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REVIEW

Vaptans for the Management of Hyponatremia in Neurocritical Care: a Systematic Review

Adam Bisiani[1] · Jessica M. Redmond[1] · Adam M. Deane[1,2] · Mark P. Plummer[1,2]

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Abstract

Hyponatremia occurs frequently following acute neurological insults and is associated with adverse outcomes. Vasopressin receptor antagonists—'vaptans'—are a recognized treatment for hyponatremia in other settings. We aimed to review the efficacy and safety of vaptans in a neurointensive care population. MEDLINE, Embase and Cochrane Library were searched from inception to July 2020. Eligible studies met the following criteria: (a) randomized controlled trials, non-randomized controlled trials, observational studies, case series and case reports; (b) adult patients (aged ≥ 18 years); (c) exposure to an acute neurological insult; (d) exposure to hyponatremia; and (e) outcome measure of sodium homeostasis. Our search retrieved 1,610 citations with 18 articles assessed for inclusion. After full text extraction, 13 studies inclusive of 272 patients met the eligibility criteria. There were four case reports, seven case series and two randomized controlled trials. Eight articles reported on intravenous conivaptan at doses ranging from 10 to 40 mg, four reported on oral tolvaptan at doses ranging from 7.5 to 15 mg and one study compared intravenous conivaptan with oral tolvaptan. All studies reported an increase in plasma sodium between 6 and 24 h after vaptan administration. Adverse events occurred frequently; 18 patients (6.8%) had an excessively rapid correction in plasma sodium, and 59 patients (22%) developed hypotension or a decrease in mean arterial pressure by > 20%. Observational data suggest vaptans effectively raise plasma sodium in the setting of acute neurological insults. However, the utility of vaptans may be limited by their side effect profile.

Keywords Vaptan · Vasopressin receptor antagonist · Neurocritical care · Hyponatremia

Introduction

Hyponatremia, defined as a serum sodium concentration below 135 mmol/L [1], is the most common electrolyte abnormality in hospitalized patients [1–3]. The incidence of hyponatremia is even greater in patients with neurological injury, complicating over a third of admissions to neurocritical care [4–6]. Hyponatremia in this population is strongly associated with morbidity and mortality [3, 7].

The clinical manifestations of acute symptomatic hyponatremia are attributable to cerebral oedema and include nausea, vomiting, headache and altered conscious state, which can progress to seizures, brain stem herniation and death [1, 7]. Overall hyponatremia-induced encephalopathy is associated with a mortality rate of 34% [8]. However, interventions to treat hyponatremia also present a significant neurologic risk, as rapid correction can lead to osmotic demyelination and irreversible brain injury [7, 8]. Accordingly, correction should be slow and not exceed 12 mmol/L in 24 h (or 0.5 mmol/L per hour) [4, 7].

The neurological pathologies most frequently associated with hyponatremia are subarachnoid haemorrhage (SAH), stroke, traumatic brain injury (TBI), pituitary surgery and brain tumours [1, 5]. These pathologies can result in release of antidiuretic hormone from the injured brain, resulting in hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [3–5]. Drug-induced SIADH secondary to frequently prescribed medications including anti-epileptics and amiodarone can

Adam Bisiani and Jessica M. Redmond contributed equally to this work

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✉ Mark P. Plummer
mark.plummer@mh.org.au

[1] Department of Intensive Care, Royal Melbourne Hospital, Melbourne, Australia

[2] Department of Critical Care, University of Melbourne, Melbourne, Australia

further exacerbate the underlying biochemical derangement [5, 8–11].

First-line treatment for hyponatremia outside of neurocritical care is fluid restriction [7]. Fluid restriction in patients with subarachnoid haemorrhage is contraindicated as it exacerbates vasospasm [12] and is controversial in all neurologically injured patients who may have impaired cerebral autoregulation and are at risk of cerebral ischemia [4, 9]. Accordingly, first-line treatment of acute hyponatremia in neurologically injured patients is hypertonic saline. This is not without risk and requires close monitoring to prevent sequelae related to rapid overcorrection of sodium and also risks tissue necrosis from extravasation [7, 13].

