Seizure 59 (2018) 28–33

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Differences in associations of antiepileptic drugs and hospitalization due to hyponatremia: A population–based case–control study

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ARTICLE INFO

Article history:
Received 11 December 2017
Received in revised form 27 April 2018
Accepted 29 April 2018

Keywords:
Antiepileptic drugs
Hyponatremia
SIADH
Adverse effect

ABSTRACT

Purpose: Hyponatremia induced by antiepileptic drugs is common, but detailed evidence is lacking. This can be problematic for the treating neurologist confronted with a patient with severe hyponatremia in need of an alternative drug. The objective of this study was to examine the association between individual antiepileptic drugs and hospitalization due to hyponatremia.
Methods: This was a register-based case–control study of patients in the general Swedish population. We included 14,359 individuals with a principal diagnosis of hyponatremia and 57,383 matched controls. The association between newly initiated (≤90 days) and ongoing antiepileptic treatment was investigated using multivariable logistic regression adjusting for concomitant drugs, medical conditions, previous hospitalizations and sociaoeconomic factors.
Results: For newly initiated antiepileptic drugs, adjusted ORs (95% CI) for hospitalization due to hyponatremia, compared to controls, were: carbamazepine 9.63 (6.18–15.33); phenytoin 4.83 (1.14–25.76); valproate 4.96 (2.44–10.66); lamotrigine 1.67 (0.70–4.08); levetiracetam 9.76 (4.02–27.59) and gabapentin 1.61 (1.08–2.38). Newly initiated oxcarbazepine treatment was only found in the hyponatremia group and not in controls. Adjusted ORs (CI) for individuals with ongoing treatment ranged from 7.97 (3.70–18.50) for oxcarbazepine to 0.83 (0.64–1.06) for gabapentin.
Conclusion: There was a strong association between newly initiated treatment with carbamazepine, oxcarbazepine and levetiracetam, and hospitalization due to hyponatremia. The corresponding association for phenytoin and valproate was moderate. The risk for hyponatremia was lower during ongoing treatment. Lamotrigine and gabapentin had the lowest risk both during initiation and ongoing treatment and may be advantageous in patients at risk of developing hyponatremia.

1. Introduction

The most frequent electrolyte disorder in hospitalized patients is hyponatremia [1]. The clinical spectrum in hyponatremia ranges from mild, non-specific symptoms such as fatigue, headache, and gait instability to life-threatening symptoms such as seizures, coma and ultimately death, secondary to brain oedema [2,3]. Pharmaceutical drugs, e.g., thiazide diuretics, antidepressants and antiepileptic drugs are common causes of both asymptomatic and symptomatic hyponatremia [4]. Since epilepsy is a common disease requiring long-term treatment with antiepileptic drugs, adverse effects such as hyponatremia can be a major problem and deaths have been described [5]. Most studies on antiepileptic drugs have been small and focused on the effect on sodium levels without addressing the clinical consequences, such as hospitalization [6,7]. This lack of evidence can be problematic for the treating neurologist, for example when confronted with a patient with severe hyponatremia, in need of an alternative drug. The aim of this study was to investigate the association between individual antiepileptic drugs and the risk of hospitalization due to hyponatremia.

2. Methods

2.1. Study design and setting

This was a retrospective Swedish population–based case–control study.

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https://doi.org/10.1016/j.seizure.2018.04.025
1059-1311/

2.2. Participants

In a hospitalized patient, the principal diagnosis reflects the condition that best motivates the admission. The attending physician in Sweden codes all admissions and specialist outpatient visits with *International Classification of Diseases* codes, 10th Revision (ICD10) [8]. All hospitalized patients 18 years or older, with a first-ever (defined as not occurring since 1 January 1997) principal ICD10 code of E87.1 (hyponatremia) or E22.2 (syndrome of inappropriate ADH secretion [SIADH]) in The National Patient Register (NPR) (see below) between 1 October 2005 and 31 December 2014 were defined as cases. Controls matched for age, sex and municipality (4 controls per case) who had not been diagnosed with hyponatremia since 1 January 1997 were selected from the Total Population Register. The study population in the present study has been described in detail in a recent publication [9].

