BMJ Best Practice

Syndrome of inappropriate antidiuretic hormone

Straight to the point of care

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Summary

Syndrome of inappropriate antidiuretic hormone (SIADH) is defined as euvolaemic, hypotonic hyponatraemia secondary to impaired free water excretion, usually from excessive arginine vasopressin (AVP) release.

Severe neurological symptoms, such as altered mental status, seizure, and coma, may result from SIADH and these are always treated with hypertonic saline, with close monitoring to avoid overcorrection of serum sodium.

Central pontine myelinolysis (osmotic demyelination syndrome) may occur with rapid correction of serum sodium in excess of 12 mmol/L/day (12 mEq/L/day).

Vasopressin receptor antagonists (also known as vaptans) are a class of medicines that compete with the antidiuretic hormone AVP for binding at the vasopressin receptor, permitting free water excretion.

Definition

The syndrome of inappropriate antidiuretic hormone (SIADH) is characterised by hypotonic hyponatraemia, concentrated urine, and a euvolaemic state. The impairment of free water excretion is caused by increased arginine vasopressin (antidiuretic hormone or AVP) release. Pseudohyponatraemia due to hyperglycaemia, hyperlipidaemia, or hyperproteinaemia should be ruled out first. Renal failure, adrenal insufficiency, and appropriate release of AVP secondary to extracellular volume depletion (hypovolaemia, due to gastrointestinal or renal loss) or intravascular volume depletion (hypervolaemia due to congestive heart failure, cirrhosis of the liver, or nephrotic syndrome) must be ruled out in order to diagnose SIADH.

Epidemiology

Hyponatraemia (serum Na <135 mmol/L or <135 mEq/L) is the most common electrolyte disorder encountered in clinical practice.[4] [5] It has been reported to occur in 15% to 28% of hospitalised patients.[6] However, the incidence of clinically significant cases of hyponatraemia (serum Na <130 mmol/L or <130 mEq/L) is between 1% and 4%.[7] The prevalence of mild hyponatraemia in people aged 75 years or older is around 16%.[8]

The incidence/prevalence of SIADH in particular is studied less thoroughly in the literature. SIADH was the most common cause of hyponatraemia in patients with cancer, accounting for around 30% of the total hyponatraemia cases.[6] Hyponatraemia is a well-recognised complication of neurosurgical conditions and in one study, SIADH was the underlying pathophysiology in 62% of cases.[9] In another study of older patients in hospital who had hyponatraemia, almost 25% of cases met the diagnostic criteria of SIADH.[10] The most common causes of SIADH were respiratory diseases (59%), followed by malignant tumours (29%), and central nervous system diseases (10%).[10]

Aetiology

Under pathological conditions, the pituitary gland and other cells may synthesise and secrete arginine vasopressin (AVP, the antidiuretic hormone) independently of serum osmolality or circulating volume.[4] Inappropriate antidiuresis may also result from increased activity of vasopressin in the collecting duct or from a gain-of-function mutation in its type 2 receptor.[4] Causes of SIADH include:[2] [4]

- Drugs: multiple drugs have been linked to increased AVP release or enhanced potential of AVP, including:[4]
    - Antidepressants such as selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, and venlafaxine
    - Anticonvulsants such as carbamazepine, oxcarbazepine, valproate, and lamotrigine
    - Antipsychotics such as phenothiazines (e.g., chlorpromazine) and butyrophenones (e.g., haloperidol)
    - Antidiabetic agents such as first-generation sulfonylureas (e.g., chlorpropamide, tolbutamide)
    - Chemotherapeutic agents such as vinca alkaloids, platinum compounds, ifosfamide, melphalan, cyclophosphamide, methotrexate, and pentostatin
    - Vasopressin analogues such as desmopressin, oxytocin, terlipressin, and vasopressin
    - Other drugs such as opioids, methylenedioxymethamphetamine (MDMA), levamisole, interferon, clofibrate, nicotine, amiodarone, proton-pump inhibitors, monoclonal antibodies, and non-steroidal anti-inflammatory drugs (NSAIDs).
- Pulmonary processes: including pulmonary infections such as bacterial pneumonia, viral pneumonia, pulmonary abscess, tuberculosis, or aspergillosis; asthma; cystic fibrosis; positive-pressure ventilation; or lung cancers, especially small cell lung cancer.[4]
- Malignancy: carcinomas (including lung, oropharynx); malignant diseases of the gastrointestinal (stomach, duodenum, pancreas) or genitourinary (ureter, bladder, prostate, endometrium) tracts; thymoma; lymphomas; sarcomas (e.g., Ewing's sarcoma); and olfactory neuroblastoma.[4]
- Central nervous system (CNS) disorders: CNS infections (encephalitis, meningitis, brain abscess, Rocky Mountain spotted fever, HIV-associated opportunistic CNS infections, malaria); vascular causes and masses (brain trauma, subdural haematoma, subarachnoid haemorrhage, stroke, and brain

tumours); other CNS disorders (hydrocephalus, cavernous sinus thrombosis, multiple sclerosis, Guillain-Barre syndrome, Shy-Drager syndrome, delirium tremens, acute intermittent porphyria).[4]
- Other stimuli for AVP release: such as anaesthesia and postoperative state, nausea, vomiting, pain, stress, and endurance exercise.[4]
- Nephrogenic syndrome of inappropriate antidiuresis or pseudo-SIADH. This is due to gain-of-function mutations in the vasopressin 2 (V2) receptor, which is constitutively active. This initiates aquaporin-2 placement into the apical membrane of cortical collecting duct cells and corresponding free water permeability, in face of appropriately low serum AVP levels.[3]

Other proposed, but unconfirmed, mechanisms include:

- The presence of an unknown antidiuretic substance (other than AVP) that stimulates the AVP V2 receptor.[1]
- Post-AVP V2 receptor defect. Aquaporin-2 channel activity is inappropriately stimulated downstream of the AVP V2 receptor. This could be via intracellular stimulation or dysfunction of the aquaporin-2 channel itself.[1]

Pathophysiology

Arginine vasopressin (AVP or antidiuretic hormone) is produced in the hypothalamus and delivered to the posterior pituitary for release into systemic circulation.

Secretion of AVP is mediated by several mechanisms. Osmotic pressure is the most sensitive and important stimulus for AVP release and is mediated by osmoreceptors in the hypothalamus. Sodium concentration greatly influences osmotic pressure. A decrease in osmolality, as minimal as 1% to 2%, rapidly suppresses AVP secretion and induces free water diuresis.[11]

Arterial pressure reduction also stimulates AVP release, but typically there must be a significant reduction of 10% to 20%, as sensed by baroreceptors in the left atrium and aorta. It appears that arterial pressure provokes AVP release by lowering the set point of the osmoregulatory system.[11] Other non-osmotic stimuli for AVP release include stress, nausea, pain, and vasovagal stimulation.

Inappropriate release of AVP can occur with malignancy, pulmonary processes, central nervous system disorders, and certain drugs. Often there is a concomitant resetting of the osmostat that also contributes to AVP effect and hyponatraemia. AVP exerts its effect by stimulating the AVP V2 receptor, located on the basolateral side of the principal cell. These receptors may also be activated by other, currently undiscovered antidiuretic substances.[3]

AVP V2 is a G-protein-coupled receptor that, when stimulated, initiates adenylate cyclase and leads to increased intracellular cyclic adenosine monophosphate (cAMP).[12] Elevated cAMP signals placement of vesicle-encased aquaporin-2 channels in the principal cell apical membrane, facilitating free water absorption in the collecting tubule.

