ORIGINAL RESEARCH

Gabapentinoids-Related Delirium Adverse Events: A Real-World Study from 2004 to 2022 Based on FAERS

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Purpose: This study comprehensively describes and evaluates the correlation between gabapentinoids and all types of delirium.

Methods: We used AERSMine to select all adverse reaction data from 2004 Q1 to the 2022 Q4 in the FDA Adverse Event Reporting System (FAERS) database, and delirium events reported by gabapentinoids drugs were included in this study. Collected and analyzed the clinical details of these reports. We have developed four models. Among the four models, reporting odds ratio (ROR) and proportional reporting ratio (PRR) were used to evaluate the potential association between and delirium. We undertook a subgroup analysis for the age and sex cohorts.

Results: A total of 2950 reports of gabapentinoids-related delirium was collected. Excluding cases with a history of delirium (Model 2), opioid drugs (Model 3), and other adverse events related to gabapentinoids drugs (Model 4), pain cases with gabapentin drugs as the main suspected drug were selected. In model 1, the reporting rates of delirium at the delirium and delirium tremens levels were higher in the gabapentinoids group than in the non-gabapentinoids group (ROR 1.09(1.05,1.13); ROR 1.54(1.16,2.04)). In model 2.3 the delira and the delirium level were higher in the gabapentinoids group (ROR 1.42(1.29,1.56), ROR 1.44(1.31,1.59); ROR 1.43 (1.30,1.58), ROR 1.46(1.33,1.61)). There is no difference in delirium levels in Model 4. Delirium levels were higher in the gabapentinoids group than in the non-gabapentinoids group in ≥65 years old. The delirium and deliria levels were higher in the male group than in the female group.

Conclusion: The delirium adverse reactions of the gabapentinoids group were significantly higher than those of non-gabapentinoids group in the first three models. However, with the removal of confounding factors, there was no significant difference in this type of adverse reaction in Model 4. In elderly and male patients, the incidence of delirium with gabapentinoids was significantly increased.

Keywords: gabapentinoids, delirium, adverse reactions, FAERS, pharmacovigilance

Introduction

Prescribed for neuropathic pain, epilepsy, and anxiety, gabapentinoids (pregabalin, gabapentin) are a class of medications with a long history of use.[1–3] Both gabapentinoids have received widespread prescriptions in the US since their initial introduction.[4] The American Pain Society recommends such drugs as a component of multimodal analgesia in the perioperative.[5] Due to the increasing use of it, the potential for negative impacts warrants worry. In 2022, Park et al[6] published in the JAMA Intern Med, conducted a retrospective cohort study and found that the use of gabapentin during surgery was linked to a slightly higher risk of delirium, considering the negative consequences of perioperative delirium, this finding raises concern about an increasingly adopted clinical practice.[6] To the best of our knowledge, the current clinical research is mainly focuses on whether they can reduce the incidence of postoperative delirium, rather than investigating whether it will cause delirium.[7,8]

Delirium is identified when there is a short-term, persistent disturbance of attention and awareness that differs from baseline and has a tendency to fluctuate.[9–11] The link between gabapentinoids and delirium is controversial, even Leung et al confirm that gabapentin could decrease postoperative delirium in older patients through clinical trial.[6,12–14] Rare adverse events (AEs) may best be discovered through spontaneous reporting, and there is currently less empirical support for gabapentinoids' potential to increase the incidence of delirium. It is important to highlight that meta-analysis depends mostly on data from published studies, which may not always provide a large enough dataset. However, millions of willingly submitted adverse event reports from consumers, manufacturers, healthcare professionals, and other stakeholders are housed in the FDA Adverse Event Reporting System (FAERS), a publicly available database in the United States. Its main objective is to make the FDA's post-marketing safety surveillance of biological and pharmaceutical products easier. Therefore, adverse reaction database mining, which makes use of information from the FAERS database, is a great way to determine whether a medicine and an adverse event are related. Due to FAERS's extensive and continuously updated repository, adverse reaction database mining grounded in FAERS can more accurately capture the dynamics of real-world research. In pharmacovigilance research, data mining in a large spontaneous adverse event reporting system database has become an essential method for doing medication safety evaluations.[15–17] We investigated the link between gabapentinoids and delirium by mining the FAERS database to respond to these questions and better comprehend the possible risk of all deliriums related to gabapentinoids.

Materials and Methods

Data Acquisition and Preprocessing

This project was approved by the Shanxi Bethune Hospital Committee (NO. YXLL-SL-2020-017). The FAERS database was used in this retrospective pharmacovigilance investigation. More than 19 million global case reports of possible medication side effects are available in this database. We used AERSMine,[18] a web-based analysis tool, to design the FAERS data from the 2004 Q1 to the 2022 Q4 on March 30, 2023.

