Introduction of Case Study & The Pharmacist’s Role in Hyponatremia Management

The Pathophysiology of Hyponatremia

Hyponatremia: Signs, Symptoms, and Clinical Burden

A Practical Approach to Hyponatremia Management: Conventional & Novel Therapies

Discussion and Q&A
Case Study
**Hyponatremia in SIADH**

- An 80-year-old woman was referred to the clinic for management of chronic hyponatremia
- Patient’s daughter explained that her mother’s symptoms had been getting increasingly worse, including
  - Weakness and feeling “shaky”
  - Unsteady gait and falls
  - Memory problems
- Poor response to fluid restriction and loop diuretics

Case Study
**History**

- Chronic systolic heart failure
- DVT
- HTN
- Anemia
- Severe pulmonary HTN
- GERD
- COPD
- Insomnia
- Anxiety
- Social history
  - Widow
  - No alcohol, cigarette, drug use
  - Lives at home with daughter
- No known drug allergies
- Family history
  - Both patients had CAD
  - Mother died from breast cancer in her 80s

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis, GERD, gastroesophageal reflux disease; HTN, hypertension.
Case Study

Current Medications

- Carvediol 25 mg bid
- Warfarin 5 mg qd
- Olmesartan 20 mg qd
- Rabeprazole 20 mg qd
- Tiotropium 18 µg inhaled qd
- Fluoxetine 10 mg qd
- Furosemide 20 mg qd

Case Study

Physical Exam

- Pleasant, alert, and oriented
- BP 122/68 mm Hg, HR 72 bpm, RR 18, temp: 97.4 °F
- HEENT: moist mucous membranes, EOMI
- Neck: supple, no JVD, no bruits
- Chest: good air entry, clear to auscultation, no rales
- Heart: S1, S2, RRR, no rub
- Abdomen: soft, nontender, normal bowel sounds
- Extremities: no edema
- Musculoskeletal: muscle strength 5/5 all extremities, sensory intact to light touch, DTRs equal in biceps and patella bilaterally

DTR, deep tendon reflex; EOMI, extraocular movements intact; HEENT, heart, eyes, ears, nose, and throat; HR, heart rate; JVD, jugular venous distension; RR, respiratory rate; RRR, regular rate and rhythm.
Case Study

Laboratory Results

<table>
<thead>
<tr>
<th></th>
<th>2 wk prior to exam</th>
<th>Day of exam</th>
<th>6 d after exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum [Na⁺]:</td>
<td>121 mEq/L</td>
<td>Serum [Na⁺]:</td>
<td>Serum [Na⁺]:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>128 mEq/L</td>
<td>121 mEq/L</td>
</tr>
<tr>
<td>Creatinine:</td>
<td></td>
<td>Creatinine:</td>
<td>Urine osmolality:</td>
</tr>
<tr>
<td>1.1 mg/dL</td>
<td></td>
<td>1.1 mg/dL</td>
<td>254 mOsm/kg</td>
</tr>
<tr>
<td>Serum [K⁺]:</td>
<td>4.6 mEq/L</td>
<td>Glucose:</td>
<td>Serum osmolality:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78 mg/dL</td>
<td>259 mOsm/kg</td>
</tr>
<tr>
<td>Serum [Ca⁺]:</td>
<td>9.4 mEq/L</td>
<td>Albumin:</td>
<td>Serum osmolality:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 g/dL</td>
<td>259 mOsm/kg</td>
</tr>
<tr>
<td>Uric acid:</td>
<td>3.6 mg/dL</td>
<td>Liver function tests:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>WNL</td>
<td>WNL</td>
</tr>
<tr>
<td>BUN:</td>
<td>22 mg/dL</td>
<td>NT-proBNP:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>350 pg/mL</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP:</td>
<td>350 pg/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen; [Na⁺], serum sodium concentration; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; WNL, within normal limits.

Many Roles of the Pharmacist

- Monitor for hyponatremia development + resolution
- Consider a more pathophysiologic approach to diagnosis and treatment
- Consider drug-related causes of hyponatremia
- Participate in clinical decision making
- Ensure optimal management of hyponatremia
- Participate in formulary decision making and address cost-containment concerns beyond acquisition costs
- Educate clinicians on hyponatremia
- Develop preventative hospital systems directed toward hyponatremia
- Ensure appropriate monitoring for morbidities of hyponatremia
Hyponatremia: Incidence

- Common definition: serum sodium concentration ([Na⁺] ≤135 mEq/L, but cut-off values vary
- Typically occurs due to excess body water diluting serum sodium as a result of excess vasopressin / AVP / ADH
- Most common electrolyte disorder seen in clinical practice
  - Occurs in up to 3.2 to 6.1 million persons annually
  - Up to 15% of hospitalized patients, 24.5% of ICU patients
  - ≈ 1 million annual hospitalizations with 1° or 2° discharge diagnosis of hyponatremia
  - Incidence increases with age

AVP, arginine vasopressin; ADH, antidiuretic hormone; ICU, intensive care unit.
Hyponatremia: Underreported, Often Mismanaged

- Clinical lab values vs ICD-9 codes 1999–2000
- 2632 cases of hyponatremia identified using lab data alone
- 66% did not have appropriate ICD-9 code
  - 94% of moderately hyponatremic patients
  - 87% of severely hyponatremic patients
- Review of 104 patients with serum [Na+] <125 mEq/L from 6-mo lab/chart data in large teaching hospital
  - 49% of diagnoses inconsistent with clinical details
  - 33% had “significant” management errors