Resulting concentrated urine, coupled with free water intake in excess of what can be excreted, leads to hyponatraemia.[1] This is especially true in the case of exercise-associated hyponatraemia, in which excessive water intake is coupled with increased non-osmotic release of AVP through stress and pain. Extracellular volume increases and plasma renin/aldosterone secretion is suppressed to cause a natriuresis, further aggravating hyponatraemia.[1]

Classification

Clinically accepted classification of SIADH[1] [2]

Type A: unregulated release of arginine vasopressin (AVP). Approximately 30% of patients. Marked increase in plasma AVP levels that fluctuate in a manner unrelated to changes in plasma osmolarity/sodium during infusion of hypertonic saline.

Type B: slow leak of AVP. Approximately 30% of patients. Milder increase in plasma AVP in comparison to type A. Plasma AVP remains stable during hypertonic saline infusion and only rises when serum sodium levels reach normal range.

Type C: reset osmostat. Approximately 30% of patients. Low AVP levels during hyponatraemic state; however, AVP levels rise inappropriately during hypertonic saline infusion before hyponatraemia is corrected.

Type D: pseudo-SIADH. Approximately 10% of patients. Low or undetectable AVP. Low levels of AVP during hyponatraemic state with apparent normal osmoregulation of AVP release. Antidiuresis occurs through an alternative mechanism, one of which is nephrogenic syndrome of inappropriate diuresis (SIAD), a genetic disorder characterised by gain-of-function mutation of vasopressin 2 receptor.[3]

Case history

Case history #1

A 76-year-old homeless man presents to the emergency department after police find him disoriented on the streets in late August. The patient gives little history, but admits to ongoing cough with productive sputum, night sweats/chills, and mild dyspnoea. He proceeds to suffer from a seizure. Vital signs demonstrate an elevated temperature at 38.7°C (101.7°F), a respiration rate of 26 breaths per minute, 94% oxygen saturation (on 3 L of O2), and pulse 87 bpm, with no evidence of orthostatic hypotension. Physical examination demonstrates a malnourished and dishevelled man in a postictal state. There is no sign of injury to the body. Crackles can be heard at the right lung base. Lab work demonstrates serum sodium of 120 mmol/L (120 mEq/L), serum creatinine of 88 micromol/L (1.0 mg/dL), and negative alcohol and toxicology screens. Chest x-ray demonstrates a large infiltrate in the right lower lung, consistent with pulmonary infection or abscess.

Approach

SIADH is largely a condition identified by abnormal serum sodium levels on laboratory testing, with variable presentations in terms of history and physical examination.[2] Chemistry panels are obtained frequently with any clinic or emergency department visit and hyponatraemia diagnosed accordingly. This prompts further investigation into the aetiology of hyponatraemia, SIADH being the most common aetiology.[16]

Risk factors

Risk factors strongly associated with SIADH include increasing age (>50 years), nursing home residence, presence of pulmonary conditions (e.g., pneumonia), malignancy, central nervous system (CNS) disease or trauma, medicine associated with SIADH induction, post-operative state and a history of endurance exercise.

History

Key points to investigate in the history include symptoms and signs of cerebral oedema, such as nausea, vomiting, headache, altered mental status, seizure, and, most alarmingly, coma. These signs can alert the physician to the possibility of hyponatraemia-induced CNS dysfunction. It is imperative to elicit the duration of these symptoms, if present.

Physical examination

There are no definitive physical examination findings that support SIADH; however, a patient may demonstrate signs of cerebral oedema, including mental status changes, increased somnolence, or coma. The patient appears euvolaemic.

Physical signs of hyper- or hypovolaemia argue against SIADH.

Signs of hypovolaemia include:

- Tachycardia
- Orthostasis
- Dry mucous membranes
- Poor skin turgor.

Signs of hypervolaemia may be due to:

- Cirrhosis (e.g., ascites or lower extremity oedema)
- Congestive heart failure (e.g., orthopnoea, paroxysmal nocturnal dyspnoea, or lower extremity oedema)
- Nephrosis (e.g., anasarca or lower extremity oedema).

There should also be an absence of physical findings consistent with adrenal insufficiency or hypothyroidism.

Investigations

Laboratory tests are used to confirm the following diagnostic criteria:[4] [5]

- Hypotonic hyponatraemia: low serum sodium and osmolality
- Euvolaemic hyponatraemia: high urine sodium, fractional excretion of sodium and urea; low urea and serum uric acid levels
- Relatively concentrated urine: elevated urine osmolality while serum sodium and osmolality are low

- Exclusion of endocrinopathy: serum TSH and cortisol levels to rule out hypothyroidism and Addison's disease, both of which cause euvolaemic hyponatraemia.

Further investigations include a diagnostic trial with normal saline infusion. This is only performed in patients with suspected volume depletion and should not be used in symptomatic hyponatraemic patients. In SIADH, serum sodium level does not improve after a normal saline infusion (1-2 L of normal saline) is administered.

Rarely, plasma arginine vasopressin level may be measured. This test may not be readily available and is only indicated in patients with non-diagnostic laboratory results or absence of SIADH aetiologies.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Including age >50 years, nursing home residence, the presence of a postoperative state, pulmonary conditions (e.g., pneumonia), malignancy, central nervous system disease or trauma, medicine associated with SIADH induction, and a history of endurance exercise.

absence of hypovolaemia (common)

- Hypovolaemia is ruled out during patient evaluation.
- Patients with tachycardia, orthostatic hypotension, dry mucous membranes, and poor skin turgor are more likely to have an alternative cause for hyponatraemia.

absence of hypervolaemia (common)

- Patients with congestive heart failure (crackles, cardiac gallops, jugular vein distension, lower extremity oedema), cirrhosis of the liver (ascites, lower extremity oedema), or nephrotic syndrome (anasarca, lower extremity oedema) are more likely to have an alternative cause for hyponatraemia.
- Pregnancy is another cause of hypervolaemic hyponatraemia.

absence of signs of adrenal insufficiency or hypothyroidism (common)

- Adrenal insufficiency (pigmentation of skin and mucosa, weight loss, hypotension) or hypothyroidism (dry coarse skin, myxoedema, hair loss, weight gain) are ruled out during patient evaluation.

nausea (common)

- May be related to brain oedema.

vomiting (common)

- May be related to brain oedema.

altered mental status (uncommon)

- May be related to brain oedema; needs rapid correction of hyponatraemia.

headache (uncommon)

- May be related to brain oedema; needs rapid correction of hyponatraemia.

seizure (uncommon)

- May be related to brain oedema; needs rapid correction of hyponatraemia.

coma (uncommon)

- May be related to brain oedema; needs rapid correction of hyponatraemia.

Other diagnostic factors

no history of recent diuretic use (common)

- Diuretics, particularly thiazides, may cause hyponatraemia.

