Risk of dementia following gabapentin prescription in chronic low back pain patients

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ABSTRACT

Introduction Gabapentin is widely used to treat chronic pain, but its association with cognitive decline and dementia remains unclear. This study examined whether gabapentin prescription is associated with dementia in adults with chronic low back pain.

Methods We conducted a retrospective cohort study using the TriNetX national database of de-identified patient records from 2004 to 2024. Adults diagnosed with chronic low back pain were included; those with prior gabapentin use, dementia, epilepsy, stroke, or cancer were excluded. Propensity score matching controlled for demographics, comorbidities, and pain medications. Patients were stratified by age and gabapentin prescription frequency. Primary outcomes were dementia and mild cognitive impairment.

Results 26,416 adults we analyzed following propensity-score matching. Patients with six or more gabapentin prescriptions had an increased incidence of dementia (RR: 1.29; 95% CI: 1.18–1.40) and mild cognitive impairment (RR: 1.85; 95% CI: 1.63–2.10). When stratified by age, non-elderly adults (18–64) prescribed gabapentin had over twice the risk of dementia (RR: 2.10; 95% CI: 1.75–2.51) and mild cognitive impairment (RR: 2.50; 95% CI: 2.04–3.05) compared to those not prescribed gabapentin. Risk increased further with prescription frequency: patients with 12 or more prescriptions had a higher incidence of dementia (RR: 1.40; 95% CI: 1.25–1.57) and mild cognitive impairment (RR: 1.65; 95% CI: 1.42–1.91) than those prescribed gabapentin 3–11 times.

Conclusions Gabapentin prescription in adults with chronic low back pain is associated with increased risk of dementia and cognitive impairment, particularly in non-elderly adults. Physicians should monitor cognitive outcomes in patients prescribed gabapentin.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The existing literature reflects mixed findings regarding the association between gabapentin and neurodegenerative processes like dementia.

WHAT THIS STUDY ADDS

⇒ The current study adds evidence of an important association, as we discovered that gabapentin prescription increases the risk of dementia and cognitive impairment for adult patients with chronic low back pain.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The findings of this study support the need for close monitoring in adult patients prescribed gabapentin to assess for potential cognitive decline. Moreover, this provides a foundation to further research whether gabapentin plays a causal role in the development of dementia and cognitive decline.

INTRODUCTION

Gabapentin, a medication approved in 1993 by the US Food and Drug Administration to treat partial seizures, has been used for the treatment of chronic pain for over 20 years.[1] Gabapentin is known to have a low abuse potential, making it an attractive alternative to opioids.[2] Over time, its use expanded, and the medication became more popular to manage chronic pain, especially neuropathic pain, as it offers not only pain-relieving effects but also potential neuroprotective benefits.[3] Despite the ever-increasing use of gabapentin, several concerns have been described, including its effects on the tripartite synapse and oligodendrocytes, as well as an increasing incidence of abuse among patients.[4 5] Additionally, studies have associated gabapentin with cognitive decline and risk of exacerbation for patients with chronic obstructive pulmonary disease (COPD).[6 7]

Gabapentin, which has a high affinity for voltage-gated calcium channels in the brain, inhibits the release of excitatory neurotransmitters in the presynaptic terminal, thereby reducing pain signaling and the occurrence of seizures.[1] Currently, there is a discrepancy on whether taking gabapentin increases a patient's risk for the development of dementia.[6 8] One large retrospective, population-based matched cohort study found an increased risk of dementia in patients taking gabapentin, especially with higher cumulative daily doses during their follow-up period. The authors found this risk for dementia to be significant for all age groups, while most pronounced in patients below age 50.[6] However, a recent analysis indicated that long-term use of gabapentin for chronic pain does not increase the risk of dementia, regardless of dosage, age, or gender.[3]

There is no consensus on the relationship between gabapentin and neurodegeneration in chronic pain patients. Moreover, the existing literature lacks a clear understanding of the impact of age in this potential relationship and potential age-related variations in drug metabolism. Thus, the

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current study aimed to investigate the risk of dementia following gabapentin prescription in chronic pain patients, followed by an age-stratified analysis. To our knowledge, no studies have performed a macro-level analysis on this topic, despite the medication's common usage and extensive research in other domains. We hope to strengthen our current understanding of this potential association, which may lead to improved care for patients with chronic pain.

