Exposure to High-Risk Medications is Associated With Worse Outcomes in Older Veterans With Chronic Pain

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Abstract: *Background:* Chronic pain is common, costly and leads to significant morbidity in older adults, yet there are limited data on medication safety. The authors sought to evaluate the association of incident high-risk medication in the elderly (HRME) with mortality, emergency department (ED) or hospital care among older adults with chronic pain. *Methods:* A retrospective Veterans Health Administration cohort study was conducted examining older veterans with chronic pain diagnoses and use of incident HRME (opioids, skeletal muscle relaxants, antihistamines and psychotropics). Outcomes evaluated included all-cause mortality, ED visits or inpatient hospital care. Descriptive statistics summarized variables for the overall cohort, the chronic pain cohort and those with and without HRME. Separate generalized linear mixed-effect regression models were used to examine the association of incident HRME on each outcome, controlling for potential confounders. *Results:* Among 1,807,404 veterans who received Department of Veterans Affairs care in 2005 to 2006, 584,066 (32.3%) had chronic pain; 45,945 veterans with chronic pain (7.9%) had incident HRME exposure. The strongest significant associations of incident HRME were for high-risk opioids with all-cause hospitalizations (odds ratio [OR] 2.08, 95% confidence interval [CI] 1.95–2.23), skeletal muscle relaxants with all-cause ED visits (OR 2.62, 95% CI 2.52–2.73) and mortality (OR 0.80, 95% CI 0.74–0.86), antihistamines with all-cause ED visits (OR 2.82 95% CI 2.72–2.95) and psychotropics with all-cause hospitalizations (OR 2.15, 95% CI 1.96–2.35). *Conclusions:* Our data indicate that incident HRME is associated with clinically important adverse outcomes in older veterans with chronic pain and highlight the importance of being judicious with prescribing certain classes of drugs in this vulnerable population.

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Chronic pain is highly prevalent in all adult groups[1] with over 50% of the U.S. population age 65 and older reporting bothersome pain in the last month.[2] Among primary care patients in the Veterans Health Administration (VHA), up to 50% of men and 75% of women patients report chronic pain.[3–5] Pain is associated with poorer self-reported health status, higher levels of emotional distress, decreased social and physical activities[3,6] and greater use of health care resources.[7,8] Although pain is common, costly and leads to significant morbidity, older adults are not well represented in clinical trials[9]; therefore, there are limited evidence to inform decisions especially with respect to medication safety in this population.[10]

Older adults with chronic pain have high rates of analgesic use[11,12] and are also highly susceptible to adverse effects (ADEs) of analgesic treatments.[10] A meta-analysis of observational studies found that the odds of being hospitalized for ADE-related conditions are 4 times higher for older compared with younger individuals. Up to 88% of ADE-related hospitalizations in older adults are potentially preventable.[13] Compared with younger adults, older adults are twice as likely to present to emergency departments (EDs) for ADE (over 177,000 emergency visits each year) and nearly 7 times more likely to be hospitalized after an emergency visit.[14] As highlighted by the Institute of Medicine,[15] preventing ADEs in older adults is a public health and patient safety priority.

The risk of ADEs increases in older adults because of a unique combination of age-related physiologic changes including altered drug absorption, decreased renal excretion, multimorbidity, polypharmacy and functional impairments.[10,16] Exposure to high-risk medications for the elderly (HRME), a Healthcare Effectiveness Data and Information Set (HEDIS) quality measure, was developed by the National Committee on Quality Assurance (NCQA) in 2006 to address this concern. The HEDIS HRME measure[17] was developed by an expert panel and includes drugs from the Beers criteria[18] for potentially inappropriate prescribing in the elderly that have been previously identified as being high risk of potentially severe outcomes.[19] This measure is now used to benchmark the quality of medication management in older adults enrolled in Medicare and other managed care plans.[20,21] Older adults with chronic pain may be at high risk of ADEs related to HRME such as opioids,[22] skeletal muscle relaxants,[23] antipsychotics[24] and sedating antihistamines, which are often prescribed in patients with pain although the evidence for their effectiveness and *safety* is lacking.

The objective of this study was to evaluate the association of incident HRME with mortality, ED or hospital care among older adults (65+) with chronic pain. To accomplish these objectives, data were used from a Department of Veterans Affairs (VA) nationwide cohort of older adults with chronic pain. The authors hypothesized that, after adjusting

for potential confounders, older adults with chronic pain and incident HRME will be more likely than those without incident HRME to experience adverse outcomes after adjusting for potential confounders.

METHODS

For this population-based cohort study, the authors used data from the VA Health Care System administrative and clinical databases. These databases are the repositories of clinical data from more than 150 VA hospitals and 850 outpatient clinics. Details regarding this study cohort have been previously published.[25,26]

Ethics Statement

The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved this study and granted a waiver of informed consent.