Classification of Hyponatremia

- Dilutional Hyponatremia
  - Total body water INCREASED
  - The most common type
- Depletional Hyponatremia
  - Total body water DECREASED

Hypervolemic
  - (edema)
  - Total body sodium INCREASED
  - Heart failure
  - Cirrhosis
  - Nephrotic syndrome
  - Renal failure

Euvolemic
  - (no edema)
  - Total body sodium UNCHANGED
  - SIADH
  - Hypothyroidism
  - Secondary adrenal insufficiency

Hypovolemic
  - Total body sodium DECREASED
  - Diarrhea
  - Pancreatitis
  - Vomiting
  - Diuretic use
  - Burns
  - Renal salt wasting
  - Trauma
  - Primary adrenal insufficiency

SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Etiologies of Hypo-osmolar Hyponatremia

Most often a complication of other illnesses in which excess water accumulates in the body at a higher rate than can be excreted

<table>
<thead>
<tr>
<th>Hypervolemia</th>
<th>Euvolemia</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>SIADH</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Tumors</td>
<td>Cerebral salt wasting</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>CNS disorders</td>
<td>Mineralocorticoid deficiency</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Drug-induced</td>
<td>Salt-wasting nephropathy</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Pulmonary diseases</td>
<td>Bicarbonaturia, glucosuria, ketonuria</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Other</td>
<td>Gastrointestinal losses</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Glucocorticoid deficiency</td>
<td>Third space losses</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Sweat losses</td>
</tr>
<tr>
<td></td>
<td>Primary polydipsia</td>
<td></td>
</tr>
</tbody>
</table>

CNS, central nervous system.


Receptor-Mediated Effects of Arginine Vasopressin (AVP)

- Plasma osmolality (Posm) is regulated by thirst and release of AVP
- Also known as antidiuretic hormone (ADH)

<table>
<thead>
<tr>
<th>Receptor subtype</th>
<th>Site(s) of action</th>
<th>Activation effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>V₁a</td>
<td>Vascular smooth muscle cells¹</td>
<td>Vasoconstriction, myocardial stimulation¹</td>
</tr>
<tr>
<td></td>
<td>Platelets¹</td>
<td>Platelet aggregation¹</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes and monocytes¹</td>
<td>Cytokine release²</td>
</tr>
<tr>
<td></td>
<td>Liver¹</td>
<td>Glycogenolysis¹</td>
</tr>
<tr>
<td>V₁b</td>
<td>Anterior pituitary¹</td>
<td>Release of ACTH¹ and β-endorphin³</td>
</tr>
<tr>
<td>V₂</td>
<td>Renal collecting duct¹</td>
<td>Renal free water absorption¹</td>
</tr>
</tbody>
</table>


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Pathophysiology of Hyponatremia

- Increased AVP concentrations increase activity of V_2 receptors in renal collecting ducts.
- This activates synthesis of adenylyl cyclase, cAMP, and PKA, enhancing expression of AQP_2 channels.
- AQP_2 channels transport water molecules from collecting duct back into circulation, resulting in decreased Posm and reduced urine volume.
- Na^+ excretion continues, resulting in hyponatremia.

Dysregulation of Normal AVP Response Complicates Many Disease States

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Prevalence of Hyponatremia in Hospitalized Patients</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure (HF)</td>
<td>~20%</td>
<td>Neurohormonal activation</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>35%</td>
<td>Neurohormonal activation</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>10%–28%</td>
<td>SIADH ± reset osmostat</td>
</tr>
<tr>
<td>AIDS</td>
<td>38%</td>
<td>SIADH</td>
</tr>
<tr>
<td>Neurologic injury (TBI, SAH, infection, intracerebral hemorrhage, massive cerebral infarction, others)</td>
<td>2.3%–36.6%</td>
<td>SIADH, idiopathic</td>
</tr>
</tbody>
</table>

During extreme exercise (marathons + triathlons), up to 25% of athletes develop hyponatremia.  

SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

2. Goldsmith SR. Am J Cardiol. 2005;95(suppl):148-21B.  
Hyponatremia: Risk Factors

### Miscellaneous conditions
- Adrenal insufficiency
- Cirrhosis
- CNS impairment
- Heart failure
- Low body weight
- SIADH
- Surgery or injury
- Very old age
- Very young age

### Drugs
- Antidepressants (TCAs, SSRIs, MAOIs)
- Antiepileptics
- Antihypertensives
- Antipsychotics
- Anticancer agents
- Diuretics
- NSAIDS
- Opiate derivatives
- Proton-pump inhibitors

CNS, central nervous system; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors.


Mechanisms of Drug-Induced Hyponatremia

↑ Hypothalamic production of AVP

↑ Effect of AVP at renal tubule level

Altered Na / H₂O homeostasis

- Antidepressants
- Antipsychotics
- Antiepileptics
- Antineoplastic agents
- Opiates

- Antidiabetic drugs
- Antiepileptics
- Antineoplastic agents
- NSAIDs

- Thiazide diuretics/indapamide
- Amiloride
- Loop diuretics

SSRI-Induced Hyponatremia

- 0.5%–32% incidence
- Most cases during first few weeks of therapy
  - Normal serum [Na+] usually achieved within 2 weeks following discontinuation of drug
- Risk factors
  - Older age
  - Concomitant diuretic therapy
  - Low body weight
  - Baseline serum [Na+] <138 mEq/L


Hyponatremia: Signs, Symptoms, and Clinical Burden

Learning Objective
- Identify the signs, symptoms, and clinical consequences of hyponatremia

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Consequences of Hyponatremia

Hyponatremia:

- Cerebral edema
- Seizures, coma
- Increased mortality risk
- Osteoporosis and fractures
- Gait disturbances and falls
- Neurologic dysfunction and decreased mental function
- Increased rate of ICU admission
- Increased hospital LOS
- Increased mortality risk
- Increased hospital LOS

Hyponatremia & Neurologic Dysfunction

SF-12* Mental Component Summary (MCS)

*The SF-12 is a subset of the SF-36 Health Survey and has been shown to reproduce at least 90% of the variance in PCS-36 and MCS-36 in both general and patient populations. Advisory Committee Meeting of the Cardiovascular and Renal Drugs Division of the US Food and Drug Administration. June 25, 2008. Available at: www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4373b1-05.pdf. Accessed March 15, 2013.
Correction of Hyponatremia Improves Mental Function

**Mean change in MCS score from baseline**
- Statistically greater mean improvement observed with tolvaptan than with placebo
- Clinically meaningful improvement in mental function

<table>
<thead>
<tr>
<th>Group</th>
<th>Total MCS</th>
<th>Cirrhosis MCS</th>
<th>CHF MCS</th>
<th>SIADH MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolvaptan</td>
<td>5.3</td>
<td>4.7</td>
<td>5.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.6</td>
<td>0.2</td>
<td>1.9</td>
<td>2.4</td>
</tr>
</tbody>
</table>


Hyponatremia, Gait Instability, & Falls

- Case-control study of 122 patients with asymptomatic chronic hyponatremia ([Na+] 126 ± 5 mEq/L), 244 matched controls
- Hyponatremic patients more often admitted for falls than controls (21.3% vs 5.3%; \( P < .001 \))
  - Frequency of falls the same—regardless of level of hyponatremia
- Gait instability significantly increased in patients with chronic hyponatremia
- Attention errors increased 1.2-fold (\( P = .001 \)) in hyponatremic patients compared with normal controls
  - Comparable to increase observed after moderate alcohol intake in healthy volunteers

Correction of Hyponatremia Stabilizes Gait

Gait stability assessed in 16 hyponatremic patients ([Na⁺] 124-130 mEq/L)
- Patients asked to walk on pressure mat
- Skew from midline of path measured as length of walk

Gait instability significantly increased in hyponatremia
- Correction of hyponatremia
- Gait stability normalized


Hyponatremia & Fractures in Ambulatory Falls

- Case-control study of bone fractures after incidental fall
  - Patients presenting with falls and fractures had significantly higher incidence of hyponatremia (13.1%) than age-matched controls (3.9%)
  - Hyponatremia drug-induced in 53% (36% diuretics, 17% SSRI),
  - Hyponatremia due to SIADH in 37%
- Hyponatremia significantly associated with fracture (P=.01)
  - Independent of age and gender
- Even mild chronic hyponatremia increases fracture risk

Bone quality should be assessed in all patients with chronic hyponatremia


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Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Hyponatremia is an Independent Risk Factor for In-Hospital Mortality

- 1-y study of 4123 patients (≥65 y) admitted to community hospital; 3.5% had admission serum [Na+] <130 mEq/L
  - Mortality increased as serum [Na+] decreased
  - Admission hyponatremia significant predictor of in-hospital mortality (RR, 1.95; P<.006)
- Even mild hyponatremia is associated with increased in-hospital mortality
- Mild hyponatremia also associated with increased mortality in an ambulatory setting

Impact of Hyponatremia on Selected Hospital Outcomes

- 558,815 hyponatremic (HN) patients selected from Premier Hospital Database from 1/1/07 to 3/31/10, matched to 558,815 non-HN control cohort using propensity score matching
- Differences in healthcare resource utilization, costs, and hospital readmissions between cohorts calculated using bivariate and multivariate statistics

<table>
<thead>
<tr>
<th></th>
<th>HN Cohort</th>
<th>Non-HN Cohort</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS, d</td>
<td>8.8 ± 10.3</td>
<td>7.7 ± 8.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hospital Admission Costs</td>
<td>$15,281 ± $24,054</td>
<td>$13,439 ± $22,198</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ICU LOS, d</td>
<td>5.5 ± 7.9</td>
<td>4.9 ± 7.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ICU Costs</td>
<td>$8525 ± $13,342</td>
<td>$7597 ± $12,695</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Increased Chance of Hospital Readmission 30 d Postdischarge</td>
<td>15%</td>
<td></td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>


RR, relative risk.
Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Symptoms Correlate with Severity & Rate of Decline in Serum [Na+]¹

- Asymptomatic presentation is common²
- May present with mild, nonspecific symptoms¹
- Degree of symptomatology is surrogate for duration of hyponatremia¹
- Symptoms from underlying disease process is also common¹

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Increasing severity of hyponatremia and rate of [Na+] decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory arrest</td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
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<tr>
<td>Delirium</td>
<td></td>
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<tr>
<td>Restlessness</td>
<td></td>
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<tr>
<td>Lethargy</td>
<td></td>
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<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td>Nausea + vomiting</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
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</tbody>
</table>


Acute Versus Chronic Hyponatremia

- Life-threatening: usually ACUTE
- Symptomatic but less impaired: usually CHRONIC

<table>
<thead>
<tr>
<th>Acute (≤48 h)</th>
<th>Chronic (&gt;48 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms include:</td>
<td>Symptoms include:</td>
</tr>
<tr>
<td>• Cerebral edema</td>
<td>• Nausea/vomiting</td>
</tr>
<tr>
<td>• Seizures</td>
<td>• Confusion or personality changes</td>
</tr>
<tr>
<td>• Increased mortality risk</td>
<td>• Neurologic dysfunction</td>
</tr>
<tr>
<td>Rapid correction reverses cerebral edema without sequelae</td>
<td>Rapid correction may cause brain dehydration and osmotic demyelination syndrome (ODS)</td>
</tr>
</tbody>
</table>
Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