Vasopressin/antidiuretic hormone receptor antagonists, or 'vaptans', are a recognized pharmacological intervention for ambulant patients with SIADH, allowing excretion of free water and retention of sodium [7, 14]. Commercially available vaptans are oral tolvaptan, mozavaptan, satavaptan and lixivaptan and intravenous conivaptan [14–16]. While these agents have been widely adopted in ward-based and outpatient management, formal recommendations on their use during neurocritical illness are lacking. Accordingly, we aimed to systematically review all currently available reports on the safety and efficacy of vaptans for the management of hyponatremia in neurocritical care.

Methods

Study Design

We conducted a systematically structured scoping review using the guidelines from the Cochrane Collaboration and Centre for Reviews and Dissemination and reported the results according to the PRISMA guideline and its extension for scoping reviews [17]. Methods and inclusion criteria were specified and documented in advance.

Inclusion and Exclusion Criteria

Eligible studies met the following criteria: (a) randomized controlled trials, non-randomized controlled trials (case control or controlled cohort), observational studies, case series and case reports; (b) study population of adult patients (aged $\geq$ 18 years); (c) exposure to an acute neurological insult including traumatic brain injury, ischemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, post-neurosurgical procedure or admission to a neurointensive care unit; (d) exposure to hyponatremia; and (e) outcome measure of sodium homeostasis reported following the administration of a vasopressor receptor antagonist—'vaptan'. We included only studies reported in English. No data or publication status restrictions were imposed.

Data Sources and Search Strategy

A librarian and two reviewers (AB and JR) searched MEDLINE (Ovid), Embase (Ovid) and Cochrane Library databases from their inception to July 2020. Searches included synonyms and combinations of the following terms: 'subarachnoid hemorrhage', 'traumatic brain injury', 'stroke', 'neurological disorder', 'neurosurgery', 'neurointensive care', 'cerebral salt wasting' and 'vaptans'. Terms were truncated in order to capture variable terminology. The full search strategies are provided in Additional File 1. We applied no language restrictions during the searches. We also reviewed reference lists of retrieved papers to identify studies not captured in the primary search.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts of all identified studies. Relevant studies were independently evaluated in full text for eligibility. Disagreements were resolved by consensus or by consultation with a third reviewer. Two reviewers independently extracted data from included studies using a standardized data collection form. Extracted information included study characteristics (author, publication year, design, sample size), participant characteristics, vaptan regimen, primary and secondary outcomes and adverse events. The supplementary files of all included studies were also examined for the purposes of data extraction. A meta-analysis of randomized, placebo-controlled, clinical trials of vaptan therapy was planned if the search yielded > 2 studies.

Results

Our search retrieved 1,610 citations with 18 full-text articles assessed for inclusion. After full-text extraction, 13 studies inclusive of 272 patients met the eligibility criteria (Fig. 1). The characteristics of the included studies are summarized in Table 1. Of the 13 included articles, there were four case reports [18–21], seven case series [22–28] and two randomized controlled trials [29, 30]. Eight articles reported on intravenous conivaptan at doses ranging from 10 to 40 mg [18, 21, 23, 26–30], four reported on oral tolvaptan at doses ranging from 7.5 to 15 mg [19, 20, 24, 25] and one study compared intravenous conivaptan and oral tolvaptan [22]. The studies failed to meet the pre-defined threshold for meta-analysis.