Risk factors

Strong

age >50 years

- Increasing age is associated with hyponatraemia.[10] [13]
- No mechanism has been delineated, but water-excretory capacity is increasingly impaired in ageing patients.
- Many older people have underlying conditions which cause SIADH and are also treated with medicines associated with SIADH, including selective serotonin-reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs).[10]

pulmonary conditions (e.g., pneumonia)

- A study found that 23% of 71 patients with pneumonia and *Streptococcus pneumoniae* bacteraemia presented with a serum sodium <135 mmol/L (<135 mEq/L).[14]
- Inappropriate arginine vasopressin (AVP) release signalled by pulmonary process, plus osmostat resetting for AVP secretion, are likely mechanisms.

nursing home residence

- About 18% of nursing home residents have been found to have serum sodium levels ≤135 mmol/L (≤135 mEq/L) compared with 8% of age-matched ambulatory individuals.[15]
- Coupled with impaired water-excretory capacity with advancing age, many of the patients also receive hypotonic fluids or low-sodium diets/tube feeds.

malignancy

- Typically lung malignancy (especially small cell lung cancer), gastrointestinal or genitourinary malignancy, lymphoma, or sarcoma.[4]

medicine associated with SIADH induction

- Drugs that are associated with development of SIADH include antidepressants such as SSRIs, tricyclic antidepressants, monoamine oxidase inhibitors, and venlafaxine; anticonvulsants such as carbamazepine, oxcarbazepine, valproate, and lamotrigine; antipsychotics such as phenothiazines (e.g., chlorpromazine) and butyrophenones (e.g., haloperidol); antidiabetic agents such as first-generation sulfonylureas (e.g., chlorpropamide, tolbutamide); chemotherapeutic agents such as vinca alkaloids, platinum compounds, ifosfamide, melphalan, cyclophosphamide, methotrexate, and

pentostatin; vasopressin analogues such as desmopressin, oxytocin, terlipressin, and vasopressin; other drugs such as opioids, methylenedioxymethamphetamine (MDMA), levamisole, interferon, clofibrate, nicotine, amiodarone, proton-pump inhibitors, monoclonal antibodies, and NSAIDs.[4]

central nervous system (CNS) disorder

- CNS causes of SIADH include infections (encephalitis, meningitis, brain abscess, Rocky Mountain spotted fever, HIV-associated opportunistic CNS infections, malaria); vascular causes and masses (brain trauma, subdural haematoma, subarachnoid haemorrhage, stroke, brain tumours); and other CNS disorders (hydrocephalus, cavernous sinus thrombosis, multiple sclerosis, Guillain-Barre syndrome, Shy-Drager syndrome, delirium tremens, acute intermittent porphyria).[4]

Weak

postoperative state

- About 4.4% of postoperative patients have been found to have developed non-osmotic arginine vasopressin release and associated hyponatraemia, often complicated by hypotonic fluid administration.[14]
- More common after organ transplantation and cardiovascular, gastroenterological, or trauma surgery. Mechanism unknown, but possibly mediated by postoperative pain and nausea.

endurance exercise

- Excessive fluid intake is the main cause.
- Elevated arginine vasopressin has been observed in some cases.

Investigations

1st test to order

Test	Result
serum sodium • SIADH presents with hypotonic hyponatraemia: low serum sodium and osmolality. • Pseudohyponatraemia can occur due to hyperglycaemia-induced water shift from the intracellular to extracellular space. This should be suspected and excluded in patients with a history of diabetes mellitus, non-compliance with diabetic therapy, polyuria, and polydipsia.	**<135 mmol/L (<135 mEq/L)**
serum osmolality • SIADH presents with hypotonic hyponatraemia: low serum sodium and osmolality.	**<275 mmol/kg (<275 mOsm/kg) H_2O**
serum urea • Usually low due to mild volume expansion.	**<3.6 mmol/L (<10 mg/dL)**
urine osmolality • Values of >100 mmol/kg H_2O (>100 mOsm/kg H_2O) indicating elevated arginine vasopressin level support the diagnosis of SIADH if present in conjunction with low serum sodium and low serum osmolality. • Low levels occur in the presence of hyponatraemia due to excessive water intake.	**>100 mmol/kg H_2O (>100 mOsm/kg H_2O)**
urine sodium • Urine sodium with normal dietary salt and water intake. • If patient is euvolaemic, results of >30 mmol/L (>30 mEq/L) are consistent with SIADH.	**>30 mmol/L (>30 mEq/L)**

Other tests to consider

Test	Result
diagnostic trial with normal saline infusion • 1 to 2 L of normal saline can be administered as a therapeutic trial if volume depletion is suspected. Serum sodium will improve in this situation, while in SIADH it will not. • A trial of normal saline should not be performed if patient is symptomatic from hyponatraemia (e.g., altered mental status, seizure, coma).	**serum sodium level does not improve after normal saline infusion; occasionally, serum sodium may even decrease**
serum uric acid • Usually not necessary. • Low serum uric acid level indicates mild volume expansion, consistent with SIADH.	**<238 micromol/L (<4 mg/dL)**
fractional excretion of sodium • Confirms euvolaemic state in people with SIADH.	**>1%**
fractional excretion of urea • Confirms euvolaemic state in people with SIADH.	**>55%**
serum TSH • Hypothyroidism should be ruled out when diagnosing SIADH.	**0.5 to 4.7 milli-international units/L**
serum cortisol level • Addisonism should be ruled out when diagnosing SIADH.	**morning level >138 nanomol/L (>5 micrograms/dL)**
serum arginine vasopressin (AVP) • AVP values vary in normal subjects with levels rising above 2.5 picograms/mL as serum sodium reaches 140 mmol/L (140 mEq/L) and beyond. • AVP not routinely recommended as urinary osmolality >100 mmol/kg H_2O (>100 mOsm/kg H_2O) is sufficient to diagnose excess AVP.[16]	**>2.5 picograms/mL during period of hyponatraemia**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Pseudohyponatraemia	• Many patients are asymptomatic. Symptoms, if present, depend on the nature and severity of the underlying cause. • Possible symptoms or signs of poorly controlled diabetes mellitus (polyuria, polydipsia) may be present if hyperglycaemia is the cause. • Eruptive xanthoma may be seen in patients with severe hyperlipidaemia. • Patients with hyperproteinaemia may show signs of multiple myeloma or other rarer causes.	• Suspicion is raised if measurement of serum glucose, lipids, and protein reveals one of these to be elevated. • Elevated serum glucose: diagnosis is confirmed if calculation of the corrected serum sodium value reveals a normal sodium level. The equation for SI units is: corrected sodium (mmol/L) = measured sodium (mmol/L) + 0.016{(glucose [mmol/L] x 18)-100}. The equation for conventional units is: corrected sodium (mEq/L) = measured sodium (mEq/L) + 0.016 [glucose (mg/dL) - 100]. • Elevated serum lipid level, particularly triglyceride: normal serum osmolarity confirms diagnosis. • Elevated serum protein, particularly, globulin (multiple myeloma): normal serum osmolarity confirms diagnosis.
Hypovolaemia	• History of poor oral intake, vomiting, diarrhoea, or diuretic use help to distinguish hypovolaemia from SIADH. • Evidence of dry mucous membranes, skin tenting, and flat neck veins can accompany hypovolaemia, although clinical assessment is poor at predicting volume status.[17]	• Central venous pressure (CVP) <8. • Urine sodium <20 mmol/L (<20 mEq/L). • Elevation in serum sodium with a diagnostic trial of 1 to 2 L of normal saline infusion.
Cerebral salt-wasting	• There is a history of intracranial bleed or trauma.	• Volume depletion (CVP <8) with a urine Na >120 mmol/L (>120 mEq/L).[18] • Fractional excretion of urea <30%.[19] • Continued high urine sodium despite hypertonic saline or water restriction.

Condition	Differentiating signs / symptoms	Differentiating tests
Hypervolaemia (e.g., CHF, cirrhosis, pregnancy)	• Dyspnoea, pulmonary oedema, elevated jugular venous pressure, ascites, lower extremity oedema.	• CVP elevated. • Urine sodium <40 mmol/L (<40 mEq/L).
Psychogenic polydipsia	• There may be a psychiatric history or excess fluid intake elicited during history.	• Urine osmolality <100 mmol/kg H_2O (<100 mOsm/kg H_2O). • 24-hour urine osmoles >600 mmol (>600 mOsm).
Poor solute intake (e.g., beer potomania, low-protein diet)	• Beer drinking or malnourished patients with poor dietary solute intake and high water intake. Low solute excretion limits water excretion, causing water retention.	• Urine osmolality <100 mmol/kg H_2O (<100 mOsm/kg H_2O). • 24-hour urine osmoles <300 mmol (<300 mOsm).
Renal failure	• Hypertension; oedema may be present.	• Elevated creatinine.
Addison's disease	• Pigmentation of skin and mucosa, weight loss, hypotension.	• Low cortisol levels. • Responds to steroid administration.
Hypothyroidism	• Dry coarse skin, myxoedema, hair loss, weight gain.	• High TSH and low serum thyroid hormone levels. • Responds to treatment with thyroid hormone.

