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The management of acute and chronic hyponatraemia

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***Abstract*:** Hyponatraemia is the most common electrolyte abnormality encountered in clinical practice; despite this, the work-up and management of hyponatraemia remain suboptimal and varies among different specialist groups. The majority of data comparing hyponatraemia treatments have been observational, up until recently. The past two years have seen the publication of several randomised control trials investigating hyponatraemia treatments, both for chronic and acute hyponatraemia. In this article, we aim to provide a background to the physiology, cause and impact of hyponatraemia and summarise the most recent data on treatments for acute and chronic hyponatraemia, highlighting their efficacy, tolerability and adverse effects.

Keywords: acute hyponatraemia, chronic hyponatraemia, syndrome of inappropriate diuresis (SIAD), vasopressin, fluid restriction, hypertonic saline, Tolvaptan

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Introduction

Hyponatraemia, defined as a plasma sodium concentration (pNa) < 135 mmol/L, is most common electrolyte abnormality in clinical practice.[1] Hyponatraemia poses diagnostic and therapeutic challenges,[2] as it is usually a pathophysiological consequence of an underlying medical condition which has led to disturbed water homeostasis.[2] Hyponatraemia can manifest with a wide range of subtle clinical symptoms. Mild chronic hyponatraemia may be asymptomatic, though nausea, malaise, headache, lethargy, muscle cramps, disorientation and restlessness may all occur. Evidence has emerged in recent years to indicate that even apparent mild hyponatraemia is associated with gait abnormalities and cognitive deficits, which lead to increased frequency of falls and consequent bone fractures.[3] In contrast, more severe hyponatraemia, with pNa < 120 mmol/L, can present with seizures, coma and cardiorespiratory arrest, particularly if the onset of hyponatraemia is rapid; acute hyponatraemia often requires emergency assessment and treatment as a consequence.[4]

Hyponatraemia has been shown to be associated with increased mortality in almost every published series in the literature spanning a diverse range of medical conditions.[5] Recent data have demonstrated that mortality rates are cause-specific. In a prospective cohort study evaluating mortality in hyponatraemia stratified by volume status, Cuesta *et al.* have demonstrated higher mortality rates for hypervolaemic and hypovolaemic hyponatraemia, compared with syndrome of inappropriate antidiuresis (SIAD), although mortality rates in SIAD remained higher than eunatraemic controls.[6] Further analysis found that mortality associated with SIAD is age-dependent, with increased risk of in-hospital death reported in patients aged < 65 years with SIAD, but not in older patients with SIAD.[7] A recent population-based cohort study from Switzerland has also demonstrated an increased risk of in-hospital mortality, as well as 30-day hospital admission, in patients with hyponatraemia; subgroup analysis failed to demonstrate increased mortality risk in patients with SIAD, however the groups were not analysed by age.[8]

Physiology of hyponatraemia

In normal physiology, plasma sodium concentration is maintained within such tight parameters that clinical conditions in which hyponatraemia occur represent major abnormalities in the physiology of water balance. This tight homeostasis is achieved through the synergistic actions of

Table 1. Classification of hyponatraemia based on volume status and urinary sodium concentration.

	Clinical features	Urine sodium < 30 mmol/L[a]	Urine sodium > 30 mmol/L[a]
Hypovolaemic	Dry mucus membranes, Decreased skin turgor, Tachycardia, Hypotension (in particular, orthostatic), Low CVP, Raised blood urea	Vomiting Diarrhoea Burns Acute pancreatitis	Diuretics Addison's disease Salt losing nephropathy Cerebral salt wasting
Euvolaemic	Normal pulse and blood pressure	SIAD with fluid restriction	SIAD ACTH deficiency Hypothyroidism
Hypervolaemic	Peripheral oedema, raised JVP, ascites, pulmonary oedema	Inappropriate intravenous fluids Cardiac Failure Cirrhosis	Renal Failure

ACTH, adrenocorticotropic hormone; CVP, central venous pressure; JVP, jugular venous pressure; SIAD, syndrome of inappropriate antidiuresis.
[a]Patients with SIAD and very low oral sodium intake can present with UNa < 30 mmol/L.

the secretion and antidiuretic effect of vasopressin (AVP) and the activation of the thirst mechanism, resulting in day-to-day variations of plasma osmolality (determined by pNa) of less than 2%.[9]

Changes in plasma osmolality are sensed by osmoreceptor cells in the organum vasculosum lamina terminalis (OVLT) and subfornical organ of the anterior hypothalamus. This initiates neural signals to the supraoptic nuclei (SON) and paraventricular nuclei (PVN), which depolarize, stimulating the synthesis and secretion of AVP.[10] AVP is synthesised along with copeptin and neurophysin II, as a preprohormone, which is then cleaved into the three component parts during transport down the axons of the magnocellular neurons to the neurohypophysis, from where AVP is released into the systemic circulation. AVP binds to the V2 receptor in the collecting duct of the kidney, generating new aquaporin-2 (AQ2) and stimulating the insertion of preformed AQ2 into the luminal membrane of the collecting tubules. This action culminates in a reduction of free water clearance and concentration of urine. Increases in plasma osmolality also simultaneously stimulate the thirst centre in the cerebral cortex. The resulting increased fluid intake, combined with actions of AVP, lead to increased plasma water and normalisation of plasma osmolality.

