Journal club

MARTA ZAMPINO,

GERIATRIC MEDICINE FELLOW

JOHNS HOPKINS SCHOOL OF MEDICINE

Discosures

- I have nothing to disclose

Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease : A Population-Based Cohort Study.

By Alvi A. Rahman, MSc; Sophie Dell'Aniello, MSc; Erica E.M. Moodie, PhD; Madeleine Durand, MD, MSc; Janie Coulombe, PhD; Jean-François Boivin, MD, ScD; Samy Suissa, PhD; Pierre Ernst, MD, MSc; and Christel Renoux, MD, PhD

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Background and Rationale

1

Gabapentinoids (gabapentin, pregabalin), are indicated for the treatment of several conditions: epilepsy, neuropathic pain, chronic pain.

2

Despite limited indications, use has surged in Europe and North America for off-label prescribing.

3

Some hypothesize that this may be linked to perception as safer alternative to opioids.

Concerns

Propensity to cause CNS depression leading to sedation and respiratory depression reported in animal and human studies.

49 case reports submitted to FDA showed severe breathing difficulties in patient using gabapentinoids

Particular concern in patients with COPD

COPD exacerbations

- Severe exacerbations are indicators of rapid disease progression and are associated with poor prognosis.

Pain and COPD

- 85% patients with COPD have 1 or more pain related diagnosis
- 27% neuropathic pain
- 70% using 1 or more prescription medication

Preventive measures

In 2016, Health Canada warned of potential serious breathing problems, recommend updated product information

In 2019, FDA released warning about breathing problems, especially for patients with respiratory factors

Study objective

- Aim: to assess whether gabapentinoid use is associated with increased risk of severe COPD exacerbation.
- Approved or off-label indication of gabapentinoids

Methods

- Time-conditional propensity score-matched, new-user cohort design

Data source

3 computerized health care databases from Quebec province in Canada

Information on demographics, medical services, dispensed outpatient prescriptions on all residents convered in the Public Prescription Insurance Plan (includes all individuals >65, welfare recipients, all residends without private insurance) = 43% of population

Records of all hospitalizations are available

Inclusion criteria

- Age 55 +
- Receiving 3 or more prescriptions for respiratory drug (LAMA, LABA, combination LAMA-LABA, or LAMA-inhaled corticosteroid on at least 2 dates within a year between 1994 and 2015

Exclusion criteria

- Diagnosis of asthma during hospitalization
- Prescription of nedocromil, ketotifen, cromolyn, antileukotrienes
- Receiving gabapentinoids prior to cohort entry

Methods

- Patient followed until date of outcome, death, end of prescription drug coverage, or end of study period (31 Dec 2015)
- Generated time-based exposure sets including comparator individuals who were not exposed to gabapentinoids up to that time point, had the same indication, age (+ or - 1 year), sex, calendar time of base cohort entry (+ or - 1 year), had a physician visit in prior 3 months
- Matched each gabapentinoid treatment initiator 1:1 without replacement on TCPS to a comparator with the closest TCPS in the exposure set
- Cohort entry: date of gabapentinoid initiation or same time in the matched nonusers

Methods

- Estimated TCPS using conditional logistic regression, including comorbid conditions measured any time before the date of matched exposure set: HTN, HLD, CAD, heart failure, stroke or TIA, DM, CKD, liver disease, cancer, OSA, dementia, anxiety, OCD, mood disorder, schizophrenia, schizotypal or delusional disorder, drug misuse, alcohol misuse.
- Also included hospitalizations for pneumonia, moderate-severe COPD exacerbations, number of bronchodilators used in 1 year prior to cohort entry.

Outcome

- Primary: severe COPD exacerbation: first hospitalization with an admission for COPD or primary diagnosis of COPD at follow up or death due to COPD exacerbation
- Secondary: moderate or severe exacerbation and respiratory failure. Moderate: prescription for oral prednisone.

Statistical analysis

- Descriptive statistics, comparing patients initiating gabapentinoid therapy with TCPS-matched comparator using standardized mean differences
- Poisson distribution for crude incidence rates and 95% CIs
- Cox proportional hazards models for hazard ratio and 95% CIs

Statistical analysis

Secondary analyses and 6 sensitivity analyses:

1. varied the grace period between successive prescriptions to 15 and 30 days.
2. repeated the primary analysis, limiting the follow-up to 1 year.
3. analysis using an intention-to-treat exposure definition with the maximum follow-up limited to 1 year.
4. excluded patients with cancer before or at cohort entry, who may be prescribed gabapentinoids or other pain medications for palliative care.
5. inverse probability of censoring weights to further account for potential informative censoring by discontinuation of study medication therapy and for competing risk fordeath from other causes. Also censored patients who used benzodiazepines or opioids during follow-up
6. computed an E-value to assess the robustness of findings to potential residual confounding.