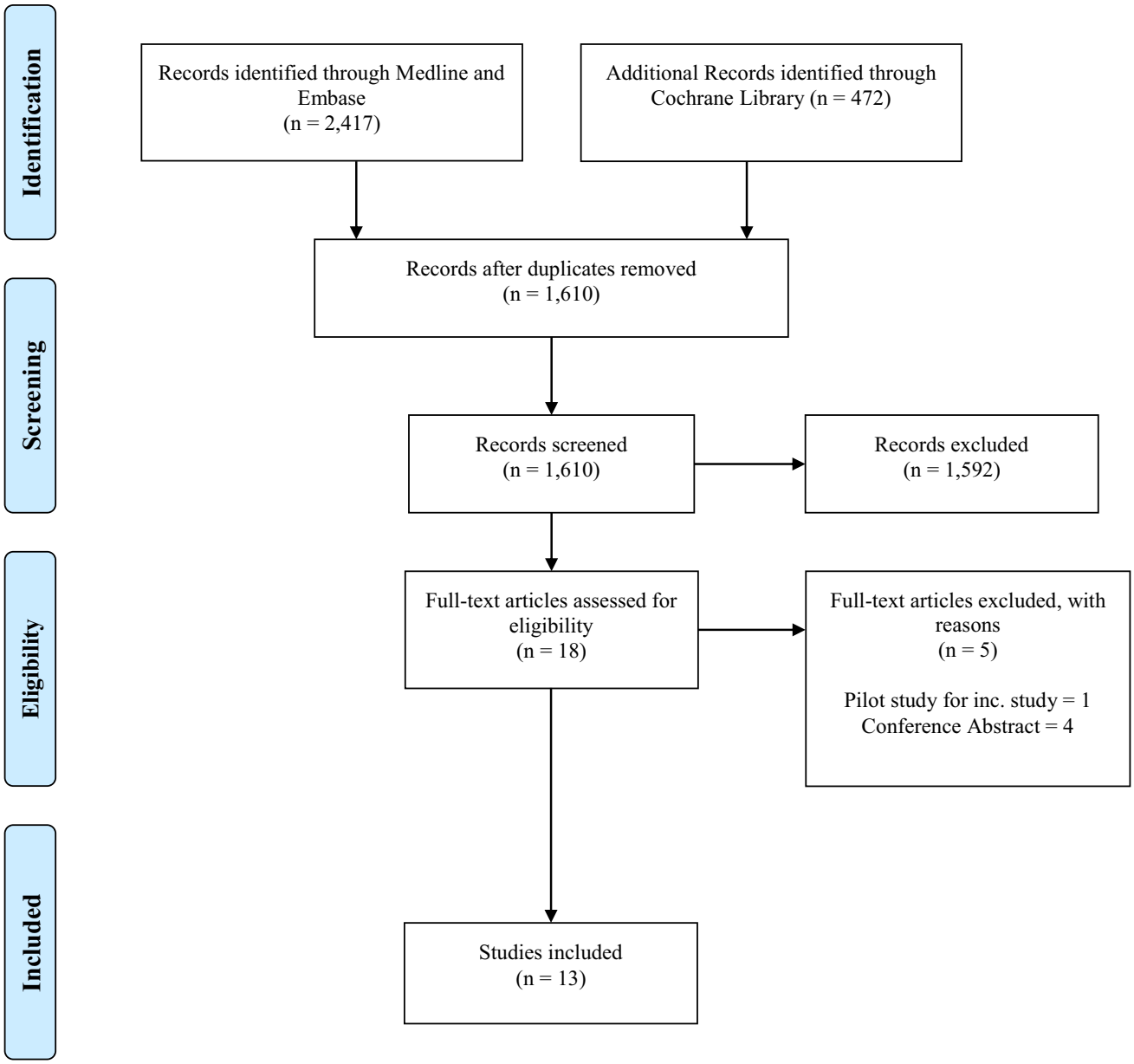

Fig. 1 PRISMA flow diagram

Case Reports

There were three case reports of vaptan use for correction of hyponatremia in patients with traumatic brain injury and one case report in a patient with an intracerebral malignancy. All cases reported an increase in serum sodium ranging from 12 to 18 mmol/L when measured between 8 and 24 h [18–21]. In three of the cases, the rate of sodium correction exceeded recommended guidelines of 0.5 mmol/L per hour [18, 20, 21].