Cause of hyponatraemia

Hyponatraemia should be initially classified by extracellular volume status into hypovolaemic, euvolaemic and hypervolaemic hyponatraemia[11] (Table 1). This is a clinical approach, based on signs which are not completely sensitive or specific, and some acumen is required for accurate classification. A clinical diagnosis of hypovolaemia can be made on the basis of orthostatic hypotension, tachycardia, dry mucous membranes and decreased skin turgor, together with laboratory clues such as raised urea to creatinine ratio, elevated uric acid concentration and urinary sodium concentration < 20 mmol/L. A definitive diagnosis is not always possible at the time of presentation – for instance the distinction between euvolaemia and mild hypovolaemia is sometimes difficult to make on clinical grounds [12] and in this scenario the US guidelines recommend a therapeutic trial of isotonic saline with close monitoring of pNa response.[13] Despite it's limitations, categorising patients according to ECF volume status and urine electrolyte excretion does allow the initiation of cause-specific investigations and treatment. This approach to classification also has implications for prognosis, as there is good evidence from recent data that outcomes vary according to volume status, with significantly higher mortality rates in hypervolaemic and hypovolaemic hyponatraemia, compared with SIAD.[6]

It is important to exclude pseudohyponatraemia which occurs if the blood sample is lipemic or has a high concentration of immunoglobulins such as in patients with myeloma; the problem is largely seen where flame photometry is used for the

measurement of electrolytes and is not seen with ion selective electrode measurements. In addition, hyperglycaemia lowers plasma sodium concentration, which needs no action other than lowering of blood glucose concentration. A discrepancy between measured serum osmolality and calculated osmolality raises the possibility of pseudohyponatraemia.[14]

SIAD

SIAD is a clinical and biochemical syndrome characterised by inappropriate urinary concentration and reduced free water excretion, in the setting of euvolaemic hyponatraemia.[9,15] Schwartz & Bartter in 1957 reported the first cases of SIAD in two patients with small-cell lung cancer and proposed the diagnostic criteria for the condition (Table 2). Although the vast majority of cases of SIAD are caused by inappropriately increased plasma AVP concentrations, a small minority of cases of SIAD result from a nephrogenic syndrome of inappropriate antidiuresis which occur due to gain of function mutations in the V2 vasopressin receptor located in the distal tubules and collecting ducts of the kidney.[15]

SIAD has been reported in a wide variety of medical conditions, including central nervous system (CNS) disorders, pulmonary disorders and malignancies. Medications account for 8–27% of cases of SIAD in hospital inpatients,[16] and an even greater proportion in elderly cohorts. Commonly implicated drugs include selective serotonin reuptake inhibitors, phenothiazine antipsychotics, carbamazepine, sodium valproate, chemotherapeutic agents particularly vincristine and cyclophosphamide, opioid analgesics and nonsteroidal anti-inflammatory agents.

Ascertainment of the key diagnostic parameters for SIAD in routine clinical practice has invariably been poor. The international hyponatraemia registry confirmed only 47% of physician diagnosed SIAD had appropriately confirmed the diagnosis with plasma and urine osmolality and urine sodium measurements, and only 27% had excluded adrenal insufficiency and/or thyroid disease.[17] The failure to make a correct diagnosis can potentially negatively impact patient outcomes.

A key differential in the diagnosis of SIAD is ACTH deficiency, as it presents with a similar biochemical picture. Mechanisms accounting for the development of hyponatraemia in adrenal insufficiency include elevated vasopressin even in the presence of plasma hypo-osmolality and impaired renal water handling in the absence of circulating free cortisol.[18] In a recent prospective series, with full ascertainment of the minimum diagnostic criteria for SIAD in 83% of cases, Cuesta *et al.* showed that 3.8% of patients presenting with euvolaemic hyponatraemia to our institution had adrenal insufficiency. ACTH deficiency should be particularly suspected in patients who develop hyponatraemia after neurosurgical conditions or withdrawal of long-term glucocorticoid treatment.[19]

Table 2. Diagnostic criteria for SIAD.

1. Hypo-osmolality: plasma osmolality $<$ 275 mOsm/kg
2. Inappropriate urine concentration: urine osmolality $>$ 100 mOsm/kg
3. Elevated Urine Sodium (UNa) $>$ 30 mmol/L with normal salt and water intake[a]
4. Euvolaemia
5. Exclusion of glucocorticoid and thyroid hormone deficiency
6. Normal renal function and absence of diuretic use, particularly thiazide diuretics

[a]SIAD patients with very low oral sodium intake can present with UNa $<$ 30 mmol/L.

Prevalence of hyponatraemia

The prevalence of hyponatraemia in the literature varies significantly depending on the patient cohort and the biochemical cut-off used to define hyponatraemia.[13] Large population studies have reported rates of 2–8%,[20–22] with higher prevalence in females, older patients and those with co-morbidities. In a study by Miller *et al.*,[23,24] 8% of ambulatory patients over the age of 60 years attending a geriatric outpatient clinic were hyponatraemic, while 18% of a similarly-aged cohort of nursing home residents were hyponatraemic. In a more recent French study, mild hyponatraemia (pNa $<$ 136 mmol/L) was present in 15.9% of 696 patients presenting to the Emergency Geriatric Medicine Unit, with a higher prevalence rate of 26.1% in patients admitted for falls.[25]

The prevalence of hyponatraemia is even higher in hospitalised patients. A prospective cohort study of 945 hospitalised patients ($>$65 years of age) showed that 34% had a pNa $<$ 135 mmol/L;[26]

higher rates (37%) were reported in a Danish study which used a higher plasma sodium cut-off of < 137 mmol/L.[27] Hyponatraemia is commonly seen in oncology patients, particularly those with small cell lung cancer,[28] and in patients with pneumonia,[29] including COVID-19 infection,[30] congestive heart failure and liver failure.[31] Hyponatraemia occurs in 10–34% of patients in the intensive care unit (ICU), and is particularly common in neurosurgical units. The highest incidence is seen following SAH (20–56%),[32–34] followed by intracranial tumours (16%), traumatic brain injury (TBI) (10–15%) [35,36] and pituitary surgery (6–25%).[37,38] SIAD is the most common underlying pathophysiology, but acute ACTH deficiency is increasingly recognised as a cause of euvolaemic hyponatraemia in this patient group.[39] Cerebral salt wasting (CSW) is another differential diagnosis in neurosurgical patients, although it is exceedingly rare. A prospective study of 100 cases of SAH by Hannon *et al.*[32] failed to reveal a single case, even after careful clinical and biochemical assessment of volume status, and some experts challenge whether the diagnosis is a real entity. CSW can be distinguished from SIAD by the demonstration of an initial period of natriuresis and hypovolaemia preceding the onset of hyponatraemia.[40]

Impact of treatment of hyponatraemia; why should we treat it?

