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Review

Syndrome of Inappropriate Antidiuresis: From Pathophysiology to Management

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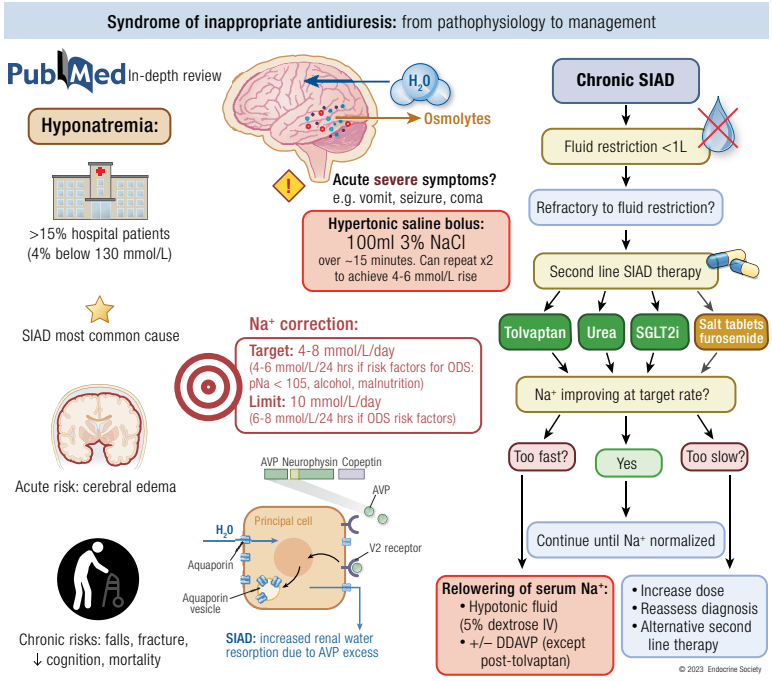
Abstract

Hyponatremia is the most common electrolyte disorder, affecting more than 15% of patients in the hospital. Syndrome of inappropriate antidiuresis (SIAD) is the most frequent cause of hypotonic hyponatremia, mediated by nonosmotic release of arginine vasopressin (AVP, previously known as antidiuretic hormone), which acts on the renal V2 receptors to promote water retention. There are a variety of underlying causes of SIAD, including malignancy, pulmonary pathology, and central nervous system pathology. In clinical practice, the etiology of hyponatremia is frequently multifactorial and the management approach may need to evolve during treatment of a single episode. It is therefore important to regularly reassess clinical status and biochemistry, while remaining alert to potential underlying etiological factors that may become more apparent during the course of treatment. In the absence of severe symptoms requiring urgent intervention, fluid restriction (FR) is widely endorsed as the first-line treatment for SIAD in current guidelines, but there is considerable controversy regarding second-line therapy in instances where FR is unsuccessful, which occurs in around half of cases. We review the epidemiology, pathophysiology, and differential diagnosis of SIAD, and summarize recent evidence for therapeutic options beyond FR, with a focus on tolvaptan, urea, and sodium-glucose cotransporter 2 inhibitors.

Graphical Abstract



Key Words: hyponatremia, syndrome of inappropriate antidiuresis (SIAD), fluid restriction, tolvaptan, urea, sodium-glucose cotransporter 2 inhibitors (SGLT2i), empagliflozin

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Abbreviations: ACTH, adrenocorticotropin; AUC, area under the curve; AVP, arginine vasopressin; *AVPR2*, gene encoding AVP V2 receptor; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CNS, central nervous system; CPM, central pontine myelinolysis; Cr, Creatinine; CRH, corticotrophin-releasing hormone; CSF, cerebrospinal fluid; CSW, cerebral salt wasting; CT, computed tomography; CTX, C-terminal crosslinking telopeptide of type 1 collagen; DDAVP, desmopressin acetate; DXA, dual-energy x-ray absorptiometry; ECF, extracellular fluid; ENaC, epithelial sodium channels; FDA, US Food and Drug Administration; FDG, fluorodeoxyglucose; FE-UA, fractional excretion of uric acid; FR, fluid restriction; GFR, glomerular filtration rate; GCS, Glasgow Coma Scale; ICP, intracranial pressure; ICU, intensive care unit; IV, intravenous; MCN, magnocellular neurosecretory cells; MDMA, 3,4-methylenedioxymethamphetamine ('ecstasy'); mOsm, milliosmole; Na^+, sodium; NaCl, sodium chloride; ODS, osmotic demyelination syndrome; OR, odds ratio; OVLT, organum vasculosum lamina terminalis; P1NP, N-propeptide of type 1 collagen; PET, positron emission tomography; pNa, plasma sodium concentration; RAAS, renin-angiotensin aldosterone system; RCT, randomized controlled trial; RR, relative risk; SAH, subarachnoid hemorrhage; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SIAD, syndrome of inappropriate antidiuresis; TSH, thyrotropin (also known as Thyroid Stimulating Hormone); UNa, urine sodium concentration; UT-A1, urea transporter A1; V2 receptor, arginine vasopressin receptor V2 (as for V1a (V1), V1b (V3) receptors).

ESSENTIAL POINTS

- Hyponatraemia is the most common electrolyte disorder, affecting around 15% of hospitalized patients - while most are mild (≥ 130 mmol/L), 4% record plasma sodium concentration (pNa) below 130 mmol/L
- Syndrome of inappropriate antidiuresis (SIAD) due to excess arginine vasopressin (AVP) despite low serum tonicity, is the leading cause of nonmild hyponatremia
- Severe symptomatic hyponatremia manifesting as vomiting, seizure, and reduced conscious state, is a medical emergency and urgent bolus hypertonic saline (100 mL of 3% NaCl, up to 3 doses) is indicated to achieve an initial pNa increase of 4 to 6 mmol/L, to reduce intracranial pressure (ICP)
- To prevent osmotic demyelination syndrome (ODS) in hyponatremia of chronic (or unknown) duration, target a pNa increase of 4 to 8 mmol/L/24 hours, and limit to 10 mmol/L/24 h (lower targets 4-6 mmol/L/24 hours for those with risk factors for ODS, eg, alcohol, malnutrition)
- Fluid restriction (FR) of less than 1000 mL/day is the first-line therapy for chronic SIAD endorsed by current guidelines, but is effective in only around half of cases
- Second-line therapies supported by current (limited) evidence include tolvaptan, urea, sodium-glucose cotransporter 2 inhibitors (SGLT2i) or high-dose salt tablets; of these, tolvaptan may be associated with the highest risk of overcorrection
- If sodium correction limit is exceeded, relowering of pNa with hypotonic fluid (oral water or intravenous [IV] 5% dextrose), with or without desmopressin to reduce urine output, is indicated

Syndrome of inappropriate antidiuresis (SIAD), previously known as syndrome of inappropriate antidiuretic hormone, is a disorder of sodium and water balance characterized by "inappropriate" (ie, nonosmotic) retention of water. The first published cases of SIAD were 2 patients with bronchogenic carcinoma with hyponatremia, yet ongoing renal sodium loss, described by Schwartz et al in 1957 (1). Through careful observation of sodium and water intake and urine output, they attributed this syndrome to sustained, inappropriate secretion of arginine vasopressin (AVP). The diagnostic criteria for SIAD later published by the same authors in 1967 have remained remarkably current (Table 1).

Over the decades since, understanding of the prevalence, pathophysiology, and complications of SIAD has progressed. Substantial advances have been made in understanding the principles of management of acute severe hyponatremia that have led to improvements in immediate mortality. A small but growing number of randomized trials have been conducted to inform management protocols. This review seeks to summarize the current understanding of SIAD, examine the evidence base informing current guidelines, and to appraise important studies conducted more recently. We aim to synthesize the literature to derive practical and clinically relevant management principles to aid the understanding of clinicians and researchers, and ultimately improve clinical outcomes.

Table 1. Criteria for diagnosis of syndrome of inappropriate diuresis

- Low serum osmolality: pOsm < 275 mOsmol/kgH_2O)
- Inappropriate urine concentration: urine osmolality > 100 mOsmol/kg H_2O
- Clinical euvolemia[a] (absence of signs of hypovolemia or hypervolemia)
- Elevated urinary sodium excretion > 30 mmol/L with normal salt and water intake[b]
- Absence of other potential causes of euvolemic hypo-osmolality (glucocorticoid insufficiency, severe hypothyroidism)
- Normal renal function[c] and absence of diuretic use (particularly thiazide diuretics)

Abbreviation: SIAD, syndrome of inappropriate diuresis.
[a]Technically, patients with SIAD retain water and become mildly hypervolemic, but compensatory pressure natriuresis partially offsets this, and most of the retained water is intracellular, hence these patients appear euvolemic on examination (2).
[b]Threshold discussed further in "Confirming a Diagnosis of Syndrome of Inappropriate Antidiuresis"—a single cutoff value has an inherent sensitivity and specificity.
[c]In practice, many patients with chronic kidney disease stage 1 to 3 are appropriately diagnosed with SIAD. Adapted from Verbalis 2013 (3) with permission, with reference to Bartter and Schwartz 1967 (4).

While one of the key characteristics of SIAD is low serum osmolality, it is more precisely referred to as low effective osmolality or tonicity. "Effective" osmolytes (eg, sodium, glucose, potassium, organic osmolytes) do not cross the cell membrane freely, so they have the capacity to create osmotic forces to influence the movement of water across cell membranes. In contrast, "ineffective" osmolytes (eg, ethanol, urea) freely cross cell membranes and therefore do not cause water shifts.

In hypotonic hyponatremia the low serum sodium concentration is primarily due to a relative excess of circulating free water, with or without a sodium deficit. Nonhypotonic hyponatremia can either be measured due to a method-dependent laboratory artifact, in which case it is termed *pseudohyponatremia*, or can be caused by excess of an effective osmolyte in the circulation (eg, hyperglycemia), in which case it is termed *translocational hyponatremia* (Fig. 1).

Pseudohyponatremia can occur in the presence of excess of lipids or proteins in the serum. This may be endogenous (eg, hypertriglyceridemia, monoclonal gammopathy) or

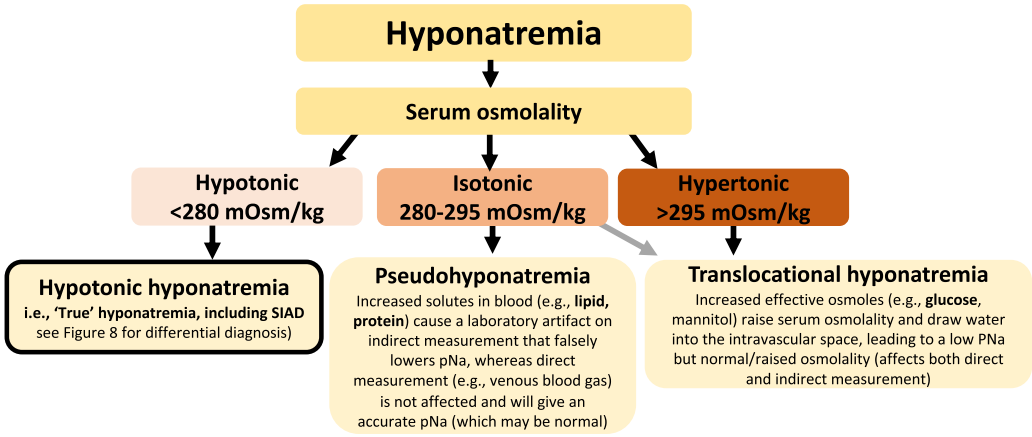

Figure 1. Classification of hyponatremia according to tonicity. Syndrome of inappropriate antidiuresis (SIAD) is the most common cause of hypotonic hyponatremia. Adapted from Sahay 2014 with permission (343), with reference to Spasovski 2014 (15).

exogenous (eg, following administration of IV immunoglobulin) (5, 6). Pseudohyponatremia is due to the electrolyte-exclusion effect, whereby an elevated proportion of blood volume is taken up by "solid" components (fats and protein) that typically constitute 7% of plasma volume, which reduces the relative fraction of plasma water (7). When plasma sodium concentration (pNa) is calculated using common indirect methods that involve dilution of the sample before measurement of sodium ions, an assumed fraction of plasma water is used in deriving the sodium concentration in the original undiluted sample. Where the true plasma water fraction is much lower, this assumption becomes incorrect, and the measured sodium ions are incorrectly assumed to be diluted over a larger plasma water volume than is really present. This pitfall can be avoided by *direct* measurement of an undiluted sample (eg, by using a blood gas analyzer).

In translocational hyponatremia, the presence of excess osmotically active solute in the plasma (most commonly glucose) draws water from the intracellular compartment to the extracellular fluid (ECF), reducing pNa, in the presence of normal or raised plasma osmolality (8, 9). Exogenous agents other than glucose that can cause this effect include mannitol, glycine, histidine-tryptophan-ketoglutarate (used during cardiac surgery and organ transplantation), maltose, and hypertonic radiocontrast media (10-14). In contrast to pseudohyponatremia, translocational hyponatremia is not a laboratory artifact, and both direct and indirect sodium measurement is affected. Correction of serum sodium for increased glucose is discussed in "Confirming a Diagnosis of Syndrome of Inappropriate Antidiuresis" (see Fig. 2).

It is also possible to have dual pathology, hence an exception to the aforementioned classifications can occur in hypotonic hyponatremia with concurrent raised ineffective osmoles (eg, acute alcohol intoxication), which can lead to a measured osmolality that is normal or even elevated despite the hypotonic hyponatremia.

In this review, the term *hyponatremia* will refer to hypotonic hyponatremia unless otherwise stated.

Categorization of hypotonic hyponatremia varies, and usually considers both clinical symptoms and the absolute pNa concentration. Biochemically, European guidelines classify hyponatremia as mild (pNa 130-135 mmol/L), moderate (125-129 mmol/L), or profound (< 125 mmol/L) (15). "Severe" hyponatremia is defined by the presence of symptoms or signs of cerebral edema including vomiting, seizures, cardiorespiratory manifestations of raised ICP, decreased conscious state or coma (eg, Glasgow Coma Scale score [GCS] < 8), and warrants emergency treatment (see "Acute Severe Hyponatremia" and "Emergency Management of Severe Hyponatremia") (15). US expert panel guidelines use the term *severe* more broadly to indicate serum sodium levels less than 125 mmol/L (3). To maintain the distinction of symptomatic severity, we use the European definitions in this review.

Another important categorization is acute vs chronic hyponatremia. Acute hyponatremia is often defined as duration less than 48 hours, whereas chronic hyponatremia is defined as duration greater than 48 hours, and for practical reasons also includes cases where duration cannot be determined. The biochemical basis for this classification is in the time taken for cerebral adaptation to hyponatremia, via the export or deactivation of intracellular effective osmoles (Fig. 3). Those with chronic hyponatremia are vulnerable to rapid correction of pNa if it outpaces the speed that intracellular osmolality can be restored. A critical consideration in the management of moderate or profound hyponatremia that is chronic, or of unknown duration, is the need to avoid excessively rapid correction of serum sodium—which can lead to ODS and permanent neurological disability or death (see "Osmotic Demyelination Syndrome").

This review is based on review of the literature (PubMed) to August 2022 using the search terms "*hyponatr(a)emia*," "*syndrome of inappropriate antidiuresis*," "*syndrome of inappropriate antidiuretic hormone*," and additional search terms specific to each section.

Epidemiology of Hyponatremia and Syndrome of Inappropriate Antidiuresis

The frequency of hyponatremia depends on the definition used, clinical setting, and population studied, but is generally reported to affect 15% to 30% of acute hospital patients to some degree (16-18). Studies reporting rates at the lower end of this range tend to include admission values only and more restrictive sodium inclusion criteria (eg, pNa < 133-135 mmol/L), whereas rates at the higher end consider the whole hospital stay and use broader criteria (eg, < 136-138 mmol/L). Table 2 summarizes large, predominantly retrospective, studies of hyponatremia

Hillier Formula
Correction of serum sodium concentration in the presence of hyperglycemia

$$\text{Corrected } (Na^+) = \text{Measured } (Na^+) + 2.4 \times \frac{(\text{glucose (mmol/L)}) - 5.5}{5.5}$$

Simplified 'rule of thumb': Corrected Na = Measured Na + 1/3 (glucose)

Adrogué-Madias Formula
Estimation of the effect of 1000 mL of intravenous fluid on the serum sodium concentration.
Total body water is calculated as 60% of the weight in kilograms for women, and 50% of the weight in kilograms for men.

$$\text{Change in serum } Na^+ \text{after 1L fluid} = \frac{(\text{Infusate } Na^+ + \text{Infusate } K^+) - \text{serum } Na^+}{\text{Total body water} + 1}$$

Fractional excretion of uric acid (FE-UA)
An alternative measure to urine sodium concentration to identify SIAD in patients despite the use of diuretics. Uric acid is excreted in the proximal tubule and its urinary concentration is not affected by common diuretics, unlike urine sodium concentration.
Raised FE-UA (>12%) has a high positive predictive value for SIAD regardless of recent diuretic use (6).

$$\text{FEUA} = \frac{\text{Urine } UA \times \text{Serum } Cr}{\text{Urine } Cr \times \text{Serum } UA} \times 100$$

Fürst Ratio (Fürst Equation)
Calculation of a Urine:Serum electrolyte ratio, which can predict response to fluid restriction.
The Fürst equation ratio has been used to assist dosing of fluid restriction:
- Fürst ratio <0.5 → fluid restriction 1000 ml/day recommended
- Fürst ratio 0.5-1 → fluid restriction 500 ml/day recommended

A Fürst ratio >1 is said to predict non-response to fluid restriction. However, one study found the Fürst ratio does not perform as well as urine osmolality >500 mOsm/kg/H_2O or urinary sodium concentration >130 mmol/L in predicting non-response (8).

$$\text{Fürst ratio} = \frac{\text{Urine } Na^+ + \text{Urine } K^+}{\text{Serum } Na^+}$$

Figure 2. Useful formulae in the management of hyponatremia. Cr, creatinine; FEUA, fractional excretion of uric acid; mOsm, milliosmoles; Na^+, sodium; UA, uric acid.

References (in order): Hiller 1999 (9), Adrogué 1997 (344), Maesaka 1998 (207), and Fürst 2000 (276).

prevalence in the inpatient and outpatient setting. Many factors relevant to hospitalization can promote antidiuresis via stimulation of AVP (including stress-related factors such as pain and nausea); other contributors may include medications (eg, diuretics), hypotonic fluid administration, or reduction in heart, kidney, or liver function.

A prospective cohort study from the Netherlands of nearly 3000 hospitalized patients with available sodium measurements over a 3-month period found that 30% had a recorded sodium level below 136 mmol/L during their admission (19). A larger Danish prospective study of more than 250 000 inpatients reported that 15% had serum sodium of less than 135 mmol/L at admission (26). Larger retrospective database studies from Singapore, the United States, and China support this range, with reported rates of sodium less than 135 mmol/L between 14.5% and 28.2% (20, 23, 25). An outlying US study of nearly 200 000 patients reported only 5.5% had hyponatremia; however, this study employed stricter criteria, requiring 2 sodium concentrations below 135 mmol/L within 24 hours of admission, which would not capture those with transient initial hyponatremia, only a single result, or hyponatremia that developed later during the hospital stay (24). Rates of profound hyponatremia are lower, with approximately 2% of patients recording sodium concentrations at or below 125 mmol/L (19, 23, 25, 26). There are specific patient subgroups with a higher risk of moderate-profound hyponatremia—for example, following pituitary surgery, where a meta-analysis showed 5.6% cases develop symptomatic hyponatremia (30, 31). Large database studies may fail to account for factors that can influence the accuracy of sodium measurements. Although many studies do seek to exclude translocational hyponatremia due to increased serum glucose (19, 20, 25), causes of pseudohyponatremia such as increased serum lipids or proteins, or erroneous results from hemolyzed (32) or contaminated blood samples, are not specifically excluded.

In the general population outside hospitals, reported incidence of hyponatremia is lower. Even so, studies drawing on pathology results in community-dwelling people may overestimate the prevalence in the general population, given that included participants may have a clinical indication for electrolyte measurement. In the aforementioned Singaporean study, the prevalence of hyponatremia in around 76 000 primary care patients was 4.3% for pNa less than 135 mmol/L, and 0.14% for pNa less than 126 mmol/L (23). Population-based studies may provide a more accurate community prevalence. A study of community-dwelling adults older than 55 years in a single suburb in the Netherlands found hyponatremia less than 136 mmol/L in 7.7% of people, though most were mild, with only 0.46% of the total population less than 130 mmol/L (28). Another population-based cross-sectional study of 14 697 adults participating in a health survey estimated overall prevalence of serum sodium below the laboratory reference range at 1.72% (applying a more stringent threshold of < 133 mmol/L for a proportion of patients) (29).

In summary, the reported prevalence of hyponatremia in hospitalized patients, of all causes, varies considerably but is mostly in the range of 15% to 30% due to differing definitions

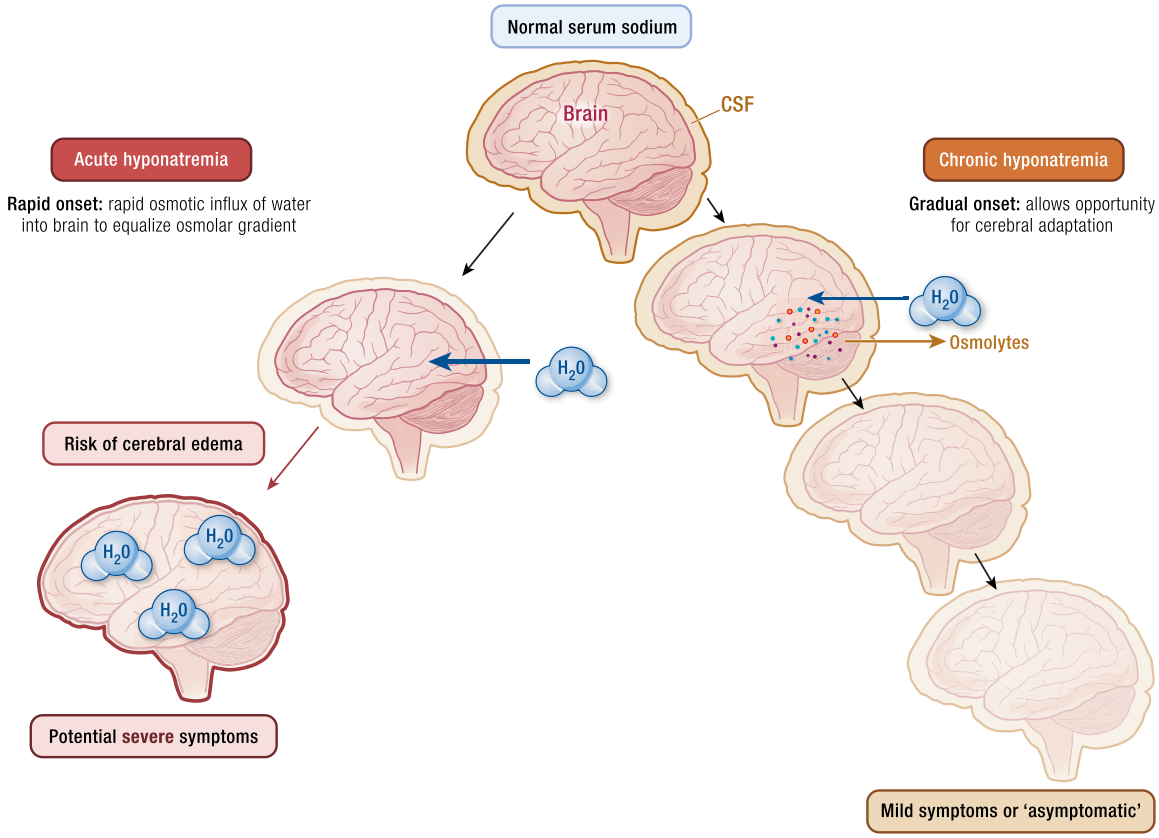

Figure 3. Schematic diagram of the development of acute vs chronic onset of hyponatremia, explaining typical difference in symptom severity. Intensity of shading is a visual representation of osmolality. Acute hyponatremia results in relatively hypotonic serum/cerebrospinal fluid (CSF) compared to brain tissue, leading to osmotic influx of water into glial cells to equalise osmolar gradient, which may cause cerebral edema and potential seizure, coma, and death. Chronic hyponatremia often occurs more gradually. As serum/CSF osmolality falls, water enters the brain more slowly and is matched by export or deactivation of brain osmolytes including sodium, potassium, and organic osmolytes (eg, myoinositol, glycerophosphorylcholine, creatine, glutamate, glutamine, taurine) to equalize the osmolar gradient (116). The resulting hypotonic brain is vulnerable to rapid correction if the reverse process happens too rapidly, which may cause osmotic demyelination syndrome (see Fig. 7).

of hyponatremia and patient populations studied. If mild hyponatremia is excluded, the percentage with serum sodium below 130 mmol/L is likely around 4% or less of patients, and those below 125 mmol/L around 2% or less. Existing studies are limited by their (mostly) retrospective design.