We used the following neurological or psychiatric AEs terms to look for cases when gabapentinoids were prescribed and any of the AEs of interest were present. The primary outcome was delirium, identified using a validated claims-based algorithm.[19,20] This algorithm consists of explicit (ie, delirium is directly mentioned) diagnosis codes for delirium. The FAERS database reports AEs from system organ class (SOC), high-level group terms (HLGT), high-level terms (HLT), and preferred terms (PT) according to the MedDRA (26.0).[21] We obtained reports of gabapentinoids-related deliria at the HLT level from AERSMine (eTables 1 and 2).

In four models, the reporting rate of gabapentinoid-related delirium was compared with different control drugs: Model 1: Other drugs excluding gabapentinoids (non-gabapentinoid drugs) without indication restrictions; Model 2: Non-gabapentinoid drugs in which pain is an indication, as pain is the risk factor of delirium;[22] Model 3: Exclude patients with a history of delirium before using gabapentinoids drugs based on model 2; Model 4: Number of reports of excluding combined use of opioid in all cases based on model 3.[23]

Statistical Analysis

Disproportionality analysis was employed to discover relevant signals. The reporting odds ratio (ROR), proportional reporting ratio (PRR), and the Bayesian confidence propagation neural network (BCPNN) were used to calculate the degree of disproportionality,[24,25] and the 95% CI for gabapentinoids-related deliriums was evaluated with various models.[26] We conducted a subgroup analysis of patients 65 and older, as well as those younger than 65. If the lower limit of the 95% CI was more than 1.0, the connection was judged statistically significant. Data analysis was performed using. The formula is as follows:

$$ROR = (a/c)/(b/d)$$

$$95\%CI = e^{\ln(ROR)\pm1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

$$PRR = [a/(a+b)]/[c/(c+d)]$$

$$95\% \text{ CI} = e^{\wedge}(\ln(ROR)\pm1.96\sqrt{1/a - 1/(a+b)+1/c - 1/(c+d)}$$

Note: a is the number of delirium AE records for gabapentinoids; b is the number of other AE for gabapentinoids; c is the number of delirium AE records for non-gabapentinoids; d is the number of other AE for non-gabapentinoids;

All data categorizations and statistics were performed using Microsoft Excel version 2023.

Results

After applying inclusion criteria, a total of 19,089,556 records (including 70,260 delirium reports) were evaluated (Figure 1).

Gabapentinoids-Related Various Delirium in HLT, and PT in Model 1

The FAERS files include 2950 gabapentinoids-related delirium reports from 2004 Q1 to 2022 Q4. In model 1, the reporting rates of delirium at the delirium, delirium tremens levels were higher in the gabapentinoids group than in the
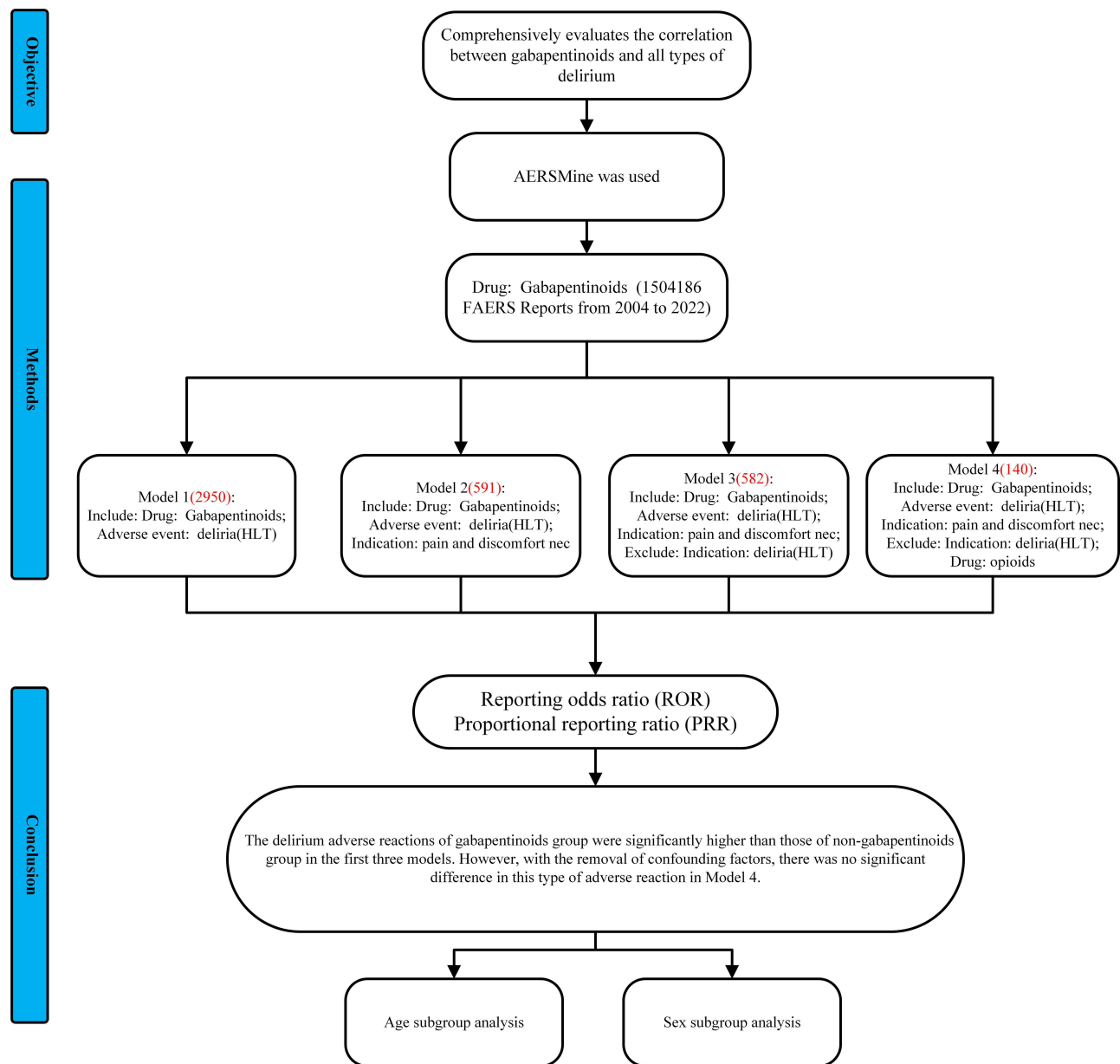