Post hoc analysis: repeated the primary analysis including neuropathic pain and other chronic pain in the TCPS for the epilepsy subcohort, and other chronic pain for the neuropathic pain subcohort

Results, main findings

- Base cohort of 156803 patients with COPD, including:

1. 356 gabapentinoid treatment initiators with epilepsy
2. 9411 with neuropathic pain
3. 3737 with other chronic pain
4. Matched to equal numbers of nonusers

- Before TCPS matching, gabapentinoid users were sicker than nonusers (comorbidities, overall health, had higher medication use across indications)
- After matching, characteristics were balanced except for CKD in patients with epilepsy

Table 1. Characteristics of Patients With COPD, by Exposure Status, Matched on Indication and TCPS

Characteristic	Epilepsy			Neuropathic Pain			Other Chronic Pain		
	Gabapentinoid Use ($n = 356$)	Nonuse ($n = 356$)	Absolute Standardized Difference	Gabapentinoid Use ($n = 9411$)	Nonuse ($n = 9411$)	Absolute Standardized Difference	Gabapentinoid Use ($n = 3737$)	Nonuse ($n = 3737$)	Absolute Standardized Difference
Mean age (SD), y*	73.2 (7.7)	73.1 (7.8)	0.01	75.5 (8.3)	75.5 (8.3)	0.00	74.3 (8.3)	74.3 (8.3)	0.00
Female sex, *n* (%)*	202 (56.7)	202 (56.7)	0.00	5424 (57.6)	5424 (57.6)	0.00	2286 (61.2)	2286 (61.2)	0.00
Region, *n* (%)									
Montreal	84 (23.6)	84 (23.6)	0.00	2010 (21.4)	2028 (21.5)	0.00	848 (22.7)	885 (23.7)	0.02
Capitale-Nationale	43 (12.1)	39 (11.0)	0.04	967 (10.3)	946 (10.1)	0.01	381 (10.2)	379 (10.1)	0.00
Estrie	13 (3.7)	17 (4.8)	0.06	547 (5.8)	570 (6.1)	0.01	270 (7.2)	278 (7.4)	0.01
Other†	216 (60.7)	216 (60.7)	0.00	5887 (62.6)	5867 (62.3)	0.00	2238 (59.9)	2195 (58.7)	0.02
Respiratory events and medications, *n* (%)‡									
Hospitalization for COPD									
0	312 (87.6)	302 (84.8)	0.08	8406 (89.3)	8355 (88.8)	0.02	3339 (89.3)	3309 (88.5)	0.03
1	34 (9.6)	37 (10.4)	0.03	778 (8.3)	789 (8.4)	0.00	310 (8.3)	324 (8.7)	0.01
≥2	10 (2.8)	17 (4.8)	0.10	227 (2.4)	267 (2.8)	0.03	88 (2.4)	104 (2.8)	0.03
Moderate or severe COPD exacerbation									
0	229 (64.3)	225 (63.2)	0.02	6037 (64.1)	6036 (64.1)	0.00	2386 (63.8)	2395 (64.1)	0.01
1	70 (19.7)	63 (17.7)	0.05	1853 (19.7)	1906 (20.3)	0.01	802 (21.5)	776 (20.8)	0.02
≥2	57 (16.0)	68 (19.1)	0.08	1521 (16.2)	1469 (15.6)	0.02	549 (14.7)	566 (15.1)	0.01