Older age is a strong risk factor for hyponatremia (25, 28, 29). This is particularly seen in hospitalized patients; in one study, those older than 80 years had an odds ratio (OR) of 10.88 (95% CI, 8.13-14.57) for developing profound hyponatremia less than 126 mmol/L in the hospital compared to patients younger than 30 years (23). Patients with hyponatremia also have higher average comorbidity scores compared to those with normal sodium (24, 25). A study of 119 nonhospitalized residential care dwellers aged 60 or older reported that 18% had hyponatremia (< 136 mmol/L), compared to 8% of age-matched community-dwelling controls (33). While the association of hyponatremia with age is clear, observational studies alone cannot definitively separate the effects of age on hyponatremia susceptibility, as it is not possible to fully adjust for age-related comorbidities. Aging and frailty reduce the capacity to maintain homeostasis in response to environmental, disease-related, and iatrogenic disturbances in water balance (34). Mechanisms may include impaired thirst sensation (35), reduced total body water, reduced glomerular filtration rate (GFR) (36), loss of urinary concentrating capacity (37, 38), decreased renal responsiveness to AVP (35), plus effects of accumulated comorbidities and medications (39). Age-associated reduction in kidney function occurs because of loss of parenchymal mass, tubulopathy, interstitial fibrosis, glomerulosclerosis, and microscopic arteriolar shunts (34, 36). Data on AVP concentrations in older individuals are controversial, with some studies suggesting higher concentrations (40-42) whereas others show no difference (43) or lower concentrations (44). There is similar controversy regarding the effect of age on the AVP response both to inhibitory (ethanol) and secretory (hypertonic saline) stimuli. One trial observed reduced free water clearance in response to ethanol with age, and a greater increase in AVP in response to hypertonic saline in older compared to younger individuals despite similar free water clearance (45). An increased AVP response could compensate for the reduced renal ability to conserve salt and water with age and may be consistent with higher rates of SIAD seen in older individuals, if confirmed.

While there is some preclinical evidence that sex steroids may modulate the secretion of AVP (46), there is no consistent effect of sex on hyponatremia rates, with some studies reporting a slight male predominance (23), some a female predominance (29) and others no effect (28).

In population-based studies, SIAD is the most common attributed cause of hyponatremia, accounting for 35% to 40% of cases. However, most retrospective studies to determine the etiology of hyponatremia are limited by an incomplete

Table 2. Prevalence of hyponatremia—summary of key studies in adults

First author, date, country	Study design and duration	Setting	Denominator (N =)	Hyponatremia prevalence		
				pNa < 135 (unless specified)	pNa < 130	pNa < 125 (unless specified)
Hospital inpatients						
Hoorn, 2006 (19) Netherlands	Prospective cohort 3 mo	Inpatients Single center	2907	30% (pNa < 136)		2.6% (pNa < 126)
Waikar, 2009 (20) US	Prospective cohort 3 y	Inpatients 2 centers	98 411	19.7% *14.5% on presentation, 12.8% after correction for hyperglycemia*		*0.6% on presentation*
Ioannou, 2021 (21) Greece	Prospective cohort 2 y	Inpatients > 65 y Single center	3621		*4.25% on presentation*	
Anderson, 1985 (22) US	Prospective cohort 3 mo	Inpatients Single center	Not reported		2.48%	
Hawkins, 2003 (23) Singapore	Retrospective database 2 y	Inpatients Single laboratory	~ 43 249 (36% of 120 137)	22.1% (28.2% Na < 136)		2.6% (Na < 126) (0.49% Na < 116)
Zilberberg, 2008 (24) US	Retrospective database 1 y	Inpatients 39 centers	198 281	*5.5% on presentation (2× pNa within 24 h of admission)*		
Hao, 2017 (25) China	Retrospective cohort study 5 y	Inpatients Single center	154 378	17.5%		1.2%
Holland-Bill, 2015 (26) Denmark	Prospective cohort 6 y	Inpatients Multicenter	279 508	*15% on presentation (16.4% of those with Na level available)*		*1.7% on presentation*
Wald, 2010 (27) US	Retrospective cohort 7 y	Inpatients Single center	53 236	*37.9% on presentation (pNa < 138)*		
Nonadmitted population (outpatients)						
Hawkins, 2003 (23) Singapore	Retrospective database	Nonadmitted patients, single laboratory	~ 76 887 (64% of 120 137)	4.3%		0.14%
Liamis, 2013 (28) Netherlands	Prospective cohort 3 y	Community-dwelling adults aged > 55 y Single suburb	5179	7.7% (pNa <136)	0.46%	
Mohan, 2013 (29) US	Population-based, cross-sectional	Adults who participated in a national health survey	14 697	1.72% (pNa < 133/135) —definition changed midstudy		

Italic text = Prevalence based on initial sodium reading only (ie, hyponatremia on admission). Includes studies based on sodium measurements only. Studies based on discharge coding are omitted because of likelihood of underestimation.
Abbreviation: pNa, plasma sodium concentration.

diagnostic workup, with 1 multicenter registry finding that less than 50% of 3087 patients with hyponatremia had all appropriate investigations performed (47). A prospective study of 121 consecutive inpatients with pNa less than 130 mmol/L at a single hospital in Germany, who were assessed by a senior endocrinologist according to a rigorous diagnostic protocol, determined that 35% had SIAD, 32% hypovolemia, 20% hypervolemia (heart failure, cirrhosis, angioedema), 7% thiazide-induced hyponatremia, 4% primary polydipsia, and 2% adrenal insufficiency (48). Another prospective study at a tertiary neurosurgical referral center in Ireland of 1323 patients admitted with pNa less than or equal to 130 mmol/L initially classified 573 (43.4%) of these patients as having SIAD, though 22 of these (3.8%) were subsequently reclassified to adrenal insufficiency after completing further investigation.

The frequencies of underlying causes of SIAD (Fig. 4) vary substantially between studies. An international multicenter registry of 1524 patients with SIAD found the cause was

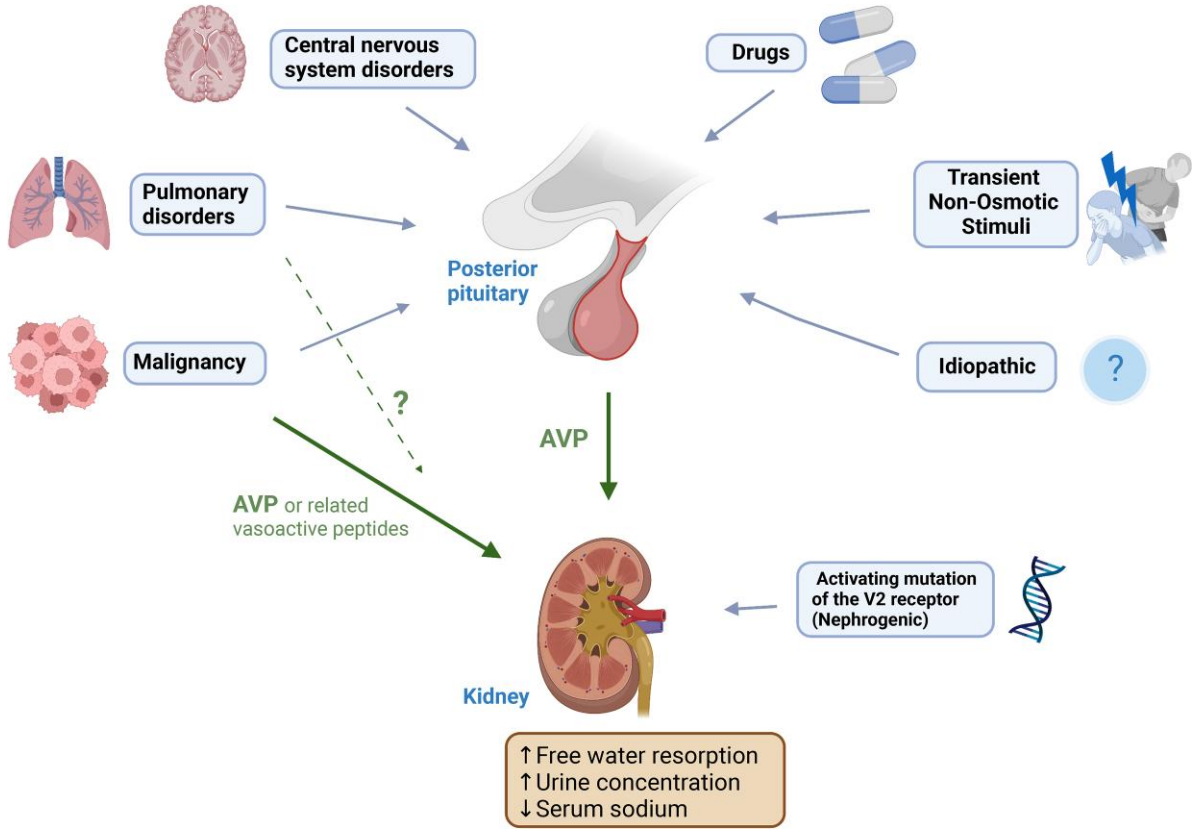

Figure 4. Causes of syndrome of inappropriate antidiuresis (SIAD). Malignancy (solid organ (particularly lung and nasopharyngeal), lymphoma). Pulmonary disorders (infection, asthma, cystic fibrosis, respiratory failure). Central nervous system disorders (infection, hemorrhage, thrombosis, trauma, tumour, hydrocephalus, autoimmune (multiple sclerosis, Guillain-Barré syndrome), multiple system atrophy, delirium tremens). Transient stimuli (nausea, pain, stress, prolonged endurance exercise, general anesthesia, pituitary surgery). Drugs (see Table 5). Idiopathic ("reset osmostat," cause not yet apparent). Hereditary (nephrogenic SIAD). AVP, arginine vasopressin. Original figure created with BioRender, with reference to Spasovski 2014 (15).

undetermined in 35.2%, malignancy in 23.6%, drug-induced in 17.8%, pulmonary disease in 10.7%, central nervous system (CNS) pathology in 8.5%, and other causes in 14.1% (49). In the aforementioned prospective German study, among 42 patients who met criteria for SIAD the attributed cause was cancer in 48%, acute bacterial infection in 19%, nausea and vomiting in 18%, and iatrogenic (from AVP analogues) in 4% (2 patients) (48). In the prospective Irish study, CNS pathology was the most frequent underlying pathology at 26% (perhaps reflecting the location at a neurosurgical specialist center), followed by pulmonary disease in 19%, malignancy in 18%, postoperative in 10%, drug-related in 8%, sepsis in 5%, and idiopathic or mixed in 4% (50). Of note, in these studies, the etiology of SIAD was determined by association, rather than causation (which would be strengthened by the demonstration that rectifying the assumed causative disease leads to resolution of SIAD). The disparate findings between these studies suggests there is more to be learned about the relative prevalence of underlying causes of SIAD.

Mechanisms and Pathophysiology of Syndrome of Inappropriate Antidiuresis

The ability of a pituitary extract to raise blood pressure was first described in 1895 (51). Later, the inhibition of urinary excretion by pituitary extract (the antidiuretic effect) was reported in 1913 (52). The amino acid structure of AVP was first described by du Vigneaud and colleagues in 1951, followed by synthesis of AVP and oxytocin in 1953—combined work for which he was awarded the 1955 Nobel Prize for Chemistry (53-55).

AVP is a 9-amino-acid peptide that is synthesized in magnocellular neurosecretory cells (MNCs) located in 2 discrete areas of the hypothalamus: the supraoptic nucleus and the paraventricular nucleus (56). AVP derives from a 164-amino-acid precursor protein (pre-pro-AVP) consisting of a signal peptide, the AVP moiety, a carrier protein (designated neurophysin II) and copeptin (a 39-amino-acid glycosylated peptide with a leucine-rich core segment) (57, 58). The precursor peptide is processed in the endoplasmic reticulum by removal of the signal peptide and addition of a carbohydrate chain (59). Additional posttranslational processing occurs during transport down the infundibulum (pituitary stalk) to axon terminals in the posterior pituitary, enzymatically separating AVP, copeptin, and neurophysin 2 (59, 60). AVP is stored in neurosecretory granules until specific stimuli including raised serum tonicity and reduced effective circulating arterial blood volume cause secretion into the circulation (Fig. 5).

There are 2 neurosecretory pathways for AVP release. First, changes in ECF tonicity are detected by osmoreceptors located in the anterior hypothalamus in the organum vasculosum of the lamina terminalis (OVLT) and subfornical organ (61-63). These osmoreceptors transduce tonicity change into alterations in the frequency or pattern of action-potential discharge, which in the setting of increasing osmolality prompts

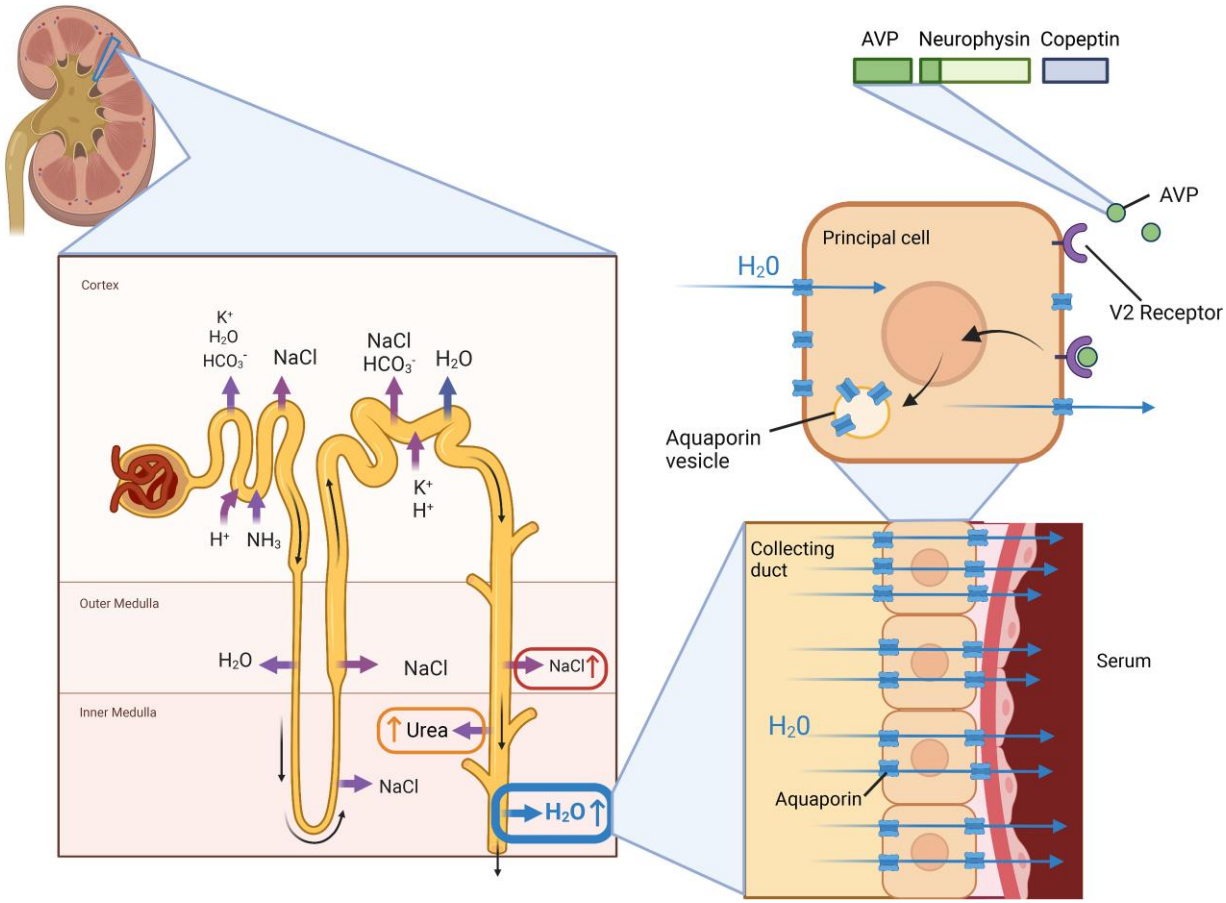

Figure 5. Mechanism of arginine vasopressin (AVP) action at renal V2 receptors. AVP interacts with the vasopressin V2 receptor on the principal cells of the renal collecting duct. When the G protein-coupled receptor V2 receptor is activated, cyclic adenosine monophosphate signaling leads to increased synthesis and deployment of aquaporins, which are stored in intracellular vesicles which then merge with the luminal cell wall. Aquaporins allow the resorption of solute-free water out of the filtrate and into serum, resulting in more concentrated urine excretion. AVP also acts on epithelial sodium channel (ENaC) urea transporters to increase sodium and urea resorption to increase medullary interstitial osmolality and hence urinary concentrating gradient. Persistent AVP stimulation "inappropriate" with respect to serum osmolality will lead to excessive water retention and a fall in serum osmolality and serum sodium concentration. Original figure created with BioRender, with reference to Christ-Crain 2019.

AVP release (56, 64). The basal electrical activity of these cells determines the osmotic "set point." The main osmotic site in the mammalian brain is the OVLT, but MNCs in the supraoptic nucleus can also operate as intrinsic osmoreceptors (65). A second neurosecretory pathway transports high concentrations of AVP from parvocellular neurons to the pituitary portal system, where it acts synergistically with corticotropin-releasing hormone (CRH) to stimulate release of adrenocorticotropic hormone from the anterior pituitary (66).

In addition to osmotic stimuli, AVP release is also influenced by peripheral baroreceptors. AVP secretion is inhibited by afferent noradrenergic input from baroreceptors in the left atrium, aortic arch and carotid sinus that detect stretch (56). A reduction baroreceptor activity, for example, following hypotension or hypovolemia, leads to increased MNC activity, prompting AVP release (67).

"Appropriate" release of AVP in response to increased tonicity or hypovolemia engages homeostatic mechanisms aiming to restore blood volume. AVP acts on 3 receptors (V1a [also known as V1], V1b [also known as V3], and V2) to enact a range of effects important for defense against dehydration, hypovolemia, and organ hypoperfusion. Activation of V1 receptors in vascular smooth muscle, hepatocytes, platelets, brain, and uterus causes vasoconstriction, glycogenolysis, platelet aggregation, aggression, and uterine contraction (akin to oxytocin), respectively (68). Activation of V3 receptors in the anterior pituitary gland stimulates the production of adrenocorticotropin (ACTH) (69). Finally, V2 receptors are located both on platelets, where they stimulate von Willebrand factor release, and in the kidney, where they mediate antidiuresis.

Renal V2 receptors are located on the basolateral membrane of principal cells in the collecting duct. Stimulation of the V2 receptor increases synthesis and insertion of aquaporin-2 water channels that increase water permeability, leading to increased reabsorption of water from the glomerular filtrate, resulting in water retention and more concentrated urine (Fig. 5). Additionally, AVP promotes water resorption by increasing the medullary interstitial osmotic gradient by increasing expression of epithelial Na^+ channels (ENaC) to increase sodium reabsorption, and by increasing urea transporters (UT-A1s) to increase urea reabsorption (70-73). These mechanisms increase the osmotic gradient in the renal interstitium to draw additional water from the filtrate, further contributing to urine concentration.

AVP can be viewed as an essential hormone to maintain tissue perfusion and defend against physiological and psychological stress. This essential importance of AVP to survival is

demonstrated by the fact that hypothalamic AVP production is highly redundant, with clinical AVP deficiency (diabetes insipidus) manifesting only if more than 90% of hypothalamic AVP neurons are destroyed (74). Experiments in rodents show that the defenses against deviations of blood volume or osmolarity from their set points are very finely tuned. In hyperosmolar states, presentation of water-predicting cues reduces AVP-secreting neuron activity within seconds, even before water ingestion begins (75). Likewise, optogenetic experiments suggest that thirst-sensing neurons can predict how water consumption will alter fluid balance in the future and can adjust water intake behavior preemptively (76), including by increasing perceived swallowing effort (77).

SIAD is a consequence of AVP activity in excess of osmotic requirements. In SIAD, antidiuresis persists despite low serum tonicity and the absence of hypovolemia. Sustained stimulation of V2 receptors promotes aquaporin insertion into the cell membrane, leading to increased reabsorption of water, increased urine concentration, and, in the context of ongoing free water ingestion, a progressive decline in plasma sodium concentration. Additionally, to compensate for ECF volume expansion, aldosterone is suppressed and atrial natriuretic peptide increases, resulting in urinary sodium loss, a phenomenon also known as "pressure natriuresis" (60). Thus, chronic hyponatremia due to SIAD is a state of whole-body sodium depletion in addition to water retention (2). Interestingly, in chronic SIAD a compensatory mechanism can occur via downregulation of V2R with reduction in aquaporin-2 expression, which can aid in limiting the free water excess (2).

SIAD has many potential underlying causes (see Fig. 4). Excess AVP activity may be due to nonosmotic release of pituitary AVP, unregulated ectopic production of AVP from a nonpituitary source (eg, paraneoplastic SIAD in malignancy), or abnormal renal sensitivity to AVP in the rare case of nephrogenic SIAD. Medications may also cause, or mimic, SIAD (Table 5). More common causes of SIAD include malignancy, CNS pathology, and pulmonary disorders. Transient nonosmotic stimuli such as nausea, pain, and stress, may also prompt AVP release. If an underlying cause of SIAD is not identified it may be deemed "idiopathic," which is sometimes due to an altered osmotic set point ("reset osmostat") where the threshold for AVP release is reset downward to defend a lower baseline serum sodium, often seen in older patients (82). Reset osmostat can be diagnosed by monitoring response to a water load, which will be excreted with serum sodium remaining stable, in contrast to other forms of SIAD where water is retained and serum sodium declines (83). See "Confirming a Diagnosis of Syndrome of Inappropriate Antidiuresis" below for further discussion on the diagnosis of SIAD and differentials.

One CNS-related cause of SIAD that deserves specific mention is SIAD following pituitary surgery. Transsphenoidal resection of pituitary or sellar lesions, with resulting manipulation of the pituitary and infundibulum, can lead to transient release of stored AVP causing SIAD (84, 85). The nadir serum sodium typically occurs between postoperative days 6 and 12 and has the potential to cause severe symptomatic hyponatremia (31). This may occur in isolation, or as part of a "triphasic response" followed by persistent AVP deficiency (diabetes insipidus) in the context of more extensive pituitary compromise (resection or damage) (84, 86). Given that the sodium nadir frequently occurs after hospital discharge, patients should be educated about the risk of delayed hyponatremia. Prevention of hyponatremia with prophylactic FR (1000 mL per day from postoperative days 4-9) with measurement of serum sodium at day 7 is recommended, provided symptoms of AVP deficiency do not occur (84, 87). If hyponatremia does occur, management is similar to other causes of chronic SIAD, though this SIAD is typically self-limiting and will resolve in around 5 days (88).

Given the frequent association between nonmalignant lung pathology (eg, pneumonia, pleural effusion) and SIAD, an unanswered question is whether AVP or AVP-like peptides can be produced in the lung, or whether this is pituitary mediated. Small cell lung carcinoma, derived from neuroendocrine cells in the lung epithelium (89), produces paraneoplastic AVP in approximately 10% to 15% of cases (90, 91). Whether nonneoplastic pulmonary neuroendocrine cells have the capacity to release AVP is not clear. An alternative hypothesis is that hypoxia and inflammatory cytokines produced in the setting of pulmonary infection such as interleukin-6 stimulate pituitary AVP release (92).

Nephrogenic SIAD is a very rare X-linked recessive condition caused by an activating mutation of the *AVPR2* gene that encodes the V2 receptor (93). There have been 21 cases reported (18 of these males), across 5 family groups (94). This mutation leads to constant activation of the V2 receptors in the renal collecting duct, causing free water retention and hyponatremia—resembling chronic SIAD, but with appropriately low AVP levels in response to hypoosmolality. Overt cases present in infancy and can be associated with severe cerebral edema. There is high phenotypic variability, however, with some cases minimally symptomatic and diagnosed only after challenge with a water load (95). Genetic testing in patients with SIAD is infrequent, hence the proportion of nephrogenic SIAD is unknown, but it is estimated to affect fewer than 1 per million population. A low serum copeptin concentration (eg, < 2.0 pmol/L, with low serum sodium and osmolality) may provide a clue to this diagnosis and prompt genetic testing (96).

