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Authors

Growdon, Matthew E
Jing, Bocheng
Morris, Earl J
et al.

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Which older adults are at highest risk of prescribing cascades? A national study of the gabapentinoid–loop diuretic cascade

Running title: Risk of gabapentinoid-diuretic cascade

Matthew E. Growdon, MD, MPH,[1,2] Bocheng Jing, MS,[1,2] Earl J Morris, PharmD, PhD,[3,4] W. James Deardorff, MD,[1,2] W. John Boscardin, PhD, [1,2,5] Amy L Byers, PhD,[1,2,6] Kenneth S Boockvar, MD,[7] Michael A Steinman, MD[1,2]

[1]Division of Geriatrics, University of California, San Francisco, San Francisco, CA, USA

[2]San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA

[3]Department of Pharmaceutical Outcomes & Policy, University of Florida College of Pharmacy, Gainesville, FL, USA

[4]Center for Drug Evaluation and Safety, University of Florida, Gainesville, FL, USA

[5]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

[6]Department of Psychiatry, Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, USA

[7]Division of Gerontology, Geriatrics, and Palliative Care, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to:

Mail: Dr. Matthew Growdon, UCSF Division of Geriatrics, 490 Illinois Street, Floor 8, San Francisco, CA 94158

Email: matthew.growdon@ucsf.edu

ORCID: https://orcid.org/0000-0001-5997-4406; @matthew_growdon

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Abstract

Background: Prescribing cascades are important contributors to polypharmacy. Little is known about which older adults are at highest risk of experiencing prescribing cascades. We explored which older veterans are at highest risk of the gabapentinoid (including gabapentin and pregabalin)–loop diuretic (LD) cascade, given the dramatic increase in gabapentinoid prescribing in recent years.

Methods: Using Veterans Affairs and Medicare claims data (2010-2019), we performed a prescription sequence symmetry analysis (PSSA) to assess loop diuretic initiation before and after gabapentinoid initiation among older veterans (≥ 66 years). To identify the cascade, we calculated the adjusted sequence ratio (aSR), which assesses the temporality of LD relative to gabapentinoid initiation. To explore high-risk groups, we used multivariable logistic regression with prescribing order modeled as a binary dependent variable. We calculated adjusted odds ratios (aORs), measuring the extent to which factors associated with one prescribing order versus another.

Results: Of 151,442 veterans who initiated a gabapentinoid, there were 1,981 patients who initiated a LD within 6 months after initiating a gabapentinoid compared to 1,599 patients who initiated a LD within 6 months before initiating a gabapentinoid. In the gabapentinoid–LD group, the mean age was 73 years, 98% were male, 13% were Black, 5% were Hispanic, and 80% were White. Patients in each group were similar across patient and health utilization factors (standardized mean difference < 0.10 for all comparisons). The aSR was 1.23 (95% CI, 1.13, 1.34), strongly suggesting the cascade's presence. People age ≥ 85 years were less likely to have the cascade (compared to 66-74 years; aOR 0.74, 95% CI: 0.56-0.96), and people taking ≥ 10 medications were more likely to have the cascade (compared to 0-4 drugs; aOR 1.39, 95% CI: 1.07-1.82).

Conclusions: Among older adults, those who are younger and those taking many medications may be at higher risk of the gabapentinoid–LD cascade, contributing to worsening polypharmacy and potential drug-related harms. We did not identify strong predictors of this cascade, suggesting that prescribing cascade prevention efforts should be widespread rather than focused on specific subgroups.

Key Points:

- In this cohort study of 151,442 older veterans who newly initiated a gabapentinoid, we identified evidence of the gabapentinoid–loop diuretic prescribing cascade.
- After adjusting for a broad range of patient and health utilization factors, the oldest adults were less likely to have the cascade, and those taking many medications were more likely to have the cascade.
- While these associations were statistically significant, we did not identify strong predictors of the gabapentinoid–loop diuretic cascade.

Why does this matter?

- Overall, we did not identify strong predictors of the gabapentinoid–loop diuretic cascade, suggesting that prescribing cascade prevention efforts should be widespread rather than focused on specific subgroups. Preventing the gabapentinoid–loop diuretic prescribing cascade is an important component of minimizing polypharmacy and concomitant drug-related harms among older adults.