Severe pneumonia	23 (6.5)	22 (6.2)	0.01	474 (5.0)	489 (5.2)	0.01	178 (4.8)	188 (5.0)	0.01
Number of bronchodilators (LABA or LAMA)									
0	51 (14.3)	52 (14.6)	0.01	1335 (14.2)	1319 (14.0)	0.00	498 (13.3)	509 (13.6)	0.01
1	175 (49.2)	173 (48.6)	0.01	4661 (49.5)	4550 (48.3)	0.02	1913 (51.2)	1916 (51.3)	0.00
2	130 (36.5)	131 (36.8)	0.01	3415 (36.3)	3542 (37.6)	0.03	1326 (35.5)	1312 (35.1)	0.01
Inhaled corticosteroids	251 (70.5)	255 (71.6)	0.02	6958 (73.9)	6980 (74.2)	0.01	2621 (70.1)	2624 (70.2)	0.00
SABA	254 (71.3)	250 (70.2)	0.02	6244 (66.3)	6263 (66.5)	0.00	2374 (63.5)	2305 (61.7)	0.04
Ipratropium	54 (15.2)	55 (15.4)	0.01	1373 (14.6)	1372 (14.6)	0.00	510 (13.6)	500 (13.4)	0.01
Prednisone	114 (32.0)	116 (32.6)	0.01	3123 (33.2)	3094 (32.9)	0.01	1238 (33.1)	1238 (33.1)	0.00
Methylxanthines	16 (4.5)	18 (5.1)	0.03	367 (3.9)	353 (3.8)	0.01	97 (2.6)	103 (2.8)	0.01
Respiratory antibiotics	221 (62.1)	229 (64.3)	0.05	5923 (62.9)	5834 (62.0)	0.02	2292 (61.3)	2281 (61.0)	0.01
Comorbidities, *n* (%)§									
Hypertension	305 (85.7)	309 (86.8)	0.03	8285 (88.0)	8255 (87.7)	0.01	3147 (84.2)	3127 (83.7)	0.01
Diabetes	129 (36.2)	118 (33.1)	0.06	3812 (40.5)	3771 (40.1)	0.01	1078 (28.8)	1041 (27.9)	0.02
Coronary artery disease	213 (59.8)	216 (60.7)	0.02	5441 (57.8)	5322 (56.6)	0.03	1836 (49.1)	1774 (47.5)	0.03
Stroke/TIA	88 (24.7)	85 (23.9)	0.02	1220 (13.0)	1233 (13.1)	0.00	323 (8.6)	321 (8.6)	0.00
Heart failure	107 (30.1)	107 (30.1)	0.00	2564 (27.2)	2528 (26.9)	0.01	775 (20.7)	766 (20.5)	0.01
Dyslipidemia	231 (64.9)	248 (69.7)	0.10	6582 (69.9)	6583 (70.0)	0.00	2365 (63.3)	2384 (63.8)	0.01
Cancer	115 (32.3)	115 (32.3)	0.00	2978 (31.6)	2943 (31.3)	0.01	1052 (28.2)	1036 (27.7)	0.01
Chronic kidney disease	91 (25.6)	67 (18.8)	0.16	2322 (24.7)	2326 (24.7)	0.00	647 (17.3)	645 (17.3)	0.00
Dementia	81 (22.8)	73 (20.5)	0.05	1133 (12.0)	1135 (12.1)	0.00	346 (9.3)	329 (8.8)	0.02
Liver disease	49 (13.8)	50 (14.0)	0.01	885 (9.4)	861 (9.1)	0.01	253 (6.8)	241 (6.4)	0.01
Obstructive sleep apnea	20 (5.6)	17 (4.8)	0.04	531 (5.6)	512 (5.4)	0.01	162 (4.3)	152 (4.1)	0.01
Anxiety	154 (43.3)	154 (43.3)	0.00	3512 (37.3)	3401 (36.1)	0.02	1145 (30.6)	1165 (31.2)	0.01
Obsessive-compulsive disorder	‖	‖	0.04	20 (0.2)	18 (0.2)	0.00	12 (0.3)	11 (0.3)	0.00
Mood disorders	58 (16.3)	56 (15.7)	0.02	678 (7.2)	660 (7.0)	0.01	258 (6.9)	219 (5.9)	0.04
