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DRUG SAFETY

Medication-induced SIADH: distribution and characterization according to medication class

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AIMS

The aims of the current study were to determine the distribution of aetiologies for the drug-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) in hospitalized patients, and to characterize them according to the different drug groups.

METHODS

A single-centre retrospective study was carried out, including all patients diagnosed with SIADH in a large community hospital and tertiary centre between 1 January 2007 and 1 January 2013 who were treated with drugs known to be associated with SIADH. Two physicians reviewed every patient's medical file for predetermined relevant clinical data.

RESULTS

The study cohort included 198 patients who had SIADH and received drugs associated with SIADH. Most patients [146 (73.7%)] were diagnosed with drug-associated SIADH, while 52 (26.3%) were diagnosed with SIADH due to other aetiologies. The Naranjo algorithm differentiated well between the two groups ($P < 0.001$). Five drug classes (antidepressants, anticonvulsants, antipsychotic agents, cytotoxic agents and pain medications) were implicated in 82.3% of patients diagnosed with drug-associated SIADH. Specific serotonin reuptake inhibitors and carbamazepine were commonly implicated. There were no clinically significant differences in the characteristics or severity of SIADH according to drug class.

CONCLUSIONS

The clinical characteristics of SIADH caused by different drugs are comparable. Patients with SIADH treated with drugs from five common medication classes will probably be diagnosed with drug-induced SIADH. Physicians should be aware of the significance of these medication classes as SIADH aetiologies.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drugs are a common cause of SIADH. The distribution of medication classes as SIADH aetiologies is unknown.
- Data regarding SIADH characteristics according to different drug classes and the likelihood of SIADH being attributed to a medication in a patient treated with a suspected drug are lacking.

WHAT THIS STUDY ADDS

- The clinical characteristics of SIADH caused by different drugs are comparable.
- Five medication classes were shown to be implicated in most cases of drug-induced SIADH.
- Most patients with SIADH treated with suspected drug had medication-induced SIADH.

Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) was described more than 50 years ago by Schwartz *et al.* [1] whose observations and diagnostic criteria remain essentially unchanged [1–4]. Medications are a common cause of SIADH [2, 5]. While many drugs have been sporadically associated with SIADH, several medication classes are more often implicated, including antidepressants, antipsychotic agents, anticonvulsants, and several pain medications and cytotoxic agents [2, 6–10]. While drug-induced SIADH is a common clinical problem, several issues remain unaddressed in the current literature. As most of the available data are derived from case reports and small case series, the distribution of the different medication classes as SIADH aetiologies is unknown. The percentage of patients with SIADH who take a suspected medication and are actually diagnosed with drug-induced SIADH is unknown. Whether these patients can be differentiated by clinical parameters from those with SIADH due to causes other than medications has not been studied. Furthermore, there are no data in the literature regarding whether different medication classes are associated with different severities and outcomes of SIADH. We conducted a single-centre retrospective study to determine the distribution of aetiologies for drug-induced SIADH in hospitalized patients, and to characterize them according to the different drug groups.

Methods

The study was approved by the hospital's Institutional Review Board. The study population included all patients older than 18 years, hospitalized between 1 January 2007 and 1 January 2013 in our institute (a large community hospital and a tertiary centre) with hyponatraemia (serum sodium ≤134 mEq l^{-1}), who met the criteria for SIADH (euvolaemia, concomitant urine osmolality ≥100 mOsm kg^{-1} and urine sodium concentration ≥30 mEq l^{-1}) and were being treated with a drug known to be associated with SIADH. Patients' medical files were reviewed by two physicians (A.S, D.S.). Exclusion criteria included: glomerular filtration rate (GFR) ≤60 ml min^{-1} (according to the Chronic Kidney Disease Epidemiology Collaboration formula) [11], use of diuretics (including thiazides, loop diuretics, aldosterone antagonists or any other diuretic), hypervolaemia or hypovolaemia (based on documented history and clinical examination), hypothyroidism and adrenal insufficiency. As serum osmolality was not routinely performed in our hospital, patients with hypertriglyceridaemia, (triglycerides ≥500 mg dl^{-1}) and any paraproteinaemia (globulin ≥3.5 g dl^{-1} or monoclonal gammopathy) were also excluded. Patients with hyperglycaemia were included if the sodium concentration was ≤134 mEq l^{-1} after adding a correction factor of 2.4 mEq l^{-1} for every 100 mg dl^{-1} increase in plasma glucose concentration [12]. For any disagreement between the physicians reviewing the patient charts, a third physician made the final decision (A.G.).

