Hyponatremia

Making sense of a common but tricky electrolyte disorder for a Sub-I

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Trivia Time!

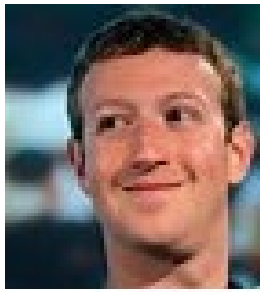
Who founded UpToDate, the widely used clinical resource?

A. Dr. Anthony Fauci

B. Dr. Burton "Bud" Rose

C. Dr. Elon Musk

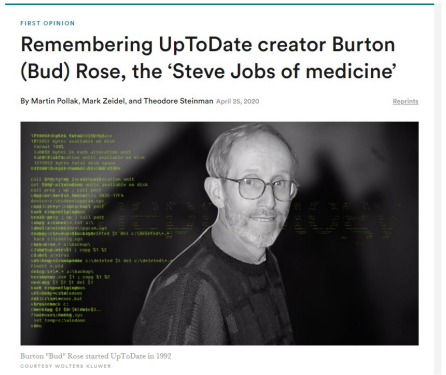
D. Dr. Mark Zuckerberg



UpToDate®

Answer

- **Dr. Burton "Bud" Rose** a nephrologist at Harvard
- UpToDate was originally focused on nephrology, before expanding to all specialties
- He created the first version of UpToDate at home in **1992**
- The early version was distributed on **floppy disks**
- He's been called the "**Steve Jobs of Medicine**"

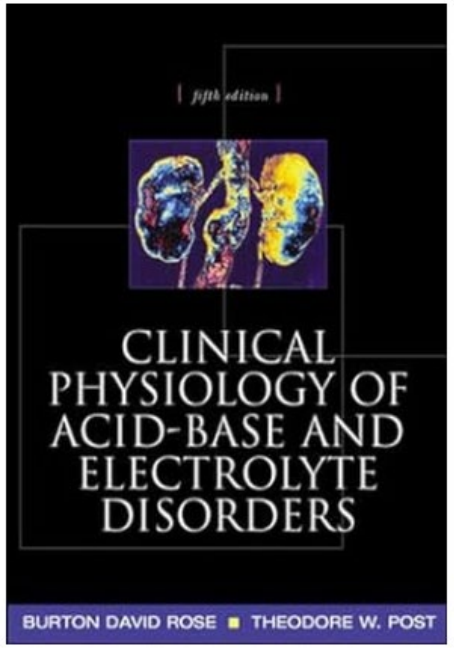

FIRST OPINION

Remembering UpToDate creator Burton (Bud) Rose, the 'Steve Jobs of medicine'

