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Reconsideration of Key Articles Regarding Medication Related Problems in Older Adults from 2011

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INTRODUCTION

This year, the oldest baby boomers turned 65 years of age. Baby boomers, which include individuals born between 1946 and 1964, represent 25% of the US population.¹ In addition, given their life experiences, this group of individuals is likely to have higher expectations for the quality of health care services, including medication safety. Thus, it is timely to discuss what new knowledge on often preventable medication-related problems (i.e., medication errors and medication adverse events) in older adults was published in 2011. Hopefully, by doing so we can begin to develop approaches to reduce medication-related problems and meet this cohort's expectations.

METHODS

Because the subject of medication-related problems is not easily accessed by interested individuals, the MEDLINE database was searched monthly by one of the authors (JTH) for articles published in 2011 in English that involved humans and the aged and contained one or more of the following terms describing medication errors: suboptimal prescribing, polypharmacy, inappropriate prescribing, underprescribing, medication dispensing errors, medication administration errors, medication non-adherence, medication non-compliance, and medication monitoring.² In addition search terms to describe medication adverse events (i.e., adverse drug events [ADE], adverse drug reactions [ADR], adverse drug withdrawal events [ADWE], and therapeutic failures [TF]) were included in these searches.² A similar search was conducted using the Google Scholar Internet search engine. In addition, a manual search for relevant articles from specific journals (i.e., New England Journal of Medicine, Annals of Internal Medicine, JAMA, Journal of the American Geriatrics Society, Journal of Gerontology: Medical Sciences, Clinical Pharmacology and Therapeutics, Pharmacoepidemiology and Drug Safety, Archives of Internal Medicine, Annals of Pharmacotherapy, Pharmacotherapy, American Journal of Health-Systems Pharmacy and Consultant Pharmacist) was conducted. Finally, additional articles suggested by the authors

were considered. Articles appearing in either *Drugs and Aging* or the *American Journal of Geriatric Pharmacotherapy* were not included as they are obvious places for readers to look for relevant articles. Similarly, no articles by any of the current authors were included.

RESULTS

A total of 111 articles were identified. There were 69 articles regarding medication errors, including 44 addressing suboptimal prescribing, 18 focused on adherence, 4 about medication administration and 3 about medication monitoring. Overall there were 42 articles about ADRs, 3 regarding ADWEs and none for TFs. Five studies of these studies that, in the authors' opinions, addressed key medication-related issues facing older people were included below.³⁻⁷ Each study is annotated and is followed by a critique along with information about how it fits with previous literature. The remaining articles identified from 2011 are listed in Appendix I.

Randomized Controlled Trials to Improve Suboptimal Prescribing

In a randomized control trial, Gallagher and colleagues sought to determine if using the STOPP/START criteria for screening elderly hospitalized patients upon 24 hours of admission and providing clinical recommendations regarding these criteria would lead to significant improvements in prescribing appropriateness at discharge and beyond, compared to usual care.³ The STOPP (Screening Tool of Older Persons potentially inappropriate prescriptions) criteria are a list of sixty-five risky medication situations, involving specific drugs, drug-drug interactions, drug-disease interactions or therapeutic duplication, to avoid in the general elderly population.⁸ The START (Screening Tool to Alert doctors to Right Treatment) criteria focus on the risk of underuse of appropriate medications for important diseases states in the elderly.⁹

The study setting was an 800 bed University-affiliated, state funded, tertiary medical center located in southern Ireland. The sample consisted of 400 patients 65 years who were admitted through the emergency department to general medicine. Exclusion criteria for this study included elderly patients who were followed by a geriatrician, psychiatrist with geriatric expertise, a clinical pharmacologist or were assessed by a specialist prior to admission. Additional exclusions included patients who were admitted to critical care units, terminal patients, and unwillingness of the patient or hospital physician to participate in the study. The included and consented patients were randomized either to the control group for usual physician and pharmacy care or to the intervention group, which in addition to usual care included a research physician who within 24 hours of admission conducted the STOPP/START criteria. After applying the STOPP/START criteria, the research physician discussed recommendations with the attending medical team and followed up with written recommendations. The main outcomes for the study were change in inappropriate prescribing (as measured by the Medication Appropriateness Index [MAI] and underprescribing (as measured by the Assessment of Underutilization [AOU] during hospitalization.^{10,11}

A total of 382 patients finished the study and were followed for 6 months after discharge. Overall, 71.1% (n=135) of intervention patients and 35.4% (n=68) of control patients has lower MAI scores at discharge than at admission with an absolute risk reduction of 35.7%. In regards to the AOU tool, 31.6% (n=60) of the intervention group patients and 10.4% (n=20) of the control patients experienced a reduction in the rate of underprescribing at discharge compared to admission (absolute risk reduction 21.2%). For both measures, these changes were sustained out to 6 months.

