SPECIAL ARTICLE

Recent Literature Update on Medication Risk in Older Adults, 2015–2016

Michael J. Koronkowski, PharmD, Todd P. Semla, PharmD, MS, AGSF,†‡ Kenneth E. Schmader, MD,§‖ and Joseph T. Hanlon, PharmD, MS, AGSF#**†††‡‡§§*

Medications can pose considerable risk in older adults. This article annotates four articles addressing this concern from 2016. The first provides national data on the use of specific prescription, over-the-counter and dietary supplements in older adults and their change over time. The second discusses the opportunity of deprescribing ineffective/unnecessary stool softeners (i.e., docusate) routinely given to older hospital patients. The third national study examines common adverse drug events in older emergency room patients. Finally, a study published demonstrating a potential association between melatonin and fractures is discussed. This manuscript is intended to provide a narrative review of key publications in medication safety for clinicians and researchers committed to improving medication safety in older adults. **J Am Geriatr Soc 2017.**

Key words: drug-related problems; polypharmacy; inappropriate prescribing; adverse drugs events

It is well known that older adults are infrequently included in randomized controlled Phase III efficacy trials for new drugs even if they are targeted for medical conditions confined to or highly prevalent in this age group.[1] Even if the Food and Drug Administration required older adults to be enrolled in such studies, the numbers would still be insufficient to detect important adverse drug events.[1] In the absence of such information, clinicians are left to extrapolate available medication information from other age groups and utilize guiding geriatric medication principles to achieve medication effectiveness while attempting to avoid medication risks (i.e., medication errors and adverse drug events).[2–7]

With the support of the new editor of Journal of the American Geriatrics Society (Dr. Applegate), we intend to continue providing this popular literature review of articles examining medication risks in older adults. We do so because searching for such literature is challenging due to the lack of specific search terms available in computerized medical literature databases. Moreover, we also hope that critique of four articles will be of interest to readers as will the list of additional articles from 2015–2016 in an online appendix (References S1) relevant to medication related problems in older adults.

METHODS

A search using OVID® was conducted and restricted to the years 2015–2016, English language, humans and all aged (65 and over) group using a combination of the following terms: medication misadventures, 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, adverse drug reactions, therapeutic failure and adverse drug withdrawal events. Preference was given to include studies that addressed unique/innovative objectives that used rigorous observational/experimental designs and reliable/valid measures. Since there is a lag time posting articles on OVID®, a similar search was conducted using Google Scholar. In addition, a manual search for relevant articles from highest impact journals from the categories of: (1) general and internal medicine (*New England Journal of Medicine*, *Lancet*, *Journal of the American Medical Association*), (2) geriatrics and gerontology (*Journal of*

From the *Department of Pharmacy Practice, College of Pharmacy, University of Illinois, Chicago, Illinois; †Department of Veterans Affairs, Pharmacy Benefits Management Services, Hines, Illinois; ‡Departments of Medicine and Psychiatry & Behavioral Sciences, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; §Department of Medicine, School of Medicine, Duke University Medical Center; ‖Geriatric Research Education and Clinical Center, Durham Veterans Affairs Medical Center, Durham, North Carolina; #Department of Medicine (Geriatrics), School of Medicine; **Department of Pharmacy and Therapeutics, School of Pharmacy; ††Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; ‡‡Geriatric Research Education and Clinical Center; and §§Center for Health Equity Research and Promotion, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania.

Address correspondence to Dr. Michael J. Koronkowski, Department of Pharmacy Practice, University of Illinois College of Pharmacy, 833 South Wood Street, Chicago, IL 60612. E-mail: koron@uic.edu

DOI: 10.1111/jgs.14887

0002-8614/17/$15.00

the American Medical Director Association, *Journal of Gerontology: Medical Sciences*, *Age and Ageing*), and (3) pharmacology and pharmacy (*Clinical Pharmacology and Therapeutics*, *British Journal of Clinical Pharmacology*, *Journal of Clinical Pharmacology*). Finally, additional articles identified by the authors were considered. Studies published by the authors, or those appearing in certain journals (i.e., *Consultant Pharmacist*, *Drugs and Aging* or the *Journal of the American Geriatrics Society*) were excluded.