Schizophrenia, schizotypal and delusional disorders	24 (6.7)	22 (6.2)	0.02	129 (1.4)	141 (1.5)	0.01	44 (1.2)	34 (0.9)	0.03
Drug misuse	24 (6.7)	24 (6.7)	0.00	304 (3.2)	268 (2.8)	0.02	91 (2.4)	75 (2.0)	0.03
Alcohol misuse	71 (19.9)	63 (17.7)	0.06	735 (7.8)	709 (7.5)	0.01	230 (6.2)	201 (5.4)	0.03
Medications, *n* (%)‡									
Antiplatelets	219 (61.5)	215 (60.4)	0.02	5657 (60.1)	5579 (59.3)	0.02	2075 (55.5)	2076 (55.6)	0.00
Oral anticoagulants	65 (18.3)	71 (19.9)	0.04	1519 (16.1)	1492 (15.9)	0.01	643 (17.2)	620 (16.6)	0.02
β-Blockers	133 (37.4)	129 (36.2)	0.02	3177 (33.8)	3137 (33.3)	0.01	1249 (33.4)	1215 (32.5)	0.02
Antiarrhythmics	186 (52.2)	188 (52.8)	0.01	4709 (50.0)	4618 (49.1)	0.02	1761 (47.1)	1708 (45.7)	0.03
NSAIDs	86 (24.2)	91 (25.6)	0.03	3209 (34.1)	3191 (33.9)	0.00	1664 (44.5)	1679 (44.9)	0.01
Opioids	151 (42.4)	146 (41.0)	0.03	4702 (50.0)	4716 (50.1)	0.00	2060 (55.1)	2067 (55.3)	0.00
Antiepileptics¶	191 (53.7)	194 (54.5)	0.02	249 (2.6)	234 (2.5)	0.01	79 (2.1)	72 (1.9)	0.01
Benzodiazepines	232 (65.2)	231 (64.9)	0.01	5270 (56.0)	5185 (55.1)	0.02	2062 (55.2)	2017 (54.0)	0.02
Antipsychotics	98 (27.5)	94 (26.4)	0.03	1102 (11.7)	1073 (11.4)	0.01	438 (11.7)	430 (11.5)	0.01
Antidepressants	125 (35.1)	137 (38.5)	0.07	3054 (32.5)	2967 (31.5)	0.02	1180 (31.6)	1166 (31.2)	0.01
Proton-pump inhibitors	264 (74.2)	260 (73.0)	0.03	6470 (68.7)	6337 (67.3)	0.03	2558 (68.5)	2534 (67.8)	0.01
Oral corticosteroids**	11 (3.1)	8 (2.2)	0.05	184 (2.0)	202 (2.1)	0.01	82 (2.2)	86 (2.3)	0.01
Hypnotics/barbiturates	25 (7.0)	18 (5.1)	0.08	70 (0.7)	55 (0.6)	0.02	22 (0.6)	16 (0.4)	0.02
Number of medication classes, *n* (%)‡									
0–8	17 (4.8)	19 (5.3)	0.03	873 (9.3)	872 (9.3)	0.00	404 (10.8)	430 (11.5)	0.02
9–11	48 (13.5)	49 (13.8)	0.01	1404 (14.9)	1507 (16.0)	0.03	649 (17.4)	695 (18.6)	0.03
12–15	105 (29.5)	101 (28.4)	0.02	2538 (27.0)	2545 (27.0)	0.00	1093 (29.2)	1104 (29.5)	0.01
≥16	186 (52.2)	187 (52.5)	0.01	4596 (48.8)	4487 (47.7)	0.02	1591 (42.6)	1508 (40.4)	0.05
Number of hospitalizations, *n* (%)‡									
0	125 (35.1)	142 (39.9)	0.10	4617 (49.1)	4454 (47.3)	0.03	1726 (46.2)	1738 (46.5)	0.01
1	104 (29.2)	96 (27.0)	0.05	2514 (26.7)	2602 (27.6)	0.02	1080 (28.9)	1061 (28.4)	0.01
≥2	127 (35.7)	118 (33.1)	0.05	2280 (24.2)	2355 (25.0)	0.02	931 (24.9)	938 (25.1)	0.00

