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FULL-LENGTH ORIGINAL RESEARCH

Symptomatology of carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy

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Abstract

Objective: To ascertain whether adverse effects experienced by people taking carbamazepine or oxcarbazepine could be attributed to carbamazepine- or oxcarbazepine-induced hyponatremia (COIH).

Methods: We performed an observational study, collecting data between 2017 and 2019 on serum sodium levels and adverse effects retrospectively in people with epilepsy while receiving treatment with either carbamazepine (CBZ) or oxcarbazepine (OXC). We defined hyponatremia as sodium level ≤134 mEq/L and severe hyponatremia as sodium level ≤128 mEq/L. Adverse effects experienced were compared between groups of individuals with and without hyponatremia.

Results: A total of 1370 people using CBZ or OXC were identified, of whom 410 had at least one episode of hyponatremia. We checked for symptoms related to the use of CBZ and OXC in 710 people (410 with and 300 without hyponatremia) and found relevant information in 688. Adverse effects occurred in 65% of people with hyponatremia compared to 21% with normal sodium levels (odds ratio [OR] 7.5, $P \leq .001$) and in 83% of people with severe hyponatremia compared to 55% in those with mild hyponatremia ($P \leq .001$). Significant predictors of adverse effects were the drug (OXC vs CBZ), and the number of concomitant anti-seizure medications. Dizziness (28% vs 6%), tiredness (22% vs 7%), instability (19% vs 3%), and diplopia (16% vs 4%) were reported more often in the hyponatremia group than in patients with normal levels.

Significance: People with COIH had a 7-fold increased risk of developing adverse effects during treatment. Clinicians should consider ascertainment of sodium levels in patients taking CBZ and OXC and act upon findings.

KEYWORDS
adverse effects, anti-seizure medication, drug treatment, sodium levels

1 | INTRODUCTION

The anti-seizure medications (ASMs) carbamazepine (CBZ) and its keto-analogue oxcarbazepine (OXC) are frequently prescribed for the pharmacological treatment of focal epilepsy. Both are also used to treat trigeminal neuralgia and bipolar disorders. Their use is limited by adverse effects including hyponatremia, as both seem to influence water reabsorption via stimulation of the vasopressin 2 receptor/aquaporin pathway causing a sodium dilution.[1] The prevalence of CBZ- or OXC-induced hyponatremia (COIH) varies greatly; for CBZ the reported estimates are between 4% and 40%, whereas for OXC they are between 23% and 73%.[2-5] High serum levels of CBZ or OXC, concomitant use of other ASMs, and being female are risk factors for COIH, as well as age >40 years.[5] A genetic predictor for COIH has not yet been identified.[6]

COIH is often assumed to be asymptomatic, but it can lead to symptoms ranging from unsteadiness and mild confusion to acute symptomatic seizures and coma. We found previously that almost half of people with COIH were symptomatic, and in 3% this led to hospital admissions.[5] The type of symptoms was not very specific for hyponatremia and often COIH was not recognized by the clinician as a potential cause. We aimed to determine whether symptoms experienced by people taking these ASMs could be attributed to COIH. We assessed symptoms that could be adverse effects in a cross-sectional cohort of people with epilepsy treated with CBZ and OXC previously described[5] and compared their occurrence in individuals with and without hyponatremia.

Key Points

- People with carbamazepine- or oxcarbazepine-induced hyponatremia experience a 7-fold increased risk of developing adverse symptoms during treatment.
- Significant predictors of adverse effects were use of oxcarbazepine (compared to carbamazepine) and number of concomitant anti-seizure medications.
- Dizziness, tiredness, instability, and diplopia were reported more often in the hyponatremia group than in patients with normal levels.

2 | METHODS

2.1 | Study design

An electronic database designed for pharmacogenomic studies (www.epipgx.eu), capturing relevant clinical data with an emphasis on ASM history, has been in use since 2010 (http://www.sein.nl/en/). It was used to identify all individuals who were prescribed CBZ or OXC and who had a serum sodium level recorded during therapy at a tertiary referral center. We defined hyponatremia as a sodium level ≤134 mEq/L, and severe hyponatremia as ≤128 mEq/L, in line with previous studies.[2,7] Levels were measured as part of routine monitoring. For each sodium level measurement, we recorded the date, serum level of CBZ or OXC (samples collected in the morning before taking the ASM), and concomitant use of other ASMs. Most individuals had several measurements, and we used the lowest recorded sodium level. Clinical characteristics, including the effect of treatment, were retrieved from case notes. Treatment outcome was recorded in three categories; failure of ASMs was defined as <50% seizure reduction with CBZ or OXC, response as seizure-freedom for at least 1 year, and moderate as seizure frequency reduction ≥50% but not seizure-free.