DIAGNOSIS

Criteria

Diagnosis of SIADH[4] [5][7]

Essential features:

- Decreased effective serum osmolality (<275 mmol/kg [<275 mOsm/kg] of H_2O)
- Urinary osmolality >100 mmol/kg H_2O (>100 mOsm/kg of H_2O) during hypotonicity
- Urinary sodium >30 mmol/L (>30 mEq/L) with normal dietary salt and water intake
- Clinical euvolaemia
- No orthostasis, tachycardia, decreased skin turgor, dry mucous membranes
- No clinical signs of excessive volume, oedema, or ascites
- Normal thyroid and adrenal function
- No recent diuretic use.

Supplemental features:

- Plasma uric acid <0.24 mmol/L (<4 mg/dL)
- Serum urea <3.6 mmol/L (<10 mg/dL)
- Fractional sodium excretion >1%, fractional urea excretion >55%
- Failure to correct serum sodium with normal saline infusion

- Abnormal result on test of water load (<80% excretion of 20 mL of H_2O/kg body weight over 4 hours), or inadequate urinary dilution (<100 mmol/kg H_2O or <100 mOsm/kg H_2O)
- Elevated plasma arginine vasopressin (AVP) levels, despite the presence of hypotonicity and clinical euvolaemia.

Screening

No evidence is available that supports screening for SIADH. However, high-risk groups such as older adults, those on offending drugs, and postoperative patients would undoubtedly benefit from baseline serum sodium levels being performed. These should be checked yearly in older patients, pre- and postoperation in ambulatory hospitalised surgical patients, especially if hypotonic fluids are administered, and 1 to 2 weeks after starting an offending drug. If antidepressant medications are started, selective serotonin-reuptake inhibitors in particular and especially in high risk groups, the patient is at most risk of developing hyponatraemia in the first 3 months of treatment. Electrolytes should be monitored closely during this period.[20]

Approach

The mainstay of treatment for SIADH is to remedy hyponatraemia with salt administration and/or water restriction. The inappropriate activation of the V2-receptor, causing excessive free water absorption in the collecting duct, has been targeted with the introduction of the vasopressin receptor antagonists (also known as vaptans). Although vasopressin receptor antagonists are a logical therapy for hyponatraemic patients with excess vasopressin, evidence of potential harms, such as overcorrection and liver toxicity, has restricted their use to certain patient groups.[4] [7] [21]

Acute hyponatraemia (≤48 hours' duration) with severe neurological symptoms

Patients are evaluated for severe symptoms of hyponatraemia (mental status changes, seizure, and coma). Acute hyponatraemia often occurs while a patient is hospitalised. As this is not of chronic duration, brain cells have not had time to compensate by releasing electrolytes and brain osmolytes. Therefore, patients with acute hyponatraemia are more susceptible to symptoms at higher serum sodium levels.

Intravenous hypertonic saline (3% sodium chloride solution) is administered and serum sodium levels checked every 2 hours, with a goal of increasing serum sodium by 1 to 2 mmol/L/hour (1-2 mEq/L/hour) until neurological symptoms resolve.[5] Subsequently, correction is slowed to elevate serum sodium by no more than 8 to 10 mmol/L (8-10 mEq/L) in a 24-hour period thereafter.[16]

There is less risk of central pontine myelinolysis (osmotic demyelination syndrome) in patients who develop hyponatraemia in ≤48 hours as compared with those with chronic hyponatraemia. Therefore, more rapid correction, although not ideal, is less dangerous in patients with acute hyponatraemia.

Furosemide may be used in addition to hypertonic saline, especially if the patient is at risk for volume overload. Furosemide helps to correct hyponatraemia by increasing free water excretion. If furosemide is used in addition to intravenous hypertonic saline, infusion rates may need to be reduced, so as to avoid overcorrection of hyponatraemia. Hypokalaemia is monitored and corrected with intravenous potassium replacement.

Investigation for an underlying disorder (e.g., malignancy, infection, pain, nausea, stress, SIADH-associated medicine, or administration of hypotonic fluid) is required. These disorders are treated and any causative medicines discontinued. All hypotonic fluids are also stopped.

Acute hyponatraemia, once corrected and any cause of SIADH removed, may be self-limiting. It may be necessary to continue free fluid restriction (of 1-1.5 L/day) after hypertonic saline therapy is discontinued. Serum sodium is monitored daily until it stabilises.

Chronic hyponatraemia (>48 hours or unknown duration) with severe neurological symptoms

These patients are also treated with intravenous hypertonic saline.[2] There is an increased risk of central pontine myelinolysis (osmotic demyelination syndrome) in chronically hyponatraemic patients, so careful monitoring is of utmost importance. Central pontine myelinolysis occurs with overcorrection of hyponatraemia where solute-poor cerebral cells are subject to shrinkage. It is characterised by demyelination of pontine, basal ganglion, and cerebellar regions, with resultant neurological symptoms, including behaviour disturbances, lethargy, dysarthria, dysphagia, paraparesis or quadriparesis, and coma. Seizures may also be seen but are less common.[22] Malnutrition, potassium depletion, and

hepatic failure increase the risk of developing central pontine myelinolysis.[22] [23] One large multi-centre study in 2023 found a high incidence of overcorrection of sodium in hospitalised hyponatraemic patients, but a relatively low incidence of osmotic demyelination syndrome. While this is an interesting finding, it does not downplay the importance of slow correction of sodium in the chronic hyponatraemic patient.[24]

Furosemide may also be used in addition to hypertonic saline, especially if the patient is at risk for volume overload, and hypokalaemia is corrected if necessary with intravenous potassium replacement.

Investigation and management of any underlying disorder is also undertaken and any causative medicine discontinued.

Following successful therapy with intravenous hypertonic saline, a vasopressin receptor antagonist is used. Vasopressin receptor antagonists compete with arginine vasopressin (AVP) for binding at the V2 receptor on the basolateral side of the principal cell and inhibit water channel insertion and free water absorption.

Conivaptan is a non-selective vasopressin receptor antagonist that affects both V1 and V2 receptors. It is currently available in some countries as an intravenous formulation for inpatient administration only.[25]

The oral vasopressin receptor antagonist tolvaptan is recommended for the treatment of hyponatraemia secondary to SIADH.[26] [27] However, due to reports of potentially fatal liver injury in patients with autosomal dominant polycystic kidney disease, tolvaptan should not be used for more than 30 days, and it should be avoided in patients with underlying liver disease including cirrhosis. The drug should be discontinued immediately in patients with signs or symptoms of liver injury (e.g., fatigue, anorexia, right upper abdominal discomfort, dark urine, jaundice, elevated LFTs). [FDA Drug Safety Communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death] (http://www.fda.gov/Drugs/DrugSafety/ucm350062.htm) Patients receiving tolvaptan should discontinue any previous fluid restriction and drink fluids freely though not excessively.[2]

Close monitoring, especially in the first 24 hours of oral therapy, is required. The concern is overcorrection of serum sodium (>12 mmol [>12 mEq] per 24 hours), which occasionally occurs with these medicines. Fluid restriction should be removed, because polyuria commonly occurs. Long-term studies have been promising in terms of sustained improved serum sodium with these agents.[28] Vasopressin receptor antagonists interact with the cytochrome P450 3A4 system, and use with other potent inhibitors is contraindicated.[29] [30]

All other patients

Mild to moderate symptoms include nausea, vomiting, or headache. In acute SIADH patients, treatment is with fluid restriction of 1 to 1.5 L/day. Vasopressin receptor antagonists are used initially for chronic SIADH patients. In both cases, investigation and management of any underlying disorder is also undertaken and any causative medication discontinued.