A Practical Approach to Hyponatremia Management: Conventional and Novel Therapies

Learning Objective
- Describe appropriate pharmacologic strategies for managing hyponatremia

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Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Treatment Overview

- Most important treatment factors
  - Severity of neurologic symptoms\(^1,2\)
  - Volume status\(^1,2\)
  - Acute vs chronic\(^2,3\)
  - Identify likely cause of hyponatremia\(^1\)

- Principles to guide treatment
  - Weigh risks and benefits\(^4\)
    - Neurologic consequences can follow both failure to promptly treat and excessively rapid rate of correction\(^3\)
    - Even modest improvement in serum \([\text{Na}^+]\) have survival benefits\(^5\)
  - Monitor serum \([\text{Na}^+]\) frequently\(^2,6\)
  - Address underlying disease and stop offending medications\(^1\)


Correct Serum \([\text{Na}^+]\) to Safe Level at Safe Rate

- Insufficient correction\(^1\)
- Too aggressive correction\(^1\)

  - Cerebral edema
  - ODS

- Raise \([\text{Na}^+]\) by <8–12 mEq/L in 1st 24 h\(^1,3\)
- Raise \([\text{Na}^+]\) by <18 mEq/L in 1st 48 h\(^1\)
- Symptomatic: 1 mEq/L/h until neurologic symptoms resolve or \([\text{Na}^+]\) ≥120 mEq/L or a total magnitude correction of 18 mEq/L is achieved\(^1,2\)

Risks of Hyponatremia & Correction: A Balancing Act

**Acute hyponatremia**
- Marked brain edema
- Minimal brain volume regulation

**Chronic symptomatic hyponatremia**
- Some brain edema
- Partial brain volume regulation

**Chronic asymptomatic hyponatremia**
- Minimal brain edema
- Complete brain volume regulation

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**Correcting Hyponatremia**

1. Add to the numerator

\[ \text{Serum } [\text{Na}^+] = \frac{\text{Na}^+_E + \text{K}^+_E}{\text{Body water}} \]

2. Subtract from the denominator

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*Na*°, exchangeable sodium; *K*°, exchangeable potassium.


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Case Study Review

80-year-old woman with multiple medical problems including HF, HTN, GERD, COPD

- She has chronic hyponatremia (current $\text{Na}^+ 121 \text{ mEq/L}$) and symptoms consistent with this diagnosis
- She has had a poor response to fluid restriction and a loop diuretic (furosemide)
- No evidence of fluid overload at this time

Etiology

What is the most likely etiology of this patient’s hyponatremia?

A. Heart failure
B. Drug-induced (SSRI)
C. Pulmonary disease
D. Drug-induced (diuretic)
Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Case Study
Next Steps

What are the treatment considerations?

What are the treatment options?

A. Hypertonic saline infusion
B. Addition of NaCl tablets
C. AVP receptor antagonist
D. Fluid restriction to <1 L/d

Treatments for Hyponatremia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline infusion</td>
<td>• Rapid response in symptomatic patients¹</td>
<td>• Complex calculations¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not be used in edema-forming disorders²</td>
</tr>
<tr>
<td>Fluid restriction</td>
<td>• Inexpensive³</td>
<td>• Slow and limited response¹,²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adherence concerns¹,³</td>
</tr>
<tr>
<td>Demeclocycline</td>
<td>• No need to limit water intake³</td>
<td>• Slow response¹,²</td>
</tr>
<tr>
<td></td>
<td>• Targets excessive AVP¹</td>
<td>• Nephrotoxic in CHF and cirrhosis¹,²</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>• Allows relaxation of fluid restriction⁴</td>
<td>• May cause volume, K⁺, + Mg⁺ depletion¹</td>
</tr>
<tr>
<td>AVP receptor antagonists</td>
<td>• Target excessive AVP⁴</td>
<td>• Not to be used in hypovolemic states⁵</td>
</tr>
<tr>
<td></td>
<td>• Aquaresis (solute-free urine output)¹,³</td>
<td></td>
</tr>
</tbody>
</table>


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The Role of Hypertonic Saline (HTS)

- Consider HTS (3% NaCl) when
  - Symptomatic hyponatremia (seizure, coma)\(^1\)
  - Acute severe hyponatremia (<24 h, <120 mEq/L)\(^2\)
  - Hyponatremia worsening on normal saline (0.9% NaCl)\(^3\)
  - Induced hypernatremic states for prevention/treatment of cerebral edema\(^4\)
- Discontinue HTS when serum \([\text{Na}^+]\) reaches 125–130 mEq/L\(^3\)
  - Exception: states of cerebral edema with Na\(^+\) augmentation
- Safety concerns: requires ICU monitoring\(^2\)
- Adrogué-Madias formula, used to predict rise in \([\text{Na}^+]\) after HTS, may underestimate correction rate, increasing risk for inadvertent overcorrection\(^1\)
- No randomized trials performed\(^1\)
- HTS may or may not be combined with loop diuretic\(^1\)

Fluid Restriction

- Standard procedure: restrict fluid to \(\leq 1\) L/d\(^1\)
- Slow rate of improvement\(^2\)
- Poor patient adherence\(^2\)
- Predictors of failure\(^3\)
  - High Uosm (>500 mOsm/kg H\(_2\)O)
  - Urine [Na\(^+\)] and [K\(^+\)] > serum [Na\(^+\)]
  - 24-h urine output <1,500 mL/d
  - Increase in serum [Na\(^+\)] <2 mEq/L in 24 h
- Not appropriate for hypovolemic hyponatremia\(^4\)

Uosm, urine osmolality.