Figure 1 The flowchart of AE records in the FAERS database.

Deliria in HLT and PT

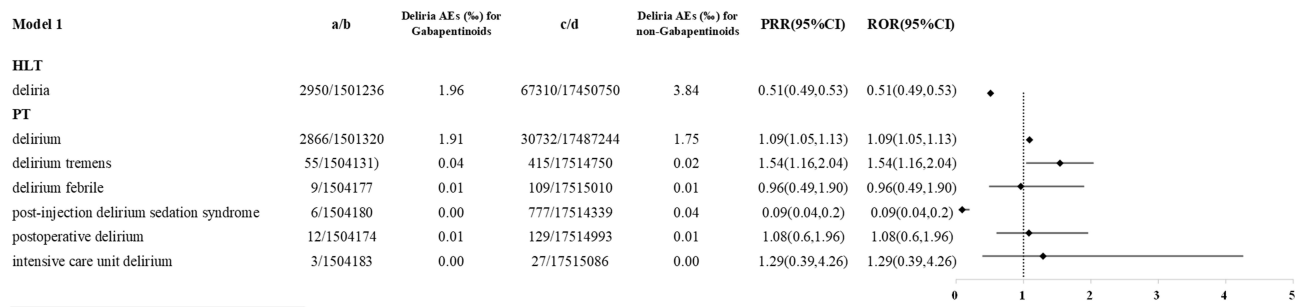| Model 1	a/b	Deliria AEs (‰) for Gabapentinoids	c/d	Deliria AEs (‰) for non-Gabapentinoids	PRR(95%CI)	ROR(95%CI)	
HLT							
deliria	2950/1501236	1.96	67310/17450750	3.84	0.51(0.49,0.53)	0.51(0.49,0.53)	
PT							
delirium	2866/1501320	1.91	30732/17487244	1.75	1.09(1.05,1.13)	1.09(1.05,1.13)	
delirium tremens	55/1504131)	0.04	415/17514750	0.02	1.54(1.16,2.04)	1.54(1.16,2.04)	
delirium febrile	9/1504177	0.01	109/17515010	0.01	0.96(0.49,1.90)	0.96(0.49,1.90)	
post-injection delirium sedation syndrome	6/1504180	0.00	777/17514339	0.04	0.09(0.04,0.2)	0.09(0.04,0.2)	
postoperative delirium	12/1504174	0.01	129/17514993	0.01	1.08(0.6,1.96)	1.08(0.6,1.96)	
intensive care unit delirium	3/1504183	0.00	27/17515086	0.00	1.29(0.39,4.26)	1.29(0.39,4.26)	

Figure 2 The reporting rates of delirium linked to gabapentinoids were compared to those of several comparators in Model 1.

non-gabapentinoids group (1.91‰ vs 1.75‰, ROR 1.09(1.05,1.13) 0.04‰ vs 0.02‰, ROR 1.54(1.16,2.04)), see Figure 2.

Gabapentinoids-Related Various Delirium in HLT, and PT in Model 2

In model 2, 591 reports of delirium related to gabapentinoids-related drugs have been reported. The reporting rates of delira and the delirium level were higher in the gabapentinoids group (6.83‰ vs 4.82‰, ROR 1.42(1.29,1.56); 6.65‰ vs 4.61‰, ROR 1.44(1.31,1.59)), see Figure 3.