Asymptomatic patients are managed with fluid restriction of 1 to 1.5 L/day and investigation and management of any underlying cause.

Persistent chronic SIADH

SIADH can persist if the underlying cause is irreversible. Fluid restriction of 1 to 1.5 L/day has been the mainstay of therapy for chronic SIADH outpatient therapy. Compliance with fluid restriction often limits this therapeutic option.

Management of any underlying disorder should continue.

If patients are intolerant to fluid restriction, tolvaptan may be used. Tolvaptan has demonstrated to be well tolerated, with most commonly reported side effects of dry mouth (4.2% to 23%), thirst (7.7% to 40.3%), and polyuria (0.6% to 31.7%) coinciding with the mechanism of action of the medication. High cost may limit the use of tolvaptan.[30] Due to reports of potentially fatal liver injury, tolvaptan should not be used for more than 30 days, and it should be avoided in patients with underlying liver disease including cirrhosis. However, in select patients with persistent chronic SIADH, tolvaptan may be continued beyond 30 days (for longer-term treatment) at the lowest effective dose with very close monitoring, although there is limited data to support this approach.[31] Patients receiving tolvaptan should discontinue any previous fluid restriction and drink fluids freely though not excessively.[2]

Sodium chloride tablets may be administered, which can increase urine output and modestly improve serum sodium levels. This is heightened by co-administration of diuretics, which lower urine osmolality and improve water excretion. Serum potassium will need to be monitored closely.[32]

Demeclocycline, a bacteriostatic antibiotic, causes diminished responsiveness of the collecting tubule to AVP. Similar to tolvaptan, demeclocycline is used without fluid restriction. Side effects such as skin photosensitivity and nephrotoxicity limit its use.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)

severe symptoms		
acute (onset ≤48 hours)	**1st**	**intravenous hypertonic saline + fluid restriction**
	plus	**treat underlying cause**
	adjunct	**furosemide**
chronic (onset >48 hours or unknown)	**1st**	**intravenous hypertonic saline**
	plus	**vasopressin receptor antagonist**
	plus	**treat underlying cause**
	adjunct	**furosemide**
mild to moderate symptoms		
acute (onset ≤48 hours)	**1st**	**treat underlying cause**
	plus	**fluid restriction**
chronic (onset >48 hours or unknown)	**1st**	**treat underlying cause**
	plus	**vasopressin receptor antagonist**
asymptomatic with sodium ≥125 mmol/L (≥125 mEq/L)		
	1st	**fluid restriction + treat underlying cause**

Ongoing (summary)

persistence of chronic SIADH		
	1st	**fluid restriction**
	plus	**treat underlying cause**
	2nd	**tolvaptan**
	3rd	**sodium chloride + furosemide**
	4th	**demeclocycline**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

severe symptoms

acute (onset ≤48 hours)

1st **intravenous hypertonic saline + fluid restriction**

» Severe neurological symptoms include altered mental status, seizure, and coma. Acute hyponatraemia may occur while a patient is hospitalised. Patients with acute development of hyponatraemia may be more susceptible to symptoms at higher serum sodium levels than those with chronic hyponatraemia.

» Intravenous hypertonic saline is required and serum sodium levels checked every 2 hours. Treatment goal is initially to elevate serum sodium by 1 to 2 mmol/L (1-2 mEq/L) per hour until neurological symptoms resolve.[22]

» In the emergency department, treatment may start with 50 mL 3% saline intravenous, followed by 200 mL intravenous infusion over 4 to 6 hours.[33] This treatment generally raises serum sodium by 8 to 10 mmol/L (8-10 mEq/L) and moves patients out of the acute neurological dangers of hyponatraemia.[33] The rate of correction is then slowed to elevate serum sodium no more than 8 to 10 mmol/L (8-10 mEq/L) in a 24-hour period thereafter.[16]

» There is a risk of central pontine myelinolysis (osmotic demyelination syndrome) in these patients. However, when hyponatraemia has developed in ≤48 hours, the risk is less than in patients with more chronic development of hyponatraemia. Therefore, more rapid correction, although not ideal, is less dangerous in patients with acute hyponatraemia.

» Acute hyponatraemia, once corrected, might be self-limiting, if the causes of SIADH are removed. It may be necessary to continue free fluid restriction (1-1.5 L/day) after hypertonic saline therapy. Serum sodium is monitored daily until it stabilises.

plus **treat underlying cause**

Treatment recommended for ALL patients in selected patient group

MANAGEMENT

Acute

» The patient is investigated for the presence of an underlying disorder, such as infection, pain, nausea, or stress, SIADH-associated medicine, or administration of hypotonic fluid, that may have led to hyponatraemia.

» These disorders are treated and causative medicines discontinued.

» All hypotonic fluids are also stopped.

adjunct **furosemide**

Treatment recommended for SOME patients in selected patient group

Primary options

» furosemide: 20 mg intravenously as a single dose initially, increase by 20 mg/dose increments every 6-12 hours according to response, maximum 600 mg/day

» Furosemide may be used in addition to hypertonic saline, especially if the patient is at risk for volume overload. It helps to correct hyponatraemia by increasing free water excretion.

» If furosemide is used in addition to intravenous 3% saline, infusion rates may need to be reduced, so as to avoid overcorrection of hyponatraemia.

» Urine sodium plus urine potassium is monitored to determine urine electrolyte and free water loss. With adequate furosemide dosing, urine sodium + urine potassium is likely to equal around 80 mmol/L (80 mEq/L) (similar to half-normal saline). Correcting for above electrolyte losses by administering 3% saline (1/6 mL per mL urine if urine electrolytes 80 mmol/L [80 mEq/L]) would lead to net free water clearance of 5/6 of urine output, which must be taken into consideration when correcting hyponatraemia.[12]

» Hypokalaemia is monitored and corrected with intravenous potassium replacement.

chronic (onset >48 hours or unknown) **1st** **intravenous hypertonic saline**

» Severe neurological symptoms include altered mental status, seizure, and coma.

» Intravenous hypertonic saline is required and serum sodium levels checked every 2 hours. Treatment goal is initially to elevate serum sodium by 1 to 2 mmol/L (1-2 mEq/L) per hour, until neurological symptoms resolve.[22]

Acute

» In the emergency department, treatment may start with 200 mL 3% saline intravenous infusion over 4 to 6 hours.[33] This treatment generally moves patients out of the acute neurological dangers of hyponatraemia.[33] The rate of correction is then slowed to elevate serum sodium no more than 10 mmol/L (10 mEq/L) in a 24-hour period.[16]

» There is an increased risk of central pontine myelinolysis (osmotic demyelination syndrome) in chronically hyponatraemic patients, so careful monitoring is of utmost importance. Central pontine myelinolysis may present with neurological symptoms, including behaviour disturbances, lethargy, dysarthria, dysphagia, paraparesis or quadriparesis, and coma.

» Seizures may also be seen but are less common.[22]

» Malnutrition, potassium depletion, and hepatic failure increase the risk of developing central pontine myelinolysis.[22] [23] One large multi-centre study in 2023 found a high incidence of overcorrection of sodium in hospitalised hyponatraemic patients, but a relatively low incidence of osmotic demyelination syndrome. While this is an interesting finding, it does not downplay the importance of slow correction of sodium in the chronic hyponatraemic patient.[24]

plus **vasopressin receptor antagonist**

Treatment recommended for ALL patients in selected patient group

Primary options

» conivaptan: 20 mg intravenously as a loading dose, followed by 20 mg infusion given over 24 hours, may increase to 40 mg infusion given over 24 hours if inadequate response, maximum 4 days total treatment

OR

» tolvaptan: 15 mg orally once daily initially Dose may be increased to 30 and 60 mg if the change in serum Na is less than 5 mEq/L until serum Na >135 mmol/L (>135 mEq/L); the dose should be titrated down if serum Na >145 mmol/L (>145 mEq/L) or an increase in serum Na >12 mmol/day (>12 mEq/day) is seen.