METHODS

Data source

This study used deidentified patient data from the US collaborative network in TriNetX, a federated health research network. TriNetX draws real-time data from its database, which contains electronic health records from 68 healthcare organizations across the USA. Patient data was retrospectively queried using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM), Current Procedural Terminology and RxNorm coding systems. Our study only used deidentified patient data, so it was exempt from Western Institutional Review Board approval, per Section §164.514(b)(1) of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. This study conforms to all the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and reports the required information accordingly (see supplementary checklist).

Patient selection

The TriNetX US Collaborative Network draws patient data up to 20 years before the time of analysis. We identified adult patients (age ≥18) diagnosed with chronic pain (ICD-10-CM G89.29), chronic pain syndrome (ICD-10-CM G89.4), lumbar radiculopathy (ICD-10-CM M54.16), or chronic low back pain (ICD-10-CM M54.5) between December 1, 2004 and November 1, 2014. This end date was chosen to assess 10-year outcomes. Patients with any prior history of gabapentin use (RxNorm 25480), dementia (ICD-10-CM F01-F03), epilepsy and recurrent seizures (ICD-10-CM G40), Alzheimer's disease (ICD-10-CM G30), cerebral infarction (ICD-10-CM I63), or cancer (ICD-10-CM C00-D49) were excluded. Initial cohorts were designed based on the presence of at least two gabapentin prescriptions or absence of gabapentin prescription following the index event, defined as the patient's initial 'pain' diagnosis (diagnosis of chronic pain, chronic pain syndrome, lumbar radiculopathy, or chronic low back pain). The 'Gabapentin' group included patients with six or more gabapentin prescriptions (RxNorm 25480) following their initial pain diagnosis. In contrast, the 'No Gabapentin' cohort involved patients with no prescription of gabapentin at any time following their initial pain diagnosis. Further cohorts were stratified by different age groups: 18–64, 18–34, 35–49, 50–64 and ≥65. Propensity score matching (PSM) was performed based on age at index event, gender, race, ethnicity, hypertension (ICD-10-CM I10), ischemic heart diseases (ICD-10-CM I20-I25), mood disorders (ICD-10-CM F30-F39), anxiety disorders (ICD-10-CM F40-F48), nicotine dependence (ICD-10-CM F17), alcohol-related disorders (ICD-10-CM F10), diabetes mellitus (ICD-10-CM E08-E13), hyperlipidemia (ICD-10-CM E78.4–78.5), pure hypercholesterolemia (ICD-10-CM E78.0), sleep disorders (ICD-10-CM G47), Parkinson's disease (ICD-10-CM G20), other degenerative diseases (ICD-10-CM