Collected data from chart reviews included demographics, weight, serum and urine sodium concentration, urine osmolality, blood urea and uric acid concentrations, patient's medications lists and the most likely SIADH aetiology. A diagnosis of drug-induced SIADH was accepted only for patients who actively took the suspected medication or had quit within 1 week prior to SIADH diagnosis. The Naranjo score, a widespread tool used to determine the likelihood of whether a suspected adverse drug effect is actually due to the drug rather than the result of other factors, was used in order to evaluate and quantify the quality of clinical diagnosis of drug-induced SIADH [13]. The score was calculated according to a predefined formula from the collected data. The Naranjo score is based on a list of 10 weighted items, including time to onset and recovery, previous reports of similar effects, the response to rechallenge, and the possibility of alternative causes. This scale allows categorical classification of adverse events as 'definite' (≥9), 'probable' (5–8), 'possible' (1–4), or 'doubtful' (0).

Patients with multiple possible aetiologies, pharmacological or nonpharmacological, for whom there was clinical uncertainty regarding the aetiology which caused the SIADH were noted. Hyponatraemia severity was defined as mild (130–134 mEq l^{-1}), moderate (125–129 mEq l^{-1}) or profound (<125 mEq l^{-1}). Usage of hypertonic saline was documented. The number of admissions due to hyponatraemia was noted. Postdischarge, steady-state short-term sodium levels were defined as the median sodium concentration during the 1–3 months following SIADH diagnosis. Follow-up time and survival until 1 June 2015 were calculated. Patients' vital status was ascertained through Israel's Ministry of Interior database.

Medications were grouped into seven categories for analysis: antidepressants, antipsychotic agents, anticonvulsants, pain medications, cytotoxic agents, others and multiple causes (more than one possible aetiology associated with patients' SIADH). Duloxetine and pregabalin, which can be used for several different indications, are used in our

institution mostly for neuropathic pain, and therefore were grouped in the pain medication category. An intergroup analysis according to specific drugs was planned.

Statistical analysis

Chi-square and/or Fisher's exact test were used to compare categorical variables. Analysis of variance (ANOVA) was used for comparison between multiple groups. Student's t-test was used to compare normally distributed continuous variables, and the Mann–Whitney U-test was used for non-normally distributed groups. All reported *P*-values are from two-sided tests.

Kaplan–Meier survival analysis, using the log-rank test, and the univariate Cox model were used to assess the effect of different variables on overall survival.

The multivariate Cox proportional hazard model was used for multivariate analysis of overall survival using the forward multiple regression test with cutoff values of 0.05 for inclusion and 0.1 for exclusion.

Results

Study cohort

There were 1287 patients with serum sodium ≤134 mEq l^{-1}, urine osmolality ≥100 mOsm kg^{-1}, urine sodium ≥30 mEq l^{-1} and GFR above 60 ml min^{-1} between 1 January 2007 and 31 December 2013 in our hospital. Of these, 732 patients did not meet the criteria of SIADH and were excluded. Of the remaining 555 patients with SIADH, 198 (35.7%) were taking a drug associated with SIADH (Figure 1). The patient demographics are depicted in Table 1. The most common medication class was antidepressants [65 patients (32.8%)], followed by anticonvulsants [41 patients (20.7%)], cytotoxic agents [28 patients (14.1%)], antipsychotic agents [22 patients (11.1%)], pain medications [19 patients (9.6%)] and other classes [seven patients (3.5%)]. Sixteen patients (8.1%) had multiple possible aetiologies for SIADH (Table 2).

From the 198 patients taking medications associated with SIADH while diagnosed with SIADH, 146 (73.7%) were diagnosed with drug-associated SIADH according to their medical charts, while 52 patients (26.3%) had other aetiologies, including malignancy-associated SIADH (20 patients), pulmonary disorders (12 patients), central nervous system disorders (12 patients) and acute pain or nausea (eight patients). The Naranjo algorithm differentiated well between the two groups, with a mean score of 6.5 ± 1.2 for drug associated SIADH *vs.* a score of 3 for SIADH due to other aetiologies, validating the clinical diagnosis of a SIADH aetiology ($P < 0.001$). Other clinical parameters available at the time of SIADH diagnosis were similar for both groups (Table 1).