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Demeclocycline

- Causes nephrogenic form of diabetes insipidus, decreasing urine concentration even in presence of high plasma AVP levels
- Dose: 600 to 1,200 mg/d in divided doses
  - Takes several days to achieve maximal diuretic effects
  - Wait 3–4 d before deciding to increase dose
- Can cause
  - Reversible azotemia
  - Nephrotoxicity (especially in patients with cirrhosis)
- Monitor renal function on regular basis, discontinue if increasing azotemia


Loop Diuretics

- Increase rate of urine flow, excretion of Na\(^+\) and Cl\(^-\)
- Allow relaxation of fluid restriction\(^2\)
- Can be used in SIADH patients when fluid restriction alone is insufficient, taking care to avoid hypovolemia from diuretic-induced sodium losses\(^3\)
- Can enhance free water excretion and help prevent volume overload in patients being treated with HTS for acute symptomatic hyponatremia\(^4\)
- Potential for volume depletion, K\(^+\) and Mg\(^2+\) depletion, ototoxicity\(^1,5\)

The Vaptans: Overview

<table>
<thead>
<tr>
<th>Agent</th>
<th>Receptor Selectivity/Affinity</th>
<th>Route</th>
<th>Urine Volume</th>
<th>Urine Osmolality</th>
<th>FDA Status</th>
<th>Therapy Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conivaptan</td>
<td>Mixed (V$_{1a}$+V$_2$); V$<em>2$ affinity 10× that of V$</em>{1a}$</td>
<td>IV$^2$</td>
<td>3–8$^1,2$</td>
<td>↑$^3,4$</td>
<td>↓$^3,4$</td>
<td>4 d$^1$</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Selective for V$_2$; V$_2$ affinity 1.8× native AVP; V$<em>2$ affinity 29×  that of V$</em>{1a}$</td>
<td>Oral$^1$</td>
<td>6–12$^1,4$</td>
<td>↑$^3,4$</td>
<td>↓$^3,4$</td>
<td>Approved 2009$^5$</td>
</tr>
<tr>
<td>Lixivaptan</td>
<td>V$_2$</td>
<td>Oral$^1$</td>
<td>7–10$^1$</td>
<td>↑$^3,4$</td>
<td>↓$^3,4$</td>
<td>Additional data requested$^8$</td>
</tr>
</tbody>
</table>


The Vaptans: Mechanism of Action

- Vaptans block effects of AVP in the kidney
- This results in fewer AQP$_2$ channels in the apical membrane
- Fewer water molecules are retained and more water is excreted in urine
- Posm eventually increases and normal plasma [Na$^+$] achieved

Conivaptan Clinical Studies

- Double-blind, placebo-controlled, randomized, multicenter study of 84 patients with euvolemic/hypervolemic hyponatremia (serum [Na⁺] 115 to <130 mEq/L); all received fluid restriction ≤2 L/d
  - Conivaptan administered 20 mg loading dose (over 30 m) with 4-d continuous infusion of either 40 mg/d or 80 mg/d
  - Mean increase in serum [Na⁺] from baseline significantly higher with conivaptan vs placebo at 24, 48, 72 h posttreatment
    - Conivaptan 80 mg: 8.1–8.8 mEq/L
    - Conivaptan 40 mg: 6.4–6.9 mEq/L
    - Placebo: 0.4–1.9 mEq/L


Conivaptan Clinical Studies (continued)

- Mean free water clearance from baseline to treatment Days 1 + 2 significantly higher with conivaptan 40 + 80 mg/d than placebo (P<.001, P=.03)
- Most common AEs: hypotension, postural hypotension, infusion site inflammation, pyrexia, hyperkalemia (no ODS)
- In an open-label extension trial, mean serum [Na⁺] was maintained over time

AE, adverse event.
Tolvaptan Clinical Studies (SALT-1, SALT-2, SALTMED)

- 2 double-blind, randomized, multicenter studies of 448 patients with euvoletic or hypervolemic hyponatremia (serum $[\text{Na}^+] < 135$ mEq/L) treated with placebo or tolvaptan, 15 mg/d
- For first 4 d, dose could be increased from 15–30 mg or from 30–60 mg
- If serum $[\text{Na}^+]$ rose above 145 mEq/L or increased too fast (>12 mEq/L in 24 h or >8 mEq/L in 8 h on Day 1), the next dose was withheld or decreased, or fluid intake was increased
- Serum $[\text{Na}^+]$ increased more in tolvaptan group than in placebo group during first 4 d ($P<0.001$) and after full 30 d of therapy ($P<0.001$)

<table>
<thead>
<tr>
<th></th>
<th>SALT-1</th>
<th></th>
<th>SALT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tolvaptan</td>
<td>Placebo</td>
<td>Tolvaptan</td>
</tr>
<tr>
<td>Baseline</td>
<td>128.5 ± 4.5</td>
<td>128.7 ± 4.1</td>
<td>129.0 ± 3.5</td>
</tr>
<tr>
<td>Day 4</td>
<td>133.9 ± 4.8</td>
<td>129.7 ± 4.9</td>
<td>135.3 ± 3.6</td>
</tr>
<tr>
<td>Day 30</td>
<td>135.7 ± 5.0</td>
<td>131.0 ± 6.2</td>
<td>135.9 ± 5.9</td>
</tr>
</tbody>
</table>


