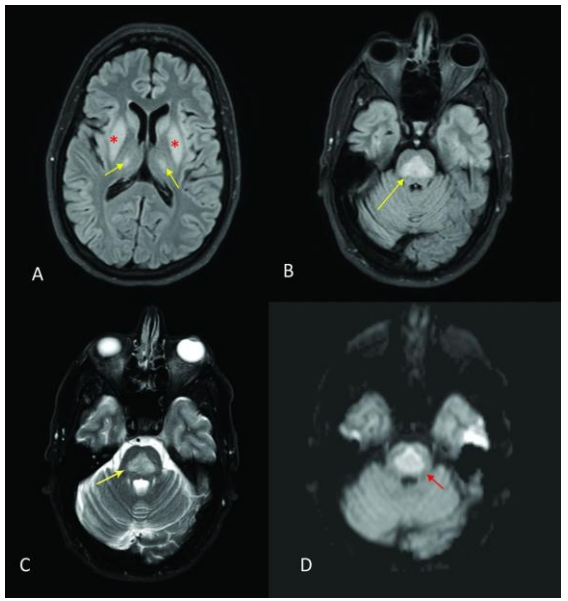
Hyponatremia Syndromes

Leticia Hernández Dávila, MD FACE
December 12, 2019



DISCLOSURES

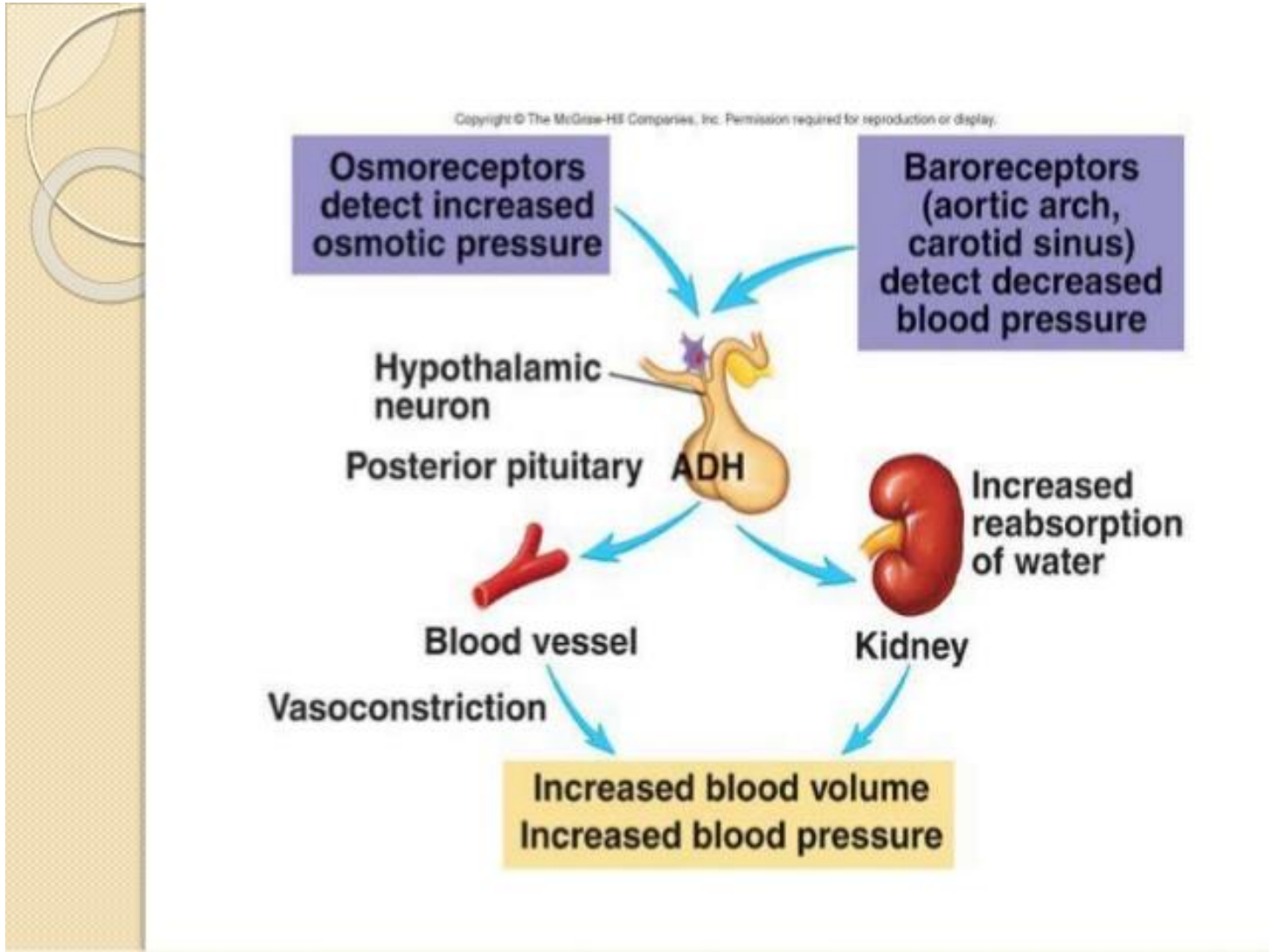
- I have no conflicts of interest to disclose.

OBJECTIVES

Topics to be reviewed during this session:

- Definition of hyponatremia
- Different causes
- Evaluation of patient with hyponatremia
- Alternatives of treatment and proper selection according to cause and patient's clinical status
- Vaptans:
  - Development
  - Function
  - Uses
  - Limitations

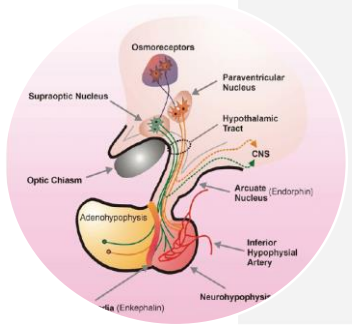
NORMAL VASSOPRESSIN (ADH) SECRETION



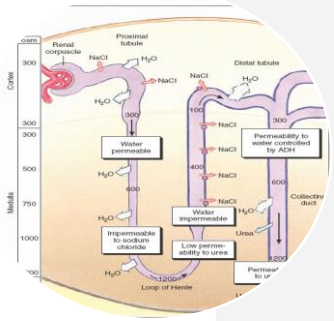
HYPONATREMIA DEFINITION

- Disturbed water homeostasis
- Heterogenous disorder
- Usually an underlying cause is complicated by hyponatremia

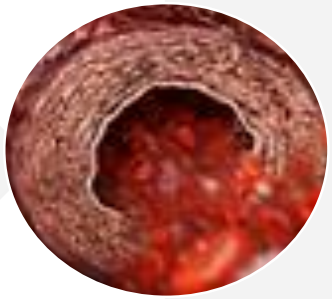
HYPONATREMIA DEVELOPMENT



Inability to suppress Vasopressin



Impairment in renal water excretion



Sodium < 135 mEq/L

Hyponatremia definition

Normal, but persistent ADH secretion

- Volume depletion
- Low tissue perfusion
  - Heart failure
  - Cirrhosis
    - Baroreceptors
      - Carotid sinus, aortic arch – regulation of sympathetic activity – release of ADH
      - Glomerular afferent arterioles – renin-angiotensin system
      - Atria and ventricles – natriuretic peptides

Abnormal ADH release – Syndrome of inappropriate Anti-Diuretic Hormone Secretion (SIADH).

EPIDEMIOLOGY

- NHANES cohort (1994-2004)
  - Prevalence general US population – 1.72%
  - 30-40% of hospitalized patients

- Retrospective review of database of 151,446 ICU's
  - 17.7% patients
    - 130-135 mEq/L -13.8%
    - 125-127 mEq/L – 2.7%
    - <125 mEq/L – 1.2%
  - Odds ratio for risk of mortality
    - 1.32 (CI 1.25-1.39), 1.89 (1.71-2.09), and 1.81 (1.56-2.10)

Journal of Intensive Care Medicine. (2016) 31(4): 223-236

CASE PRESENTATION

70-year-old woman admitted to ER after suffering a fall.