2.3. Variables

In Table 1, all variables included in the multiple logistic regression analysis are shown, along with their definitions. Antiepileptic drugs included in the analysis were: carbamazepine, oxcarbazepine, phenytoin, valproate, lamotrigine, levetiracetam, and gabapentin. ICD10 codes, Anatomical Therapeutic Chemical (ATC) codes, and parameters from the Longitudinal integration database for health insurance and labor market studies (LISA)-register were used to define potential confounders. A documented dispensing within 90 days prior to the index date was used to define antiepileptic drug exposure. Almost all patients in Sweden

Table 1
Variables included in the multiple logistic regression analysis and their definition.

Variables	Codes
Antiepileptic drugs	**ATC codes beginning with**
Carbamazepine	N03AF01
Oxcarbazepine	N03AF02
Phenytoin	N03AB02
Valproate	N03AG01
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Gabapentin	N03AX12
Other drugs	
Furosemide	C03C
Thiazides	C03A, C09BA, C09DA
Fluoroquinolones	J01MA
Macrolides	J01FA
Trimethoprim sulfamethoxazole	J01EE
Citalopram	N06AB04
Escitalopram	N06AB10
Sertraline	N06AB06
Other SSRIs[a]	N06AB03, N06AB05, N06AB08
Tricyclic antidepressants	N06AA
Mirtazapine	N06AX11
Venlafaxine	N06AX16
Other antidepressants	N06AX03, N06AX12, N06AX18, N06AX21, N06AX22, N06AX26, N06AG02
Proton pump inhibitors	A02BC
Amiodarone	C01BD01
Tramadol	N02AX02
Diseases	**ICD10 codes beginning with**
Renal diseases	N17-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Sepsis	A41
Pneumonia	J18
Meningitis	G00-G07
Ischemic heart disease	I20-25
Malignant disease	C
Congestive heart failure	I50
Pancreatic disease	K85, K860-1
Inflammatory bowel disease	K50-K51
Liver diseases	K70-77 Procedure codes JJB, JJC
Cerebrovascular diseases	I60-64, I69
Hypothyroidism	E03, E06.3
Malnutrition	E43.9, E41.9
Chronic obstructive pulmonary disease	J44
Pulmonary embolism	I26
	Combination of ATC- and ICD-10 codes, each beginning with
Alcoholism	**ATC:** N07BB03, N07BB04, N07BB01, N07BB05, N07BB
	ICD10: E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Adrenal insufficiency	**ATC:** N07BB03, N07BB04, N07BB01, N07BB05, N07BB
	ICD10: E27, K70.3, K70.4, K70.1
Diabetes	**ATC:** A10A, A10AB
	ICD10: E10-E14
Other factors	
Education	Increasing levels of education from 1–6, continuous variable
Income	Income in Swedish crowns during 1 year, continuous variable
Unemployment	Number of days, continuous variable
Drug use	Number of dispensed drugs 90 days prior to index date, categorised into <4, 4–7, 8–12 and >12 drugs
Previous hospitalization	>2 days within 2 years prior to index date

[a] Selective serotonin reuptake inhibitors.

on long–term treatment repeat their drug–dispensing every third month. Chronic diseases (using the documented ICD10 codes) were controlled for since 1 January 1997 to index date, and infectious diseases were controlled for within 90 days before the index date (Table 1). Subjects were divided into two groups, those with newly initiated antiepileptic drug therapy (started within 90 days from index date), and those who had received the drug 91–454 days from index date.

2.4. Data sources/measurement

The unique Swedish personal identification number enabled unambiguous linkage between three population-based registers: NPR, The Swedish Prescribed Drug Register (SPDR) and the LISA-register which is a register based on socioeconomic data [8,10,11]. The NPR has data on all hospital admissions in Sweden including all ICD10 codes since 1997. The SPDR covers all prescriptions dispensed since 1 July 2005 for the entire Swedish population. The LISA register was used to control for socioeconomic factors.

2.5. Statistical analysis

Univariable and multivariable logistic regression was used to analyse the association between hyponatremia and different antiepileptic drugs. Individuals never exposed to any of the drugs or diagnosed with any of the disease included in the model (see Table 1) were used as the reference group. The relationship between hyponatremia and different antiepileptic drugs in cases and controls was presented as crude and adjusted (for potential confounders) odds ratios (OR), with 95% confidence intervals (95% CI). A P-value <0.05 was considered significant. R version 3.3.2 was used for all calculations [12].

