

SIAD: practical recommendations for diagnosis and management

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Abstract Hyponatremia is the commonest electrolyte disturbance encountered in hospitalized patients, and the syndrome of inappropriate antidiuresis (SIAD) is the most frequent underlying disorder. There is a well-recognized relationship between hyponatremia and increased morbidity and mortality. Therefore, to provide appropriate treatment is critical to improve the clinical outcome related to SIAD-hyponatremia. There have been important advances in the treatment of SIAD over the last decade, leading to the publication of several clinical guidelines. In particular, the introduction of the vasopressin-2 receptor antagonists provides a potent pharmacological tool to target the underlying pathophysiology of SIAD. The evidence base recommendations of the available therapies for SIAD are discussed in this study. Fluid restriction is considered the first-line therapy by the recent published guidelines, but it is certainly ineffective or unfeasible in many patients with SIAD. We discuss a number of relevant points to the use of fluid restriction in this study, including the lack of good evidence-based recommendations to support its use. Conversely, the clinical efficacy of oral tolvaptan in SIAD supported by good quality randomized, placebo controlled, clinical trials. However, the cost of the therapy and the need for long-term safety data may limit its widespread use. Finally, new recommendations for the management of

acute hyponatremia with a focus on the use of bolus therapy with 3 % hypertonic sodium chloride are described in this study.

Keywords Hyponatremia · SIAD · SIADH · Vaptans · Tolvaptan

Introduction

The syndrome of inappropriate antidiuresis (SIAD) is the commonest cause of hyponatremia in clinical practice [1]. SIAD occurs secondary to a wide variety of diseases and also as a complication of medical or surgical therapy. As a consequence, SIAD may present to almost every clinician in medicine, though once recognized, referral to an endocrinologist or nephrologist is usually the next step. In recent years, the huge increase in the number of published papers on hyponatremia has contributed to an increased knowledge of the clinical sequelae of low plasma concentrations. Hyponatremia has been associated with an increase in mortality in almost every condition with which it is associated, including internal medicine patients [2], intensive care patients [3], patients with pneumonia [4], patients in the community [5], and cancer patients [6]. In addition, there is evidence of increased morbidity associated with hyponatremia of all degrees of severity [1].

Unfortunately, there is far less data available on the clinical impact of hyponatremia due to SIAD. Most of the available literature is derived from the analysis of the effects of hyponatremia of all causes. In addition, much of the published data are retrospective, and the ascertainment of diagnostic criteria for SIAD is poor in those studies, which have aimed to target SIAD, as distinct from all-cause hyponatremia [7, 8]. In a recent study supported by the Italian

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Endocrine Society, less than half of clinicians surveyed used validated biochemical parameters to diagnose SIAD [9]. This is, therefore, a major gap in our knowledge of the effects of SIAD, and on the clinical impact of treatment. As the causation of SIAD may be different from the aetiology of hypovolemia hyponatremia, for instance, as it is not possible always to discern the effect of the precipitating illness on the excess mortality associated with hyponatremia [10], one cannot simply assume that the morbidity and mortality rates for hyponatremia are the same in patients with SIAD. In this review, we have attempted to present a practical approach to the diagnosis and management of SIAD, while recognizing the deficiencies in the literature, and basing our recommendations on clinical experience, and the recently published guidelines on hyponatremia [11, 12].

Aetiology of SIAD

SIAD is a clinical and biochemical syndrome characterized by euvoletic hyponatremia, with inappropriate urinary concentration and reduced free water excretion, due in almost all cases to elevated plasma concentrations of vasopressin (AVP) [13]. However, not always the antidiuretic effect is secondary to high plasma vasopressin levels, as in the nephrogenic syndrome of inappropriate antidiuresis; they are undetectable due to gain-of-function mutations in the V2 vasopressin receptor. Hence, the term “syndrome of inappropriate antidiuresis (SIAD)” is more precise than the syndrome of inappropriate antidiuretic hormone secretion (SIADH); commonly quoted in the medical literature. The first classic report of SIAD described two patients with bronchogenic carcinoma and hyponatremia [14] in whom the experimental alternation of water restriction and fluid loading demonstrated sustained antidiuresis. The authors postulated that an excess of circulating “antidiuretic hormone” reduced renal free water clearance, resulting in dilutional hyponatremia. The subsequent development of a radioimmunoassay for arginin vasopressin identified high circulating levels of this antidiuretic hormone in patients diagnosed with SIAD [15], proving their hypothesis.

