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Supplementary References

COMPLETE METHODS

Study Design, Data Sources, and Population:

We conducted a cohort study using the 2013 standard analytic and Medicare payment files in the United States Renal Data System (USRDS), which includes clinical and prescription drug data from 2011.[1] This study was not considered human subjects research by the University of California, San Francisco Committee on Human Research.

Diagnoses Associated with Gabapentin and Pregabalin Use:

Gabapentin is FDA-approved for the treatment of epilepsy and post-herpetic neuralgia,[2] but it is commonly used off-label for conditions such as neuropathic pain, diabetic neuropathy, trigeminal neuralgia, and restless legs syndrome.[3] Pregabalin is FDA-approved for the treatment neuropathic pain associated with diabetic peripheral neuropathy, post-herpetic neuralgia, adjunctive therapy for partial onset seizures, and fibromyalgia, and it is also approved for the treatment of generalized anxiety disorder in Europe.[4, 5] We were interested in capturing the prevalence of both on-label and off-label diagnoses associated with gabapentin and pregabalin use, including specific diagnoses that have been evaluated in hemodialysis patients (e.g., neuropathic pain, pruritus, and restless legs syndrome).[6-15] Diagnoses of interest were captured using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (**Supplementary Table 1**).

Gabapentin and Pregabalin Exposure Variables:

Ascertainment of gabapentin and pregabalin exposure was started in January 2011, and we delayed ascertainment of the outcomes until February 2011 to allow for determination of prior exposure.

Gabapentin and pregabalin exposure were modeled as separate time-varying predictors. Our database was structured such that there was a record for every person for each day of observation. With this database structure, we defined periods of medication possession as the period starting from the date of service of a prescription continuing until the days supply of the prescription was completed.[16] The time at risk began on the first day of the prescription claim. Gaps between prescriptions were considered as periods of non-exposure. For each period of medication possession, we calculated a daily dose averaged over the duration of the prescription and classified periods of exposure into the following dose categories for gabapentin (0 mg, >0-100 mg, >100-200 mg, >200-300 mg, >300 mg) and pregabalin (0 mg, >0-100 mg, >100 mg).

Outcome Variables:

We examined first episode of altered mental status, fall, and fracture requiring an emergency room visit or hospitalization during 2011 in separate models. Using our continuous database structure, we were able to assign event dates to the outcomes of interest, and we stopped classifying days as time at risk after the occurrence of the first events. Outcomes were ascertained from the revenue, physician/supplier, and institutional claims files using ICD-9-CM diagnosis and Current Procedural Terminology (CPT) codes (**Supplementary Table 2**). The sensitivity, specificity, and positive predictive value for using ICD-9-CM codes to identify fall (73-95%, 88-97%, and 62-86%, respectively)[17, 18] and fracture (75-100%, 97-100%, and 69-99%, respectively)[19-21] were generally higher than those for delirium (3-50%, 99-100%, and 28-100%).[22-25] Delirium represents a subset of altered mental status, and we defined altered mental status using a broad listing of ICD-9-CM codes that captured terms including delirium and alteration of mental status or consciousness, confusion,

encephalopathy, hallucination, intoxication, and drug-induced delirium, delusion, hallucination, and psychosis.[22-31] We based our methodology for coding fall and fracture on prior work examining these outcomes among patients with end-stage renal disease in the USRDS.[32-37] Fractures of interest included those of the hip, femur, pelvis, leg, foot, arm, hand, or axial skeleton. We included emergency room visits in which there was a code for the outcomes and hospitalizations in which the outcomes were identified as the primary diagnosis according to standard USRDS methodology.[38]

Statistical Analysis:

We calculated the prevalence of at least one prescription for gabapentin and pregabalin during 2011, and among those with at least one prescription for these agents, we calculated the prevalence of at least one high dose prescription (defined as >300 mg for gabapentin and >100 mg for pregabalin). For Table 1, patients were categorized into two groups: receipt of at least one prescription for gabapentin or pregabalin in 2011 or no use of these agents in 2011. Baseline characteristics are presented as means and standard deviations or medians with interquartile ranges for continuous variables and percentages for categorical variables. We compared characteristics of those who received gabapentin or pregabalin versus those who did not using Mann-Whitney and chi-squared tests. We calculated outcome rates, expressed as the number of events per 100 person-years, with follow-up time partitioned according to gabapentin dose category (0 mg, >0-100 mg, >100-200 mg, >200-300 mg, >300 mg) and pregabalin dose category (0 mg, >0-100 mg, >100 mg). Among individuals with at least one prescription for gabapentin and pregabalin in 2011, we ascertained diagnoses associated with use of gabapentin and pregabalin according to whether a relevant ICD-9-CM code was present

within 60 days prior to the date of service of each prescription in the Medicare Part D prescription drug file.

For each predictor and outcome analysis, we constructed a Cox model using a time-varying definition of gabapentin and pregabalin exposure in order to compare the hazard of each outcome during each dose category compared to no use. We controlled for the following potential confounders: baseline demographic characteristics (i.e., age, duration on dialysis, sex, race, geographic location of ESRD network as defined by US Census geographic divisions, body mass index, comorbidities [i.e., alcohol dependence, coronary artery disease, cancer, other cardiac disease, dysrhythmia, congestive heart failure, cerebrovascular disease, diabetes, drug dependence, opioid dependence, hypertension, inability to ambulate, inability to transfer, chronic obstructive pulmonary disease, peripheral vascular disease, tobacco dependence, liver disease, dementia, depression, seizures/epilepsy], and medication burden (i.e., total number of unique medications prescribed at baseline). We also adjusted for duration of gabapentin and pregabalin exposure to account for the possibility of differential associations according to shorter duration of exposure (less than 30 days) compared to longer duration of exposure (greater than or equal to 30 days). Comorbidities were ascertained using the USRDS Medical Evidence Report and ICD-9-CM diagnosis and procedure codes. Specifically, we included diagnoses indicated at the time of dialysis initiation on the USRDS Medical Evidence Report or present on two outpatient claims or one inpatient claim during 2010 in the institutional claims or physician/supplier files (**Supplementary Table 3**).[39-42] We adjusted for use of concomitant medications that could affect risk of the outcomes (e.g., benzodiazepines, antidepressants with anticholinergic properties) as a time-varying covariate. We included anticholinergic antidepressants

in particular because their side effects (e.g., sedation, orthostatic hypotension) could predispose to fall and fracture.[43, 44]

Patients were censored from the study cohort at the time of death, kidney transplantation, change in modality, uncertain or recovered function, withdrawal from dialysis, loss to follow-up, discontinuation of Part D coverage or end of the study period. We also performed a sensitivity analysis to account for potential misclassification of the exposure related to the Medicare Part D coverage gap (i.e., "donut hole") that occurs every calendar year, beginning when the initial coverage limit has been exceeded and ending when catastrophic coverage begins.[38] The Part D program offers a low-income subsidy (LIS) that provides full or partial coverage during the coverage gap. Medication persistence and adherence have been shown to be higher in patients with end-stage renal disease who have the LIS.[45] Thus, we performed an analysis restricting to patients with the LIS.[46] We considered a two-tailed p-value <0.05 to be statistically significant. We used SAS version 9.4 (SAS Institute, Inc., Cary, NC) for all analyses.

Supplementary Table 1: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes for Ascertainment of Diagnoses Associated with Gabapentin and Pregabalin Use