We scored symptoms of adverse effects (AEs; Table 4) present at the time of hyponatremia, which could not be explained by another cause or comorbidity. From patients with normal sodium levels, we selected the 300 individuals with the most recent measurements (between 2006 and 2016) and scrutinized for AEs during the use of CBZ/OXC at times when sodium levels were known. We used the same strategy for both groups.

The starting point was the date when the lowest sodium level was measured. We checked the records of visits/contacts prior and following this date. In case of several measurements in a continuous period, records were checked over this period for adverse events. The individual must have been continuously receiving CBZ or OXC over the period, but the dosage could vary. If dosage changed, records were included only if sodium levels were available for the different dosages. For the hyponatremia group also only when all the sodium measurements within the continous period were l ≤ 134 mEq/L.

Usually, with normal sodium levels the measurements were scattered and not close in time. When measurements were obtained within 1 year with no dosage change between measurements, all records of the continuous period in-between were included. When measurement intervals were >1 year, only the records prior and following the date of assay were included.

In people who trialed CBZ and OXC (n = 13) only the period with the lowest sodium level was used in the analysis. In the subgroup analysis (stratified by CBZ/OXC use) the ASM trial appropriate to the group was used.

2.2 | Statistics

Having AEs or not was modeled as a dichotomous variable. Hyponatremia was modeled as either a dichotomous variable or a categorical variable. The association between hyponatremia

TABLE 1 Descriptives

Variables		Hypo Na (N = 388)		Normal Na (N = 300)		*p*-value	Having symptoms				
							Yes (N = 313)		No (N = 375)		*P*-value
Sex, N (%)	Male	188	(48.5)	152	(50.7)	.56	150	(47.9)	190	(50.7)	.49
Treatment outcome,[a] N (%) (missing 17)	failure	157/375	(41.9)	67/296	(22.6)		125/303	(41.3)	99/368	(26.9)	
	response	76/375	(20.3)	106/296	(35.8)		65/303	(21.5)	117/368	(31.8)	
	moderate	142/375	(37.9)	123/296	(41.6)	<.001	113/303	(37.3)	152/368	(41.3)	<.001
Concomitant ASMs[b] (missing 22)	Monotherapy	74/371	(19.9)	99/295	(33.6)	<.001	58/302	(19.2)	115/364	(31.6)	<.001
Mean age (SD), years		47.3	(15.0)	40.9	(17.0)	<.001	45.8	(16.2)	43.4	(16.1)	.06
Mean sodium level (SD), mEq/L		129.6	(3.9)	139.7	(6.0)		131.0	(5.9)	136.47	(4.9)	<.001
Mean drug level (SD), mg/L (CBZ, missing 34; OXC, missing 23)	CBZ	8.3	(2.2)	7.6	(2.1)	.001	8.2	(2.3)	7.8	(2.1)	.07
	OXC	22.0	(7.0)	20.1	(6.9)	.12	21.8	(6.4)	20.8	(7.6)	.38

Abbreviations: ASM, anti-seizure medication; CBZ, carbamazepine; Hypo Na, hyponatremia; OXC, oxcarbazepine.

[a]Treatment outcome is a categorical variable with groups failure (<50% seizure frequency reduction), response (seizure freedom >1 year), and moderate (seizure frequency reduction ≥50%, not seizure-free).

[b]Concomitant ASMs = dichotomous variable (mono vs polytherapy)

TABLE 2 Univariate analysis, showing the frequencies of adverse symptoms for each group.

No. (%)	N	Hypo Na		Normal Na		*P*-value	Na<128		Na 128-134		Na >134		*P*-value
Total	688	251/388	(64.7)	62/300	(20.7)	<.001	111/134	(82.8)	140/254	(55.1)	62/300	(20.7)	<.001
CBZ	524	163/276	(59.1)	52/248	(21.0)	<.001	62/79	(78.5)	101/197	(51.3)	52/248	(21.0)	<.001
OXC	177	98/125	(78.4)	10/52	(19.2)	<.001	54/62	(87.1)	44/63	(69.8)	10/52	(19.2)	<.001

Note: Thirteen people trialed CBZ and OXC; in the total analysis each individual appeared only once.