SIAD has been reported to occur in association with a wide variety of conditions. Most published series report that the commonest causes of SIAD include malignancy, CNS disorders, pulmonary disease, and medication, though the relative frequencies of each vary according to the study. For instance, the results from the recently published multi-centre hyponatremia registry [8] show that tumors were the commonest cause (24 %) in a large European and US cohort, followed by drugs (18 %), pulmonary disease (11 %), and CNS disease (9 %). In addition, a recent single-center retrospective study of 555 patients with SIAD showed that malignancy and medication were the

commonest cause of SIAD [16]. In contrast to the results of these studies, in our hospital, which is the site of the Irish National Neurosurgical service, CNS disease is the commonest cause of SIAD (Table 1).

In our series, intracranial disease is the commonest cause of SIAD; we have reported hyponatremia in over 50 % of patients with subarachnoid haemorrhage in retrospective [17] and prospective studies [18].

There have been reports of SIAD in association with most types of malignancy. Bronchogenic carcinoma, in particular, has been well described to cause SIAD, since the original reports of Schwartz and Bartter [14], and approximately 15 % of cases of small cell lung cancer can develop SIAD. The incidence in non-small cell carcinoma of the lung is lower at 0.4–2 %. We have demonstrated that hyponatremia occurs in 3 % of intracranial tumors, almost all of which is due to SIAD; the incidence of hyponatremia rises to 15 % after neurosurgery [19]. SIAD also occurs frequently in head and neck tumors, haematological malignancies, urological tumors, and gastroenterological cancers. SIAD is often due to true ectopic secretion in malignancy, and immunostaining for AVP has been demonstrated in malignant cells derived from a bronchogenic tumor and other tumors. As AVP is derived directly from the tumor, tumor regression with successful treatment can lower plasma AVP concentrations and normalize plasma sodium concentration [20].

Diagnosis of SIAD

The diagnostic criteria for SIAD have been well defined in the literature, and have stood the test of time (Table 2). However, in clinical practice, there are three quite separate key steps in the diagnostic approach to SAID.

1. Confirmation of euvoletic hyponatremia.
2. Exclusion of other causes of euvolemia, particularly secondary adrenal failure.
3. Identification of the underlying cause of SIAD.

Confirmation of euvoletic hyponatremia

Hyponatremia in clinical practice can be divided into the broad categories of hypovolemia, euvoletic, and hypervolemic hyponatremia [12, 21]. The distinction is important, as the treatment pathway for each is different, and erroneous application of the treatment for hyponatremia may be harmful; for instance, applying fluid restriction to a patient who is already dehydrated will not only fail to correct hyponatremia, but also worsen the patient’s condition by rendering him more hypovolemia. Identification of hypervolemic hyponatremia is usually straightforward, as

Table 1 Description of the aetiology in patients with SIAD in a prospective cohort of 353 patients in Beaumont Hospital, Dublin, Ireland (unpublished observations)

	Aetiology of SIAD	<i>n</i>
CNS, (<i>n</i> = 108, 30 %)	Subarachnoid haemorrhage	20
	Ischaemic stroke	12
	Intracranial tumor	18
	Traumatic brain injury	9
	Haemorrhagic	9
	Hydrocephalus	9
	Miscellaneous	31
	Pulmonary diseases, (<i>n</i> = 96, 27 %)	Lobar pneumonia
Other respiratory tract infections	31	
	Bronchiectasis	9
	Miscellaneous: pneumothorax, pulmonary fibrosis, pulmonary embolism etc.	11
Malignancy, (<i>n</i> = 90, 25 %)	Lung cancer	30
	SCLCA <i>n</i> = 14	
	NSCLCA <i>n</i> = 21	
	Gastrointestinal malignancy	25
	Urological malignancy	9
	Haematological malignancies	9
Drug-related, (<i>n</i> = 31, 9 %)	Other malignancies	15
	Carbamazepine	14
	Oxcarbazepine	4
	SSRI	8
	Other	4
Postoperative, (<i>n</i> = 28, 8 %)	Orthopedic surgery	20
	Other surgeries	8

CNS central nervous system, SSRI selective serotonin reuptake inhibitor, CA carcinoma

the clinical signs of peripheral and sacral oedema, elevated jugular venous pressure, and the presence of pulmonary oedema or ascites are generally within the skill set of most clinicians, even those at an early stage of their careers. In contrast, although profound hypovolemia manifests as tachycardia, hypotension, dry skin, and mucous membranes, it is not easy to differentiate between mild dehydration and euvoolemia. In addition, some patients have multiple comorbidities, which may be responsible for hyponatremia; the elderly patient who presents with vomiting is taking diuretics for cardiac failure, and has pneumonia, would be a common example. A number of algorithms have been suggested [12, 21, 22] to aid the differentiation between the three types of hyponatremia. Although accurate application of all algorithms still needs clinical acumen and experience, they do offer a guide to the difficult approach to complex patients. To sophisticate the approach to the difficult patient with hyponatremia, the copeptin to urine sodium ratio has

