cognitive decline, and sometimes to unnecessary and costly hospitalizations and nursing home placements.

For example, recent attention at KP has focused on suggesting safer alternatives to skeletal muscle relaxants and long-acting benzodiazepines. Educational presentations to practitioners include suggestions for safer medications, as well as nonpharmacologic interventions, in treating musculoskeletal pain. Another initiative provided education about alternatives to antihistamines such as diphenhydramine, hydroxyzine, and promethazine. Specific recommendations were made regarding alternatives (based on the indication, such as sleep or cough) including nonpharmacologic treatment strategies as appropriate.

KP regions have programs devoted to caring for patients who are older, frail, or have multiple chronic conditions. Many such programs include the opportunity for a clinical pharmacy specialist to participate in evaluating and reconciling those patients' medications, especially during transitions in care settings such as from hospital to home.

In KP of Georgia, one such program includes an interdisciplinary team consisting of a geriatrician, nurse care manager, nurse, and clinical pharmacy specialist. The team evaluates and treats older patients identified as high risk through predictive modeling based upon chronic medical conditions and other factors. Much of the work is conducted telephonically, using the electronic health record to document and communicate recommendations to the patients and their treating physicians. In many cases, the clinical pharmacist works closely with the patient's primary care physician (PCP) to implement changes under the PCP's supervision. The team thoroughly evaluates overall functional and health status, including review of all prescribed and over-the-counter medications and supplements, and makes recommendations for changes to optimize regimens and patient safety. Annual program evaluation includes measurement of number of program enrollees identified as having been prescribed medications on the Healthcare Effectiveness Data and Information Set (HEDIS) high risk list, and whether the team recommended/made changes to the regimen. New tools are being developed to enhance the team's effectiveness in addressing this issue.

Are "Medications to be Avoided" Really Avoidable?

All medications have some risk of causing adverse effects. However, medications can increase survival and enhance quality of life and are therefore widely used and highly valued therapies for acute and chronic diseases in older patients.[3] Based on data from the Medical Expenditure Panel Survey, 91.5% of adults aged 65 years or older in 2005 had at least 1 chronic condition, and 96.5% of prescription medication expenditures were attributable to those with at least 1 chronic condition; more than one-half the medical expense of this group was associated with treatment of chronic conditions.[4]

Polypharmacy is often appropriate, but the number of medications along with the physiologic changes associated with aging can increase the prospect of adverse drug reactions and serious drug-drug interactions. Adverse drug events (ADEs) are a major problem in the elderly, contributing to drug-related morbidity and mortality at an estimated annual cost of $76.6 billion in the ambulatory setting in the United States in 1995.[5] The addition of each new drug to a treatment regimen increases the risk of an adverse drug event. For instance, in an ambulatory care setting in 2003, Gandhi et al. determined that the mean number of ADEs per patient increased by 10% (95 percent confidence interval [CI] = 6%-15%) for each additional medication.[6] The manifestation of adverse effects in elderly patients may not be obvious because the effects can be similar to problems frequently experienced by elderly persons, such as increased frequency of falls, excessive sedation, increased confusion, urinary retention, decreased oral intake, or a general failure to thrive. These manifestations, when not recognized as drug-related, can result in the physician's prescribing another medication to mitigate the ADE.[7]

In the manuscript that we reviewed for *JMCP*, the authors examined the prevalence of same-year DDIs and PIMs according to the Beers criteria in a sample of elderly Medicare Part D beneficiaries. The Beers list is a validated screening tool used to determine the potential risk of adverse events associated with prescribing PIMs in the elderly.[8-10] In 1991, Beers et al. published criteria to assess medications that were inappropriate for use in nursing home residents.[8] The list, which was derived by consensus opinion on prescribing indicators from a panel of 13 experts, consisted of 19 medications/classes to be avoided in nursing home residents, such as antihypertensives, psychotropics, oral hypoglycemic agents, nonsteroidal anti-inflammatory drugs and analgesics regardless of diagnosis, dose and dosing frequency.[8]