Abbreviations: CBZ, carbamazepine; Hypo Na, hyponatremia; Na, sodium in mEq/L; OXC, oxcarbazepine.

TABLE 3 Stepwise logistic regression with outcome having adverse symptoms

	N = 666		95% CI			
Step	Dependent variables	Odds ratio	Lower	Upper	*P*-value	R2
1	Hyponatremia	7.348	5.152	10.479	<.001	0.254
2	Hyponatremia	6.932	4.848	9.914	<.001	0.265
	OXC/CBZ	1.716	1.149	2.561	.007	
3	Hyponatremia	6.582	4.591	9.436	<.001	0.277
	OXC/CBZ	1.775	1.185	2.660	.004	
	N concomitant ASMs	1.308	1.077	1.588	.007	

Note: Treatment outcome, sex, and age had no significant influence. N concomitant ASMs, continuous variable with values from 0-5.

Abbreviations: ASM, anti-seizure medication; N, number.

TABLE 4 Frequencies of specific symptoms in people with hyponatremia vs normal sodium levels, and shown for three sodium level categories

Symptoms, N (%)	Hypo Na (388)		Normal Na (300)		*P*-value	Na <128 (134)		Na 128-134 (254)		Na >134 (300)		*P*-value
Behavioral disturbance	8	(2,1)	2	(0,7)	.13	6	(4,5)	2	(0,8)	2	(0,7)	.005
Cognitive slowing	31	(8,0)	0		**<.001**	13	(9,7)	18	(7,1)	0		**<.001**
Concentration problems	30	(7,7)	4	(1,3)	**<.001**	15	(11,2)	15	(5,9)	4	(1,3)	**<.001**
Confusion	19	(4,9)	2	(0,7)	**.001**	11	(8,2)	8	(3,1)	2	(0,7)	**<.001**
Diplopia	60	(15,5)	12	(4,0)	**<.001**	27	(20,1)	33	(13,0)	12	(4,0)	**<.001**
Dizziness	108	(27,8)	19	(6,3)	**<.001**	47	(35,1)	61	(24,0)	19	(6,3)	**<.001**
Falls	29	(7,5)	1	(0,3)	**<.001**	13	(9,7)	16	(6,3)	1	(0,3)	**<.001**
Gait disturbance	16	(4,1)	2	(0,7)	.005	10	(7,5)	6	(2,4)	2	(0,7)	**.002**
Headache	35	(9,0)	9	(3,0)	**.001**	21	(15,7)	14	(6,7)	9	(3,0)	**<.001**
Increased seizure frequency	37	(9,5)	0		**<.001**	21	(15,7)	16	(6,3)	0		**<.001**
Instability	75	(19,3)	8	(2,7)	**<.001**	32	(23,9)	43	(16,9)	8	(2,7)	**<.001**
Nausea/vomiting	36	(9,3)	1	(0,3)	**<.001**	22	(16,4)	14	(5,5)	1	(0,3)	**<.001**
Personality change	5	(1,3)	0		.05	2	(1,5)	3	(1,2)	0		.16
Somnolence	45	(11,6)	6	(2,0)	**<.001**	24	(17,9)	21	(8,3)	6	(2,0)	**<.001**
Tiredness	84	(21,6)	20	(6,7)	**<.001**	40	(29,9)	44	(17,3)	20	(6,7)	**<.001**
Other symptoms	53	(13,7)	18	(6,0)	**.001**	27	(20,1)	26	(10,2)	18	(6,0)	**<.001**

Note: Bonferroni correction for multiple testing; *P* significant at .003125 (0.05/16); significant *P*-values are marked bold. Other symptoms were: allergy, hair loss, memory problems, mood disorders, skin problems, tremor, and nonspecific complaints. Hypo Na; hyponatremia

TABLE 5 Frequencies of specific symptoms in people with hyponatremia vs normal sodium levels, stratified for CBZ and OXC use