Introduction

Prescribing cascades occur when a medication causes adverse effects that are treated with a second medication.[1,2] Such cascades are under-recognized contributors to polypharmacy among older adults and have been linked with harms including emergency room visits and hospitalizations,[3] increased pill burden,[1] reduced quality of life,[4] and additional costs to individuals and health systems.[5,6]

Despite progress in the detection of prescribing cascades at a population level,[7–12] little is known about which groups of older adults are at highest risk of experiencing cascades; such information would be helpful to guide targeted efforts to mitigate the effects of prescribing cascades.[7] Most studies involving rigorous epidemiologic methods have primarily focused on the detection of specific cascades across large populations, with subgroup analyses by various factors construed as a secondary aim.[8–11] In many of these studies, stratified results are unadjusted, therefore making it challenging to disentangle which factors confer the highest risk of experiencing the prescribing cascade. For example, if a study indicated that people with dementia had a disproportionately high burden of a given prescribing cascade,[11] with unadjusted results it is unclear if this excess risk was in fact driven by another factor (e.g., age).

The present study focuses on one specific cascade—the gabapentinoid (including gabapentin and pregabalin)–loop diuretic (LD) prescribing cascade—with the central aim of exploring which older patients are at highest risk of experiencing this prescribing cascade. Given little prior work in this area, our goal was to conduct an exploratory analysis considering a broad array of potential high-risk groups. The results can inform future hypothesis-driven testing of potential pathways that could be targeted to reduce the risk of experiencing a prescribing cascade. Gabapentinoids were originally developed as antiseizure drugs but are now prescribed mostly for treatment of pain and other conditions; peripheral edema is an established adverse drug effect of gabapentinoids, estimated to affect between 2% and 16% of users.[8,12,13] In some cases, clinicians may respond to gabapentinoid-associated edema by prescribing a loop diuretic (either by misinterpreting the edema as a new condition or by doing so intentionally), thereby leading to a prescribing cascade.

We chose to focus on the gabapentinoid–LD cascade for several reasons. First, gabapentinoid prescribing has increased dramatically in recent years in the US—tripling between 2009 and 2020, with disproportionate increase among older adults and those with multimorbidity[14]—due to frequent off-label use for a variety of medical conditions and a perception by prescribers that it has a favorable safety profile.[15–20] Second, the gabapentinoid–LD prescribing cascade has been identified in prior studies involving data sources from the US, Canada, and Denmark, making it an emblematic prescribing cascade through which to investigate those groups at highest risk of prescribing cascades.[8,11] Moreover, rich US Veterans Affairs (VA) clinical and prescribing data represent a unique opportunity to investigate which groups of older veterans are at highest risk of experiencing the gabapentinoid–LD prescribing cascade.

Methods

Design

We conducted a prescription sequence symmetry analysis (PSSA) to assess the potential association between gabapentinoid use and loop diuretic use and to identify those groups at highest risk of experiencing this cascade. Briefly,

PSSA is a self-controlled study design that has been used in numerous studies to identify prescribing cascades.[6,21,22] In this case-only design, individuals are selected who initiated two drugs of interest during the observation period: a medication suspected of causing a drug-induced adverse event (i.e., index drug, in this case, a gabapentinoid) and a medication potentially used to treat the adverse event (i.e., marker drug, in this case, a loop diuretic).

The PSSA method assesses the temporal ordering of these two drugs, exploiting the fact that if no relationship exists between index and marker drugs, recipients of both drugs would be equally likely to receive them in either order. By contrast, in the case of a prescribing cascade, a higher proportion of initiations of the marker drug would occur after the index drug compared with before. An attractive feature of the PSSA design is that it inherently controls for time-invariant patient characteristics (e.g., sex and some demographic and environmental factors). This is because the analytic cohort comprises individuals who started on both index and marker drugs; factors that are stable over time during the observation period cannot predict the sequencing of these drugs.[23]

Data source

We used national outpatient VA pharmacy data merged with VA and Medicare claims data from fiscal years 2010-2019. This research was approved by the institutional review boards of the San Francisco VA Health Care System and the University of California, San Francisco School of Medicine. We adhered to the Strengthening the Reporting of Studies in Epidemiology (STROBE) reporting guideline (**Supplementary Table S1**).[24]