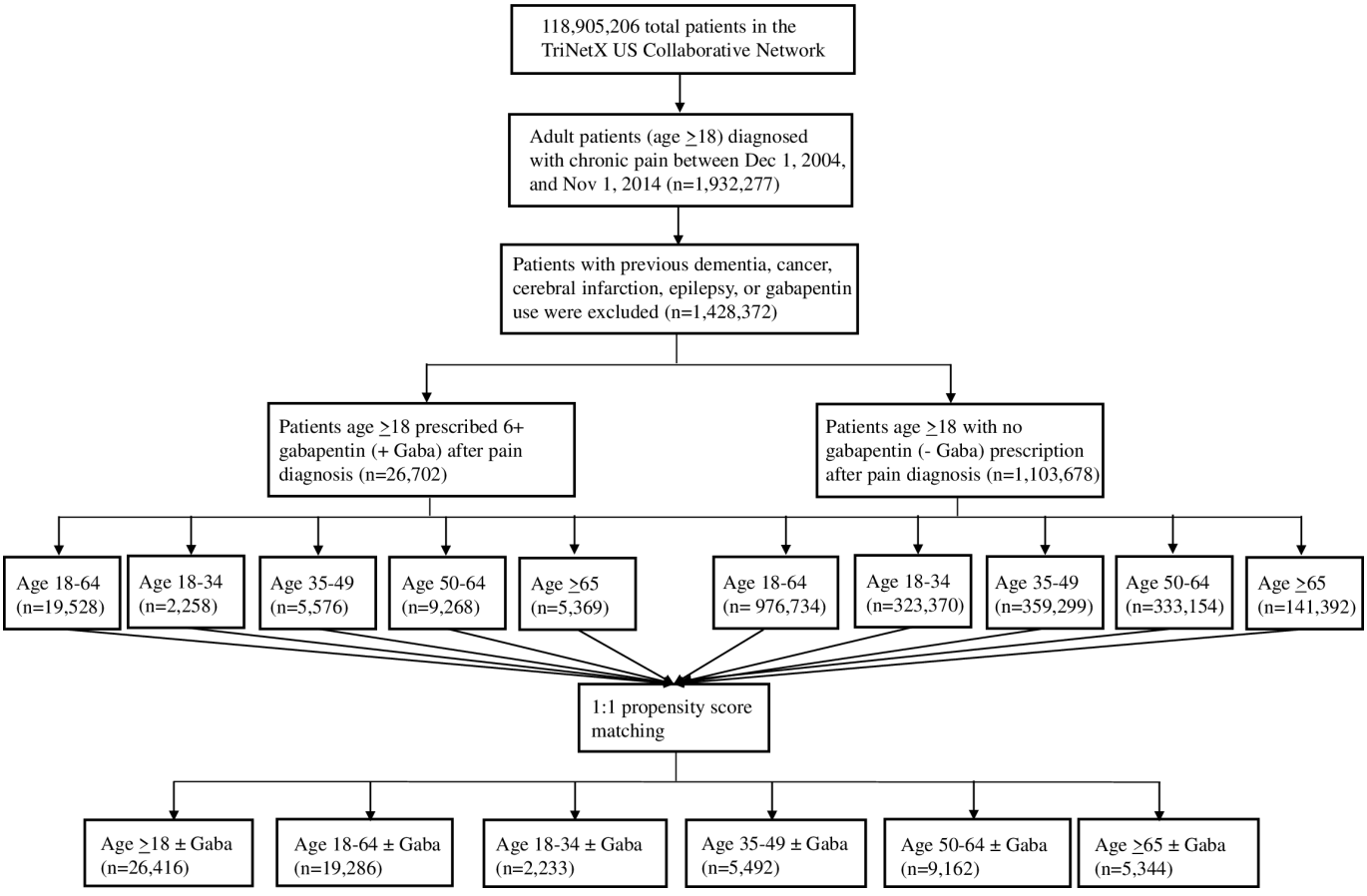

Figure 1 Flowchart of patient selection and cohort design.

G31; includes mild cognitive impairment (MCI), frontotemporal dementia, dementia with Lewy bodies and unspecified cerebral degeneration), and intracranial injury (ICD-10-CM S06). Our PSM also matched for prescription of a variety of pain medications, including opioids (VA CN101), tricyclic antidepressants (VA CN601), duloxetine (RxNorm 72625), venlafaxine (RxNorm 39786), benzodiazepines (VA CN302), skeletal muscle relaxants (VA MS200), milnacipran (RxNorm 588250), carbamazepine (RxNorm 2002), oxcarbazepine (RxNorm 32624), lamotrigine (RxNorm 28439), and lidocaine (RxNorm 6387). A subanalysis included the 'Gabapentin 12+' cohort, consisting of patients with at least 12 gabapentin prescriptions following their back pain diagnosis, and the 'Gabapentin 3 to 11' cohort, which consisted of patients with between 3 and 11 gabapentin prescriptions.

Outcomes measured

Following PSM, we examined several outcomes within 10 years following the index event of the patient's first pain diagnosis. Our primary outcome was the occurrence of dementia, including vascular dementia, dementia in other diseases, unspecified dementia, and Alzheimer's disease, using ICD-10-CM codes F01, F02, F03, G30. Secondarily, we examined the incidence of MCI through ICD-10-CM G31.84.