- Cognitive and motor impairment with gradual deterioration since about 2 weeks prior to fall.
- Medical history:
  - Breast cancer – 60 yrs
  - HTN, dyslipidemia
  - Depression
- Medications:
  - Clonidine (transdermal) 5 mg/week
  - Atorvastatin 20 mg qd
  - Clopidrogel 75 mg qd
  - Paroxetine 20 mg qd

Case adapted from:
Endocrine (2017) 55: 311-319

Case Presentation

- Physical examination
  - BP 135/86, HR 75 bpm

- Laboratory workup:
  - Na 124 mmol/L
  - CXR normal, ECG normal, 2 D echo – normal, Head CT Scan – subcortical arteriosclerotic encephalopathy.

HYPONATREMIA

CLASSIFICATION

CLASSIFFICATION OF HYPONATREMIA

Classification	Criteria	Limitations of Clinical Utility
Moderate (125–129 mmol/L) versus severe/profound[a] (<125 mmol/L)	Absolute S_{Na} concentration	Symptoms do not always correlate with degree of hyponatremia
Acute versus chronic	Time of development (cutoff 48 h)	Time of development not always known
Symptomatic versus asymptomatic	Presence of symptoms	Many symptoms aspecific; chronic hyponatremia may be symptomatic
Hypotonic, isotonic, or hypertonic	Measured serum osmolality	Ineffective osmoles (e.g., urea, ethanol) are also measured
Hypovolemic, euvolemic, hypervolemic	Clinical assessment of volume status	Clinical assessment of volume status has low sensitivity and specificity

JASN May 2017, 28 (5) 1340-1349

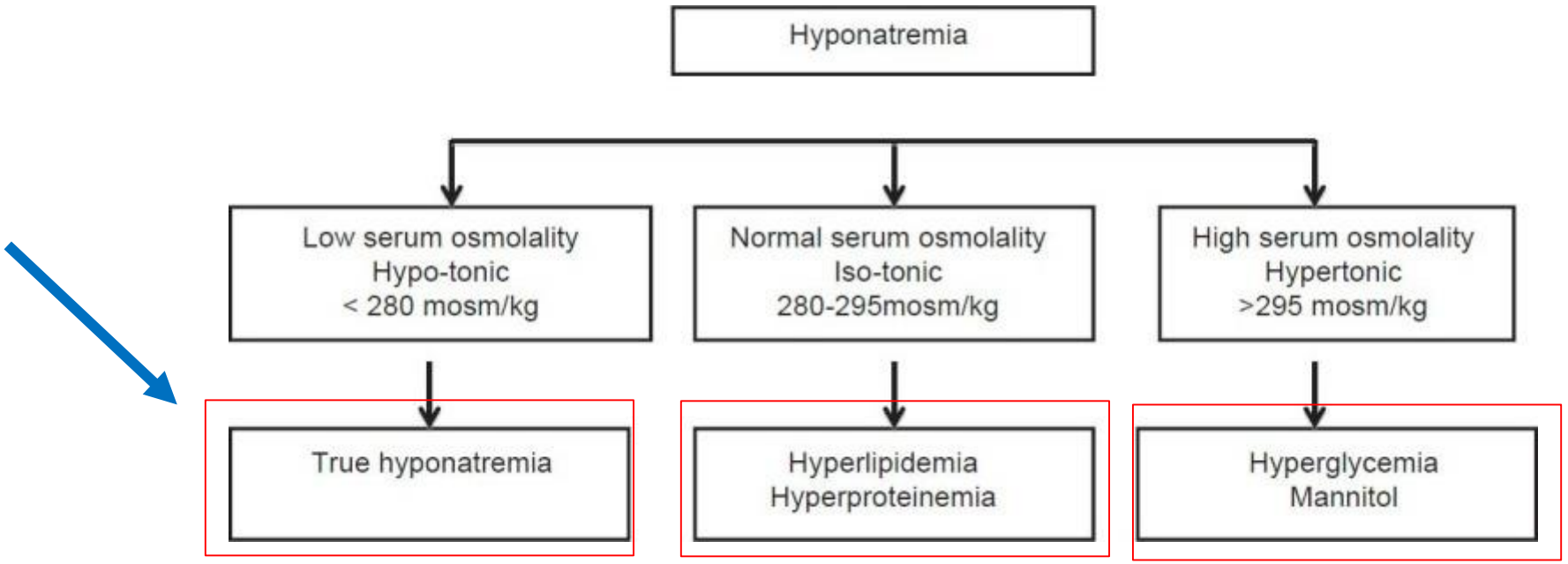
HYPONATREMIA: ACUTE VS. CHRONIC

	ACUTE	CHRONIC
Symptom onset	<48 hrs	>48 hrs
Sodium concentration		Usually > 120 mEq/L
Symptoms	▪ Seizures ▪ Impaired mental status ▪ Coma ▪ Death	▪ Nausea ▪ Vomiting ▪ Loss of appetite ▪ Frequent falls, gait disturbances (elderly)

Indian J Endocrinol Metab. 2014 Nov-Dec; 18(6): 760–771.

Am J Med. 2006 Jan;119(1):71.e1-8.

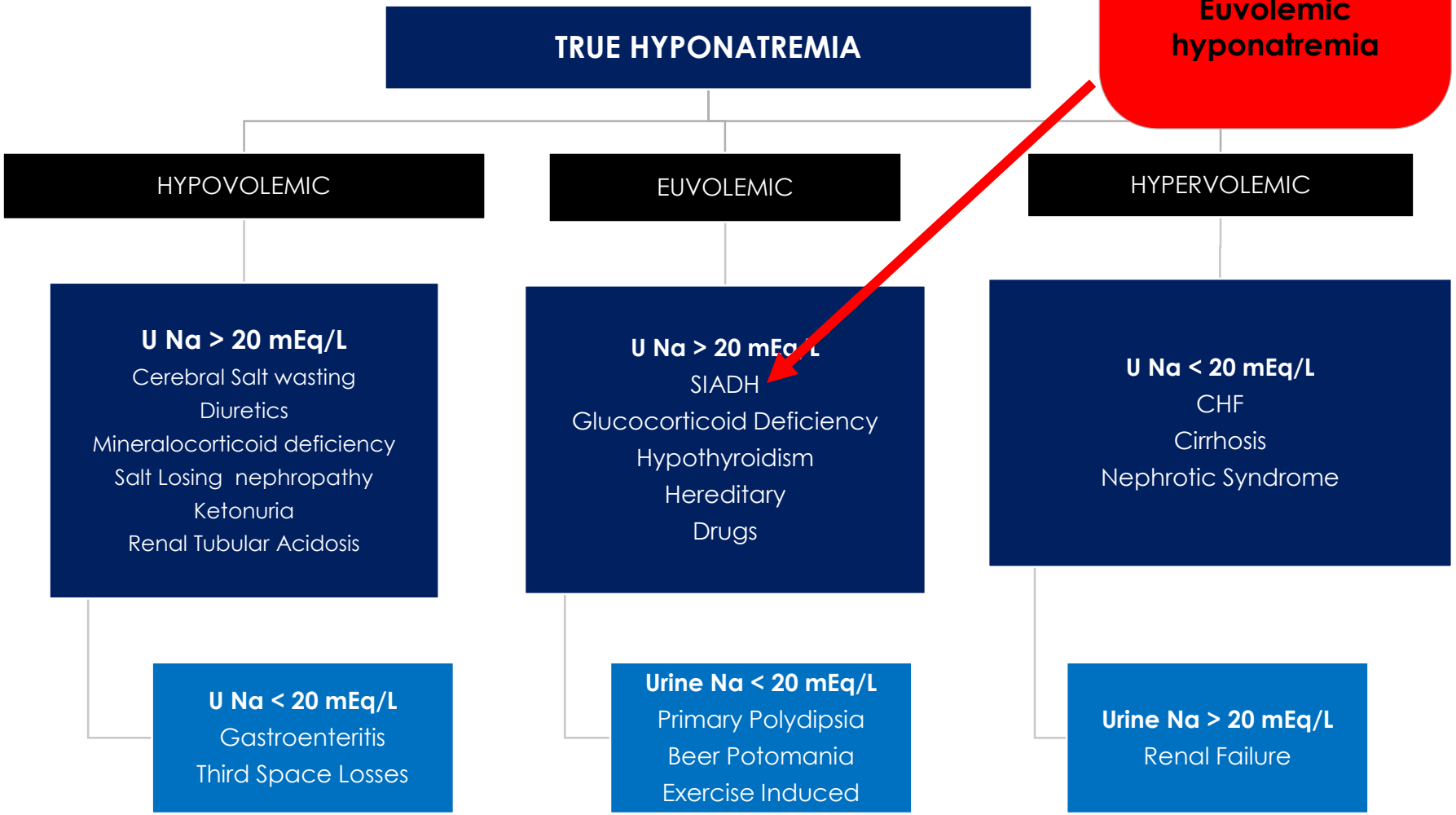
HYPONATREMIA CLASSIFICATION - TONICITY



Indian J Endocrinol Metab. 2014 Nov-Dec; 18(6): 760–771.