Case Series

There were seven case series of vaptan use to treat hyponatremia in mixed neurointensive care populations, totalling 216 patients [23–28]. All case series reported an increase in plasma sodium at 12, 24 or 48 h [23–28]. Five case series reported fluid balance as a secondary outcome; two reported no change in fluid balance post vaptan administration [24, 27] and three reported a negative fluid balance, post tolvaptan [22, 25] and conivaptan [22, 26]. The largest case series

Table 1 Characteristics of included studies

Author (year)	Design	Population (*n*)	Regimen	Primary outcome	Results	Secondary outcomes	Adverse events
Dhar et al. (2010) [18]	Case report	TBI (1)	Conivaptan: IV 20 mg bolus	△ Na at 8 h	↑ 18 mEq/L (128 → 146)	↑urine output (1L/h), ↓ ICP	Nil
Graziani et al. (2011) [19]	Case report	TBI (1)	Tolvaptan: PO 15 mg	△Na at 24 h	↑ 12 mmol/L (124- > 136)	↓ oedema on CT	Nil
Onuigbi et al. (2017) [20]	Case report	TBI (1)	Tolvaptan: PO 15 mg	△ Na	↑ 18 mEq/dL (121 → 139) in 18 h	Urine output: 6325 mL/24 h	Rapid correction of Na
Sughrue et al. (2010) [21]	Case report	Brain tumour (1)	Conivaptan: IV 20 mg bolus + 20 mg over 24 h	△ Na	↑ 16 mmol/L (121 → 137) in 8.5 h	Nil	Rapid correction of Na
Der-Nigoghossian et al. (2017) [22]	Case series	NeuroICU (36)	Conivaptan: 20 mg IV ± 20 mg/24 h (*n* = 5) Tolvaptan: PO 15 mg ± 15–30 mg OD for 1–2 days (*n* = 31)	△ Na at 24 h	Conivaptan: 5.2 (4.3) mEq/L Tolvaptan: 7.9 (5.5 mEq/L)	Conivaptan -△ fluid balance 303 (893) ml Tolvaptatn -△ fluid balance 1129 (1360) ml	Rapid correction of Na (17%) Hypotension (47%)
Human et al. (2012) [23]	Case series	NeuroICU (124)	Conivaptan: IV 10, 20 or 40 mg bolus	△Na at 12 h	↑ 4 [2–7 mEq/L	Daily urine output ↑ 2600 [1810–3470] mEq/L	Rapid correction of Na (4%) Drop in MAP > 20% from baseline (29%)
Jeon et al. (2012) [24]	Case series	NeuroICU (17)	Tolvaptan: PO 15 mg ± repeat dose at 24 h	△ Na at 24 h △ Na at 48 h	Single: ↑ 5.7 (2.1) mEq/L Double: ↑ 5.3 (5) mEq/L Single: ↑ 7.4 (2.2) mEq/L Double: ↑ 9.9 (5.5) mEq/L	No change in net fluid balance, GCS, ICP or CPP	Rapid correction of Na (12%)
Llompart-Pou et al. (2017) [25]	Case series	NeuroICU (8)	Tolvaptan: PO 7.5 mg or 15 mg	△ Na at 24 h	↑ 5 (4–8) mEq/L	-△ Fluid balance 1600 [500, 3000)]ml	Rapid correction of Na (13%)
Marik et al. (2013) [26]	Case series	NeuroICU (32)	Conivaptan: IV 20 mg bolus	△ Na at 24 h	↑ 4.3 (2.6) mEq/L	-△ Fluid balance 783 (440) mL	Nil
Potts et al. (2011) [27]	Case series	NeuroICU (13)	Conivaptan: IV 20–30 mg daily for 1–4 days	△ Na at 12 h △ Na at 24 h	↑ 7.5 (5.1) mEq/L ↑ 6.8 (6.7) mEq/L	No change in fluid balance	Hypotension (23%)
Wright et al. (2009) [28]	Case series	NeuroICU (22)	Conivaptan: IV 20–40 mg/day for 1–5 days	Na rise ≥ 6 mEq/L	19 patients (86%) achieved goal rise	Nil	Peripheral infusion site reaction (31%) Hypotension (5%)

Table 1 (continued)

