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Year in Review: Medication Mishaps in the Elderly

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Abstract

Objective—This paper reviews articles from the past year that examined medication mishaps (i.e., medication errors and adverse drug events [ADEs]) in the elderly.

Methods—The MEDLINE and EMBASE databases were searched for English-language articles published in 2010 using a combination of search terms including: *medication errors*, *medication adherence*, *medication compliance*, *suboptimal prescribing*, *monitoring*, *adverse drug events*, *adverse drug withdrawal events*, *therapeutic failures*, and *aged*. A manual search of the reference lists of the identified articles and the authors' article files, book chapters and recent reviews was conducted to identify additional publications. Five studies of note were selected for annotation and critique. From this literature search, this paper also provides a selected bibliography of manuscripts published in 2010 (excluding those previously published in the *American Journal of Geriatric Pharmacotherapy* or by one of the authors) that address various types of medication errors and ADEs in the elderly.

RESULTS—Three studies addressed types of medication errors. One study examined underuse (due to prescribing) as a type of medication error. This was a before-and-after study from the Netherlands reported that those who received comprehensive geriatric assessments had a reduction in the rate of under-treatment of chronic conditions over a third (from 32.9% to 22.3%, $p < 0.05$). A second study focused on reducing medication errors due to the prescribing of potentially inappropriate medications. This quasi-experimental study found that a computerized provider order entry clinical decision support system decreased the number of potentially inappropriate medications ordered for patient's ≥ 65 years of age who were hospitalized (11.56 before to 9.94 orders per day after, $p < 0.001$). The third medication error study was a cross-sectional phone survey of managed-care elders. This study found that more blacks than whites had low antihypertensive medication adherence as per a self-reported measure (18.4% vs. 12.3% respectively; $p < 0.001$). Moreover, blacks compared to whites used more complementary and alternative medicine (CAM) for the treatment of hypertension (30.5% vs. 24.7%, respectively; $p = 0.005$). In multivariable analyses stratified by race, among blacks, those that used CAM were more likely than those that did not to have low antihypertensive medication adherence (prevalence rate ratio 1.56, 95% confidence interval 1.14–2.15, $p= 0.006$).

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The remaining two articles each addressed some form of medication adverse events. A case-control study of Medicare Advantage patients revealed for the first time that skeletal muscle relaxant use was significantly associated with an increased fracture risk (adjusted odds ratio 1.40, 95% confidence interval 1.15–1.72; $p < 0.001$). This increased risk was even more pronounced with the concomitant use of benzodiazepines. Finally, a randomized controlled trial across 16 centers in France used a one-week educational intervention about high-risk medications and ADEs directed at rehabilitation health care teams. They found that the rate of ADEs in the intervention group was lower than that in the usual care group (22% vs. 36%, respectively, $p = 0.004$).

CONCLUSION—Information from these studies may be used to advance health professionals' understanding of medication errors and ADEs and may help guide research and clinical practices in years to come.

Keywords

medication errors; suboptimal prescribing; medication adherence; drug monitoring; adverse drug events; aged

INTRODUCTION

Medication mishaps in the elderly range from medication errors to medication-related adverse patient events (MRAPEs).[1] Older adults are at an increased risk of experiencing medication mishaps because of their frequent use of multiple medications (i.e., polypharmacy) and the pharmacokinetic and pharmacodynamic changes that occur with aging.[2] In fact, it is estimated that elderly people have four times greater odds of being hospitalized for a medication mishap than those <65 years of age (16.6% vs. 4.1%).[3] As the geriatric population continues to grow, critical evaluation of the literature may help to identify current problems and develop solutions for the future. Therefore, an updated review of medication mishaps among older adults remains timely and practical.

METHODS

MEDLINE and EMBASE databases ere searched for articles from published in 2010 in English involved humans, and contains one or more of the fallowing terms: *medication errors*, *medication adherence*, *medication compliance*, *suboptimal prescribing*, *monitoring*, *adverse drug events*, *adverse drug withdrawal events*, *therapeutic failures*, and *aged*. A manual search of the reference lists of the identified articles and the authors' article files, book chapters, and recent reviews was conducted to identify additional publications. Those studies that, in the authors' opinions, addressed key medication-related issues facing older people were included in the review. Articles were categorized according to a previously described classification system for medication errors and MRAPEs.[1] Selected additional articles of interest from 2010 have been categorized and are listed in a bibliography (Appendix 1).