COPD = chronic obstructive pulmonary disease; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; NSAID = nonsteroidal anti-inflammatory drug; TCPS = time-conditional propensity score; TIA = transient ischemic attack; SABA = short-acting β-agonist.
* Matching variable in addition to duration of COPD, calendar year of cohort entry, indication for gabapentinoids, and TCPS.
† Includes missing information (2.1% for gabapentinoid users, 0.2% for nonusers).
‡ Measured in the year before cohort entry.
§ Measured any time before cohort entry.
‖ Cells with a value <6 were suppressed owing to privacy restrictions.
¶ Excludes gabapentinoids.
** Excludes prednisone.

Table 2. Additional Characteristics of Patients With COPD for Each Indication, Measured in the Year Before Cohort Entry*

Characteristic	Gabapentinoid Users	Nonusers	Absolute Standardized Difference
Epilepsy			
Patients, *n*	356	356	–
Hospitalization for epilepsy	23 (6.5)	18 (5.1)	0.06
Carbamazepine	38 (10.7)	37 (10.4)	0.01
Lamotrigine	12 (3.4)	14 (3.9)	0.03
Levetiracetam	31 (8.7)	36 (10.1)	0.05
Phenobarbital/primidone	24 (6.7)	18 (5.1)	0.07
Phenytoin	102 (28.7)	105 (29.5)	0.02
Topiramate	†	†	0.03
Valproic acid	28 (7.9)	25 (7.0)	0.03
Other antiepileptic drugs	6 (1.7)	6 (1.7)	0.00
Number of distinct antiepileptics			
0	165 (46.3)	162 (45.5)	0.02
1	145 (40.7)	152 (42.7)	0.04
≥2	46 (12.9)	42 (11.8)	0.03
Neuropathic pain‡	182 (51.1)	153 (43.0)	0.16
Other chronic pain‡	148 (41.6)	124 (34.8)	0.14
Neuropathic pain			
Patients, *n*	9411	9411	–
Type of neuropathic pain			
Diabetic	1087 (11.6)	1129 (12.0)	0.01
Herpetic	2051 (21.8)	2009 (21.3)	0.01
Other/unspecified	6273 (66.7)	6273 (66.7)	0.00
Hospitalization for diabetes mellitus or hypoglycemia	115 (1.2)	123 (1.3)	0.01
Metformin	1990 (21.1)	1971 (20.9)	0.01
Sulfonylureas	1142 (12.1)	1149 (12.2)	0.00
α-Glucosidase inhibitors, meglitinide derivatives, and thiazolidinediones	380 (4.0)	400 (4.3)	0.01
DPP-4/SGLT2 inhibitors	253 (2.7)	276 (2.9)	0.01
Insulin	900 (9.6)	895 (9.5)	0.00
Muscle relaxants	793 (8.4)	725 (7.7)	0.03
Other chronic pain‡	4170 (44.3)	3425 (36.4)	0.16
Other chronic pain			
Patients, *n*	3737	3737	–
Type of pain			
Back	972 (26.0)	1004 (26.9)	0.02
Neck	126 (3.4)	123 (3.3)	0.00
Fibromyalgia	192 (5.1)	195 (5.2)	0.00
Osteoarthritis	1284 (34.4)	1256 (33.6)	0.02
Other	1163 (31.1)	1159 (31.0)	0.00
Intravenous corticosteroids	249 (6.7)	239 (6.4)	0.01
Orthopedic surgery	166 (4.4)	178 (4.8)	0.02
Muscle relaxants	401 (10.7)	394 (10.5)	0.01

COPD = chronic obstructive pulmonary disease; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium–glucose cotransporter-2.
* Values are numbers (percentages) unless otherwise indicated.
† Cells with a value <6 were suppressed owing to privacy restrictions.
‡ Included as a covariate in the time-conditional propensity score model in a post hoc analysis.

Results, main findings

Mean follow up time:

1. Patients with epilepsy: 1.5 years, gabapentinoid treatment duration: 0.6 years
2. Patients with neuropathic pain: 1.6 years, gabapentinoid treatment duration 0.5 years
3. Patients with other chronic pain: 1.6 years, gabapentinoid treatment duration 0.5 years

Results, main findings

Gabapentinoid use was associated with increased risk for severe COPD exacerbation across all indications:

Table 3. Adjusted HRs for Severe COPD Exacerbation Associated With the Use of Gabapentinoids, by Indication and Overall

Exposure	Patients, *n*	Events, *n*	Person- Years, *n*	Incidence Rate (95% CI)*	Adjusted HR (95% CI)†
Epilepsy					
Nonuse	356	90	838	10.7 (8.7-13.2)	1.00 (Reference)
Gabapentinoid use	356	46	205	22.4 (16.8-29.9)	1.58 (1.08-2.30)
Neuropathic pain					
Nonuse	9411	2142	24 645	8.7 (8.3-9.1)	1.00 (Reference)
Gabapentinoid use	9411	712	4646	15.3 (14.2-16.5)	1.35 (1.24-1.48)
Other chronic pain					
Nonuse	3737	756	10 298	7.3 (6.8-7.9)	1.00 (Reference)
Gabapentinoid use	3737	258	1842	14.0 (12.4-15.8)	1.49 (1.27-1.73)
Overall cohort					
Nonuse	13 504	2988	35 780	8.3 (8.0-8.6)	1.00 (Reference)
Gabapentinoid use	13 504	1016	6693	15.1 (14.2-16.1)	1.39 (1.29-1.50)