RESULTS

A total of 157 articles were identified. After reviewing the abstracts, 47 were excluded leaving 52 for 2015 and 58 for 2016. Two authors (JTH, MJK) independently reviewed the full text for these 110 articles and reached consensus on the 10 top articles for each year (References S1). We then chose 4 of the 10 articles from 2016 that were thought to be particularly unique/important to describe further and critique below.[8–11]

Polypharmacy and Drug Interactions

Using the National Social Life, Health, and Aging Project (NSHAP), Qato and colleagues conducted a longitudinal analysis describing the changes in prescription and non-prescription medication prevalence patterns and major drug–drug interaction risk in community-dwelling older adults 62–85 years of age.[8] The NSHAP is a United States (US), nationally representative, in-home interview survey that included direct medication visualization during 2005–2006 (n = 2,351, avg. age 70.9 years) and 2010–2011 (n = 2206, avg. age 71.4). Concurrent use of medications was defined as the regular use of at least 2 medications. Major drug–drug interactions were assessed using Micromedex. The authors found that polypharmacy (i.e., the use of 5 or more prescription medications) increased from 31% of older adults in 2005–2006 to 36% by 2010–2011. Furthermore, when non-prescription products of any type are included, the rate of polypharmacy increased substantially from 53% to 67%. Significant increases in statins (34–46%), antiplatelet therapy (33–43%), and omega-3 fish oils (5–19%) were demonstrated. The rate of potential major drug–drug interactions increased from 8% to 15% between 2005–2006 and 2010–2011. It should be noted that most of the increased risk for potential major drug–drug interactions involved medications (i.e., statins, antiplatelets such as clopidogrel and aspirin, NSAIDs) and dietary supplements (i.e., omega-3 fish oils) increasingly used in the 2010–2011 findings.

These results are consistent with a large body of research that has documented a rise in medication use among older adults. Inexorable prescribing and self-medication practices is driven in part by an aging population, but also by aggressive marketing and application of chronic disease management guidelines that do not account for the complexities of multimorbidity.[12] A strength of the Qato study was the use of a nationally recognized dataset which included an in-home survey with medication visualization to verify medication use and its ability to assess prescription and self-medication practice patterns of use in the similar cohort over a sequential 5-year time period. While the study demonstrated the use of statins, antiplatelet, and omega-3 fatty acids fish oils therapies increased significantly over this time period it does not tell us if this is appropriate use, overtreatment, led to any positive or adverse outcomes, or what to do about this. There are older adults with multiple chronic conditions who would benefit from adequate multidrug regimens.[13] While these agents may be indicated in older people; it is not without potential harm. Polypharmacy is associated with increased healthcare utilization, functional and cognitive impairment, geriatric syndromes (i.e., delirium, falls and frailty), adverse drug events, and mortality.[14] As healthcare providers, complex drug regimens should be monitored and challenged routinely, and simplification strategies should be employed when it can improve health. Systematic efforts to address polypharmacy in older adults should include: (1) creating an awareness that options exist to tailor therapy; (2) patient engagement through discussion of options and their benefits and risks; (3) exploration of patient preferences for the different options; and (4) decision making that includes monitoring and re-evaluation of medication use.[15]

Transitions of Care Interventions and Deprescribing

MacMillan et al. conducted a cohort study to examine docusate prescribing/deprescribing during hospitalization at two academic health sciences centers in Toronto, Canada.[9] A random sample of 500 patients was selected of whom 452 patients whose median age was 75 years had complete data. They found that 53% received docusate before admission and that only 13% of admission docusate users had the drug discontinued during their hospital stay. Among the 47% not taking docusate before admission, 33.2% of these patients became new users. Therefore, a total of 263 of 452 (58.2%) received an order for docusate at hospital discharge. Opioid use at discharge was seen in 185 patients (40.9%) of which 14.6% received no laxative and 13.0% received just docusate.

The issue of deprescribing, defined as the process of tapering, stopping, and monitoring drugs, has been receiving considerable attention in the literature. It implies that a medication may be inappropriate/unnecessary and that polypharmacy, a major risk factor for adverse drug reactions in older adults, can be reduced.[16] To date most of the emphasis has been on the use of preventative medications by older patients at the end of life with dementia or cancer (i.e., statins, bisphosphonates).[17] The study by MacMillan focuses on the use of docusate, a stool softener that has not been demonstrated to be effective as a laxative and as seen in this study was often prescribed in combination with stimulant and osmotic agents. This study also reminds us that continuing docusate during hospitalization may reflect prescriber inertia. Finally, hospitalization can lead to starting a "drive by drug" like docusate. Other examples of "drive by" drugs during hospitalization include inappropriate/ineffective/unnecessary medications such as antipsychotics, expectorants, vitamins, and proton pump inhibitors for stress ulcer prophylaxis.[17,18] A strength of the MacMillan et al. study is the use of a