SIAD has been classified into a number of distinct pathophysiological categories based on evaluation of AVP concentrations (Fig. 6). This was pioneered by Zerbe and colleagues (97), who measured AVP concentration before and after raising the serum osmolality with hypertonic saline in patients with SIAD, and identified 4 patterns of AVP response, known as types A to D. These phenotypes correlate with certain etiologies; however, whether the categories are clinically meaningful or simply a vehicle for better understanding pathophysiology is less clear. Type A refers to a persistently raised AVP concentration regardless of an increase in serum osmolality, which occurs in the most common forms of SIAD due to ongoing "inappropriate" AVP secretion either from the pituitary or a paraneoplastic source (98). Type B is characterized by a lower osmotic threshold for AVP secretion ("reset osmostat"), with serum sodium typically stably maintained at a lower level of 125 to 135 mmol/L, in which AVP will still suppress at lower osmolarities than this (unless another intercurrent pathology occurs). This pattern may be more common in older age. Rarer patterns include type C, characterized by an abnormal AVP response only at low osmolalities, potentially due to dysfunction of inhibitory neurons in the hypothalamus, and type D, in which AVP is undetectable, either because of secretion of an unidentified antidiuretic substance from tumor cells, or alternatively, a gain-of-function mutation in the V2 receptor (ie, nephrogenic

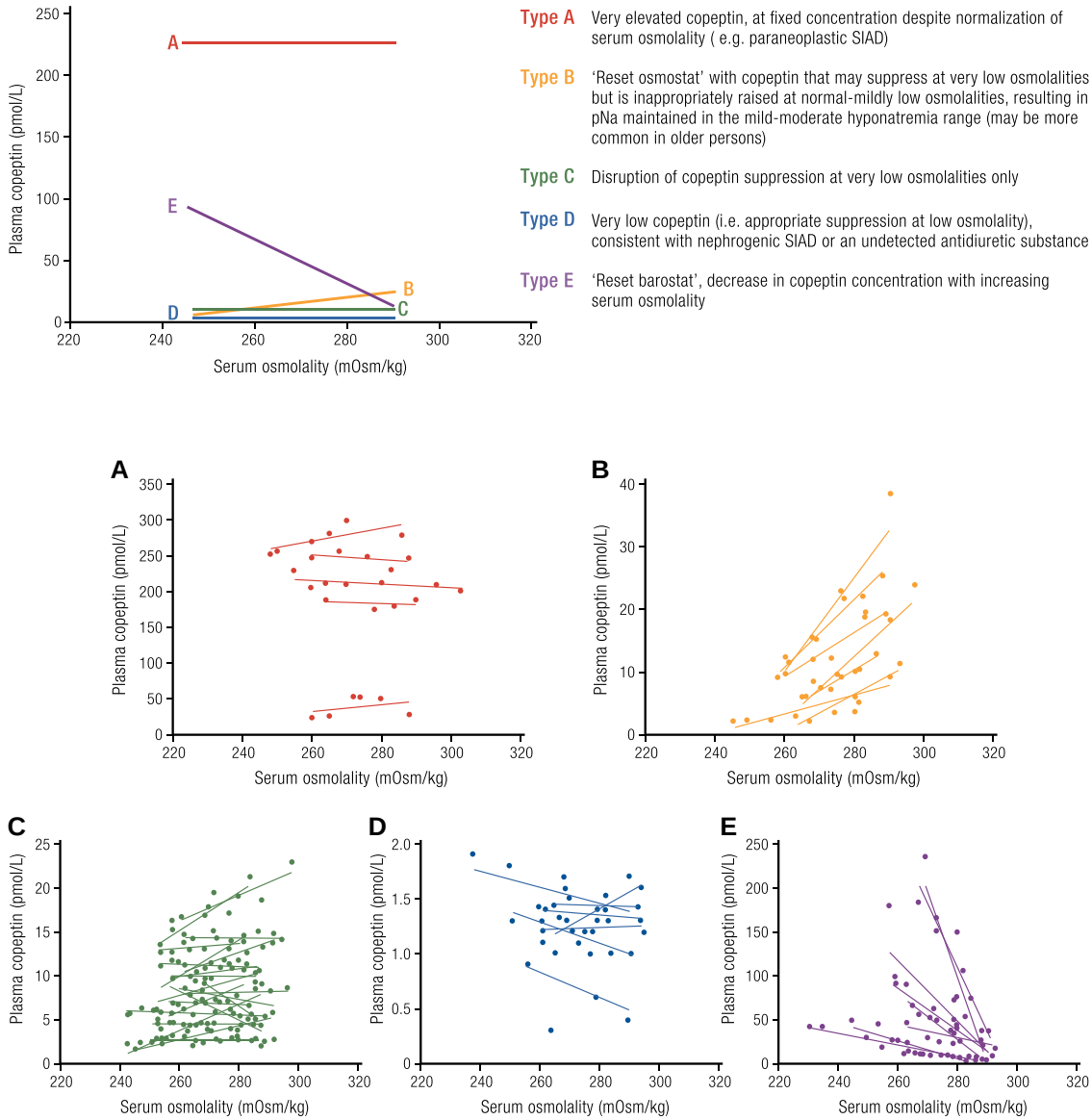

Figure 6. Biochemical subtypes of syndrome of inappropriate antidiuresis (SIAD), categorized according to 5 patterns of copeptin (types A-E), based on copeptin measurement when hyponatremic, and after infusion of hypertonic saline to normalized serum sodium. This illustrates distinct phenotypes of SIAD based on arginine vasopressin response—the clinical significance of which is not clear. Upper graph is an original figure, adapted from A-E below. A-E are reproduced from Fenske 2014 (96) with permission.

SIAD) (93). More recently, the same patterns have been shown for copeptin, even pointing to a fifth novel SIAD subtype discovered in 20% of patients that was characterized by a linear decrease in copeptin concentrations with increasing serum osmolality (type E), which may represent a "reset barostat," or could be consistent with resolution of acute type A SIAD (96) (see Fig. 6). Whether treatment responses and patient outcomes will vary according to SIAD subtype is still to be investigated.

Symptoms, Morbidity, and Mortality of Hyponatremia

Acute Severe Hyponatremia

Acute severe hypotonic hyponatremia is a medical emergency. It can lead to cerebral edema, due to osmotic influx of water into the brain, causing raised ICP within the confined skull, and potential cerebral herniation and death (see Fig. 3) (99). "Severe" symptoms indicative of imminent adverse outcomes may include vomiting, seizure, somnolence (GCS score < 8), coma, or cardiorespiratory manifestations of increased ICP (Cushing reflex) such as bradycardia, widened pulse pressure, and irregular breathing (100). The presence of severe symptoms warrants urgent intervention (see "Emergency Management of Severe Hyponatremia"). Moderately severe symptoms that may precede these include nausea, confusion, and headache (15). Rapid progression can occur, especially in the case of acute water ingestion when there is water in the stomach that is still to be absorbed, or in the context of inappropriate hypotonic IV fluid administration.

Historically, severe acute hyponatremia was observed to have very poor clinical outcomes. A 1986 case series of 15 women, mean age 41 years, with documented postoperative acute hyponatremia due to SIAD who presented with seizures and mean nadir sodium 108 mmol/L, reported that 27% of

patients died, 13% had limb paralysis, and 60% had a persistent vegetative state (100). Lack of active intervention in severe hyponatremia is associated with worse neurological outcomes. A prospective observational study of 53 women, mean age 62 years, with severely symptomatic hyponatremia (including 41% with respiratory failure), mean pNa 111 mmol/L, found that treatment with hypertonic saline before respiratory failure was associated with better neurological outcomes, with an average Cerebral Performance Category after 4 months of 1 out of 5 (indicating normal function or slight disability) in treated patients, compared to a mean score of 4.6 out of 5 (where 4 represents persistent vegetative state, and 5 indicates death) in those treated with FR alone (101). In a more contemporary retrospective study of 255 patients across 2 tertiary hospitals presenting with serum sodium less than 120 mmol/L from 2000 to 2007 (of whom 40% presented with neurological symptoms, and 49 had serum sodium ≤ 110 mmol/L), a mortality rate of 10% was seen, and 1.6% had permanent neurologic sequalae due to ODS (discussed further in "Osmotic Demyelination Syndrome"). With the advent of international guidelines and a growing evidence base and clinical expertise, outcomes may continue to improve. A recent study retrospectively assessed the benefit of active management of hyponatremia in patients with severe hyponatremia (defined as pNa < 120 mmol/L), by longitudinally reviewing outcomes at a single Irish center in 2005, 2010, and 2015 (102). The greatest improvement was seen between 2005 and 2010, with rates of specialist referral increasing from 32% to 68%, rates of active management in patients with pNa less than 120 mmol/L increasing from 63% to 88%, and an associated reduction in mortality from 51% to 15% over that 5-year period. Across the whole cohort, specialist consultation was associated with a 91% reduction in mortality risk (102). These assembled data support intervention in severe symptomatic hyponatremia, typically with bolus hypertonic saline, as being critical to improving morbidity and mortality (see "Emergency Management of Severe Hyponatremia").

Biochemical and symptomatic severity are not always well correlated, as patients with chronic hyponatremia may have very low serum sodium concentrations with minimal symptoms due to cerebral adaptation, yet patients with an acute precipitous fall in serum sodium, even to concentrations above 120 mmol/L, may present with severe symptoms (103). The presence of severe symptoms should prompt treatment with careful bolus hypertonic saline aiming for an increment in serum sodium of 4 to 6 mmol, based on clinical improvements seen in published cases (104). There is clinical evidence to support a 50% reduction in ICP with a pNa increase of this magnitude (105). A retrospective observational study of 68 patients with transtentorial herniation due to cerebral hemorrhage, stroke, or tumor but with normal serum sodium concentration (mean pNa 140 mmol/L), were administered a small, 30- to 60-mL bolus of very concentrated hypertonic saline (NaCl 23.4%, equivalent Na^+ to 240 mL of 3% NaCl) (105). ICP reduced from 23 to 11 mm Hg over 24 hours, and reversal of herniation occurred in 75% of cases, predicted by a 5-mmol/L or greater increase in pNa ($P = .001$) (105). There was no control group comparison, however—and this was not a hyponatremic cohort (105). Collectively, however, these studies illustrate the rationale for active intervention with hypertonic saline in symptomatic hyponatremia to reduce ICP and improve morbidity and mortality.

In patients definitively known to have acute hyponatremia, it is thought that pNa can be corrected (or allowed to correct) more rapidly, as the second phase of cerebral adaptation to low pNa (depletion of organic osmolytes) has not yet occurred (see Fig. 3) (106). In practice, however, when a patient presents to hospital for care, it is often unclear whether their hyponatremia is acute or chronic. Even if there is a compelling history of water intoxication, endurance exercise with hypotonic fluid consumption, or recreational 3,4-methylenedioxymethamphetamine (MDMA/"ecstasy") use that supports acuity, unless a reliable normal pNa measurement within the previous 24 hours it is available, it is not possible to confirm. While symptom-defined severe hyponatremia should always prompt treatment with hypertonic saline to achieve the initial small increment in serum sodium described earlier, in most cases it is necessary to assume chronicity and adopt conservative serum sodium correction targets from that point to avoid the risk of ODS (see "Osmotic Demyelination Syndrome").

There is at least one reported case of atypical ODS occurring following correction of acute hyponatremia (107). A study in rats showed that that while rapid correction of acute hyponatremia is usually well tolerated, some risk of ODS may remain (108). In this experiment, acute profound hyponatremia (mean pNa 106 mmol/L) was A, induced rapidly and then reversed after 5 hours; B, induced over 10 hours, then corrected after 24 hours; or C, induced gradually over 48 hours then reversed after 72 hours (ie, chronic hyponatremia) (108). Correction was achieved through either rapid or slow infusion of hypertonic saline. All rats in group A with rapid onset and reversal of hyponatremia survived with good neurological outcomes. Those in group B all survived, but 2 of 12 (17%) of those rapidly corrected after 24 hours had adverse neurological outcomes, compared to 100% good neurological outcomes with slow correction in this group. As expected, the worst outcomes were in the model of chronic hyponatremia (group C) following by rapid correction, which led to neurological deterioration in 10 of 12 rats, 7 of which died (108). This study did not observe harm related to slow correction for any duration of hyponatremia.

Although the conventional cutoff for "acute" hyponatremia onset is considered 48 hours, clinically we favor a more conservative less-than-24 hours definition, provided this is confirmed with pathology results, before permitting rapid correction, to minimize ODS risk.

Osmotic Demyelination Syndrome

A critically important consideration in hyponatremia of chronic or unknown duration is managing the risk of ODS by avoiding excessively rapid correction of serum sodium concentration, which can damage the protective neural myelin sheath as a consequence of osmotic stress—with severe, potentially fatal, consequences. ODS was first reported in 1959, in a series of individuals presenting with rapidly evolving flaccid quadriplegia, pseudobulbar palsy, and then death within weeks, who were found to have distinctive pontine lesions at autopsy, on a background of alcohol abuse and malnutrition (109). It was only in the 1980s after preclinical studies in animals demonstrated demyelination after rapid correction of chronic hyponatremia that causation was established (110), supported by concordant patient observations (111).

When hyponatremia is chronic, brain cells adapt to the reduced serum tonicity by decreasing intracellular osmolytes

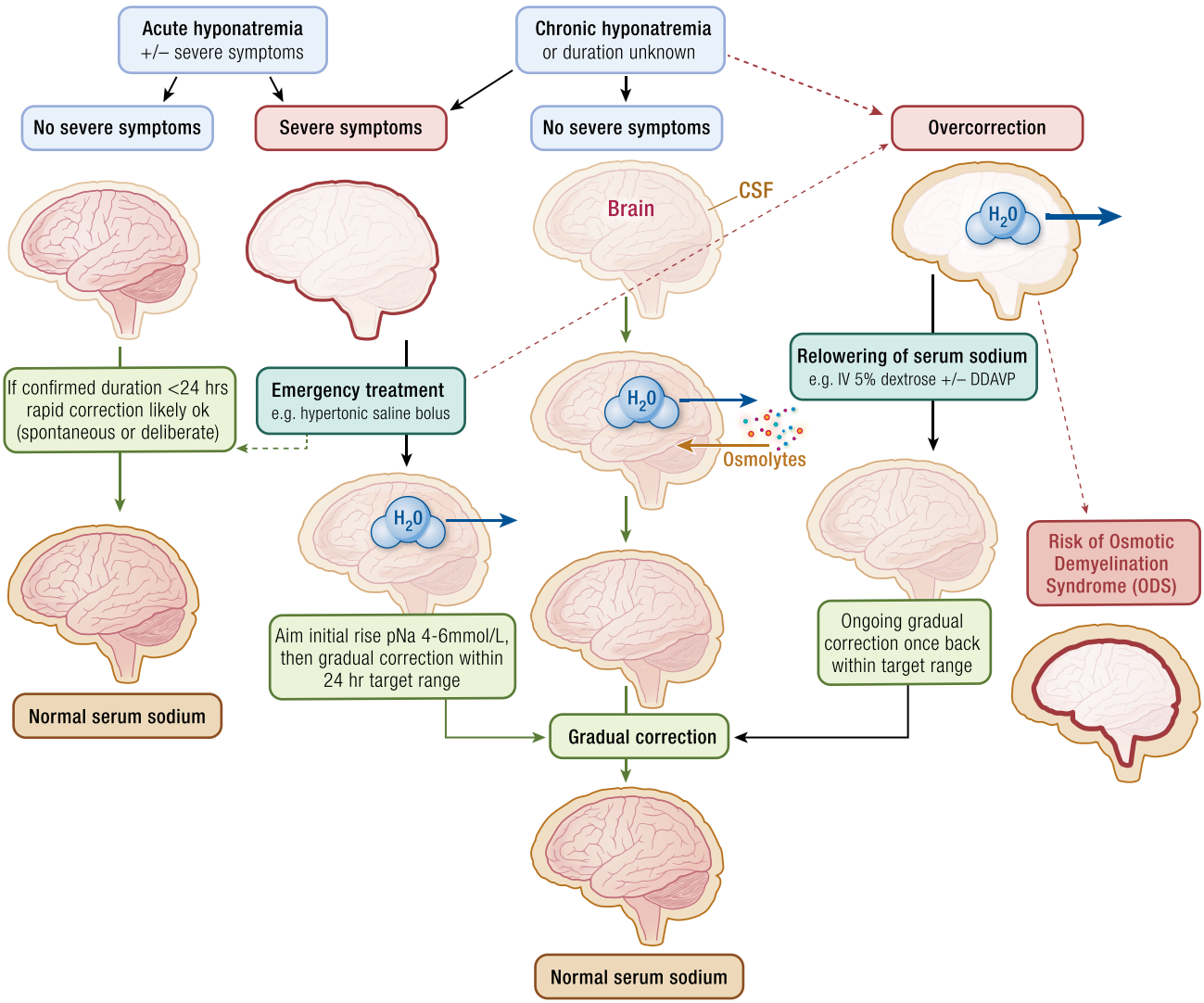

Figure 7. Principles of management of acute vs chronic hyponatremia, and potential risks. Intensity of shading is a visual representation of osmolality. In acute hyponatremia, cerebral osmolar adaptation has not yet occurred so it is acceptable to allow (or induce) rapid correction of serum sodium, with low risk of ODS. We advocate a cutoff of hyponatremia duration less than 24 hours rather than 48 hours to maximize the safety of this approach. In hyponatremia with severe symptoms of any (or unknown) duration, emergency management with bolus hypertonic saline is indicated to prevent progression of potentially life-threatening cerebral edema (see "Emergency Management of Severe Hyponatremia"). Once the target initial increment of serum sodium rise is achieved (eg, 4-6 mmol/L) and/or if symptoms improve, ongoing correction is determined by duration of hyponatremia. If duration is unknown, it is safest to assume it to be chronic and aim for gradual correction. In chronic hyponatremia, gradual correction of serum sodium allows for restoration of brain tissue osmolality toward the normal range with the import or synthesis of osmolytes (sodium, potassium, organic osmolytes as discussed in Fig. 3), and slow exit of excess intracellular water. The typical target rate of correction is 5 to 8 mmol/L per 24 hours, or lower for those with risk factors for ODS. If rapid correction of serum sodium above the target rate occurs (overcorrection, eg, > 10 mmol/L within 24 hours), it is advised to relower serum sodium (eg, with IV dextrose 5%, and/or desmopressin (DDAVP), see "In Case of Overcorrection: Relowering of Plasma Sodium" below) to prevent the rare complication of ODS. ODS can occur as a consequence of rapid exit of intracellular water damaging the myelin sheath, particularly in the pons, and can cause devastating neurological outcomes or death. Onset of symptoms of ODS is often delayed. Subsequent correction after relowering should be gradual. H_2O, water; DDAVP, desmopressin (arginine vasopressin analogue); IV, intravenous; ODS, osmotic demyelination syndrome.

(eg, electrolytes [sodium, potassium, chloride] and nonelectrolyte organic osmolytes). This lowers the tonicity gradient between brain tissue and serum, reducing water influx and lessening the risk of cerebral edema (Fig. 7). This adaptation to hyponatremia occurs in 2 phases—the initial phase involves rapid exit of electrolytes through volume-sensing channels occurring over minutes to hours (112, 113), to avert life-threatening sequelae of cerebral edema such as seizure or brain herniation (though a degree of edema may still occur, and can still have severe clinical consequences) (114). The second phase of adaptation that occurs over hours to days involves extrusion of intracellular organic osmolytes (eg, myoinositol, betaine, glutamine, taurine, γ-aminobutyric acid) via organic osmolyte transporters (113, 115). The extent of cerebral adaptation is the basis for a distinction between "acute" and "chronic" hyponatremia, frequently defined below or above 48 hours' duration, as chronic hyponatremia is assumed to have been present for long enough for depletion both of electrolytes and organic osmolytes to occur —though in reality, this occurs as a gradual continuum. When hyponatremia is corrected, brain electrolyte concentrations recover much faster than organic osmolytes, which can take up to 5 days to return to baseline levels, often being resynthesized (116, 117). Gradual correction of chronic

hyponatremia allows sufficient time for safe reversal of the adaptation process.

Excessively rapid correction of chronic hyponatremia means that serum and cerebrospinal fluid (CSF) (ie, extracellular) tonicity increases faster than brain intracellular tonicity is able to rise, given that organic osmolytes in particular are unable to be rapidly restored (116). This leads to osmotic shift of water out of hypotonic brain cells, with subsequent neuronal dehydration leading to cellular crenation (shrinkage and surface deformity). This in turn leads to disruption of cellular junctions and the blood-brain barrier, leading to oligodendrocyte damage and demyelination of neurons (118). The myelin sheath that protects axons is composed of foot processes of oligodendrocytes, supported by astrocytes that maintain homeostasis and form the blood-brain barrier. These glial cells (astrocytes, oligodendrocytes) are thought to be most susceptible to osmotic damage from rapid sodium correction because they form the interface between brain cells and CSF that is responsible for water exchange, and contain a high concentration of aquaporins (119, 120). This may also mean they may become relatively more depleted of organic osmolytes than other cells (121). Another vulnerability factor of glial cells is that hyponatremia has been shown to downregulate a neutral amino acid transporter prevalent in oligodendrocytes that is important for osmoadaptation (122). The exact pathophysiology of demyelination is incompletely understood, but the combined insult of crenation and an influx of intracellular cations (sodium, potassium) to compensate for the absence of organic osmolytes leads to protein aggregation and DNA fragmentation, prompting apoptosis. Approximately 24 hours after the osmotic insult, astrocytes and oligodendrocytes begin to die. Myelin damage from ODS is classically most apparent in the pons (hence it was previously known as central pontine myelinolysis), but extrapontine myelinolysis can affect other areas such as the basal ganglia and thalamus in around 10% of cases (111). The pons is white-matter rich and has a higher surface area to volume ratio than some other parts of the brain. It has been observed in animal studies that the midbrain and striatum, adjacent to the pons, demonstrate slower recovery of organic osmolytes after chronic hyponatremia compared to other areas of the brain, which may also explain the preponderance of demyelination lesions for these areas (123). This could be due to a less-permeable blood-brain barrier to organic compounds in the pons, as it has been shown that drug concentrations are lower in this region compared to other areas of the brain (124), postulated to perhaps have a protective effect against toxins for this crucial area that controls basic functions like respiration (125).

Symptoms of ODS typically present in a delayed manner, one or more days after overcorrection occurs. Clinically, patients with severe symptomatic hyponatremia may initially improve as the pNa rises; however, with the onset of ODS this may be followed by neurologic deterioration that is progressive and sometimes permanent. ODS symptoms include dysarthria, dysphagia, flaccid quadriparesis that later become spastic, horizontal gaze paralysis, "locked-in" syndrome, and coma (111). Clinical features associated with extrapontine myelinolysis include tremor, ataxia, parkinsonism, dystonia, and catatonia. The 2 largest contemporary case series to date, a report of 83 individuals with ODS in Sweden and 45 cases in the United States, reported 7.2% and 13% in-hospital mortality, respectively (126, 127). After 3 to 6 months of follow-up, around 60% of patients were functionally independent, while the remainder of survivors had persistent functional limitations.

Table 3. Risk factors for development of osmotic demyelination syndrome following correction of chronic hyponatremia, based on observational data

Extremely low serum sodium concentration < 105 mmol/L (or < 113 mmol/)
Severe symptoms of hyponatremia: decreased conscious state, vomiting
Hypokalemia
Alcohol abuse
Malnutrition
Advanced liver disease
Hypotonic urine (indicating water loss/spontaneous correction)

Adapted from Verbalis 2013 (3) with permission, with reference to Woodfine 2019 (128).

Risk factors for ODS, other than an extremely low initial sodium concentration (eg, < 105 mmol/L) and rapid correction (eg, > 12 mmol/L in 24 hours), include hypokalemia, alcohol abuse, malnutrition, and advanced liver disease (Table 3) (3, 128, 129). These factors may impair the ability of glial cells to import or resynthesize organic osmolytes (130). Reduced endothelial cell membrane concentration of Na-K-ATPase with hypokalemia may also impair the transport of electrolytes, further predisposing glial cells to injury associated with the rapid rise in the serum sodium concentration (131).

ODS may occur as the result of overcorrection that is either iatrogenic (eg, excessive administration of hypertonic saline) or spontaneous (eg, a negative water balance due to increased urinary electrolyte-free water clearance after resolution of a temporary nonosmotic stimulus to AVP). Higher-risk clinical scenarios for overcorrection include a reversible cause of hyponatremia (eg, cessation of potentially causative medications [eg, thiazide and thiazide-like diuretics, selective serotonin reuptake inhibitors, desmopressin]), glucocorticoid replacement in adrenal failure, or provision of solute in patients with malnutrition and low solute intake (eg, alcohol abuse ('beer potomania'), or poor "tea and toast" diet in older individuals).