Acute

» Following successful therapy with intravenous hypertonic saline, an intravenous vasopressin receptor antagonist is commenced.

» Conivaptan is a non-selective vasopressin receptor antagonist and affects both V1 and V2 receptors. Therefore, it is recommended that the patient is monitored for hypotension. This may occur with V1 receptor blockade and resultant vasodilation. Other adverse effects include a risk of infusion site reactions in up to 50% of patients.[16]

» Tolvaptan, a selective V2 receptor antagonist, has been demonstrated to be safe and effective, if monitored closely at initiation.[30] Serum sodium should be checked at baseline and 8 hours after the first dose, and then daily during titration period (up to 14 days).[28] Due to reports of potentially fatal liver injury, tolvaptan should not be used for more than 30 days, and it should be avoided in patients with underlying liver disease including cirrhosis. The drug should be discontinued immediately in patients with signs or symptoms of liver injury (e.g., fatigue, anorexia, right upper abdominal discomfort, dark urine, jaundice, elevated LFTs).

» An increase in urine output is expected following treatment. Patients receiving tolvaptan should discontinue any previous fluid restriction and drink fluids freely though not excessively.[2]

plus **treat underlying cause**

Treatment recommended for ALL patients in selected patient group

» The patient is investigated for the presence of an underlying disorder, such as infection, pain, nausea or stress, SIADH-associated medicine, or administration of hypotonic fluid, that may have led to hyponatraemia.

» These disorders are treated and causative medicines discontinued.

» All hypotonic fluids are also stopped.

adjunct **furosemide**

Treatment recommended for SOME patients in selected patient group

Primary options

» furosemide: 20 mg intravenously as a single dose initially, increase by 20 mg/dose increments every 6-12 hours according to response, maximum 600 mg/day

Acute

» Furosemide may be used in addition to hypertonic saline, especially if the patient is at risk for volume overload. It helps to correct hyponatraemia by increasing free water excretion.

» If furosemide is used in addition to intravenous 3% saline, infusion rates may need to be reduced, so as to avoid overcorrection of hyponatraemia.

» Urine sodium plus urine potassium is monitored to determine urine electrolyte and free water loss. With adequate furosemide dosing, urine sodium + urine potassium is likely to equal around 80 mmol/L (80 mEq/L) (similar to half-normal saline). Correcting for above electrolyte losses by administering 3% saline (1/6 mL per mL urine if urine electrolytes 80 mmol/L [80 mEq/L]) would lead to net free water clearance of 5/6 of urine output, which must be taken into consideration when correcting hyponatraemia.[12]

» Hypokalaemia is monitored and corrected with intravenous potassium replacement.

mild to moderate symptoms

acute (onset ≤48 hours)

1st **treat underlying cause**

» Mild to moderate symptoms include nausea, vomiting, or headache.

» The patient is investigated for the presence of an underlying disorder, such as infection, pain, nausea, or stress, SIADH-associated medication, or administration of hypotonic fluid, that may have led to hyponatraemia.

» These disorders are treated and causative medications discontinued.

» All hypotonic fluids are also stopped.

plus **fluid restriction**

Treatment recommended for ALL patients in selected patient group

» Fluid restriction of 1 to 1.5 L/day is required.

» Acute hyponatraemia, once corrected, might be self-limiting, if the causes of SIADH are removed.

» Serum sodium is monitored daily until it stabilises.

Acute

chronic (onset >48 hours or unknown)

1st **treat underlying cause**

» The patient is investigated for the presence of an underlying disorder, such as infection, pain, nausea, or stress, SIADH-associated medicine, or administration of hypotonic fluid, that may have led to hyponatraemia.

» These disorders are treated and causative medicines discontinued.

» All hypotonic fluids are also stopped.

plus **vasopressin receptor antagonist**

Treatment recommended for ALL patients in selected patient group

Primary options

» conivaptan: 20 mg intravenously as a loading dose, followed by 20 mg infusion given over 24 hours, may increase to 40 mg infusion given over 24 hours if inadequate response, maximum 4 days total treatment

OR

» tolvaptan: 15 mg orally once daily initially Dose may be increased to 30 and 60 mg if the change in serum Na is less than 5 mEq/L until serum Na >135 mmol/L (>135 mEq/L); the dose should be titrated down if serum Na >145 mmol/L (>145 mEq/L) or an increase in serum Na >12 mmol/day (>12 mEq/day) is seen.

» Vasopressin receptor antagonists are recommended initially for patients with chronic SIADH without severe neurological symptoms.

» Conivaptan is a non-selective vasopressin receptor antagonist and affects both V1 and V2 receptors. Therefore, it is recommended that the patient is monitored for hypotension. This may occur with V1 receptor blockade and resultant vasodilation. Other adverse effects include a risk of infusion site reactions in up to 50% of patients.[16]

» Tolvaptan, a selective V2 receptor antagonist, has been demonstrated to be safe and effective, if monitored closely at initiation. Serum sodium should be checked at baseline and 8 hours after the first dose, and then daily during titration period (up to 14 days).[28] Due to reports of potentially fatal liver injury, tolvaptan should not

Acute

		be used for more than 30 days, and it should be avoided in patients with underlying liver disease including cirrhosis. The drug should be discontinued immediately in patients with signs or symptoms of liver injury (e.g., fatigue, anorexia, right upper abdominal discomfort, dark urine, jaundice, elevated LFTs). » An increase in urine output is expected following treatment. Patients receiving tolvaptan should discontinue any previous fluid restriction and drink fluids freely though not excessively.[2]
asymptomatic with sodium ≥125 mmol/L (≥125 mEq/L)		
	1st	**fluid restriction + treat underlying cause** » Fluid restriction of 1 to 1.5 L/day is required. » The patient is investigated for the presence of an underlying disorder, such as infection, pain, nausea, or stress, SIADH-associated medication, or administration of hypotonic fluid, that may have led to hyponatraemia. » These disorders are treated and causative medications discontinued. » All hypotonic fluids are also stopped.

Ongoing

persistence of chronic SIADH

1st **fluid restriction**

» Fluid restriction of 1 to 1.5 L/day has been the mainstay of therapy for chronic SIADH therapy.

» Compliance with fluid restriction often limits this therapeutic option.

plus **treat underlying cause**

Treatment recommended for ALL patients in selected patient group

» The patient is investigated for the presence of an underlying disorder, such as infection, pain, nausea, or stress, SIADH-associated medicine, or administration of hypotonic fluid, that may have led to hyponatraemia.

» These disorders are treated and causative medicines discontinued.

» All hypotonic fluids are also stopped.

2nd **tolvaptan**

Primary options

» tolvaptan: 15 mg orally once daily initially Dose may be increased to 30 and 60 mg if the change in serum Na is less than 5 mEq/L until serum Na >135 mmol/L (>135 mEq/L); the dose should be titrated down if serum Na >145 mmol/L (>145 mEq/L) or an increase in serum Na >12 mmol/day (>12 mEq/day) is seen.

» If the patient is intolerant to fluid restriction, tolvaptan may be used.