Study population

We assembled a cohort of older adults receiving care in the VA who newly started a gabapentinoid during the period of January 1, 2013 to August 31, 2019. We required individuals to be age $\geq$ 66 years to allow for $\geq$ 1 year of Medicare eligibility. We defined new users as those receiving a new gabapentinoid fill without any gabapentinoid fills during the preceding year; we set the date of this new gabapentinoid fill as the index date. Among new users of gabapentinoids, we limited the cohort to those individuals who newly started a loop diuretic within 6 months before or after the index date. We adopted this observation window for several reasons: (1) given that most—but not all—gabapentinoid-induced edema occurs in the first few months after prescription, loop diuretic use beyond this window is less likely to be attributable to gabapentinoid-induced edema[25]; (2) to allow for detection of gabapentinoid-induced edema over time given available evidence which suggests that gabapentinoid-induced edema is more likely with higher doses and following dose increases[11,25,26]; and (3) balancing between the various observation windows (90, 180, and 360 days) adopted in a prior PSSA study of this prescribing cascade.[11]

To improve measurement of prescribing within the VA's integrated health system, we excluded older adults who were enrolled in Medicare Part D or Medicare Advantage (given that utilization data may not be complete for these individuals,[27] and in line with our prior studies[28,29]) from one year prior to and six months after the index date. Additionally, we limited our sample to individuals who received at least 80% of their outpatient care in VA settings and were therefore expected to regularly receive drugs from VA pharmacy sources. In line with prior studies, we excluded

individuals with a diagnosis of congestive heart failure, chronic kidney disease, liver disease, and/or venous insufficiency (defined by International Classification of Diseases [ICD]-9 and ICD-10 codes in the 1 year prior to the index date) given that loop diuretics are often used for the treatment of edema in these conditions.[10,11] Finally, in keeping with prior PSSA studies, we excluded individuals who filled both index and marker drugs on the same date.[10,11]

Study drugs

The exposure drugs of interest (index drugs) were gabapentinoids, including gabapentin and pregabalin, at any dose. The outcome drugs of interest (marker drugs) were loop diuretics commonly used for edema including furosemide, torsemide, bumetanide, and ethacrynic acid. We required fills to have a dispensed quantity of 14 or more pills to exclude very short-term or highly intermittent use.

Key variables

Demographic variables included age, sex, and race/ethnicity (using categories based on the Research Triangle Institute definitions found in Medicare claims[30]). Chronic disease covariates included the Deyo adaptation of the Charlson comorbidity index (calculated from VA and Medicare claims during the 2 years before initiation of whichever drug [index or marker] came first). We also determined the presence of specific comorbidities including dementia, diabetes, myocardial infarction, chronic obstructive pulmonary disease, cerebrovascular disease, malignancy, chronic pain, neuropathy, and epilepsy. We used a 2-year look-back period in claims for these comorbidities except for dementia, for which we used a 3-year look-back period in line with prior studies.[31,32] We defined baseline chronic medication use as those with fills of greater than or equal to 14 pills in the 6 months prior to the index date. We determined additional healthcare utilization variables including presence of hospitalization in the prior year and, as measures of potential intensity and dispersion of care, overall number of outpatient clinic visits in the prior year, and number of distinct types of clinic visits in the past year (e.g., primary care vs cardiology).

Statistical analysis

The primary effect measure of a PSSA is the sequence ratio. We first calculated a crude sequence ratio (cSR) by dividing the number of individuals with the initial marker drug claim after the initial index drug by the number of individuals with the initial marker drug claim before the index drug claim. We assessed the cSR graphically by visually inspecting the histogram depicting marker drug initiation relative to index drug initiation for asymmetry. To adjust for secular trends in medication use (e.g., increasing use of gabapentinoids during the course of the observation period), we then calculated the null-effect sequence ratio.[22] The null-effect sequence ratio has been previously described and represents an expected sequence ratio based on the probability of the sequencing of initiation of marker drugs after index drugs in the absence of a causal association.[21,23,33] Next, we calculated an adjusted sequence ratio (aSR) with 95% confidence intervals (CI) by dividing the cSR by the null-effect ratio.[34] To estimate the incidence rate of the gabapentin–LD prescribing cascade among all older adults initiating a gabapentinoid with PSSA, we calculated the difference in the number of patients