Table 2 Standard criteria for the diagnosis of SIAD

1. Plasma hyposmolality (<275 mOsm/kg)
2. Inappropriate urine concentration (urine osmolality >100 mOsm/kg)
3. Urine sodium >30 mmol/l
4. Clinical euvoolemia
5. Exclusion of hypothyroidism or secondary adrenal failure

been recommended to distinguish between hypovolemic hyponatremia and SIAD [23]. The same authors have also demonstrated that the measurement of fractional uric acid excretion is highly predictive of SIAD in patients on thiazide diuretics, in whom the same differentiation between euvoolemia and hypovolemia is often a clinical challenge [24]. Although the published data in these studies were convincing, neither of these measurements are widespread in clinical practice; they should be considered in difficult clinical cases, however. Many clinicians take an empirical approach to those cases where it is difficult to distinguish between mild hypovolemia and euvoolemia, and administer 0.9 % sodium chloride intravenously, on the premise that it will be beneficial to patients with hypovolemia, without causing harm to those with SIAD.

Exclusion of other causes of euvolemic hyponatremia

Once euvoolemia has been established on clinical and biochemical grounds, the next step is to exclude conditions, which can manifest in a similar presentation to that of SIAD. Primary polydipsia rarely causes hyponatremia, but if water intake exceeds the capacity for free water clearance, plasma sodium concentration can fall; in this circumstance, urine osmolality will be <100 mOsm/kg, indicating suppression of AVP secretion, and no antidiuretic action. In SIAD, by definition (Table 2), urine osmolality will exceed 100 mOsm/kg, indicating inappropriate urine concentration. Once inappropriate elevation of urine osmolality has been established, the next step is to exclude hypothyroidism and glucocorticoid deficiency. Although hyponatremia occasionally occurs in severe hypothyroidism, and has been reported, for instance, after radioiodine therapy [25], the continued inclusion of thyroid function tests in routine investigation of SIAD has been challenged [26]. The relationship between hypothyroidism and hyponatremia is considered to be so tenuous that some authors have advised that the discovery of hypothyroidism in someone with hyponatremia should not necessarily be regarded as cause and effect, and the search for alternative causes of SIAD should continue [27]. Currently, the measurement of thyroid function remains as part of the investigations of SIAD, though causative hypothyroidism is extremely rare.

The investigation of underlying glucocorticoid deficiency in SIAD is, in contrast to the investigation of hypothyroidism, very important. Addison's disease presents differently from SIAD with hypovolemia, hypotension, hyperkalemia, and hypoglycaemia, but secondary adrenal failure, with preservation of mineralocorticoid secretion, presents with biochemical features that closely mimic SIAD. If adrenal failure is sufficient to cause hyponatremia, glucocorticoid deficiency is severe, potentially life threatening, but easily treatable. It is, therefore, essential not to miss this differential diagnosis. The true incidence of adrenal failure in euvoletic hyponatremia is not known. This partially reflects the retrospective nature of most of the studies in hyponatremia, and is partly due to the poor ascertainment of data on hypothalamic/pituitary/adrenal (HPA) axis function [7, 28–31]. Tzoulis and Bouloux found that in routine clinical practice, only 35 % of patients with all-cause hyponatremia had basal measurements of plasma cortisol, and only 2 % had synacthen testing. Even in prospective studies of SIAD patients, the documentation of the integrity of the HPA axis has been poor; in the large, multinational, prospective hyponatremia registry study, only had a 33 % documented measurements of HPA axis function [8]. A retrospective study of 185 patients admitted to a specialist endocrine unit over 20 years, with all-cause hyponatremia, found that 28 patients had cortisol deficiency, almost all secondary to pituitary failure [32]. However, as the patients were admitted to an endocrine unit, there may have been a bias toward endocrine hyponatremia in this retrospective series. A recent prospective, observational study of 298 patients with all-cause hyponatremia <125 mmol/L found that 36 % had SIAD, and in the SIAD cohort, 3 % had evidence of central adrenal insufficiency, although the criteria for making this diagnosis was unclear. If this figure is correct—and confirmatory prospective data in SIAD is required—it would suggest that a sizable minority of patients diagnosed with SIAD have indeed hyponatremia, which is attributable to steroid deficiency.

The figure is higher in patients with euvoletic hyponatremia due to neurosurgical conditions. Hyponatremia occurs in 50 % of patients with subarachnoid haemorrhage [19]; 90 % are euvoletic, and 10 % of these have hyponatremia due to acute ACTH/cortisol deficiency, as opposed to SIAD [18]. Hyponatremia following traumatic brain injury (TBI) is less common occurring in 15–20 % of cases [33, 34], but the incidence of transient ACTH/cortisol deficiency following TBI is very high, and could be responsible for up to 80 % of cases of post-TBI hyponatremia [34]. It is, therefore, particularly important to consider steroid deficiency in neurosurgical hyponatremia, where vascular insults to the pituitary can lead to transient—or permanent—ACTH/cortisol deficiency.