The strengths of this study included the use of a randomized control trial design, the application of time effective intervention tools (i.e., STOPP/START criteria) and the use of reliable and valid measures of suboptimal prescribing. However, no information was provided on several key study design features, including how many prescribers had patients in both intervention and control groups, who specifically applied the MAI/AOU, and whether they were blind to group status. Moreover, despite the good inter-rater reliability reported for the MAI and AOU for a sample of patients, it is customary to use two raters for these main outcomes and have any discordances resolved by consensus. In addition, the study did not measure the impact of the intervention on the distal outcomes of ADEs, and was underpowered to detect between groups in falls, health services use, or death. Finally, it is not clear how generalizable the study findings are to other hospitalized older patients given that there was only one study site. To improve translation of results to other settings, it would have been helpful to have had more detail regarding what disciplines were part of the medical team, what the preexisting relationships were between the research physician and the team prescribers (e.g., if they were residents), and how familiar they were with START/STOPP criteria before the study.

In conclusion, this study was a good first attempt to show that educating health care professionals about the START/STOP criteria as it pertains to their specific patients can be effective at reducing suboptimal prescribing. Future multi-hospital studies that include ADEs as outcome measures are needed, as well as similar studies in other care settings (e.g., primary care, nursing homes). Finally, these tools need to be studied using other healthcare disciplines as interventionists to evaluate whether the acceptance rate shown in this study can remain high among non-physician healthcare professionals.

A paper by Patterson et al. describes a cost-effectiveness analysis of a previously published cluster randomized controlled trial of an intervention using the Fleetwood Northern Ireland (NI) model of pharmaceutical care in a nursing home population.⁴ In this intervention consultant pharmacists were trained to assess nursing home residents' clinical and prescribing information, perform a medication review, and interact with the prescribing general practitioners and any other relevant healthcare practitioners to discuss recommendations to improve inappropriate prescribing of psychoactive medications. The previously reported study showed that the intervention resulted in fewer residents receiving inappropriate psychoactive medication in the intervention arm (19.5%) than those in the standard care (50.4%; OR=0.26, 95% CI=0.14-0.49).¹² The primary outcome for the current analysis was the cost per patient per each inappropriate psychoactive drug avoided. The cost of the intervention was estimated at \$11.56 per resident per month. The overall costs per resident in intervention homes were \$4,922 for mean health resources (i.e., medication, labs, outpatient visits and hospitalization) and intervention costs. This was lower than the cost of health care resources used by the usual care group (\$5,053; p=0.80). In addition, analysis using a willingness-to-pay threshold of \$2000 found that the probability of the intervention being cost effective was 93%. This finding was robust to the sensitivity analyses conducted.

This study is the first of its kind to assess the cost effectiveness of this type of intervention in nursing homes, although, the outcome measure is similar to the one used by Chisholm-Burns et al., in a recent review that examined cost-effectiveness of pharmacist interventions in hospitals and ambulatory care settings.¹³ There are several limitations to the study which are important to discuss. The first is that the analysis was performed on the cohort of patients for which there was complete 12 month data. This could have misclassified the true expenditure of healthcare resources for this population since those who died were not included in the analyses. Also there was no measure of health-related quality of life included in this study which prohibits an understanding of how these medication changes affected nursing home residents' quality of life, an important outcome in this population. Another

alternative could have been to measure health care costs due to ADEs and calculate an incremental cost ratio per ADE avoided.

In conclusion, this study provides policy-makers the cost outcome data to support the use of this type of intervention in the nursing home population to reduce the use of inappropriate psychoactive medications. This is a clinically important public health issue due to the considerable adverse effects of psychoactive medications. Moreover, reductions in inappropriate psychoactive medications have been somewhat resistant to mandatory regulatory initiatives and typical consultant pharmacist activities in the US. Further well designed studies are needed to determine the impact of clinical pharmacist activities on other medication types in nursing home patients.