ODS is relatively rare, despite overcorrection occurring relatively frequently. In a recent retrospective study of 1490 patients presenting with a pNa of less than 120 mmol/L over a 16-year period, 41% experienced an increase in pNa greater than 8 mmol/L/24 hours, but only 9 (0.5%) developed magnetic resonance imaging–documented ODS (all but 1 of whom had at least 1 risk factor for ODS) (132). It is possible that ODS is underdiagnosed, particularly in those who are asymptomatic or minimally symptomatic, if they do not happen to undergo a magnetic resonance imaging scan (133). It may also be underreported by clinicians, given that it is considered a potentially preventable complication (113).

Unfortunately, there are cases reported of ODS occurring despite gradual correction. A 2021 literature review identified 21 published cases of ODS in individuals with a pNa increase of less than or equal to 10 mmol/L per day, of whom 12 had a maximum sodium increase of less than or equal to 8 mmol/L/day, most of whom had additional risk factors (134). Three of these cases of ODS occurred despite maximum recorded daily pNa increments of only 4 mmol/L (133, 135), all 3 patients had a history of malnutrition, and it is possible that unmeasured fluctuations in pNa before admission may have occurred.

As ODS can be a devastating outcome, overcorrection should be scrupulously avoided to reduce risk. For this reason,

Table 4. Recommended plasma sodium concentration daily correction targets and limits in current hyponatremia guidelines

	General hyponatremia	Hyponatremia with risk factors for ODS
US expert opinion (3)	Target: 4-8 mmol/24 h Limit: 10-12 mmol/24 h	Target: 4-6 mmol/L/24 h Limit: 6-8 mmol/L/24 h
EU guidelines (15)	Target: 5 mmol/L/24 h Limit: 10 mmol/L/24 h in first 24 h, 8 mmol/L/24 h subsequent days	Same as general

Abbreviations: EU, European Union; ODS, osmotic demyelination syndrome.

recommended sodium correction targets often err on the conservative side for safety, particularly in those with risk factors for ODS for whom a daily correction limit of 6 to 8 mmol/L per 24 hours is endorsed by US expert opinion guidelines (Table 4). It is the net 24-hour change in pNa rather than the precise hourly rate of correction that is most important (136).

The management of patients who develop ODS is outside the scope of this review, but in brief, there are no established therapies. To maintain correction within the goal range, relowering of serum sodium with hypotonic fluid and/or desmopressin may be required if pNa targets are surpassed, and can still be beneficial even for those who have developed early symptoms of ODS (see "In Case of Overcorrection: Relowering of Plasma Sodium"). Case reports describe good outcomes after treatment of ODS with glucocorticoids (137), plasmapheresis (138-140), IV immunoglobulin (141), and zolpidem (142); however, it is unclear if improvements occurred as the result of these interventions. Glucocorticoids have been assessed in animal models of ODS and have shown reduced histological damage, but there are conflicting data with respect to mortality benefit (143, 144). Nevertheless, glucocorticoid therapy after overcorrection is recommended in US expert guidelines for those with baseline a pNa less than 120 mmol/L (3). Preclinical studies have demonstrated that administration of osmolytes such as urea or myo-inositol can protect against myelinolysis (121, 145) but they are not routinely recommended for this particular indication (see "Urea" for urea use). Plasmapheresis, which may remove "myelotoxins" from the circulation, and/or restore organic osmolytes, is the experimental therapy most frequently reported to have benefit and requires further evaluation (138-140). Supportive care measures such as intubation and ventilation, and in patients who survive, prolonged neurorehabilitation may be required. Optimal management of ODS when it does occur is an important area for future research.

Chronic Hyponatremia

In chronic hyponatremia of duration greater than 48 hours, the brain adapts to a lower pNa, with a corresponding reduction in brain tissue osmolality, because of an influx of water and export of osmolytes (see Fig. 3). Chronic hyponatremia was previously considered to be "asymptomatic," but it is now recognized that while severe symptoms may be absent, it can be associated with cognitive impairment, falls, fractures, plus vulnerability to acute exacerbations of hyponatremia. Clinical features associated with chronic hyponatremia may include nausea, vertigo, confusion, muscle cramps, weakness, headache, restlessness, dysarthria, and hyporeflexia (99, 146). There is preclinical evidence to suggest that cellular function, for example, enzymatic activity, is compromised when intracellular osmolality is reduced (113, 147). Furthermore, the intracellular organic osmolytes that become depleted in chronic hyponatremia can play a vital role in neurotransmission and protein synthesis, factors that may explain clinical sequelae of chronic hyponatremia (113).

The evidence linking clinical symptoms to chronic hyponatremia is largely observational, and there is no prospective interventional study to demonstrate conclusively that correction of chronic hyponatremia, which is commonly biochemically mild, can improve such features. The literature is potentially further confounded by the fact that clinical features attributable to hyponatremia are nonspecific and have a relatively high background prevalence in the normonatremic population. Observational studies can never fully adjust for confounders, and reverse causality remains a possibility, meaning that hyponatremia may be a marker of poor health, rather than a pathogenic mediator. Likewise, there is a recognized association between chronic hyponatremia and increased mortality, though causation, or the direction thereof, is not yet established. For some of these chronic hyponatremia-associated clinical features, there is mechanistic evidence from preclinical studies supporting biologic plausibility, as discussed later.

Cognition

Chronic hyponatremia is associated with impaired cognitive function—an effect accentuated at lower serum sodium concentrations. A prospective population cohort study in 2550 older Australians correlated serum sodium with results from the Audio Recorded Cognitive Screening tool, finding that scores for individuals with mild hyponatremia (130 mmol/L) were lower than those with normal sodium, representing a 5% reduction in cognitive function (148). A more extensive cognitive evaluation was performed in a prospective observational study of 130 hospitalized patients with moderate-profound euvolemic hyponatremia (mean 122 mmol/L; range, 119-126 mmol/L) comparing results in a comprehensive battery of validated neurocognitive, mood, and motor assessments (ie, the Mini-Mental State Examination, Timed Up-and-Go Test, Trail-Making Tests, among others) undertaken before treatment for hyponatremia, then repeated at the time of discharge, and compared to 50 matched normonatremic hospitalized controls (146). Scores across all domains were significantly worse in hyponatremic patients compared to those with normal serum sodium ($P < .001$), and the odds of pathological test results in the aforementioned measures were significantly increased for those with more profound hyponatremia of less than 120 mmol/L (146). In this study, correction of hyponatremia led to improvement in cognitive performance. This built on the work of earlier, smaller studies of fewer than 20 hyponatremic individuals that found impairment in attention and alertness when serum sodium was low improved when levels normalized (149, 150).

Potential explanations for cognitive impairment may include cerebral depletion of organic osmolytes, including the neurotransmitter glutamate, or slower neuronal processing (151, 152). There is also evidence that hyponatremia may negatively

affect mood, with one study finding Beck Depression Inventory scores indicative of depression in 50% patients with profound hyponatremia (146). In the SALT trials of tolvaptan therapy, mental health scores improved in tolvaptan-treated patients with baseline pNa below 130 mmol/L compared to the placebo group, in line with serum sodium correction (153). As low mood is known to affect cognitive performance, this may be an additional potential mechanism.

Only 2 randomized trials have sought to assess whether correction of hyponatremia can have positive cognitive outcomes. The INSIGHT trial was a pilot study that assessed a composite score of reaction time, psychomotor speed, and processing speed in 57 participants with chronic hyponatremia before and after a 3-week intervention with tolvaptan or placebo (151). Baseline cognitive performance was impaired compared to age-matched normative values, across the whole study population (mean pNa 129 mmol/L). In the tolvaptan-treated group, who had a significant improvement in plasma sodium levels compared to placebo ($P < .001$), there was no significant difference in the primary composite cognitive outcome relative to the placebo group ($P = .08$), who remained hyponatremic. One individual cognitive measure of the 3 components of the composite score reached statistical significance, which was faster psychomotor speed in the tolvaptan group ($P = .03$). This was deemed clinically significant for those with initial sodium less than 130 mmol/L (treatment effect 0.27; 95% CI, .04-.51)—representing a subgroup of only 12 tolvaptan-treated patients, and was not corrected for multiple comparisons (151). Most participants in this small study had mild-moderate hyponatremia, and it may have been underpowered, but failure to achieve a statistically significant change in the primary outcome implies that raising plasma sodium with tolvaptan may not improve cognitive outcomes. More recently, a crossover randomized trial of a 4-week intervention with the SGLT2i empagliflozin and placebo in 14 patients showed a statistically significant increase both in pNa and cognitive function as assessed by the Montreal Cognitive Assessment in the empagliflozin group. However, whether this beneficial effect was caused by the increase of sodium or related to empagliflozin treatment remains unclear (154).

Falls

An increased risk of falls associated with hyponatremia is consistently reported in observational studies. A case-control study compared 122 patients (mean age 72 years) admitted to the hospital with hyponatremia (mean pNa 126 mmol/L; range, 115-132 mmol/L) of unclear duration (classified as chronic after exclusion of those with seizures or polydipsia), with 244 controls matched for age and sex. This study observed that a higher proportion of patients with hyponatremia were admitted for falls (21.3% vs 5.3%) compared to controls, with a remarkably high adjusted OR of 67, although CIs were wide (95% CI, 7.5-607; $P < .001$) (150). There was no correlation between the severity of hyponatremia and frequency of falls in this study (150). More modest but still significantly increased falls risk was seen in another case-control study of 243 patients with hyponatremia admitted to an Australian internal medicine unit (mean age 80 years, mean sodium not reported, but 67% between 130 and 134 mmol/L) where hyponatremia less than 135 mmol/L was independently associated with falls on admission with OR 3.12 (95% CI, 1.84-4.38; $P < .001$) compared to unmatched controls (155). A study in Japan of 2948 hospitalized patients, approximately 10% of whom had hyponatremia, found on multivariate analysis that serum sodium less than 135 mmol/L was a statistically significant risk factor for falls (OR 1.75; 95% CI. 1.02-3.01; $P < .05$) (156). A further study of 969 patients admitted to a French acute geriatric unit, 111 of whom had mild chronic hyponatremia (pNa 130-135 mmol/L), found that mild hyponatremia was statistically significantly associated with falls (OR 3.02; 95% CI, 1.84-4.96; $P < .001$) compared to those with normal sodium levels (157). Owing to the potential for residual confounding these observational reports, while suggestive, cannot prove a causal role for hyponatremia in producing falls.

The mechanism for increased falls in hyponatremia may be due to impairments in gait, attention, and nerve conduction from low sodium concentrations. A direct assessment of gait was performed in a substudy of 12 outpatients with chronic hyponatremia (mean pNa 128 mmol/L) who completed a task quantifying unsteadiness over 3 tandem steps in comparison to matched normonatremic controls (150). Hyponatremic patients had impairment that was equivalent to that seen after moderate alcohol intake in controls (0.55 g of alcohol per kg body weight [~ 3-5 standard drinks]; mean blood alcohol concentration 0.06 g/100 mL—just above the legal driving limit in many European countries). Importantly, gait steadiness improved after normalization of serum sodium, which may suggest that the risk of falls associated with hyponatremia may be modifiable with normalization of serum sodium (150). A follow-up study noted greater effects of hyponatremia on attention and balance in older compared to younger adults (158). Another small, mechanistic, uncontrolled study assessed muscle strength, nerve conduction and mobility (Timed Up-and-Go Test) in 11 patients before and after correction of hyponatremia (mean pNa 122-136 nmol/L). There was no change in muscle strength, but a significant improvement in velocity of neural signal on peripheral nerve conduction studies, and faster completion of Timed Up-and-Go Test on normalization of serum sodium. Impaired peripheral nerve conduction may be an important contributor to falls in hyponatremia (152). However, in a small, randomized controlled study using empagliflozin to increase sodium levels no effect on gait was seen, so this is not a consistently observed benefit. Hence, further study into the relationship between falls and hyponatremia is needed (154).

Fracture

Cohorts who have experienced skeletal fracture are consistently observed to have a higher prevalence of hyponatremia than cohorts without fracture (159-162). The largest case-control study, in a US database of 2.9 million patients, matched those with osteoporosis (N = 30 517) and fragility fracture (N = 46 256) with an equal number of controls based on age, sex, and race, without these conditions (163). A history of recent or chronic hyponatremia was associated with significantly higher rates of osteoporosis (OR 12.09; 95% CI, 9.34-15.66), and increased fragility fracture (OR 11.21; 95% CI, 8.81-14.26) on multivariate logistic regression. The odds of osteoporosis or fracture increased with decrease in median serum sodium (163).

Deterioration of bone density and quality in hyponatremia likely contributes to fracture risk (164-166). A pivotal study established an animal model of profound hyponatremia in

male rats (using desmopressin infusion and liquid diet to achieve mean pNa 110 mmol/L, for at least 3 months), and reported a 30% reduction in bone mineral density on dual-energy x-ray absorptiometry (DXA) in hyponatremic rats compared to normonatremic controls receiving desmopressin and a solid diet (165). Subsequent assessment with microcomputed tomography and histomorphometric analysis of bone samples showed a reduction in trabecular and cortical bone volumes, hypothesized to have occurred via increased resorption and decreased bone formation to attempt to counteract the hyponatremia (165). An alternative explanation for bone loss could be that these profoundly hyponatremic rats had reduced physical activity in the context of a subcutaneous infusion and a feeding tube in situ, although no changes in behavior or locomotive activity were reported.

Lower bone mineral density with hyponatremia has also been observed in humans. Analysis of data from a subset of a cross-sectional study ("NHANES III") analyzed more than 5000 community-dwelling adults older than 50 years with available serum sodium and DXA results. Researchers reported a 2.9-fold increased odds of radiographic osteoporosis at the hip on DXA scan in the hyponatremic subgroup (N not reported, mean pNa 133 mmol/L) compared with normonatremic participants (165). Lower bone mineral density in chronic mild hyponatremia was also seen in a retrospective Danish registry study that assessed serial DXA scans in 58 patients with mild hyponatremia (pNa 130-137 mmol/L) compared to more than 800 unmatched normonatremic controls, reporting lower bone mineral density in hyponatremic patients (mean hip T score −2.2 vs −1.6; $P < .05$) (167).

There are a number of proposed mechanisms for hyponatremia-associated bone loss. Early radioisotope studies observed that around one-third of total body sodium is stored in bone, acting as a reservoir (168). When serum sodium levels fall, it is thought that bone matrix resorption by osteoclasts increases to release sodium into the circulation (168). By this logic, chronic hyponatremia would be expected to cause a deterioration in bone architecture, mechanisms that have been recently reviewed by Barsony and Verbalis (165). A recent study by these authors described upregulatory changes in gene expression in osteoclasts exposed to hyponatremia (169). Furthermore, bone contains AVP receptors (both V1 and V2), which may mediate another important mechanism for bone loss in SIAD. Administration of AVP to wild-type mice enhanced formation of bone-resorbing osteoclasts and reduced bone-forming osteoblasts in one animal study (170). Conversely, disruption of AVP receptor V1 signaling with either the administration of an V1 antagonist, or targeted deletion of the gene *AVPra1* in a knockout mouse model, both lead to increased bone mass and reduced bone turnover (170, 171). Interestingly, administration of the V2 inhibitor tolvaptan did not affect bone formation or mass, suggesting that V1 is the more relevant AVP receptor in bone (171).

A new body of evidence for a negative effect of hyponatremia on bone may emerge from assessment of serum bone turnover markers such a C-terminal crosslinking telopeptide of type 1 collagen (CTX), considered to be a marker of bone resorption, and N-propeptide of type 1 collagen (P1NP), a marker of bone formation. A small, longitudinal pilot study prospectively measured serial bone turnover markers over 1 week in patients with subarachnoid hemorrhage (SAH) (172). Eight patients developed mild-moderate hyponatremia (mean pNa 131 mmol/L), and 14 maintained normal serum sodium and acted as controls. The authors observed a reduction in P1NP in patients who became hyponatremic ($P = .02$), indicating reduced bone formation activity (172). CTX levels rose in both groups over time ($P = .001$) potentially due to reduced mobility, but there was no between group difference, indicating no effect of hyponatremia on a surrogate measure of bone resorption in this very small data set. Another study assessed bone turnover markers by way of a prespecified post hoc analysis of a larger short-term trial of empagliflozin in hyponatremia and found that P1NP levels rose in those patients in whom hyponatremia corrected after 5 days, which would imply that resolution of hyponatremia might have a positive effect on osteoblast function (173). CTX rose over the 5 days in the whole cohort of hyponatremic patients whether it was corrected or not. P1NP did not change in those who remained hyponatremic (173). Caution needs to be exercised in interpretating studies reporting changes in bone turnover biomarkers. Markers of bone formation and markers of bone resorption are measuring coupled bone remodeling events, occurring in different basic multicellular units, and occurring on different time scales. Therefore, differential changes in biomarkers such as P1NP and CTX, especially if measured in the short term, have their limitations in inferring net gain or loss of bone mineral (174, 175).

This assembled evidence does support a contribution of chronic hyponatremia to loss of bone mineral density and increased fracture risk, and while several mechanisms have been proposed, this process is not fully understood. It remains to be determined whether correction of hyponatremia reduces risk of fracture.

Mortality

A consistent association between hyponatremia and increased mortality is observed. Whether this is because multimorbid patients with serious underlying conditions are prone to develop hyponatremia, or whether hyponatremia itself is an independent risk factor, is not entirely clear and needs to be clarified in properly designed intervention studies.

A 2013 meta-analysis identified 81 studies comparing death rates in patients with or without hyponatremia, including a total of more than 850 000 patients (nearly 148 000 with hyponatremia) (176). Hyponatremia was significantly associated with an increased risk of overall mortality (relative risk [RR] 2.60; 95% CI, 2.31-2.93; $P < .0001$), and this was maintained after adjustment for age, sex, and diabetes mellitus. The association was relatively consistent when analyzed by individual underlying condition (heart failure, cirrhosis, pulmonary infection, myocardial infarction). There was an inverse relationship between serum sodium concentration and mortality —indicating higher risk with lower sodium concentrations. The mean difference in serum sodium between individuals who died compared to survivors was 4.8 mmol/L (pNa 130.1 vs 134.9 mmol/L), so even hyponatremia in the mild range was associated with risk. A causal relationship was not able to be established, by the nature of this analysis. The consistency associated irrespective of the underlying condition suggests that the underlying mechanism, if hyponatremia is indeed causal, is not disease-specific.

A follow-up meta-analysis by the same group in 2015 sought to clarify this association by determining whether an improvement in serum sodium was associated with reduced risk of mortality. In total, 15 observational studies

encompassing 13 816 patients, mean follow-up almost 3 years, that assessed the effects of an improved, or normalized, serum sodium on mortality were included. An improvement in serum sodium, through various interventions, was achieved in 53.2% of patients. Serum sodium improvement was associated with a reduced risk of death (OR 0.57; 95% CI, 0.30-0.81; $P = .002$). A majority of the included patients had heart failure, which may limit applicability to the broader chronic hyponatremia cohort. Subsequent retrospective studies have reported that active management of hyponatremia is associated with improved mortality, discussed further in "Management of Chronic Syndrome of Inappropriate Antidiuresis" (102, 177).

The Hyponatremia Intervention Trial (HIT) is a large, international, multicenter, randomized controlled trial (RCT) currently underway aiming to recruit 2278 hospitalized participants with pNa less than 130 mmol/L to be allocated 1:1 to receive either targeted correction of sodium concentration or standard care (178). The trial will include patients with hyponatremia irrespective of underlying cause or volume status. Targeted correction will aim to be achieved by adhering to predetermined diagnostic and treatment algorithms. The primary outcome will be death or rehospitalization within 30 days, and secondary outcomes will include measures of falls, fractures, hyponatremia recurrence, quality of life, and adverse events (eg, ODS). The results of this trial will provide high-quality evidence to confirm or refute the hypothesis that intervention to correct hyponatremia improves clinical outcomes.

Data regarding the mortality risk of SIAD specifically are conflicting, with some studies showing increased mortality and some potentially showing reduced mortality compared with other causes of hyponatremia. A prospective observational study in Ireland evaluated mortality outcomes in 1323 hyponatremic patients (43.3% with SIAD) compared to matched controls (179). SIAD was associated with increased mortality compared to normonatremic controls (RR 1.76; 95% CI, 1.08-2.8). However mortality risk in SIAD was not as high as for other causes of hyponatremia. Hypervolemic patients had an RR of mortality of 2.9 compared to SIAD, and hypovolemic patients had an RR of 1.6 (179). A recent Swiss retrospective population-based cohort study of 47 176 medical inpatients with hyponatremia (11.9% with SIAD) using propensity-score matching found no significant effect of hyponatremia on mortality as a whole, but sensitivity stratification by non-SIAD and SIAD hyponatremic patients showed opposing results (180). While non-SIAD hyponatremic patients had a 10% higher risk for in-hospital mortality, SIAD seemed to be associated with reduced mortality—however, 30-day readmission, intensive care unit (ICU) admission, and length of hospital stay were all increased in SIAD (180). SIAD is known to be underrecorded in hospital coding, hence the accuracy of SIAD classification in this study may be low (181). This is particularly relevant when assessing mortality rates, as if a patient dies of an underlying malignancy, anecdotally, the hospital discharge documentation is even less likely to record comorbid SIAD.

Potential reasons for a less pronounced effect on mortality in SIAD (if this is a true effect confirmed in future studies) are unclear and remain speculative. It has been shown that paradoxically, mortality rate seems to be lower in patients with pronounced hyponatremia (< 120 mmol/L) compared to patients with a milder hyponatremia (179, 182). Interestingly, the degree of hyponatremia varies according to hyponatremia etiology, and notably, SIAD seems to predispose to very low sodium concentrations (182). In patients with pNa below 120 mmol/L, the therapeutic approach has been shown to be different, with a higher percentage of ICU admission and of hypertonic saline administration as well as a more rapid initial sodium correction rate (182). This could possibly explain the lower mortality rates but higher ICU admission rates in these patients. However, since exact sodium concentrations were not known, this remains speculative. An alternative explanation for the "protective" role of SIAD might be the exact opposite, that is, that patients with SIAD had milder hyponatremia. Finally, the severity of the intercurrent diseases, medical complications during hospitalization, or the proportion of patients receiving palliative care might not have been distributed in a comparable way in both groups.

Regardless of cause, hyponatremia as a whole is associated with increased mortality, and timely diagnosis and treatment are important in improving clinical outcomes.

Initial Evaluation and Treatment of Hyponatremia

Emergency Management of Severe Hyponatremia

Initial management of hyponatremia includes assessment of neurological symptoms and signs to determine whether urgent treatment of severe hyponatremia with hypertonic saline is required. As discussed in "Acute Severe Hyponatremia," severe hyponatremia can cause cerebral edema leading to seizures, coma, or death, and urgent intervention is recommended with a 100-mL bolus of hypertonic (3%) sodium chloride administered over approximately 15 minutes. An initial dose should be followed by clinical reassessment and a repeat dose if no clinical response, until this target increment has been achieved (3, 183) (Fig. 8). The goal is to achieve an initial sodium increase of 4 to 6 mmol. According to the Adrogué-Madias formula to estimate the effect of fluid administration on pNa, 100 mL of NaCl 3%, containing 51.3 mmol of Na^+, may be expected to increase serum sodium by 1 to 1.5 mmol/L in most adults of average size (50-80 kg) (assuming no urinary electrolyte-free water clearance in the same interval) (184, 185) (see Fig. 2).

Hypertonic saline is the agent of choice because it is immediately effective and titratable; it will reliably increase serum sodium irrespective of the underlying etiology, at least initially, as its osmolality (1026 mOsmol/L) exceeds that of maximal urine osmolality. It is not recommended to continue hypertonic saline beyond resolution of acute severe symptoms because of the risk of serum sodium overcorrection, which can occur in around 20% of cases (unless the hyponatremia is documented to be of acute duration < 24 hours, and rapid correction is tolerated) (see "Acute Severe Hyponatremia" and Fig. 7) (49, 183). Overcorrection risk is significantly higher if more than 2 boluses of 100 mL, or more than a single bolus of 150 mL, of 3% NaCl, are given (183, 186). It has long been recognized that hypertonic saline will not necessarily have a long-term therapeutic effect in SIAD, as the administered sodium will eventually be excreted in the urine (1, 4, 187); however, its immediate efficacy may be lifesaving.