Tolvaptan Clinical Studies (SALT-1, SALT-2, SALTMED continued)

- Increase in serum $[\text{Na}^+]$ in tolvaptan group sustained 30 d
- Most common AEs: thirst, dry mouth, polyuria (no ODS)
- In an open-label study, increases in serum $[\text{Na}^+]$ were significant and maintained over the long term (mean follow up 701 d)


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SIADH Cost Analysis

- **Cost estimate methods**
  - HCUP 2009 Nationwide Inpatient Sample database
  - 21,718 patients hospitalized for SIADH: mean LOS 5.7 d, mean hospital cost $8667
  - Used tolvaptan treatment duration of 4 d at $250/dose
  - LOS reduction estimate based upon SALT-1 and SALT-2 trials
    - SIADH patients receiving tolvaptan had shorter hospital LOS (4.98 vs 6.19 d)

- **Results**
  - Cost offset model estimated LOS reduction of 1.11 d and total cost offset of $694 per admission
  - 95% CI for cost offset using Monte Carlo simulation was $73–$1405
  - Cost-neutral break-even mean duration of tolvaptan inpatient use: 6.78 d
  - Use of tolvaptan to treat these 21,718 patients identified in the HCUP population would result in total cost offset >$15 million

CI, confidence interval.  

Bioavailability of Tolvaptan Administered via NG Tube

- Tolvaptan 15 mg crushed and administered via NG tube vs oral tablet swallowed intact (each with 240 mL H₂O)
- Randomized crossover study in 28 healthy fasted adults

<table>
<thead>
<tr>
<th>Relative Bioavailability</th>
<th>Est. Ratio of Geometric Means With NG vs Oral Administration, %</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>88.9</td>
<td>80.1–98.6</td>
</tr>
<tr>
<td>AUC_{t} (ng * h/mL)</td>
<td>74.3</td>
<td>68.1–81.0</td>
</tr>
<tr>
<td>AUC_{∞} (ng * h/mL)</td>
<td>74.2</td>
<td>68.1–80.9</td>
</tr>
</tbody>
</table>

- Administration with NG tube compared with oral intact tablet
  - C_{max} ≈ 10% lower and AUC_{t} and AUC_{∞} ≈ 25% lower
  - No evidence of different aquaretics
  - 24-h urine output 2.8% lower with NG tube

AUC, area under the curve; C_{max}, maximum concentration; NG, nasogastric 
Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

The Vaptans: Contraindications & Precautions

Conivaptan/tolvaptan\(^1,2\)
- Do not use with potent CYP3A and P-glycoprotein inhibitors, or in hypovolemic or anuric patients
- Use with caution in patients with hepatic or renal impairment
- Monitor serum [Na\(^+\)] and neurologic status

Conivaptan\(^1\)
- Do not use in patients with known allergy to corn or corn products
- May cause significant infusion site reactions

Tolvaptan\(^2\)
- Do not use in patients unable to respond appropriately to thirst
- Liver injury noted in study of ADPKD patients (incidence of ALT >3x ULN in 4.4% [42/958] of tolvaptan patients vs 1.0% [5/484] of placebo patients)
- Therefore, limit treatment to 30 d, discontinue treatment if hepatic injury suspected, avoid use in patients with underlying liver disease

ADPKD, autosomal dominant polycystic kidney disease; ULN, upper limit of normal.


The Vaptans: Drug–Drug Interactions

Conivaptan\(^1\)
- Substrate/inhibitor of CYP3A
- Concomitant use of conivaptan and potent CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, or indinavir) is contraindicated
- Generally avoid CYP3A substrates
- Exposure to coadministered digoxin may be increased and digoxin levels should be monitored

Tolvaptan\(^2\)
- Substrate of CYP3A
- Concomitant use of tolvaptan and potent CYP3A inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, or indinavir) is contraindicated
- Avoid use with CYP3A inducers and moderate CYP3A inhibitors
- Does not significantly change pharmacokinetics of other CYP3A substrates
- Coadministration with digoxin results in 1.3-fold increase in digoxin Cmax
- Coadministration with P-gp inhibitors may require dose reduction of tolvaptan


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Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Monitoring Patients on Conivaptan

- Only for use in hospitalized patients
- Administer through large veins, change infusion site every 24 h to minimize risk of vascular irritation
- Monitor serum [Na⁺] and neurologic status appropriately, as serious neurologic sequelae can result from overly rapid correction (>12 mEq/L in 24 h)
- Discontinue conivaptan if patient develops undesirably rapid rate of rise of serum [Na⁺], and carefully monitor serum [Na⁺] and neurologic status
  - If serum [Na⁺] continues to rise, do not resume treatment
  - If hyponatremia persists or recurs, and patient has had no evidence of neurologic sequelae of rapid rise in serum [Na⁺], conivaptan may be resumed at reduced dose


Monitoring Patients on Tolvaptan

- Medication MUST be started and re-started in the hospital
- Obtain serum [Na⁺] every 4-6 h for 48 h
  - In clinical trials, no patients had evidence of ODS
  - In postmarketing surveillance, cases of ODS have been identified in which HTS was administered concomitantly or in close approximation to tolvaptan
- As many as 35% of patients (especially those with highest Uosm) may need concomitant water restriction to see rise in serum [Na⁺]
- After 48 h, vast majority reach steady state and can be safely discharged with outpatient monitoring
  - Check serum [Na⁺] once a week for the first month
  - Outpatient administration should be limited to ≤30 d per label.
  - If administration is continued, [Na⁺] should be monitored monthly if stable, and patient should be closely monitored for any signs of liver impairment

