



Journal club

MARTA ZAMPINO.
GERIATRIC MEDICINE FELLOW
JOHNS HOPKINS SCHOOL OF MEDICINE

1

Disclosures

- I have nothing to disclose

2

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
(Annals of Internal Medicine, 2024)

3

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.

4

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

5

COPD exacerbations

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

6

Pain and COPD

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

7

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

8

Study objective

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

9

Methods

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

10

Data source



3 computerized health care databases from Quebec province in Canada



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



Records of all hospitalizations are available

11

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

12

Exclusion criteria

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

13

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

14

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.

15

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.

16

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

17

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 for death 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

18

Results, main findings

- Base cohort of 156803 patients with COPD, including:
 - 356 gabapentinoid treatment initiators with epilepsy
 - 9411 with neuropathic pain
 - 3737 with other chronic pain
 - 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

19

Characteristic	Subcohort n = 356	Nonusers n = 156,447	Relative Difference	Subcohort n = 9411	Nonusers n = 156,447	Relative Difference	Subcohort n = 3737	Nonusers n = 156,447	Relative Difference
Baseline									
Female sex, n (%)	202 (56.7)	202 (56.7)	0.00	104 (11.2)	104 (11.2)	0.00	52 (13.9)	52 (13.9)	0.00
Age, mean (SD)	64.0 (14.0)	64.0 (14.0)	0.00	64.0 (14.0)	64.0 (14.0)	0.00	64.0 (14.0)	64.0 (14.0)	0.00
Weight, mean (SD)	70.0 (15.0)	70.0 (15.0)	0.00	70.0 (15.0)	70.0 (15.0)	0.00	70.0 (15.0)	70.0 (15.0)	0.00
Height, mean (SD)	170.0 (6.0)	170.0 (6.0)	0.00	170.0 (6.0)	170.0 (6.0)	0.00	170.0 (6.0)	170.0 (6.0)	0.00
Respiratory events and medications, n (%)									
0	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
1	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
2	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
3	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
4	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
5	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
6	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
7	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
8	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
9	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
10	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
11	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
12	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
13	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
14	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
15	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
16	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
17	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
18	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
19	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
20	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
21	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
22	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
23	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
24	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
25	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
26	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
27	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
28	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
29	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
30	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
31	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
32	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
33	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
34	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
35	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
36	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
37	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
38	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
39	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
40	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
41	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
42	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
43	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
44	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
45	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
46	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
47	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
48	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
49	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
50	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
51	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
52	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
53	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
54	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
55	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
56	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
57	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
58	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
59	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
60	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
61	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
62	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
63	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
64	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
65	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
66	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
67	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
68	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
69	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
70	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
71	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
72	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
73	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
74	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
75	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
76	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
77	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
78	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
79	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
80	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
81	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
82	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
83	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
84	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
85	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
86	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
87	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
88	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
89	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
90	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
91	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
92	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
93	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
94	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
95	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
96	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
97	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
98	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
99	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00
100	10 (2.8)	10 (2.8)	0.00	5 (0.5)	5 (0.5)	0.00	2 (0.5)	2 (0.5)	0.00

20

Characteristic	Subcohort Users	Nonusers	Relative Difference
Epilepsy			
Female sex	356	356	0.00
Hospitalization for epilepsy	23 (6.5)	18 (5.1)	0.06
Carbamazepine	28 (7.9)	21 (6.0)	0.05
Levetiracetam	31 (8.7)	24 (6.8)	0.05
Phenytoin/phenytoin	24 (6.7)	18 (5.1)	0.07
Phenytoin/phenytoin	162 (45.7)	155 (49.1)	0.05
Topiramate	28 (7.9)	21 (6.0)	0.05
Valproic acid	28 (7.9)	21 (6.0)	0.05
Other antiepileptic drugs	41 (11.5)	41 (11.5)	0.00
Number of distinct antiepileptics			
0	162 (46.3)	162 (49.3)	0.02
1	145 (40.7)	142 (40.2)	0.04
2	46 (12.9)	42 (11.8)	0.03
3	18 (5.1)	12 (3.4)	0.14
4	18 (5.1)	12 (3.4)	0.14
5	18 (5.1)	12 (3.4)	0.14
6	18 (5.1)	12 (3.4)	0.14
7	18 (5.1)	12 (3.4)	0.14
8	18 (5.1)	12 (3.4)	0.14
9	18 (5.1)	12 (3.4)	0.14
Neurologic pain			
Female sex	9411	9411	0.00
Hospitalization for pain	1087 (11.6)	1129 (12.0)	0.01
Topiramate	2057 (22.0)	2097 (22.1)	0.00
Other antiepileptics	4277 (46.0)	4277 (46.0)	0.00
Topiramate for diabetic neuropathy or trigeminal	127 (1.4)	127 (1.4)	0.00
Topiramate	112 (1.2)	112 (1.2)	0.00
Suboxone	112 (1.2)	112 (1.2)	0.00
Other antiepileptics, myofascial, dystonia, and fibromyalgia	408 (4.4)	408 (4.4)	0.00
OPR A-2, T-2 inhibitors	23 (0.2)	23 (0.2)	0.00
Topiramate	191 (2.0)	191 (2.0)	0.00
Other antiepileptics	417 (4.4)	417 (4.4)	0.00
Other chronic pain	417 (4.4)	417 (4.4)	0.00
Other chronic pain			
Female sex	3737	3737	0.00
Hospitalization for pain	191 (2.4)	194 (2.4)	0.02
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)	155 (1.9)	0.00
Topiramate	123 (1.5)	123 (1.5)	0.00
Other antiepileptics	155 (1.9)		