HYPONATREMIA – CLASSIFICATION DUE TO VOL

60 % of all causes of hyponatremia. Most common cause of Euvolemic hyponatremia



Indian J Endocrinol Metab. 2014 Nov-Dec; 18(6): 760–771.

CAUSES OF SIADH

SYNDROME OF INAPPROPRIATE ADH SECRETION:

TYPE	% OF CASES	PATOPHYSIOLOGY
A	40-70%	Random ADH release, independent of plasma osmolality. • Ej. Neoplasms.
B	20-40%	Reset Osmostat – lower [Na+] 125-130 perceived as normal. • Pharmacologic agents • Brainstem degenerative disorders • Chronic infections. • More common in elderly
C	10%	ADH not inhibited by H2O load. Dysregulation of ADH synthesis.
D	<5%	Normal or low levels of ADH • Gain of function mutation of V2 receptors.

J. Endocrinol. Invest. 33: 671-682, 2010

MAJOR KNOWN CAUSES OF SIADH

- Pulmonary disorders
  - Tuberculosis, viral/bacterial pneumonia, asthma, atelectasia, pneumothorax, HIV
- Ectopic production
  - Malignancies
    - Pulmonary microcitoma
    - Nasopharyngeal tumors
    - GI/pancreatic malignancies
    - GU tract malignancies
    - Mesothelioma
    - Lymphoma, sarcoma

J. Endocrinol. Invest. 33: 671-682, 2010

MAJOR KNOWN CAUSES OF SIADH

- Increased hypothalamic/hypophyseal ADH release
  - Infections
    - Meningitis, encephalitis, sarcoidosis, abcesses, herpes, HIV
  - Vascular
    - Thrombosis, SAH, SDH, temporal arteritis
    - Psychosis
    - Post-surgical
    - Guillain-Barre
  - Drugs
    - Antidepressants: carbamazepine, TCAs, SSRIs, phenothiazines, haloperidol, quinolones, leveteiracetam
    - NDMA (ecstasy)
    - Cyclophospamide
    - Chlorpropamide
    - NSAIDs

J. Endocrinol. Invest. 33: 671-682, 2010

MAJOR KNOWN CAUSES OF SIADH

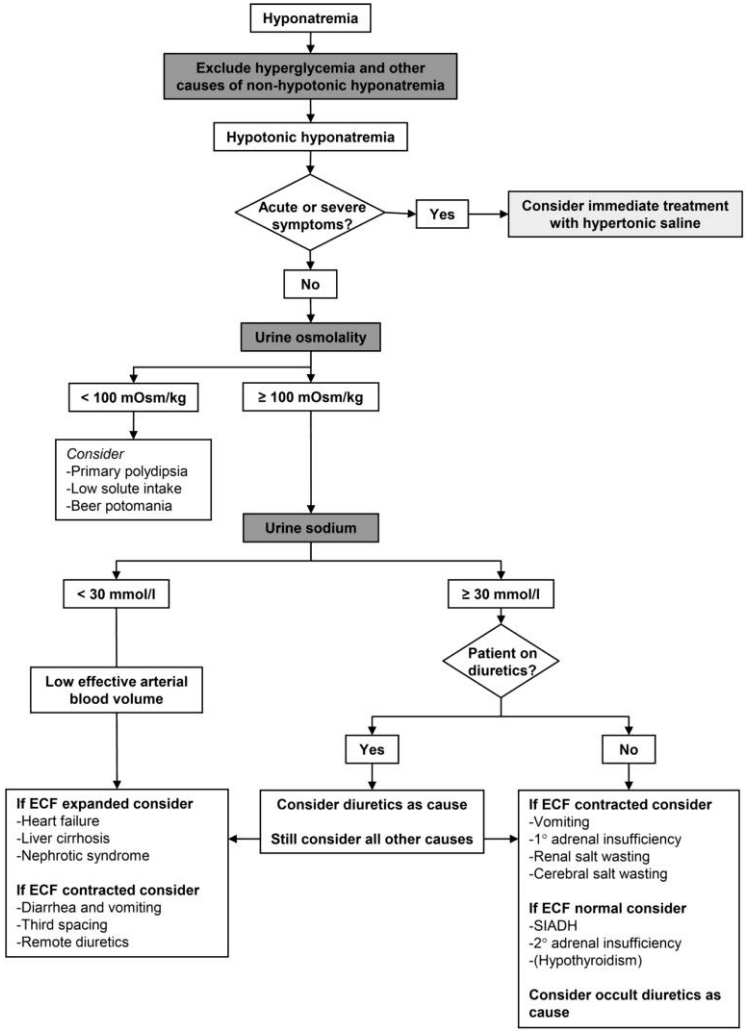
- Amplification of effects of ADH at the receptors
  - Drugs: cyclophosphamide, chlorpropamide

- Release of non-ADH antidiuretic peptides
  - Prolactinoma, Waldeström macroglobulinemia.

J. Endocrinol. Invest. 33: 671-682, 2010

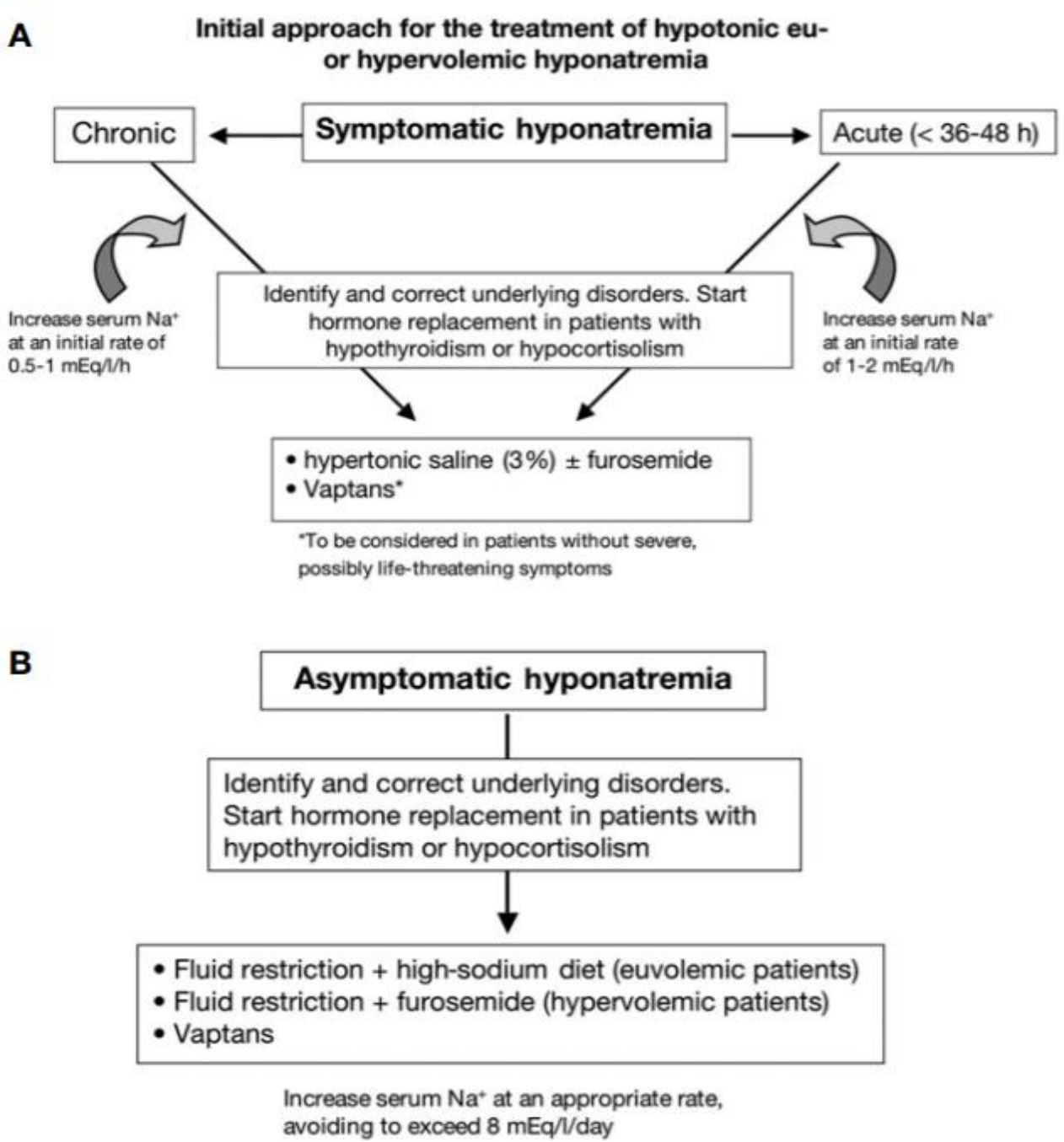
MANAGEMENT

Diagnostic algorithm for hyponatremia.