The other clinical scenario in which to carefully consider the possibility of adrenal failure leading to hyponatremia is the recent steroid therapy. There is good evidence that inhaled steroids are an underestimated cause of adrenal suppression [35]; in patients with hyponatremia and previous steroid inhalation, an early morning cortisol has been shown to be highly predictive of adrenal suppression [35].

Establishing the aetiology of SIAD

Once the diagnosis of SIAD is confirmed on the basis of the criteria in Table 2, and adrenal insufficiency has been excluded, investigations to establish the underlying aetiology of SIAD should be instituted. The extent of biochemical and radiological investigations should be individualized at the discretion of the clinician, but in the absence of an obvious diagnosis—a history of carbamazepine therapy, or a lung mass in a smoker presenting with weight loss—we would recommend CT scans of brain, thorax, abdomen, and pelvis as a minimum prelude to more specialized investigations. A normal chest X-ray is insufficient to exclude lung cancer, and CT thorax is always preferable. Careful clinical history is crucial, and an accurate drug history may reveal medications known to cause SIAD, such as serotonin reuptake inhibitors and carbamazepine. Candidate medications should be stopped where possible, and replaced by alternative agents, which do not effect plasma sodium concentrations.

Management of SIAD

There have been a number of guidelines, recommendations, and clinical algorithms published in recent years on the management of hyponatremia due to SIAD, and there has been significant disagreement between some of them over which therapies to recommend, particularly for the second-line therapy of chronic hyponatremia. However, the common principles are that the indications for treatment are different if the onset of hyponatremia is acute, as opposed to chronic, and that the urgency of treatment is fundamentally based on the presence of symptoms of cerebral irritation, rather than the absolute level of plasma sodium concentration.

Chronic hyponatremia due to SIAD

Chronic hyponatremia is defined as hyponatremia that has taken more than 48 h to develop. In clinical practice, most cases of chronic hyponatremia have had low plasma sodium concentrations for much longer than this. The reason to distinguish chronic hyponatremia from that of acute onset is the capacity of the brain to adapt to

plasma hypo-osmolality. When hyponatremia is chronic, there is leakage of idiogenic osmoles from the brain into the plasma; this reduces the osmotic difference across the blood brain barrier, and reduces the tendency for water to move from the plasma into the brain, causing cerebral oedema. This has two effects in chronic hyponatremia, both of which are clinically relevant;

1. Symptoms of cerebral irritation due to brain oedema are less likely.
2. Rapid reversal of hyponatremia is more likely to cause osmotic demyelination syndrome.

With this in mind, the decision to treat hyponatremia in chronic SIAD needs to be carefully considered. There may be little that needs active intervention, and the consequences of overaggressive intervention can be catastrophic. The decision to treat is complex and may be based on a number of parameters;

1. The time course of SIAD. Some cases of SIAD are temporary and may need no specific therapy. For instance, mild hyponatremia associated with pneumonia may resolve very quickly, simply with antibiotic treatment of the infection. Drug-induced SIAD may simply need withdrawal of the causative medication. Therefore, not every case of SIAD necessarily needs specific therapy
2. The potential hazards of treatment. SIAD associated with infection may need intravenous antibiotics and intravenous fluids for circulatory support: fluid restriction in this circumstance may be more hazardous than leaving hyponatremia untreated. SIAD is a common complication of subarachnoid haemorrhage, but neurosurgeons are traditionally hostile to intervention with fluid restriction, because of a fear that it will precipitate cerebral vasospasm. In both of these circumstances, fluid restriction is undesirable, and the decision to treat, with other therapies, is based on the presence of symptoms of cerebral irritation.
3. Symptoms. Hyponatremia is associated with gait instability and falls [36], increased rate of fracture [37] deterioration in concentration and cognition, and the development of osteoporosis [38], so treatment may be targeted to reverse the symptoms and improvement in quality of life. Unfortunately, the evidence base for symptomatic treatment of SIAD is sparse. The SALT studies [39] did show an improvement in the SF-12 questionnaires in the cohort actively managed with tolvaptan, the SALT studies included a patient cohort composed of both SIAD and hypervolaemic hyponatremia. Although the evidence base for outcome-based therapy is lacking, if symptoms are typical for those

associated with hyponatremia, intervention with treatment of SIAD is justified on clinical grounds.