Diagnosis	ICD-9-CM Codes
Neuropathic pain	053.20, 053.21, 053.22, 249.0, 249.6, 250.0, 250.6, 337.1, 337.20, 337.21, 337.22, 337.29, 337.9, 338.0, 349.89, 349.9, 350, 350.01, 350.1, 350.2, 350.50, 350.8, 350.9, 354.4, 354.9, 355.40, 355.71, 355.8, 355.9, 356.0, 356.01, 356.9, 357.2, 357.4, 585.9, 722.30, 723.8, 724.3, 724.4, 729.2, 780.96
Pruritus	698, 698.0, 698.1, 698.2, 698.3, 698.4, 698.8, 698.9
Restless legs syndrome	333.94
Seizures/epilepsy	345.0, 345.1, 345.2, 345.3, 345.4, 345.5, 345.6, 345.7, 345.8, 345.9
Fibromyalgia	729.1
Bipolar	296.0, 296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.1, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.4, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.5, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.6, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.89
Depression	296.2, 296.3
Attention deficit hyperactivity disorder	314.00, 314.01, 314.8
Anxiety	293.84, 300.0, 300.00, 300.01, 300.02, 300.09, 300.21, 300.22, 300.23, 300.29, 300.3, 308.3, 309.81
Periodic limb movement of sleep	327.51
Insomnia	307.40, 307.41, 307.42, 307.47, 307.48, 327.00, 327.01, 327.02, 327.09, 780.50, 780.52, 780.55, 780.56, 780.59
Migraine	346.00, 346.01, 346.10, 346.11, 346.9
Withdrawal seizures	291.81, 292.0

Supplementary Table 2: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis and Current Procedural Terminology (CPT) Codes for Altered Mental Status, Fall, and Fracture Ascertainment

Outcome	ICD-9-CM Codes	CPT Codes
Altered mental status	292.11, 292.12, 292.2, 292.81, 292.84, 292.89, 292.9, 293.0, 293.1, 298.9, 348.30, 348.39, 349.82, 760.72, 760.77, 780.02, 780.09, 780.1, 780.97	
Fall	E880.0, E880.1, E880.9, E884.9, E884.2, E884.3, E884.4, E884.5, E884.6, E885.0, E885.9, E888.0, E888.1, E888.8, E888.9	
Fracture		
Hip/femur	733.14, 733.15, 820.xx, 821.xx	27125, 27220, 27222, 27226, 27227, 27228, 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27254, 27500, 27501, 27502, 27503, 27506, 27507, 27508, 27509, 27510, 27511, 27513, 27514
Pelvis	808.xx	27190, 27193, 27194, 27215, 27216, 27217, 27218, 27200, 27202
Leg/foot	733.16 (path tibia), 822.xx (patella), 823.xx (tibia & fibula), 824.xx (ankle), 825.xx (tarsal, metatarsal), 826.xx (phalanges)	27350, 27520, 27524, 27530, 27532, 27535, 27536, 27538, 27540, 27750, 27752, 27756, 27758, 27759, 27760, 27762, 27766, 27767, 27768, 27769, 27780, 27781, 27784, 27786, 27788, 27792, 27808, 27810, 27814, 27816, 27818, 27822, 27823, 27824, 27825, 27826, 27827, 27828, 28315, 28400, 28405, 28406, 28415, 28420, 28430, 28435, 28436, 28445, 28450, 28455, 28456, 28465, 28470, 28475, 28476, 28485, 28490, 28495, 28496, 28505, 28510, 28515, 28525, 29851, 29855, 29856
Arm/hand	733.11 (path humerus), 733.12 (path radius), 812.xx (humerus), 813.xx (radius & ulna), 814.xx (carpal bone, wrist), 815.xx (metacarpal), 816.xx (phalanges), 817.xx (multiple)	23600, 23605, 23610, 23615, 23616, 23620, 23625, 23630, 23665, 23670, 23675, 23680, 24500, 24505, 24506, 24510, 24515, 24516, 24530, 24531, 24535, 24536, 24538, 24540, 24542, 24545, 24546, 24560, 24565, 24566, 24570, 24575, 24576, 24577, 24579, 24581, 24582, 24583, 24585, 24586, 24587, 24588, 24620, 24625, 24635, 24650, 24655, 24660, 24665, 24666, 24670, 24675, 24680, 24685,