	CBZ					OXC				
Symptoms, N (%)	Hypo Na (276)		Normal (248)		*P*-value	Hypo Na (125)		Normal (52)		*P*-value
Behavioral disturbance	3	(1,1)	1	(0,4)	.37	5	(4)	1	(1,9)	.49
Cognitive slowing	23	(8,3)	0		**<.001**	11	(8,8)	0		.03
Concentration problems	7	(2,5)	4	(1,6)	.46	23	(18,4)	0		**.001**
Confusion	8	(2,9)	1	(0,4)	.03	11	(8,8)	1	(1,9)	.10
Diplopia	34	(12,3)	9	(3,6)	**<.001**	27	(21,6)	2	(3,8)	.004
Dizziness	70	(25,4)	15	(6,0)	**<.001**	42	(33,6)	4	(7,7)	**<.001**
Falls	20	(7,2)	0		**<.001**	9	(7,2)	1	(1,9)	.17
Gait disturbance	12	(4,3)	2	(0,8)	.01	6	(4,8)	0		.11
Headache	20	(7,2)	8	(3,2)	.04	16	(12,8)	1	(1,9)	.03
Increased seizure frequency	13	(4,7)	0		**.001**	25	(20,0)	0		**.001**
Instability	43	(15,6)	5	(2)	**<.001**	34	(27,2)	3	(5,8)	**.001**
Nausea/vomiting	20	(7,2)	1	(0,4)	**<.001**	19	(15,2)	0		**.003**
Personality change	3	(1,1)	0		.10	2	(1,6)	0		.36
Somnolence	29	(10,5)	4	(1,6)	**<.001**	20	(16,0)	2	(3,8)	.03
Tiredness	40	(14,5)	18	(7,3)	.008	50	(40,0)	2	(3,8)	**<.001**
Other symptoms	22	(8,0)	15	(6,0)	.39	33	(26,4)	3	(5,8)	**.002**

Note: Bonferroni correction for multiple testing; *P* significant at .003125 (0,05/16), significant *P*-values are marked bold. Other symptoms were: allergy, hair loss, memory problems, mood disorders, skin problems, tremor, and nonspecific complaints.

Abbreviations: CBZ, carbamazepine; Hypo Na, hyponatremia; OXC, oxcarbazepine.

and the risk of having AEs was analyzed with chi-square tests. The association between hyponatremia and different specific symptoms were also analyzed with chi-square tests. To correct for multiple comparisons, we used the Bonferroni method.

A stepwise logistic regression model was used to analyze the significance of clinical variables influencing the risk of having AEs. Hyponatremia, use of CBZ or OXC, treatment outcome, sex, age, and number of concomitant ASMs used were included as covariates. The type of ASM co-used was modeled separately with hyponatremia to test the influence on the risk of having AEs. In a final model only the significant covariates were included.

Serum drug level was included as a covariate to analyze the influence of hyponatremia on the risk of having AEs in the subgroups of both CBZ and OXC use.

Relationships between dichotomous variables were assessed with 2x2 tables and analysis of variance (ANOVA) was used to compare means.

Those with missing AEs data were excluded.

Statistical analysis was carried out using SPSS version 22.0 for Windows (SPSS Inc).

2.3 | Ethics

The Ethical Committee of UMC Utrecht approved the study, and all participants provided written informed consent for data retrieval.

2.4 | Data availability statement

Anonymized data will be shared on receipt of a reasonable request from a qualified investigator.

3 | RESULTS

We identified 1370 people using CBZ or OXC, of whom 410 had at least one episode of hyponatremia. We checked for CBZ/OXC-related AEs in 710 people (410 with and 300 without hyponatremia) and found pertinent information in 688. Reports of AEs were identified in 313 people (45%). Thirteen individuals had trials of treatment with OXC and with CBZ. People who developed hyponatremia were significantly older than those with normal levels. Mean drug levels did not differ between symptomatic and nonsymptomatic individuals (Table 1).

Hyponatremia and having AEs were independently associated with a higher frequency of failure of ASM treatment and use of combination therapy instead of monotherapy (Table 1).

In those hyponatremic, 65% experienced AEs compared to 21% in people with normal levels ($P < .001$). In those with severe hyponatremia, 83% experienced AEs, whereas this was 55% in mild hyponatremia ($P < .001$, Table 2).