between those initiating a loop diuretic after gabapentinoid initiation and those initiating a loop diuretic before gabapentinoid initiation, and divided the result by the number of patients initiating a gabapentinoid between 2013 and 2019. We adjusted the estimated incidence rate by the length of the exposure window and presented it in terms of person-years.[6] This allowed us to better quantify the incidence of the gabapentin–LD prescribing cascade over a prespecified time period and to more effectively compare our findings against other research on this prescribing cascade.

To identify those older veterans at highest risk of experiencing the prescribing cascade, we constructed a series of logistic regression models with prescribing order modeled as a dichotomous variable. This method allows for multivariable adjustment of the odds ratio (OR) indicating the sequence of index drug before marker drug compared to the opposite order and has been used in prior studies.[6,35,36] The resultant adjusted OR sheds light on those factors in which the skewness of the sequencing was most pronounced.[22] Specifically, the OR represents the odds of the gabapentinoid–LD sequence divided by the odds of the LD–gabapentinoid sequence; therefore, an OR>1 represents a higher odds of the gabapentinoid–LD sequence compared to the opposite sequence. We examined these relationships with logistic regression models adjusting for all measured patient and healthcare utilization characteristics. In secondary analyses, we performed stratified analyses, comparing the aSR across key variables of interest (described above).[6,10]

We used SAS, version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) for all analyses.

Results

Cohort description

After applying the exclusion criteria, we identified 151,442 veterans who initiated a gabapentinoid. The analytic cohort included 1,981 patients who initiated a loop diuretic within 6 months after initiating a gabapentinoid compared to 1,599 patients who initiated a LD within 6 months before initiating a gabapentinoid (**Supplemental Figure S1**). Patients in the gabapentinoid–LD group had a mean age of 73 years, 98% were male, 13% were Black, 5% were Hispanic, and 80% were White. Most patients (98%) were prescribed gabapentin (as opposed to pregabalin, which during the follow-up period required a non-formulary drug request in VA). Patients in the comparator group (LD–gabapentinoid) were similar across these and other measured patient and health utilization factors (**Table 1**; standardized mean difference [SMD] <0.10 for all comparisons). The proportion of patients in each group who were exposed to concomitant medications known to be associated with edema (**Supplementary Table S2**) in the 6 months prior to the index date was similar between groups (gabapentinoid–LD: 57%; LD–gabapentinoid: 58%; SMD -0.02).

Prescription sequence symmetry analysis

Among the analytic cohort of older veterans prescribed both a gabapentinoid and a loop diuretic within the 6-month period, the loop diuretic was initiated nearly one-quarter more often after gabapentinoid initiation than before (aSR, 1.23; 95% CI, 1.13, 1.34). Excess initiation of LD after gabapentinoid was observed throughout the follow-up period, but

most prominently in the first 5 months (**Figure 1**). Among 151,442 veterans who initiated a gabapentinoid between 2013 and 2019, the estimated incidence rate of the cascade was 4.8 prescribing cascade events per 1,000 gabapentinoid-initiator years.

Analysis of high-risk groups

The results of the analysis of predictors of the gabapentinoid–LD prescribing order are shown in **Table 2**. After adjustment for all measured patient and health utilization factors, two factors were associated with prescribing order. First, people age ≥ 85 years were less likely to have the prescribing cascade (compared to 66-74 years; aOR 0.74, 95% CI: 0.56-0.96). Second, people taking more medications at baseline were more likely to have the prescribing cascade (baseline medication count 5-9 vs 0-4, aOR: 1.22, 95% CI: 0.93-1.60; ≥ 10 vs 0-4, aOR 1.39, 95% CI: 1.07-1.82).

Stratified analyses

Stratified analyses (**Figure 2**) revealed overlapping 95% CIs across stratum levels of all factors. For the specific strata of age ≥ 85 years and baseline medication count ≥ 10 (those that emerged as significant predictors above), the stratified analyses revealed similar findings to the main results (e.g., among those taking ≥ 10 medications at baseline, aSR: 1.28, 95% CI 1.15-1.43 compared to those taking 0-4 medications, aSR: 1.01, 95% CI: 0.75-1.36).