Statistical analysis

PSM was used to limit bias and avoid the influence of potential risk factors for dementia in our analysis. The TriNetX system uses a 1:1 greedy nearest-neighbor PSM method, using logistic regression models to generate cohorts of comparable size and characteristics. In the current study, PSM was based on demographics, medical diagnoses related to cognitive decline, and other pain medications. We defined well-matched covariates as those with a standardized mean difference <0.1. Analytic tools within TriNetX were used to calculate t-tests and risk ratios (RRs) with 95% CIs.

RESULTS

Patient demographics

At the time of our query, there were 118 905 206 patients in the TriNetX US Collaborative Network. Of these patients,

Table 1 Demographics and comorbidities for adult patients in the gabapentin versus no gabapentin cohorts before and after propensity score matching

	Before propensity score matching			After propensity score matching		
Variable: avg. (SD) or n (%)	Gabapentin	No gabapentin	Standardized mean difference	Gabapentin	No gabapentin	Standardized mean difference
Sample size, n	26 681	1 103 678		26 416	26 416	
Demographics						
Mean age at index in years, mean (SD)	52.4 (13.4)	44.8 (15.2)	0.531	52.4 (13.4)	53.0 (13.8)	0.048
Sex, n (%)						
Female	15 312 (57.9)	589 205 (54.2)	0.076	15 308 (58.0)	15 426 (58.4)	0.009
Male	11 089 (42.0)	494 088 (45.4)	0.070	11 084 (42.0)	10 972 (41.5)	0.009
Race and ethnicity, n (%)						
White	19 072 (72.2)	717 113 (66.0)	0.135	19 063 (72.2)	19 368 (73.3)	0.026
Black	4336 (16.4)	172 490 (15.9)	0.015	4336 (16.4)	4097 (15.5)	0.025
Not Hispanic or Latino	20 445 (77.4)	685 056 (63.0)	0.318	20 436 (77.4)	20 621 (78.1)	0.017
Comorbidities, n (%)						
Hypertension	10 924 (41.3)	156 668 (14.4)	0.630	10 915 (41.3)	10 850 (41.1)	0.005
Diabetes mellitus	5843 (22.1)	59 477 (5.5)	0.497	5834 (22.1)	5621 (21.3)	0.020
Ischemic heart diseases	3058 (11.6)	33 119 (3.05)	0.332	3050 (11.5)	2886 (10.9)	0.020
Hyperlipidemia, unspecified	6611 (25.0)	98 195 (9.03)	0.435	6605 (25.0)	6304 (23.9)	0.027
Pure hypercholesterolemia	2478 (9.4)	43 007 (4.0)	0.219	2476 (9.4)	2430 (9.2)	0.006
Other hyperlipidaemia	4644 (17.6)	67 808 (6.2)	0.356	4638 (17.6)	4528 (17.1)	0.011
Nicotine dependence	5145 (19.5)	69 120 (6.36)	0.399	5140 (19.5)	4904 (18.6)	0.023
Alcohol-related disorders	1785 (6.8)	21 014 (1.9)	0.238	1782 (6.7)	1656 (6.3)	0.019
Intracranial injury	683 (2.6)	12 370 (1.1)	0.107	683 (2.6)	660 (2.5)	0.006
Parkinson's disease	140 (0.5)	1704 (0.2)	0.064	138 (0.5)	133 (0.5)	0.003
Sleep disorders	4904 (18.6)	57 318 (5.3)	0.419	4897 (18.5)	4687 (17.7)	0.021
Mood disorders	7747 (29.3)	98 248 (9.0)	0.533	7738 (29.2)	7496 (28.4)	0.020
Anxiety disorders	6168 (23.3)	88 930 (8.2)	0.425	6160 (23.3)	6090 (23.1)	0.006
Medications, n (%)						
Opioids	17 113 (64.8)	261 679 (24.1)	0.898	17 104 (64.7)	17 319 (65.6)	0.017
Benzodiazepines	10 312 (39.0)	111 700 (10.3)	0.708	10 303 (39.0)	10 399 (39.4)	0.007
Skeletal muscle relaxants	7700 (29.1)	82 181 (7.6)	0.581	7691 (29.1)	7536 (28.5)	0.013
Lidocaine	7165 (27.1)	82 815 (7.6)	0.533	7157 (27.1)	6907 (26.1)	0.021
Tricyclic Antidepressants	2434 (9.2)	18 789 (1.7)	0.334	2427 (9.2)	2231 (8.4)	0.026
Duloxetine	1329 (5.0)	8187 (0.8)	0.257	1325 (5.0)	1203 (4.6)	0.022
Venlafaxine	1057 (4.0)	9363 (0.9)	0.205	1055 (4.0)	911 (3.4)	0.029
Lamotrigine	380 (1.4)	3480 (0.3)	0.120	379 (1.4)	326 (1.2)	0.018

