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Medication Misadventures in Older Adults Literature From 2013

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Abstract

This is the second year that editors of the *Journal of the American Geriatrics Society* have been gracious enough to allow us to compile the latest literature regarding medication misadventures (i.e., medication errors and adverse drug events) for its readers. As noted in some recent well written comprehensive reviews, medication errors due to suboptimal drug use continues to be very common in older adults.^{1–3} We believe that it is important to summarize this literature in a single place because it is very difficult to compile using standard literature search techniques as they often miss key studies. We hope you find these articles informative and useful in the conduct of high quality clinical research and care of older adults.

METHODS

A search of Medline and Google Scholar restricted to 2013 was conducted using a combination of the terms: elderly, aged, 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. 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 *Consultant Pharmacist*, *Drugs and Aging*, and the *Journal of the American Geriatrics Society* were excluded because they are obvious places for readers to easily find relevant articles.

RESULTS

A total of 58 articles were identified. The abstracts of these articles were read and reviewed by each of the authors who reached consensus to which articles to highlight this year.

Preference was given to studies that were innovative and used rigorous observational or experimental study designs and reliable, valid measures. Below we annotate and critique data from two randomized controlled trials and one large cohort study. Appendix S1 (online only) briefly provides summaries of 20 other important medication misadventure articles, 11 of which involve medication errors and the remaining 9 articles deal with adverse drug events.

Article 1: Pharmacists intervene to reduce suboptimal prescribing

Previously investigators from Sweden conducted a randomized controlled trial of a clinical pharmacist intervention in 400 older hospitalized patients (80+).⁴ They reported that there was a statistically significant reduction in drug-related readmissions in the intervention vs the control group in the 12-month follow-up period.⁴ In 2013, this same group of investigators reported the impact that the clinical pharmacist intervention had on suboptimal prescribing as measured by an explicit and implicit measure for potentially inappropriate prescribing (i.e., Screening Tool of Older Persons' Prescriptions [STOPP] criteria and Medication Appropriateness Index [MAI], respectively), and for potential underutilization measured by explicit criteria (Screening Tool to Alert doctors to Right Treatment [START]).⁵ Between hospital admission and discharge, MAI scores improved more in the intervention group than control group patients (MAI mean change -3.5 vs 1.3, respectively; $P < 0.001$). Similarly the average number of potentially inappropriate medications per the STOPP criteria was reduced more in the intervention vs the control group (-0.5 vs 0.2, respectively; $P < 0.001$). Also of note, the number of necessary medications omitted as per the START criteria was reduced only in the intervention group (-0.30 vs 0; $p < 0.001$). In addition, secondary analyses were conducted to determine the relationship between these three separate suboptimal prescribing measures and drug-related readmissions. There was a positive association between scores for MAI and STOPP and drug-related readmissions (Relative Risk 8–9% and 30–34% respectively) but not for the START criteria.⁵

This study is important in that it reaffirms the benefit of clinical pharmacist interventions in the framework of randomized controlled trials on improving potentially inappropriate medications in older adults as per the MAI. In fact this is the fifth such study to demonstrate this.⁶ Moreover, two additional randomized controlled trials using an educational intervention found similar improvements in MAI scores.⁶ It also provides additional evidence of the MAI's predictive validity with important health outcomes; in this case drug-related readmissions.⁶ It is interesting to note that in contrast with the findings from another study, improvement in potentially inappropriate prescribing as per the STOPP criteria was not associated with adverse drug events.⁷ Moreover, this study, to the best of our knowledge, is the first to demonstrate the relationship between a potential global measure of underuse of medications and an important health outcome; in this case drug-related readmissions.²

Like most studies there are several potential limitations worth noting. First the study was conducted retrospectively in a single site and whether the findings generalize to other hospitals or other settings is unknown. No information was provided as to whether the single evaluator of suboptimal prescribing was blinded to study group. Also, it is customary to use

two evaluators (as opposed to only one as in this trial) with the MAI unless adequate interrater reliability is shown by the same group of investigators. The measurement of drug-related admissions was not well described suggesting that structured causality algorithms for adverse drug reactions and therapeutic failure were not utilized.⁸ Finally, as study group was not included in the multivariable models, one cannot conclude with full confidence that the reductions in drug-related admissions were due to improvement in suboptimal prescribing although it is highly suggestive.