Ewout J. Hoorn, and Robert Zietse JASN 2017;28:1340-1349

JASN Journal of the American Society of Nephrology



J. Endocrinol. Invest. 33: 671-682, 2010

Treatment and Limits of Correction of Severe Hyponatremia.

Table 1. Treatment and Limits of Correction of Severe Hyponatremia.*

Duration	Related Behavior or Condition	Clinical Features	Initial Therapeutic Goal	Limit of Correction and Management of Overcorrection
Several hours	Self-induced water intoxication associated with psychosis, running in marathons, use of 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy")	Headache, delirium, vomiting, seizures, coma, neurogenic pulmonary edema, brain swelling with risk of fatal herniation	100-ml bolus of 3% saline three times as needed for severe symptoms; increase plasma sodium concentration by 4–6 mmol/liter in first 6 hr	Excessive correction not known to be harmful
1–2 days	Postoperative hyponatremia, especially in women and children; hyponatremia associated with intracranial disease	Headache, delirium, vomiting, seizures, coma, neurogenic pulmonary edema, brain swelling with risk of fatal herniation	100-ml bolus of 3% saline three times as needed for severe symptoms; increase plasma sodium concentration by 4–6 mmol/liter in first 6 hr	Avoid increasing plasma sodium concentration by >10 mmol/liter/day
Unknown or ≥2 days	Conditions associated with high risk of the osmotic demyelination syndrome (plasma sodium concentration, 105 mmol/liter or less; hypokalemia, alcoholism, malnutrition, liver disease)†	Malaise, fatigue, confusion, cramps, falls, 10% incidence of seizures with plasma sodium concentration <110 mmol/liter, minimal brain swelling, and no risk of herniation	Extra caution indicated for conditions associated with high risk of osmotic demyelination syndrome; 100- ml bolus of 3% saline if needed for seizures; increase plasma sodium concentration by 4–6 mmol/liter in first 24 hr	Avoid increasing plasma sodium concentration by >8 mmol/liter/day; consider lowering again if limit is exceeded, especially in patients with high risk of the osmotic demyelination syndrome

* Severe hyponatremia is defined as a plasma sodium concentration below 120 mmol per liter. In the absence of urinary loss of water, 1 ml of 3% saline per kilogram of body weight will increase the plasma sodium concentration by approximately 1 mmol per liter.

† The osmotic demyelination syndrome may develop when the plasma sodium concentration is increased rapidly in outpatients who became hyponatremic while drinking normal amounts of water and in hospitalized patients who became hyponatremic over 2 or more days.

Sterns RH. N Engl J Med 2015;372:55-65.

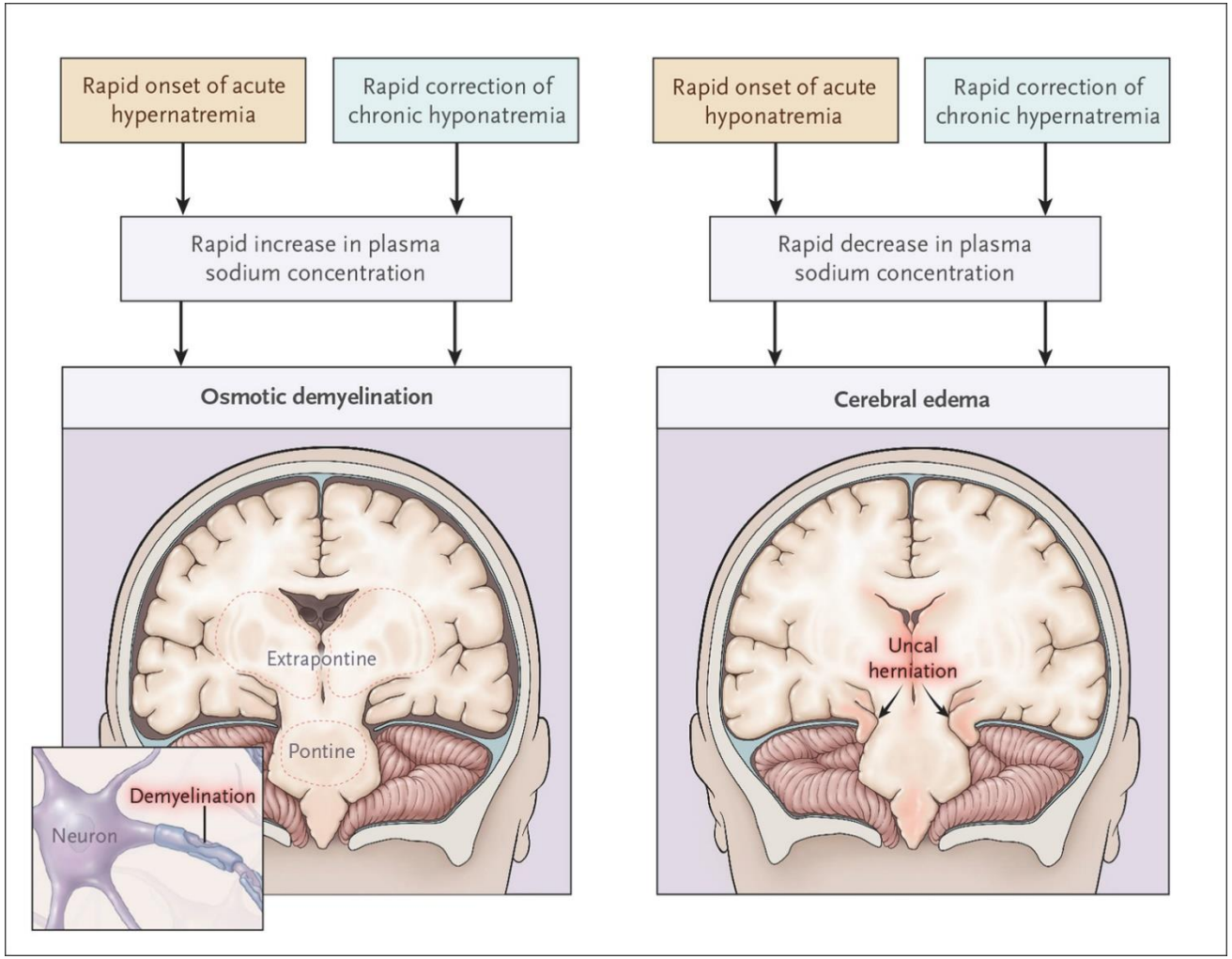
The NEW ENGLAND JOURNAL of MEDICINE

Comparison of the United States and European guidelines

Subject	United States Guideline	European Guideline
Acute or symptomatic hyponatremia	Severe symptoms: Bolus 3% NaCl (100 ml over 10 min × 3 as needed)	Severe symptoms: Bolus 3% NaCl (150 ml over 20 min 2–3 times as needed)
	Moderate symptoms: Continuous infusion 3% NaCl (0.5–2 ml/kg per h)	Moderate symptoms: Bolus 3% NaCl (150 ml 3% over 20 min once)
Chronic hyponatremia		
SIAD	Fluid restriction (first line)	Fluid restriction (first line)
	Demeclocycline, urea, or vaptan (second line)	Urea or loop diuretics + oral NaCl (second line)
		Do not recommend or recommend against vaptan[a]
		Recommend against lithium or demeclocycline
Hypovolemic hyponatremia	Isotonic saline	Isotonic saline or balanced crystalloid solution
Hypervolemic hyponatremia	Fluid restriction	Fluid restriction
	Vaptans[b]	Recommend against vaptan
Correction rates	Minimum: 4–8 mmol/L per d, 4–6 mmol/L per d (high risk of ODS)	No minimum
	Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)	Limit: 10 mmol/L per d
Management of overcorrection	Baseline $S_{Na} \geq 120$ mmol/L: probably unnecessary	Start once limit is exceeded
	Baseline $S_{Na} < 120$ mmol/L: start relowering with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L per d	Consult an expert to discuss infusion containing electrolyte-free water (10 ml/kg) with or without 2 μg desmopressin iv

JASN May 2017, 28 (5) 1340-1349

Consequences of Rapid Changes in the Plasma Sodium Concentration.