While acute hyponatraemia is a medical emergency which can lead to death if untreated, chronic hyponatraemia has long been thought of as a benign condition and is often left under-investigated and untreated. However, there is now emerging evidence of the positive impact of treating chronic hyponatraemia on outcomes such as cognition, gait, and quality of life. In a seminal study by Renneboog *et al.*,[41] active treatment of chronic hyponatraemia (with urea in the majority of cases) led to improvements in gait parameters and reaction times. In a follow-up study, the same group demonstrated lower baseline scores of tandem gait and attention, and greater gains when hyponatraemia was actively managed, in elderly patients compared with younger subjects with the same degree of hyponatraemia.[42] More recently, Brinkkoetter *et al.*[43] have shown that an increase of pNa of at least 5 mmol/L in patients aged > 70 years leads to improvements in cognitive scores (Mini Mental State Exam, MMSE) and scores of independence (Barthel index of Activities of Independent Living) compared with eunatraemic controls. Largest effect sizes were seen in patients with euvolaemic hyponatraemia and multivariable linear regression analysis confirmed change in pNa to be an independent predictor in MMSE improvement. It has yet to be proven in prospective studies that treatment of hyponatraemia reduces risk of falls and fractures; these studies are awaited.

A 2015 meta-analysis has reported, for the first time, that improvement in plasma sodium in hyponatraemic patients is associated with a reduction in overall mortality (OR 0.57, $p = 0.002$), which persisted at 12 months; the greatest reduction was seen in older patients and those with lowest plasma sodium at baseline.[44] While a cause-effect relationship cannot be extrapolated from the data included in this analysis, this report provided the first evidence for a potential mortality benefit from treating chronic hyponatraemia. More recent data from our group has demonstrated that increased specialist input and active management of severe hyponatraemia over a 10-year period, were associated with a fall in mortality rates, to rates comparable with moderate hyponatraemia.[45]

Treatment of hyponatraemia

General approach. There are a number of key issues which influence the implementation of optimum management of hyponatraemia. Accurate assessment of the underlying cause of hyponatraemia is essential to institute cause-specific therapy. There are causes of hyponatraemia where simply treatment of the underlying cause reverses hyponatraemia without specific treatment for the electrolyte disorder; in community-acquired pneumonia for instance, SIAD reverses to normal with antibiotic therapy and resolution of infection.[29] Equally, volume status is essential to quantify, as the treatment of hypovolaemic hyponatraemia, with intravenous saline, is very different to that of hypervolaemic hyponatraemia, for which the therapeutic intervention is diuretic therapy (Figure 1).

Awareness of the chronicity of low plasma sodium concentration is the key issue that determines the urgency of treatment and the speed of reversal of hyponatraemia. Patients with acute hyponatraemia require emergency treatment to prevent cerebral herniation and death. In contrast, patients with chronic hyponatraemia are much less likely to develop neurological symptoms as cerebral

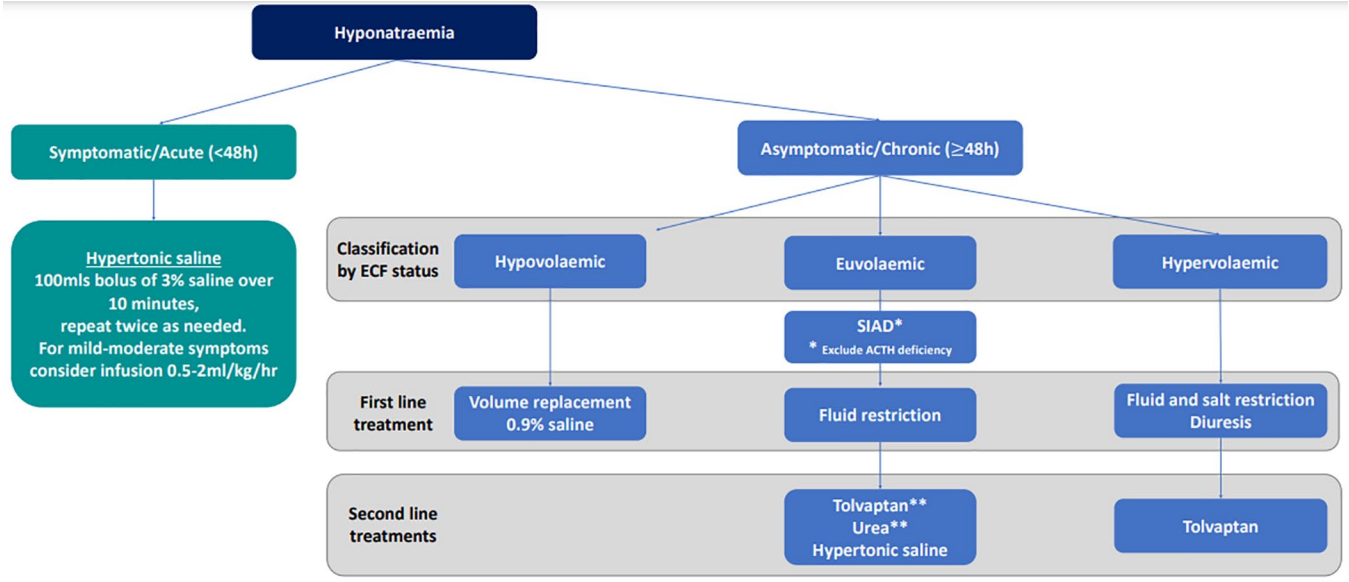

Figure 1. General approach to treatment of hyponatraemia.

adaptation protects against the development of raised intracranial pressure. In addition, patients with chronic hyponatraemia are particularly vulnerable to osmotic demyelination (ODS) if there is a rapid rise in extracellular tonicity caused by overaggressive treatment. Therefore, risk-benefit analysis favours a slow rise in pNa in this patient group. First described in 1959, osmotic demyelination syndrome occurs when correction of chronic hyponatraemia exceeds the ability of the brain to reverse compensatory mechanisms. Failure to recapture organic solutes as pNa rises results in an inverse osmotic gradient leading to dehydration of the cells and possible demyelination of white matter,[46] characterised clinically by spastic quadriparesis and pseudobulbar palsy, and in most severe cases 'locked in' syndrome.