Several drugs were associated with SIADH within every medication class (Table 3). The most commonly reported antidepressant was citalopram, with 19 cases of SIADH. Other selective serotonin reuptake inhibitors (SSRIs) were associated with 17 additional reports. Carbamazepine, the most commonly reported anticonvulsant, was associated with 19 cases of SIADH. Vincristine was the most commonly associated cytotoxic agent, with 10 associated cases. Other medication classes had more diverse representation, with risperidone and duloxetine the most commonly reported drugs for antipsychotic agents and pain medications, associated with five cases each.

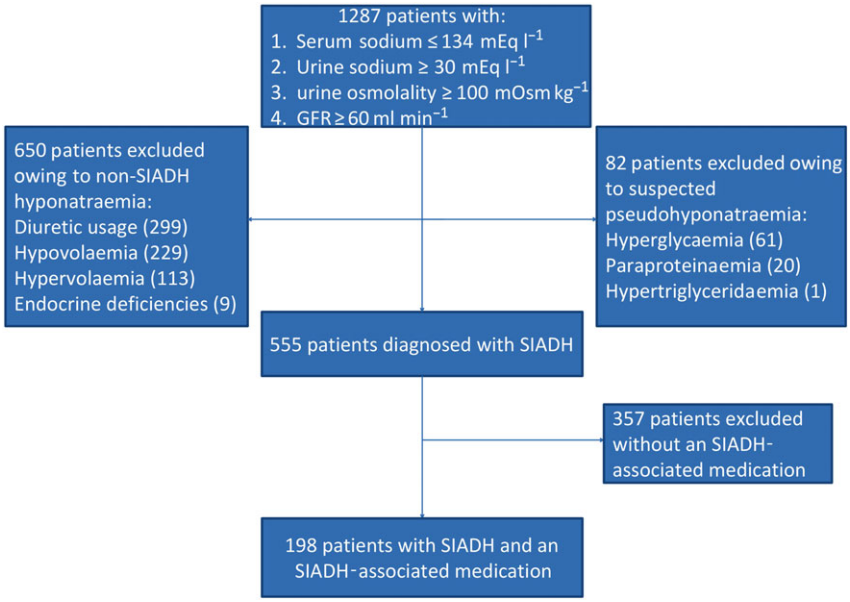

Figure 1
Flow chart of patient selection process

Table 1

Characteristics of patients with SIADH receiving SIADH-associated medications, grouped according to SIADH aetiology

	Study population	Medication-associated SIADH	SIADH d/t other aetiologies	*P*
No. of patients	198	146 (73.7%)	52 (26.3%)	
Average age, years (SD)	66.6 (17.3)	67.9 (16.9)	63.1 (17.8)	0.1
Male gender (%)	88 (44.5%)	64 (43.8%)	24 (46.2%)	0.87
Weight (kg)	66 (15.1)	66.2 (16.2)	65.2 (11.8)	0.74
Average serum sodium concentration, mEq l^{-1} (SD)	125.9 (5.9)	125.3 (6.2)	127.4 (4.6)	0.02
Average urine sodium concentration, mEq l^{-1} (SD)	79.4 (37.5)	77.8 (38.5)	83.8 (34.4)	0.3
Average urine osmolality, mOsm kg^{-1} (SD)	416.4 (173.7)	408 (166.1)	440.7 (193.3)	0.28
Average urea concentration, mg dl^{-1} (SD)	26.9 (8.6)	26.7 (8)	27.5 (10.1)	0.64
Average uric acid concentration, mg dl^{-1} (SD)	3.3 (1.2)	3.4 (1.3)	3 (1.1)	0.06
Oral NaCl usage (%)	51 (25.8%)	35 (24%)	16 (30.8%)	0.54
Hypertonic saline usage (%)	21 (10.6%)	18 (12.3%)	3 (5.8%)	0.29
Hospitalizations due to hyponatraemia (%)	65 (32.8%)	53 (36.3%)	12 (23.1%)	0.09
Average serum sodium concentration at 1–3 months, mEq l^{-1} (SD)	134.1 (4.3)	134.4 (4.3)	133.3 (4.3)	0.16
Survival at end of follow-up	89 (44.9%)	77 (52.7%)	12 (23.1%)	<0.001
Average Naranjo score (SD)	5.6 (1.8)	6.5 (1.2)	3 (0)	<0.001

d/t, due to; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SD, standard deviation

Analysis according to aetiology

The distribution of aetiologies of SIADH according to medication class is presented in Table 2. Demographics differed among patients on different medication classes. Serum urea and uric acid concentration, as well as urine osmolality and sodium concentration, were comparable between patients on different medication classes. Hypertonic saline usage was similar for patients with SIADH caused by different drug classes. The percentage of patients receiving drugs from the different classes who were diagnosed with drug-induced SIADH, as compared with other SIADH aetiologies, were similar. There was a statistically significant difference in the short-term sodium concentration but the absolute difference was clinically insignificant.