Hypertonic saline is typically administered in a high-dependency setting or emergency resuscitation bay to allow for frequent monitoring. It is safe to administer NaCl 3% through a either a peripheral or central line (188). Despite

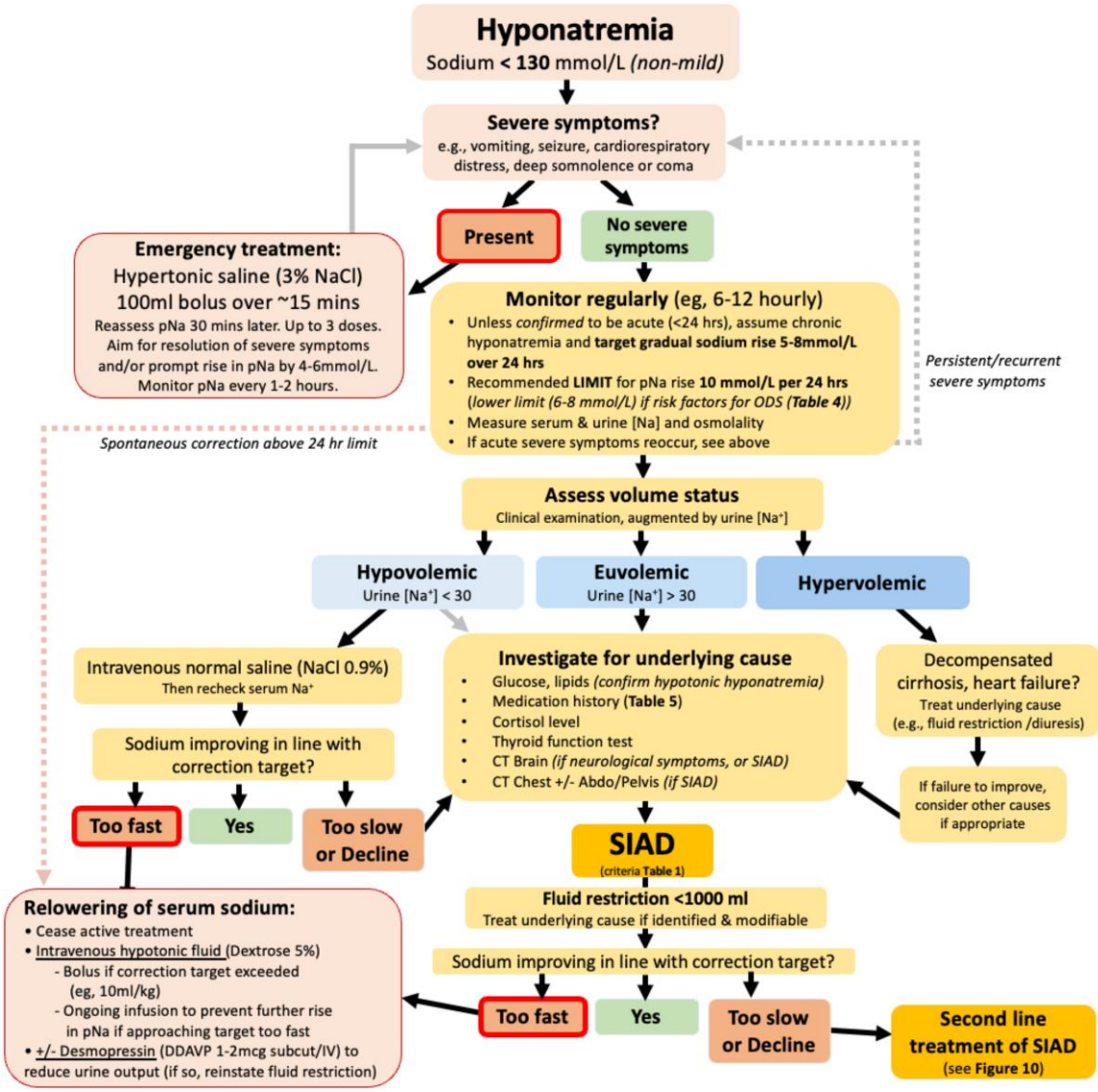

Figure 8. Diagnosis and initial management of nonmild hyponatremia while confirming a diagnosis of SIAD. CT, computed tomography; IV, intravenous; Na^+, sodium; NaCl, sodium chloride; ODS, osmotic demyelination syndrome; pNa, plasma sodium concentration; SIAD, syndrome of inappropriate antidiuresis; subcut, subcutaneous. Original figure, with reference to guidelines by Spasovski 2014 and Verbalis 2013 (3, 15).

this, some administration protocols erroneously call for a central line or place other restrictions on 3% NaCl use, such as a requirement for ICU admission. Resulting delays in hypertonic saline due to administrative barriers can have fatal consequences (189). In response to such restrictions, alternative approaches are sometimes used to circumvent these requirements, for example, using 2% hypertonic saline in some US hospitals instead of 3%. However, the osmolality of 2% NaCl (684 mmol/L) is not reliably higher than maximally concentrated urine and its use may delay symptomatic improvement; therefore, is not an adequate substitute for 3% NaCl. We recommend that nonevidence-based protocols that differ from current best practice be amended to facilitate peripheral administration of 3% NaCl and emergency administration in any hospital setting with appropriate monitoring, rather than recommending work-around alternative therapies.

Two recent studies have compared bolus vs slow infusion of hypertonic saline, and both reported results in favor of a bolus regimen. An Irish observational study compared outcomes for 22 hyponatremic patients (mean baseline pNa 120 mmol/L) treated with bolus 100 mL 3% NaCl, up to 3 doses, compared to a historical cohort of 28 patients managed with a relatively slow 20 mL/hour 3% NaCl infusion (183). Bolus hypertonic saline was associated with a faster elevation of serum sodium at 6 hours (median increase 6 mmol/L vs 3 mmol/L with infusion; $P < .0001$), and significantly greater improvement in GCS at 6 hours (median improvement 3 points vs 1 point; $P < .0001$), though with a greater need for reversal with IV dextrose and/or desmopressin, which occurred for 5 of 22 bolus patients (23%) vs none of the infusion patients ($P = .008$). There were no cases of ODS in either group, and pNa was similar at 24 hours. The nonrandomized and retrospective data for the control group limits the comparison, but the authors concluded that the faster neurological improvement with bolus therapy supports this regimen.

A larger randomized trial from Korea (SALSA) allocated 178 patients with hyponatremia pNa less than 125 mmol/L (mean pNa 118 mmol/L) to either bolus NaCl 3% (2 mL/kg,

or 100 mL if weight unknown; repeated if persistent symptoms or insufficient pNa increment) or continuous infusion (0.5-1 mL/kg/h, titrated to aim for pNa increment 5-9 mmol/24 hours—a higher initial rate than the Irish historical cohort) (186). They concluded that both therapies were effective and safe, with no statistically significant difference in overcorrection risk (17.2% with bolus vs 24.2% with infusion; $P = .26$); however, rapid intermittent bolus therapy had reduced requirement for therapeutic relowering and better efficacy in achieving improved pNa at 1 hour, supporting bolus therapy as the preferred treatment—consistent with current guidelines (186). Anecdotally, the exception is in cases of confirmed acute hyponatremia of less than 24 hours' duration, where both bolus and infusion NaCl 3% may be required to achieve deliberate rapid sodium increase. A recent retrospective study compared a larger volume initial bolus 250ml with 100ml bolus and did not observe increased rates of overcorrection (190) - but this is not widely reccommended at this stage.

After achieving an initial modest sodium increase, sufficient to prevent acute outcomes related to raised ICP, the focus turns to prevention of further rapid sodium rise to avoid overcorrection and ODS. Indeed, often the real challenge in managing severe hypotonic hyponatremia of chronic (> 24 hours) or unknown duration is to prevent this potentially deleterious overshoot. Relowering of serum sodium with IV 5% dextrose, with or without desmopressin to reduce urine output may be required, typically in a high-dependency setting, to maintain sodium rise ideally to 5 to 8 mmol above baseline within 24 hours, with a limit of no more than 10 to 12 mmol within 24 hours (see "In Case of Overcorrection: Relowering of Plasma Sodium") (3, 15). In patients with risk factors for ODS (see Table 3), one should aim for even slower corrections, 4 to 6 mmol within 24 hours and a limit of 8 mmol/L in any 24-hour period (3, 15), especially as such an increment is generally sufficient to prevent adverse clinical outcomes from acute hyponatremia-associated increase in ICP (see "Acute Severe Hyponatremia").

An alternative approach that has been proposed is "proactive DDAVP," that is, early empirical coadministration both of desmopressin (DDAVP) and hypertonic saline (191, 192). The rationale is that overcorrection is frequently the result of a spontaneous water diuresis following resolution of transient SIAD, interruption of polydipsia, or cessation of a causative medication. This spontaneous water clearance can be prevented with preemptive desmopressin (193). The advantage of this approach would be that the rate of correction can be more precisely controlled with hypertonic saline alone (bolus or infusion), without variable outputs to contend with. However, by potentiating SIAD through the administration of an AVP analogue before overcorrection occurs or appears imminent, this approach risks exacerbation or prolonging of hyponatremia symptoms—especially in the presence of ongoing fluid input. In patients with a chronic cause of SIAD (eg, paraneoplastic SIAD), desmopressin is unlikely to have any effect as the underlying cause of antidiuresis is likely to continue. The only data for this proactive approach stem from an uncontrolled observational study in 24 patients with pNa less than 120 mmol/L, predominantly secondary to thiazide diuretics, treated with desmopressin 1 to 2 mcg every 8 hours and weight-based hypertonic saline titrated to achieve a pNa increase of 6 mmol/L in 24 hours. Overall, participants had a mean increase in serum sodium 5.8 mmol/L over 24 hours, 2 patients experienced a decline in serum sodium by 1 to 2 mmol/L after 4 hours, and 2 patients had an above-target increase in serum sodium greater than 10 mmol/L at 24 hours, but no adverse effects were reported (191). Currently there is insufficient evidence to support this strategy, and instead we endorse a "reactive" or "rescue" approach to desmopressin therapy, in keeping with current guidelines.

Another alternative therapy for acute severe hyponatremia that is not in wide use, and that we do not recommend, is the use of more highly concentrated sodium chloride (eg, 23.4% or 29.2% NaCl) via central venous access. This therapy has been investigated as an alternative treatment to mannitol to raise plasma tonicity in traumatic brain injury to reduce cerebral herniation (105, 194, 195). There are no quality data in hyponatremia to support its use, especially when considering the expected higher risks of overcorrection, and the potential adverse sequelae of extravasation with these formulations.

Treating the potentially reversible neurotoxicity of severe hyponatremia may help clarify its contribution to clinical symptomatology (eg, altered conscious state) in sick patients with multiple potential causes for their symptoms. If symptoms do not improve with the modest pNa increments suggested earlier, alternative or additional causes should be sought.

Confirming a Diagnosis of Syndrome of Inappropriate Antidiuresis

Review of history, medications, and clinical examination can all assist in determining the cause of hyponatremia (see Fig. 8). There are many potential causes of hyponatremia, and SIAD is considered a diagnosis of exclusion. Evaluation of urine and serum osmolality and sodium concentrations are some of the most useful investigations in establishing whether the diagnostic criteria for SIAD are met, alongside clinical assessment of volume status (see Table 1).

Measurement of serum osmolality aids in excluding nonhypotonic causes of hyponatremia, such as pseudohyponatremia (due to raised lipids or protein) or translocational hyponatremia (due to raised glucose, or exogenous effective osmolytes, eg, mannitol) (see "Introduction"). For this reason, it is useful to obtain serum glucose and lipid profile in most patients to ensure accurate sodium assessment.

If the glucose is raised, the anticipated serum sodium concentration can be calculated according to the formula from Hillier et al (see Fig. 2) (9). This formula adds 2.4 mmol/L to the measured serum sodium concentration for every 5.5-mmol/L (100 mg/dL) incremental rise in serum glucose, to give the anticipated serum sodium concentration if the hyperglycemia was corrected. This is necessary only for significantly raised glucose concentrations, as for glucose levels below 10 mmol/L (180 mg/dL) this amounts to correction of pNa by 1 mmol/L or less.

Volume status and urine sodium concentration

Assessment of volume status (to approximate ECF volume) is a frequently used method of classifying hyponatremia, though the accuracy of clinical examination has been shown to be poor (196-198). Although features indicative of hypovolemia such as dry mucous membranes, decreased skin turgor, prolonged capillary refill, hypotension, and postural tachycardia are frequently mentioned in diagnostic algorithms, a systematic review found that few clinical signs of hypovolemia have

proven utility, with widely ranging sensitivities between 29% and 85%, specificity 58% to 95%, and variable interobserver agreement (198). The most difficult distinction, which is critical in guiding initial management (ie, FR vs volume administration), is between apparent euvolemia in SIAD and mild hypovolemia. In one study, clinical assessment correctly identified only 47% of hypovolemic patients compared to the gold-standard method of diagnosing hypovolemic hyponatremia: serum sodium improvement with IV isotonic saline solution (0.9% NaCl) (199). In hypovolemia, volume replacement with IV 0.9% saline treatment reduces the hypovolemic stimulus to AVP secretion, leading to improvement in serum sodium, in part by urinary dilution leading to excretion of excess free water. However, in SIAD, where AVP does not respond to the volume stimulus, the urine remains concentrated despite the IV fluid. Hence, IV 0.9% saline is not an effective treatment in SIAD as it may lead to a further reduction in serum sodium, as the water component is retained, coupled with ongoing renal sodium loss (3). In this scenario, 0.9% NaCl (osmolality 308 mOsmol/L) may be hypotonic relative to the concentrated urine (commonly > 500 mOsmol/L in SIAD) leading to net free water retention, worsening the hyponatremia. Consequently, this treatment should be reserved for patients with either clinical or biochemical indicators of ECF volume depletion—low urine sodium (UNa) concentration—despite the limitations of these assessments.

UNa concentration is a very useful discriminator of ECF volume status. This is because in hypovolemic hyponatremia the mechanisms to conserve sodium remain intact, resulting in low UNa excretion—however, in SIAD there is ongoing renal sodium loss. UNa concentrations can vary considerably, even in serial samples hour to hour (200), so the exact value is not as useful as whether it is above or below an approximate threshold of 30 mmol/L (according to current European guidelines, or 20-30 mmol/L according the expert panel guidelines (3, 15)). Because of measurement variability and other factors, it is difficult to determine a strict UNa cutoff for diagnosis. Different sources have set the UNa threshold for SIAD diagnosis at varying levels, including greater than 20 mmol/L (201), greater than 30 mmol/L (199, 202), greater than 40 mmol/L (203), or even greater than 50 mmol/L (204). The original description of SIAD by Bartter and Schwartz referred to "continued renal excretion of sodium" without quantifying a threshold (4), an approach also taken by some contemporary sources (205), perhaps to avoid this controversy. Because UNa is a continuous variable under multifactorial influence, setting a higher threshold will increase the specificity of SIAD diagnosis but decrease sensitivity, and vice versa for a lower threshold (Fig. 9) (199). Given this variability, and because volume status can change over time, repeated UNa measurements may be useful. Logically, the closer to the threshold, the greater the value in continued reevaluation. A low UNa may also develop with resolution of transient SIAD as the retained water begins to be excreted, so this finding does not totally rule out SIAD having been present. Clinical history and assessment of urine output are key to differentiating this scenario from hypovolemia.

Factors that may affect the accuracy of UNa include metabolic alkalosis and dietary solute intake. In the setting of metabolic alkalosis, UNa is not a reliable indicator of volume status (due to excretion of bicarbonate with sodium). In such cases, the urine chloride concentration, which is also typically low in hypovolemia, can be used instead (203). This assessment assumes normal salt and water intake, as low solute intake can lead to a low UNa even in SIAD—which reduces the specificity for diagnosing hypovolemia as a differential.

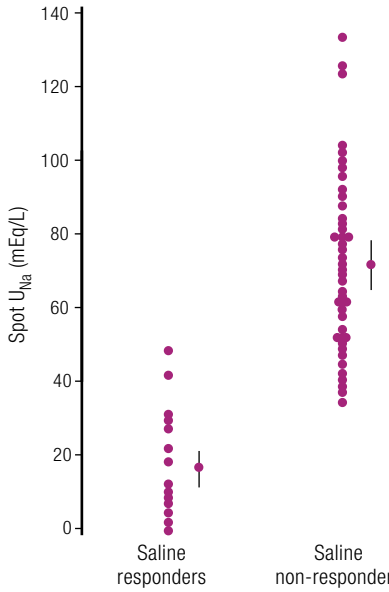

Figure 9. Identifying a urine sodium threshold for diagnosis of syndrome of inappropriate antidiuresis (SIAD) vs hypovolemic hyponatremia: urine sodium concentrations (UNa) in a prospective assessment of 58 patients with plasma sodium concentration less than 130 mmol/L, classified according to response to intravenous 0.9% saline rehydration (gold standard assessment of volume status). This study recommended a threshold of UNa greater than 30 mmol/L to differentiate hypovolemia (saline responders) from SIAD (saline nonresponders). Spot UNa in saline responders and nonresponders. All individual values as well as the mean ± 1 SEM are included. Figure reproduced from Chung 1987 with permission (199).

It is important to note that hyponatremia due to adrenal insufficiency and diuretics is usually volume responsive and characterized by a high UNa, hence these are important differentials to consider (discussed later). It has been suggested that calculating fractional excretion of uric acid (FE-UA) is another measure that can assist in diagnosing SIAD, potentially useful in patients on diuretics in whom UNa may be less reliable (206) (see Fig. 2). This is because uric acid is excreted in the proximal tubule and hence is not subject to interference from common diuretics (207). In one study, a raised FE-UA (> 12%) had a 100% positive predictive value for diagnosis of SIAD regardless of recent diuretics (206). A challenge, however, is that such results may not be obtained at the point of care quickly enough to influence treatment decisions.

Clinically apparent ECF excess in the form of edema is usually indicative of other differential diagnoses for SIAD such as decompensated heart or liver failure. However, assessment is complicated by the fact that peripherally edematous patients may be intravascularly volume depleted, resulting in a baroreceptor-mediated AVP stimulus. Other clinical signs associated with hypervolemia include pleural effusion and ascites, provided these are transudative (exudative effusions or ascites, eg, related to malignancy or infection can co-occur with SIAD). Hyponatremia is an independent marker of mortality in cirrhosis (208) and heart failure (209) and occurs because of a reduction in effective circulating volume and release

of AVP in an attempt to compensate. In these conditions management of the underlying pathology, if possible, for example, with FR or volume diuresis, is the optimal approach rather than specific sodium-directed therapy.

Cerebral salt wasting (CSW) is a somewhat controversial entity that is sometimes invoked as a differential for SIAD in the setting of hyponatremia after a cerebral insult (eg, traumatic brain injury, SAH, tumor, or stroke) (210). The postulated pathophysiology of CSW involves the release of natriuretic peptides (eg, B-type natriuretic peptide [BNP, also known as brain natriuretic peptide]) and/or reduced sympathetic stimulation to the kidney, inhibiting sodium resorption and suppressing the renin-angiotensin-aldosterone system—leading to renal salt and water loss causing hyponatremia, which can be exacerbated by provision of hypotonic fluids (210, 211). The main differentiating factor between CSW and SIAD is volume status, as patients with CSW become hypovolemic. In contrast to SIAD, the treatment approach in CSW aims to replace salt and water—with isotonic fluid, salt tablets, and/or fludrocortisone (212, 213).

There is, however, ongoing debate about the existence and frequency of CSW. Hyponatremia with UNa loss after cerebral injury was first described in 1950, before the recognition of SIAD (214). Subsequently, it has been proposed that SIAD or adrenal insufficiency may explain many such cases. A carefully conducted prospective study of 100 patients with SAH who underwent detailed endocrine evaluation, including serial measurements of AVP, BNP, and cortisol, determined that of 49 who developed hyponatremia, the majority (36/49) were due to SIAD and the remainder were attributed to glucocorticoid insufficiency, incorrect IV fluids, or hypovolemia—but no cases of CSW were found (215).

There are no standardized diagnostic criteria for CSW to differentiate from SIAD, beyond clinical volume status (as discussed earlier, an unreliable measure). BNP is usually raised in cases of suspected CSW, and is typically not raised in SIAD—but this is not specific (216). Fractional excretion of uric acid remains raised after correction of serum sodium in CSW, whereas it reduces in SIAD (207); however, this means that FE-UA is not a useful differentiator while pNa remains low (see Fig. 2). A novel natriuretic protein, haptoglobin-related protein without signal peptide (Hpr-WSP), has been proposed as an alternate marker, but has not been externally validated (217).

It is useful to be aware of CSW as a potential differential diagnosis for SIAD given contrasting management approaches, but it appears to be very rare compared to SIAD and other causes of hyponatremia, even in neurosurgical populations.

No role for measuring arginine vasopressin or copeptin

Investigations that have not been proven useful in the differential diagnosis of hypotonic hyponatremia so far include measurement of AVP, which rapidly degrades ex vivo, and copeptin, the more stable cleavage product of AVP that is a biochemical surrogate for AVP action. Both AVP and copeptin are elevated in most cases of hyponatremia, including SIAD ("inappropriately") as well as in hypovolemia ("appropriately," in response to reduced effective circulatory blood volume), hence measurement does not assist in discriminating between these causes (218). Hyponatremia due to primary polydipsia, or profoundly low solute intake reducing renal electrolyte-free water excretory capacity, has been shown to have a low copeptin, reflecting the AVP-independent pathophysiology (219, 220). Nephrogenic SIAD, caused by an activating mutation in the vasopressin V2 receptor, will also lead to suppressed AVP and copeptin. Identifying this rare differential may be an exception where copeptin testing in hyponatremia could be useful - a low copeptin result (without evidence of polydipsia) can be followed by confirmatory *AVPR2* gene testing (93, 96). A recent study investigating copeptin as a marker of response to hypertonic saline therapy in 100 hyponatremic patients found that a lower copeptin was associated with higher rate of overcorrection; however, this is may be due to resolution of the underlying cause of SIAD by the time copeptin was measured, which would be more readily reflected in increased urine output with lower urine osmolality (221). Urine osmolality is generally a fairly good surrogate indicator of AVP activity (provided that renal function is not markedly impaired) that is more readily accessible, hence low urine osmolality is often sufficient to raise suspicion of differentials such as polydipsia or low solute intake.

Adrenal and thyroid function

Adrenal insufficiency is an important and treatable cause of hyponatremia that can mimic SIAD and must be excluded in all patients with hyponatremia. Importantly, in patients with clinical suspicion of adrenal insufficiency, empirical glucocorticoid replacement should be commenced immediately, rather than waiting for diagnostic confirmation (3). A random cortisol and ACTH may be drawn before glucocorticoid administration to assist in later clarifying whether this should continue, but treatment should be started without waiting for the result. In one prospective study of 1323 hospital patients with hyponatremia pNa less than 130 mmol/L who were prospectively assessed by a consultant endocrinologist, adrenal insufficiency was the underlying cause in 3.8% of patients initially thought to have SIAD (50). Hyponatremia can be caused both by primary and secondary adrenal insufficiency, through common and differing mechanisms. Because cortisol suppresses AVP production, both primary and secondary adrenal insufficiency increase AVP secretion (222, 223). There is evidence that CRH from the hypothalamus, which is increased both in primary and secondary adrenal insufficiency, stimulates AVP production (224). There may also be hemodynamic stimuli to AVP secretion from hypotension in both contributing to hyponatremia. In addition, in primary adrenal insufficiency there is loss of aldosterone production, leading to renal salt wasting, and more pronounced clinical hypovolemia and hyperkalemia, that are not seen in secondary adrenal insufficiency where the renin-angiotensin aldosterone system (RAAS) remains intact. Renal salt wasting due to mineralocorticoid deficiency in primary adrenal insufficiency is likely why hyponatremia is more common with that underlying cause, occurring in 84% patients in a case series of 272 patients with Addison disease (225), whereas in ACTH deficiency this figure is likely between 10% and 40% (226).