Subgroup analysis showed that hyponatremia was associated with a higher frequency (78%) of AEs when related to

use of OXC rather than with the use of CBZ (59%) (Table 2, $P = .007$ Table 3).

We modeled the contribution of clinical cofactors to having AEs. We found that, apart from hyponatremia, which of the two drugs used (OXC higher risk than CBZ) and the number of ASMs used concomitantly were significantly predictive of outcome (adjusted R2 = 0.28, Table 3). The type of ASM co-used did not influence the outcome of having AEs (data not provided). Serum drug level was analyzed as clinical cofactor within the subgroups of CBZ and OXC. In both ASM groups, drug levels had no significant influence on the association between hyponatremia and having AEs (Table S1).

Table 4 shows the frequencies of specific symptoms in patients with hyponatremia and patients with normal sodium levels. Table 4 also indicates frequencies of symptoms for severe and mild hyponatremia. Data stratified by CBZ or OXC use are in Table 5.

Dizziness (28%), tiredness (22%), instability (19%), and diplopia (16%) were most frequently reported and significantly more often in the hyponatremia group than in patients with normal levels (Table 4). Cognitive slowing, concentration problems, confusion, falling, headache, increased seizure frequency, nausea, and somnolence were also reported significantly more often in the hyponatremia group. These were even more frequently seen in severe hyponatremia than in mild hyponatremia.

In the separate analysis for OXC use (Table 5) tiredness was the most frequent symptom in the hyponatremic individuals, reported in 40% compared to 4% in those with a normal sodium level.

4 | DISCUSSION

CBZ and OXC are widely used, and physicians should be aware of the high prevalence of COIH, which is often assumed to be asymptomatic. We found that patients with hyponatremia experienced a 7-fold increased odds of AEs.

The symptoms related to hyponatremia are not very specific. Hyponatremia signs, whether or not related to the use of ASMs, can include nausea, vomiting, malaise, headache, dizziness, confusion, drowsiness, and fatigue.[8] Similar symptoms can be seen with higher CBZ/OXC drug levels or with individual intolerability for these drugs.[9] Reports about side effects caused by CBZ and OXC describe rash, dizziness, headache, fatigue, and drowsiness, but sodium levels were not taken into account in these reports.[10,11]

We cannot determine whether hyponatremia is the direct cause of the AEs or whether low sodium levels increase vulnerability to adverse effects of the ASMs. The drug levels of the ASMs did not influence the association between hyponatremia and having AEs and they were not significantly different between those symptomatic and those asymptomatic. Does the finding that ASM levels were not associated with having symptoms tell us that the symptoms are more likely to be caused by hyponatremia rather than the direct adverse effects of the ASM itself? This would only be the case when we assume that these direct adverse effects are highly dose dependent. A relationship between dose and adverse effects has been described for OXC, but titration schedule and concomitant ASMs also played an important role.[12]

AEs were seen more frequently with OXC than with CBZ. Our earlier study suggests that OXC is associated with lower sodium levels and more frequent severe hyponatremia.[5] This could provide some support to the notion that lower sodium levels are more likely to cause symptoms and is in line with the finding of a higher frequency of AEs in the severe hyponatremia group.

In the hyponatremia group, fewer individuals had a good response to their treatment and more were on polytherapy. The outcome of epilepsy treatment did not influence the association between hyponatremia and having AEs, but the number of co-prescribed ASMs did (Table 3). A recent study showed that polytherapy with three or more ASMs was associated with more adverse effects, with no difference between monotherapy and duotherapy.[13] In earlier studies, no association was found between the number or load of ASMs and adverse effects.[14,15] We showed previously that the number of concomitant ASMs influenced the risk of COIH. With increasing numbers of concomitant ASMs used, sodium levels dropped, suggesting a higher risk of hyponatremia-related symptoms.[5]

Because hyponatremia seems to be symptomatic in a considerable number of people treated with CBZ/OXC, the clinical importance of this finding needs to be understood. Mild chronic hyponatremia was described earlier as causing neurocognitive deficits, gait disturbance, and falls.[16] Treatment of chronic mild hyponatremia improved neurocognitive and neuromuscular function.[17] This suggests the need to treat COIH, even if mild, to improve overall functioning. Management can be either by fluid restriction or by switching to another ASM.