Severity of hyponatraemia

Of the 198 patients included in the study cohort, 53 (26.8%) had mild hyponatraemia, 84 (42.4%) had moderate hyponatraemia and 61 (30.8%) had profound hyponatraemia. The serum sodium concentration was significantly lower for patients with drug-associated SIADH compared with those with SIADH associated with other aetiologies but the absolute difference was not clinically significant (Table 1). Hyponatraemia severity was also associated with age ($P < 0.001$) and with hypertonic saline therapy ($P < 0.001$). However, hyponatraemia severity was unrelated to patient weight ($P = 0.35$), urine sodium concentration ($P = 0.32$) or urine osmolality ($P = 0.09$). Serum sodium concentration was comparable for patients on most medication classes, except for cytotoxic agents, which were associated with milder hyponatraemia.

Survival

Median follow-up for the study cohort was 35 months (interquartile range 10–58 months). Overall survival at the end of follow-up was 44.9%. Survival at follow-up was considerably better for patients with drug-associated SIADH (52.7%) than for those with SIADH associated with other aetiologies (23.1%). This remained significant on multivariate analysis, with a hazard ratio (HR) of 0.35 [95% confidence interval (CI) 0.22, 0.56]. This difference in survival was driven mainly by the poor survival of patients with malignancy-related SIADH (5%). Survival also differed according to medication class (Table 2), driven mainly by better survival of patients with SIADH associated with anticonvulsants and worse survival of patients with multiple possible SIADH aetiologies. Additional factors associated with survival on multivariate analysis were age (HR 0.98 per year; 95% CI 0.96, 0.99; $P = 0.001$) and short-term hyponatraemia grade (HR 0.94 per grade; 95% CI 0.89, 0.99; $P = 0.01$). Hyponatraemia severity at SIADH diagnosis was not predictive of long-term survival ($P = 0.22$).

Discussion

This was a single-centre, retrospective study aiming to describe the distribution of the different medication classes

Table 2

Patient characteristics according to medication class

	Study population	Antidepressants	Anticonvulsants	Antipsychotic agents	Anticancer agents	Pain medications	Others[a]	Multiple[b]	*P*
No. of patients	198	65	41	22	28	19	7	16	
Average age, years (SD)	66.6 (17.3)	74.4 (12.3)	62.1 (17.5)	68 (17.2)	56.5 (18.4)	71 (15.6)	59.6 (22.9)	60.4 (18)	<0.001
Male gender (%)	88 (44.5%)	25 (38.5%)	20 (48.8%)	14 (63.6%)	13 (46.4%)	7 (36.8%)	1 (14.3%)	8 (50%)	0.2
Average weight, kg (SD)	66 (15.1)	60.7 (14)	70.4 (12.4)	79.3 (18.6)	67.4 (15)	61.5 (13.5)	78.3 (23.4)	61.8 (10)	0.006
Average serum sodium concentration, mEq l^{-1} (SD)	125.9 (5.9)	124.8 (5.1)	125.2 (5.1)	124.2 (8.6)	130 (3.1)	124.3 (7.2)	124.3 (7.7)	129.7 (2.9)	<0.001
Average urine sodium concentration, mEq l^{-1} (SD)	79.4 (37.5)	73.9 (32.5)	79.6 (37.5)	69.5 (37.9)	99.1 (43.4)	82.2 (40.1)	88.4 (46.7)	73.4 (29.7)	0.11
Average urine osmolality, mOsm kg^{-1} (SD)	416.4 (173.7)	387.5 (156.9)	381.1 (169.6)	397.3 (187.1)	482.6 (166.5)	457 (180)	515.6 (227.9)	445.2 (181.2)	0.1
Average urea concentration, mg dl^{-1} (SD)	26.9 (8.6)	28.6 (7.1)	23.6 (9)	27.6 (9.7)	28.6 (7.3)	27.9 (8.7)	22.4 (6.9)	25.7 (11.5)	0.07
Average UA concentration, mg dl^{-1} (SD)	3.3 (1.2)	3.4 (1.2)	3.3 (1.4)	3.5 (1.2)	3.3 (1.3)	3.2 (1.3)	2.2 (0.4)	2.8 (0.8)	0.44
Hypertonic saline usage (%)	21 (10.6%)	9 (13.8%)	3 (7.3%)	3 (13.6%)	1 (3.6%)	3 (15.8%)	1 (14.3%)	1 (6.2%)	0.56
Average Naranjo score (SD)	5.6 (1.8)	5.8 (1.9)	5.7 (1.75)	5.6 (1.1)	6.4 (1.6)	5.7 (2.4)	6 (0)	3 (0)	<0.001
Medication-associated SIADH (%)	146 (73.7%)	50 (76.9%)	32 (78%)	19 (86.4%)	26 (92.9%)	12 (63.2%)	7 (100%)	--	0.12
Average serum sodium concentration at 1–3 months, mEq l^{-1} (SD)[c]	134.1 (4.3)	134.8 (3.6)	132.7 (4.4)	132.5 (4.2)	136 (3.2)	134.8 (5.5)	135 (6)	132 (4.3)	0.01
Survival at end of follow-up	89 (44.9%)	29 (44.6%)	23 (56.1%)	11 (50%)	9 (32.1%)	8 (42.1%)	5 (71.4%)	4 (25%)	0.14