Discussion

In this analysis of a nationally representative sample of older veterans, we report two key findings. First, our PSSA underscores the presence of the gabapentinoid–LD prescribing cascade in national US VA prescribing data (aSR of 1.23 [95% CI, 1.13, 1.34]), suggesting an excess of individuals prescribed loop diuretic after gabapentinoid versus before gabapentinoid. Second, among older veterans, those who were younger and those taking multiple medications were at higher risk of the gabapentinoid–LD prescribing cascade—findings that emerged from analyses adjusted for patient and health utilization factors. Overall, we did not find evidence of strong predictors of the cascade in this population despite considering a broad array of patient and system factors, suggesting that efforts to mitigate the gabapentinoid–LD prescribing cascade should be broad-based rather than targeting specific subgroups.

Our findings confirm the presence of the gabapentinoid–LD prescribing cascade in the US veteran population, as previously identified in other studies from the US, Canada, and Denmark.[8,11] Prior studies have used both PSSA and retrospective cohort designs to examine this particular cascade. The most comparable of these was a PSSA conducted by Vouri et al., in which the authors reported an aSR of 1.24 (95% CI: 1.21-1.28) for the gabapentinoid–LD cascade among US adults ≥ 65 years with commercial insurance.[11] The concordance of our findings (regarding the strength of the detected PSSA signal) is noteworthy for two reasons. First, veterans who use the VA for healthcare have rates of multimorbidity and functional impairment exceeding those of non-veterans as well as being predominantly male.[37–39] Second, the VA is an integrated healthcare system. In such an ecosystem—in which prescribing and dispense history, clinical documentation, and provider-to-provider communication are inherently facilitated relative to patients covered by commercial insurance—

one might expect prescribers to be able to communicate better and potentially prevent prescribing cascades. Nevertheless, we observed remarkably similar aSRs between studies, underscoring the persistence of this prescribing cascade in disparate types of patients and delivery settings.

With our study, we sought to push the field of prescribing cascade research beyond detection of cascades to a better understanding of those groups at highest risk of experiencing a prescribing cascade. To this end, we explored a broad array of patient and health services factors that could potentially increase the risk of experiencing prescribing cascades. We hypothesize that prescribing cascades result from a complex interplay between aspects of a patient's physiology and comorbidity burden (e.g., renal function, which modifies the risk of adverse drug events such as gabapentinoid-induced edema; diagnoses that drive prescribing of certain drugs); specific medications and doses; and prescriber and system factors (e.g., awareness of potential cascades by a given provider, fragmentation of care). As such, we cast a broad net in our exploration of factors, with the goal of generating foundational knowledge to inform future studies focused on specific aspects of the aforementioned factors (e.g., renal function). In doing so, we recognize the inherent limitations to which contextual factors can be derived from administrative data. For example, a detailed understanding of the medical decision-making processes giving rise to prescribing cascades (e.g., whether a prescriber was aware of a potential cascade) is impossible to glean from administrative data. Further exploration of prescriber knowledge and decision-making with respect to prescribing cascades remains an important area for further qualitative inquiry.[40]