3. Results

During the nine–year study period, 14,359 individuals with a principal diagnosis of hyponatremia 18 years or older and 57,382 matched controls were identified. The mean age was 74 ± 14 years, and the majority were women (72%). A selection of medical conditions and the different antiepileptic drugs in the study population at index date are shown in Table 2. Overall, the cases had a greater burden of disease. Moreover, the cases had more frequently been prescribed antiepileptic drugs. Hypertension, ischemic heart disease, diabetes and alcoholism were the most common concomitant medical conditions, while the most commonly prescribed antiepileptic drugs were carbamazepine, gabapentin and valproate.

The association between exposure to antiepileptic drugs and hospitalization due to hyponatremia is shown in Fig. 1. Adjusted ORs ranged from 1.03 for gabapentin to 13 for oxcarbazepine. Fig. 2 shows the associations (adjusted OR) after separating newly initiated antiepileptic drug treatment from ongoing treatment. For newly initiated antiepileptic drugs and newly developed hyponatremia necessitating hospitalization, adjusted ORs ranged from 1.61 for gabapentin to 9.62 for carbamazepine. All individuals who had been newly initiated on oxcarbazepine had developed hyponatremia (n = 16) and thus calculation of OR was not performed. For ongoing treatment, the adjusted ORs were lower for all antiepileptic drugs. Phenytoin, lamotrigine, levetiracetam and gabapentin did not significantly increase the risk for hospitalization due to hyponatremia during ongoing treatment. However, both phenytoin and levetiracetam treatment increased the risk significantly during initial treatment (adjusted OR 4.83 and 9.76, respectively) (Fig. 2).

4. Discussion

This is the first study reporting on the risk for hospitalization due to hyponatremia in patients with newly initiated vs. chronic use of different antiepileptic drugs. Especially carbamazepine and oxcarbazepine were associated with a vastly increased risk. In contrast, the risk associated with lamotrigine and gabapentin, were not significantly, or only mildly, elevated. Levetiracetam was associated with a high risk in newly initiated treatment while the

Table 2
Medical characteristics and different type of antiepileptic drugs among cases (diagnosed with hyponatremia) and controls at index date.

	Number (%) of total cases (n = 14,359)	Number (%) of total controls (n = 57,382)
Diagnosis		
Hypertension	8818 (61.4)	15336 (26.7)
Ischemic heart disease	2808 (19.6)	7880 (13.7)
Diabetes	2423 (16.9)	6581 (11.5)
Alcoholism	2285 (15.9)	1028 (1.8)
Congestive heart failure	1900 (13.2)	4493 (7.8)
Cerebrovascular diseases	1884 (13.1)	4540 (7.9)
Chronic obstructive pulmonary disease	1477 (10.3)	1958 (3.4)
Adrenal insufficiency	821 (5.7)	405 (0.7)
Renal diseases	631 (4.4)	1098 (1.9)
Liver diseases	553 (3.9)	417 (0.7)
Pancreatic disease	327 (2.3)	513 (0.9)
Antiepileptic drugs, total		
Carbamazepine	634 (4.4)	321 (0.6)
Oxcarbazepine	51 (0.4)	11 (0.02)
Phenytoin	55 (0.4)	73 (0.1)
Valproate	203 (1.4)	128 (0.2)
Lamotrigine	105 (0.7)	131 (0.2)
Levetiracetam	114 (0.8)	70 (0.1)
Gabapentin	198 (1.4)	331 (0.6)
Antiepileptic drugs, newly initiated treatment		
Carbamazepine	128 (0.9)	31 (0.05)
Oxcarbazepine	16 (0.1)	0 (0.0)
Phenytoin	10 (0.07)	4 (0.007)
Valproate	49 (0.3)	12 (0.02)
Lamotrigine	22 (0.2)	12 (0.02)
Levetiracetam	45 (0.3)	6 (0.01)
Gabapentin	65 (0.5)	69 (0.1)