Study Design, Setting and Sample

The cohort consisted of veterans aged 65 years and older on October 1, 2005 and veterans who received VA care (n = 1,807,404) during fiscal year (FY) 2005 (October 1, 2004 to September 30, 2005) and FY 2006 (October 1, 2005 to September 30, 2006). From that population, the sample was restricted to veterans who had diagnoses of chronic pain [neuropathic, nocireceptive and mixed] defined using *ICD-9-CM* codes[27] at least 2 times, 7 or more days apart during FY 2004 to 2006 (Appendix 1). To examine incident use, individuals who had previous exposure to outpatient prescriptions for any HRME in FY 2005 were excluded from the analyses.

Data Sources

The authors used inpatient and outpatient demographic, health care utilization and comorbidity data from the VA National Patient Care Database. Pharmacy data extracted from VA Pharmacy Benefits Management (PBM) data set and vital status information obtained from the Vital Status file were

described in greater detail in previous publications.[26] Encrypted patient identifiers linked information across these databases.

Outcomes

The outcome measures examined were all-cause mortality, ED visits or inpatient hospital care. Outcomes were evaluated from initial HRME exposure to 1 year after the index date. Secondary outcomes were inpatient admissions or ED visits, because of falls or nonspine fractures. Both primary and secondary outcomes were selected based on clinical importance and as potential surrogate markers for falls and fractures.

Independent Variables

The authors evaluated the 4 types of most commonly[25] used HEDIS HRME: opioids, skeletal muscle relaxants, antihistamines and psychotropics. Drug exposure was defined using the VA product name, which identifies any dose or formulation of that drug (Table 1). The authors identified incident HRME by drug category. The authors attempted to evaluate incident use of indomethacin and oral ketorolac; however, the sample size (n = 925) was too small to evaluate our outcomes of interest.

Covariates

The authors identified patient demographic characteristics (ie, age, sex and race/ethnicity) between FY 2004 and FY 2006. Race/ethnicity was categorized as white, black, Hispanic (of any race), other and missing. Missing demographic data on race/ethnicity are common in VA files; however, several years
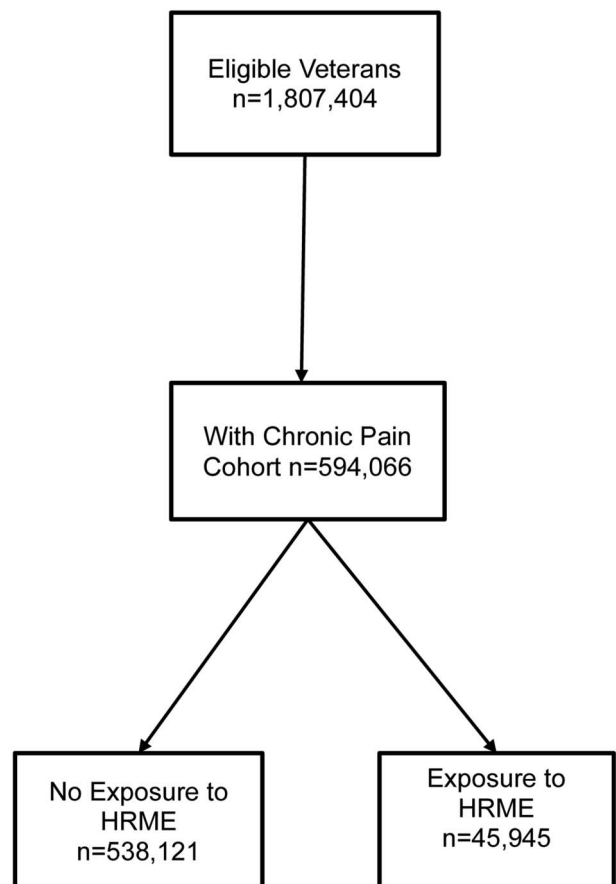
TABLE 1. High risk medications in older adults with chronic pain

Drug group	Drugs included	Concerns regarding use
Opioids	Propoxyphene, meperidine and pentazocine	Confusion, falls, fractures, dependency and withdrawal
Skeletal muscle relaxants	Methocarbamol, cyclobenzaprine, carisoprodol, chlorzoxazone, metaxalone and orphenadrine	Anticholinergic ADEs, excessive sedation and weakness; questionable effectiveness
Antihistamines	Diphendydramine, hydroxyzine, promethazine, cyproheptadine, dexchlorpheniramine and tripelennamine	Confusion and sedation, anticholinergic ADEs
Psychotropics	Diazepam, chlordiazepoxide, flurazepam, thioridazine, meprobamate and barbiturates	Excessive sedation, falls, central nervous system and extrapyramidal side effects, dependency

FIGURE 1. Derivation of study cohort.