By Martin Pollak, Mark Zeidel, and Theodore Steinman April 25, 2020 Reprints

Burton "Bud" Rose started UpToDate in 1992

COURTESY WOLTERS KLUWER



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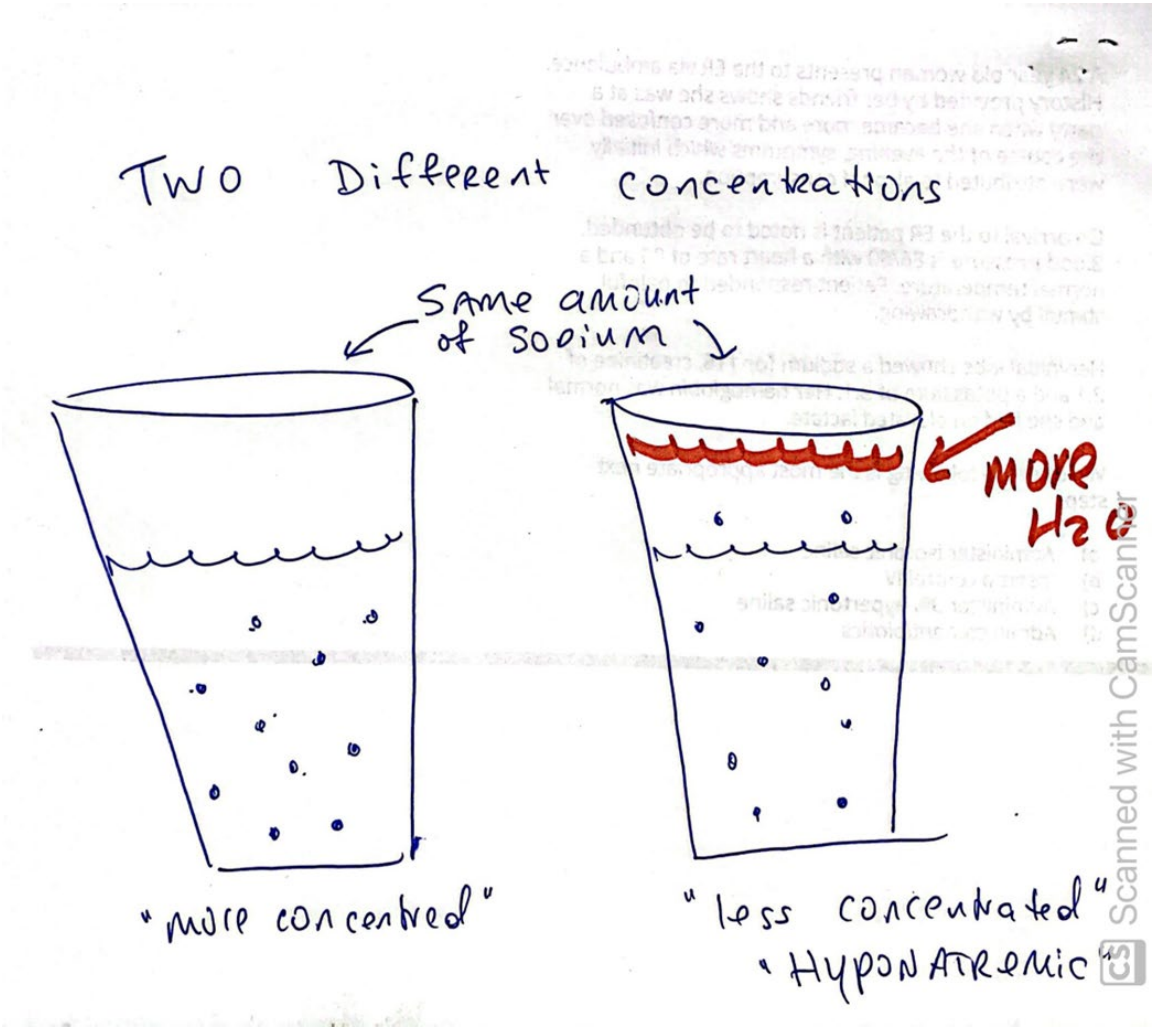
Objectives

- Understand why low sodium levels drop
- Learn how ADH affects sodium
- See how water moves through nephron
- Know what triggers ADH release
- Understand how the brain adapts to low sodium
- Identify clinical categories of hyponatremia
- Know the basic treatments for each category
- Practice using this knowledge to cases

What Does Hyponatremia Really Mean?

- Hyponatremia = “low sodium”… or is it?
  - ↓ Sodium?
  - ↑ Water?
  - Or both: too much water and too little salt
- Understanding this concept is the key to treatment.

Hyponatremia = Water Problem



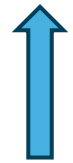
Sodium is **diluted**, *not* lost.

Too much water compared to sodium = hyponatremia

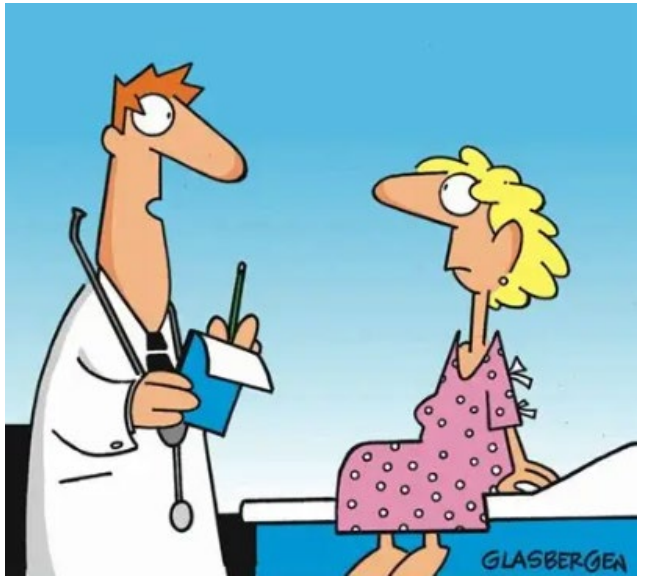
Often, there is confusion about this concept. When sodium levels are too low, the common advice is to simply **eat more salt**. Even worse, some might suggest **drinking more water**, which can exacerbate hyponatremia.