Gabapentinoids-Related Various Delirium in HLT, and PT in Model 3

In model 3, 582 gabapentinoids-related delirium reports have been reported. The reporting rates of deliria and the delirium level were higher in the gabapentinoids group (6.73‰ vs 4.71‰, ROR 1.43(1.30,1.58); 6.56‰ vs 4.50‰, ROR 1.46(1.33,1.61)), see Figure 4.

Gabapentinoids-Related Various Delirium in HLT, and PT in Model 4

In model 4, 140 gabapentinoids-related delirium reports have been reported. There is no difference in delirium levels between the gabapentinoids group and the non-gabapentinoid group, see Figure 5.

Delirium with Gabapentinoids Stratified by Age

We have added subgroup analysis on age (≥65 and <65) to the results of our study on four models (Figure 6 and eTable 3). Among patients who model 1, 2 and 3, the delirium levels were higher in the gabapentinoids group than in the non-gabapentinoids group in ≥65 years old (ROR 2.04(1.93, 2.16); ROR 1.28(1.13, 1.46); ROR 1.32(1.16,1.50); ROR 1.30 (1.15, 1.48)). There is no difference between gabapentinoids group and the non-gabapentinoids group in the <65 years old.
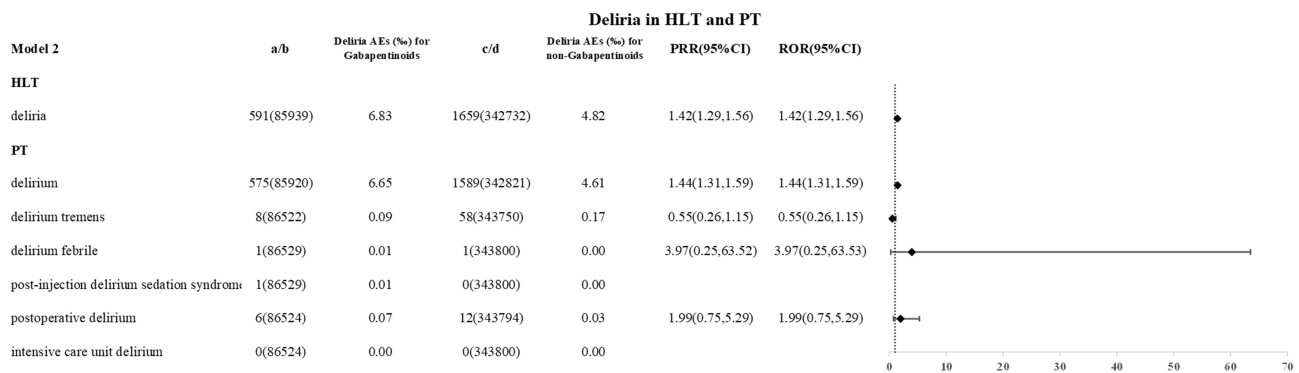
Deliria in HLT and PT

Model 2	a/b	Deliria AEs (‰) for Gabapentinoids	c/d	Deliria AEs (‰) for non-Gabapentinoids	PRR(95%CI)	ROR(95%CI)	
HLT							
deliria	591(85939)	6.83	1659(342732)	4.82	1.42(1.29,1.56)	1.42(1.29,1.56)	
PT							
delirium	575(85920)	6.65	1589(342821)	4.61	1.44(1.31,1.59)	1.44(1.31,1.59)	
delirium tremens	8(86522)	0.09	58(343750)	0.17	0.55(0.26,1.15)	0.55(0.26,1.15)	
delirium febrile	1(86529)	0.01	1(343800)	0.00	3.97(0.25,63.52)	3.97(0.25,63.53)	
post-injection delirium sedation syndrome	1(86529)	0.01	0(343800)	0.00			
postoperative delirium	6(86524)	0.07	12(343794)	0.03	1.99(0.75,5.29)	1.99(0.75,5.29)	
intensive care unit delirium	0(86524)	0.00	0(343800)	0.00			

Figure 3 The reporting rates of delirium linked to gabapentinoids were compared to those of several comparators in Model 2.