The Impact of Different Drug Benefits on Medication Use and Adherence

Stuart et al. compared patterns of medication use and adherence among Medicare beneficiaries with diabetes receiving prescription drug benefits from Medicare Part D Prescription Drug Plans (PDP) versus retiree health plans (RHPs).⁵ The authors used the 5% random sample from the 2006 Chronic Conditions Warehouse (CCW) to identify PDP enrollees and the 2006 Thomson/Reuters MarketScan Medicare Supplemental and Coordination of Benefits database to identify Medicare enrollees with drug coverage through retiree health plans. A total of 45,613 PDP and 211,919 RHP beneficiaries aged 67 or older with diabetes and continuous enrollment in these plans were identified. Utilization patterns of three medication classes were examined, including antidiabetic medications, renin-angiotensin-aldosterone system (RAAS) inhibitors, and antihyperlipidemics. Three measures of annual drug utilization were defined for each class: 1) prevalence of use of at least one drug; 2) duration of therapy (DOT) during the year, defined as the number of days between the dates of the first fill for a medication in the class and the last fill for a medication in the class plus day supply on the last fill or December 31st; and 3) refill adherence using a weighted average medication possession ratio (MPR), equal to the sum of days supply for all medications in the class divided by the sum of the DOTs for each medication.

Unadjusted analyses revealed that PDP enrollees were older, more often female, and more likely to have specific comorbidities, and had lower drug utilization per most of the measures. Propensity score-matched analysis revealed meaningfully lower prevalence of use of antihyperlipidemic agents (60.5% versus 69.4%), but enrollees' use of antidiabetic agents (73.7% versus 75.9%) and RAAS inhibitors (66.6% versus 67.3%) was not markedly different across PDP versus RHP plans. Furthermore, although PDP enrollees exhibited MPRs that were 1-3% lower than those of RHP enrollees, duration of therapy was actually longer, ranging from <1 day for antihyperlipidemics to 16 days longer (all $p < .0001$).

This study adds to a growing literature on the impact of Part D on prescription medication use, including numerous studies showing increased overall utilization and adherence to medications.¹⁴⁻¹⁹ This study is unique in that it is the first to suggest that Part D enrollees' patterns of drug utilization and refill adherence do not differ markedly from those of enrollees in retiree health plans, which have historically been considered the best available source of prescription drug coverage for older adults. Other study strengths were removing Part D low income members from the sample and the use of matched pairs by propensity scores. However, this study has some important limitations to consider when interpreting results. First, although this study may alleviate some concerns that the idiosyncratic features of Part D, most notably the coverage gap, may decrease patients' utilization of chronic medications compared to RHPs, the authors' lack of payment information and plan characteristics prevented them from directly examining the impact of cost-sharing differences on drug use and adherence. Second, inclusion of only those PDP beneficiaries

who were enrolled continuously from January through December 2006 (i.e., the “early adopters” of Medicare Part D), may have resulted in a PDP sample that is more motivated or engaged in their healthcare and likely to utilize and adhere at higher than average rates. The propensity score analyses could not control for confounding from unmeasured characteristics such as these. In addition, the authors did not have 2005 drug utilization data, which prevented them from including days supply of medications carried over from the prior year and led to underestimates of therapy duration. This underestimation may be more marked for RHP beneficiaries, who likely had more generous coverage and higher utilization in the prior year compared to new PDP enrollees. Both of these design features may have inflated estimates of PDP utilization relative to the RHP group. Also, while ubiquitous in the literature, the use of a simple yearly MPR is a somewhat imprecise measure of refill adherence patterns compared to other available options.²⁰ Moreover, the policy relevance of this study could have been improved by also examining proportion of days covered (PDC), the medication adherence measure likely to be adopted by CMS in future pay for performance initiatives. Finally, the generalizability of results to beneficiaries with other chronic diseases besides diabetes is unknown.

In conclusion, this study shows that Part D benefits resulted in similar drug use and adherence as more generous employer benefits. However, nearly one third of diabetes patients (risk equivalent to having coronary heart disease) did not use recommended antilipemics. Future studies investigating the impact of Part D benefit design on health outcomes in diabetes (e.g., hemoglobin A1c, micro- and macro-vascular complications, health services use) and medication use and adherence in other chronic diseases are needed.

Studies of Adverse Drug Events with Specific Medication Classes

Stephenson et al. conducted a population-based, nested case-control study to determine the risk of acute urinary retention (AUR) in older adults using inhaled anticholinergic bronchodilator agents (IACs) to treat chronic obstructive pulmonary disease (COPD).⁶ The study linked multiple health care administrative databases to identify 565,073 individuals with COPD (identified by a validated algorithm) aged 66 years and older living in Ontario, Canada between April 1, 2003 and March 31, 2009. Individuals were excluded if they had a previous radical cystectomy or a previous AUR event in the year prior to COPD cohort enrollment.