Article 2: Choosing a thiazide

The Panel Members of the Eighth Joint National Commission (JNC 8) recommend thiazide diuretics as a first line drug for treating hypertension in older adults but they do not specify an individual thiazide diuretic.⁹ The ACCF/AHA guideline for treating hypertension in the elderly equally recommends three thiazide diuretics (i.e., bendroflumazide, hydrochlorothiazide [HCTZ] or chlorthalidone).¹⁰ The first agent is not widely used in North America. Therefore, which agent should clinicians choose for the treatment of hypertension in our older patients? Both HCTZ and chlorthalidone are widely available and inexpensive. Chlorthalidone compared to HCTZ has a longer duration of action and thus may cause more metabolic abnormalities.¹⁰ However, this information about adverse drug events (ADEs) must be tempered by efficacy data from a recent meta-analysis of some randomized placebo controlled studies in adults that favor chlorthalidone especially for systolic blood pressure reduction.¹¹ There is no randomized controlled trial comparing the benefits and risks of these two agents in older adults to help answer this question.

Given this background, investigators from Canada observationally examined the effectiveness and safety of both of these agents to address this issue.¹² This retrospective population-based cohort study included 10,384 patients newly treated with chlorthalidone and 19,489 patients newly treated with hydrochlorothiazide aged 66 years or older between January 1993 and March 2010. They linked high quality health databases that had been used in prior studies to collect the independent and dependent variables and employed propensity scoring to adjust for differences in the two groups. The outcome for effectiveness was a composite of death or hospitalization with acute myocardial infarction, heart failure, or ischemic stroke. The outcomes for safety were hospitalization with hypokalemia or hyponatremia and all-cause hospitalization. The starting dose of chlorthalidone was 12.5, 25, and 50 mg per day in 11%, 70%, and 10% of patients, respectively. The starting dose of hydrochlorothiazide was 12.5, 25 and 50 mg per day in 67%, 24%, and 5% of patients, respectively.

The results showed little difference between the groups in the composite effectiveness outcome (3.2 events per 100 person-years in the chlorthalidone group vs. 3.4 events per 100 person-years in the hydrochlorothiazide group). Likewise, there was no difference in all cause hospitalization between the groups. However, hospitalization with an admission diagnosis of hypokalemia was more frequent in the chlorthalidone group (0.69 events per 100 person-years) compared with the hydrochlorothiazide group (0.27 events per 100 person-years; adjusted hazard ratio 3.06, 95% CI 2.04 to 4.58). Hospitalization with an admission diagnosis of hyponatremia was also more frequent in the chlorthalidone group

(0.69 events per 100 person-years of follow-up) compared to the hydrochlorothiazide group (0.49 events per 100 person-years; adjusted hazard ratio 1.67, 95%CI 1.24 to 2.28).

This study is important because the findings showed no difference in effectiveness between the two drugs but increased harm via hypokalemia and hyponatremia in chlorthalidone treated patients compared to hydrochlorothiazide-treated patients. The authors concluded that hydrochlorothiazide is safer than chlorthalidone in elderly patients at typically prescribed doses. The findings should be interpreted in the light of prior studies that found chlorthalidone to be superior to hydrochlorothiazide for health outcomes. Furthermore, in this study, patients treated with chlorthalidone were less likely to also be taking an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker which could affect rates of hypokalemia between the groups. At baseline, 0.8% in both groups were taking a potassium-sparing diuretic, but no information is provided on the use of potassium supplements during the trial. The possibility of residual confounding or group differences in unmeasured characteristics is a potential limitation in all cohort studies. Episodes of clinically significant electrolyte abnormalities could have been missed because of the use of administrative codes to identify these events. The absolute risk difference was small for hypokalemia and hyponatremia. Furthermore, the maintenance doses of the drugs were not reported.