Sterns RH. N Engl J Med 2015;372:55-65.

The NEW ENGLAND JOURNAL of MEDICINE

Landmarks in Vasopressin Biology.

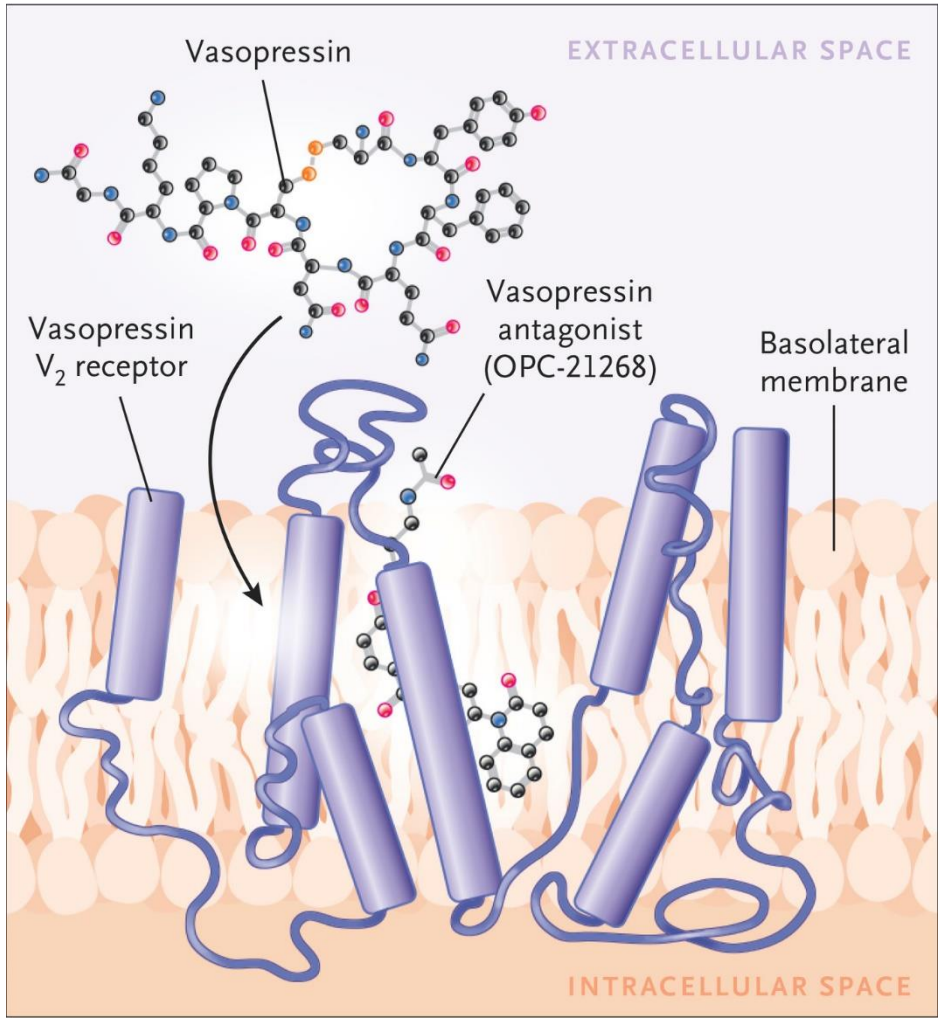
Table 1. Landmarks in Vasopressin Biology.

Year	Landmark
1895	Discovery that the use of pituitary extracts increases blood pressure
1898	Discovery that pressor activity resides in the posterior lobe
1913	Discovery that the use of pituitary extracts decreases urine excretion
1947	Discovery that vasopressin is released under osmotic control
1952	Report on the structure and amino acid sequence of vasopressin
1957	Localization of the osmoreceptor in the anterior hypothalamus
1957	Reports of patients with presumed vasopressin-mediated hyponatremia
1970s–1980s	Synthesis of numerous polypeptide antagonists
1973–1975	Reports of nonosmotic release of vasopressin baroreceptors
1973	Development of radioimmunoassay for vasopressin
1982	Identification of gene encoding vasopressin carrier — neurophysin II — on chromosome 20
1991	Discovery of water channels
1992–1994	Cloning of human vasopressin V_1 and V_2 receptors
1992	Development of nonpeptide oral vasopressin antagonists
1994	Cloning of vasopressin-regulated water channel
2004–2008	Approval of vasopressin antagonists for treatment of hyponatremia

Berl T. N Engl J Med 2015;372:2207-2216.

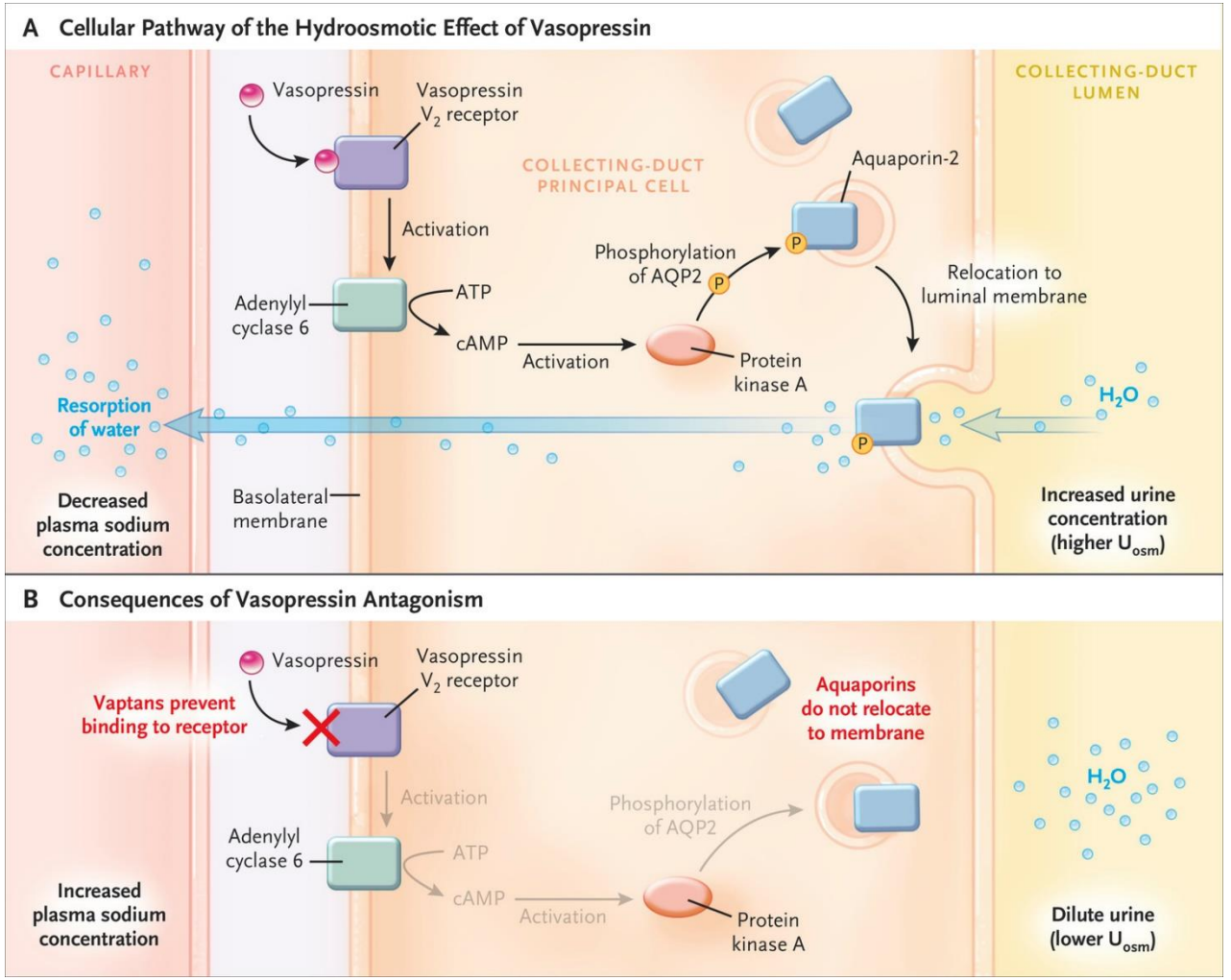
The NEW ENGLAND JOURNAL of MEDICINE

Binding of Vasopressin to Its Receptor and Location of Antagonist.