In 1997, based on the consensus opinion of a panel of 6 experts, Beers published a revised set of criteria for potentially inappropriate drug use associated with 28 medications/classes to avoid in ambulatory people aged 65 years or older regardless of their place of residence (community or nursing home).[9] In 2001, Zhan et al. utilized an expert panel to classify the Beers criteria drugs into 3 categories: (a) drugs that should always be avoided in older adults, (b) drugs that may be appropriate in rare circumstances, and (c) drugs that have some indications for use in the elderly population but "are often misused."[10] Subsequently, in 2003, Fick et al. published another revised list that identified 48 drugs/classes and 20 drug-disease combinations to avoid in older adults.[11]

Even though the Beers criteria have evolved over the years, we question the use of the Beers criteria to evaluate DDIs and PIMs in the elderly, considering previous studies of the relationship between the Beers criteria and ADEs. Page and Ruscin studied how frequently ADEs in the acute care setting are related to medications on the Beers list and the occurrence of ADEs or other negative outcomes in older hospitalized adults who were prescribed medications on the Beers list.[12] A retrospective review was conducted of 389 patients; of those, 107 (27.5%) patients were prescribed 116 Beers criteria medications, and 124 (31.9%) patients experienced 131 ADEs. However, only 12 (9.2%) of the 131 ADEs were attributed to medications on the Beers list. The authors concluded that reductions in the risk of ADEs and the associated morbidity and mortality in acute care of the elderly require more comprehensive interventions than elimination of use of drugs in the Beers list.[12]

Jano and Aparasu (2007) conducted a systematic review of 18 studies of health care outcomes associated with inappropriate medication use based on Beers criteria.[13] Most of the 18 studies were retrospective cohort analyses conducted in diverse health care settings with patients aged 65 years or older. An evidence of association was considered if 50% of the findings were statistically significant. In the community setting, inappropriate medication use was associated with more inpatient and emergency department visits; however, there was no evidence of association between PIM use and mortality or utilization of other health care resources, and the evidence was inconclusive in regards to quality of life and costs. Among nursing home patients, there was no evidence of association of Beers PIMs with mortality, and evidence was deficient for an association with inpatient and emergency department visits. The evidence was also insufficient to make any generalizations in the hospital settings when Beers PIMs were used in this patient population. When comparing the 18 studies across all health care settings, Jano and Aparasu found that Beers PIM use was associated with ADEs and increased costs but not with other outcome measures. There is a need to strengthen the validity of the Beers criteria in all health care settings as adverse health care impact was observed only in the community setting in the systematic review by Jano and Aparasu.[13]

Gallagher and O'Mahony compared Beers criteria to the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP).[14] A Delphi consensus technique was used to establish the content validity of STOPP, a new screening tool for older patients' medicines comprising 65 clinically significant criteria for potentially inappropriate prescribing in older people. Each criterion is accompanied by a concise explanation as to why the prescribing practice is potentially inappropriate. In the study by Gallagher and O'Mahony, 715 acute hospital admissions were

evaluated and compared with STOPP and Beers criteria: 226 PIMs were identified by the Beers list in 177 patients (25%), but only 43 of these patients (24%) presented with an associated ADE compared with the STOPP tool that identified 336 PIMs in 247 patients (35%), of whom 82 (33%) presented with an associated ADE. Thus, STOPP criteria were associated with a significantly higher number of patients requiring hospitalization as a result of PIM-related ADEs than were the Beers criteria.[14]

Beers criteria have been utilized over the past 18 years to examine potentially inappropriate prescribing in the elderly, but overall the studies have not linked Beers criteria to ADEs.[12-14] In 2005, the American Medical Directors Association (AMDA) and the American Society of Consultant Pharmacists (ASCP) published a joint position statement that expressed significant reluctance for use of the Beers criteria because they were based on the consensus of a panel of 12 experts rather than the use of an evidence-based methodology. AMDA and ASCP concluded that undoubtedly the list can be used as a reference to address potential problems with prescribing certain medications in elderly patients, but clinical judgment should be utilized, considering the patient's total clinical picture.[15] Practitioners will be better able to apply the Beers list and provide patient-centered care if they understand the principles underlying proper prescribing for patients in nursing home facilities. Medical directors and consultant pharmacists should work with facility staff to ensure appropriate medication use by proper interpretation of the criteria.[15] Although the Beers list provides a basis for considering whether medications are appropriate in general for elderly patients, an individualized drug regimen should be developed for each patient based on the individual's condition. For example, a patient with depression refractory to or intolerant of other medications may benefit from addition of fluoxetine, although it is generally recommended that safer alternatives exist.[10]