random sample, documenting not only medications started in the hospital but those taken at home and continued. One potential concern is the lack of accounting for other constipating drugs besides opioids and employment of a multivariable model with data from the random sample to help identify predictors of docusate new prescribing or deprescribing to guide future intervention studies. Of course, generalizability to other countries like the US is unknown as well as the impact on health outcomes. Nonetheless, this study reminds us that deprescribing is everyone's job whether they started the medication or not and the perfect time to start this process is the hospital setting where, if necessary, complicated tapering can be started and monitoring for unlikely withdrawal events or return of the unknown underlying disease is readily available.

Adverse Drug Events and Healthcare Utilization

Shebab et al. at the US Centers for Disease Control and Prevention used the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event (NEISS-CADES) to describe the characteristics of emergency department (ED) visits for adverse drug events in the US (2013–2014) and describe changes in ED visits for adverse drug events since 2005–2006.[10] The NEISS-CADES is a nationally representative, size-stratified probability sample of US hospitals. Data abstractors at each hospital review the clinical records for any clinician diagnosed adverse drug events that were the reason for the ED visit. Cases in which prescription or over the counter medications, dietary supplements, homeopathic products, or vaccines were implicated in the adverse event were included. Potentially inappropriate medications for older adults included all drugs in the American Geriatrics Society 2015 Beers Criteria.[4]

The results showed that overall there were 4.0 (95% CI 3.1–5.0) ED visits for adverse drug events per 1,000 individuals in 2013–2014. However, the rate of ED visits for adverse events was highest among older adults aged ≥65 years old at 9.7 (95% CI, 6.6–12.9) per 1,000 individuals. Compared with 2005–2006, rates of ED visits among older adults ED visits nearly doubled from 5.2 (95% CI, 3.2–7.2) to 9.7 (95% CI, 6.6–12.9) per 1,000 individuals. Overall, an estimated 27% of ED visits for adverse drug events resulted in hospitalization but rates were highest for individuals aged ≥65 years with a 43.6% hospitalization rate. Among older adults, anticoagulants, diabetes agents and opioid analgesics were the most common drugs associated with adverse drug events (59%). Medications to avoid in the Beers criteria accounted for only 1.8% of ED visits for adverse drug events.

This study confirms that rates of ED visits for adverse drug events, and subsequent hospitalization, is highest among older adults. The investigators used a powerful surveillance system but the method of measuring adverse drugs events by clinician diagnosis limits the internal validity since researchers did not have detailed information on how the medications were being prescribed or used. Additionally, emergency departments within computerized integrated health care systems such as the Veterans Administration and Kaiser Permanente were not eligible. These exclusions are noteworthy since these institutions offer unique opportunities to address adverse drug events.[19,20] It is important to note, these findings likely underestimated adverse drug event rates since clinicians, not infrequently, miss adverse event diagnoses and investigators have developed adverse drug event measurement techniques that reliably find adverse drug events using systematic or algorithmic approaches that do not rely on clinical diagnosis.[19,20] Either way, the findings of the study highlight the fact that older adults remain a critically important subgroup for medication safety efforts. Furthermore, it appears those efforts need to be directed towards anticoagulants, hypoglycemic, and opioids. Although Beers criteria drugs to avoid will continue to be important, these medications were responsible for a very small proportion of ED visits for adverse drug events. However, this does not preclude that being exposed to Beers criteria drugs is a risk factor/marker for adverse drug events.

Adverse Drug Events and Negative Outcomes

Frischer et al. accessed the United Kingdom's (UK) The Health Improvement Network (THIN) to study whether an association exists between melatonin, hypnotics, and fractures.[11] THIN consists of an electronic medical record for >1500 general practitioners in >380 practices in the UK. A prolonged-release formulation of melatonin is approved as a hypnotic in the UK for patients 55 years and older. Using a matched cohort design, patients 45 years of age and older were separated into 4 groups. Three groups were identified based on receipt of prescriptions between July 2008 and June 2013 for melatonin and none for other hypnotics (n = 1,371), receipt of ≥2 prescriptions for a hypnotic benzodiazepine (n = 880) or a "Z-drug" (zolpidem or zopiclone; n = 1,148) and none for melatonin. The fourth group "matched to criteria" received neither a prescription for melatonin nor a hypnotic during the same time period (n = 2,751). The study's outcome was any fracture occurring after entering the study. Numerous confounders, covariates and comorbidities were controlled for including age, gender, smoking and alcohol use status and body mass index (BMI kg/m^2). The model also included prescription medications, pre-study fracture as well as cardiovascular, pulmonary, psychiatric, dementia, diabetes, gastrointestinal, musculoskeletal, and ophthalmic disorders.