RESULTS

Potential Under-Prescribing

Tulner et al. published the results of an observational study assessing the impact of comprehensive geriatric assessment (CGA) on the prevalence of under-treatment in the elderly.[4] Under-treatment can be defined as the omission of indicated drug therapies for the treatment or prevention of a disease, and it has been associated with increased morbidity and mortality as well as decreased quality of life.[2]

In 2004, 807 geriatric outpatients were recruited for a prospective descriptive study of CGA from the Geriatric Day Clinic of an Amsterdam, Netherlands hospital.[4] From this initial group, 516 were identified as having at least one of 10 commonly under-treated disease (i.e., hypertension, angina pectoris, cerebrovascular accident [CVA], transient ischemic attack, peripheral arterial disease, myocardial infarction [MI], heart failure, atrial fibrillation, diabetes mellitus, osteoporosis) or requiring preventive therapy for a potential adverse drug event (ADE) (i.e. bisphosphonates for long-term corticosteroid use, proton pump inhibitors [PPIs] for long-term non-steroidal anti-inflammatory [NSAID] use, laxatives for long-term morphine use). Patients were considered under-treated if lacking any drugs indicated for the above conditions in accordance with 2004 guidelines from the Dutch College of General Practitioners (Dutch GPs). Other national and international interdisciplinary guidelines were used when Dutch GP guidelines were unavailable for specific disease states (e.g., CVA, MI). Treatment drugs of interest were antihypertensives, antithrombotics, oral anticoagulants (OACs), ACE inhibitors, beta blockers, anti hyperglycemics, and bisphosphonates. As a secondary objective, the prevalence of contraindications for OACs, other antithrombotics, and beta blockers was investigated; no other reasons were considered adequate for justifying under-treatment.

In the Geriatric Day Clinic, geriatricians and geriatric residents conducted CGAs, which consisted of a complete medical and medication history, assessment using the Medication Appropriateness Index, and an evaluation of current complaints and functional limitations. Potential problems with under-prescribing were discussed by both the study physician and pharmacist, and decisions were made about the changing or prescribing of medications.

Just over half (53%) of the patients were female and the average age was 81.5 years. Prior to CGA, 32.9% (n=170) of patients were identified as being under-treated. Following CGA, under-treatment was significantly reduced (22.3%, $p<0.01$). Examples of conditions whose under-treatment was resolved with CGA included prescribing of bisphosphonates in those taking chronic oral steroids and giving PPIs to those receiving chronic NSAIDs. One factor associated with under-treatment at follow-up was polypharmacy (≥5 medications) (76.5% vs. 68.8% in those without polypharmacy; $p = 0.068$). Similarly, patients with contraindications to medications (e.g., antithrombotics, beta blockers) were more likely to be under-treated than not (49.6% vs. 11.2%; $p < 0.01$).

This study illustrates that nearly one-third of elderly outpatients from Europe before CGA had evidence of under-treatment. This rate is considerably less than the 50–66% rate of under-treatment reported for elderly outpatients in the United States.[5] This research also supports previous findings from a randomized controlled trial that CGA reduces suboptimal prescribing, including under-treatment, in the aged.[6]

This study is limited by its lack of a control group, unblinded evaluation of under-treatment, and lack of control for historical or confounding factors that might have influenced the study findings. Additionally, this study is based on data collected in one hospital in the Netherlands in 2004 and guidelines from that year; as such, differences in other populations, prescriber practices, and treatment and prevention guidelines may limit the study's generalizability.

Potential Inappropriate Prescribing

Mattison et al. conducted a quasi-experimental study (before-and-after without a control group) to determine whether a computerized provider order entry (CPOE) with clinical decision support (CDS) system could decrease orders for potentially inappropriate medications (PIMs), as defined by a subset of Beers list medications in hospitalized older patients.[7,8] The study involved inpatients ≥ 65 years who were admitted to a large urban

academic medical center in Boston, Massachusetts. The "before" period was between June 1, 2004 to November 29, 2004, and the "after" period was from March 17, 2005 to August 30, 2008. The main outcome measure was the rate of orders for PIMs before and after the CPOE with CDS system was deployed. Prescribers received alerts requiring responses before confirming their orders. Each alert contained an explanation for the warning, a list of conditions that could place a patient at increased risk, and, where appropriate, advised an alternative medication or dose reduction. During the course of the study, the mean rate of ordering PIMs decreased from 11.56 before to 9.94 orders per day after the implementation of a CPOE with CDS system (difference, 1.62; $p < 0.001$). There was no evidence that the effect waned over time. There were also no appreciable changes in the rate of medication orders that were not targeted after CPOE with CDS implementation or for which only dose reduction was recommended. These effects persisted when analyzed with autoregressive models that accounted for secular trends and season ($p < 0.001$). The authors concluded that specific alerts embedded into a CPOE system, used in patients ≥ 65 years, can decrease the number of orders of PIMs quickly and specifically.