In the multivariable logistic regression analysis, most factors did not reach a standard cut-off for statistical significance. Of those that did, we found that older adults age ≥ 85 years were less likely to experience the cascade (compared to 65-74 years; aOR 0.74, 95% CI: 0.56-0.96). This finding is somewhat surprising as one might expect older adults to be at heightened risk of developing an adverse drug event such as gabapentinoid-induced edema.[41] However, it is also possible that prescribers are generally more aware of potential adverse drug effects and/or cascades in this population and therefore less likely contribute to a prescribing cascade (e.g., by stopping or decreasing the dose of the first medication rather than starting a second)[42] or that older patients are more often exposed to deprescribing efforts due to changing goals of care. Investigating these possibilities represents a promising avenue for future research. Additionally, we found that older adults taking ≥ 10 medications at baseline were more likely to experience the cascade (compared to 0-4 medications; aOR 1.39, 95% CI: 1.07-1.82); there was a suggestion of a potential dose-response relationship in the baseline medication use findings (people taking 5-9 medications compared to 0-4 medications; aOR 1.22, 95% CI: 0.93-1.60). One potential explanation for these findings is that with increased levels of polypharmacy, it may be harder to attribute drug side effects to a given drug; in this scenario, prescribers might be more likely to prescribe a second drug to treat the adverse effect of a previously prescribed drug. Importantly, one should interpret both findings with caution given the risk of multiple hypothesis testing. In general, these findings extend prior PSSA work on the gabapentinoid–LD cascade by Vouri et al.,[11] which took a univariable approach to examining heterogeneity of effects between subgroups (e.g., by stratification). Despite the previously discussed salient differences in populations between our studies, in their stratified analysis, results were generally concordant with those presented here, with little variance in stratified aSR estimates around an overall study aSR of 1.24 (for a 180-day follow-up window).

A central takeaway from our study is that we did not identify strong predictors of the gabapentinoid–LD prescribing cascade. This was evident both in terms of the relatively weak adjusted ORs for age and polypharmacy discussed above as well as in the stratified (unadjusted) analysis, which showed relatively little variance in stratified aSR estimates around the overall study aSR of 1.23. The confidence limits on our estimates were sufficiently narrow to support the notion that we were unlikely to have missed a major risk factor due to insufficient power. These results suggest that efforts to prevent and mitigate prescribing cascades (e.g., via provider education or point-of-care clinical decision tools) among older adults should be broad-based, rather than focusing on a particular subgroup. Additionally, the overall incidence rate of the gabapentinoid–LD cascade in our cohort was relatively low—estimated at 4.8 prescribing cascade events per 1,000 gabapentinoid-initiator years—which suggests it may be worthwhile to focus efforts on a group of prescribing cascades, rather than any given cascade in isolation. To this end, the 2022 international Delphi panel delineating a consensus-based list of nine clinically relevant cascades representing potentially inappropriate prescribing is a promising development.[43] Finally, there is an ongoing need to supplement large epidemiological studies of prescribing with deeper forms of inquiry (such as qualitative inquiry into decision-making and patient perspectives around cascades[40,42] and novel artificial intelligence methods aimed at medication optimization[44]) aiming to disentangle the decision-making processes giving rise to prescribing cascades and to identify promising avenues to detect and avoid prescribing cascades among older adults.

This study has several limitations. First, we were unable to discern the indication for loop diuretic prescription from pharmacy claims; as such, we could not confirm that the dispensed loop diuretic was used to treat gabapentinoid-induced edema. However, a key benefit of the PSSA study design is its proven ability to detect prescribing cascades in the absence of the indication for prescribing.[6,45] Additionally, in line with prior studies, we restricted our cohort to older veterans without documentation of diagnoses often treated with loop diuretics to address this issue. Second, our study took place in the VA health system, which is the largest integrated health system in the US but serves a predominantly male population; thus, our findings may not be generalizable to female patients. The number of women included in our analysis was small; while still feasible to conduct PSSA with small sample sizes,[45] the resultant confidence intervals for the effect estimate and subgroup analysis among women were quite wide. Additionally, while our analytic cohort has broad demographics in line with other national cohorts of older veterans in terms of age and sex, our inclusion criteria (e.g., including those who initiated a gabapentinoid and excluding patients with a diagnosis of heart failure) yield an analytic cohort with some key differences compared to other national studies of older veterans—for example, a lower burden of heart failure and higher burden of diabetes and polypharmacy.[46,47] Third, while PSSA offers many inherent benefits in the study of prescribing cascades (such as controlling for time-invariant factors that may affect prescribing order),[6,21] this analytic technique requires developing a cohort of new users of both gabapentinoids and loop diuretics, which may further limit generalizability. However, there is little reason to suspect that the occurrence of this prescribing cascade in these individuals is markedly different from a broader population of individuals initiating a gabapentinoid. Finally, our analysis focused solely on the gabapentinoid–LD prescribing cascade; it is plausible that exploration of high-risk groups would vary in studies focused on other prescribing cascades, which represent a promising area for future research.