Berl T. N Engl J Med 2015;372:2207-2216.

Cellular Effects of Vasopressin and Consequences of Vasopressin Antagonism.



Berl T. N Engl J Med 2015;372:2207-2216.

Inhibitory Constants and Pharmacokinetics of Two Vasopressin Antagonists.

Table 2. Inhibitory Constants and Pharmacokinetics of Two Vasopressin Antagonists.

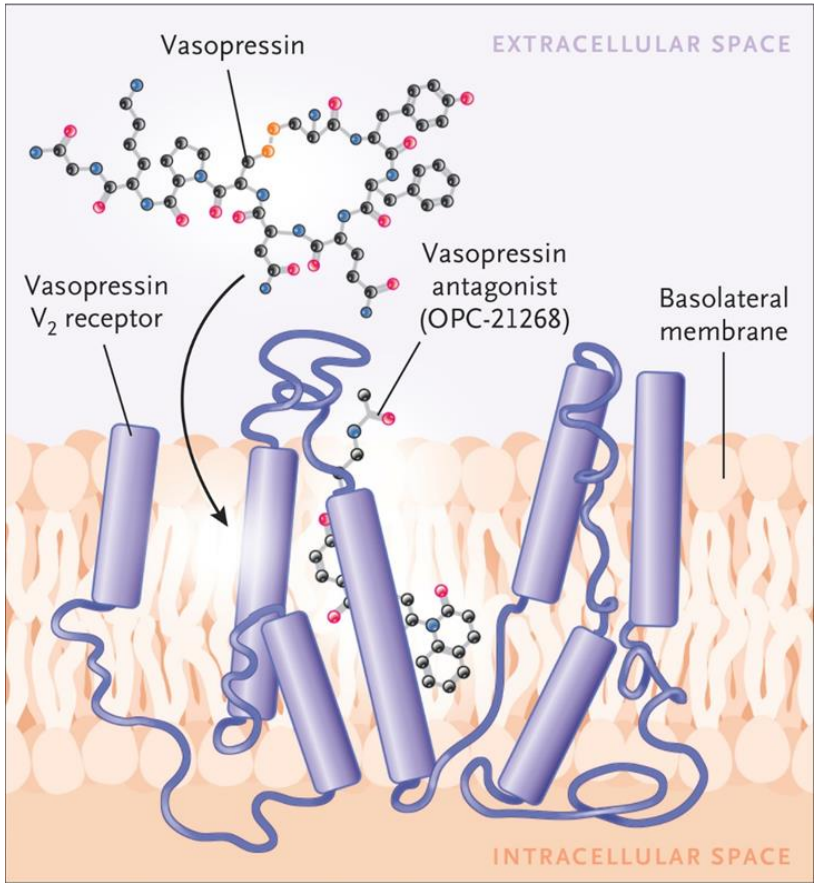
Variable	Conivaptan	Tolvaptan
Inhibitory constant of vasopressin antagonist*		
V_1 receptor — nM	6.3	12.3
V_2 receptor — nM	1.1	0.4
V_2:V_1 selectivity ratio	5.7	29.0
Pharmacokinetics of vasopressin antagonists†		
Dose	Intravenous administration, 40 mg daily for 4 days	Oral administration, 15 to 60 mg daily
Half-life — hr	6–10	6–8
Time to maximum aquaresis after administration — hr	2	2
Protein binding — %	95–99	99
Oral bioavailability — %	40–50	40–50
Primary metabolism	CYP3A4	CYP3A4
Urinary excretion — %	<1	<5

* Data are adapted from Tahara et al.[25] and Yamamura et al.[26] The inhibitory constant (Ki) is the inhibitor level that produces half the maximal rate, so a smaller Ki value indicates a more potent inhibitor.
† Data are adapted from Costello-Boerrigter et al.[27]

Berl T. N Engl J Med 2015;372:2207-2216.

The NEW ENGLAND JOURNAL of MEDICINE

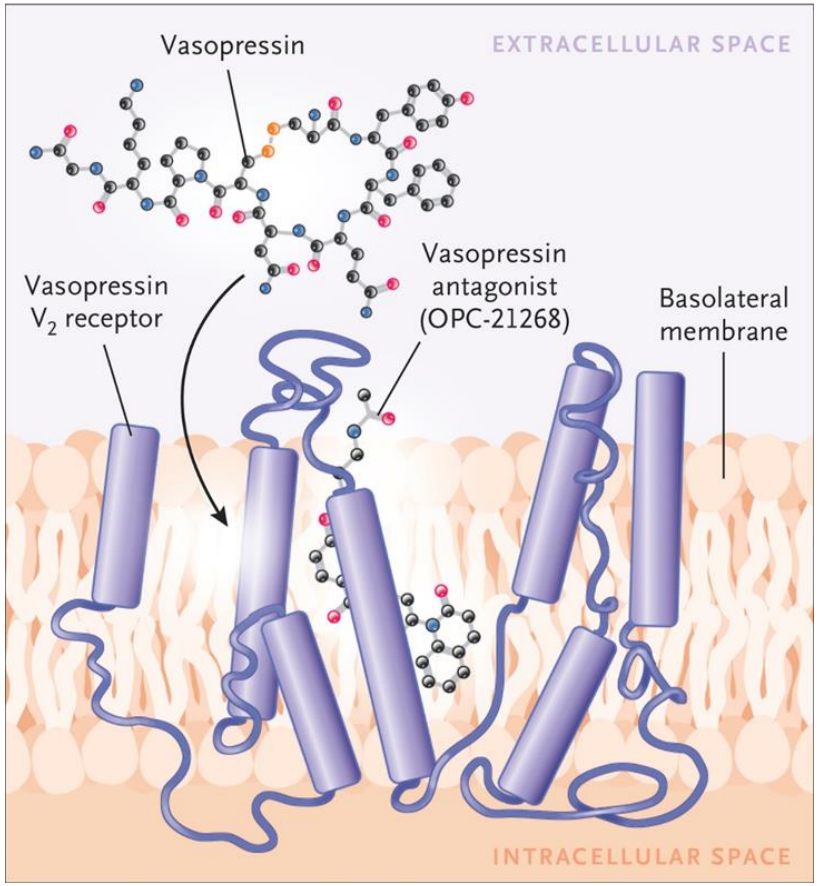
VAPTANS - Trials



- Assessment of the Efficacy and Safety of Intravenous Conivaptan in Euvolemic and Hypervolemic Hyponatremia.
  - Conivaptan (40 mg IV)
    - Increase mean Na by 6.3 mmol/L.

Am J Nephrol 2007;27:447–457

VAPTANS - Trials



- Study of Ascending Levels of Tolvaptan in Hyponatremia 1 & 2.
  - Multicenter, randomized, double-blind, placebo-controlled.
  - Euvolemic and hypervolemic hyponatremia.
- Tolvaptan 30 mg qd
  - Increase mean Na by 3.6 and 4.4 mmol/L.

Am J Nephrol 2007;27:447–457

Demographic and Baseline Characteristics of Patients in the SALT-1 and SALT-2 Trials.