		25500, 25505, 25510, 25514, 25515, 25520, 25525, 25526, 25530, 25535, 25540, 25541, 25545, 25560, 25565, 25570, 25574, 25575, 25600, 25604, 25605, 25606, 25607, 25608, 25609, 25622, 25624, 25628, 25630, 25635, 25645, 25650, 25651, 25652, 25680, 25685, 26600, 26605, 26607, 26608, 26615, 26645, 26650, 26665, 26720, 26725, 26727, 26735, 26740, 26742, 26746, 26750, 26755, 26756, 26765, 29847
Axial	807.0x-807.1x, 807.2-807.3 (ribs/sternum); 810.xx, 811.xx (clavicle, scapula)	21800, 21820, 23500, 23505, 23515, 23570, 23575, 23585

Altered mental status was defined using a broad listing of ICD-9-CM codes that captured terms including delirium and alteration of mental status or consciousness, confusion, encephalopathy, hallucination, intoxication, and drug-induced delirium, delusion, hallucination, and psychosis.[22-31] We based our methodology for coding fall and fracture on prior work examining these outcomes among patients with end-stage renal disease in the USRDS.[32-37] Fracture for a given type required the presence of both an ICD-9-CM diagnosis code and CPT code.[32, 34-37] In order to maximize the ability to ascertain incident fractures, we excluded vertebral fractures and required that no fracture of given type occurred within the previous 30 days.[47]

Supplementary Table 3: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis and Procedure Codes for Comorbidity Ascertainment

Comorbidity	ICD-9-CM Codes
Alcohol dependence	291.x, 303.x, 305.x
Coronary artery disease	00.66, 36.0x, 410.x, 411.x, 413.x
Cancer	140.x-165.x, 170.x-172.x, 174.x, 175.x, 180.x-209.x, 238.6, 273.3
Other cardiac disease	v42.2, v43.3, 394.x-397.1, 424.x, 746.3-746.6
Dysrhythmia	37.7x, 37.8x, 37.9x, v45.00, v45.01, v45.02, v45.09, v53.31, v53.32, 426.x, 427.0, 427.1, 427.20, 427.3x, 427.4x, 427.81, 427.9, 996.01, 996.04
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.13, 404.91, 428.x
Cerebrovascular disease	433.x, 434.x, 435.x, 436.00, 437.x, 438.x
Diabetes	249.x, 250.x, 357.2, 362.0x
Drug dependence	292.x, 304.x, 305.x
Opioid dependence	304.x, 305.5
Hypertension	401.0, 401.1, 401.9, 402.x, 403.x, 404.x, 405.x
Chronic obstructive pulmonary disease	490, 491.x-496
Peripheral vascular disease	38.03, 38.04, 38.05, 38.08, 38.33-38.48, 39.22-39.29, v43.4, 440.2x, 440.3x, 440.4x, 441.x, 443.x, 445.x, 447.10, 557.10, 557.90
Tobacco dependence	305.1x
Liver disease	v42.7, 070.x, 456.1, 456.21, 570-573.x
Dementia	290.x, 294.1x, 331.x
Depression	296.2x, 296.3x, 296.5x, 296.82, 300.40, 301.12, 309.0, 309.10, 311
Seizures/epilepsy	345.x

Supplementary Table 4: Dose of Gabapentin and Pregabalin by Diagnosis

Diagnosis	**Gabapentin Dose (mg)** Median (25^{th}-75^{th} Percentile)	**Pregabalin Dose (mg)** Median (25^{th}-75^{th} Percentile)
Neuropathic pain	300 (200-600)	100 (58-150)
Anxiety	300 (200-600)	100 (75-150)
Insomnia	300 (200-600)	100 (50-150)
Fibromyalgia	300 (200-667)	100 (63-150)
Pruritus	300 (200-600)	100 (58-150)
Restless legs syndrome	300 (200-600)	100 (50-150)
Bipolar	300 (209-600)	100 (70-150)
Migraine	386 (300-700)	150 (75-200)
Seizures/epilepsy	300 (200-870)	100 (50-150)
Withdrawal seizures	300 (300-900)	150 (75-200)
Periodic limb movement of sleep	300 (200-600)	133 (75-150)
Attention deficit hyperactivity disorder	366 (300-750)	150 (50-250)