How does hyponatremia develop:

(1) **Excess** water intake + (2) **Impaired** water excretion

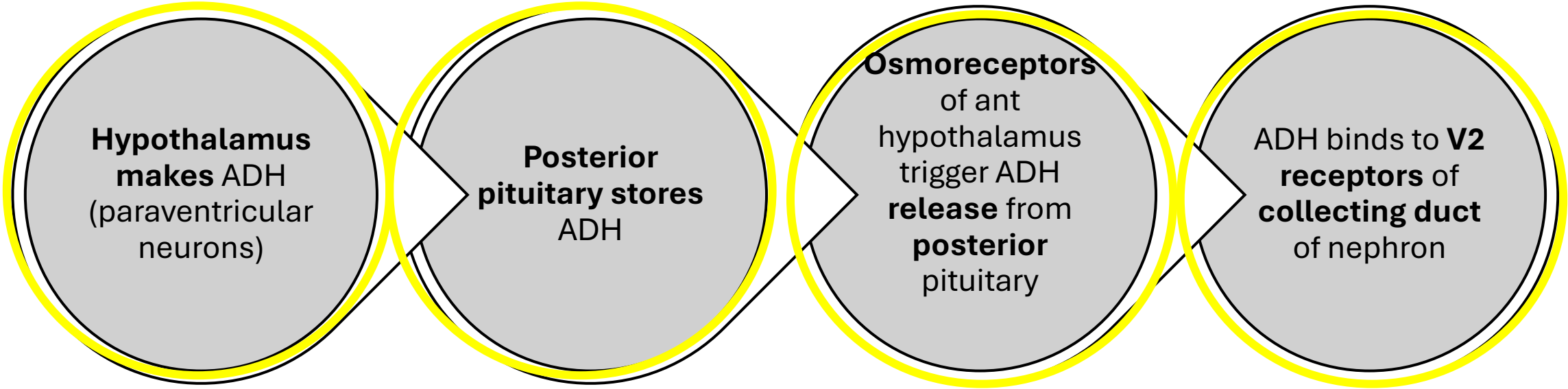


💡 ADH is usually the key driver of impaired water excretion



Good news! Your sodium levels are perfectly fine. It looks like all you need to do is cut back on the all-you-can-drink water parties!

ADH: The Water-Retaining Hormone



V2 Receptor Activation → **Aquaporin** Insertion → Water **Reabsorption** ↑
(*Water Reabsorption Requires an **Osmotic Gradient**)

https://youtu.be/MR8BABoFTP8

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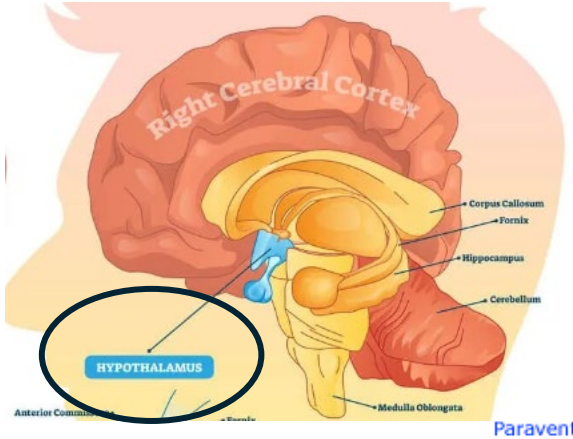