A low serum cortisol (eg, morning cortisol < 140 nmol/L [< 5 mcg/dL], depending on the cortisol assay) in patients without recent confounding medication (eg, exogenous glucocorticoids), is usually suggestive of primary or secondary adrenal insufficiency. The gold-standard investigation for primary adrenal insufficiency is an $ACTH_{1–24}$ stimulation test (also known as the short synacthen test or the cosyntropin stimulation test), in which 250 mcg of corticotropin is administered parenterally, and cortisol levels measured after

30 and 60 minutes. A peak cortisol concentration below the local laboratory cutoff for the assay (eg, stimulated cortisol < 500 nmol/L [< 18 mcg/dL]) is consistent with primary adrenal insufficiency (227). A random serum cortisol concentration within the lower part of the normal range may be falsely reassuring in patients who are acutely unwell, who would be expected to be mounting a stress response of cortisol secretion. Therefore, a screening cutoff of morning cortisol greater than 300 nmol/L (> 10.9 mcg/dL) to exclude adrenal insufficiency in hyponatremia is recommended by some experts based on prospective data (50). Depending on the etiology and clinical presentation, a cortisol level greater than 300 nmol/L may still be inappropriate for a patient under physiologic stress, so this threshold does not definitively exclude pathology, although whether more subtle hypothalamic-pituitary-adrenal axis insufficiency causes hyponatremia is not clear (50). Those with a morning cortisol less than 300 nmol/L (< 10.9 mcg.dL) may proceed to further evaluation with ACTH and a short synacthen test, unless acutely unwell. Empirical stress-dosing with hydrocortisone should be considered in hyponatremic patients with clinical features suspicious for adrenal insufficiency, a history of long-term exogenous glucocorticoid therapy, and those who are hypotensive or otherwise unwell, to avoid delaying potentially life-saving treatment. There is no universal dosing recommendation for glucocorticoid replacement in this circumstance, but in general patients with hemodynamic instability may benefit from higher IV dosing (eg, 100 mg hydrocortisone stat, then 50 mg IV every 6 hours (227, 228)), with care to monitor for overcorrection of serum sodium. Water diuresis following initiation of glucocorticoid therapy is supportive of adrenal insufficiency as the underlying cause of hyponatremia. Consequently, there is a high risk of serum sodium overcorrection, and requirement for relowering therapy if correction targets are exceeded (see "In Case of Overcorrection: Relowering of Plasma Sodium"). When correcting secondary adrenal insufficiency in patients with pituitary disease, it is important to be aware of the possibility of unmasking underlying AVP deficiency (central diabetes insipidus) concealed by the stimulation of residual AVP production by cortisol deficiency—which can exacerbate overcorrection risk further (229).

It is widely recommended to check thyroid function in the workup of hyponatremia. There is limited evidence for hypothyroidism contributing substantially to hyponatremia, and a causative relationship is controversial (230). An important study compared serum sodium in 999 patients with newly diagnosed hypothyroidism compared to 4875 euthyroid controls, and while there was a correlation, this amounted to a tiny 0.14-mmol/L fall in pNa for every 10-mU/L rise in thyrotropin (TSH), supporting the conclusion that there was no clinically relevant association between hypothyroidism and hyponatremia (231). Another retrospective study of 33 000 patients found no difference in rates of hyponatremia between the 445 hypothyroid patients with TSH greater than 40 mU/L and euthyroid controls (232). Hyponatremia occurring in profound hypothyroidism may be a consequence of myxedema, cardiac failure, and systemic hypotension. If hypothyroidism is identified it should be treated, but not assumed to be the sole underlying cause of low serum sodium. Of note, in otherwise unexplained "SIAD," TSH and free thyroxine should both be measured, as reliance on a normal or even slightly increased TSH can miss profound secondary hypothyroidism in very rare cases (though the hyponatremia in that context can be caused by secondary adrenal insufficiency rather than hypothyroidism). Treatment of hypothyroidism should be delayed until glucocorticoid replacement is established, to avoid precipitating adrenal crisis via restoration of basal metabolic rate with thyroid replacement (233). Given the potential shared autoimmune pathophysiology of primary hypothyroidism (Hashimoto disease) and primary adrenal insufficiency (Addison disease), it is important to rule out adrenal insufficiency in at-risk patients with increased TSH before thyroid replacement as well. Interestingly, TSH can be raised as the result of primary adrenal insufficiency and then correct after glucocorticoid replacement, which is another reason to be alert to adrenal insufficiency as the more common cause of hyponatremia than thyroid dysfunction (234).

Medications

Medications are an important cause of hyponatremia to consider. Medications can cause SIAD through stimulating AVP release, potentiating its action, contributing to altered osmotic set point, or being a direct AVP analogue (Table 5). Medications with a natriuretic effect can mimic SIAD by causing hypovolemic hyponatremia with an increased UNa concentration. Thiazide diuretics are one of the most common causes of hyponatremia (235) and are an important differential diagnosis for SIAD. Up to 13% of patients taking thiazides develop hyponatremia (236). Thiazide diuretics act at the sodium-chloride cotransporter in the distal convoluted tubule to block sodium resorption, which impairs urinary dilution, resulting in free water retention and sodium excretion that can contribute to hyponatremia (237). A genetic susceptibility to thiazide-associated hyponatremia has been identified, with approximately 50% of those affected found to have a single-nucleotide variation in the *SLCO2A1* gene encoding a prostaglandin transporter expressed in the renal collecting duct, a variant that activates water resorption in the collecting duct despite suppression of AVP (238, 239). Thiazide-induced hyponatremia is likely to reoccur with repeat exposure, so should be recorded as an adverse reaction in the medical record (240, 241). A rechallenge study in 11 patients with a history of previous thiazide-induced hyponatremia found that a single dose of hydrochlorothiazide 50 mg caused a fall in serum sodium (mean 5.5 mmol/L) in 6 hours, but minimal change in controls (241). Other medications that cause hyponatremia and resemble SIAD through salt-wasting diuresis include the antibiotic trimethoprim (and by extension, trimethoprim-sulfamethoxazole), especially at higher doses (242, 243). Of course, these common medications and underlying organic SIAD also frequently coexist, so the presence of potentially hyponatremia-causing medication does not rule out SIAD.

Identifying an underlying cause of syndrome of inappropriate antidiuresis

SIAD can have a wide variety of causes (see Fig. 4), some of which may be clear based on clinical history and examination, and some revealed through additional investigation. There are no current guidelines that direct how to investigate for an underlying cause of SIAD, but imaging of the brain and chest with computed tomography (CT) scanning is generally recommended to identify causative CNS or lung pathology (244, 245). If brain and chest imaging is negative, CT imaging of

Table 5. Medications that can cause hypotonic hyponatremia

- AVP release stimulants or potentiators
  - Antidepressants
    - SSRIs and SNRIs (on initiation (78))
    - Tricyclics (eg, amitriptyline)
    - MAOI
  - Antiepileptics
    - Carbamazepine, oxcarbazine, sodium valproate, lamotrigine
  - Antipsychotics
    - Phenothiazines (eg, chlorpromazine, thiridazine)
    - Butyropenones (eg, haloperidol)
  - Cancer therapy
    - Vinca alkaloids (eg, vincristine)
    - Alkalating agents (cyclophosphamide, melphalan, ifosfamide)
    - Methotrexate, pentostatin
  - Miscellaneous
    - Tramadol (79), MDMA ("ecstasy"), interferon, NSAIDs, ACEI (rarely), nicotine, amiodarone, proton pump inhibitors, nicotine, clofibrate, monoclonal antibodies, levamisole, first-generation sulphonylureas (chlorpropramide, tolbutamine), ginkgo biloba (80)
- AVP receptor activation
  - AVP analogues: desmopressin, vasopressin, terlipressin (terlipressin a rare cause due to selective V1 receptor activity)
  - Receptor crosstalk: oxytocin
- Reset osmostat
  - Carbamazepine
  - Venlafaxine
- Natriuretic agents that may mimic SIAD (ie, due to increased urine sodium concentration)
  - Thiazides, indapamide, amiloride, loop diuretics
  - Platinum compounds (eg, cisplatin)
  - Trimethoprim (including co-trimoxazole)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AVP, arginine vasopressin; MAOI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; NSAID, nonsteroidal anti-inflammatory drug; SIAD, syndrome of inappropriate diuresis; SNRI, serotonin and norepinephrine (noradrenaline) reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors. Adapted from Liamis Am J Kid Dis 2008 (81) with permission, with additional reference to Spasovski 2014 (15).

the abdomen and pelvis may be considered to complete screening for underlying malignancy. If no cause is identified on cross-sectional imaging, SIAD may be provisionally regarded as "idiopathic." Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan has been used to investigate further for malignancy, particularly in younger patients with unexplained SIAD (246, 247). There are also cases reported of FDG-PET aiding diagnosis of nonmalignant, non-SIAD causes of hyponatremia, including congenital adrenal hyperplasia and adrenal tuberculosis (248, 249). Even if initial evaluation is negative, periodic reevaluation in an individualized fashion, even in the absence of intercurrent new clinical features, may be useful, as in some patients SIAD may precede a clinically detectable underlying malignancy for months, if not years (eg, nasal neuroendocrine tumors) (250, 251). An additional investigation that could be considered in rare circumstances may be a Gallium-68 DOTATE PET scan, which has been reported to aid diagnosis of occult neuroendocrine tumors causing SIAD (252, 253). Measurement of copeptin, a surrogate for AVP, has not been shown to be a reliable marker of underlying malignancy (254, 255).

If a reversible underlying cause of SIAD is identified, treatment of this, if possible, should improve hyponatremia without specific sodium-directed therapy. For those with persistent hyponatremia due to SIAD, management options are discussed next.

Management of Chronic Syndrome of Inappropriate Antidiuresis

There is little high-level evidence to guide chronic SIAD treatment because of the difficulty of conducting randomized trials due to the heterogeneity of patients with this condition, severity of illness that makes placebo therapy ethically difficult, and the potential for resolution of conditions perpetuating the nonosmotic release of AVP, which can confound trials of SIAD treatments (256, 257). However, this tendency for "autocorrection" of hyponatremia due to SIAD, if caused by a reversible underlying condition, makes rigorous RCTs even more important to confirm any apparent benefits in observational studies. A 2017 systematic review of chronic hyponatremia treatments did not identify RCTs of any treatments other than vaptans, but since then new RCTs have emerged (258). Published RCTs of therapies for chronic hypotonic hyponatremia to date are summarized in Table 6.

Current guideline-directed management of hyponatremia is largely based on expert opinion and is expected to evolve with new evidence over the coming years. Trials are currently in progress comparing protocolized low-dose tolvaptan vs FR in SIAD (271), and evaluating empagliflozin in inpatients and outpatients with euvolemic and hypervolemic chronic hyponatremia (NCT04447911). Despite controversies in approach, there is retrospective evidence that active management of inpatients with hyponatremia by specialist physicians (endocrinologists or nephrologists, depending on local practice) may improve mortality and reduce length of hospital stay (102, 272). This was reported in an audit of a single Irish center over a 5-year period from 2005 to 2010, that found increasing rates of specialist referral (32%-68%) and use of active hyponatremia management strategies for pNa less than 120 mmol/L (63%-88%) was associated with a 91% reduction in mortality risk ($P < .001$) (102). A UK single-center study compared 18 individuals with hyponatremia less than 127 mmol/L (mean pNa 120.7 mmol/L) who received

Table 6. Randomized controlled trials in management of chronic hypotonic hyponatremia

Trial	Intervention	Commercial funding?	Mean baseline pNa, mmol/L	N =	Primary end point/s	Primary end point met? (bold if primary end point related to pNa)
Nonvaptans						
Garrahy 2020 (259) Ireland Single center Inpatients and outpatients	FR vs No treatment Open-label Randomized 1:1	No	127	46	Change in pNa d 4, d 30	**Yes** *D 4: pNa increase 3 mmol/L with FR, vs 1 mmol/L no Tx (P = .005)* *D 30: pNa increase 4 mmol/L FR vs 1 mmol/L no Tx (P = .04)*
Krisanapan 2020 (260) Thailand Single center Inpatients "EFFUSE-FLUID"	FR vs FR + furosemide vs FR + furosemide + salt tablets open-label, randomized 1:1:1	No	125.5	92	Change in pNa at d 4, 7, 14, and 28	**No** *D 4 mean pNa increase 5 mmol/L in all groups—not significant across groups (P = .7)*
Refardt 2020 (261) Switzerland Single center Inpatients	Empagliflozin vs placebo (all with FR) Double-blind, randomized 1:1	No	125	87	Change in pNa at d 5	**Yes** *D 5 pNa rise 10 mmol/L with empagliflozin (Empa + FR) vs 7 mmol/L with placebo (FR only) (P = .04)*
Refardt 2023 (154) *Switzerland* *Single center* *Outpatients*	Empagliflozin vs placebo Double-blind, randomized 1:1, crossover	No	131	14	Change in pNa at 4 wk	**Yes** *D 28 pNa increase to 134 mmol/L with empagliflozin vs 130 mmol/L with placebo (P = .004)*
Vaptans[b]						
Schrier 2006 (153) International, Multicenter 92 sites Outpatients (HF/ cirrhosis/SIAD) "SALT1 & SALT2"	Tolvaptan (15-60 mg) vs placebo Double-blind 1:1	Yes	129	448	Change in average AUC for pNa d 4, d 30	**Yes** *D 4 mean AUC 3.62 for tolvaptan vs 0.25 for placebo (P < .001) Mean pNa increase 5.3 mmol/L tolvaptan vs 1 mmol for placebo after 4 d*
Chen 2014 (262) China Multicenter 49 sites Inpatients (SIAD)	Tolvaptan (15 mg) vs placebo 1:1 Double-blind 1:1	Yes	126	37	Change in pNa AUC at d 4, d 7	**Yes** *D 4 mean pNa increase 8.1 mmol/L for tolvaptan vs 1.9 mmol/L for placebo (P < .001)*
Li 2011 (263) China, Multicenter 11 sites Inpatients (HF)	Tolvaptan (15-60 mg) vs placebo 1:1 Double-blind 1:1	Yes	[a]	65	Change in pNa d 4, d 7	**Yes** *D 4 pNa increase 5.6 mmol/L for tolvaptan vs 2.5 mmol/L for placebo (P < .05)*
Salahudeen 2014 (264) US, Single center Inpatients (cancer)	Tolvaptan (15 mg) vs placebo Double-blind 1:1	Yes	129	30	Sodium correction (> 135 mmol/) at d 14	**Yes** *94% normalized pNa in tolvaptan group vs 8% placebo (P < .001)*
Rossi 2007 (265) International, Multicenter 45 sites Inpatients (HF) Substudy of "ACTIV in CHF"	Tolvaptan (30/60/ 90 mg) vs Placebo Double-blind 1:1:1:1	Yes	133	69	Change in wt 24 h, Composite HF end point 60 d	Yes for wt, no for composite end point *66.2% of patients had increase in pNa ≥ 2 mmol/L*
Gheorghiade 2006 (266) US, Multicenter 9 sites Inpatients (HF, cirrhosis, SIAD)	Tolvaptan (10-60 mg) vs placebo plus FR (1200 mL/d) Double-blind 2:1	Yes	129	23	Change in pNa at discharge	**Yes** (*underpowered—did not meet recruitment target*) *Rise in pNa 5.7 mmol/L tolvaptan* vs *1.0 mmol/ for placebo + FR at discharge (P = .0065)*
Gheorghiade 2003 (267) US, Multicenter: 30 sites Outpatients (HF)	Tolvaptan (30/45/ 60 mg) vs placebo Double-blind 1:1:1:1	Yes	[a]	70	Change in body wt d 14	Yes, reduction in wt ~ 1 kg with tolvaptan (P < .001) *pNa > 135 in 80% tolvaptan vs 40% placebo (P < .05)*

(*continued*)

Table 6. Continued

Trial	Intervention	Commercial funding?	Mean baseline pNa, mmol/L	N =	Primary end point/s	Primary end point met? (bold if primary end point related to pNa)
Nonvaptans						
Subgroup "tolvaptan-CHF"						
Hauptman 2013 (268) International, Multicenter 359 sites Inpatients (HF) Subgroup of "EVEREST"	Tolvaptan (30 mg) vs placebo Double-blind 1:1	Yes	131	475	All-cause mortality and cardiovascular death or HF hospitalization	No *D 1: rise pNa 4.9 mmol/L tolvaptan vs 1.2 mmol/L placebo.* *D 7: rise pNa 4.9 mmol/L tolvaptan vs 1.2 mmol/L placebo*
Verbalis 2016 (151) US, Multicenter 16 sites Outpatients "INSIGHT"	Tolvaptan (15 mg) vs placebo Double-blind 1:1	Yes	129	57	Composite neurocognitive score at 7 and 21 d	No *Significant increase in pNa at 30 d in tolvaptan group pNa 7 mmol/L vs 2 mmol/L with placebo (P < .01)*
Annane 2009 (269) International, Multicenter 17 sites Inpatients	Conivaptan oral (20 mg 2×/d/40 mg 2×/d) vs placebo, all FR 2000 mL/d Double-blind 1:1:1	Yes	125	83	Change in pNa AUC at d 5	**Yes** *D 5: pNa increase 9.1 mmol/L conivaptan 80 mg 2×/d, rise 6.9 mmol/L with conivaptan 20 mg 2×/d vs 1.8 mmol/L with placebo (P = .0001)*
Ghali 2006 (270) International Multicenter 21 sites Inpatients "Coniv-oral study"	Conivaptan oral (20 mg 2×/d/40 mg 2×/d) vs placebo, all FR 2000 mL/d Double-blind 1:1:1	Yes	124	74	Change in pNa AUC at d 5	**Yes** *D 5: pNa rise 8.2 mmol/L conivaptan 40 mg 2×/d, 6.4 mmol/L for conivaptan 20 mg 2×/d vs 3.4 placebo (P = .002)*

Abbreviations: AUC, area under the curve; HF, heart failure; FR, fluid restriction; pNa, plasma sodium concentration; SIAD, syndrome of inappropriate antidiuresis; Tx, treatment. **Bold** text indicates whether primary outcome in hyponatremia was met. Original table, with reference to Bhandari et al 2017 (258).
[a]Not reported, or unable to access full text in English, French, or German.
[b]Only trials of tolvaptan and conivaptan included.

prompt endocrine specialist input with 23 historical controls (mean Na 124.1 mmol/L), observing faster time to achieving a sodium increase of 5 mmol/L or greater (3.5 days vs 7.1 days; $P = .005$), and reduced length of stay in the intervention group (10.9 vs 14.5 days; $P = .004$) (272). A large Swiss multicenter international RCT, currently recruiting, has been designed to definitively evaluate the hypothesis that correction of hyponatremia in hospitalized patients reduces the risk of death or rehospitalization (ClinicalTrials.gov identifier: NCT03557957) (178).

It is worth noting that chronic mild-moderate hyponatremia due to a reset osmostat may not be amenable to correction when compared to other causes of SIAD—as due to increased thirst above the new osmotic set point, FR, and other therapies are unlikely to be effective.

Potential treatments for hyponatremia in SIAD are discussed and evaluated next, and a proposed management algorithm based on best available current evidence is summarized in Fig. 10.

Fluid Restriction

In patients with SIAD, FR is the first-line therapy currently recommended by EU and US hyponatremia guidelines, though evidence for efficacy is limited (3, 15). FR has the advantages of being free and readily accessible; however, limitations include patient adherence, accuracy of fluid balance monitoring in real-world conditions, potential competing need for concurrent medications that require coadministration of oral or IV fluid, and potentially poor tolerability with respect to thirst and quality of life (273). Interestingly, the osmotic threshold for thirst is lower in those with chronic SIAD, which may contribute to discomfort with FR—in a study comparing water intake post hypertonic saline infusion in 8 patients with chronic SIAD and 8 healthy controls, onset of thirst occurred at a significantly lower serum osmolality in those with SIAD, 264 vs 285 mOsml/kgH_2O (274).

There is no universally recommended FR limit. For FR to be effective, there must be negative fluid balance—with electrolyte-free water output exceeding input. For this reason, US recommendations suggest FR that is 500 mL below the 24-hour urine output, which is a "rule of thumb" to achieve this (given the difficulty of measuring insensible losses) (3). For consistency, most available studies evaluate FR in the range of 500 to 1000 mL (260). The efficacy of a 1000-mL FR was recently evaluated in comparison to no treatment, in a randomized trial in 46 patients (mean age 73 years) with chronic asymptomatic hyponatremia, mean baseline pNa 127 mmol/L (259). This trial observed a modest early rise in serum sodium of 3 mmol/L in fluid-restricted patients, compared to 1 mmol/L with no treatment (allowed ad libitum fluid intake, average intake 1.5 L). However, 39% patients assigned to FR did not respond, with serum sodium persistently below 130 mmol/L after 3 days. Notably, 9 of 23 (39%) participants receiving no treatment achieved pNa greater than or equal to 130 mmol/L after 4 days, illustrating a relatively high

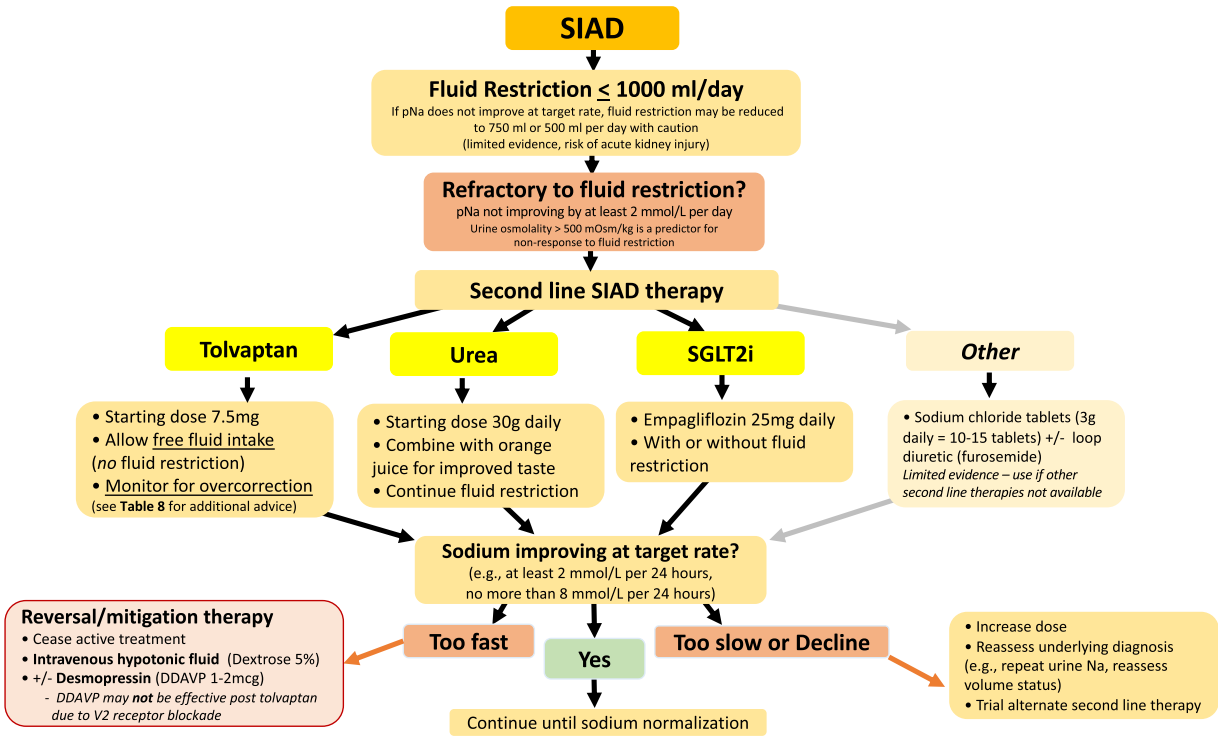

Figure 10. An approach to management of syndrome of inappropriate antidiuresis (SIAD), based on current limited evidence base. pNa, plasma sodium concentration.

rate of "spontaneous correction" even in chronic hyponatremia. These results were similar to the Thai EFFUSE-FLUID trial of 92 participants with hyponatremia, mean age 59 years, that evaluated FR (limit 500-1000 mL), determined based on urine/serum electrolyte ratio (ie, Fürst ratio, discussed later) with or without furosemide and oral salt tablets. This trial reported a mean increase in pNa of 5 mmol/L after 4 days in the 31 patients allocated to FR alone; however, there was no control group (260). In the group allocated to FR alone, 52% had pNa persistently below 130 mmol/L after 4 days and 26% had pNa less than 130 mmol/L after 30 days. Regarding the "dose" of FR, across this study as a whole, 57% participants were allocated to FR less than 1000 mL and 43% to less than 500 mL, based on prespecified criteria for urine:serum electrolyte ratio. Adherence to FR was much lower, with the 500 mL limit (43% vs 79% for the 1000 mL limit) suggesting this tighter limit was not as well tolerated (260). In a Swiss prospective observational trial, total daily fluid intake (above or below 500 mL) was not significantly associated with nonresponse to FR, indicating marginal benefit to a tighter restriction. In general, a FR limit of 1000 mL per day is the most widely studied, and any benefits to a restriction limit below this are unproven.