Cases were defined as individuals with a hospitalization, emergency department visit, or same-day surgery with a primary diagnosis of AUR (International Classification of Disease, Tenth Revision [ICD-10] code R33). The date of the AUR event was used as the index date for cases and selected controls. Controls were individuals with COPD residing in the province with no previous AUR event and who remained free from AUR events. Controls were randomly selected from the study time period and were matched 5:1 with cases on age (+/- 1 year).

IAC exposure (short acting such as ipratropium and long acting such as tiotropium) was identified using the Ontario Drug Benefit database, which contains records of all publicly funded medications dispensed to residents of the province aged 65 and older. Patterns of IAC use for the 180 days prior to the index date were classified into the following 4 groups: (1) new IAC users (new IAC prescription within 30 days of index date with no prior prescription within 30-180 days of the index date); (2) current users (IAC prescription occurring 30-180 days prior to the index date with sufficient days supplied to extend to within 30 days of the index date); (3) past users (IAC prescription occurring 30-180 days prior to the index date where the days' supply ends 30 days prior to the index date); and (4) nonusers (no prescriptions within 180 days of the index date). A second analysis was

conducted among new IAC users to evaluate the risk of AUR by the different types of IAC regimens (short-acting IAC, long-acting IAC, combination therapy).

Potential confounders included age, Charlson comorbidity index, comorbidities associated with AUR risk (diabetes, benign prostatic hyperplasia, prostate cancer, urinary incontinence, neurologic disease, and anticholinergic burden from other medications). Proxies for COPD disease severity included duration of COPD, oral or inhaled corticosteroid use, long-acting β -agonist use, number of outpatient visits, number of specialty pulmonology visits, hospitalizations for COPD, and ICU admissions. Analyses were conducted separately for men and women.

Among men, IAC exposure (new, current) was associated with an increased risk of an AUR event compared to nonusers of IAC. The increased risk in new and current users was similar (new users: AOR = 1.42; 95% CI, 1.20 – 1.68; current users: AOR = 1.36; 95% CI, 1.26 – 1.46). AUR risk among past IAC users was not significantly different than nonusers (AOR = 1.18; 95% CI, 1.00 – 1.35). A subgroup analysis of high-risk men suggested the risk of AUR associated with new IAC use may be particularly high in men with underlying benign prostatic hyperplasia (AOR = 1.81; 95% CI, 1.46-2.24). Results also suggest that men receiving combination IAC therapy may be at nearly double the risk of AUR compared to monotherapy users of a short- or long-acting IAC. Among women, no significant association was found between IAC exposure and AUR events.

Stephenson et al's finding that IAC use may increase the risk of AUR in older men with COPD is important because IACs are widely considered as one of the first-line therapies for treating persistent symptoms of COPD based on results from carefully selected patients enrolled in randomized, controlled efficacy trials.²¹ While the beneficial anticholinergic effects of IACs are thought to be localized in the lungs, a small yet growing body of empirical evidence suggests that IACs may cause clinically important systemic anticholinergic effects in certain subgroups of COPD patients.²²⁻²⁴ Moreover, the fact that COPD treatment guidelines are equivocal in their recommendations regarding the choice between long-acting anticholinergics and long-acting β -agonists as the preferred first-line therapy for COPD suggests that safety information gleaned from large, post-marketing surveillance studies such as Stephenson et al's may inform patients and providers in their initial choice between long-acting COPD medication options. The results of the current study suggest that healthcare providers should closely monitor male COPD patients who initiate IAC therapy for signs of acute urinary retention, particularly if the male patient has concurrent benign prostatic hyperplasia.

Several limitations of this study are worth noting. The use of a proxy measure for severe COPD such as the use of methylxanthines (e.g., theophylline) may have been informative. Information about the sensitivity and specificity of the approaches used to classify cases with AUR and/or BPH is not provided raising the question of misclassification. In particular for BPH, the study investigators could have ascertained the use of specific α -1 antagonists (e.g., prazosin) and/or 5- α -reductase inhibitors (e.g., finasteride) used most commonly for this condition. It is also notable that neither dose-response nor medication adherence analyses were not done despite this being computationally possible.²⁵ This latter point is important because inhaler adherence is reduced in older adults due to their having more problems with cognition, hand-eye coordination and arthritis in the hands.²⁵ We also cannot rule out the possibility of reverse causality (AUR $\rightarrow$ discontinued IAC use) because COPD patients with AUR events occurring before the 1-year study period that may have resulted in discontinued use of IAC would be classified as nonusers in this study. Threats to internal validity of the current study due to potential confounding are also of concern. It is not clear why other drugs that can be prescribed for urge incontinence and have the same

mechanism of action as IACs (i.e., decreases detrusor contractility) were not pulled out as a separate variable from the anticholinergic use measure. The anticholinergic load measure is likely an underestimate as it would not include the use of over the counter medications (e.g., first generation antihistamines such as diphenhydramine). Moreover, it is controversial as to which anticholinergic measure is best for use in such studies.²⁶