4. Prevention of complications. There is no evidence to suggest that treatment of hyponatremia will prevent complications, such as osteoporosis or fracture, and further work in this area is needed.
5. Reduction in mortality. Almost every cross-sectional study of hyponatremia has demonstrated increased mortality in the hyponatremic, compared with the normonatremic group. However, most of the studies in the literature have not distinguished between hyponatremia due to SIAD and that due to other causes, including hyper- and hypovolemic hyponatremia. Therefore, there is no evidence from prospective randomized trials that treatment of hyponatremia due to SIAD improves survival.

In the absence of the type of evidence usually required to treat, the management of SIAD should be aimed at the underlying condition, with judicious use of intervention on clinical grounds. There are a number of therapeutic options, which have reviewed in recent guidelines and recommendations produced from US/Ireland [12], Europe [11], Britain [21], and Spain [40]. Each has produced distinct views on treatment algorithms, with the principle difference being that the European guidelines were unable to recommend the use of vaptans, whereas the other three clinical recommendations all acknowledged the role of vaptans in certain circumstances.

Fluid restriction

All of the recently published guidelines concur that fluid restriction should be the first-line therapy for mild-to-moderate hyponatremia secondary to SIAD. This is despite the acknowledged absence of any randomized controlled trials that prove the efficacy or safety of fluid restriction. Furthermore, the results reported from the hyponatremia registry showed that fluid restriction was no better than no treatment at all, in patients with SIAD [8]. The registry reported the results of physician-selected treatment for SIAD, so there was no randomization in this study. Despite the lack of supportive evidence and concerns about efficacy, fluid restriction tends to be the first-line therapy in SIAD. It is certainly cheaper than other therapies and can be used easily in non-specialized units. It is free of serious side effects. In chronic use patients find it very difficult to persevere with. The downward resetting of the thirst threshold [41] dictates that many patients continue to experience thirst at plasma osmolalities where thirst would be expected physiologically to be suppressed, and therefore, they cannot maintain treatment goals in the medium to long term. In addition, fluid restriction cannot always be adhered

to in hospital, because of the therapeutic need to administer intravenous antibiotics, intravenous fluids, or maintain nutritional support.

For fluid restriction to be effective, there are a number of important caveats.

1. Fluid restriction must include all fluids, including intravenous injections, soups, and fruit.
2. Fluid restriction should be limited to 500 mL less than daily urine volume [12].
3. Many patients respond slowly and several days of restriction are needed to reach normonatremia; many patients never normalize plasma sodium completely.
4. Sodium intake must be maintained to replace urinary losses from natriuresis.

It is recognised that fluid restriction is not effective in all patients. The US guidelines documented a number of parameters, which predict poor response to fluid restriction [12]. Urine osmolality is a bioassay for the action of AVP; the higher the urine osmolality, the greater the plasma concentrations of AVP; urine osmolality >500 mOsm/kg is strongly predictive of poor response to fluid restriction. Both the US [12] and the British guidelines [21] recommend the application of the Furst formula (urine Na⁺/urine K/plasma sodium) [42], with a ratio >1 strongly predictive of failure to respond to fluid restriction. The need to administer a fluid intake >1.5 l/day because of intravenous antibiotics also predicts failure to respond, as does low urine volume (<1.5 l/24 h). Unpublished data from our unit suggest that over 50 % of prospectively studied patients with SIAD have data at diagnosis, which predicts poor response to fluid deprivation. Therefore, many clinicians who treat hyponatremia are beginning to question the role of fluid restriction as the first-line therapy for SIAD.

Demeclocycline

Demeclocycline is a tetracycline derivative, which induces nephrogenic diabetes insipidus, with a resultant increase in free water clearance [43]. The rise in plasma sodium that occurs is variable and unpredictable. Hyponatremia from excess renal water losses can occur. The side effect profile includes reversible azotemia, and sometimes nephrotoxicity, especially in patients with cirrhosis, hepatic dysfunction, and photosensitive skin rashes [44]. A recent systematic analysis failed to identify any supporting evidence for safety or efficacy in the literature [45], and in many countries, it is not licensed for use in the treatment of SIAD. As a result, in the multinational hyponatremia registry study, only 3 % clinicians selected demeclocycline as the first-line therapy for SIAD [8]. Despite this, it is included as the second-line therapy in most clinical guidelines.