In summary, we identified evidence of the gabapentinoid–LD prescribing cascade among older US veterans, in agreement with prior studies. To investigate which groups of older adults were at highest risk of experiencing the gabapentinoid–loop diuretic prescribing cascade, we considered a broad array of patient and health system factors. Overall, we did not identify strong predictors of the prescribing cascade, suggesting that efforts to mitigate prescribing cascades among older adults should be broad-based and not focused on specific subgroups.

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Author Contributions: MEG, BJ, EJM, WJD, and MAS contributed to the design and conduct of the study, and data collection and management. MEG, BJ, WJB, and MAS contributed to the analysis of the data. All authors contributed to the interpretation of the data, and preparation, review, and approval of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MEG is the guarantor.

Sponsor's Role: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation or approval of the manuscript; or the decision to submit the manuscript for publication. The views expressed herein are those of the authors and do not necessarily represent the views of the US Department of Veterans Affairs, the US government, the University of California, San Francisco, or other affiliated organizations.

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Data sharing: No additional data are available for sharing owing to a data use agreement with the US Department of Veterans Affairs. The statistical code used in programming and/or analysis can be made freely available to others.

Table 1: Analytic Cohort Characteristics

Characteristic	Veterans With Loop Diuretic Initiated Before Gabapentinoid (N=1599)	Veterans With Loop Diuretic Initiated After Gabapentinoid (N=1981)	SMD
Age in years			0.08
66-74	1115 (69.7%)	1398 (70.6%)	
75-84	352 (22.0%)	464 (23.4%)	
85+	132 (8.3%)	119 (6%)	
Sex: Female	41 (2.6%)	50 (2.5%)	-0.003
Race/Ethnicity			0.08
Non-Hispanic White	1263 (79.0%)	1593 (80.4%)	
Non-Hispanic Black	219 (13.7%)	247 (12.5%)	
Hispanic	81 (5.1%)	98 (4.9%)	
Asian/Pacific Islander, American Indian/Alaska Native, Unknown, and Other	36 (2.3%)	43 (2.2%)	
Myocardial infarction	151 (9.4%)	175 (8.8%)	-0.02
Diabetes	850 (53.2%)	1132 (57.1%)	-0.08
Cerebrovascular disease	281 (17.6%)	356 (18%)	-0.01
Chronic Obstructive Pulmonary Disease	633 (40.0%)	762 (38.5%)	-0.02
Dementia	76 (4.8%)	110 (5.6%)	-0.04
Malignancy	398 (24.9%)	458 (23.1%)	0.04
Chronic Pain	54 (3.4%)	70 (3.5%)	-0.01
Neuropathy	66 (4.1%)	98 (4.9%)	-0.04
Epilepsy	4 (0.3%)	5 (0.3%)	<0.001
Charlson Comorbidity Index ≥ median (3)	913 (57.1%)	1177 (59.4%)	-0.05
Baseline medication count ≥ 5	1386 (86.7%)	1760 (88.8%)	-0.07
0-4	150 (9.4%)	149 (7.5%)	0.06
5-9 (polypharmacy)	394 (24.6%)	463 (23.4%)	
10+ (hyperpolypharmacy)	1055 (66.0%)	1369 (69.1%)	
Type of gabapentinoid: gabapentin (vs pregabalin)	1571 (98.2%)	1927 (97.3%)	-0.07
Hospitalization in past year	278 (17.4%)	307 (15.5%)	0.05
Number of clinic visits in past year ≥ median (23)	821 (51.3%)	970 (49%)	0.05
Number of distinct clinical specialties visited in past year ≥ median (4)	993 (62.1%)	1228 (62%)	0.002
Index year			0.05
2013-2015	844 (52.8%)	999 (50.4%)	
2016-2019	755 (47.2%)	982 (49.6%)	

Footnote: SMD: Standardized mean difference. Epilepsy is included in this table for descriptive purposes but was not retained for further analyses given its exceedingly rare prevalence in the cohort.