This study is an important addition to the literature on the important and common issue of the choice between hydrochlorothiazide and chlorthalidone for the treatment of hypertension in older adults. The study is an outstanding reminder to prescribers of the importance of monitoring electrolytes when prescribing these medications and the classic geriatric prescribing dictum of “starting low”, and sometimes, “staying low” with drug dosage.

Article 3: Reducing anticholinergic burden in the frail elderly

There are numerous measures of anticholinergic medication use.¹³ One of the most commonly studied measures is the Anticholinergic Drug Scale (ADS).¹⁴ This measure was first introduced in 2002 by Carnahan et al. and further validated in 2006.¹⁴ Anticholinergic drugs included in the ADS is in part based upon their serum anticholinergic activity (SAA, as quantified by displacement of a known anticholinergic from muscarinic rat brain receptors). The ADS utilizes an ordinal scale from 0–3 where level 2 and 3 drugs are considered to be highly anticholinergic.¹⁴

A randomized single-blind pharmacist intervention study from Norway used the ADS as a process outcome measure.¹⁵ Eighty seven older patients residing in 21 nursing homes with an ADS score ≥ 3 were randomized. The pharmacist’s intervention consisted of performing a drug regimen review and communicating with prescribing physicians the alternatives to anticholinergic drug (s). While the median ADS score in the intervention group was reduced from 4 to 2, no change in median ADS scores were noted in the control group ($p < .0001$). Despite this change in ADS score, no improvement was seen in four cognitive function scales or a measure of adverse drug effects (i.e., saliva flow).

What are some possible reasons for this conundrum? One possibility is misclassification of drugs that did not possess anticholinergic properties. The most common anticholinergic

medication changed in this study was furosemide. A recent review of anticholinergic measures concluded that there was insufficient evidence suggesting that furosemide had anticholinergic properties.¹³ Another possibility is that insensitive measures of cognitive function were used. Indeed only one global measure (the Mini-Mental State Exam [MMSE]) of cognitive function and three CERAD memory subscales were utilized in the study. Perhaps more sophisticated neuropsychological testing that addressing areas such as executive function may have detected improvement in cognition. It is important to note that only one other randomized controlled intervention trial of anticholinergic drug withdrawal also conducted in 15 nursing home patients has been published.¹⁶ They too found no improvement in cognitive function as determined by the MMSE. Both studies may also have been underpowered to detect statistically significant changes. A recent study of 102 older Canadians was published that simultaneously compared the impact of four anticholinergic measures including the ADS on 7 sensitive neuropsychological tests.¹⁷ Using a standardized regression based approach they found that increase in anticholinergic burden as determined by any of the four measures were associated with an increased risk of cognitive decline as measured by only two of the sensitive neuropsychological tests (i.e., Trail-Making Test Part B for one AC measure and free and cued recall delayed memory test for the other three measures on of which was the ADS). As concluded by a recent comprehensive review of this topic, studies with larger sample sizes, duration, and methods for measuring anticholinergic drugs are warranted.¹⁸

CONCLUSIONS

One of the studies highlight that the rate of adverse drug effects may be different for different agents within a therapeutic class. Another study reminds us of the importance of conducting predictive validity studies for measures of suboptimal prescribing, in this case anticholinergics, with important health outcomes before using them in intervention studies and/or quality improvement errors. Finally, one study showed that both explicit and implicit measures of suboptimal prescribing can be improved by a clinical pharmacist intervention as well as reducing drug-related readmissions to hospital. Hopefully, health policy makers and clinicians will find this information helpful in improving the quality of care for older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Semla serves on the Omnicare, Inc. Pharmacy and Therapeutics Committee and he is a member of AARP's Caregiving Advisory Panel. He is an author and editor for LexiComp, Inc; his spouse is an employee of AbbVie and owns stock in AbbVie, Abbott Labs, and Hospira.

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