1 932 277 adult patients (age ≥18 years) received a back pain diagnosis between December 1, 2004 and November 1, 2014 (figure 1). Patients with prior history of gabapentin use, dementia, Alzheimer's disease, cerebral infarction, cancer, or epilepsy were excluded, yielding a total of 1 428 372 patients in our analysis. Of this population, patients were assigned to the gabapentin cohort or no gabapentin cohort based on the presence or absence of gabapentin prescription following initial pain diagnosis. The gabapentin group contained 26 702 patients, and the no gabapentin cohort contained 1 103 678 patients. These cohorts were further stratified into separate adult age groups, forming the following cohorts: age 18–34 gabapentin (n=2258), age 18–34 no gabapentin (n=323 370), age 35–49 gabapentin (n=5576), age 35–49 no gabapentin (n=359 299), age 50–64 gabapentin (n=9268), age 50–64 no gabapentin (n=333 154), age 18–64 gabapentin (n=19 528), age 18–64 no gabapentin (n=976 734), age ≥65 gabapentin (n=5369), age ≥65 no gabapentin (n=141 392), as depicted in figure 1.

Each direct comparison was preceded by matching demographics and comorbidities through PSM. Table 1 demonstrates variables before and after PSM for the gabapentin and no gabapentin groups for all adult patients. Following PSM, there were 26 416 patients in each group for the gabapentin versus no gabapentin analysis. The gabapentin group had a mean±SD age of 52.4±13.4 years, and the no gabapentin group had an average age of 53.0±13.8. The gabapentin group contained 15 308 (58.0%) female and 11 084 (42.0%) male patients, while the no gabapentin group consisted of 15 426 (58.4%) female and 10 972 (41.5%) male patients. There were 19 063 (72.2%) white and 4336 (16.4%) black patients in the gabapentin group. In the no gabapentin group, 19 368 (73.3%) patients and 4097 (15.5%) patients were white and black, respectively. 20 436 (77.4%) and 20 621 (78.1%) patients identified as not Hispanic or Latino in the gabapentin and no gabapentin groups, respectively. All covariates were well matched with a standardized mean difference of <0.1 (table 1).