2. Faculty recommendations.

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Case Study

Treatment Course

- Patient admitted
- Fluid restriction discontinued
- Tolvaptan therapy initiated at 15 mg/d
- Uptitrated to tolvaptan 30 mg/d after 24 h

Case Study

Response to Therapy

- Urine volume increased, urine osmolality decreased, and serum $[\text{Na}^+]$ increased by 4.5 mEq/L/d over first 48 h

- Patient discharged after 3 d with $[\text{Na}^+]$ 136 mEq/L

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Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Treatment Algorithm

Euvolemic hyponatremia

- Fluid restriction; vaptan under select circumstances:
  - Inability to tolerate fluid restriction or failure of fluid restriction
  - Prevention of worsened hyponatremia with increased fluid administration
  - Unstable gait and/or high fracture risk
  - Serum [Na⁺] <125 mEq/L
  - To correct serum [Na⁺] to safer levels for surgery/procedures or ICU/hospital discharge
  - Therapeutic trial for symptom relief

Hypovolemic hyponatremia

- Vaptan ± fluid restriction

Hypervolemic hyponatremia

- Saline or HTS ± fludrocortisone

Level 1: No or minimal symptoms

- Fluid restriction; vaptan under select circumstances:
  - Inability to tolerate fluid restriction or failure of fluid restriction
  - Prevention of worsened hyponatremia with increased fluid administration
  - Unstable gait and/or high fracture risk
  - Serum [Na⁺] <125 mEq/L
  - To correct serum [Na⁺] to safer levels for surgery/procedures or ICU/hospital discharge
  - Therapeutic trial for symptom relief

Level 2: Moderate symptoms

- Vaptan ± fluid restriction

Level 3: Severe symptoms

- HTS followed by fluid restriction ± vaptan

Top 10 Take-Aways

1. Role of AVP in pathophysiology of SIADH and hypervolemia
2. Hyponatremia has real impacts on costs and outcomes
3. Chronic consequences of hyponatremia
4. When hyponatremia is present, consider drug-related causes
5. Be vigilant for cognitive dysfunction at any level of hyponatremia
6. Treatment algorithm
7. Vaptans are necessary "tool" in the treatment algorithm
8. Rate of serum [Na⁺] correction important
9. Monitor, monitor, monitor during [Na⁺] correction for safety
10. Know vaptan AEs, drug interactions

Role of AVP in Edematous Disorders

- **CHF**
  - Decreased cardiac output

- **Cirrhosis**
  - Decreased peripheral resistance due to splanchnic vasodilation

  - Arterial underfilling
  - Stimulation of arterial baroreceptors
  - Nonosmotic release of AVP
  - Impaired H₂O excretion
  - Hypervolemic hyponatremia

Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Classification Algorithm

- [Na+] < 135 mEq/L
  - Assess serum osmolality
    - > 295 mOsm/kg
      - Hyperosmolar
        - Hyperglycemia
        - Mannitol
    - 275-295 mOsm/kg
      - Normo-osmolar
        - Pseudohyponatremia
          - Na-free irrigant solutions
    - < 275 mOsm/kg
      - Hypo-osmolar
      - Assess urine osmolality
        - ≥ 100 mOsm/L
          - (inappropriately concentrated)
          - Impaired water excretion
          - Excessive water intake
        - < 100 mOsm/L
          - (maximally dilute)
          - Polydipsia
        - Assess volume status
          - Hypervolemia
            - Increased ECF volume
          - Euvolemia
            - Normal ECF volume
          - Hypovolemia
            - Reduced ECF volume

ECF, extracellular fluid.


SIADH: Pathophysiology

- Caused by excessive levels of AVP as a result of disease, drug-induced pituitary release of AVP, or ectopic production of AVP
- AVP secretion not suppressed appropriately when Posm falls below the osmotic threshold
- The inability to suppress AVP secretion results in
  - Impaired renal water excretion
  - Increased total body water
  - Hyponatremia
- “Dilute serum, nondilute urine”


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Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Essential Criteria for Diagnosis of SIADH

- ↓ Effective osmolality of the ECF ($P_{\text{osm}} < 275 \text{ mOsm/kg H}_2\text{O}$)
- Inappropriate urinary concentration ($U_{\text{osm}} > 100 \text{ mOsm/kg H}_2\text{O}$) with normal renal function at some level of hypo-osmolality
- Clinical euvolemia (no signs of hypovolemia or hypervolemia)
- Elevated urinary Na excretion despite normal salt and H$_2$O intake
- No other potential causes of euvoletic hypo-osmolality

$P_{\text{osm}}$, plasma osmolality; $U_{\text{osm}}$, urinary osmolality.