While this study adds to previous knowledge that information technology interventions may improve the quality of prescribing for older adults, it also has some potential limitations worth noting.[9] First, the lack of random assignment and a control group reduces the ability to establish causality. Although study analyses factored in the time period to address historical factors that could account for the findings, it did not control for other potential patient, prescriber, or health system factors that could result in confounding the relationship between the intervention and outcome measure. Second, no information was provided about the impact of the intervention on patient outcomes. This is important given the questionable relationship between PIM and ADEs.[10] Third, the CPOE with CDS system used a non-scientific method for alert development and was unable to distinguish between orders for new vs. chronic PIMs, and lacked linkage with an electronic medication administration system to determine if medication had actually been administered. Finally, the generalizability of the study is limited as the investigators developed their own software programs to conduct the intervention that are not available to the public.

Medication adherence

Krousel-Wood et al. reported on the association between complementary and alternative medicine (CAM) use and antihypertensive medication adherence in older black and white adults in a sample of patients enrolled in a large managed care organization.[11] The authors included 2,180 participants (black, n=670; white, n=1,510) with hypertension who completed the baseline interview of the Cohort Study of Medication Adherence among Older Adults (CoSMO). Participants were telephoned to complete the baseline survey, consisting of an assessment of sociodemographic factors, clinical factors, healthcare system factors, antihypertensive medication treatment-related variables, CAM use for blood pressure management, and adherence to antihypertensive medication. CAM use was assessed with items from a previously validated survey and included three domains: (1) health food (e.g., fish oil, fiber, L-arginine, co-enzyme Q10), (2) herbal supplements (e.g., garlic, snakeroot, yarrow, Chinese herbs), and (3) relaxation techniques (e.g., yoga, meditation, other relaxation techniques). [12] A CAM use variable was created for those who reported use from any of these domains at least several times or on a regular basis in the year prior. Self-reported antihypertensive adherence was evaluated with the 8-item Morisky Medication Adherence Scale (MMAS-8), which has previously been shown to be reliable and valid.[13,14] A dichotomous antihypertensive adherence variable was created using the MMAS-8 score to identify subjects with low medication adherence (low adherence < 6 vs. not low ≥ 6). Finally, the following question was asked to assess potential cost-related nonadherence: "In the last year, have you ended up taking less high blood pressure

medication than was prescribed because of the cost?" All analyses were stratified by race to assess for any racial differences in the effect of CAM use on medication adherence.

Overall, the sample had relatively low self-reported nonadherence, with 14.1% of participants having an MMAS-8 score < 6. About a quarter of the sample (26.5%) used CAM in managing their blood pressure. Bivariate analysis revealed that significantly more blacks than whites were CAM users (30.5% vs. 24.7%; $P = 0.005$) and that more blacks had low antihypertensive medication adherence (18.4% vs. 12.3%; $P < 0.001$). After adjusting for sociodemographic characterics, depression, and cost-related nonadherence, the risk of low antihypertensive medication adherence associated with CAM use was increased in blacks (prevalence ratio 1.56; 95% confidence interval 1.14–2.15) but not in whites (prevalence ratio 0.95; 95% confidence interval 0.70–1.29).

The study findings are important because they clearly showed that CAM use was more common in older blacks and may have a negative effect on antihypertensive medication adherence. The greater use of CAM in black subjects is in consistent with some studies but not with others where blacks used less CAM than whites. [15]. However, since older adults often do not report CAM use to their primary care physicians, the study's results reinforce the recommendation to question about the use of non-prescription medications when taking a medication history. Another key finding from this study is the importance of assessing cost-related nonadherence when evaluating medication adherence in older adults, as this factor was shown to be significantly associated with low adherence in both blacks and whites.

Some potential limitations of this study include the cross-sectional design and self-reported nature of the data, both of which can lead to potential bias. Moreover, outcomes such as blood pressure control that could be influenced by medication adherence were not assessed in this study. Finally, the study was focused on one disease and included older adults with from only one region of the United States. Thus, further research is needed with other co-morbid conditions and other populations to improve the generalizability of the results.

Medication Related Adverse Patient Events

Golden et al. conducted a case-control study of a nationwide Medicare Advantage (MA) population to identify the risk of fracture injuries for patients prescribed skeletal muscle relaxants (i.e., carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol).[16] Cases and controls were identified from the population of persons ≥ 65 years who were enrolled for at least 90 days in a MA plan between June 2004 and May 2007. Cases were defined as having at least one ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) code for fracture in their medical record and at least one prescription within the three months prior to the date of the fracture event. Controls were persons who had been prescribed at least one drug within the three months prior to the matched case's fracture event, but who did not have an ICD-9-CM code for fracture in their medical record during the study period. Controls were matched 1:1 with cases on age, sex, state of residence, specific MA plan, coverage period, and Charlson co-morbidity index. After adjusting for other potential covariates, (i.e., age, fibromyalgia, urinary incontinence, unspecified disorders of the back, diagnoses associated with the use of skeletal muscle relaxants, and the use of antidepressants or atypical antipsychotics), those exposed to skeletal muscle relaxants had an increased risk of a fracture (odds ratio = 1.40; 95% CI 1.15–1.72). However, there was no significant increase in risk for persons exposed to combinations of ≥ 2 skeletal muscle relaxants over that found for the use of a single skeletal muscle relaxant. An increased risk was also seen for both long-acting benzodiazepines (OR = 1.90; 95% CI 1.49–2.43) and short-acting benzodiazepines (OR = 1.33; 95% CI 1.15–1.55). The combination of a potentially inappropriate skeletal muscle

relaxant with either a long- or short-acting benzodiazepine was associated with an even greater risk, with ORs of 2.66 (95% CI 1.94–3.65) and 1.86 (95% CI 1.45–2.40), respectively.