Deliria in HLT and PT
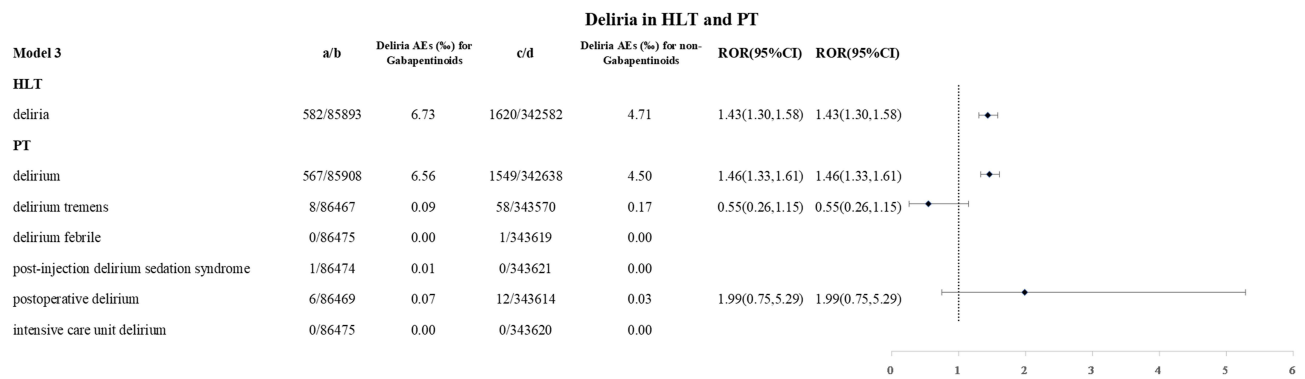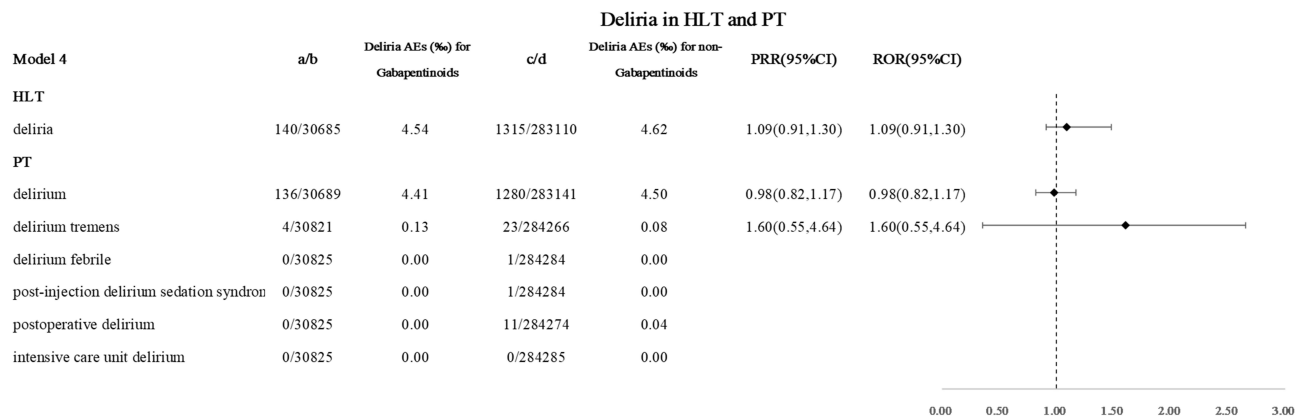
Model 3	a/b	Deliria AEs (‰) for Gabapentinoids	c/d	Deliria AEs (‰) for non-Gabapentinoids	ROR(95%CI)	ROR(95%CI)
HLT						
deliria	582/85893	6.73	1620/342582	4.71	1.43(1.30,1.58)	1.43(1.30,1.58)
PT						
delirium	567/85908	6.56	1549/342638	4.50	1.46(1.33,1.61)	1.46(1.33,1.61)
delirium tremens	8/86467	0.09	58/343570	0.17	0.55(0.26,1.15)	0.55(0.26,1.15)
delirium febrile	0/86475	0.00	1/343619	0.00		
post-injection delirium sedation syndrome	1/86474	0.01	0/343621	0.00		
postoperative delirium	6/86469	0.07	12/343614	0.03	1.99(0.75,5.29)	1.99(0.75,5.29)
intensive care unit delirium	0/86475	0.00	0/343620	0.00		