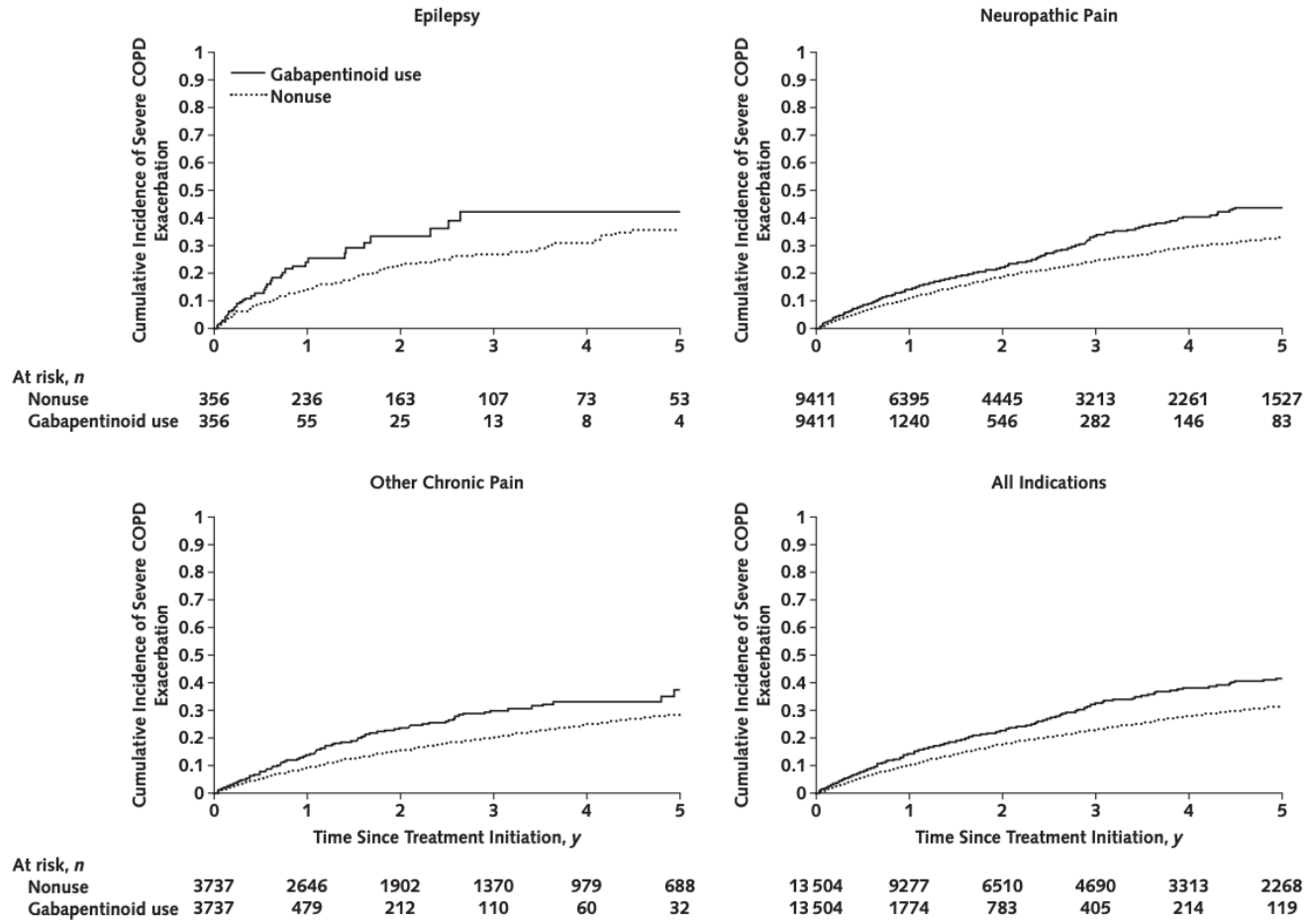
COPD = chronic obstructive pulmonary disease; HR = hazard ratio.
* Per 100 persons per year.
† After matching on duration of COPD, indication for gabapentinoids, age, sex, calendar year of cohort entry, and time-conditional propensity score.

Results

The cumulative incidence curves diverged shortly after gabapentinoid treatment initiation.

Peak increase in risk after 6 months of continuous use (suppl figure 1)

Figure 1. Cumulative incidence of severe COPD exacerbation among patients using gabapentinoids and TCPS-matched nonusers in epilepsy, neuropathic pain, other chronic pain, and all indications.