Author (year)	Design	Population (*n*)	Regimen	Primary outcome	Results	Secondary outcomes	Adverse events
Galton et al. (2011) [29]	Open-label RCT	Normonatremic TBI (10)	Conivaptan: 20 mg IV bolus vs usual care	Safety	Rapid correction of Na: 2 in intervention vs 1 in control	Δ Na at 24 h: No difference Δ ICP at 4 h (−8 (7.7) vs +2.5 (4.4) mmHg, $P<0.05$) ↑ urine output at 24 h (3959 (505) vs 2174 (717) mL, $P<0.01$)	Nil other
Naidech et al. (2011) [30]	Open-label RCT	NeuroICU (6)	Conivaptan: IV 20 mg bolus + 20 mg/24 h vs usual care	Δ Na at 6, 12, 18, 24, 36, and 48 h	Δ Na was greater at 6 h with conivaptan (7.0 ± 1.7 vs −0.6 ± 2.1 mmol/L, $P<0.01$)	No change in GCS	Hypotension in conivaptan arm (66%)

CPP cerebral perfusion pressure, *CT* computed tomography, *GCS* Glasgow Coma Score, *ICP* intracranial pressure, *IV* intravenous, *Na* sodium, *PO* per oral, *TBI* traumatic brain injury

Data are mean (SD) or median (IQR)

by Human and colleagues of 124 neuroICU patients reported a three-fold increase in urine output following a bolus dose of conivaptan, but did not report overall fluid balance [23]. Rapid correction of sodium was reported in four case series [22–25], with a reported incidence of 4–17%, and overall occurred in 14 patients (6.5%). Hypotension was reported in three series of conivaptan use [22, 27, 28] with incidence between 23 and 47%, and overall was reported in 21 patients (9.7%). The incidence of hypotension was not reported in the case series by Human et al.; however, 36/124 patients (29%) had > 20% decrease in mean arterial pressure following conivaptan [23]. In a case series of intravenous conivaptan administration, five of 16 patients receiving conivaptan through a peripheral cannula developed an infusion site reaction (31%) [28].

Randomized Controlled Trials

There have been two open-label randomized controlled trials comparing intravenous conivaptan with usual care in patients with acute neurological insults [29, 30]. In a single-centre feasibility study, Galton and colleagues randomized 10 normonatremic adult patients with severe traumatic brain injury to 20 mg of intravenous conivaptan or usual care (five in each arm) [29]. The primary endpoint was drug safety determined by the number of events of rapid sodium correction as well as 'drug-related adverse events'. Two patients in the intervention arm and one patient in the control arm reached the pre-defined threshold for rapid sodium correction (> 1 mEq/L in 4 h) [29]. There were no other serious adverse events. Conivaptan was associated with an increase in sodium at 4 h (ΔNa 3.4 ± 1.9 mmol/L vs. − 0.4 ± 1.9 mmol/L, $P<0.02$) and a fall in intracranial pressure (ΔICP − 8.0 ± 7.7 mmHg vs. 2.4 ± 4.4 mmHg, $P<0.05$). These differences did not persist at 24 h. Conivaptan doubled the daily urine output (3959 ± 594 ml vs. 2174 ± 717 ml, $P<0.01$).

In a separate single-centre trial, Naidech and colleagues aimed to randomize twenty hyponatremic neurocritical care patients to conivaptan or usual care [30]. Recruitment was slow, and the study was ceased after enrolling six patients (3 in each arm). Within the limitations of the small sample size, conivaptan was associated with an increase in sodium at 6 h but not at 12, 18, 24 or 48 h. Two patients in the conivaptan arm developed hypotension [30].

Discussion

We conducted a systematic review to evaluate the safety and efficacy of vasopressin receptor antagonists for the management of hyponatremia in neurocritical care. We identified four relevant case reports, seven case series and

two small randomized controlled trials, including 264 patients with acute neurological insults who had received vaptan treatment. We identified that only 16 patients had been randomized to vaptan use or not in a neurointensive care setting. Of the two open-label randomized controlled trials, Galton and colleagues [29] recruited patients with normal plasma sodium levels, and Naidech and colleagues [30] failed to recruit more than half the required sample size.