Incidence of dementia and MCI for gabapentin versus no-gabapentin patients

Diagnosis of dementia within 10 years of initial pain diagnosis was the primary outcome assessed in this study. Our initial analysis compared all adult patients (age ≥18) prescribed gabapentin versus those not prescribed gabapentin, revealing a higher incidence of dementia in the gabapentin group (table 2; RR: 1.29; 95% CI 1.18 to 1.40). Additionally, patients in the gabapentin group were more likely to be diagnosed with MCI (table 2; RR: 1.85; 95% CI 1.63 to 2.10). Following this overall analysis, we explored age-dependent differences by first stratifying the cohort into elderly (age≥65) and non-elderly (age 18–64) groups. In the elderly cohort, the gabapentin group showed increased incidence of both dementia (table 2; RR: 1.28; 95% CI 1.15 to 1.42) and MCI (table 2; RR: 1.53; 95% CI 1.28 to 1.83). Similarly, among non-elderly adults, dementia (table 2; RR: 2.10; 95% CI 1.75 to 2.51) and MCI (table 2; RR: 2.50; 95% CI: 2.04 to 3.05) were more commonly diagnosed in patients prescribed gabapentin compared with those who were not. We then further stratified the non-elderly group into narrower age ranges: 18–34, 35–49 and 50–64 years. For patients aged 18–34, there was no significant difference in dementia or MCI incidence between exposure groups (table 2; RR for MCI: 1.00; 95% CI 0.42 to 2.39). In contrast, patients aged 35–49 who were prescribed gabapentin had an increased likelihood of both dementia (table 2; RR: 2.44; 95% CI 1.41 to 4.23) and MCI (table 2; RR: 3.50; 95% CI 2.18 to 5.61). A similar pattern was observed in the 50–64 age group, where gabapentin exposure was associated with elevated incidence of dementia (table 2; RR: 2.28; 95% CI 1.86 to 2.80) and MCI (table 2; RR: 2.22; 95% CI 1.75 to 2.82).

Table 2 Incidence of dementia and mild cognitive impairment (MCI) diagnosis stratified by age within 10 years after pain diagnosis among patients prescribed versus not prescribed gabapentin

Age group	Outcome	Gabapentin n (%)	No gabapentin n (%)	Risk ratio (95% CI)
≥18	Dementia	1124 (4.3)	875 (3.3)	**1.29 (1.18 to 1.40)**
	MCI	678 (2.6)	367 (1.4)	**1.85 (1.63 to 2.10)**
≥65	Dementia	691 (12.9)	541 (10.1)	**1.28 (1.15 to 1.42)**
	MCI	297 (5.6)	194 (3.6)	**1.53 (1.28 to 1.83)**
18–64	Dementia	367 (1.9)	175 (0.9)	**2.10 (1.75 to 2.51)**
	MCI	332 (1.7)	133 (0.7)	**2.50 (2.04 to 3.05)**
18–34	Dementia	≤10 (1.0)	0 (0)	–
	MCI	≤10 (1.0)	≤10 (1.0)	1.00 (0.42 to 2.39)
35–49	Dementia	44 (0.8)	18 (0.3)	**2.44 (1.41 to 4.23)**
	MCI	77 (1.4)	22 (0.4)	**3.50 (2.18 to 5.61)**
50–64	Dementia	294 (3.2)	129 (1.4)	**2.28 (1.86 to 2.80)**
	MCI	213 (2.3)	96 (1.0)	**2.22 (1.75 to 2.82)**

Bold values represent statistical significance.

Comparison of dementia and MCI by gabapentin prescription frequency

To assess potential dose-dependent effects of gabapentin exposure on cognitive outcomes, we compared patients with 12 or more gabapentin prescriptions (gabapentin 12+) to patients with 3–11 gabapentin prescriptions (gabapentin 3 to 11). Among all adult patients (age ≥18), those in the 12+ prescription group had a higher incidence of both dementia (table 3; RR: 1.40; 95% CI 1.25 to 1.57) and MCI (table 3; RR: 1.65; 95% CI 1.42 to 1.91) relative to those with 3–11 prescriptions. In elderly patients (age ≥65), this trend persisted as the 12+ prescription group had increased rates of dementia (table 3; RR: 1.37; 95% CI 1.19 to 1.57) and MCI (table 3; RR: 1.50; 95% CI 1.20 to 1.88) compared with the 3–11 group. Similarly, in non-elderly adults (age 18–64), those with 12+ prescriptions had greater incidence of both dementia (table 3; RR: 1.57; 95% CI 1.28 to 1.93) and MCI (table 3; RR: 1.80; 95% CI 1.43 to 2.26). Further stratification revealed consistent findings. Among patients aged 18–34, the incidence of dementia remained very low, with no clear difference between exposure groups. For MCI, risk was comparable across the 18–34 groups (table 3; RR: 1.00; 95% CI 0.42 to 2.39). In the 35–49 age group, patients with ≥12 prescriptions were more likely to be diagnosed with dementia (table 3; RR: 1.59; 95% CI 0.87 to 2.91) and MCI (table 3; RR: 2.10; 95% CI 1.25 to 3.51). Finally, among patients aged 50–64, the 12+ prescription group showed a significantly elevated risk of dementia (table 3; RR: 1.98; 95% CI 1.54 to 2.54) and MCI (table 3; RR: 2.02; 95% CI 1.50 to 2.71) relative to those with 3–11 prescriptions.