Supplementary Table 5: Total Number of Days Spent within Each Dose Category and Number and Percentage of Individuals with at Least One Prescription in Each Dose Category during Follow-up

Gabapentin	**Total Number of Days** Median (25^{th}-75^{th} Percentile)	**n (%)**
>0-100 mg	70 (31-172)	5524 (4)
>100-200 mg	76 (31-172)	5524 (4)
>200-300 mg	75 (31-177)	9532 (7)
>300 mg	92 (31-194)	10841 (8)
Any dose	117 (38-229)	25737 (18)
Pregabalin	**Total Number of Days** Median (25^{th}-75^{th} Percentile)	**n (%)**
>0-100 mg	76 (31-178)	3670 (3)
>100 mg	88 (31-195)	2421 (2)
Any dose	93 (31-211)	5501 (4)

Note: Follow-up time spanned from February 2011 until the time of an outcome, censoring event, or 12/31/11. A given person could contribute to multiple dose categories.

Supplementary Table 6: Risk of Altered Mental Status, Fall, and Fracture by Gabapentin and Pregabalin Dose Category (Low-Income Subsidy Sensitivity Analysis)

	Altered Mental Status				Fall				Fracture			
Dose Category	*Crude HR (95% CI)*	*p-value*	*Adjusted HR[a] (95% CI)*	*p-value*	*Crude HR (95% CI)*	*p-value*	*Adjusted HR[a] (95% CI)*	*p-value*	*Crude HR (95% CI)*	*p-value*	*Adjusted HR[a] (95% CI)*	*p-value*
Gabapentin												
None	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
>0-100 mg	1.34 (1.17-1.53)	<.001	1.06 (0.93-1.21)	0.40	1.64 (1.37-1.96)	<.001	1.28 (1.07-1.53)	0.007	1.27 (0.96-1.69)	0.10	0.99 (0.75-1.32)	0.97
>100-200 mg	1.68 (1.49-1.90)	<.001	1.33 (1.18-1.50)	<0.001	1.88 (1.58-2.23)	<.001	1.42 (1.20-1.69)	<0.001	1.47 (1.15-1.89)	0.003	1.14 (0.89-1.46)	0.31
>200-300 mg	1.81 (1.65-1.98)	<.001	1.42 (1.29-1.55)	<0.001	1.76 (1.53-2.03)	<.001	1.35 (1.17-1.55)	<0.001	1.28 (1.03-1.60)	0.03	1.04 (0.83-1.30)	0.73
>300 mg	1.93 (1.77-2.09)	<.001	1.51 (1.39-1.64)	<0.001	2.12 (1.89-2.38)	<.001	1.56 (1.39-1.75)	<0.001	1.74 (1.45-2.08)	<.001	1.38 (1.15-1.65)	0.0005
Pregabalin												
None	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
>0-100 mg	1.89 (1.63-2.19)	<.001	1.47 (1.27-1.70)	<0.001	1.57 (1.24-1.97)	0.0001	1.17 (0.93-1.47)	0.19	1.80 (1.30-2.49)	0.0004	1.41 (1.02-1.95)	0.04
>100 mg	1.84 (1.56-2.18)	<.001	1.47 (1.24-1.74)	<0.001	2.16 (1.72-2.72)	<.001	1.65 (1.31-2.08)	<0.001	1.66 (1.15-2.38)	0.006	1.40 (0.97-2.02)	0.07

Abbreviations: HR = hazard ratio, CI = confidence interval

Based on 108,901 (77%) of the cohort that received the low-income subsidy for the entire study duration.

[a]Results are adjusted for age, sex, race, duration on dialysis, network, body mass index, alcohol dependence, coronary artery disease, cancer,

other cardiac disease, dysrhythmia, congestive heart failure, cerebrovascular disease, diabetes, drug dependence, opioid dependence, hypertension, inability to ambulate, inability to transfer, chronic obstructive pulmonary disease, peripheral vascular disease, tobacco dependence, liver disease, dementia, depression, seizures/epilepsy, medication burden, concomitant medications, and duration of gabapentin or pregabalin exposure.

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