Figure 4 The reporting rates of delirium linked to gabapentinoids were compared to those of several comparators in Model 3.
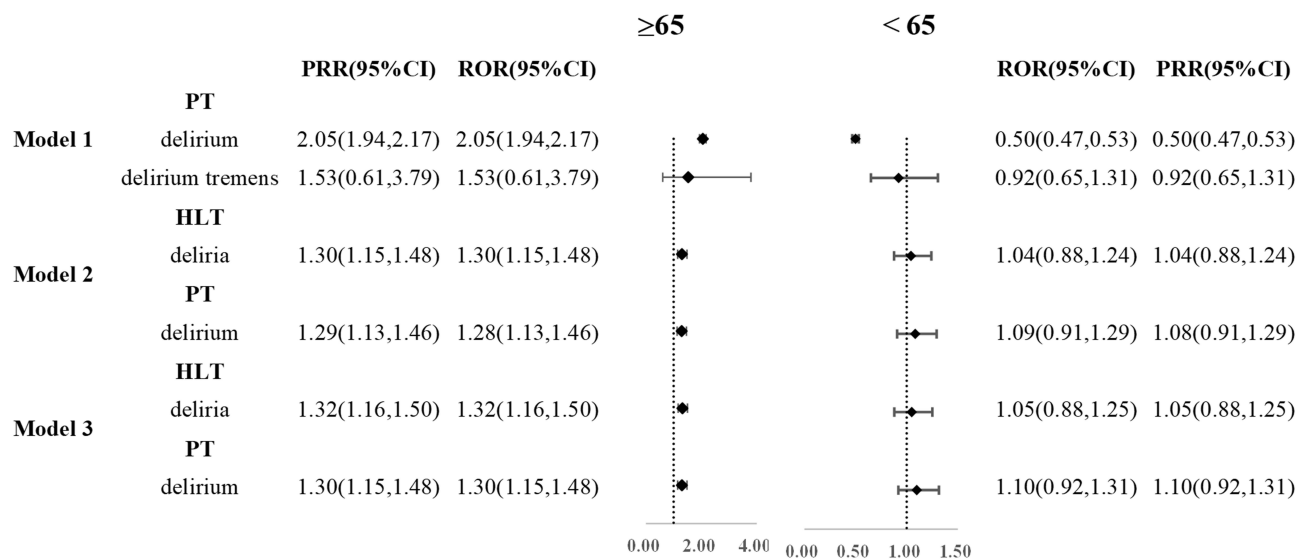
Deliria in HLT and PT

Model 4	a/b	Deliria AEs (‰) for Gabapentinoids	c/d	Deliria AEs (‰) for non-Gabapentinoids	PRR(95%CI)	ROR(95%CI)
HLT						
deliria	140/30685	4.54	1315/283110	4.62	1.09(0.91,1.30)	1.09(0.91,1.30)
PT						
delirium	136/30689	4.41	1280/283141	4.50	0.98(0.82,1.17)	0.98(0.82,1.17)
delirium tremens	4/30821	0.13	23/284266	0.08	1.60(0.55,4.64)	1.60(0.55,4.64)
delirium febrile	0/30825	0.00	1/284284	0.00		
post-injection delirium sedation syndrom	0/30825	0.00	1/284284	0.00		
postoperative delirium	0/30825	0.00	11/284274	0.04		
intensive care unit delirium	0/30825	0.00	0/284285	0.00		

Figure 5 The reporting rates of delirium linked to gabapentinoids were compared to those of several comparators in Model 4.

		≥65				<65	
		PRR(95%CI)	ROR(95%CI)			ROR(95%CI)	PRR(95%CI)
	PT						
Model 1	delirium	2.05(1.94,2.17)	2.05(1.94,2.17)			0.50(0.47,0.53)	0.50(0.47,0.53)
	delirium tremens	1.53(0.61,3.79)	1.53(0.61,3.79)			0.92(0.65,1.31)	0.92(0.65,1.31)
	HLT						
Model 2	deliria	1.30(1.15,1.48)	1.30(1.15,1.48)			1.04(0.88,1.24)	1.04(0.88,1.24)
	PT						
	delirium	1.29(1.13,1.46)	1.28(1.13,1.46)			1.09(0.91,1.29)	1.08(0.91,1.29)
	HLT						
Model 3	deliria	1.32(1.16,1.50)	1.32(1.16,1.50)			1.05(0.88,1.25)	1.05(0.88,1.25)
	PT						
	delirium	1.30(1.15,1.48)	1.30(1.15,1.48)			1.10(0.92,1.31)	1.10(0.92,1.31)

Figure 6 Delirium ROR and PRR of gabapentin versus non-gabapentin were stratified by age.

	a	b	a'	b'	PRR(95CI)	ROR(95CI)
Model 1	**PT**					
	delirium	1327	193099	1049	1093484	7.16(6.60, 7.76)	7.16(6.60, 7.76)
	delirium tremen	5	194421	37	1094496	0.76(0.29, 1.94)	0.76(0.29, 1.94)
Model 2	**HLT**					
	deliria	339	24659	170	43566	3.52(2.93, 4.24)	3.52(2.93, 4.24)
	PT					
	delirium	330	24668	165	43536	3.53(2.93, 4.24)	3.53(2.93, 4.24)
Model 3	**HLT**					
	deliria	333	24641	167	43543	3.52(2.92, 4.24)	3.52(2.92, 4.24)
	PT					
	delirium	324	24650	163	43547	3.51(2.90, 4.24)	3.51(2.90, 4.24)

Figure 7 Delirium ROR and PRR occurred at different age in patients taking gabapentinoids.
Note: a is the number of delirium AE records for ≥65; b is the number of other AE for ≥65; a' is the number of delirium AE records for <65; b' is the number of other AE for <65; a' and b' replace c and d of the original formula, respectively.

