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RESEARCH NOTES

An evaluation of a potential calcium channel blocker–lower-extremity edema–loop diuretic prescribing cascade

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ABSTRACT

Objectives: Dihydropyridine calcium channel blockers (DH-CCB) are associated with lower-extremity edema (LEE). Loop diuretics have been used inappropriately to treat DH-CCB-associated LEE, constituting a prescribing cascade (PC). The aim of this work was to identify the prevalence and factors associated with potential DH-CCB–LEE–loop diuretic PC.

Methods: The 2014 National Ambulatory Medical Care Survey was used to identify patient visits in which a DH-CCB was continued. The definition of a potential PC was the continuation or initiation of a loop diuretic in the absence of congestive heart failure, cancer, obstructive sleep apnea, chronic kidney disease or end-stage renal disease, obesity, or resistant hypertension. Multivariable logistic regression was used to identify factors related to a potential PC, including demographic information, number of medications, number of patient visits in the previous 12 months, and comorbid conditions.

Results: Among the estimated 47.5 million patient visits in which a DH-CCB was continued, 4.6% had a potential PC. Visits in patients 65 to 84 years of age (odds ratio [OR] 2.56, 95% CI 1.20–5.43) and 85 years of age and older (OR 3.89, 95% CI 1.76–8.61) were more likely to have potential PC compared with patients 18 to 64 years of age. Visits in patients with 5 to 7 (OR 3.75, 95% CI 1.72–8.19), 8 to 11 (OR 2.20, 95% CI 1.09–4.44), and 12 or more (OR 5.23, 95% CI 2.29–11.94) medications were more likely to have potential PC compared with patients with 4 or fewer medications.

Conclusion: A potential DH-CCB–associated LEE loop diuretic PC was present in approximately 2.2 million patient visits in which DH-CCB was continued. Older age and an increasing number of concomitant medications were associated with this potential PC.

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Hypertension is the most common condition in the United States, present in one-third of adults 18 years of age or older.¹ Calcium channel blockers (CCBs) are considered as a first-line option to treat hypertension in the absence of compelling comorbidities.² Dihydropyridine (DH) CCBs are a particularly useful treatment option in older adults, because this class of

medication does not require routine electrolyte monitoring or cause hypovolemia.^{3–6}

A disadvantage of DH-CCBs is the potential for lower-extremity edema (LEE), which occurs in 12.3% of patients.⁵ LEE is due to increased hydrostatic pressure from precapillary arteriolar dilation, which causes fluid to shift to the interstitial space and pooling of fluid in lower extremities.^{7–12} The risk of LEE due to DH-CCBs appears to be dose and duration dependent; more than 25% of patients on high-dose DH-CCBs for more than 6 months experience LEE.⁵ Although not recommended, diuretics have been used to treat DH-CCB-associated LEE.¹¹ This approach results in a prescribing cascade (PC) in which a loop diuretic is prescribed to LEE arising from an unrecognized adverse event of a DH-CCB.^{13,14} This treatment strategy should be avoided,

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because DH-CCB–associated LEE is not the result of hypervolemia.^{7,11,12,15,16} Excessive diuresis in a euvolemic patient can lead to dehydration and consequences such as falls and increased hospitalizations.^{17–23} It is unknown how many providers are aware of this PC; moreover, it may be increasingly difficult to identify a PC in a patient with a complex medication list. Currently, the potential DH-CCB–LEE–loop diuretic PC has not been described in the literature beyond 1 case report.²⁴

The present study aimed to estimate the prevalence of the potential DH-CCB–LEE–loop diuretic PC and associated factors with the use of a nationwide sample of ambulatory medical care visits in the United States.

Methods

Data source

We performed a cross-sectional observational study of the publicly available National Ambulatory Medical Care Survey (NAMCS) database. The NAMCS is an annual national probability sample of patient visits to non–federally employed providers.²⁵ Medications that patients were taking before the visit and continued at the conclusion of the visit were classified as “continued.” Medications initiated during the visit were classified as “new.” The NAMCS does not include medications discontinued during the visit.