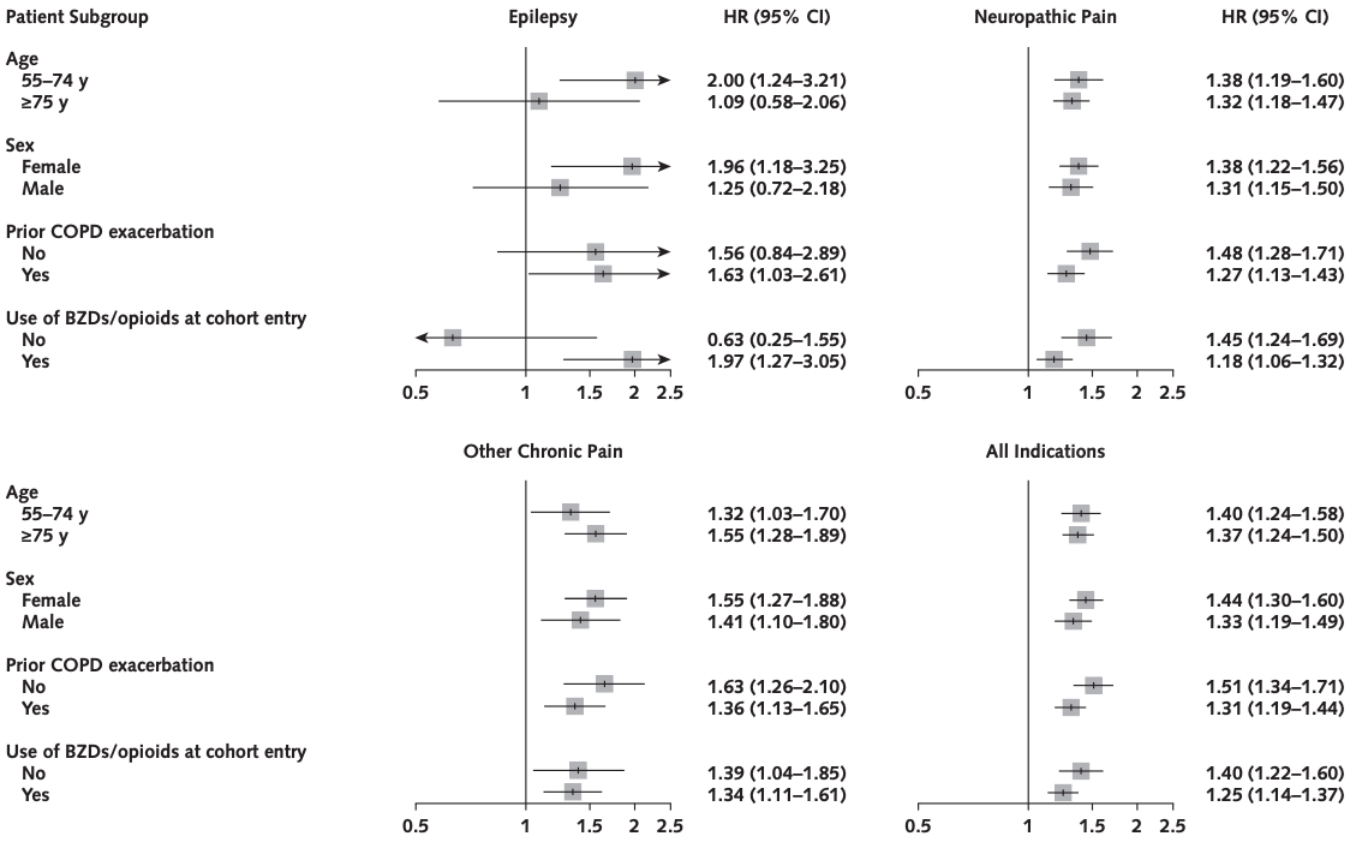
COPD = chronic obstructive pulmonary disease; TCPS = time-conditional propensity score.

Results

In stratified analyses, estimates in patients with epilepsy had uncertainty

In patients with neuropathic/other pain risk observed regardless od age, sex, number of prior COPD exacerbations, prior use of ICS, number of respiratory meds, opioid or BZD use at entry.

Figure 2. Forest plot summarizing adjusted HRs for severe COPD exacerbation associated with gabapentinoid use, stratified by pertinent patient characteristics, in epilepsy, neuropathic pain, other chronic pain, and all indications.