Tolvaptan is a vasopressin V2 receptor antagonist, and conivaptan is a combined vasopressin V1a and V2 receptor antagonist [15, 31]. The V1a receptor is a G-coupled receptor that activates phospholipase C to increase free calcium and is located in vascular smooth muscle, platelets, hepatocytes and myometrium [14, 31]. Conivaptan antagonism of the V1a receptor on vascular smooth muscle attenuates calcium entry into the cell, decreasing vasoconstriction and total peripheral resistance and thereby effecting hypotension [15, 31]. The V2 receptor is found in the basolateral membrane of the renal collecting tubule and in response to antidiuretic hormone agonism leads to the insertion of aquaporin 2 water channels into the luminal membrane causing renal water retention [14]. Antagonism of the V2 receptor conversely results in aquaresis or excretion of water without electrolytes [31]. Accordingly, by removing excess water rather than just increasing salt stores, there is face validity that vaptans may be an attractive alternative to traditional treatment regimens for SIADH in a neurointensive care population.

Consistent with this known mechanism of action, this review demonstrates that vaptans raised plasma sodium and induced aquaresis. The most robust data comes from the case series by Human et al. whereby 124 patients were treated with conivaptan with a median (IQR) baseline sodium of 132 (129–133) mEq/L and had a median rise in sodium of 4 (2–7) mEq/L over 6–12 h [23]. In this study, the degree of aquaresis after conivaptan was strongly associated with the natremic response; in regression analysis, plasma sodium rose by 2 mmol/L for every litre of urine output [23]. This review has highlighted that serious adverse events occurred frequently; 18/264 patients (6.8%) had an excessively rapid correction in plasma sodium, 59/264 patients (22%) developed hypotension or a decrease in baseline mean arterial pressure by > 20% and, in the only study specifying peripheral administration of intravenous conivaptan, 5/16 patients (31%) developed an infusion site reaction. No patients developed central pontine demyelinosis. Large volume diuresis and hypotension are particularly harmful in the neurointensive care setting whereby intravascular volume depletion is known to exacerbate vasospasm in subarachnoid haemorrhage [12], and hypotension can precipitate cerebral ischaemia in patients with impaired cerebral autoregulation or elevated intracranial pressure [4, 9].

Implications

Our review has demonstrated that there is a lack of robust data on the efficacy of vasopressin receptor antagonists for the management of hyponatremia in a neurointensive care setting. Moreover, we have demonstrated an alarming frequency of adverse effects suggesting that any blinded trial comparing vaptans with hypertonic saline for the management of hyponatremia in a neurointensive care population would require careful oversight. It should be noted that the use of vaptans is contraindicated in hypovolemic hyponatremia and severe hyponatremia (serum sodium < 120 mmol/L) and any trial should be restricted to a nonhypovolemic hyponatremic population [32]. Given our findings, the off-label use of vaptans in a neurocritical care setting outside of a clinical trial is not recommended. This is consistent with earlier clinical practice guidelines which recommended against vasopressin receptor antagonists in profound hyponatremia as a level 1C GRADE recommendation, i.e. a strong recommendation based on low quality evidence [33].

Strengths and Limitations

To our knowledge, this is the first systematic review of the efficacy and safety of vasopressin receptor antagonists/vaptans for the management of hyponatremia in the setting of acute neurological insults. To increase the breadth of the review, we included case series and case reports, acknowledging that these yield a lower quality of evidence. Due to only 16 patients being randomized to a vaptan or control (usual care), we were unable to conduct a meta-analysis. Finally, we only included studies in the English language; however, there is no evidence of a systematic bias when non-English papers are excluded [34].

Conclusions

Limited observational data suggests that vasopressin receptor antagonists, so-called ‘vaptans’, can raise plasma sodium in the setting of hyponatremia following acute neurological insults. Their clinical utility however may be limited by their side effect profile, with relatively high rates of hypotension and overly rapid sodium correction. The use of vaptans outside of a clinical trial is not recommended.

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Author Contribution AB, JR, AD and MP were all involved with study conception and design, analysis and interpretation of data, drafting the article and revising the manuscript and approving the final manuscript for submission.

Data Availability All data and search terms are provided.

Code Availability Not applicable.

Declarations

Ethics Approval Ethics approval was not required.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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