While multivariable conditional logistic regression was used to adjust for a number of potential confounders, the use of propensity score or instrumental variable methods may have provided better control for confounding by indication/contraindication and unmeasured confounding differences in IAC prescribing tendencies of providers.²⁷ The finding regarding combination of short and long acting anticholinergics being risky but neither as monotherapy alone is not clinically sensible. This is because there is no advantage to using this combination given that the onset of action is delayed with even with short acting agents. Moreover, guidelines and clinicians recommend short acting beta 2 agonists as prn rescue agents.²¹ Finally, adjusted odds ratios of less than 2.0 require further confirmation by future samples before causality can be confirmed given that achieving statistical significance is more likely in studies such as the current one that have large sample sizes.

Miller and colleagues compared the risk of fracture associated with initiating treatment with opioids to that of nonsteroidal anti-inflammatory drugs (NSAIDS).⁷ This retrospective cohort study involved 17,310 participants in two statewide pharmaceutical benefit programs for persons aged 65 and older. Participants were included if they had a diagnosis of osteoarthritis or rheumatoid arthritis and filled a prescription for an opioid or NSAID prescription without having filled one in the previous six months. Mean age at initiation of analgesia was 81 and 85% of the participants were female. Utilizing diagnostic and procedure codes from Medicare data of participants, study outcomes of fracture of the hip, humerus or ulna, or wrist were identified. The authors included 38 variables to control for possible confounders associated with increasing fracture risk. Among the 12,436 participants who initiated opioids, there were 587 fracture events (4.72%) compared to 38 fracture events (0.78%) among the 4,874 initiators of NSAIDS (HR = 4.9, 95% CI = 3.5-6.9). The authors further compared the risk of fracture with those initiating NSAIDS to the risk of fracture associated with dose of opioid, duration of action, and duration of use of opioids. Higher dose of opioids were associated with higher fracture risk. Short-acting opioids were associated with a greater risk of fracture (HR=5.1, 95% CI=3.7-7.1) compared to long-acting opioids (HR=2.6, 95% CI=1.5-4.4). This differential risk of fracture was apparent for the first 2 weeks after starting opioids, but did not persist thereafter.

This study has a number of strengths. First it provides observational evidence that use of opioids may contribute to the risk of fractures in the older patients. This is consistent with the results of a meta-analysis of six older opioid studies.²⁸ More recently, four additional studies (2 by this group of authors) have suggested that opioids increase the risk of injuries/fractures.²⁹⁻³² Moreover, the authors conducted both dose- and duration-response analyses to further support the main findings. Finally, they conducted sophisticated matched propensity score analyses. There are several potential limitations to the study to consider. It is notable that the authors did not restrict the fracture outcome to hips only since this has the highest sensitivity and specificity using ICD-codes and almost always are treated in hospitals. While the authors controlled for a variety of confounders, they were unable create variables to include in the final analyses for pain severity and extent of pain relief, use of over the counter NSAIDs and body mass index. This last factor is particularly important, as it is a key component in the FRAX fracture risk prediction models.³³ In addition, important risk factors for falls such as functional status, cognition, and depression were also not controlled.³⁴ Finally, the generalizability in beyond this predominantly female sample from New Jersey and Pennsylvania enrolled in Pharmaceutical Assistance programs is unclear.

In conclusion, this study provides further evidence that opioids increase the risk of fractures. It is important to note, however, that NSAIDs still results in over 41, 000 hospitalizations and 3,000 deaths per year due to gastrointestinal injury in older adults and the overall rate of fractures with opioids is small. Finally, studies are needed to determine whether the risk of severe pain is a greater risk for falls/fractures than opioids used in low doses.

CONCLUSIONS

These studies should provide health care professionals and health policy makers further information about medication-related problems in older adults. Hopefully in the future this information will lead to improvements in medication safety in older adults.

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Appendix I. Articles from the 2011 Scientific Literature Regarding Medication Errors and Adverse Events in Older Adults

A. Medical Errors

1. Suboptimal Prescribing

1.1 Polypharmacy

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B. ADVERSE DRUG EVENTS

1.0 Adverse Drug Reactions

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2.0 Adverse Drug Withdrawal Events

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