Table 2: Multivariable Analyses of Prescribing Order in the Prescription Sequence Symmetry Analysis

Characteristic	Odds Ratio (Unadjusted)	p value	Odds Ratio (Adjusted)	p value
Age, years [ref: 66-74 years]				
75-84	1.05 (0.90-1.23)	0.54	1.06 (0.90-1.25)	0.49
≥ 85	0.72 (0.55-0.93)	0.01	0.74 (0.56-0.96)	0.02
Female sex	0.98 (0.65-1.50)	0.94	1.00 (0.66-1.53)	0.98
Race/ethnicity [ref: Non-Hispanic White]				
Non-Hispanic Black	0.89 (0.74-1.09)	0.26	1.07 (0.68-1.68)	0.77
Hispanic	0.96 (0.71-1.30)	0.78	0.94 (0.58-1.52)	0.80
Asian/Pacific Islander, American Indian/Alaska Native, Unknown, and Other	0.95 (0.60-1.48)	0.81	1.00 (0.58-1.71)	0.99
Dementia	1.18 (0.87-1.59)	0.28	1.22 (0.89-1.66)	0.21
Diabetes	1.18 (1.03-1.34)	0.02	1.07 (0.92-1.25)	0.40
Cerebrovascular disease	1.03 (0.87-1.22)	0.76	1.00 (0.84-1.20)	0.99
Malignancy	0.91 (0.78-1.06)	0.22	0.92 (0.77-1.10)	0.34
COPD	0.95 (0.83-1.09)	0.49	0.94 (0.82-1.09)	0.43
Myocardial infarction	0.93 (0.74-1.17)	0.53	0.91 (0.71-1.15)	0.41
Chronic Pain	1.05 (0.73-1.50)	0.80	1.08 (0.75-1.56)	0.69
Neuropathy	1.21 (0.88-1.66)	0.24	1.12 (0.80-1.57)	0.50
Charlson Comorbidity Index ≥ median (3)	1.10 (0.96-1.26)	0.16	1.11 (0.93-1.32)	0.24
Baseline medication count [Ref: 0-4]				
5-9 (polypharmacy)	1.18 (0.91-1.54)	0.21	1.22 (0.93-1.60)	0.15
10+ (hyperpolypharmacy)	1.31 (1.03-1.66)	0.03	1.39 (1.07-1.82)	0.01
Type of gabapentinoid: gabapentin (vs pregabalin)	0.64 (0.40-1.01)	0.05	0.64 (0.40-1.02)	0.06
Hospitalization in past year	0.87 (0.73-1.04)	0.13	0.89 (0.74-1.07)	0.22
Number of clinic visits in past year ≥ median (23)	0.91 (0.80-1.04)	0.16	0.86 (0.73-1.00)	0.06
Number of distinct clinical specialties visited in past year ≥ median (4)	1.00 (0.87-1.14)	0.95	1.00 (0.84-1.16)	0.89
Index year [Ref: 2013-2015]	1.10 (0.96-1.25)	0.16	1.10 (0.96-1.26)	0.18

Footnote: LB: Lower bound; UB: Upper bound. The odds ratios represent the result of logistic regression models with prescribing order modeled as a dichotomous variable (indicating the sequence of gabapentinoid before loop diuretic compared to the opposite order). Adjusted results reflect adjustment for all listed factors.

Figure 1: Prescription Sequence Symmetry of Initial Loop Diuretic Prescription Within 6 Months of Initial Gabapentinoid Prescription Among Older Veterans

Legend: The Figure presents the results in a common format among prescription sequence symmetry analyses. In the absence of an association between gabapentinoid and loop diuretic use, we would expect the pattern to be symmetrical around time 0. The relative excess volume of patients on the right-hand side of the figure (gabapentinoid preceding loop diuretic) compared to the left-hand side (gabapentinoid following loop diuretic) may be attributable to a gabapentinoid-loop diuretic prescribing cascade and is captured in the sequence ratio (SR) measure.

Figure 2: Stratified Prescription Sequence Symmetry Analysis by Key Patient and Health Utilization Factors

Legend: CSR: Crude sequence ratio; NSR: Null sequence ratio; ASR: Adjusted sequence ratio; COPD: chronic obstructive pulmonary disease. The summary dotted line indicates the overall study adjusted sequence ratio of 1.23. “Other” race refers to Medicare claims categorizations of Asian/Pacific Islander, American Indian/Alaska Native, Unknown, and Other.

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