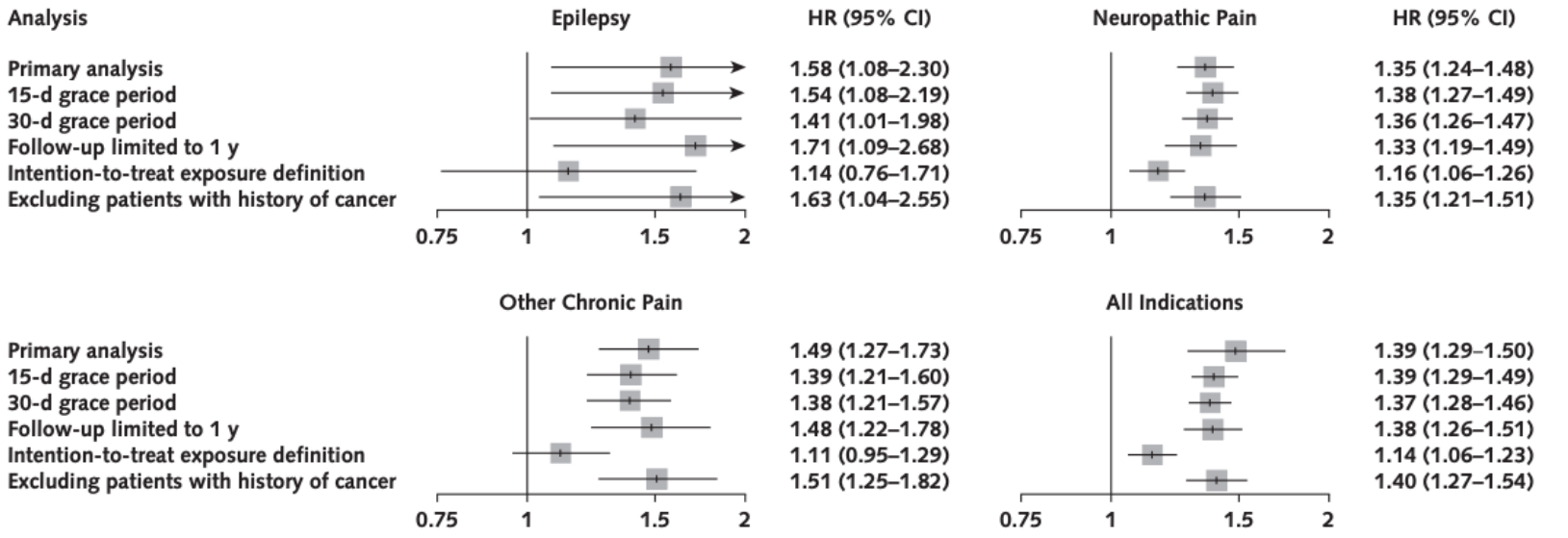


BZD = benzodiazepine; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

Subgroup analysis

Results consistent with primary analysis

Figure 3. Forest plot summarizing the results of primary and sensitivity analyses for the association between the use of gabapentinoids and the risk for severe COPD exacerbation in epilepsy, neuropathic pain, other chronic pain, and all indications.



COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

Subgroup analysis

- Risk of severe exacerbation similar in gabapentin or pregabalin
- Association still present in patients with undocumented indication
- Compared with NSAIDs, gabapentinoids remains associated with risk for severe exacerbation
- Gabapentinoids also associated with increased risk for moderate-severe exacerbation and respiratory failure

Discussion – strengths

- Large sample, multiple indications
- Matched exposed and unexposed patients on indication, COPD duration, age, sex, calendar time and TCPS

Limitations

- Definition of COPD: use of medications, due to limited validity of ICD codes
- Possible misclassification of asthma among prescribed LABA-ICS
- More likely to capture age>65 because covered by insurance for prescription medications
- Data on outpatient visits to ED not available
- Lack of information on previous or current smoking
- Could not exclude patients with pain in the subcohort of patients with epilepsy
- Opioid/BZD use is another potential confounder, but was well balanced between groups
- Race and ethnicity not available – possible residual confounding

Clinical implications

- Need for caution when prescribing gabapentinoids to COPD patients, especially those with additional risk factors (polypharmacy, older age, renal impairment, concurrent CNS depressants).

Summary and recommendations

- Gabapentinoids are associated with increased risk of severe COPD exacerbation, and prescribers should carefully weigh risks and benefits in this population.

References

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