Mean age at study entry was 64.7 years with an average enrolled time of 2.6 years; neither differed between the 4 groups. Among the melatonin group, 79% were dispensed melatonin once or twice, while 21% were dispensed it 3 times or more. Relative to the control group (no study drug exposure), adjusted hazard ratios (HR) for the ≥3 exposure groups were melatonin HR 1.44 (95% CI, 1.01–2.04); hypnotic benzodiazepines HR 1.26 (95% CI, 0.82–1.92); and Z-drugs HR 1.52 (95% CI, 1.04–2.23). Musculoskeletal problems, a pre-study fracture, female gender, and a lifetime receipt of >500 prescriptions were significantly associated with any fracture, while being overweight (BMI 25–29.9) was significantly protective.

Melatonin is an alternative to other hypnotic drugs associated with falls and/or fractures in older adults. This

study signals an increased risk of fracture after exposure to melatonin and needs to be replicated before any conclusion can be made to avoid melatonin. Melatonin is believed to have positive effects on bone by stimulating growth and inhibiting osteoclast activity.[21] Thus, the mechanism by which melatonin might increase fracture risk is unclear. As noted by its authors, the study has several limitations including its non-randomized design, unmeasured or errors in measuring confounders, and not controlling for the severity of comorbid conditions. It also appears that exposure to melatonin and other hypnotics were not equal based on differing inclusion criteria. Finally, selection bias is another limitation if melatonin was selectively prescribed in an effort to avoid prescribing a benzodiazepine hypnotic or Z-drug to patients believed to be at risk for a fall or fracture.

DISCUSSION

There were numerous post marketing published articles assessing medication risk in older adults in 2015–2016. The selected literature describes advancements with direct application to support change in practice targeting medication safety. The first study highlights the increasing use of multiple medications, including supplements, by older adults in the US and the potential risk for a major drug–drug interaction among commonly used medications. Another study demonstrates the ongoing impact of overprescribing docusate especially during care transitions and the need for greater awareness and safety initiatives targeting deprescribing to address this form of potentially inappropriate prescribing. The third study reinforces the dramatic increase in emergency department and hospital healthcare utilization among older adults resulting from adverse drug events with commonly prescribed drug classes: anticoagulants, diabetic agents, and opioid analgesics. Lastly, a recent study demonstrated the association of melatonin and non-benzodiazepine sedative hypnotic agents with a significant increased risk of fracture. Together, these studies, along with the supplemental bibliography material (References S1) shines a spotlight on the continued challenge of medication risk associated with multidrug therapy in older adults. Healthcare providers must improve awareness of these medication safety findings in order to initiate patient and system level strategies to address unnecessary, ineffective and harmful prescribing. Doing so, will require a patient centered team approach leveraging existing systems to improve overall safety in the medication use process of initiating, monitoring and discontinuing medications.

ACKNOWLEDGMENTS

We would like to thank Jennifer Naples, PharmD and Beth Thomas for their help compiling these articles.

Conflicts of Interest: Dr. Koronkowski serves on the OptumRx, Inc. Pharmacy and Therapeutics Committee, Dr. Semla is an editor for LexiComp, Inc. His spouse is an employee of Abbvie and owns shares in Abbvie and Abbott Labs.

Author Contributions: All authors contributed to the writing of this article and approved the final version before submission.

Sponsor's Role: None.

Funding: This article was supported by grants from the Donoghue Foundation, National Institute on Aging (R01-AG050302, R01-AG05123, U13-AG047008, T32-AG 021885, P30-AG028716 and P30-AG02482706), Agency for Health Research and Quality (R18-HS023779), a VA Health Services Research Grants (IIR 12-379, IIR 14-297, IIR 14-306, IIR 15-115) and Health Services Research Administration, Geriatric Workforce Enhancement Program Grant (U1-QHP2870).

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

References S1. Recent Literature Update on Medication Risk in Older Adults, 2015–2016.

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