d/t, due to; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SD, standard deviation; UA, uric acid

[a]Others: three patients on vasopressin analogues, two on sulphonylureas and two with SIADH due to unidentified herbal medications

[b]Multiple: multiple possible aetiologies, clinical uncertainty regarding which aetiology caused the SIADH

[c]Data on short-term sodium concentration available for 162 (81.8%) patients

Table 3

Medications associated with SIADH, according to medication classes

Antidepressants *n* = 50	Anticonvulsants *n* = 32	Antipsychotic agents *n* = 19	Cytotoxic agents *n* = 26	Pain medications *n* = 12	Others *n* = 7
Citalopram (19)	Carbamazepine (19)	Risperidone (5)	Vincristine (10)	Duloxetine (5)	Desmopressin (3)
Escitalopram (11)	Phenytoin (6)	Haloperidol (3)	Cyclophosphamide (9)	Pregabalin (3)	Glibenclamide (2)
Amitriptyline (9)	Valproate (5)	Quetiapine (2)	Cisplatin (2)	Tramadol (3)	Herbal preparations (2)
Paroxetine (5)	Lamotrigine (1)	Chlorpromazine (2)	Ifosfamide (2)	Oxycodone (1)	
Mirtazapine (3)	Phenobarbital (1)	Fluphenazine (2)	Cytarabine (1)		
Sertraline (1)		Clotiapine (1)	Busulfan (2)		
Doxepin (1)		Zuclopenthixol (1)			
Venlafaxine (19)		Perphenazine (1)			
		Thioridazine (1)			
		Olanzapine (1)			

SIADH, syndrome of inappropriate antidiuretic hormone secretion; *n*, number of medications associated with SIADH reported for each medication class

as SIADH aetiologies. The study cohort included 198 patients who were diagnosed with SIADH and were treated with drugs reported to be associated with SIADH. Several of our findings might have implications for clinical practice. The majority of the patients in this cohort (73.7%) were diagnosed with drug-associated SIADH. Thus, when a patient diagnosed with a SIADH is treated with a medication known to be associated with this condition, it is more likely that the patient will have drug-associated SIADH than SIADH due to other causes.

A complementary finding is that 82.3% of drug-associated SIADH cases were associated with five medication classes – namely, antidepressants, anticonvulsants, antipsychotic agents, cytotoxic agents and pain medications. Thus, although numerous case reports exist tying a wide range of drugs to SIADH, in real-world practice most cases are associated by a limited, well-described and relatively small number of drugs. We are not aware of similar reports regarding this clinically frequent condition in the published literature.

The most common medication class associated with SIADH in the present cohort was antidepressants. SSRIs were the most common antidepressants reported as an SIADH etiology. These are commonly prescribed drugs, making it possible that their prevalence in our cohort simply reflected their prevalence among the general population. However, previous studies have reported the strong correlation between SSRI usage and hyponatraemia, especially among older adults, with a prevalence of up to 32% in some reports, and suggestions for clinical alternatives have been published [14, 15]. Similarly, carbamazepine was the most common anticonvulsant associated with SIADH in the present cohort, in accordance with the published literature [8]. We believe that these findings reflect the real-world nature of our cohort.