Close monitoring of pNa is recommended during the active correction phase. Hourly urine output monitoring is very helpful, as often treatment of the underlying cause of hyponatraemia (e.g. volume replacement in hypovolaemic hyponatraemia) can lead to suppression of AVP, and a rapid aquaresis, resulting in rapid rise in pNa. Both European and American consensus guidelines recommend that plasma sodium rise in chronic hyponatraemia generally should not exceed 10 mmol/l per 24 hours, with the US guidelines specifying that the rise should ideally be restricted to <8 mmol/l.[11,13] The US guidelines also include revised targets for patients deemed to be at greater risk of osmotic demyelination, such as those with liver disease, alcohol misuse, hypokalaemia or malnutrition. In these scenarios, targets are revised downwards to a maximum recommended elevation in plasma sodium of < 6 mmol/l and should not exceed 8 mmol/L in 24 hours (Table 3).

In patients with acute hyponatraemia, when the acuity of onset is certain, the rise in pNa need not be restricted. Both guidelines now recommend 3% hypertonic saline bolus in the treatment for acute and symptomatic hyponatraemia, the goal being an initial brisk rise in pNa to reduce cerebral oedema. In chronic symptomatic hyponatraemia, the goal then quickly shifts to maintaining 24- and 48-hour correction within the safe thresholds for chronic hyponatraemia.

Reversal of overcorrection. If overcorrection is anticipated based on trend in pNa and urine output, further hyponatraemia-targeted therapy should be held and treatment instigated to prevent overcorrection. Plasma sodium concentration can be kept stable either with the administration of

Table 3. Targets for elevation in plasma sodium concentration recommended to avoid osmotic demyelination in chronic hyponatraemia.[13]

Patient	Target rise pNa/ 24 h (mmol/L)	Maximum rise pNa/ 24 h (mmol/L)
Standard patient	4–8	10–12
High risk patient (pNa < 105 mmol/L, hypokalaemia, alcoholism, advanced liver disease, malnutrition)	4–6	8

IV hypotonic fluids (enteral water or IV 5% dextrose) to match urine output or the administration of 2–4 mcg parenteral desmopressin to clamp urine output and prevent further aquaresis. If overcorrection does occur, therapeutic relowering of pNa can be considered, by administering 2–4 mcg parenteral desmopressin with bolus of 3 ml/kg hypotonic fluids, until target pNa is reached.[13] The US guidelines stipulate that this is probably only necessary if starting pNa was <120 mmol/L,[13] although the European guidelines do not make this distinction.[33] It should be emphasised that the clinical impact of therapeutic re-lowering of pNa has not been well studied, and both guidelines include the caveat that the therapeutic approaches to overcorrection of hyponatraemia are not validated in prospective randomised controlled trials.

Treatment of acute hyponatraemia

The administration of hypertonic saline is the recommended treatment of choice for acute hyponatraemia. In a major therapeutic policy change, bolus 3% hypertonic saline is now recommended to treat symptomatic acute hyponatraemia in place of continuous infusion of 3% saline.[11,13] This bolus approach was first applied in the management of exercise induced hyponatraemia.[2] The aim of this approach is to achieve a rapid early rise in pNa of 4–6 mmol/L over the initial four hours of treatment, a target derived from neurosurgical data in which an increment of 5 mmol/L reverses clinical signs of trans-tentorial herniation and reduces intracerebral pressure by nearly 50% within an hour of hypertonic saline administration in eunatraemic patients[47] This is a potentially life-saving treatment for cerebral oedema secondary to hyponatraemia, as the increased extracellular sodium concentration immediately removes water from the intracellular space.

The European guidelines recommend the administration of 150 ml of hypertonic saline over a period of 20 minutes, at which point a repeat plasma sodium measurement is taken, and another infusion of 150 ml 3% hypertonic saline commenced; this can be repeated twice or until a rise in pNa of 5 mmol/L is achieved.[11] If hyponatraemia is presenting with moderate symptoms, then a once off bolus of 150 ml hypertonic saline can be administered.[11] The US guidelines differ slightly; in symptomatically severe hyponatraemia they recommend 100 ml bolus hypertonic saline over 10 minutes to be repeated up to twice more. In patients with moderate symptoms of hyponatraemia, the US guidelines recommended a continuous slow infusion of 3% normal saline at a rate of 0.5–2 ml/kg per hour.[13] Patients should be in a monitored environment, with close supervision of neurological status, urine output and pNa.

In 2019, Garrahy *et al.*[48] compared prospectively collected clinical and biochemical outcomes in patients with symptomatic hyponatraemia secondary to SIAD treated with 100 ml boluses of 3% saline and compared them to a historical cohort treated with the traditional continuous infusion of 3% saline (20 ml/hr, rate adjusted according to response) (Figure 2). We found that bolus 3% saline resulted in a faster initial rise within the first six hours of treatment (6 mmol/L *versus* 3 mmol/L, $p < 0.0001$) with quicker restoration in GCS compared to traditional continuous infusion. Following twenty-four hours of closely observed treatment, plasma sodium concentrations were similar in both groups. Interventions to prevent overcorrection such as intravenous dextrose/dDAVP were more frequently used in the bolus group (5/22 *versus* 0/28, $p = 0.008$), particularly in those patients who received three boluses.[48] The following year, the SALSA randomised controlled clinical trial found that both weight-based rapid bolus infusion and slow continuous infusion of 3% hypertonic saline were efficacious and safe. The incidence of overcorrection, the primary endpoint of the study, was similar in both groups occurring in 17.2% in the rapid infusion group compared with 24.2% in the continuous infusion group, $p = 0.26$. However, the incidence of therapeutic re-lowering treatment was significantly lower in the rapid infusion group, 41.4% *versus* 57.1%, $p = 0.04$. A greater rise in plasma Na was achieved in the first hour of treatment in the rapid bolus infusion group, supporting the role of bolus hypertonic saline in acute life-threatening

hyponatraemia.[49] There were no cases of ODS in either study. More recently, in 2021, in an observational study by Chifi *et al.*, 28% of patients with moderate or severely symptomatic hyponatraemia treated with 150 ml boluses of hypertonic saline were given 5% dextrose/or dDAVP to re-lower plasma sodium concentration, which was successful in maintaining rise of pNa within target in less than half of cases. Patients treated with bolus hypertonic saline, however, had less fluctuations in pNa and reached correction thresholds more often than those treated with 'conventional' treatments.[50]