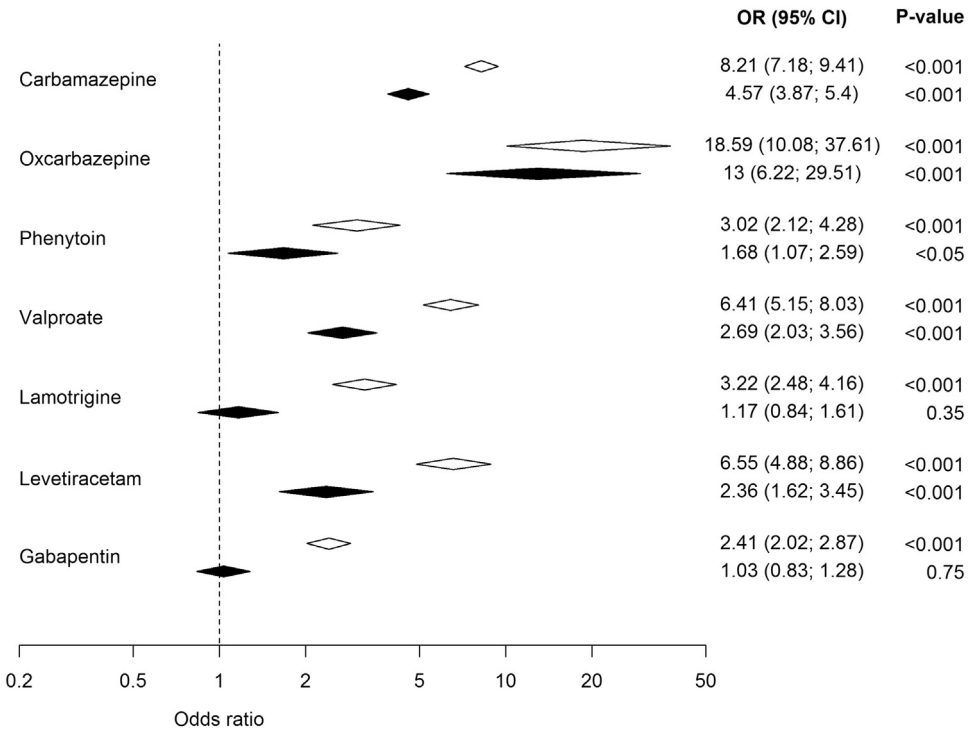

Fig. 1. The crude (white) and adjusted (black) odds ratio (OR), including 95% confidence intervals (95% CI) for hospitalization due to hyponatremia in patients with different antiepileptic drugs.

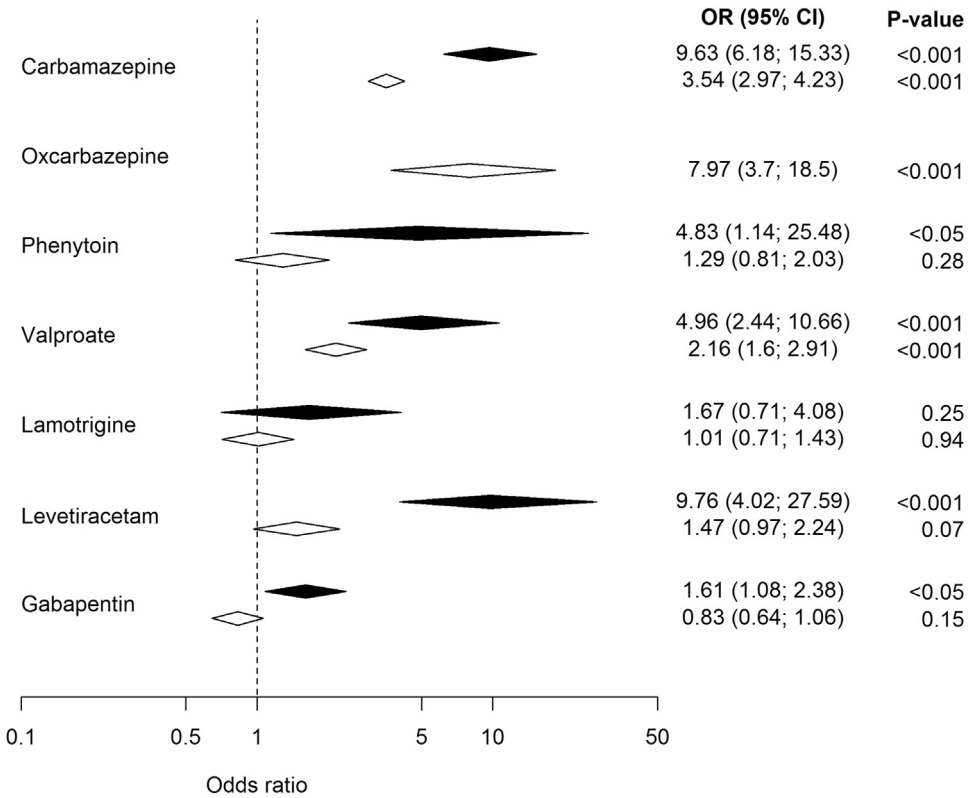

Fig. 2. The odds ratio (OR), including 95% confidence intervals (95% CI) for hospitalization due to hyponatremia in patients with ongoing (white) and newly initiated antiepileptic drug treatment (black). Newly initiated oxcarbazepine could not be shown since only 16 had been newly initiated on this treatment and all had been diagnosed with hyponatremia.

risk during ongoing treatment was only mildly and not significantly elevated.