An analysis aimed at characterizing patients with drug-induced SIADH and differentiating them by clinical parameters from patients with SIADH due to other aetiologies failed to demonstrate significant differences. Other than the Naranjo score, which, predictably, was considerably higher in the first group, no other clinical parameter could assist clinicians in this differentiation. Thus, clinical judgement, supported by the Naranjo algorithm, is still the physician's main tool when approaching these patients.

A comparison between the different medication classes also failed to demonstrate clinically useful findings. Although different drugs cause SIADH through a variety of pathophysiological mechanisms [16], the severity, characteristics, treatment and prognosis of SIADH were mostly comparable between medication subgroups. Although there were statistically significant differences in regard to several clinical parameters, mostly they either reflected differences in the patient populations treated with different drugs (e.g. in age or weight) or were too small to be statistically significant (e.g. serum sodium concentration). Thus, it can be said that drug-induced SIADH is probably a homogeneous clinical entity, regardless of the culprit medication.

Patients with multiple possible aetiologies of SIADH had similar clinical characteristics to the rest of the study cohort. This finding has some clinical significance. It is not uncommon for physicians to prefer not to prescribe a drug known to be associated with SIADH when a patient already takes a medication which might cause a similar side effect, owing to concerns of severe hyponatraemia. Our findings do not support this practice. It is possible that patients who take several SIADH-associated drugs have a higher prevalence of hyponatraemia, but of unchanged severity. This probably reflects no synergy in SIADH causation between different drugs: each either causes SIADH or it does not. This observation should be validated in a prospective study.

The overall survival of patients with drug-induced SIADH was considerably better than for those with SIADH due to other aetiologies. However, this difference was probably due to patient comorbidities, as demonstrated by the poor survival rate of cancer patients. Similarly, survival differences between patients with drug-associated SIADH according to medication classes are probably attributable to

the differences in patient populations, rather than differences in drugs, as SIADH characteristics were mostly comparable. Patients with multiple potential SIADH aetiologies had poor survival, possibly due to more comorbidities in this group. Age and short-term hyponatraemia have also been demonstrated to predict survival in this cohort. Both have been previously reported as prognostic factors in this patient population, thus further bolstering our data validity [5].

Our study had several limitations. As this was a single-centre study from a large tertiary hospital, the study population might have overrepresented patients with multiple comorbidities and complicated medical conditions. Furthermore, only patients whose urine was analysed for sodium concentration and osmolality could be diagnosed with SIADH, making it likely that severe or chronic cases of hyponatraemia were overrepresented in our cohort. As serum osmolality is not routinely performed in our hospital, patients with possible pseudohyponatraemia (hyperglycaemia, paraproteinaemia and hypertriglyceridaemia) were excluded, but we could not verify that all of the patients included in the study fulfilled the SIADH diagnostic criterion of low serum osmolality. Likewise, hypoadrenalism was not formally excluded for all patients. An additional limitation was that SIADH aetiology and several exclusion criteria were subjective and based on the chart reviews. Therefore, although at least two physicians reviewed every file, it is possible that some of the included patients should have been excluded (e.g. due to inappropriate volume status documentation). In addition, SIADH aetiology might have been misinterpreted in some patients; however, the Naranjo algorithm strongly supported the clinical decisions regarding SIADH aetiology. Another potential limitation was the lack of analysis with regard to specific drugs due to the diverse representation of specific drugs reported in the present cohort. However, as SIADH characteristics were similar between different medication classes, it is reasonable to assume that no major differences would have been demonstrated. Several drugs, most notably duloxetine and pregabalin, could potentially be classified in more than one category; however, data analysis using different categories for these drugs showed similar results.

In conclusion, we report on the real-world distribution of different medications as aetiologies for drug-induced SIADH. Most cases are associated with five major drug classes. Most patients with SIADH treated with a medication which belongs to these classes will be diagnosed with drug-associated SIADH. The Naranjo algorithm successfully differentiates between drug-induced SIADH and SIADH due to other aetiologies in patients treated with these medications. The clinical characteristics of drug-induced SIADH are comparable between different medication classes. We are unaware of similar reports in the literature. We believe that these findings might be of interest to health professionals caring for patients with drug-associated SIADH.

Competing Interests

There are no competing interests to declare.

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