» Tolvaptan, a selective V2 receptor antagonist, has been demonstrated to be safe and effective, if monitored closely at initiation. Serum sodium should be checked at baseline and 8 hours after the first dose, and then daily during titration period (up to 14 days).[28] Due to reports of potentially fatal liver injury, tolvaptan should not be used for more than 30 days, and it should be avoided in patients with underlying liver disease including cirrhosis. However, in select patients with persistent chronic SIADH, tolvaptan may be continued beyond 30 days (for longer-term treatment) at the lowest effective dose with very close monitoring, although there is limited data to support this approach.[31] The drug should be discontinued immediately in patients with

Ongoing

signs or symptoms of liver injury (e.g., fatigue, anorexia, right upper abdominal discomfort, dark urine, jaundice, elevated LFTs). An increase in urine output is expected following treatment. Fluid restriction should be avoided.

3rd **sodium chloride + furosemide**

Primary options

» sodium chloride: 2-3 g/day orally
-and-
» furosemide: 40 mg orally once daily

» If the patient is intolerant to fluid restriction, sodium chloride tablets may be administered, which can increase urine output and modestly improve serum sodium levels. This is heightened by co-administration of diuretics, which lower urine osmolality and improve water excretion.[32]

» Serum potassium will need to be monitored closely.

4th **demeclocycline**

Primary options

» demeclocycline: 900-1200 mg/day orally given in 3-4 divided doses initially, followed by 600-900 mg/day given in 3-4 divided doses

» If the patient is intolerant to fluid restriction, demeclocycline may be used.

» Demeclocycline is a bacteriostatic antibiotic that causes diminished responsiveness of the collecting tubule to arginine vasopressin (AVP).

» Demeclocycline is used without fluid restriction.

» Side effects such as skin photosensitivity and nephrotoxicity limit use.[16] Effects of therapy vary widely and therefore will require close monitoring.

Emerging

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

SGLT2 inhibitors have been proposed as a novel treatment of SIADH as they increase urinary glucose excretion with concomitant osmotic diuresis. In one trial of patients with SIADH treated with fluid restriction, use of empagliflozin had a larger increase in plasma sodium levels compared to placebo.[34]

Primary prevention

Patients with a history of malignancy (especially of pulmonary origin) or of taking offending drugs require regular monitoring for the development of SIADH with chemistry panels and asked specific questions concerning signs and symptoms of hyponatraemia. A chemistry panel every 6 months after diagnosis of a malignancy and 1-2 weeks after starting an SIADH-associated medicine, with a repeat test after 1-2 months, is usually sufficient.

Several strategies to avoid hospital-induced hyponatraemia, which is often SIADH-related, include avoidance of hypotonic fluids prior to surgical procedures, control of nausea and pain, and close monitoring of older adult patients and those on SIADH-associated medicines.

Patient discussions

Patients with a history of malignancy, especially of pulmonary origin, or those receiving SIADH-associated medicines, should be educated about the signs and symptoms of hyponatraemia, including nausea, vomiting, lethargy, and seizures. The importance of compliance with follow-up appointments and laboratory work is emphasised. Patients may require specific advice concerning appropriate fluid restriction.

FOLLOW UP

Monitoring

Monitoring

It may be necessary to continue free fluid restriction (1-1.5 L/day) after hypertonic saline therapy and to monitor serum sodium daily until it stabilises.

Patients with a history of malignancy (especially of pulmonary origin) or of taking offending medicines require regular monitoring for the development of SIADH. A chemistry panel every 6 months after diagnosis of a malignancy and 1 to 2 weeks after starting an SIADH-associated medicine, with a repeat test after 1-2 months, is usually sufficient.

Complications

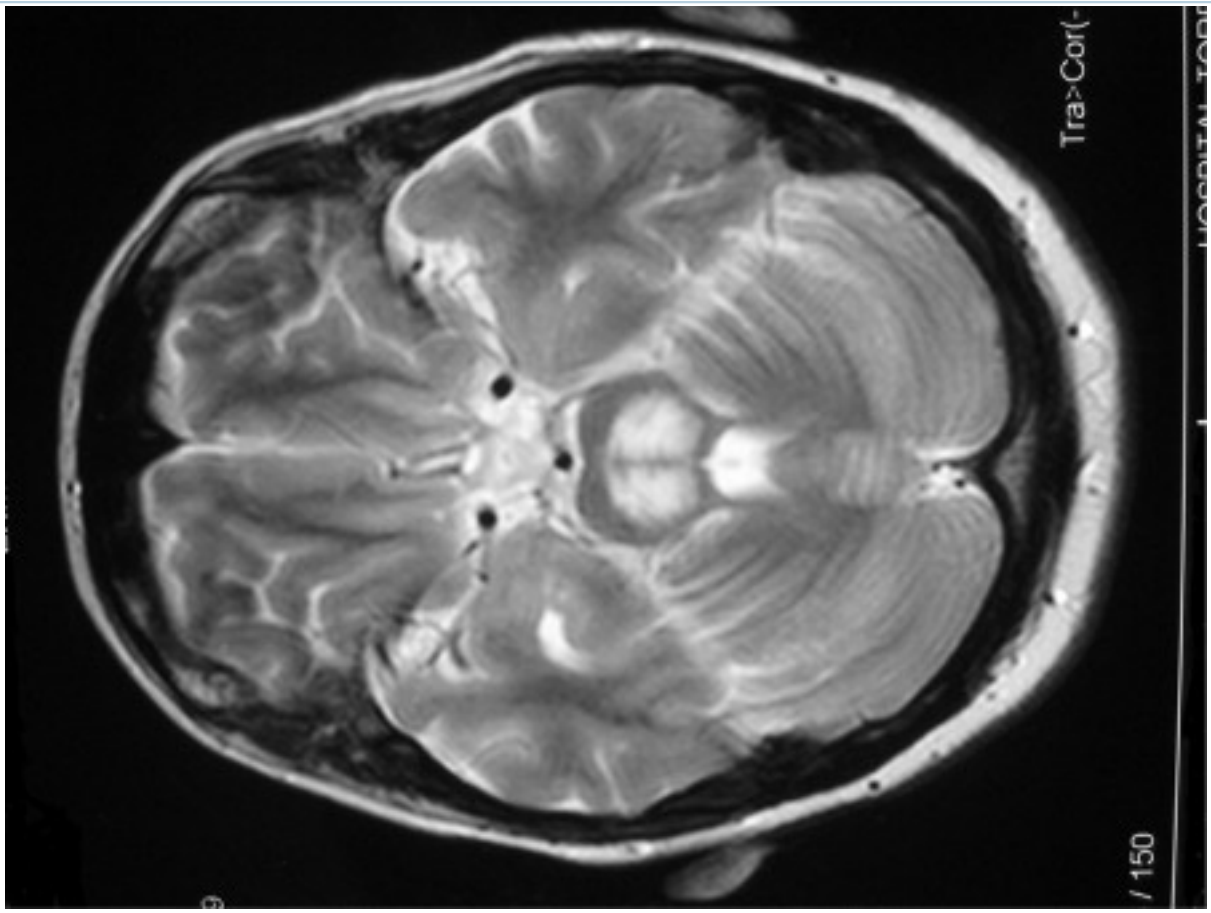
Complications	Timeframe	Likelihood
untreated hyponatraemia	**variable**	**medium**
Chronic hyponatraemia, if left untreated, can contribute to altered mentation, abnormal gait, osteoporosis, falls, and increased risk of significant fractures. Outpatient maintenance of SIADH-related hyponatraemia is of utmost importance to avoid associated increased morbidity and mortality.		
central pontine myelinolysis (CPM or osmotic demyelination syndrome)	**variable**	**low**

Occurs in people with longstanding SIADH who undergo overaggressive treatment of hyponatraemia.[35]

The brain adapts slowly to hyponatraemia by secretion of intracellular solutes such as sodium and potassium initially, followed by amino acids and myoinositol (organic osmolytes).

Overcorrection of hyponatraemia can subject solute-poor cerebral cells to shrinkage and CPM.