Table 1. Demographic and Baseline Characteristics of Patients in the SALT-1 and SALT-2 Trials.*

Characteristic	SALT-1		SALT-2		P Value		
	Tolvaptan (N=102)	Placebo (N=103)	Tolvaptan (N=123)	Placebo (N=120)	SALT-1	SALT-2	SALT-1 and SALT-2
Age — yr							
Mean	60±14	60±13	62±15	63±14	0.94	0.66	0.72
Range	18–86	35–90	27–92	28–100			
Female sex — no. (%)	50 (49)	41 (40)	48 (39)	47 (39)	0.21	1.00	0.39
Race — no. (%)					0.26	0.47	0.56
White	71 (70)	76 (74)	118 (96)	109 (91)			
Black	13 (13)	17 (17)	1 (1)	3 (2)			
Hispanic	13 (13)	9 (9)	3 (2)	6 (5)			
Other	5 (5)	1 (1)	1 (1)	2 (2)			
Mean body weight — kg	78±23	75±22	73±19	75±21	0.44	0.39	0.96
Mean height — cm	167±10	170±11	168±11	167±9	0.02	0.42	0.14
Fluid status — no. (%)					0.38	0.80	0.70
Euvolemic	61 (60)	67 (65)	63 (51)	60 (50)			
Hypervolemic	41 (40)	34 (33)	58 (47)	60 (50)			
Cause of hyponatremia — no. (%)					0.63	0.96	0.70
Chronic heart failure	35 (34)	33 (32)	36 (29)	34 (28)			
Cirrhosis	25 (25)	21 (20)	38 (31)	36 (30)			
SIADH and other	42 (41)	49 (48)	49 (40)	50 (42)			
Mean serum sodium — mmol/liter	128.7±4.5	128.8±4.1	129.5±3.5	129.1±4.5	0.85	0.37	0.60
Degree of hyponatremia — no. (%)					0.89	1.00	0.93
Mild	49 (48)	51 (50)	64 (52)	62 (52)			
Mean serum sodium — mmol/liter	132.4±1.5	132.1±1.3	132.3±1.6	132.4±1.3	0.37	0.56	0.88
Marked	53 (52)	52 (50)	59 (48)	58 (48)			
Mean serum sodium — mmol/liter	125.4±3.5	125.5±3.2	126.6±2.5	125.5±3.8	0.84	0.07	0.26
Mean score on SF-12 Health Survey†							
Physical Component Summary	33.4±10.7	33.9±10.5	33.0±10.6	33.1±10.8	0.78	0.95	0.81
Mental Component Summary	42.4±11.6	44.7±11.9	44.3±11.9	44.9±11.6	0.15	0.89	0.30

* Mild hyponatremia was defined as a baseline serum sodium concentration of 130 to 134 mmol per liter. Marked hyponatremia was defined as a serum sodium concentration of less than 130 mmol per liter. SIADH denotes syndrome of inappropriate antidiuretic hormone secretion. Race was self-reported. Plus–minus values are means ±SD.
† Scores on the Physical Component Summary of the SF-12 range from 5 to 69, and those on the Mental Component Summary range from 8 to 73, with higher scores indicating better functioning.

Schrier RW et al. N Engl J Med 2006;355:2099-2112.

The NEW ENGLAND JOURNAL of MEDICINE

Results of Efficacy Analysis.

Table 2. Results of Efficacy Analysis.*

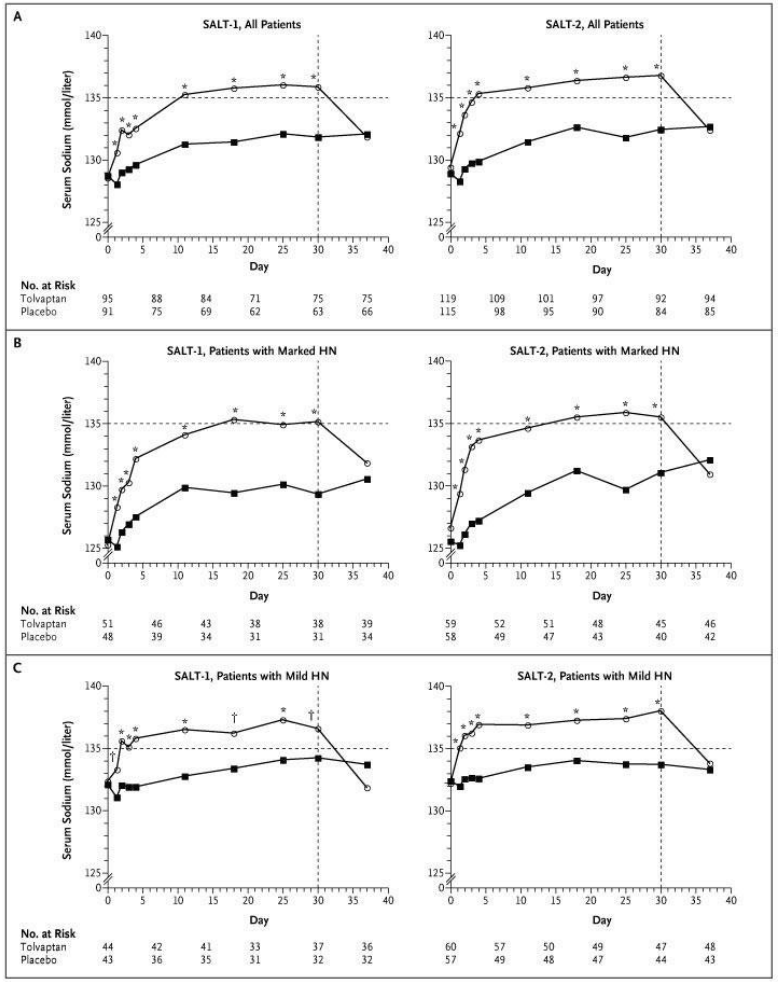
Variable	SALT-1			SALT-2		
	Tolvaptan (N=102)	Placebo (N=103)	P Value	Tolvaptan (N=123)	Placebo (N=120)	P Value
Primary end point: change in average AUC for serum sodium — mmol/liter						
All patients						
Day 4	3.62±2.68	0.25±2.08	<0.001	4.33±2.87	0.42±2.56	<0.001
Day 30	6.22±4.10	1.66±3.59	<0.001	6.20±3.92	1.84±3.83	<0.001
Mild hyponatremia						
Day 4	2.52±1.95	−0.32±2.27	<0.001	3.59±2.34	0.18±2.01	<0.001
Day 30	3.87±3.01	0.68±2.78	<0.001	4.68±2.91	0.94±2.89	<0.001
Marked hyponatremia						
Day 4	4.56±2.88	0.76±1.77	<0.001	5.06±3.16	0.7±2.99	<0.001
Day 30	8.24±3.84	2.54±4.01	<0.001	7.60±4.31	2.72±4.41	<0.001
Absolute change in serum sodium — mmol/liter						
Baseline	128.5±4.5	128.7±4.1		129.±3.5	128.9±4.5	
Day 4						
Mean	133.9±4.8	129.7±4.9	<0.001	135.3±3.6	129.6±5.2	<0.001
No. of patients	95	88		115	112	
Day 30						
Mean	135.7±5.0	131.0±6.2	<0.001	135.9±5.9	131.5±5.7	<0.001
No. of patients	95	89		114	98	
Categorical change in hyponatremia — no./total no. (%)						
Baseline						
Mild hyponatremia	49/102 (48)	51/103 (50)		64/123 (52)	62/120 (52)	
Marked hyponatremia	53/102 (52)	52/103 (50)		59/123 (48)	58/120 (48)	
Day 4						
Normal	38/95 (40)	12/89 (13)	<0.001	65/118 (55)	12/114 (11)	<0.001
Marked hyponatremia	12/95 (13)	44/89 (49)	<0.001	12/118 (10)	46/114 (40)	<0.001
Day 30						
Normal	50/95 (53)	22/89 (25)	<0.001	69/118 (58)	28/114 (25)	<0.001
Marked hyponatremia	7/95 (7)	31/89 (35)	<0.001	18/118 (15)	37/114 (32)	0.002
Fluid status						
Urine output on day 1 — ml	3218±1646	2076±1534	<0.001	3185±2543	1914±1366	<0.001
Fluid intake on day 1 — ml	1825±1057	1492±945	0.04	2129±2110	1705±1396	0.09
Difference on day 1 — ml	−1533±1429	−636±1275	<0.001	−1059±1877	−185±870	<0.001
Patients requiring fluid restriction — %	9.3	17.5	0.08	9.2	16.8	0.08

* The range for mild hyponatremia, defined as a baseline serum sodium concentration of 130 to 134 mmol per liter, was conservatively extended to 130 to 135 mmol per liter for the analysis of categorical change. Marked hyponatremia was defined as a serum sodium concentration of less than 130 mmol per liter. Patients whose serum sodium concentrations were evaluated at baseline and one or more times after baseline were included in the efficacy analysis. P values are for the comparison of the change in serum sodium concentrations from baseline to day 4 and from baseline to day 30 between the placebo group and the tolvaptan group. Plus–minus values are means ±SD. AUC denotes area under the curve.