Most of our knowledge about antiepileptic drugs and hyponatremia is based on smaller observational studies, or case reports, which have not been able to compare the different antiepileptic drugs [7]. However, a recently published registry-based study by *Gandhi* et al., investigated the 30-day risk of hospitalization after the initiation of carbamazepine or valproate/phenytoin/topiramate compared to nonuse in older adults (>65 years old) [6]. Similarly to us, they found a relative risk of 8.2 for carbamazepine while for valproate/phenytoin/topiramate it was 2.6. However, they did not present data including younger adults or risks associated with chronic use. Furthermore, they did not include data on oxcarbazepine, lamotrigine, levetiracetam or gabapentin.

Both carbamazepine and oxcarbazepine (a derivate of the former) are known to cause hyponatremia with an occurrence of 4.8–31.3% and 0.14–73.3%, respectively [7,13–18]. In our study, chronic use of oxcarbazepine was associated with the highest risk of hospitalization due to hyponatremia. Moreover, patients with newly initiated oxcarbazepine treatment were only found in the hyponatremia group and not in controls. Carbamazepine was also associated with a very high risk of hyponatremia and both drugs necessitate caution when prescribed in individuals susceptible to hyponatremia.

Phenytoin has been shown to inhibit the release of antidiuretic hormones [19] and has been thought not to induce hyponatremia. However, we found an increased risk of hyponatremia in patients using phenytoin (adjusted OR 1.68) but when analyzing newly initiated vs. ongoing treatment only the former was a significant risk factor (adjusted OR 4.83). *Gandhi* et al. found an increased risk associated with newly initiated phenytoin (adjusted RR 4) and also reported it to be increased compared to valproate [6]. In contrast, we found valproate to be associated with a slightly higher OR for hyponatremia. Moreover, ongoing use of valproate, but not of phenytoin, was associated with hyponatremia. Previous data on valproate–induced hyponatremia is limited to anecdotal case-reports [7,20].

Three case reports describe lamotrigine–induced hyponatremia [7], but we were unable to corroborate these findings. On the contrary, lamotrigine did not appear to induce severe hyponatremia and may therefore be considered in patients with a predisposition for hyponatremia.

Levetiracetam has been considered safe to use in patients predisposed for hyponatremia with only five case reports of hyponatremia in the literature [7,21–23]. Surprisingly, we found a marked increased risk in patients newly initiated on levetiracetam with a magnitude similar to that of carbamazepine. This finding was based on a relatively small number of observations (n = 22) and should therefore be interpreted with caution. Furthermore, it could be speculated that levetiracepam, is preferentially prescribed for patients at risk of hyponatremia, or a history of hyponatremia. However, the results indicate that particular care may be taken also at the initiation of levetiracetam.

A post-marketing survey of gabapentin showed that 6 months after the initial prescription (n = 3100) only two patients had developed hyponatremia [24], however, there was very scarce information about the cases and probably sodium was not checked regularly. Our study showed a mild increase in hospitalization due to hyponatremia within 90 days of the first prescription but a non–significant decrease in risk during chronic use. Thus, gabapentin seems to carry a very low over-all risk of inducing hyponatremia.