We performed a subgroup analysis by age of gabapentinoids patients on four models (Figure 7). The results confirmed that among patients who model 1, 2 and 3, the delirium levels were higher in the ≥65 group than the <65 group (Figure 7) (ROR 7.16(6.60, 7.76); ROR 3.52(2.93, 4.24); ROR 3.53(2.93, 4.24); ROR 3.52(2.92, 4.24) ROR 3.51(2.90, 4.24)).

Delirium with Gabapentinoids Stratified by Sex

We have added stratified research on sex to the results of our study on four models (Figure 8, eTable 4 and eFigure 1). For gabapentinoids patients, the results confirmed that among patients who model 1, 2 and 3, the delirium and deliria levels were higher in the male group than in the female group (ROR 1.71(1.58, 1.84); ROR 1.66(1.54, 1.80); ROR 9.13 (4.46, 18.67); ROR 1.29(1.09, 1.54); ROR 1.23(1.03, 1.47); ROR 1.31(1.10, 1.56); ROR 1.24(1.04, 1.49)).

Discussion

The connection of gabapentinoids with all forms of delirium was investigated in the FAERS database by continuously removing influencing factors in four models, and a thorough pharmacovigilance analysis of delirium AEs was carried out at the HLT/PT levels. According to disproportionality studies, gabapentinoids are linked to delirium at the PT level in the first four models, and when we finally attempted to rule out the effects of opioids, there was no significant difference in delirium adverse reactions between the gabapentinoids group.

In the current clinical practice, anticonvulsants (such as sodium valproate and gabapentin) are often used to treat delirium, but there are limited data on their use.[27,28] Previous researchers believe that gabapentin may prevent delirium by improving pain control and reducing opioid dose.[29] To date, several studies investigated whether gabapentin could reduce perioperative delirium. Pinto F W's study found that gabapentin could reduce the occurrence of delirium in Analgesia in Oncologic Pediatric Patients.[12] In 2006, Leung et al confirmed that adding gabapentin to the treatment of postoperative pain
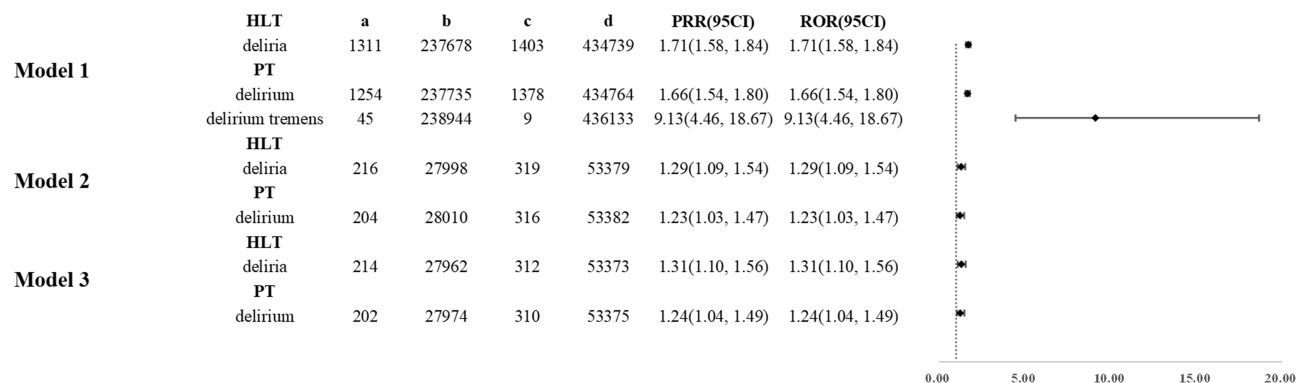
	HLT	a	b	c	d	PRR(95CI)	ROR(95CI)
Model 1	deliria	1311	237678	1403	434739	1.71(1.58, 1.84)	1.71(1.58, 1.84)
	PT						
	delirium	1254	237735	1378	434764	1.66(1.54, 1.80)	1.66(1.54, 1.80)
	delirium tremens	45	238944	9	436133	9.13(4.46, 18.67)	9.13(4.46, 18.67)
Model 2	**HLT**						
	deliria	216	27998	319	53379	1.29(1.09, 1.54)	1.29(1.09, 1.54)
	PT						
	delirium	204	28010	316	53382	1.23(1.03, 1.47)	1.23(1.03, 1.47)
Model 3	**HLT**						
	deliria	214	27962	312	53373	1.31(1.10, 1.56)	1.31(1.10, 1.56)
	PT						
	delirium	202	27974	310	53375	1.24(1.04, 1.49)	1.24(1.04, 1.49)