While the above-mentioned studies differ in design, inclusion criteria, control group and bolus dose, in general, they demonstrate that bolus hypertonic saline produces a quicker initial rise in pNa when clinically needed in acute hyponatraemia, but carries a significant risk of overcorrection. Cautious monitoring of urine output and pNa is required, along with early implementation of stalling or re-lowering measures where the duration of hyponatraemia is not known to be acute, to reduce the risk of ODS. An alternative strategy proposed by some experts to mitigate this risk of overcorrection is to administer desmopressin at the onset of treatment. This acts to clamp urinary losses of electrolyte free water, and 3% saline is then titrated according to plasma sodium response.[51] While a recent retrospective study failed to show any reduction in overcorrection with this 'pro-active' approach,[52] it may be of use in those at a particularly high risk of rapid water diuresis with overcorrection of plasma sodium, e.g. hypovolaemic hyponatraemia, thiazide induced hyponatraemia, glucocorticoid deficiency and primary polydipsia, where treatment of the underlying condition results in restoration of the kidneys ability to excrete electrolyte-free water.[11]

Treatment of chronic hyponatraemia

Treatment of chronic hyponatraemia should be directed at reversal or removal of the underlying cause. Patients with chronic hyponatraemia are much less likely to develop neurological symptoms but are at higher risk of osmotic demyelination. Therefore, risk benefit assessment favours a slower rise in plasma sodium concentration in this patient group.

Treatment of SIAD. Treatment of the underlying cause of SIAD is always the first therapeutic step, e.g. removal of offending medication or treatment of pneumonia. Key aspects of currently available treatments for SIAD are summarised in Table 4.

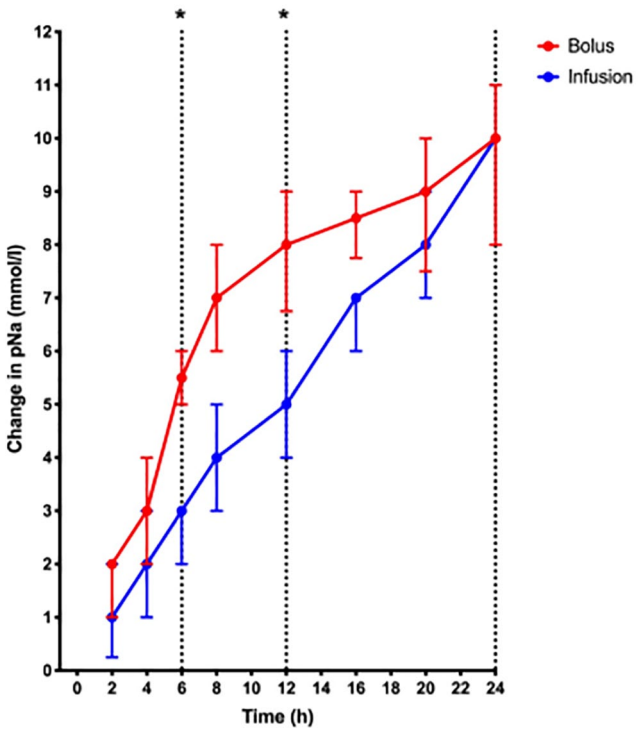

Figure 2. Change in plasma sodium concentration from baseline in patients with SIAD treated with bolus 3% saline (red) and slow infusion of 3% saline (blue).
Data expressed as median and IQR. Asterisks indicate a *p*-value of less than 0.05.
pNa; plasma sodium concentration, h; hours.
With permission, from Garrahy et al. (Garrahy, Dineen and Hannon, 2019).

Until recently, the majority of data for treatments of SIAD were observational and/or retrospective. The SALT trials published in 2006 were the first randomised controlled trials of a hyponatraemia treatment, and in the past two years there have been a further three randomised controlled trials investigating treatment options for SIAD. The results of these studies are summarised in Table 5.

Fluid restriction. Fluid restriction is the recommended first-line treatment for SIAD across all international guidelines,[11,13] and the most commonly employed treatment strategy for hyponatraemia in clinical practice.[17] Despite being the first-line treatment, observational data from the large Hyponatraemia Registry study reported that less than half of patients (44%) with SIAD treated with fluid restriction corrected their pNa by >5 mmol/L and that the majority of patients required additional treatment to reach clinical goals.[57] Several clinical and biochemical factors have been

Table 4. Comparison of treatment options for chronic SIAD.

Treatment	Dose	Advantages	Disadvantages
Fluid restriction	Aim 500 ml/day below 24 h urine output	Inexpensive Safe	Often ineffective. May be difficult to achieve. Can lead to caloric restriction. Contraindicated in SAH.
Urea	15–60 mg daily	Effective	Lack of availability. Poor palatability. Reversible renal impairment.
Demeclocycline	600–1200 mg daily in divided doses	Inexpensive	Takes 3–4 days to achieve effect. Reversible renal impairment. Rash.
Tolvaptan	15–60 mg daily, often 7.5 mg suffices	Effective	Relatively expensive. Not universally reimbursable. Requires supervision for first dose. Risk of overcorrection.

proposed as predictors of response to FR, Table 6.[13,58] In a two centre analysis of patients embarking on fluid restriction for SIAD, 40% of patients had one predictor of failure to respond to FR, and 60% had two predictors.[59] It is therefore hardly surprising that FR does not deliver the clinical impact that clinicians require.