Urea

Urea is an interesting agent, which has no widespread available formulation and is not licensed for use in SIAD. However, it increases free water clearance and decreases natriuresis, leading to an elevation in plasma sodium concentration. The disadvantages include poor palatability and the development of azotemia at higher doses. A recent systematic review found no randomized controlled trials to support the use of urea in SIAD [46]; six trials were reviewed, but all were retrospective and considered to have significant bias or methodological problems. Some of these retrospective, non-randomized studies do, however, suggest that urea is effective in treating hyponatremia in SIAD due to subarachnoid hemorrhage [47] and in the management of critical care patients [48, 49], and case reports have reported efficacy in infants with chronic SIAD [50] and nephrogenic syndrome of inappropriate antidiuresis [51]. A small, non-randomized study conducted in SIAD patients has suggested that the effect of urea treatment on hyponatremia may be comparable with that of vaptans in the reversal of hyponatremia [52]. Despite these considerations, urea has been recommended as “the first choice” second-line therapy for SIAD in the European Guidelines [11]. Clinical use of urea is concentrated mainly in Belgium, though it is acknowledged by those who advocate for the use of urea that prospective, randomized studies are necessary [53].

Furosemide plus sodium chloride supplementation

The theory behind this therapy is that the loop diuretic will induce a natriuresis and an aquaresis, and that the oral sodium chloride will replace the renal sodium loss. There will be a net aquaresis, therefore, with a consequent rise in plasma sodium concentration. Enthusiasts for this treatment anecdotally claim that it effectively produces an equivalent aquaresis to vaptans or demeclocycline, without the cost implication of the former, or the unpredictability and side effect profile of the latter. Although it could be argued that the combination of loop diuretic and sodium chloride makes physiological sense, there are no data from randomized controlled trials to support this form of treatment.

Vasopressin receptor antagonists

Plasma AVP concentrations are measurable in almost all cases of SIAD [13], always inappropriately high to the low plasma osmolality, and the antidiuretic effect of AVP is the mechanism responsible for the development of hyponatremia in SIAD. Vasopressin receptor antagonist drugs (vaptans) are, therefore, a logical treatment of SIAD in that they specifically target the causative mechanism of the

hyponatremia. Vaptans competitively bind to the V2 receptor, displacing AVP from the binding site and allowing an increase in free water clearance. Clinical studies show that plasma sodium concentration rises steadily and predictably in most patients, though care must be taken to check for overcorrection, particularly if the initial plasma sodium is <120 mmol/l. Conivaptan [54] is available for intravenous use in heart failure in the US and in Europe, and tolvaptan is licensed as an oral agent, for the treatment of SIAD.

The SALT studies, conducted simultaneously in Europe and the US, showed that tolvaptan was effective in causing an elevation of plasma sodium concentration. The study had a randomized, placebo-controlled design, comparing the effect of tolvaptan with placebo, in a mixed cohort of patients with either SIAD or hypervolemic hyponatremia [39]. Plasma sodium concentration raised more in the tolvaptan than the placebo group, without the need for fluid restriction. The maximum recommended correction rate for plasma sodium was exceeded in <2 % of cases, with the greatest elevation in plasma sodium in those with the lowest baseline plasma sodium concentration; no case of osmotic demyelination was reported, but the guidelines for the use of tolvaptan do caution careful measurements of plasma sodium concentrations. A subgroup analysis of the minority SIAD cohort subsequently confirmed the clinical efficacy of tolvaptan in this subgroup [55]. Discontinuation of tolvaptan after 30 days was associated with a drop in plasma sodium concentration; the SALTWATER 4 years of follow-up study showed that long-term tolvaptan continued to be effective [55].

A careful literature review shows that the only prospective randomized control trial data on the treatment of SIAD is for the vaptans. The authors of the European guidelines elected to downgrade the value of the results of these trials on the basis of the industry sponsorship of the SALT studies [39]. Although industry sponsorship is a serious consideration in evidence-based guidelines, the decision to consign well-designed studies, which provide the only evidence base for the treatment of SIAD, to the status of case reports seems unnecessarily doctrinaire. There is no doubt that further studies comparing the use of vaptans with the existing first-line therapies, such as fluid restriction, would be valuable, however.

Although the view of the authors would be that vasopressin-receptor blockade constitutes a physiological, effective, and evidence-based therapy for SIAD, there are some caveats to be considered. Clinicians should be cautious in the use of vaptans in patients with severe hyponatremia (<120 mmol/l). Although the SALT studies contained only a few patients with severe hyponatremia, the largest elevations in plasma sodium—and, therefore, the greatest potential for overcorrection—occurred in those with the lowest

baseline plasma sodium concentrations. Furthermore, it is not clear whether the patients with overcorrection were derived from the hypervolemic or euvolemic cohorts in these studies. However, it would seem sensible to exercise caution, and frequent monitoring of electrolytes, in patients with SIAD and severe hyponatremia, if vaptans are used. The US recommendations noted a number of safety recommendations for the use of vaptans, which are documented in Table 3, along with additional concerns.