DISCUSSION

Gabapentin is a common treatment for chronic pain, and its increasing use has prompted further investigation into its adverse effects.[6] It provides substantial pain relief for postherpetic neuralgia and diabetic neuropathy; however, for other chronic neuropathic pain conditions, it remains limited.[9–11] Gabapentin is often favored due to its relatively low number of

Table 3 Incidence of dementia and mild cognitive impairment (MCI) diagnosis stratified by age within 10 years after pain diagnosis among patients with 12+ gabapentin prescriptions versus patients with between 3–11 gabapentin prescriptions

Age group	Outcome	Gabapentin 12+ N (%)	Gabapentin 3–11 n (%)	Risk ratio (95% CI)
≥18	Dementia	723 (4.9)	516 (3.5)	**1.40 (1.25 to 1.57)**
	MCI	454 (3.1)	275 (1.8)	**1.65 (1.42 to 1.91)**
≥65	Dementia	428 (14.3)	313 (10.4)	**1.37 (1.19 to 1.57)**
	MCI	185 (6.2)	123 (4.1)	**1.50 (1.20 to 1.88)**
18–64	Dementia	228 (2.2)	145 (1.4)	**1.57 (1.28 to 1.93)**
	MCI	205 (2.0)	114 (1.1)	**1.80 (1.43 to 2.26)**
18–34	Dementia	≤10 (1.0)	0 (0)	–
	MCI	≤10 (1.0)	≤ 10 (1.0)	1.00 (0.42 to 2.39)
35–49	Dementia	27 (1.0)	17 (0.7)	1.59 (0.87 to 2.91)
	MCI	44 (1.7)	21 (0.8)	**2.10 (1.25 to 3.51)**
50–64	Dementia	178 (3.7)	90 (1.9)	**1.98 (1.54 to 2.54)**
	MCI	131 (2.7)	65 (1.3)	**2.02 (1.50 to 2.71)**

Bold values represent statistical significance.

drug interactions and few serious adverse effects.[12] Nonetheless, Derry *et al* found the most common side effects to be sedation, dizziness, gait instability, and somnolence.[13] While existing literature identifies several risks, there lacks a strong understanding of how gabapentin impacts cognitive function and whether it contributes to neurodegenerative processes. Thus, the current study aimed to explore the relationship between gabapentin and dementia in chronic pain patients.

Our initial analysis yielded an increased risk of dementia in adults (age ≥18) in the gabapentin cohort compared with the no gabapentin cohort (table 2). Among non-elderly patients (age 18–64), gabapentin prescription was associated with a greater likelihood of dementia compared with those not prescribed gabapentin (table 2). This association was relatively stronger in the elderly (age ≥65) patients, who also showed an increased risk for dementia and MCI (table 2). Moreover, when comparing varying frequencies of gabapentin prescriptions (≥12 vs 3–11 prescriptions) in adults, we observed elevated risk for both dementia and MCI in the higher prescriptions group (table 3). Shem *et al* corroborate our findings, reporting a decline in memory, executive function, and attention in spinal cord injury patients taking gabapentin.[14] Oh *et al* similarly reported associations between gabapentin and neurocognitive decline, including functional status decline and motor function change among older adults with initially normal cognition.[15] Additional evidence from HIV patients showed gabapentin users experienced more functional impairment, mental fog, and drowsiness.[16] In contrast, a randomized study of 40 healthy volunteers found that while topiramate impaired cognition, gabapentin had minimal effects.[17] While our findings and previous literature indicate that gabapentin increases dementia risk, particularly in non-elderly patients, some studies have reported conflicting results. One study of over 200 000 chronic pain patients aged >50 years found no increase in dementia risk following gabapentin use.[3] Yilmaz *et al* found that gabapentin, when combined with pregabalin, is well tolerated in elderly adults and can effectively treat agitation in dementia patients.[18] Similarly, Leach *et al* describe that gabapentin was well tolerated and did not affect cognition, but led to sedation at high doses in patients with a history of seizures.[19]