FR is often ineffective. In a large international registry of 1524 patients with SIAD, mean pNa 124 mmol/L, FR was unsuccessful in 55% of cases (49). In a Swiss prospective observational study of 106 patients with SIAD (pNa < 125 mmol/L), 41% did not respond to FR (pNa increment ≤ 3 mmol/L in 24 hours) (275). Factors predicting a poor response to FR include a) high urine osmolality (> 500 mOsm/L), b) low urine volume (< 1500 mL/day), and c) high UNa concentration (or high urine/serum electrolyte ratio ie, $(U_{Na} + U_K)/pNa > 1$; ie, "Fürst ratio') (3, 275, 276) (see Fig. 2). These factors all imply a lack of urinary free water clearance. In the Swiss trial, urine osmolality greater than 500 mOsm/kg/H_2O predicted nonresponse to FR with specificity of almost 90% (OR 34.8; 95% CI, 1.2-1038.3; $P = .04$) (275). Urine sodium of 130 mmol/L or greater was the most highly significant predictor of nonresponse to FR (OR 15.0; 95% CI, 2.4-95.8; $P = .004$) and while the closely-related Fürst ratio greater than 1 also predicted nonresponse, it performed less well (OR 2.7; 95% CI, 1.0-7.6; $P = .05$). In contrast, the serum copeptin was not associated with response to FR (275). One or more predictors of nonresponse are seen in up to 60% patients with SIAD, which may explain why FR is often ineffective (277).

FR involves limiting intake of all liquids, not solely water. In patients prescribed an FR where there is difficulty adhering to the limit, review of medications may reveal opportunities for substitution of therapy. In many instances, oral tablets that can be taken with a sip of water will require less fluid intake than formulations that are effervescent or dissolved in water, or IV preparations.

In patients with persistent SIAD not responding to FR, without other causes of hyponatremia or mimics of SIAD as listed earlier, and without severe symptoms necessitating hypertonic saline, the question regarding choice of second-line therapy arises, especially for those with sodium below 125 mmol/L (according to regulatory approval thresholds and prescribing guidelines for second-line agents), or with (nonsevere) symptoms (278). As seen earlier and advocated in US guidelines, early second-line therapy may be considered in those with a lower likelihood of FR response, eg, urine osmolality greater than 500 mOsm/kg/H_2O (3). Potential adverse effects of chronic hyponatremia (see "Chronic Hyponatremia") support the rationale for treatment, although to date there has been no dedicated primary end point RCT that has unequivocally

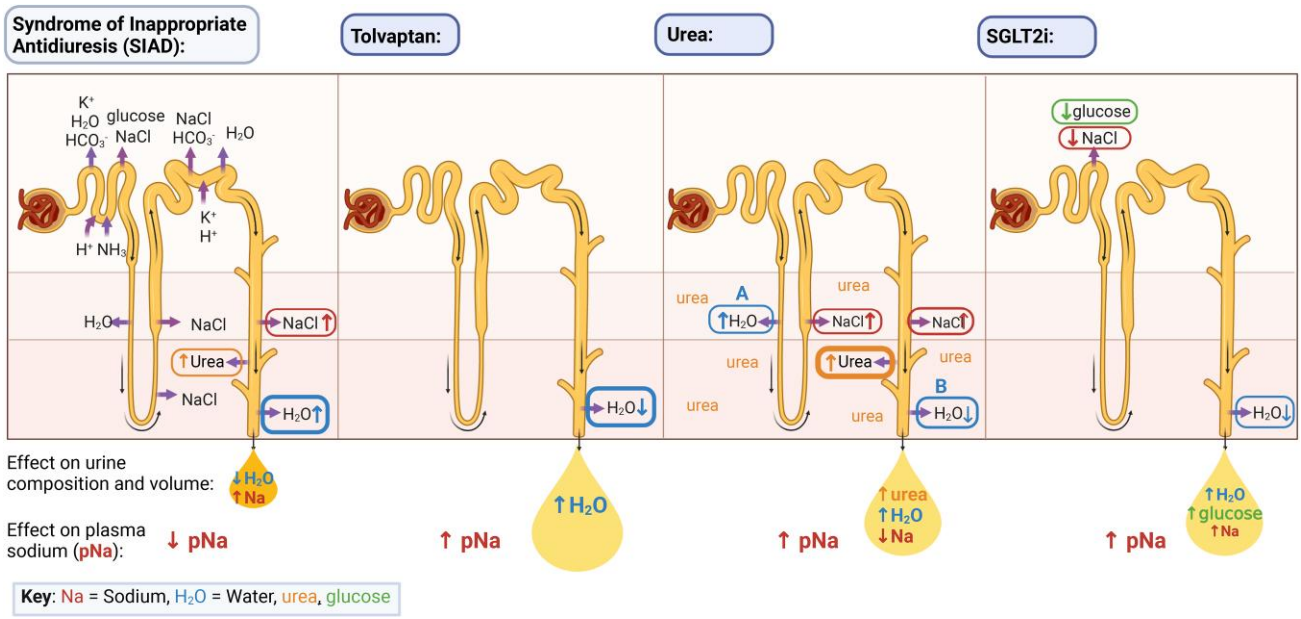

Figure 11. Renal physiology in SIAD, and mechanisms of action of tolvaptan, urea, and SGLT2i at the nephron. **SIAD**: Nonosmotic increase in circulating AVP leads to increased water resorption in the collecting duct via aquaporins, plus reduced sodium resorption in the proximal convoluted tubule, ascending limb, and distal convoluted tubule, resulting in concentrated urine production and decreased serum sodium concentration (see Fig. 5). AVP also promotes water retention by upregulating expression of UT-A1s to increase reabsorption of urea, augmenting medullary interstitial osmolality and hence urinary concentrating ability. **Tolvaptan**: blockade of AVP V2 receptor leads to reduced water resorption in the context of reduced aquaporins, resulting in a free water diuresis leading to a rise in serum sodium. **Urea**: Administration of urea leads to increased concentration of urea both in the filtrate and the renal interstitium. This leads to A, increased water resorption in the descending limb due to the osmotic effect of urea, initially leading to an elevated sodium concentration in the filtrate in the descending limb. This leads to increased sodium resorption by passive diffusion in the ascending limb, reducing sodium loss. Later, the osmotic draw of urea in the filtrate leads to B, reduced water resorption in the collecting duct, resulting in an osmotic diuresis and rise in serum sodium. **SGLT2i**: SGLT2i inhibitors act at the sodium-glucose cotransporter in the proximal tubule to reduce resorption of glucose and sodium. The primary effect is glycosuria (even in those without diabetes mellitus), accompanied by increased water excretion due to an osmotic diuresis. There is a transient increase in sodium excretion as well; however, the net effect on plasma sodium level is to increment when used in hyponatremia. AVP, arginine vasopressin; SIAD, syndrome of inappropriate diuresis; SGLT2i, sodium-glucose cotransporter 2 inhibitor. Original figure created with biorender.com, with reference to Decaux 1980 regarding urea physiology (306).

established that correcting mild to moderate hyponatremia leads to clinically important long-term health benefits.

Tolvaptan

Tolvaptan is an oral vasopressin V2 receptor antagonist that blocks AVP action in the kidney, inducing a water diuresis (termed *aquaresis* to differentiate this from the effect of diuretics that induce a natriuresis) to raise plasma sodium concentration (Fig. 11). Until recently, vaptans were the only available treatment for hyponatremia evaluated in placebo controlled, randomized clinical trials (see Table 6) (258). Treatment with a V2 receptor antagonist addresses the underlying pathophysiology of SIAD, although it is not effective in patients with rare nephrogenic SIAD (activating V2 receptor or aquaporin mutations). The IV alternative conivaptan is also approved but is not in widespread use because of CYP3A4 drug interactions and impracticalities surrounding IV administration (interestingly, the main trials on conivaptan were conducted with an oral formulation (269, 270)). Other V2 receptor antagonists that have been investigated but are not widely approved or used include lixivaptan, satavaptan, and mozavaptan (258).

The efficacy of tolvaptan vs placebo in raising serum sodium was established in the SALT-1 and SALT-2 trials. These studies recruited 448 participants with a mean age of 61 years. The 2 trials had an identical design (1 conducted at 50 international sites and the other at 42 US sites), enrolling patients with chronic mild-to-moderate hyponatremia, mean baseline serum sodium 129 mmol/L (SD 4.1), who were electively admitted to the hospital for trial initiation (153). Euvolemic and hypervolemic patients both were enrolled—30.8% had heart failure, 26.8% had cirrhosis, 24.6% had SIAD, and 17.8% "other" (153, 279). These trials compared 30 days of tolvaptan or placebo in addition to standard care (fluid intake recommendations as per treating clinician: no protocolized FR). Both trials demonstrated greater improvement in their primary end point of serum sodium area under the curve (AUC) with tolvaptan by day 4 (~ 4 mmol/L) than with placebo (~ 1 mmol/L). The initial dose of tolvaptan was 15 mg daily, with uptitration to 30 mg or 60 mg daily if there was limited response (< 5 mmol/L increase in pNa). Participants with pNa less than 120 mmol/L "in association with neurological impairment" were excluded (153). Adverse effect rates were similar between the 2 groups, the most common being thirst, dry mouth, weakness, nausea, dizziness, and urinary frequency.

Tolvaptan was approved in the United States and Europe in 2009; then Japan, Taiwan, and Hong Kong in 2010; Canada, China, Indonesia, and Korea in 2011; and Australia in 2012 (280). The US Food and Drug Administration (FDA) approval, which formed a template for many other regions, was for treatment of clinically significant hypervolemic or euvolemic hyponatremia, defined as serum sodium less than 125 mmol/L, or hyponatremia that is symptomatic and has resisted correction

Table 7. Rates of overcorrection with tolvaptan in postmarketing observational studies in hyponatremia

First author, y	Setting	No.	Mean pNa, mmol/L (rounded)	Tolvaptan dose, mg (initial dose)	Overcorrection rate (pNa > 12 mmol/L in 24 h unless otherwise specified[b]
Prospective observational					
Arima 2021 (289)	Multicenter, Japan	16	127	7.5	**6.3%**
Han 2018 (290)	8 sites, Korea	39	127	15	**13%**
Kleindienst 2020 (286)	1 site, Germany	86	128	7.5 (in 55%) 3.75 (in 45%)	**44%**[b] for 7.5 mg **37%**[b] for 3.74 mg [b]Defined as pNa > 10 mmol/L (post pituitary surgery)
Castello 2017 (291)	1 site, Italy (emergency department)	23*	125	15 (in 52%) 7.5 (in 47%)	**41.7%** for 15 mg **0%** for 7.5 mg
Retrospective observational					
Rajendran 2012 (292)	1 site, UK	14*	120	15	**0%**
Verbalis 2016 (49)	92 sites, international	225	124	15	**12.1%**
Tzoulis 2016 (283)	2 sites, UK	61	120	15 (7.5 in some, not quantified)	**18%**
Humayun 2017 (284)	1 site, UK	31	118	15	**0%** (3%[b] > 10 mmol/L)
Morris 2018 (288)	5 sites, US	28	121	15	**25%**
Kim 2020 (293)	1 site, Korea	77[a]	126	15 (in 86%; range, 7.5-30)	**18.2%** (**31.2%**[b]> 10 mmol/L)
Estilo 2021 (285)	48 sites, EU/UK	252	123	15 (in 75%; range, 3.75-60)	**24.6%** (≥ 12)
Chatzimavridou-Grigoriadou 2021 (287)	1 site, UK	55	118	7.5	**30.9%** (≥ 12) *Concurrent demeclocycline in 40%, + FR in some*
Pose-Reino 2021 (294)	8 sites, EU/UK	100	123	7.5 (in 72%) 15	**3%**
Indirli 2021 (295)	1 site, Italy	14	126	7.5 (in 57%) 15 (in 42%)	**64.2%**[b] [a]Defined as pNa > 10 mmol/L (post pituitary surgery)

Abbreviations: EU, European Union; FR, fluid restriction; IV, intravenous; pNa, plasma sodium concentration; SIAD, syndrome of inappropriate antidiuresis; UK, United Kingdom; US, United States. **Bold** text indicates overcorrection rate for clarity.
[a]Includes patients with and without confirmed SIAD (eg, hypervolemic hyponatremia included).
[b]Overcorrection defined differently from greater than 12-mmol/L sodium increase within 24 hours.

with FR (278, 280). The sodium threshold from the FDA approval is not evidence based, but instead based on expert opinion regarding which patients with hyponatremia are likely to benefit from treatment in general (278). In Europe and Taiwan, tolvaptan is approved for euvolemic hyponatremia caused by SIAD only (106, 281). In Japan, tolvaptan is approved but for use in heart failure, and it is mozavaptan that is approved in SIAD (282).

Postapproval observational studies of tolvaptan have reported efficacy in hospitalized patients with lower serum sodium concentrations than the SALT trials but have identified potential risks (283-285). While the SALT trials reported excessively rapid correction of hyponatremia (defined as an increase in sodium > 12 mmol in 24 hours) in 1.7% of overall tolvaptan-treated patients (5.6% in the SIAD subgroup), observational studies of tolvaptan in moderate to profound hyponatremia have reported highly variable rates of biochemical overcorrection (variably defined, usually ≥ 12 mmol/L over 24 hours) in patients with initial pNa less than 125 mmol/L, ranging from 0% to 30% of cases (283-288) (Table 7). The largest data sets are an international hyponatremia registry that included 225 patients with SIAD treated with tolvaptan, which observed overcorrection (pNa > 12 mmol/L in 24 hours) in 12.1% of cases (49), and an international pharmacovigilance study of 252 tolvaptan-treated patients that observed overcorrection in 24.6% of cases (285). One reason for the higher rates of overcorrection in clinical practice compared to the SALT trials may be that in clinical practice tolvaptan is used second-line, which selects for patients with more severe SIAD. Some of these studies describe use that differs from standard practice, including combining tolvaptan with FR, or the concurrent use of additional therapies (49, 287). Higher rates still of overcorrection are reported in observational studies in which tolvaptan has been used in less highly selected patient groups, including those likely to contain participants with acute hyponatremia, post pituitary surgery, or in emergency department populations, which are likely to contain individuals with readily reversible SIAD (286, 291, 295).

A lower initial dose of tolvaptan, 7.5 mg, has become more widely prescribed in recent years as there is some evidence of lower overcorrection risk. In 2 small trials (each < 15 patients), no incidents of overcorrection (> 12 mmol/L in 24 hours) were seen with the 7.5-mg dose, yet with the standard

15-mg dose 13% to 40% overcorrected (291, 296). However, the risk is not completely eliminated, as even an ultra-low dose of 3.75 mg did not prevent overcorrection greater than 10 mmol/L per 24 hours in a study of patients with acute post-neurosurgical hyponatremia, with overcorrection rates above 30% both for the 3.75 and 7.5 mg doses in this acute cohort (286). Notably, these studies were not designed to determine the degree to which tolvaptan use rather than autocorrection following resolution of reversible stimuli to AVP secretion contributed to the overly rapid rise in pNa, as there was no placebo control group. The ultra-low dose of 3.75 mg is in many cases impractical and inaccurate as it requires quartering a triangular tablet with current formulations in many markets. An alternative approach, to achieve an even lower overall dose, is to administer 7.5 mg every second day; however, there are no published data to support this, and this strategy does not reduce the risk of overcorrection with the initial dose. The potential for overcorrection on initiation means that in our experience tolvaptan is best prescribed as single doses, with ongoing therapy reviewed daily.

Risk factors for overcorrection of sodium following tolvaptan include lower initial serum sodium, presence of cancer, lower body mass index (BMI), lower blood urea nitrogen (BUN), increased GFR, and concurrent use of other treatments for hyponatremia (eg, hypertonic saline, diuretics, FR, demeclocycline) (283, 287, 288, 290, 293). Lower initial sodium is an intuitive risk, especially as the onset of thirst as the serum sodium enters the normal range for those with a higher sodium starting point would be expected to be protective against overcorrection. The increased risk with cancer may arise from increased severity of paraneoplastic SIAD that could arise from higher AVP concentrations that have been correlated with tolvaptan response in one small study (297), or may relate to cachexia and low BMI (254). There are no data available to indicate whether copeptin concentrations can predict response to tolvaptan. In patients with a lower BMI, a given volume of water excreted represents a higher proportion of total body water compared to those with higher BMI, there is a higher likelihood of raising serum sodium concentration rapidly, plus the tolvaptan dose would have a lower volume of distribution in those with lower BMI, hence higher serum concentration and greater capacity to counteract AVP. A lower BUN may represent hypotonicity and may correlate with a greater degree of AVP excess (288). Higher GFR may contribute to overcorrection risk via improved delivery of tolvaptan to its site of action in the collecting duct, and greater renal free water clearance response, compared to those with reduced renal function (288).

Only one case of ODS in association with tolvaptan monotherapy has been published, occurring in a patient with decompensated cardiac failure in whom tolvaptan was administered for 4 days at increasing doses up to 30 mg daily, despite an initial rise in serum sodium from 126 to 142 mmol/L (16 mmol in 24 hours) after the first dose—continuing to a peak sodium of 187 mmol/L after 3 further doses of tolvaptan (298). Obviously, this case was mismanaged, but at least 10 further unpublished cases of ODS following tolvaptan have been reported to the FDA (299, 300), which prompted a letter of warning from the manufacturer (301). Even if uncommon, such cases highlight the importance of conservative dosing, daily reassessment, and specialist oversight of ongoing therapy to guard against the development of ODS, particularly in patients at higher risk of ODS (see Table 3). Importantly, there is a scarcity of prospective RCT evidence to guide tolvaptan usage in multimorbid hospital inpatients with pNa less than 125 mmol/L (the US FDA recommendation), in whom it has the most potential utility.

Current international hyponatremia guidelines differ in their recommendations regarding the use of tolvaptan (106). US expert panel recommendations, while acknowledging insufficient evidence for tolvaptan use with serum sodium less than 120 mmol/L, endorse its use as a second-line treatment, with appropriate monitoring and prompt intervention if the recommended rate of serum sodium increase is exceeded, and even raise the possibility that it may be a potential first-line therapy option in the future (3). European guidelines, however, recommend against the use of tolvaptan in moderate-profound hyponatremia, primarily out of concern regarding the potential risk of excessively rapid serum sodium correction (15). Other potential concerns raised about tolvaptan include cost (302) and risk of liver function derangement seen with sustained higher-dose tolvaptan therapy used for autosomal dominant polycystic kidney disease (up to 120 mg daily) (303). A US FDA safety notice was issued in 2013 limiting the use of tolvaptan in hyponatremia to less than 30 days' duration, and removing the indication for patients with cirrhosis (304). Safe long-term tolvaptan use for up to 4 years has been reported in 111 participants in the SALTWATER trial (the SALT trial extension study), though 1 patient with cirrhosis developed hepatorenal syndrome and died, which was considered "possibly related" to tolvaptan use (305). So far, there are no reported cases of liver dysfunction directly attributed to the lower doses and typically short durations of tolvaptan in SIAD.

We use tolvaptan as a second-line therapy in selected inpatients and occasional outpatients with SIAD, typically when refractory to FR. Safety information recommends initiation and reinitiation in the hospital to allow monitoring. Careful patient selection is important, plus close monitoring of serum sodium and urine output, readiness to administer IV dextrose if correction targets are exceeded, and daily reevaluation of each dose. Based on existing evidence and clinical experience, we have developed the following recommendations for tolvaptan use (Table 8), which form the basis of an inpatient RCT protocol that is currently underway (ACTRN12619001683123), aiming to provide a prospective evidence base to evaluate these recommendations (271). We use tolvaptan less frequently in outpatients because of the product information recommending against long-term use, high cost, and limited monitoring capacity—in this situation we prefer oral urea.

Urea

Urea is recommended as a second-line treatment after FR both in the European hyponatremia guidelines and the US expert panel recommendations, despite an absence of randomized trials (3, 15). Urea is a product of hepatic nitrogen metabolism that is renally excreted and exerts an osmotic effect to promote free water excretion. In SIAD, in which urine osmolality remains inappropriately high due to persistent AVP action, osmotic intake becomes an important determinant of urine volume. In addition to the main antidiuretic action of AVP (via vasopressin V2 receptors, to increase aquaporin insertion in the renal collecting duct), AVP also promotes water retention by upregulating expression of UT-A1s to increase reabsorption of urea, augmenting medullary interstitial osmolality and therefore urinary concentrating ability (72). In

Table 8. Practical suggestions to optimise the safety of tolvaptan use in inpatient hyponatremia

- Exclude other causes of hyponatremia, especially hypovolemia. Avoid use in patients with end-stage kidney disease or substantial liver function abnormality
- Do not use in combination with other treatments for hyponatremia
- Ensure free access to water once tolvaptan is administered (no fluid restriction), and ensure patient physically and cognitively able to drink unaided (and/or ability to provide IV fluid if required to counteract overcorrection)
- Prescribe as a once-off "stat" order to avoid unintentional ongoing therapy
- A low initial dose of tolvaptan 7.5 mg is preferred
- Give tolvaptan early in the morning if possible so most of the aquaresis occurs in afternoon/evening rather than overnight (for ease of monitoring and to minimize patient sleep disruption)
- Monitor fluid intake and output (with or without indwelling urinary catheter)
- Recheck serum sodium 6 and 12 h post tolvaptan dose
- If serum sodium increase > 6 mmol within 6 h, or 8 mmol within 12 h (301), initiate preemptive treatment with IV 5% dextrose matched to rate of urine output to ameliorate further sodium increase, with ongoing frequent monitoring of serum sodium. If serum sodium then reduces to within these targets, dextrose should be paused.
- In the event of overcorrection serum sodium increase > 10 mmol/L, bolus IV dextrose is our preferred reversal agent, as DDAVP action may be blocked by tolvaptan (in vivo evidence is lacking)

Abbreviations: IV, intravenous; DDAVP, desmopressin.

hyponatremic patients, treatment with exogenous urea overwhelms this mechanism by achieving a high concentration of urea in the glomerular filtrate, which induces an osmotic diuresis and reduces natriuresis, resulting in increased electrolyte-free water clearance (see Fig. 11) (306, 307). Urea administration is a much more efficient means of solute supplementation than oral sodium chloride administration. For example, a 15-g sachet of urea provides a renal solute load of 250 mOsm, whereas a single 600-mg sodium chloride tablet provides a renal solute load of 20.6 mOsm, and a 1000-mg NaCl tablet provides 34 mOsm. In other words, a 30-g dose of urea provides the same solute load as 14 to 25 salt tablets, depending on their strength (see Table 9).

Urea has been in clinical use since at least 1980; however, its uptake had been limited; an international hyponatremia registry published in 2016 of more than 1000 patients with SIAD in the United States and European Union reported use of urea in only 0.2% of patients (49). The main barriers to uptake appear to have been difficult access and concern about tolerability (in particular, bitter taste), which can be ameliorated by combining it with citric acid, sucrose and bicarbonate, or a small volume of orange juice (3, 15). The dose of urea endorsed by the EU guidelines is 0.25 to 0.5 g/kg/day (ie, 15-30 g daily for a 60-kg patient), and US guidelines recommend 15 to 60 g daily, and use of doses up to 90 g daily is reported (3, 15, 308). In general, 30 g daily is a commonly recommended starting dose (178, 309). Clinicians should be aware that urea therapy causes an increase in serum urea concentration and BUN usually double baseline, but this does not necessarily represent deterioration in renal function or hypovolemia (308). Urea powder is low cost, at less than USD $3 per 30-g dose (309). Proprietary flavored formulations that may be more palatable are also available in the United States and elsewhere by special order, albeit more expensive (eg, "Ure-Na" approximately USD $7.50 per 30-g dose).

Table 9. Expected efficacy of urea (ure-Na) vs oral sodium chloride (600-mg NaCl tablets) for an illustrative 70-kg woman (total body water 35 L) with hyponatremia due to syndrome of inappropriate antidiuresis (pNa 125, UOsm 500)

	Urea	Sodium chloride
Formulation	21-g sachet of powder	Tablet
Contents	Urea 15 g = 249.5 mmol	600 mg NaCl = 10.3 mmol Na + 10.3 mmol Cl
Renal solute load	250 mOsm	21 mOsm
Water loss[a]	500 mL (1 sachet)	42 mL (1 tablet) *420 mL (10 tablets)*
Net water balance if taken with 140 mL water	−360 mL (1 sachet)	+98 mL (1 tablet) *−280 mL (10 tablets)*
Anticipated change in pNa[b]	+1.3 mmol/L (1 sachet)	+ *1.0 mmol/L (10 tablets)*

Italic refers to calculations for 10 x 600 mg sodium chloride tablets.
Abbreviation: pNa, plasma sodium concentration.
[a]Assuming urine osmolality of 500 mOsm/L
[b]Using the Adrogué-Madias formula (184) and assuming total body water of 35 L and pNa 125 mmol/L.