The other key issue for vaptans—which applies to all therapies for SIAD—is the lack of strong outcome data to justify reversing mild/moderate hyponatremia. Although no one would dispute that severe acute hyponatremia with neurological compromise is a medical emergency, for which treatment is potentially life-saving, the scenario with chronic hyponatremia is less clear cut. The SALT studies did show an improvement in the SF-12[®] Mental Component Score readings in the tolvaptan-treated patients, compared with those on placebo, providing data on improved quality of life after improvement in hyponatremia [39]. There was also a trend toward reduced hospital stay in the tolvaptan group [39], and a recent review did highlight data, which indicates that the high unit cost of vaptans could be offset to a degree by the reduction in hospital stay and associated morbidity [56]. There is no doubt, however, that the need for better outcome studies, and comparison of effectiveness with other treatment modalities is keenly felt [57]. Until these data are available, the significant cost issue with vaptans, which has limited the availability of the drugs in some jurisdictions, will make it difficult for some physicians to justify the use of the most effective therapy at our disposal for the treatment of SIAD.

A summary of the key aspects of the main therapies for SIAD is shown in Table 3.

Acute hyponatremia

Acute hyponatremia, defined as hyponatremia which develops in less than 48 h, is different clinically and therapeutically from chronic hyponatremia. Acute hyponatremia allows no time for cerebral adaptation to occur, and brain oedema is more likely to occur. Acute hyponatremia is more likely to present with neurological symptoms directly related to the electrolyte imbalance, and hyponatremia-related death is a strong possibility [58, 59]. Arieff's classical paper documents the huge discrepancy between the high likelihood of coma, fits and death in acute hyponatremia, compared with chronic [60].

In acute hyponatremia, the presence of neurological symptoms—particularly confusion, altered conscious level, or seizures—raises the potential for cerebral herniation, and a high mortality rate [61–64]. There is a very high mortality attached to this dreaded complication.

Table 3 Summary of key aspects of therapies for SIAD

	Evidence	Practicality	Capacity for over-correction of pNa	Side effects
Fluid restriction	Nil	Cheap Poor patient tolerability Close supervision needed Ill patients may need fluid support	Unlikely	Dry mouth Patient tolerability
Demeclocycline	Nil	Available Careful monitoring for side effects	No data, but clinical experience indicates a risk	Thirst Diarrhoea Photosensitivity Liver disease Renal disease
Urea	Non-randomized observational studies	No license or available preparation Needs on site preparation by pharmacy; cost dependent on pharmacy	Reported in literature Monitoring essential	Unpleasant taste Headache
Furosemide and oral salt	Anecdotal	Readily available Cheap	No data available	Thirst Hypokalemia Uraemia
Vaptans	Good RCT data	Full license for SIAD Expensive and not universally reimbursable	Reported in literature Monitoring essential	Thirst Polyuria Raised LFTs

pNa plasma sodium, *RCT* randomized controlled trials, *LFTs* liver function tests

The traditional approach to therapy for acute symptomatic hyponatremia has been low dose infusion of hypertonic (3 %) sodium chloride, with a therapeutic goal of a progressive increase in plasma sodium concentration, of up to 12 mmol/l, over 24 h. However, current thinking is that an initial increase of 4–6 mmol/L in plasma sodium concentration is effective in reducing mortality in acute hyponatremia [63]. This is based on the results of studies in normonatremic cerebral oedema, which demonstrated that hypertonic saline infusion to cause an increase of 5 mmol/l in plasma sodium concentration can reduce intracranial pressure and reverse clinical signs of cerebral herniation [65]. To reflect this, the US/consensus has recommended that the initial treatment of acute hyponatremia should be aimed at an initial increase in plasma sodium of 4–6 mmol/l over 4 h, using intravenous boluses of 3 % sodium chloride [12]. The new recommendations have not been submitted to prospective review, but the evidence base for treatment of this life-threatening situation is small. The main hazard with rapid treatment of hyponatremia is the potential for osmotic demyelination to develop as a consequence of therapy. Osmotic demyelination is characterized by neurological sequelae, which vary from transient confusion to spastic quadriparesis and a high mortality. It is much more likely to occur in patients with alcoholism and/or malnutrition.

Careful adherence to a schedule of frequent (two hourly) monitoring of plasma sodium is recommended to identify over-rapid correction. The targets for avoidance of osmotic demyelination are summarized in Table 4, including the lower targets for high risk groups, such as those with alcoholism or malnutrition.

Once the initial target of 4–6 mmol/l rise over the first 4–6 h has been achieved, mortality rates will have been significantly reduced, and subsequently, a low dose hypertonic saline infusion can be used, if it is considered clinically necessary, to slowly increase plasma sodium, within the recommended parameters in Table 4, over the initial 24 h. Overcorrection is less likely to cause osmotic demyelination in patients with acute hyponatremia, but in cases where overcorrection is profound, or the duration of hyponatremia is uncertain, or the patient is at risk because of alcohol or malnutrition; plasma sodium can be re-lowered to safe limits with either intravenous dextrose, desmopressin, or both, according to clinician preference and experience [12].