The Furst equation ratio, calculated by dividing the sum of urinary sodium and potassium concentrations by plasma sodium, has been utilised to predict the degree of fluid restriction which is required for effective elevation of pNa.[60] In patients with a ratio greater than 1 (concentrated urine), a 500 ml fluid restriction per day is advised for correction of hyponatraemia. Clearly, this stringent target is extremely difficult to adhere, as downwards re-setting of the thirst threshold in SIAD dictates that patients continue to experience thirst despite hyponatraemia.[61] This undoubtedly impacts negatively on long-term compliance with fluid restriction.[62] Where compliance is maintained, the rigour of this degree of fluid restriction may predispose to volume depletion.[56,63] In addition, fluid restriction may not always be possible in the clinical context of adjunctive therapies; for example a patient with SIAD due to underlying neoplastic disease may not be possible to fluid restrict because of the requirements for intravenous fluids as part of chemotherapy.

Although fluid restriction has been recommended as first-line treatment for SIAD, for years there were no data on safety and efficacy. However, a recent prospective randomised controlled trial from our group compared fluid restriction with no hyponatraemia treatment, in ambulatory patients with chronic SIAD who had no reversible or transient cause. The results of this study demonstrated that patients with SIAD, who were fluid restricted to 1 L/day, had an early rise in pNa which was maintained at 30 days and significantly greater than that seen in untreated patients (3 *versus* 1 mmol/L after 3 days, $p = 0.005$). Although fluid restriction was statistically better than 'no treatment', the rise in plasma sodium concentration was modest, and less than one in five patients treated with fluid restriction had a rise in pNa of $\geqslant 5$ mmol/L after 3 days of treatment. Fewer than half of patients achieved this target after 30 days of fluid restriction. The proportion of patients achieving a pNa $\geqslant 130$ mmol/L was 61% and 71% after 3 and 30 days treatment respectively.[54] While the modest improvements in pNa and the favourable safety profile, justify the position of FR as first-line therapy, the data from this study challenge the effectiveness of the treatment in a significant proportion of patients. This highlights the need for effective and affordable second-line treatments for chronic SIAD.

The rise in plasma sodium concentration in two other recently published randomised trials was greater than that which was published in our study. In a comparison of empagliflozin *versus* FR, and a separate analysis of frusemide *versus* FR, the rise in pNa in the FR groups was 7 and 5 mmol/L after 3 days, respectively. However, neither study restricted inclusion to patients with chronic SIAD, so the higher rise in pNa in these studies may have reflected a cumulative effect of FR and the treatment and/or resolution of the underlying cause of hyponatraemia.

Table 5. Summary of recent randomised controlled trials investigating treatments for SIAD.

	N	Patient type	Treatment groups	Primary outcome	Results	Adverse events
Schrier *et al.*,[53] NEJM 2006	448	Euvolaemic or hypervolaemic hyponatraemia, pNa < 135 mmol/L	1. Tolvaptan (Tolv), starting dose 15 mg, titrated according to response 2. Placebo (P)	Change in pNa day 4 and 30	Day 4: Tolv *versus* P, 4 mmol/L *versus* 0 mmol/L, $p < 0.001$. Day 30: Tolv *versus* P, 6 mmol/L versus 2 mmol/L, $p < 0.001$	Tolv: thirst, dry mouth, increased urination, 1.8% overcorrection
Garrahy *et al.*,[54] JCEM 2020	46	Chronic SIAD (transient/ reversible causes excluded), pNa < 130 mmol/L	1. Fluid restriction 1 L/*d* (FR) 2. No active hyponatraemia treatment (NoTx)	Change in pNa day 4 and 30	Day 4: FR *versus* No Tx, 3 mmol/L *versus* 1 mmol/L, $p = 0.005$ Day 30: FR *versus* No Tx, 4 mmol/L *versus* 1 mmol/L, $p = 0.04$	Nil directly attributed to treatment, no overcorrection
Refardt *et al.*,[55] JASN 2020	92	SIAD, pNa < 130 mmol/L	1. Fluid restriction 1 L/d plus Emplagliflozin (FR + Empa) 2. Fluid restriction 1 L/*d* (FR)	Change in pNa day 5	Day 5: FR + Empa *versus* FR alone, 10 mmol/L *versus* 7 mmol/L, $p = 0.04$	No cases of hypotension or hypoglycaemia, four patients had deterioration in renal function, two patients in FR + Empa group had overcorrection of pNa, requiring loosening of FR
Krisanapan *et al.*,[56] AJKD 2020	88	SIAD, pNa < 130 mmol/L	1. Fluid restriction 1 L or 500 ml/day (depending on urine to plasma electrolyte ratio) (FR) 2. Fluid restriction plus furosemide (FR + Furos) 3. Fluid restriction plus furosemide plus sodium chloride (FR + Furos + NaCl)	Change in pNa day 4, 7, 14, 28	Day 4: FR *versus* FR + Furos *versus* FR + Furos *versus* NaCl, 5 mmol/L *versus* 4 mmol/L *versus* 6 mmol/L, $p = 0.7$ Day 28: FR *versus* FR + Furos *versus* FR + Furos *versus* NaCl, 6 mmol/L *versus* 8mmol/L *versus* 9 mmol/L, $p = 0.8$	Acute kidney injury in 10% FR, 17% FR + Furos and 32% FR + Furos + NaCl, p 0.07. Hypokalaemia (<3 mmol/L) in 13%, 23% and 42%, respectively, $p = 0.01$. Overcorrection in 6%, 7% and 13%, respectively, $p = 0.7$.

Vasopressin receptor antagonists. The development of vasopressin receptor antagonists (VRA) represented a major advance in SIAD treatment. This class of drug competitively bind to the V2 receptor in the collecting duct, displacing vasopressin, promoting free water clearance and rise in pNa.[64] Tolvaptan is an oral selective antagonist of V2 receptor available in Europe and USA, while conivaptan is an intravenous antagonist of V1 and V2 receptors available in the USA.