In 2006, the National Committee on Quality Assurance began to review use of high-risk medications in the elderly as a part of HEDIS to assess the quality of care for older Americans. HEDIS used an expert panel and a modified Delphi process to classify the 2003 Beers criteria drugs into 3 categories: (a) always avoid, (b) rarely appropriate, or (c) appropriate for some indications.[16-18] The HEDIS 2006 Drugs to be Avoided in the Elderly (DAE) measure was created to evaluate (a) the percentage of never or rarely appropriate medications in Medicare members aged 65 years or older who received at least 1 high-risk medication and (b) the percentage of Medicare members aged 65 years or older who received at least 2 different high-risk medications.[16] Beginning in 2008, HEDIS changed the formal name of this DAE measure to Use of High-Risk Medications in the Elderly.[16] Another HEDIS measure, Drug-Disease Interactions in the Elderly (DDE), better targets inappropriate prescribing, addressing the percentage of potentially harmful drug-disease interactions in patients aged 65 years or older who receive specific types of medications with an underlying disease, condition or health concern, including history of falls, dementia, and renal failure.[17] Because both the DAE and DDE HEDIS measures have undergone expert review, and the DAE measure focuses on a more targeted list of medications, it is more appropriate and useful to examine DDIs and PIMs with the HEDIS measures instead of the Beers criteria.

Although the HEDIS list is based on the Beers 2003 criteria, it includes a number of medications that were not originally on the Beers 1997 list and excludes a number of drugs that were thought by the original Beers list developers to be the most problematic.[9,10,16] In the September 2006 issue of *JMCP*, Pugh et al. assessed potentially inappropriate prescribing in an elderly Department of Veterans Affairs (VA) population using the HEDIS 2006 quality measure.[18] In the VA population in Pugh et al.'s study, 19.6% of patients were exposed to a HEDIS 2006 drug, similar to the exposure rate in other studies where 20%-25% of patients received drugs identified as inappropriate by the 1997 Beers criteria.[18] Unfortunately, Pugh et al.'s analysis, like most of the studies in the literature, did not link exposure to actual adverse patient outcomes.

The choice of medications prescribed is based on the prescriber's knowledge of pharmaceuticals and the associated risk of use in the elderly. Because relatively few physicians are specially trained in care of the elderly, many physicians caring for older patients may not be aware of pharmacological issues related to aging.[19] Appropriate training of health care professionals is essential to ensure appropriate understanding of pharmacotherapy for older patients based on pharmacokinetics and pharmacodynamics, as well as ways to minimize adverse drug reactions.

Curtailing ADEs: A Potential Role for Pharmacists

Optimal drug use in the elderly is a topic of increasing importance as the population ages and more medications come to market. ADEs can be minimized and their occurrence can be managed but not totally eliminated. Medications identified as high risk should, ideally, not be prescribed at all or, at most, prescribed sparingly with frequent follow-up to ensure patient well-being. However, in a commentary regarding the implementation of the Beers criteria, Crownover and Unwin emphasize that patients may legitimately need a medication on the Beers list; thus, collaboration between prescribers and pharmacists is essential to determine when one of the medications on the list is potentially appropriate.[20]

Health care professionals play an essential role in educating the elderly about appropriate dosing of medications and potential side effects. Pharmacists are a critical part of this process, in ensuring proper medication use in the elderly through medication counseling, medication therapy management services required by the Centers for Medicare & Medicaid Services (CMS), and use of drug utilization evaluations to ensure that medications are being prescribed and monitored appropriately. Pharmacists can also work in conjunction with physicians to decrease ADEs by obtaining an accurate medication and medical history, aligning

medications with disease states, identifying medications that may be treating side effects of another medication, and ensuring medication reconciliation at every care transition if new medications are ordered or existing orders are rewritten. Practitioners should avoid prescribing inappropriate medications for the elderly if possible and use drug therapy only when it is essential, helping to ensure maximum therapeutic benefit, minimal side effects, and overall compliance.

DISCLOSURES

The authors report no conflicts of interest related to the subjects in this commentary.

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