Prognosis in SIAD

The difficulty in obtaining good data for prognosis in SIAD is again related to the lack of prospective data and the lack

Table 4 Targets for elevation in plasma sodium in hyponatremic patients, with lowered targets in patients at high risk of ODS (ODS = Osmotic Demyelination Syndrome)

	Ideal rise of plasma sodium in first 24 h (mmol/l)	Maximum rise in plasma sodium in first 24 h (mmol/l)
Normal risk patient	8	12
High risk of ODS Plasma sodium <105 mmol/l Hypokalemia Alcoholism Malnutrition Advanced liver disease	6	8

of differentiation of SIAD from all-cause hyponatremia in the literature. Although there is clear evidence from the studies already referenced in this review that hyponatremia is associated with increased mortality, two questions are still unresolved. The first is how much mortality and morbidity is related to hyponatremia, rather than the underlying condition causing electrolyte imbalance. The second is whether the mortality reported to be associated with hyponatremia is related to SIAD, as opposed to other conditions producing hyponatremia—for example, the hypervolemic hyponatremia associated with high mortality conditions, such as cardiac or hepatic failure.

Evidence is slowly accumulating that the mortality and morbidity associated with hyponatremia is partly due to the low plasma sodium, as opposed to the underlying condition. No one would doubt that some conditions that cause hyponatremia have high morbidity or mortality. However, a case–controlled study of 139 patients with all-cause hyponatremia, and 254 matched controls showed that hyponatraemic patients were three times more likely to die than matched controls [66]. Retrospective analysis of a small cohort of patients has also shown that death rates are three times higher if specific treatment for hyponatremia is not administered during hospital admission [67]. The SALT studies did not show a decrease in mortality in the vaptan-treated group, but the mortality rate in chronic hyponatremia is relatively low, and the studies were underpowered to make this association, which was not a primary endpoint [39]. There is a clear need, therefore, for appropriately powered prospective studies to examine the value of therapy of hyponatremia on mortality.

Prognosis in SIAD is also difficult to determine because of the relatively few studies conducted specifically in SIAD. One retrospective review of SIAD patients showed that the mortality was lower than in a control group of patients with hyponatremia and acute kidney injury [68]. However, a surprising statistic from this study was the 5 year mortality of 81 % in the SIAD patients, with most of the early mortality in patients with malignancy or severe infection, suggesting that the nature of the disease which precipitates SIAD is a major determinant of survival. This would be supported

by a single centre retrospective review of 555 patients with SIAD, which indicated that long-term survival was dependent on the aetiology of SIAD, with higher mortality when SIAD was due to malignancy [16]. The difficulty in separating out the effect of hyponatremia from the morbidity of malignancy has been previously referenced [10], but evidence from smaller disease-specific studies suggests that hyponatremia may independently effect prognosis. A number of studies have reported shorter survival in patients with small cell lung cancer [69], hepatocellular cancer [70], malignant pleural mesothelioma [71], metastatic renal carcinoma [72], and a wide variety of other tumours [6]. However, prospective studies are still needed.

Summary

There has been an explosion in interest in the clinical effects of hyponatremia in recent years. Disease-specific therapy for SIAD is now available in the form of vasopressin receptor antagonists, but basic information on natural history, response to treatment and mortality, in SIAD is not available. There is a huge need to clinicians who are interested in SIAD collaborating to conduct the trials needed to provide the science which forms the foundation of an evidence base for logical treatment of SIAD.

Compliance with ethical standards

Dr Martin Cuesta and Professor Thompson have received honoraria (speakers) from Otsuka Pharmaceutical Company. All the studies had local ethical approval (Ethics Committee in Beaumont Hospital, Dublin, Ireland).

Conflicts of interest Professor Christopher Thompson and Dr Martin Cuesta have received a speaker honorarium from Otsuka Pharmaceutical Company. Dr Aoife Garrahy has no conflict of interest.

Ethical approval “This article does not contain any studies with animals performed by any of the authors.” “This article contains unpublished observations from human participants which were approved by the Ethics Committee in Beaumont Hospital. An informed consent was considered not necessary as it was classified as a prospective audit in the management of SIAD, reflecting best practice in the study of this condition”

Informed consent “This article contains unpublished observations from human participants which were approved by the local Ethics Committee in Beaumont Hospital. An informed consent was considered not necessary as it was classified as a prospective audit in the management of SIAD, reflecting best practice in the study of this condition”.

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