Although not fully elucidated, SIADH is believed to be the major contributor of antiepileptic drug-induced hyponatremia [4,7]. However, some studies have demonstrated that antiepileptic drug–induced hyponatremia can occur without ADH levels being affected [20,25,26]. Some antiepileptic drugs may have a direct effect on renal tubules and/or increase the tubular response to ADH [7]. Carbamazepine and oxcarbazepine are thought to stimulate the vasopressin-2 receptor and upregulate aquaporin-2 expression and thus have antidiuretic properties regardless of ADH-levels [27], which may explain their increased risk of hyponatremia compared to most other antiepileptic drugs. Of the five previously published cases with levetiracepam-induced hyponatremia [7, 21–23], four had a predisposition to SIADH. Whether a peripheral process (such as a direct effect on renal tubules), as discussed above, could be a contributing factor to levetiracepam-induced hyponatremia remains speculative. Interestingly, we found that newly initiated therapy was associated with a markedly increased risk as compared to ongoing treatment within each drug group. We have recently shown a similar pattern in antidepressant–induced hyponatremia [9]. The reason may be that individuals carrying factors that predispose for the development of severe hyponatremia, are forced to stop treatment shortly after the commencement of certain antiepileptic drugs, leaving a group of patients that are less vulnerable. This temporal association between initiation of treatment and hospitalization for hyponatremia also point to a true causal relationship, something that is often difficult to establish in hyponatremia. Our results may have important clinical implications. For a patient with a predisposition for hyponatremia (e.g. females, elderly and individuals with low body weight) [1] lamotrigine or gabapentin may be considered while carbamazepine and oxcarbazepine should be used more carefully. In patients experiencing clinically significant hyponatremia, i.e. symptomatic hyponatremia leading to hospitalization, after recent initiation of carbamazepine, oxcarbazepine, phenytoin, valproate or levetiracetam, an alternative treatment could be lamotrigine or gabapentin.

The current study has limitations, but also strengths. In spite of capturing all cases hospitalized due to a principal diagnosis of hyponatremia in the entire country for nine years, the number of cases for each individual antiepileptic drug was relatively small. Even though we did study the relative risks of newly initiated antiepileptic drugs, the case–control design restricts the possibility to investigate the importance of the duration of drug therapy. To explore this more in depth, a longitudinal cohort study is needed which would also permit determining absolute risks (incidences) associated with respective antiepileptic drugs. Despite the adjustment for a wide range of drugs, diagnoses and socioeconomic factors, residual confounding factors could be present. Finally, knowledge on the plasma levels of hyponatremia was lacking. On the other hand, by including only cases hospitalized with a principal diagnosis of hyponatremia we know that the hyponatremia was severe and by basing the outcome on the principal diagnosis, the validity is far superior to an outcome that also includes secondary diagnoses (www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18692/2012-4-18.pdf). This was confirmed by our previously published validation of hyponatremia as the principal diagnosis demonstrated a 100% exposure to hyponatremia with a mean plasma sodium level of 121 mmol/L [9]. Importantly, 89% had in fact been hospitalized mainly due to hyponatremia [9]. Thus, the sensitivity of ICD-codes to detect low plasma sodium is low but those diagnosed with hyponatremia all have low plasma sodium levels. Since this was an epidemiological study data on clinical relevant symptoms related to hyponatremia (e.g. confusion, altered mental state, changes in seizures frequency) at admission were not available. However, the validation study mentioned above did show that the vast majority of patients indeed were admitted due to symptoms of hyponatremia. Another strength of this study, besides including only clinically relevant hyponatremia, is the unique Swedish personal identification number, which enabled us to unambiguous linkage between population-based registers with almost complete coverage.

Moreover, we could adjust for a large number of factors that could contribute to hyponatremia so that the contribution of the antiepileptic drug could be estimated with better precision and validity. Furthermore, since this study is very large we could compare different propensities for causing severe hyponatremia in a wide variety of antiepileptic drugs.

5. Conclusion

The current study indicates a strong association between newly initiated treatment with carbamazepine, oxcarbazepine or levetiracetam, and hospitalization due to hyponatremia. The corresponding association for phenytoin and valproate was moderate. In contrast, the risk for hospitalization due to hyponatremia was lower during ongoing treatment with antiepileptic drugs. Lamotrigine and gabapentin seem to result in the lowest risk both during initiation and ongoing treatment and may be considered in patients at risk of developing hyponatremia.

Conflict of interest

Drs. Jakob Skov and Buster Mannheimer report personal fees from Otsuka Pharma Scandinavia AB, outside the submitted work. Drs. Henrik Falhammar, Jonatan D Lindh, Jan Calissendorff, Shermineh Farmand, and David Nathanson report no disclosures relevant to the manuscript.

Ethics approval

The study was approved by the Regional Ethical Review Board in Stockholm. For this type of retrospective study formal consent was not required.

Availability of data and material

The register data used is not publicly available due to sensitive information. Data access can be requested from the National Board of Health and Welfare in Sweden after ethical approval.

Funding

The cost for retrieval of the data was funded by a clinical trial investigating for the development of diabetic neuropathy (Cebix incorporated).

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