Study population

Visits of nonpregnant patients 18 years of age or older who continued on DH-CCB (Appendix 1) were analyzed. The 2014 NAMCS dataset was selected, because it contains more detail compared with previous years.²⁶ The number of medications that could be abstracted expanded from 10 to 30 in 2014. The number of fields for diagnosis codes and reasons for visit expanded from 3 to 5, and the number of check boxes available to identify comorbidities, regardless of diagnosis codes, was expanded from 14 to 23.

Outcome variable

We assessed new or continued use of a loop diuretic (Appendix 1), which served as a marker for a potential DH-CCB–LEE–loop diuretic PC. Individual loop diuretics were combined into 1 variable, because these medications have the same mechanism of action. However, there are many scenarios in which concomitant use of a DH-CCB and a loop diuretic may not be a PC. Loop diuretics are used to maintain euolemia in patients predisposed to hypervolemia, such as congestive heart failure (CHF).²⁷ Cancer, venous thromboembolism (VTE), obstructive sleep apnea (OSA), chronic kidney disease (CKD) or end-stage renal disease (ESRD), and obesity may be associated with LEE, which can also lead to the prescribing of a loop diuretic.^{12,28} The use of a loop diuretic is also a treatment strategy for resistant hypertension.^{28–30} Resistant hypertension was defined as the use of a loop diuretic in visits with 3 or more classes of antihypertensives (Appendix 1), not including DH-CCB. Conditions that may be associated with loop diuretic use were identified based on diagnosis codes, reasons for visit, and the statement “regardless of the diagnoses previously

entered, does the patient now have <variable>, when applicable” (Appendix 2).

We assessed the percent of visits in which a loop diuretic was continued or new among visits in which a DH-CCB was continued. The outcome of potential PC was defined as a new or continued loop diuretic in the absence of CHF, cancer, VTE, OSA, CKD, ESRD, obesity, or resistant hypertension. A secondary definition of a potential PC outcome was also explored in a sensitivity analysis that included a continued or new loop diuretic in the absence of CHF. The conditions of cancer, VTE, OSA, CKD, ESRD, obesity, and resistant hypertension were removed in this secondary analysis because loop diuretic use in patient visits with these conditions may still constitute a PC (e.g., not all cancers result in LEE). We also explored the number of patient visits with potential PC coded that was coded for LEE (Appendix 2).

Independent variables

Older age and female sex increase the risk for DH-CCB–associated LEE, whereas the concomitant use of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker may reduce this risk and may reduce the risk for this potential PC.⁵ Additional factors such as race, geographic region, and number of visits in the previous 12 months categorized in quartiles were examined. Race (e.g., White/European, Black/African American, Asian, Native Hawaiian/Other Pacific Islander, or American Indian/Alaskan Native) was extracted from the patient chart to the NAMCS patient record. Owing to low counts of Native Hawaiian/Other Pacific Islander and American Indian/Alaska Native, these were combined with Black/African American, and race was classified as white and non-white. The number of concomitant medications, excluding DH-CCBs, loop diuretics, and potassium chloride, were classified with the use of quartiles. Potassium chloride was not in the number of concomitant medications, because it is often prescribed with loop diuretics to treat hypokalemia.³¹ Comorbid conditions were also examined as predictors for potential PC because these may be markers for increased disease burden.

Statistical analyses

Data were analyzed using the sampling visit weights. These weights produce national estimates of the number of visits and associated characteristics.²⁵ SAS PROC SURVEYFREQ and PROC SURVEYLOGISTIC were used to account for the clustered nature of the survey.^{32,33} The DOMAIN procedure was used to ensure appropriate variance estimates.^{32,33}

The number of visits was rounded to the nearest thousand.²⁵ The percentage of visits in which a loop diuretic was used among patients who continued DH-CCBs was described along with the percentage of patients with a potential PC. Univariate analyses were used to examine factors potentially associated with a potential DH-CCB–LEE–loop diuretic PC. Weighted odds ratios (ORs) and 95% CIs were calculated with the use of PROC SURVEYLOGISTIC. All variables with *P* less than 0.2 were included in the initial multivariable logistic regression model. Variables were removed with the use of backward selection. Variables with greater than 30% missingness,

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