Figure 8 Delirium ROR and PRR occurred at different sex in patients taking gabapentinoids.
Note: a is the number of delirium AE records for ≥65; b is the number of other AE for ≥65; a' is the number of delirium AE records for <65; b' is the number of other AE for <65; a' and b' replace c and d of the original formula, respectively.

decreased the incidence of postoperative delirium through the pilot research trial.[14] However, he proposed an opposite viewpoint with an RCT in 2017.[30] In a post-hoc analysis of an RCT of 161 patients (mean age, 63 years), Dighe et al[31] reported that the incidence of delirium in the gabapentin group and the placebo group were 12% and 9%. In another RCT of 697 patients (mean age, 73 years) undergoing orthopedic surgery, Leung et al[30] showed that 24.0% in the gabapentin group and 20.8% in the placebo group had delirium, although the difference in the delirium incidence was not statistically significant. More and more evidence has questioned the ability of gabapentin to reduce postoperative delirium, our study found that although the risk of delirium was not demonstrated in model 4, an increased risk of delirium was found in models 1, 2, and 3, and it can also provide evidence support for future research.

The 2-subunit of calcium channels, which are present in both the peripheral and central nervous systems, is the primary target of gabapentin's action,[13,32,33] which may explain its delirium adverse effects. Delirium is associated with various underlying factors including preexisting diseases, metabolic or sleep disorders, psychotropic drug use, and altered sensory function.[34] This may explain the delirium adverse effects of gabapentinoids in models 1, 2, and 3 found in our study.

Our study indicates that there is no difference in ROR between gabapentinoids and non-gabapentinoids drugs when opioid drugs are excluded (model 4). Opioids are the most likely drugs to induce delirium and may have a significant confounding effect on reports of delirium response to gabapentinoids drugs in the real world.[35,36]

Research suggests that age and sex may be risk factors for delirium. Some studies reported that patients aged ≥65 years and men had a significantly increased incidence of delirium than those aged 40 to 65 years and women, respectively,[37,38.] Park et al[6] research subjects are elderly people, and older age is a common risk factor for delirium among rehabilitation inpatients.[39–41] Our results showed that the age difference in delirium adverse reactions between gabapentin group and non-gabapentin group was significant, but the gender difference was not significant. Therefore, we stratified the age and sex of the patients taking gabapentin, and the results showed that the incidence of gabapentinoids-induced delirium increases significantly in older and male patients. However, there is a large amount of data with unknown gender in the database, which also reduces the reliability of our study results (eTable 3).

In order to ensure the reliability of the results, we gradually designed four models. However, due to the complexity of post-operative medication, it is difficult for us to control unexpected bias, which will lead to the ambiguity of our results, so this is also part of the limitations of our study.

Limitations

FAERS cannot establish a causal relationship between gabapentinoids and delirium. The reporting habits may be impacted by recent publications of AEs in the literature and media attention. Comorbidities and concurrent medications confuse the link between a drug and an adverse event. FDA claims that the submitted information has not been examined by a medical expert. Manufacturers, consumers, and healthcare professionals may all submit FAERS data. A submission's source must be taken into account. Incomplete or missing data can be found in FAERS. In other instances, the age was not provided or the medicine names were spelled incorrectly. Due to the inability to obtain the patient's medication dose, it is impossible to rule out the bias in delirium caused by different medication doses. Not every adverse event or medication mistake involving a product is reported to FDA. Additionally, ROR only looks into a risk of AEs reporting that is elevated rather than a risk of AEs incidence in general.[42] Due to the small number of ROR reports, several confidence intervals, such as delirium febrile 3.97(0.25,63.53) in model 2, are quite large. The number of cases in Model 2–4 and the age and sex stratified analyses was small, and it may address the reliability of the conclusions. The FAERS database has the advantage of having a huge sample size, although there are some flaws, it is very important for discovering new and rare AEs.

Conclusion

Because gabapentinoids are so widely used, there are worries regarding safety, particularly in delirium. Our research offered fresh, practical proof of the safety of gabapentinoids for treating delirium. Using the FAERS database reveals that the reporting rates of delirium were higher in the gabapentinoids group than in the non-gabapentinoids group at the delirium levels in model 1,2,3, but no difference in delirium levels between the gabapentin group and the non-gabapentinoid group in the model 4. In elderly and male patients, the incidence of delirium with gabapentinoids was significantly increased. Given the advantages of

the gabapentinoids group, the increased ROR does not suggest that doctors should limit the use of gabapentinoids, but rather that they should maintain the necessary level of awareness for any potential side effects.

Data Sharing Statement

This study analyzed publicly available datasets. These data can be found in the following locations: 1) https://research.cchmc.org/aers/explore.jsp; 2) https://fis.fda.gov/sense /app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-D58b-4203-a8aa-6d3021737452/state/analysis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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