This study is important since falls and fall-related injury remain a very important public health problem for adults ≥ 65 years with 28–35% of community-dwelling persons from this age group falling at least once per year and 5% of falls resulting in fractures.[17] Moreover, it provides further justification for the inclusion of skeletal muscle relaxants on the Beers list as PIMs.[8] Prior to this study, there have only been two studies showing a link between anticholinergic drug use and falls in the elderly.[18,19] This study also indicates that the use of central nervous system medications from two drug classes appears to significantly increases the risk of fracture. This is consistent with recent work showing that CNS polypharmacy increases the risk of recurrent falls in community-dwelling elders.[20]

This study has some limitations worth noting. There is a high probability that there was bias in the measurement of the outcome. No attempt was made to confirm by medical record review that a fracture actually occurred and was not due to other causes such as a motor vehicle accident or cancer. Moreover, not all fractures come to the hospital for treatment. For example, in older adults, skeletal compression fractures can be a common manifestation of osteoporosis sometimes found inadvertently through x-ray tests. In addition, ICD-9 codes for fractures other than the patella or hip have positive predictive values less than 93%.[21,22] The authors note that data which would enable these factors to be included in the analysis were not generally present in the investigators' MA claims database. There is also potential misclassification of exposure. Cases and controls qualified as being exposed to a muscle relaxant or benzodiazepine if pharmacy records showed at least one prescription within the three months prior to the date of a case fracture diagnosis. However, since skeletal muscle relaxants are usually indicated for short-term use this might have led to the inclusion of persons who were no longer taking the medication. In addition, dispensing of medications may not represent the medication being administered or taken. One also cannot rule out the presence of confounding due to other known risk factors for falls and fractures such as gait, depression, cognitive impairment, mobility limitations, impaired activities of daily living, and history of falls.[17]

Trivalle et al. published the results of a randomized controlled study designed to reduce the rate of ADEs in 576 older hospitalized patients from 16 centers in France.[23] After a two-week lead-in period, these 16 units were randomized to control (usual care) or educational intervention. The one-week educational intervention consisted of the education of rehabilitation health-care teams about important geriatric pharmacotherapy topics (i.e., risk of NSAIDs, benzodiazepines and anticholinergics, appropriate use of opioids including the need for slow titration and regular laxative regimens, and the need to calculate estimated creatinine clearance for renally cleared drugs and adjust dose accordingly). The follow-up period consisted of two weeks. The main outcome was probable ADEs (i.e., drug came before event, known effect, improvement with medication stoppage, and not due to patient's clinical condition). These potential ADEs were detected by an investigator who reviewed the medical record and talked with nurses and physicians taking care of patients. The preventability of probable ADEs was evaluated by a multidisciplinary team of physicians and pharmacists. Overall, there were 122/475 (25.7%) ADEs in the intervention and control wards before randomization and this was reduced to 38/196 (19.4%) in those wards randomized to the intervention group by the end of the study. In contrast, there were 63/241 (26.1%) ADEs in the control group after the intervention. Overall, 28% of ADEs were deemed preventable.

The importance of this study is that it is only the fifth randomized controlled study to examine ADEs/adverse drug reactions (ADRs) as the main outcome.[24–27] Moreover, it appears to be the first randomized controlled trial of an intervention to reduce ADEs in the hospital setting restricted to the elderly. However, there are some potential issues with this study. First, the statistical analysis did not take into account clustering since the unit of randomization was hospital units as opposed to patients. There is also potential misclassification because a formal validated ADR causality algorithm (e.g., Naranjo) was not utilized.[28] No information was noted about whether the ADE evaluators were blinded to group assignment. Finally, the generalizability to hospitals from other countries is unknown.

CONCLUSIONS

Information from these studies may be used to advance health professionals' understanding of medication errors and ADEs and may help guide research and clinical practices in years to come.

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Appendix 1. Selected Bibliography of Manuscripts Published in 2010 on Medication Mishaps in the Elderly*

MEDICATION ERRORS

Suboptimal prescribing

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* Excludes those previously published in the *American Journal of Geriatric Pharmacotherapy* or by one of the authors