Most Common Diagnoses in Hospitalized Patients With Hyponatremia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Hyponatremia Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia, organism unspecified</td>
<td>6.0%</td>
</tr>
<tr>
<td>Septicemia</td>
<td>5.5%</td>
</tr>
<tr>
<td>Disorders of fluid, electrolyte, and acid–base balance (including hyponatremia)</td>
<td>5.3%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5.3%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.0%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3.9%</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Costs of Hyponatremia

- Direct costs estimated at $1.6 to $3.6 billion annually\(^1\)
  - Hospitalization costs account for \(\approx 70\%\) of total cost of illness
- Associated with worse clinical and economic outcomes\(^2\)
- Patients with hyponatremia have
  - 10\% to 32\% increased risk of requiring ICU stay\(^2,3\)
  - Adjusted mean LOS of 3.06 d longer\(^4\)
  - Adjusted OR of 1.64 for requiring discharge to short- or long-term care facility\(^5\)
- 41.2\% higher cost at 6 mo; 45.7\% higher at 1 y\(^6\)


Costs of Admission Hyponatremia

(adjusted for clinical & demographic variables)

<table>
<thead>
<tr>
<th>Level</th>
<th>ICU Admission</th>
<th>Total Costs</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (135–145 mEq/L)</td>
<td>22% ICU admission</td>
<td>$17,085</td>
<td>6-d</td>
</tr>
<tr>
<td>Mild-Moderate (130–134 mEq/L)</td>
<td>26% ICU admission</td>
<td>$18,054</td>
<td>8-d</td>
</tr>
<tr>
<td>Moderate-Severe (≤129 mEq/L)</td>
<td>32% ICU admission</td>
<td>$19,519</td>
<td>8-d</td>
</tr>
</tbody>
</table>

Difference = $2434
Difference = $969


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Hyponatremia: Obstacles and Opportunities for Clinical Pharmacists

Hyponatremia Associated with Increased Mortality in Patients in the ICU

- Retrospective study in 77 medical, surgical, and mixed ICUs in Austria
- 151,486 adults admitted consecutively over 10 y (1998–2007)
  - Borderline (130 ≤ [Na⁺] < 135 mEq/L) hyponatremia: 13.8%
  - Mild hyponatremia (125 ≤ [Na⁺] < 130 mEq/L): 2.7%
  - Severe hyponatremia ([Na⁺] < 125 mEq/L): 1.2%
- Independent mortality risk with increasing severity of hyponatremia
  - Borderline: OR, 1.32 (95% CI, 1.25–1.39)
  - Mild: OR, 1.89 (95% CI, 1.71–2.09)
  - Severe: OR, 1.81 (95% CI, 1.56–2.10)


Change in Serum [Na⁺] & Mortality

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR for Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In-hospital</td>
</tr>
<tr>
<td>Normonatremia (n=42176)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Resolution of hyponatremia (n=3794)</td>
<td>1.26</td>
</tr>
<tr>
<td>Persistent hyponatremia (n=4524)</td>
<td>2.37</td>
</tr>
<tr>
<td>Acquired hyponatremia (n=1974)</td>
<td>2.44</td>
</tr>
</tbody>
</table>

Failure to Measure Plasma & Urinary Osmolalities Associated With Increased Hyponatremia Mortality

- 113 patients with severe hyponatremia (serum [Na⁺] ≤ 120 mEq/L)
- Relationship between investigation for hyponatremia and mortality

Impact of Hyponatremia on Cost in Hospitalized Patients With HF

- 115,969 patients hospitalized for CHF
- Grouped by serum [Na⁺]Eq/L

<table>
<thead>
<tr>
<th></th>
<th>Serum [Na⁺], mEq/L</th>
<th>Risk-Adjusted Attributable Hospital Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatremia</td>
<td>&gt;145</td>
<td>$99</td>
</tr>
<tr>
<td>Normonatremia (ref)</td>
<td>136–145</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>131–135</td>
<td>$509</td>
</tr>
<tr>
<td>Severe hyponatremia</td>
<td>≤ 130</td>
<td>$1132</td>
</tr>
</tbody>
</table>
Meta-analysis: Vaptans for Hyponatremia

- 15 randomized, controlled trials of vaptans with or w/o fluid restriction
- Primary result: Normal or significant increase in serum $[\text{Na}^+]$ at 3-7 d
- Vaptan treatment significantly increased
  - Early response rate (11 trials): RR, 3.15; 95% CI, 2.27–4.37
  - Late response rate (4 trials): RR, 2.27; 95% CI 1.79–2.89
- Rates of hypernatremia (5 trials): RR, 2.21; 95% CI, 0.61–7.96
- No cases of ODS


Effect of Serum $[\text{Na}^+]$ & Tolvaptan on LOS in Hospitalized Patients With HF

- Objectives of this post-hoc analysis of EVEREST trial
  - Compare LOS between normonatremic (n=1789) and hyponatremic (n=216) patients who were randomized to placebo
  - Evaluate the effect of tolvaptan (n=225) compared with placebo (n=216) on LOS in hyponatremic patients
- LOS in hyponatremic vs normonatremic patients
  - Serum $[\text{Na}^+] < 135$ mEq/L: LOS + 3.06 d ($P < .001$)
  - More severe hyponatremia: LOS + 5.17 d ($P < .001$)
- LOS tolvaptan vs placebo
  - 1.72 d shorter vs placebo ($P = \text{NS}$)
  - 2.12 d shorter in patients with more severe hyponatremia ($P = \text{NS}$)

**Post-hoc Exploratory Analysis**  
**EVEREST: CV Mortality & Morbidity**

![Graph showing the effect of tolvaptan on hyponatremia](image)


---

**Economic Benefits of Tolvaptan in Hyponatremic HF Patients**

- **Hospital cost and LOS** for DRG hospitalizations of adult HF patients with complications, comorbidities estimated from HCUP 2008 NIS database
- **Reductions in LOS associated with tolvaptan** estimated from EVEREST trial data for hyponatremic patients
- **Cost offset model** used to evaluate impact of tolvaptan on LOS and hospital cost
  - LOS reduced 0.81 d among HF hospitalizations
  - $265 total cost savings per admission (based on wholesale acquisition cost of $250/d)
  - Supports clinical and economic benefit of tolvaptan use
- **Study limitation**: Clinical trial patient profiles and relative LOS reductions may not be applicable to real-world patient populations