The cognitive effects of gabapentin have been explored in several patient populations outside of chronic pain. In patients with a seizure history, two studies demonstrated no cognitive decline following gabapentin administration.[19 20] One study found that patients with spinal cord injury taking gabapentin demonstrated a decrease in cognitive function 1 week postinitiation.[14] Moreover, Oh *et al* discovered cognitive decline in healthy elderly patients following gabapentin initiation.[15] In terms of neurotoxicity, gabapentin combined with opioids has been linked to increased hospitalization risk and altered mental status.[21] There is additional risk for gabapentin abuse in patients with a history of substance use.[22] One case report showed overuse and abuse of gabapentin leading to posterior reversible encephalopathy syndrome, illustrating the potential neurotoxicity of the drug.[23] Another report describes gabapentin-induced altered mental status in a patient with uremia.[24]

Antiseizure drugs, including gabapentin, suppress neuronal excitability or enhance inhibitor neurotransmission, potentially leading to adverse cognitive effects.[25] However, the precise mechanism remains to be fully elucidated. Preclinical studies reflect that gabapentin can alter neural activity by modulating calcium channel function through the alpha2delta-1 ($\alpha2/\delta-1$) subunit of voltage-gated calcium channels.[12 26] Oh *et al* postulate that gabapentin may provide a neuroprotective effect through blocking calcium channels in the brain, despite inconclusive evidence.[15] Further research in rodents demonstrates gabapentin's ability to reduce pain sensitivity and activate spinal glial cells by modulating VGCC $\alpha2/\delta-1$ subunits.[27] Microglial activation and astrocytic dysfunction are central to the pathophysiology of dementia, providing a potential mechanism for gabapentin's role in neuroinflammation and neurodegeneration.[28] Chronic gabapentin exposure has also been linked to reduced neurogenesis and synaptic plasticity in memory-related brain regions.[29] One study in healthy males found gabapentin increased gamma-aminobutyric acid (GABA) levels—potentially via stimulating glutamic acid decarboxylase activity and inhibiting GABA transaminase.[30] Gabapentin's ability to reduce calcium influx into glutamatergic terminals could contribute to its effects, but its impact on chronic glutamate and GABA modulation requires further investigation. The relationship between these acute changes and therapeutic efficacy in epilepsy or neuropathic pain remains to be explored.

The current study has several limitations, including its retrospective nature and inherent constraints of the TriNetX database. We did not control for dose or duration of gabapentin use, introducing a key variable to address in future studies. This study does not establish causality but rather examines the association between gabapentin and dementia. Despite efforts to control for confounders through propensity score matching, the possibility of residual confounding remains. As this is a database study, there may have been patients lost to follow-up, underdiagnosed, or inconsistently coded. Our study features several key strengths, including our large national sample, 10-year follow-up, age-based subgroup analysis, and prescription frequency analysis. We also excluded prior gabapentin prescriptions and used propensity score matching to control for demographics and dementia risk factors.

The current study aimed to investigate the relationship between gabapentin prescription and dementia in chronic low back pain patients on a national level. Our findings indicate an association between gabapentin prescription and dementia or cognitive impairment within 10 years. Moreover, increased gabapentin prescription frequency correlated with dementia incidence. Our results support the need for close monitoring

in adult patients prescribed gabapentin to assess for potential cognitive decline. We hope the current study promotes further research to delineate whether gabapentin plays a causal role in the development of dementia and the underlying mechanisms of this relationship.

Contributors NBE—guarantor, study conception and design, data analysis, manuscript writing, and revisions. IHY—manuscript writing, data analysis, and revisions. BY—manuscript writing. GVA—study conception and design, and manuscript editing. CK—study conception and design, and manuscript editing.

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