A limitation of our study is that there was no consistent information available on sodium levels prior to starting CBZ/OXC. For further studies, a prospective cohort with baseline sodium levels, follow-up measurements at regular intervals, and monitoring the effect of treatment of COIH is recommended.

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CONFLICT OF INTEREST

BB, JH, AS, MMcC, G-JdH, JWS, DL, and BPK have no disclosures relevant to this work.

AUTHOR CONTRIBUTIONS

BB, JWS, and BPK conceptualized and designed the study. BB, JA, and AS contributed by acquisition and analysis of data. BB, JWA, DL, and BPK drafted the manuscript. MMcC and G-jdH revised the manuscript for intellectual content. All approved the final version.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Berghuis B, de Haan GJ, van den Broek MP, Sander JW, Lindhout D, Koeleman BP. Epidemiology, pathophysiology and putative genetic basis of carbamazepine- and oxcarbazepine-induced hyponatremia. Eur J Neurol. 2016;23(9):1393–9.
2. Dong X, Leppik IE, White J, Rarick J. Hyponatremia from oxcarbazepine and carbamazepine. Neurology. 2005;65(12):1976–8.
3. Van Amelsvoort T, Bakshi R, Devaux CB, Schwabe S. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. Epilepsia. 1994;35(1):181–8.
4. Nielsen OA, Johannessen AC, Bardrum B. Oxcarbazepine-induced hyponatremia, a cross-sectional study. Epilepsy Res. 1988;2(4):269–71.
5. Berghuis B, van der Palen J, de Haan GJ, Lindhout D, Koeleman BPC, Sander JW, *et al*. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. Epilepsia. 2017;58(7):1227–33.
6. Berghuis B, Stapleton C, Sonsma ACM, Hulst J, de Haan GJ, Lindhout D, *et al*. A genome-wide association study of sodium levels and drug metabolism in an epilepsy cohort treated with carbamazepine and oxcarbazepine. Epilepsia Open. 2019;4(1):102–9.
7. Kim YS, Kim DW, Jung KH, Lee ST, Kang BS, Byun JI, *et al*. Frequency of and risk factors for oxcarbazepine-induced severe and symptomatic hyponatremia. Seizure. 2014;23(3):208–12.
8. Hague J, Casey R, Bruty J, Legerton T, Abbs S, Oddy S, *et al*. Adult female with symptomatic AVPR2-related nephrogenic syndrome of inappropriate antidiuresis (NSIAD). Endocrinol Diabetes Metab Case Rep. 2018;2018(1):1–5.
9. Martinez W, Ingenito A, Blakeslee M, Barkley GL, McCague K, D'Souza J. Efficacy, safety, and tolerability of oxcarbazepine monotherapy. Epilepsy Behav. 2006;9(3):448–56.
10. Koch MW, Polman SK. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Cochrane Database Syst Rev. 2009(4):CD006453.
11. Besi E, Boniface DR, Cregg R, Zakrzewska JM. Comparison of tolerability and adverse symptoms in oxcarbazepine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headaches using the Liverpool Adverse Events Profile (AEP). J Headache Pain. 2015;16:563.
12. Barcs G, Walker EB, Elger CE, Scaramelli A, Stefan H, Sturm Y, *et al*. Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. Epilepsia. 2000;41(12):1597–607.
13. Joshi R, Tripathi M, Gupta P, Gulati S, Gupta YK. Adverse effects & drug load of antiepileptic drugs in patients with epilepsy: Monotherapy versus polytherapy. Indian J Med Res. 2017;145(3):317–26.
14. Canevini MP, De Sarro G, Galimberti CA, Gatti G, Licchetta L, Malerba A, *et al*. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. Epilepsia. 2010;51(5):797–804.
15. Deckers CL, Hekster YA, Keyser A, Meinardi H, Renier WO. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. Epilepsia. 1997;38(5):570–5.
16. Rondon-Berrios H, Berl T. Mild chronic hyponatremia in the ambulatory setting: significance and management. Clin J Am Soc Nephrol. 2015;10(12):2268–78.
17. Refardt J, Kling B, Krausert K, Fassnacht M, von Felten S, Christ-Crain M, *et al*. Impact of chronic hyponatremia on neurocognitive and neuromuscular function. Eur J Clin Invest. 2018;48(11):e13022.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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