Schrier RW et al. N Engl J Med 2006;355:2099-2112.

The NEW ENGLAND JOURNAL of MEDICINE

Mean Serum Sodium Concentrations According to the Day of Patient Visit.



Schrier RW et al. N Engl J Med 2006;355:2099-2112.

The NEW ENGLAND JOURNAL of MEDICINE

Adverse Events.

Table 3. Adverse Events.*

Variable	SALT-1		SALT-2	
	Tolvaptan (N=100)	Placebo (N=101)	Tolvaptan (N=123)	Placebo (N=119)
Total patient-days of drug exposure	2669	2292	3228	3055
	no. of patients (%)			
Adverse events occurring during study (all causes)	88 (88)	83 (82)	91 (74)	85 (71)
Serious adverse events	31 (31)	35 (34)	33 (27)	30 (25)
Withdrawal because of adverse events	9 (9)	17 (17)	14 (11)	9 (8)
Adverse events (potentially study-related)	50 (50)	34 (34)	42 (34)	29 (24)
Serious adverse events	2 (2)†	6 (6)‡	6 (5)§	4 (3)¶
Withdrawal because of adverse events	4 (4)‖	7 (7)**	4 (3)††	1 (1)‡‡
	Tolvaptan Group (N=223)		**Placebo Group (N=220)**	
Common adverse events — body system and MedDRA preferred term§§				
Gastrointestinal disorders				
Ascites	14 (6)		13 (6)	
Constipation	16 (7)		4 (2)	
Diarrhea (not organ-specific)	12 (5)		12 (6)	
Dry mouth	28 (13)		9 (4)	
Nausea	18 (8)		13 (6)	
Vomiting (not organ-specific)	7 (3)		19 (9)	
General disorders				
Fatigue	12 (5)		11 (5)	
Peripheral edema	16 (7)		15 (7)	
Thirst	32 (14)		10 (5)	
Weakness	21 (9)		10 (5)	
Infections and infestations				
Urinary tract infection (not organ-specific)	13 (6)		8 (4)	
Metabolism and nutritional disorders				
Hyperglycemia (not organ-specific)	12 (5)		2 (1)	
Hyperkalemia	12 (5)		11 (5)	
Nervous system disorders				
Dizziness	15 (7)		11 (5)	
Headache (not organ-specific)	15 (7)		15 (7)	
Renal and urinary tract disorders				
Urinary frequency	15 (7)		6 (3)	
Vascular disorders				
Hypotension (not organ-specific)	15 (7)		14 (6)	

* Patients who received at least one dose of the study medication (tolvaptan or placebo) were included in the safety analysis. MedDRA denotes the *Medical Dictionary for Regulatory Activities*.
† Serious adverse events in this group included dehydration with hypotension (1 patient) and increased serum creatinine concentrations.
‡ Serious adverse events in this group included acute renal failure (2 patients), rash (2 patients), cardiac failure (twice in 1 patient), and vomiting.
§ Serious adverse events in this group included dehydration with dizziness (1 patient), syncope, acute renal failure, ascites, increased serum sodium concentrations, *Escherichia coli* sepsis, and respiratory failure (1 patient).
¶ Serious adverse events in this group included hepatic encephalopathy, acute dyspnea and edema (1 patient), worsening anemia, increased serum creatinine concentrations with lower hemoglobin and hematocrit values, and dyspepsia (1 patient).
‖ Serious adverse events in this group included rash (2 patients) and nocturia.
** Serious adverse events in this group included rash (2 patients), acute renal failure (2 patients), dysgeusia, decreased serum sodium concentrations, vomiting, and aggravated hyponatremia.
†† Serious adverse events in this group included urinary frequency, exanthema, muscle weakness, and hypernatremia.
‡‡ The serious adverse event in this group was increased serum creatinine concentration.
§§ Common adverse events are defined as events occurring in more than 5% of patients.

Schrier RW et al. N Engl J Med 2006;355:2099-2112.

The NEW ENGLAND JOURNAL of MEDICINE

LIMITATION IN THE USE OF VAPTANS

- Too slow to be used in patients with severe central neuron system symptoms
  - Dependence on free water excretion
- No use in patients with hypovolemic hyponatremia
  - Possible hypotension
- Adverse events
  - Urinary frequency
  - Thirst
  - Mouth dryness
  - Constipation
- Severe adverse events
  - Acute liver injury -> Not to be use in patients with liver injury
- FDA recommends limiting use to 30 days

Recommendations for the Use of Vaptans in the Treatment of Hyponatremia.

Table 3. Recommendations for the Use of Vaptans in the Treatment of Hyponatremia.

Hyponatremia Classification	Expert Panel Recommendation*	European Clinical Practice Guideline†
Hypovolemic hyponatremia	Vaptan is not a treatment option.	Vaptan is not a treatment option.
Euvolemic hyponatremia		
Asymptomatic	Vaptan is a treatment option.	Vaptan is not a treatment option.
Moderate-to-severe central nervous system symptoms	Vaptan is not a treatment option.	Vaptan is not a treatment option.
Hypervolemic hyponatremia		
Asymptomatic	Vaptan is a treatment option, except in patients with liver disease.	Vaptan is not a treatment option.
Moderate-to-severe central nervous system symptoms	Vaptan is not a treatment option.	Vaptan is not a treatment option.

* Data are adapted from Verbalis et al.[53]

† Data are adapted from Spasovski et al.[32] These guidelines were developed by members of three medical societies: the European Society of Intensive Care Medicine, the European Society of Endocrinology, and the European Renal Association–European Dialysis and Transplant Association.

Berl T. N Engl J Med 2015;372:2207-2216.

The NEW ENGLAND JOURNAL of MEDICINE

CASE PRESENTATION

70-year-old woman admitted to ER after suffering a fall.

- Cognitive and motor impairment with gradual deterioration of neurologic status since about 2 weeks prior to fall.
- Medical history:
  - Breast cancer – 60 yrs
  - HTN, dyslipidemia
  - Depression
- Medications:
  - Clonidine (transdermal) 5 mg/week
  - Atorvastatin 20 mg qd
  - Clopidrogel 75 mg qd
  - Paroxetine 20 mg qd

Case adapted from:
Endocrine (2017) 55: 311-319

Case Presentation

- Physical examination
  - BP 135/86, HR 75 bpm, Temp: 37.1 ^{0}C
  - Clear to auscultation
  - Euvolemic
  - No severe neurologic deficits
- Laboratory workup:
  - Na 124 mmol/L
  - CXR normal, ECG normal, 2 D echo – normal, Head CT Scan – subcortical arteriosclerotic encephalopathy.
  - TSH and cortisol wnl
  - Urine sodium 63 mmol/L, serum osmolality 271 mOsm/kg, urine osmolality 301 mOsm/kg.

Case adapted from:
Endocrine (2017) 55: 311-319

Case presentation

- Initial management
  - Discontinuation of paroxetine
  - Increase in sodium in 48 hrs to 126 mmol/L
  - No clinical improvement in neurological function
  - Therapy with Tolvaptan 15 mg daily started
    - Na increase to 139 mmol/L in 4 days.
    - Discontinuation of tolvaptan
      - Psychiatry consultation for change of antidepressant Tx. - > Bupropion.

Case adapted from:
Endocrine (2017) 55: 311-319

Conclusions

- Hyponatremia is a common electrolyte derangement in hospitalized patients
- This condition may cause significant morbidity and mortality
- Adequate management requires a careful history, examination and selection of studies for identification of cause(s).
- Determination of chronicity and neurologic status of patient are of utmost importance for determination of therapy
- Available options for therapy include:
  - Fluid restriction
  - 3% SS
  - Vaptans

THANKS FOR YOUR ATTENTION!!