There are a number of observational studies of urea, but no randomized trials to date. The largest is a review of 69 patients with hyponatremia prescribed urea, with mean nadir pNa 122 mmol/L and mean age 67 years, that reported 64% patients achieved a serum sodium greater than 130 mmol/L by 72 hours, compared to 52.9% in an unmatched FR cohort —which was not a statistically significant difference (309). In the 56 patients who had failed to respond to other prior treatments including FR, the mean pNa increment after commencing urea was 6.9 mmol/L over 72 hours, though with no control group for this measure. Notably, urea was administered in conjunction with FR (500-1000 mL) in more than 80% cases, and both urea dose and the FR limit were often escalated during the treatment course. Urea dose of 30 g or greater per day was associated with benefit, as no patient receiving less than 30 g urea achieved serum sodium greater than 135 mmol/L after 72 hours. Side effects occurred in 21% of patients, most commonly distaste, nausea, and hypokalemia, though none led to discontinuation. There were no cases of overcorrection (pNa > 10 mmol/L in 24 h) observed. It is difficult to separate the effect of urea from the concurrent, tightening FR in this nonrandomized study, but it was safe and well tolerated. Another retrospective observational study of 58 hyponatremia patients treated with urea (7.5-90 g/d) reported a mean increase in pNa of 7 mmol/L over 4 days, with no instances of rapid correction (308). A case series of 36 cancer patients with SIAD (mean pNa 123 mmol/L) treated with urea at an initial dose of 15 to 30 g daily without FR had a mean 24-hour sodium increase of 5 mmol/L, with 86% patients achieving pNa greater than 135 mmol/L after 30 days with no cases of overcorrection (310).

In patients unable to be fluid-restricted, there are also reports of urea efficacy with concurrent IV isotonic saline. A retrospective study of 50 ICU patients with mild-moderate hyponatremia (mean pNa 128 mmol/L) receiving urea 0.5 to 1 mg/kg/day reported that the majority normalized pNa within 48 hours despite fluid intake of more than 2 L/day—though 6 patients developed hypernatremia (maximum Na 155 mmol/L) (311). Another study of 42 patients with SIAD

in the context of SAH, mean pNa 127 mmol/L, prescribed isotonic 0.9% saline 3 L/day as part of their SAH management and treated with urea (median dose of 50 g daily) leading to a mean time to pNa normalization of 3 days (312).

Overcorrection with urea has been described. In the aforementioned SAH study, 4 patients (9.5%) had sodium increments of 12 mmol/L or greater within 24 hours (312). In an ICU series of 35 patients with symptomatic severe hyponatremia (mean pNa 111 mmol/L) treated with urea and normal saline, 34% had an increment in pNa greater than 12 mmol/L in 24 hours; however, there was no control group and this patient population was at high baseline risk of spontaneous sodium overcorrection. There have been no published cases of ODS due to urea therapy despite these instances of overcorrection, though the body of literature for urea use is smaller than for many other therapies. Interestingly, it seems possible that urea may have a protective effect against ODS. A preclinical study induced rapid sodium correction (> 30 mmol/L in 24 h) in rats with 3 different agents—hypertonic saline, lixivaptan, and urea. Despite similar increases in pNa, urea-treated animals had lower mortality, fewer neurological symptoms, and reduced histological markers of demyelination (313). The postulated mechanism is that the additional urea itself may aid in replenishing intracellular osmolytes in brain tissue, thereby increasing resilience to rapid osmolar shift; however, whether this applies to humans is uncertain.

Overall, the evidence base for the use of urea is limited by the retrospective observational nature of most current studies, heterogeneous inclusion criteria, and lack of control groups—which are particularly important in hyponatremia given the potential for autocorrection. Despite the limited evidence base, there is support for its use as an adjunct therapy to FR in chronic SIAD not responsive to FR alone in current guidelines, given its lower cost, low risk, and potential efficacy (3, 15, 314).

The only study to compare vaptans and urea, indirectly, was a small, single-arm trial in 12 participants with chronic SIAD (mean pNa 125 mmol/L, mean age 73 years) comparing sequential long-term treatment with a vaptan (tolvaptan or satavaptan), followed by urea 15 to 30 g/d after a treatment interruption. The authors reported a good response to treatment with both agents (mean pNa on treatment 135 mmol/L with both) and no difference in tolerability (315). However, methodologic limitations including the small size of the study do not allow accurate inferences to be made. This is an important topic for future research.

Current clinical practice differs across different centers, but urea is being increasingly used (see Fig. 10). Considerations that may make urea the preferred second-line therapy include risk factors for overcorrection, frailty, requirement for longer-term SIAD therapy to prevent recurrent hyponatremia-associated hospitalization (given the 30-day treatment limit for tolvaptan), and specific contraindications to tolvaptan (eg, deranged liver function). Though there are no direct published comparisons of overcorrection rate, clinical experience and the available literature of overcorrection in urea and tolvaptan individually suggest urea may carry a lower risk.

Sodium-Glucose Cotransporter 2 Inhibitors

SGLT2is, approved for treatment of diabetes and heart failure (316, 317), may be beneficial in SIAD. The SGLT2 in the proximal renal tubule is responsible for 90% of renal glucose resorption and 65% of sodium resorption (318). Inhibition of SGLT2 leads to glycosuria, accompanied by an osmotic diuresis (see Fig. 11) (319). Due to the increased free water excretion, SGLT2is have been investigated in SIAD as a novel therapy. A randomized trial of 87 inpatients with SIAD compared 4 days of empagliflozin 25 mg or placebo, in addition to 1000-mL FR, in patients with a mean baseline pNa of 125.5 mmol/L (261). pNa increased by 10 mmol/L over 4 days in the empagliflozin plus FR group, compared to 7 mmol/L with placebo and FR ($P = .04$). Comorbid type 2 diabetes mellitus was present in 14% of participants, equal between empagliflozin and placebo arms. pNa overcorrection occurred in 2 patients in the empagliflozin arm (5%), compared to 1 in the placebo arm. The only other potentially related adverse event was decreased renal function in 7% empagliflozin participants that later resolved. There was no hypotension or hypoglycemia observed. The relatively high sodium increment in the placebo group (ie, FR alone) suggests that at least in some patients, reversible stimuli to AVP secretion may have been present. It is worth noting that the causes of SIAD were unbalanced between the 2 groups; therefore, the rates of autocorrection may have differed. However, the higher rate of malignancy (a nonreversible stimulus) in the SGLT2i group would if anything excepted to bias the response rate in favor of the placebo group. No biomarkers, including copeptin, were predictive of response to empagliflozin (320).

A second, randomized controlled crossover study in 14 patients (50% female, median age 72 years, 2 with type 2 diabetes) compared a 4-week treatment with empagliflozin 25 mg/d to placebo in outpatients with chronic SIAD-induced hyponatremia, without concomitant FR (154). The etiology of chronic SIADs ranged from drug-induced (antiepileptic [n = 3] and antidepressants [n = 1], which could not be stopped), to pulmonary (n = 3) or CNS disorders (n = 2) to stress induced due to chronic pain (n = 1). In 4 patients, the etiology remained idiopathic. Median baseline pNa was 131 mmol/L and increased following treatment with empagliflozin to 134 mmol/L, whereas no increase was seen with placebo (130 mmol/L). This resulted in a serum sodium increase of 4.1 mmol/L ($P = .004$) on empagliflozin as compared to placebo. Treatment with empagliflozin was generally well tolerated. Increased thirst was reported in about half of all patients under both treatments, and a few patients reported headache and vertigo; nausea was reported only on placebo. No events of sodium overcorrection, hypoglycemia, hypotension, or urinary tract or genital infection occurred during the observation period. Of the 7 reported adverse events, 5 were potentially related to empagliflozin treatment. On placebo, 2 of the reported 7 adverse events were judged to be potentially related to the study intervention.

Experience with SGLT2 therapy for other indications has shown a risk of ketoacidosis in patients with type 2 diabetes, particularly in patients who are unwell in the hospital (321), potentially limiting the indication for this therapy in multimorbid hospital inpatients—though no episodes of ketoacidosis occurred in the trial. A larger trial in chronic euvolemic and hypervolemic hyponatremia is currently underway (NCT04447911). The accessibility, clinical familiarity, and relative safety of SGLT2is may see them become a widely used therapy in SIAD—if efficacy is established.

Oral Sodium Chloride (Salt Tablets)

Hyponatremia due to SIAD is predominantly caused by water retention rather than sodium deficiency (though a total body

sodium deficit can accumulate in chronic SIAD due to compensatory pressure natriuresis). While intuitively attractive, salt tablets do not address this underlying cause, though there are some pathophysiologic mechanisms by which salt tablets may plausibly have benefit. In the context of low solute intake or natriuresis from loop diuretics, low-dose salt tablets may supplement sodium intake to replace sodium lost via physiological mechanisms. Alternatively, high-dose NaCl tablets can produce a renal solute load (akin to urea), as osmotic intake is important in affecting urine volume in SIAD, in which AVP concentrations are relatively static. Therefore, ingestion of sufficient salt could increase urine volume and endogenous water clearance. However, the osmotic equivalent of 30 g of urea, to facilitate up to 1000 mL of water clearance, is 15 000 mg of NaCl—far above the typical dosing of salt tablets published in hyponatremia (see Table 9). The use of salt tablets is further limited by palatability, potential nausea, and thirst. The mechanism by which salt tablets induce thirst in humans with hypotonic hyponatremia has not been studied, but preclinical studies have reported that experimentally increasing the osmolality of gastrointestinal fluid stimulated thirst-promoting medical preoptic nucleus glutaminergic neurons in mice (322). The aforementioned 2016 international registry study of SIAD treatment (n = 1524) reported use of salt tablets in 18% cases, often in combination with other therapies (49). In the 2014 European guidelines, oral sodium chloride was recommended as a second-line therapy in combination with loop diuretics, though this was classified as a weak recommendation with a low-quality evidence base, and though this combination is uncommonly used in clinical practice (only 0.3% of registry patients) (15, 49). Salt tablets are not mentioned in the US expert panel recommendations (3).

Even in high sodium-loss states, normal dietary sodium intake is almost always adequate to maintain normal plasma sodium concentration (323). The usual recommended daily dietary sodium intake (~ 100 mmol/d) contains twice as much sodium as a typical dose of salt tablets (3 g daily, eg, 5×600 mg tablets = 51 mmol Na^+)—and many Western diets exceed these sodium guidelines (324). This quantity of sodium is equivalent to just over half a teaspoon of table salt (2.85 g = 47.4 mmol), or 100 mL of hypertonic (3%) sodium chloride solution (51.3 mmol). Some recommended regimens for salt tablets are even higher, 9 g per day (3×1 g, 3 times daily = 154 mmol) aiming to produce an osmotic diuresis (325).

The only RCT of sodium chloride tablets evaluated them in combination with FR and furosemide, in a trial of 92 patients with SIAD (260). The trial involved 3 open-label arms: FR alone; FR + furosemide (20-40 mg daily); and FR + furosemide + salt tablets (3 g [51 mmol] per day, 10×300 mg tablets, in divided doses). Mean baseline pNa was 125 mmol/L. This study, the highest-quality evidence to date, found no difference in time taken for serum sodium concentration to normalize in those patients prescribed salt tablets compared to FR and furosemide, or FR alone ($P = .5$), and found higher rates of treatment withdrawal due to adverse events (20%, vs 6% and 10% in other arms; $P = .03$), namely increased acute kidney injury ($P = .07$) and significant hypokalemia less than or equal to 3.0 mmol/L ($P = .01$) (260). By increasing thirst, salt tablets may increase water intake and worsen hyponatremia if the amount of fluid intake exceeds that of the extra urine volume excreted via salt-mediated solute diuresis (326). Whether higher doses of oral sodium chloride without furosemide are effective and safe has not been subject to RCTs.

Sodium supplementation may have a role where there is suspected solute depletion from long-term diuretic therapy or a low-solute diet in tandem with SIAD. Despite their popularity, there is no compelling evidence for efficacy of salt tablets in SIAD.

Loop Diuretics

Loop diuretics, such as furosemide, increase urinary salt and water excretion via inhibition of the sodium-potassium-chloride cotransporter in the Henle loop to reduce reabsorption of these solutes. They are listed in the European guidelines as a second-line therapy for SIAD in combination with salt tablets (weak recommendation, low-quality evidence), but are not endorsed in the international expert panel recommendations (3, 15). The guideline recommendation was made on the strength of several case series, though only 1 of these included patients with SIAD rather than patients with heart failure and cirrhosis, and that report from 1973 included only 5 patients (327).

Loop diuretics are useful in the treatment of hypervolemia; however, in the absence of volume excess, natriuresis may cause volume depletion, which stimulates AVP release, thereby worsening hyponatremia. The randomized trial discussed earlier that evaluated FR with and without furosemide and salt tablets to prevent hypovolemia in SIAD found no significant benefit to the addition of frusemide 20 to 40 mg daily compared with FR alone, but in fact observed increased rates of acute kidney injury and hypokalemia (260). Furosemide increases urinary potassium excretion, which can be potentiated by increased sodium in the distal nephron (328). Because of this recent evidence, we do not recommend loop diuretics for euvolemic hyponatremia.

Demeclocycline

Demeclocycline is recommended as an alternative therapy in the US expert opinion guidelines but recommended against in European guidelines because of side effects. Demeclocycline, a tetracycline derivative, can induce renal AVP resistance (nephrogenic diabetes insipidus), thereby promoting dilute urine excretion (329). This effect is unpredictable, occurring in 33% to 60% of patients (329, 330), with the maximal diuretic effect taking 3 to 4 days to develop (3). Potential adverse effects include gastrointestinal intolerance, nephrotoxicity, and a photosensitive skin rash (331).

A recent systematic review of demeclocycline for SIAD did not find any good-quality evidence to support its use (331). Two small RCTs of demeclocycline 600 to 1200 mg daily were identified, but only one of those studies enrolled hyponatremic patients (mean baseline pNa 131 mmol/L), with a sample size of 9, and showed no significant difference between demeclocycline and placebo (332). The remaining evidence from cohort studies and case reports describe some effect; however, concerns remain regarding unreliable onset of action and poor safety profile, particularly nephrotoxicity (333). Overcorrection and ODS have been reported (334). Considering these risks, and given the availability of alternatives, we do not recommend demeclocycline for treatment of SIAD.

Lithium

Given that lithium may also induce nephrogenic diabetes insipidus, it has been explored as a potential treatment for SIAD. However, adverse neurological symptoms and lack of

predictable effect mean that it is not clinically useful for SIAD, and use of lithium is recommended against in European hyponatremia guidelines (15, 333).

Apelin Analogues

New research is exploring the use of an apelin-17 analogue in SIAD (335). Apelin is a neurovasoactive peptide that acts both on apelin receptors in the hypothalamic magnocellular vasopressinergic neurons to reduce AVP secretion, and on apelin receptors in the renal collecting duct, where it reduces aquaporin expression via crosstalk with the V2 receptor (the opposite effect of AVP), promoting free water excretion (336). An apelin analogue was compared with tolvaptan and placebo in an animal model of SIAD and both active agents demonstrated an aquaretic effect, causing an increase in pNa of 10 mmol/L, but there was no significant difference between the apelin analogue and tolvaptan (335). This class has not yet been trialed in humans, and it remains to be seen whether it will offer any advantage over V2 receptor inhibition with vaptans.

In Case of Overcorrection: Relowering of Plasma Sodium

Overcorrection of serum sodium can occur as a consequence of any sodium-raising intervention, or may occur spontaneously with the resolution of a reversible stimulus for AVP secretion or cessation of excessive water input, and subsequent aquaresis. There is no evidence that spontaneous overcorrection of chronic (> 48 h) hyponatremia is any safer than iatrogenic overcorrection. To maintain the rate of correction within the target range, "relowering" of serum sodium can be achieved with administration of hypotonic fluid, with or without iatrogenic AVP therapy (desmopressin, DDAVP) to suspend urine output (see Figs. 8 and 10), and of course ceasing any active sodium-increasing therapy. Because the symptoms of ODS are delayed by several days, relowering remains essential for patients who are asymptomatic—but may also improve symptoms and outcomes for those with early clinical ODS (337).

The precise serum sodium threshold to commence relowering is not definitively established and may depend on clinical factors reflecting ODS risk. European guidelines recommend prompt intervention for relowering for any serum sodium increase greater than 10 mmol/L during the first 24 hours, or greater than 8 mmol/L in any subsequent 24-hour period (15). A US expert panel recommends consideration of relowering if correction exceeds 10 to 12 mmol/L/day for those at low-moderate risk of ODS, but endorses a more conservative threshold of 6 to 8 mmol/L within 24 hours for relowering in those at higher risk of ODS, defined broadly as pNa less than 120 mmol/L (plus additional factors in Table 3) (3).

Relowering of serum sodium is based on sound physiologic principles, preclinical data, and case series in humans; however, RCT evidence for the best strategy is lacking (337). In an animal model of ODS in which serum sodium in rats was reduced below 115 mmol/L for 3 days, then excessively corrected with hypertonic saline (rise pNa > 25 mmol/L for at least 12 hours), relowering with oral water bolus to achieve a correction gradient of less than 20 mmol/L per day improved mortality and histological severity of ODS compared to more modest correction that was still greater than 20 mmol/L/day, or no relowering (143, 338). In fact, all rats in which the 24 hour sodium increase was limited to less than 20 mmol/L with relowering had good neurological outcomes though mild brain lesions were seen in 20%, compared to a 100% rate of histological brain damage and 57% mortality in the overcorrected control rats (338).

Three retrospective observational studies in humans assess relowering therapy to date, all of which use the administration of desmopressin in hyponatremia to identify such cases. The first study included 6 patients who had pNa increase above 12 mmol/L within 24 hours who were administered DDAVP and IV 5% dextrose to actively reduce serum sodium, and in all 6, pNa was reduced by 2 to 9 mmol/L, with no adverse consequences observed (339). A further 14 patients in the same study were administered DDAVP following a pNa increase below 12 mmol/L to prevent a further increase, of whom 5 also received IV dextrose—and with these interventions no patient exceeded the target 24-hour pNa limit (339). Another study identified 20 consecutive patients admitted to an ICU with severe symptomatic hyponatremia, treated with DDAVP and hypotonic fluid to treat or prevent overcorrection (340). As expected, DDAVP decreased the rate of correction, decreased urine output, and reduced the magnitude of pNa increase, with no adverse effects observed. The largest observational study so far in Canada evaluated 254 instances of DDAVP use in hyponatremia, plus concurrent hypotonic fluids in 90 of these cases (35.9%). This cohort represented 17.5% of 1450 total severe hyponatremia presentations at that center over 10 years. This study observed reduced rates of change of pNa and lower mortality (3.9% vs 9.4%) in these patients compared to those who did not receive DDAVP (341). Four patients in this cohort were diagnosed with ODS (0.28%), of whom 2 received DDAVP during their admission and 2 did not—however, none of the 4 received hypotonic fluid. Of the 2 patients with ODS despite DDAVP, 1 had a pNa increase greater than 8 mmol/L (but not > 12 mmol/L) in 24 hours, and in the other a pNa increase was not reported as the initial pNa was "< 100," and both had additional risk factors for ODS. These data support the stricter 8-mmol/L limit for pNa correction in those at higher risk of ODS—and support the logical conclusion that while DDAVP is effective to prevent further increase, hypotonic fluid is also necessary to achieve relowering.

Electrolyte-free water administration (eg, oral water, or IV 5% dextrose) is critical in managing overcorrection. The European guidelines recommend a bolus of 10 mL/kg of electrolyte-free water over 1 hour (eg, 500-1000 mL over 1 h for patients 50-100 kg) (15). International expert panel guidelines recommend commencing an infusion of 3 mL/kg/h of IV 5% dextrose (ie, 150-300 mL/h for patients weighing 50-100 kg) continuing, with hourly monitoring, until the pNa has returned below the 24-hour limit (3). We favor the larger upfront bolus in line with the European guidelines, then reassessment before any ongoing infusion. The Adrogué-Madias formula can be used to estimate the sodium-lowering effect of 1000 mL of dextrose 5% with the caveat that this formula assumes no net electrolyte-free water clearance or retention occurs as the dextrose is administered (184) (see Fig. 2). If the pNa is rising faster than desired but has not yet exceeded the maximum target, an infusion of dextrose 5% can be used to prevent further increments. As a rule of thumb, matching the rate of fluid input to hourly urine output (an imperfect indicator of electrolyte-free water clearance) should stabilize pNa in this instance.

Desmopressin, an AVP analogue, may be administered either IV or subcutaneously at a dose of 1 to 2 mcg, to reduce

urine output and prevent further increments in pNa (3, 15, 339, 342). DDAVP is particularly useful in polyuric patients, in situations when a reversible stimulus to AVP is no longer present and accumulated free water is being rapidly excreted (heralded by hypotonic polyuria, ie, low UNa and osmolality). In this context, rather than "chasing" polyuria by attempting to match urine output with high volumes of 5% dextrose or oral free water, urine output is curtailed, allowing judicious administration of electrolyte-free water to actively relower serum sodium, usually in an intensively monitored setting (eg, high dependency or ICU) with frequent (eg, 1-2 hourly) serum sodium monitoring. Clinicians should be aware that desmopressin may not be effective in halting overcorrection from tolvaptan because of AVP receptor blockade, depending on the duration of tolvaptan effect at the renal collecting duct cells. DDAVP is contraindicated for patients with primary polydipsia, in which oral fluid intake cannot be reliably restricted.

A systematic review of DDAVP in hyponatremia identified 3 different approaches: "proactive" DDAVP in high-risk patients in combination with hypertonic saline before any correction (not widely recommended, as discussed in "Emergency Management of Severe Hyponatremia"), "reactive" in response to actual or anticipated above-target pNa increase, or "rescue" after pNa limits have been exceeded or on development of neurological symptoms (342). Although there have been no prospective comparisons, a follow-up retrospective study (as mentioned earlier) concluded that a reactive strategy to maintain pNa within the target range if overcorrection is deemed likely, was best supported by their data (341).

In summary, relowering pNa with electrolyte-free water and/or DDAVP to achieve a safe net 24-hour correction is an important tool that may be required during the often delicate management of hyponatremia, to minimize the risk of adverse outcomes.

Conclusion and Directions for Future Research

Hyponatremia is the most common electrolyte disorder in hospitals and is associated with short- and long-term morbidity and mortality, though causality remains to be clarified in future trials. SIAD is a frequent cause, but is a diagnosis of exclusion that requires careful workup. Approximately half of patients with SIAD do not respond to first-line therapy with FR. There is a lack of high-quality evidence to definitively guide second-line management of hypotonic hyponatremia, with only tolvaptan and empagliflozin subject to RCTs compared with placebo.

Based on current guidelines, and new information published since, tolvaptan and urea have emerged as the most effective second-line therapies in SIAD if FR fails. There is a need for further research such as RCTs of FR with and without urea (the use of placebo comparison complicated by urea's distinctive taste); tolvaptan vs FR; and comparison of second-line therapy after FR with tolvaptan, urea, or SGLT2is. Trials conducted in inpatients with moderate-severe hyponatremia reflecting real-world clinical care needs are lacking. It is possible that with further evidence, medications such as vaptans or urea may ultimately complement or supersede FR as the first-line treatment for SIAD, where targeted treatment addressing the underlying cause is not effective or if there are clinical or biochemical characteristics to suggest FR is unlikely to succeed.

Tolvaptan, urea, and SGLT2is (as all active hyponatremia treatments) carry a potential risk of sodium overcorrection —likely tolvaptan more so, though direct comparison is lacking. Close monitoring and readiness to administer prophylactic hypotonic fluid and/or DDAVP are key when prescribing medication to raise serum sodium concentration, to ensure optimal patient outcomes.

AREAS FOR FUTURE RESEARCH

Diagnosis
- Identify point-of-care markers that can reliably diagnose SIAD and distinguish it from other causes of hyponatremia
- Investigate whether subtypes of SIAD predict treatment response to vaptans or other therapeutic options
- Identify markers (eg, genetic variation) that make patients more prone to SIAD and/or medication-associated hyponatremia (eg, thiazide induced)
- Investigate value of copeptin measurement in the diagnosis of nephrogenic SIAD
- Determine the degree to which chronic hyponatremia is a causal mediator of associated adverse clinical outcomes (eg, osteoporosis, fracture, falls, neurocognitive decline, and mortality)

Management
- Evaluate the effect of treatment of hyponatremia on outcomes in patients with SIAD
- Comparison of bolus hypertonic 3% NaCl treatment with fixed dose vs weight-adapted dose
- Comparison between FR and other therapies
- RCTs of urea and SGLT2is to prove efficacy and safety
- Followed by comparison between different second-line therapies (tolvaptan, urea, SGLT2is)
- Therapeutic approaches to ODS
- RCTs to determine whether implementation of standardized diagnostic and treatment pathways can improve clinical outcomes in hospital patients
- RCTs to determine whether correction of chronic hyponatremia improves adverse clinical consequences

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