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

22

Results, main findings

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

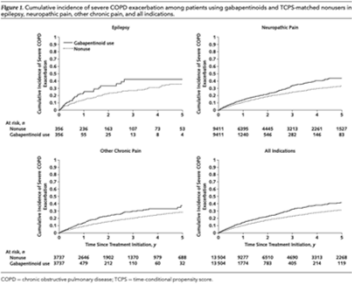
Table 3. Adjusted HRs for Severe COPD Exacerbation Associated With the Use of Gabapentinoids, by Indication and Overall					
Exposure	Patients, n	Events, n	Person-Years, n	Incidence Rate (95% CI)*	Adjusted HR (95% CI)†
Epilepsy					
None	356	90	838	10.7 (8.7–13.2)	1.00 (Reference)
Gabapentinoid use	356	46	205	22.4 (16.8–29.9)	1.58 (1.08–2.30)
Neuropathic pain					
None	9411	2142	24 645	8.7 (8.3–9.3)	1.00 (Reference)
Gabapentinoid use	9411	712	4646	15.3 (14.2–16.5)	1.35 (1.24–1.48)
Other chronic pain					
None	3737	754	10 278	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					
None	13 504	2988	35 780	8.3 (8.0–8.6)	1.00 (Reference)
Gabapentinoid use	13 504	1016	6693	15.1 (14.0–16.1)	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.

23

Results

The cumulative incidence curves diverged shortly after gabapentinoid treatment initiation.
Peak increase in risk after 6 months of continuous use (suppl figure 1)

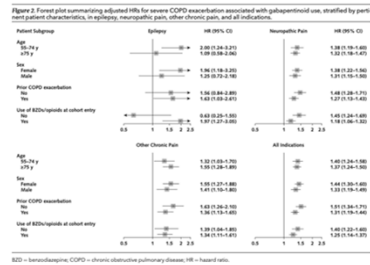


24

Results

In stratified analyses, estimates in patients with epilepsy had uncertainty

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

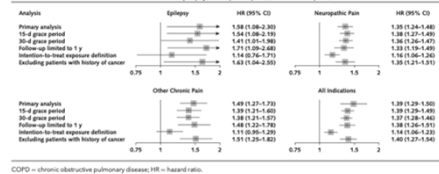


25

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.



26

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

27

Discussion – strengths

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

28

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

29

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).

30

Summary and recommendations

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

31

References

[Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study](#). Rahman AA, Dell’Anello S, Moodie EEM, et al. *Annals of Internal Medicine*. 2024;177(2):144-154. doi:10.7326/M23-0849

- [Respiratory Concerns of Gabapentin and Pregabalin: What Does It Mean to the Pharmacovigilance Systems in Developing Countries?](#) Shrestha S, Pataian S. *F1000Research*. 2020;9:32. doi:10.12688/f1000research.21962.1
- [A Clinical Overview of Off-Label Use of Gabapentinoid Drugs](#). Goodman CW, Brett AS. *JAMA Internal Medicine*. 2019;179(5):695-701. doi:10.1001/jamainternmed.2019.0086
- [Gabapentinoid Pharmacology in the Context of Emerging Mouse Liability](#). Evoy KE, Peckham AM, Covey JR, Tidgewell KJ. *Journal of Clinical Pharmacology*. 2021;61 Suppl 2:S89-S99. doi:10.1002/cph.1833
- [Risk of Severe Exacerbation Associated With Gabapentinoid Use in Patients With Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study](#). Otaeye O, Dell’Anello S, Ermer P, Sussaa S, Renoux C. *Cope*. 2025;22(1):2534002. doi:10.1089/25422955.2025.2534002
- [Prevalence of Gabapentinoids and Central Nervous System Depressant Drugs and Their Association With Risk Factors for Respiratory Depression in Primary Care Patients](#). Fernández-Lu E, Barco-Gómez MC, Gómez-García L, et al. *Clinical Drug Investigation*. 2022;42(5):437-439. doi:10.1007/s40261-022-01144-8
- [Gabapentinoids and Risk for Exacerbation of Chronic Obstructive Pulmonary Disease](#). Kimura Y, Jo T, Inoue N, et al. *Annals of the American Thoracic Society*. 2025. doi:10.1513/AnnalsATS.202411.123000
- [Risk of Adverse Outcomes During Gabapentinoid Therapy and Factors Associated With Increased Risk in UK Primary Care Using the Clinical Practice Research Datalink: A Cohort Study](#). Muller S, Bailey J, Bagep R, et al. *Pain*. 2024;165(10):2282-2290. doi:10.1097/j.pain.0000000000003239

32