CPM is characterised by demyelination of pontine, basal ganglion, and cerebellar regions with resultant neurological symptoms, including behaviour disturbances, lethargy, dysarthria, dysphagia, paraparesis or quadriparesis, and coma.



Pontine demyelination in axial T2 MRI sequences
From: P. J. Serrano-Castro, G. Alonso-Verdegay, G. López-Martínez, et al. BMJ Case Reports 2009; doi:10.1136

Seizures may also be seen, but are less common.[22]

Complications	Timeframe	Likelihood
One case study of patients with hyponatraemic encephalopathy, reported in early 2015, included 71 hyponatraemic episodes in which patients were treated with aggressive 3% NaCl resuscitation.[36] Twelve of the patients in the study died of comorbid conditions prior to 6-month follow-up. Of those who were re-evaluated, no patient demonstrated neurological symptoms consistent with cerebral demyelination. Malnutrition, potassium depletion, and hepatic failure increase the risk of developing CPM.[22] [23] CPM occurs more frequently in long-standing SIADH, due to brain adaptation to hyponatraemia. It can also occur in acute SIADH (duration ≤48 hours), but this is less likely. To treat overcorrection of hyponatraemia (either as a result of aggressive salt administration or of spontaneous water diuresis after offending medicines are discontinued), free water is replenished through increased oral intake or hypotonic fluids.		

Prognosis

Persistent SIADH

If the underlying cause is found and treated successfully, SIADH typically resolves. If the underlying condition persists, SIADH is difficult to manage, secondary to difficulty complying with necessary fluid restriction or medicines. Oral vasopressin antagonists such as tolvaptan offer hope for more successful long-term management of SIADH, and it has been used in selected patients with careful monitoring.[31]

Diagnostic guidelines

Europe

Clinical practice guideline on diagnosis and treatment of hyponatraemia (https://www.ese-hormones.org/publications/guidelines)

Published by: European Society of Endocrinology, European Society of Intensive Care Medicine, European Renal Association-European Dialysis and Transplant Association

Last published: 2014

Treatment guidelines

United Kingdom

Emergency management of severe symptomatic hyponatraemia in adult patients (https://www.endocrinology.org/clinical-practice/clinical-guidance/society-for-endocrinology-guidance)

Published by: Society for Endocrinology

Last published: 2016

Europe

Clinical practice guideline on diagnosis and treatment of hyponatraemia (https://www.ese-hormones.org/publications/guidelines)

Published by: European Society of Endocrinology, European Society of Intensive Care Medicine, European Renal Association-European Dialysis and Transplant Association

Last published: 2014

Online resources

1. FDA Drug Safety Communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death (http://www.fda.gov/Drugs/DrugSafety/ucm350062.htm) *(external link)*

Key articles

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Images

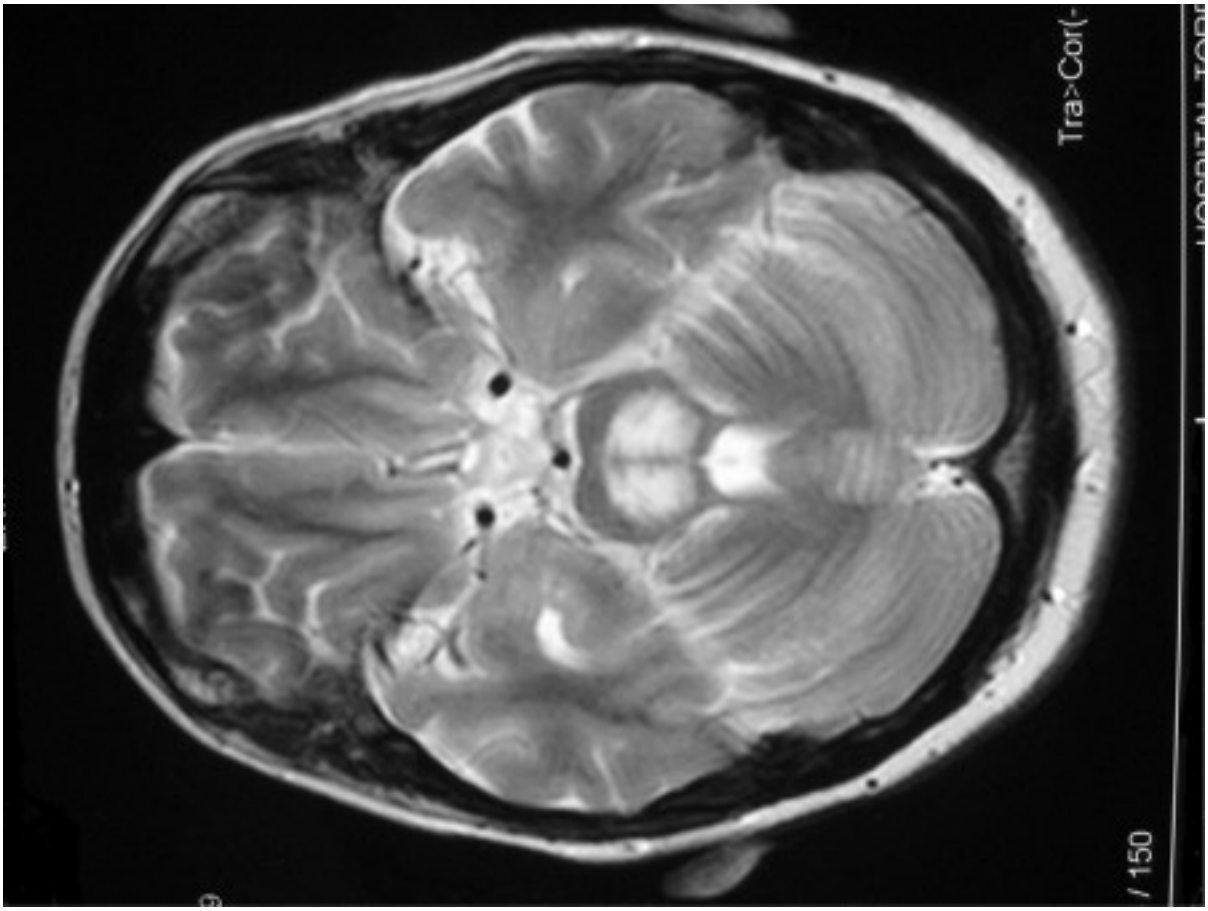

Figure 1: Pontine demyelination in axial T2 MRI sequences

From: P. J. Serrano-Castro, G. Alonso-Verdegay, G. López-Martínez, et al. BMJ Case Reports 2009; doi:10.1136

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Figure 1 – BMJ Best Practice Numeral Style

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4-digit numerals: 1000

numerals < 1: 0.25

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

BMJ Best Practice

Contributors:

// Authors:

Megan Dixon, MD

Nephrologist
Arizona Kidney Disease and Hypertension Center, Phoenix, AZ
DISCLOSURES: MD declares that she has no competing interests.

Yeonghau Howard Lien, MD, PhD

Professor Emeritus of Medicine
Division of Nephrology, University of Arizona, Tucson, AZ
DISCLOSURES: YHL is an author of a reference cited in this topic.

// Peer Reviewers:

Maryam Gondal, MD

Assistant Professor
Nephrology, Yale University, New Haven, CT
DISCLOSURES: MG declares that she has no competing interests.

Judith H. Veis, MD

Associate Director
Nephrology, Washington Hospital Center, Washington, DC
DISCLOSURES: JHV declares that she has no competing interests.

Laurie Solomon, MD, FRCP

Consultant Nephrologist
Renal Unit, Lancashire Teaching Hospitals, Fulwood, Preston, UK
DISCLOSURES: LS declares that he has no competing interests.