In the large multicentre, randomised double-blind placebo controlled trials, SALT1 and SALT2, tolvaptan was shown to produce an effective rise in plasma sodium concentration at day 4 and day 30 in patients with euvolaemic and hypervolaemic hyponatraemia, compared to patients in the placebo group.[53] Subsequent subgroup analysis confirmed the efficacy of tolvaptan in the SIAD cohort in the study.[65] Plasma sodium concentration fell following cessation of the drug

Table 6. Predictors of failure to respond to fluid restriction.

1	Urine osmolality >500 mOsm/kg H_2O
2	Sum of urine sodium plus potassium exceeds plasma sodium concentration
3	24-hour urine volume 1500 ml
4	Increase in plasma sodium concentration <2 mmol/L/day in 24–48 hours despite fluid restriction ⩽1 L per day

With permission, from Verbalis JG *et al.*[13]

at 30 days, confirming that the positive effect was related to tolvaptan and not spontaneous recovery of hyponatraemia. The long-term safety of tolvaptan has been confirmed in the SALTWATER study, a multicentre open-label four-year extension of the SALT-1 and SALT-2 trials.[66] Plasma sodium concentrations were well maintained over the long-term with a favourable adverse effect profile. The most commonly reported adverse effects related to tolvaptan therapy include urinary frequency and polyuria, both of which are expected due to the mechanism of action of the drug, and good indicators that the drug is functioning. Patients also reported thirst, dry mouth and polydipsia. We have previously reported two cases (and encountered a third) of acquired resistance to tolvaptan. All three cases occurred in patients with SIAD associated with small cell lung cancer, and resistance to tolvaptan effect occurred despite increasing doses of the drug. Resistance to the aquaretic effects of tolvaptan occurred in the setting of progression of malignant disease, with escalating plasma AVP concentrations which we postulate overwhelmed the drug at the V2 receptor.[67]

The European guidelines specifically advised against the use of tolvaptan, because of concerns about overcorrection of hyponatraemia.[11] Overcorrection was reported in 1.8% of patients treated with tolvaptan in the SALT studies,[68] and no patient displayed symptoms of osmotic demyelination. However, subsequent real world studies have reported much higher rates of overcorrection, 12.1–31%.[17,69,70] Overcorrection is a possibility with all effective therapies for hyponatraemia, and the key issues are awareness of the possibility, frequent monitoring of plasma sodium concentration in the 24 hours after initiation of therapy, and willingness to correct early with dextrose or dDAVP. Concurrent use of other hyponatraemia treatments should be avoided. Overcorrection is more likely where the starting plasma sodium concentration is very low.[69,71] A case series of 61 hospital inpatients by Tzoulis *et al.* reported a significant negative correlation between baseline plasma sodium concentration and 24 hour sodium rise; 29% of patients with starting pNa <125 mmol/L exceeded the safe rate for pNa correction at any timepoint compared with none of those with pNa ⩾125 mmol/L.[69,71] Lower doses of tolvaptan (7.5 mg or less) are efficacious,[70,72,73] and may be safer, though it is important to stress that plasma sodium responses to lower doses of tolvaptan have not been subjected to rigorous prospective study.

Tolvaptan has been utilised in the treatment of SIAD post-pituitary surgery, with a German group reporting that tolvaptan 7.5 mg was more efficacious than fluid restriction in correcting hyponatraemia in this cohort of patients. However, it should be noted with caution that one third of patients treated with tolvaptan had overcorrection of pNa, most likely because the aquaretic effect of tolvaptan are compounded by the transient self-correcting nature of SIAD in this clinical context.[74]

The principal drawback to vaptan therapy perceived by most clinicians is the cost of the drugs, which are not uniformly reimbursable in all countries. Although there have been cost/benefit analyses which have sought to justify the use of vaptans,[75] they remain prohibitively expensive given that the main indication is for chronic SIAD, which may need prolonged therapy, particularly in the absence of data on reduction of hard clinical end points.

Demeclocycline. Demeclocycline is a tetracycline derivative that has been used clinically since the 1970s to treat chronic hyponatraemia secondary to SIAD.[76] The mode of action in the treatment of hyponatraemia is not yet fully established, however, it has been observed that it interferes with the action of vasopressin on the renal ducts inducing diabetes insipidus in 60% of individuals with SIAD.[1,76,77] Unfortunately, the onset of action is erratic, usually occurring between 3 and 5 days, but often occurring much later,[76–79] and this means that dose adjustment is less predictable. Side effects include nausea and vomiting, renal failure, skin photosensitivity and antibiotic resistance.[80,81] Renal failure is normally reversible on

cessation of the drug.[78] In some patients polyuria can be profound and can lead to hypernatraemia if fluid intake is restricted.[1,82] There are no prospective randomised controlled data to support the use of demeclocycline, and it is no longer universally recommended across consensus guidelines for hyponatraemia management.

Urea. Oral urea has been used to treat hyponatraemia in SIAD since 1980.[83] It is an osmotically active agent that increases urinary free water excretion and decreases urinary sodium excretion.[83] In an 1981 study by Decaux & Genette, seven patients with confirmed SIAD with a mean pNa of 115 ± 6 mmol/l and mean urine osmolality of 514 ± 79 mOsm/kg H_2O were administered between 30 and 60 g of urea once daily. After treatment, a significant rise in serum Na to 136 ± 3.5 mmol/l ($p < 0.001$) was demonstrated, with a concomitant rise in urine osmolality to 652 ± 95 mOsm/kg H_2O ($p < 0.001$).[84] Retrospective studies have shown urea to be effective in SIAD induced by SAH and in critical care patients,[85] as well as in twelve patients who transitioned to urea therapy following 12 months of vaptan therapy in a clinical trial.[86] A more recent retrospective non-controlled study from the US (n = 58) compared outcomes in patients treated with an oral commercially available formulation of urea and those treated by other means, over a one year period. Treatment with urea resulted in a statistically significant rise in pNa following 24 hours (2.8 mmol/L *versus* –0.5 mmol/L in the non-urea group; $p < 0.05$),[87] and a median rise in pNa of 6 mmol/L over 4 days, without overcorrection or other adverse events.[87] Contraindications to the use of urea in the treatment of hyponatraemic include liver cirrhosis, adrenal insufficiency and states of hypovolemia.[88]

SGLT-2 inhibitors. Sodium glucose co-transport 2 inhibitors (SGLT-2i) are a well-established class of antidiabetic medication. They act by promoting osmotic diuresis *via* urinary glucose excretion and therefore offer a promising new management option for SIAD.[55] Preliminary data from Refardt *et al.*[89] demonstrated significantly increased urinary water excretion in healthy volunteers with artificially induced SIAD within 6 hours of receiving a dose of empagliflozin, an oral SGLT2 inhibitor; this suggests the drug may have a beneficial effect on hyponatraemia acutely. The same group recently published a double-blind randomised placebo-controlled trial, in which hospitalised patients with SIAD were randomised to standard treatment of 1000 ml/day fluid restriction with or without empagliflozin once daily for 4 days. Patients treated with empagliflozin had a greater increase in pNa compared to those treated with standard fluid restriction alone, 10 *versus* 7 mmol/L, $p = 0.04$.[55] Empagliflozin may be a favourable treatment option in the treatment of hyponatraemia going forward, however, long-term efficacy or safety data in the outpatient setting are not yet available. There are however extensive data on the use of empagliflozin in patients with type 2 diabetes, renal disease and heart failure; the drug has been shown to have a favourable safety profile, beneficial cardio-protective and renal protective profiles and therefore may be an excellent treatment option for comorbid patients with SIAD.[55,90,91]

Apelin. In normal physiological conditions, apelin and AVP are released in proportional concentrations dependent on plasma osmolality. Water resorption occurs once AVP binds to V2-R, increasing aquaporin-2 insertion. Apelin is a neuro-vasoactive peptide that works centrally to inhibit AVP release and at the level of the collecting duct promoting water excretion through its action on apelin-R counteracting the antidiuretic effect of AVP. A recent investigation has proven that a metabolically stable K17F analogue, LIT01-196, restores water homeostasis in SIAD in animal models. LIT01-196 inhibits the antidiuretic effect of AVP, by increasing urine output and reducing urinary osmolality, thereby causing a rise in pNa. This study illustrates metabolically stable apelin analogues have a potential role in the treatment of hyponatraemia in patients with SIAD, pending appropriate clinical trial data.[64]

Treatment of hypervolemic hyponatraemia

A combination of fluid and salt restriction and loop diuretics, plus neurohormonal antagonism is the recommended first-line approach for hyponatraemia in the settings of heart and liver failure. Vaptans offer an attractive alternative or adjunct to loop diuretics, as they are potassium neutral and cause less neuro-hormonal activation from intravascular volume depletion compared with diuretics, and tolvaptan is an FDA-approved treatment for hypervolaemic hyponatraemia. Forty-three percent of patients recruited into the SALT RCTs of tolvaptan mentioned earlier had hypervolemic hyponatraemia, and although

subgroup analyses of this group were not published separately, tolvaptan was shown to produce a significantly greater rise in pNa compared with placebo in the overall group.[53] Several large RCTs have subsequently confirmed tolvaptan's beneficial effect on plasma sodium, weight and dyspnoea in heart failure patients,[92,93] while in patients with hyponatraemia and ascites, short term tolvaptan use has been shown to normalise plasma sodium in 27–50% of patients.[94] The routine use of tolvaptan is not recommended in patients with cirrhosis, based on the liver injury seen in higher doses used in the TEMPO trial.[95]

Treatment of hypovolaemic hyponatraemia

Volume replacement with isotonic saline, and specific management of the underlying cause, form the approach to management of hypovolaemic hyponatraemia. Correction of hypovolaemia eliminates the stimulus for AVP secretion resulting in a rapid aquaresis which can potentially lead to overcorrection, and thus careful monitoring is required. Treatment of thiazide diuretic induced hyponatraemia requires particular caution as withdrawal of the drug combined with correction of hypovolaemia may result in a rapid aquaresis

Conclusion

Acute symptomatic hyponatraemia is a medical emergency, and current practice guidelines have adapted to recommend the use of bolus hypertonic saline in this setting; however recent trial data have emphasised that caution must be taken to prevent overcorrection when the duration of hyponatraemia is unclear. Chronic asymptomatic hyponatraemia is traditionally thought of as clinically benign and is thus often underinvestigated and undertreated. Traditional treatments for SIAD have been limited to date by poor efficacy, side-effects, cost or lack of supportive randomised control trial data. The past two years have seen the publication of several much-needed prospective randomised controlled trials that have demonstrated modest effects of fluid restriction in patients with chronic SIAD, albeit with good tolerability and safety, thereby emphasising the need for second-line therapies. Cost-reduction, more widespread reimbursement and use of a lower starting dose may allow expansion of the use of tolvaptan in treatment of SIAD. Recent studies have also given cause for optimism for potential future treatments such as empagliflozin; an RCT examining use of the drug in chronic euvolemic and hypervolemic hyponatraemia is underway.

Treatment of hyponatraemia must be individualised to the patient, taking into account the acuity and cause of hyponatraemia, the indications for treatment, and treatment goals. For example, it is reasonable to consider an initial trial of fluid restriction in an asymptomatic patient with incidentally noted chronic SIAD. On the other hand, correction of hyponatraemia may be more urgent in patients awaiting chemotherapy for example, and in this scenario early consideration of a low dose of dose of tolvaptan (7.5 mg) is appropriate.

It is becoming increasingly clear that treatment of chronic hyponatraemia is associated with reduction in length of hospital stay, improvements in gait and mentation, and a reduction in mortality. Mortality rates associated with hyponatraemia have been shown to differ according to volume status, and this should be considered when designing and interpreting future outcome studies. Prospective studies, employing effective treatments that will increase plasma sodium concentration by a clinically significant amount, in a large enough cohort to classify patients by volume status, are required to confirm the long-term clinical benefits of chronic hyponatraemia treatment.

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