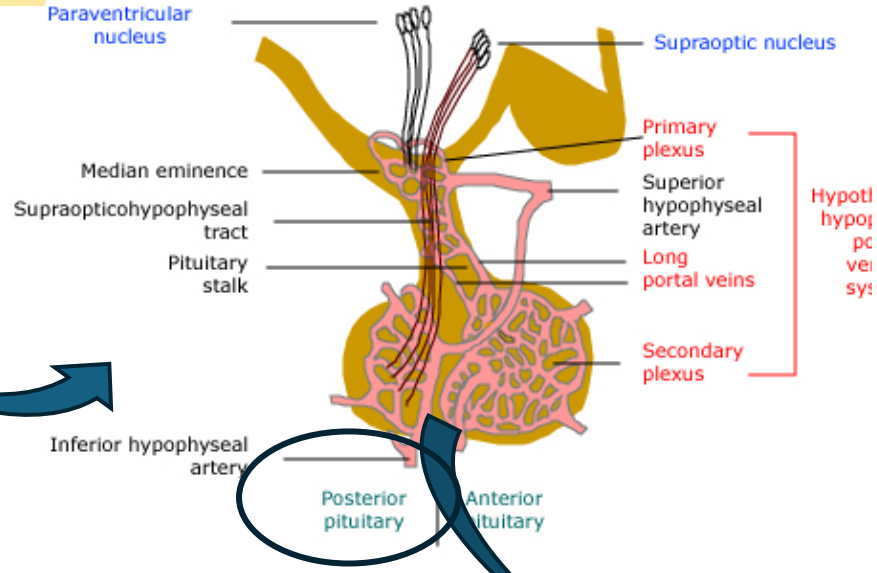

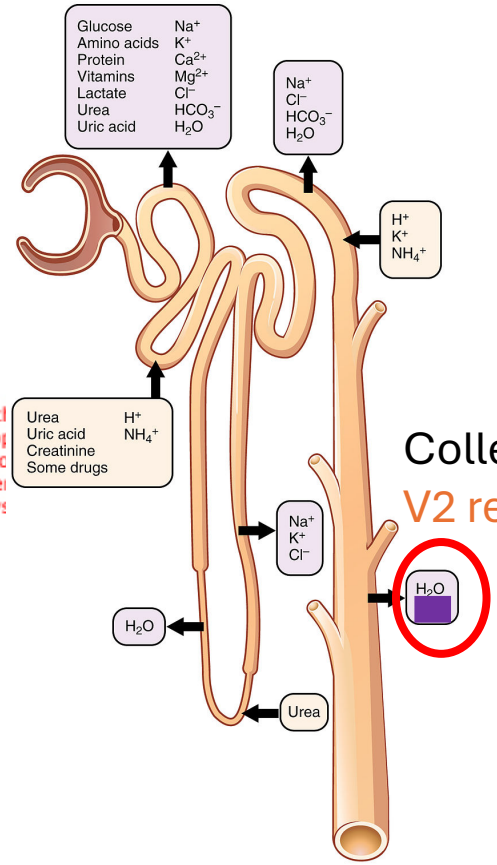

Collecting tubule

V2 receptors

Water reabsorption via AQP channels down the **gradient**

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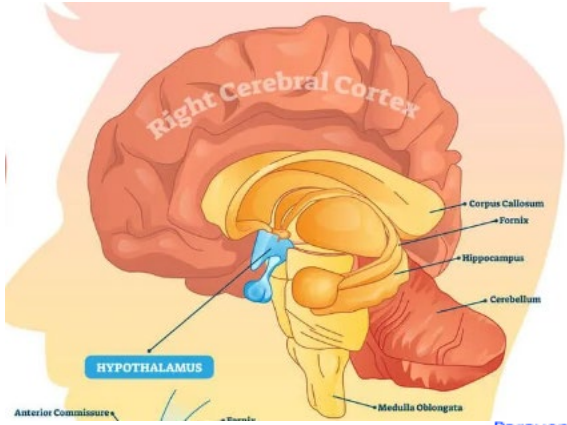
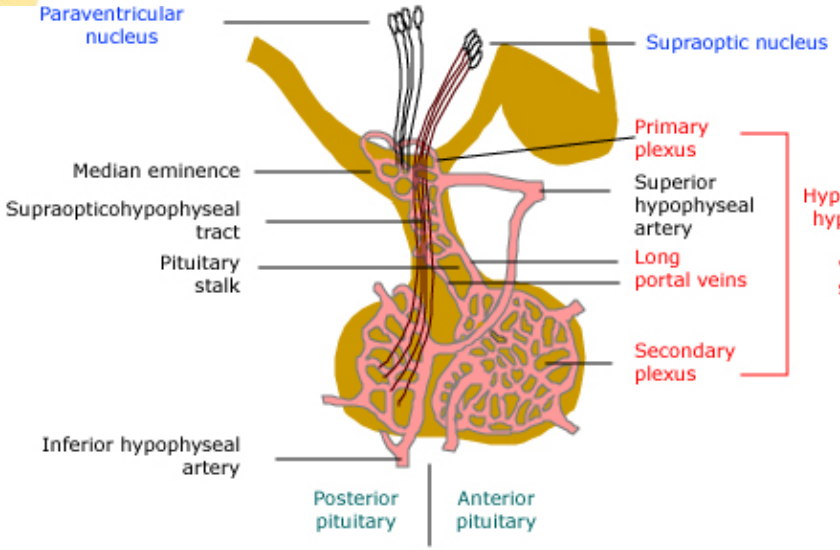
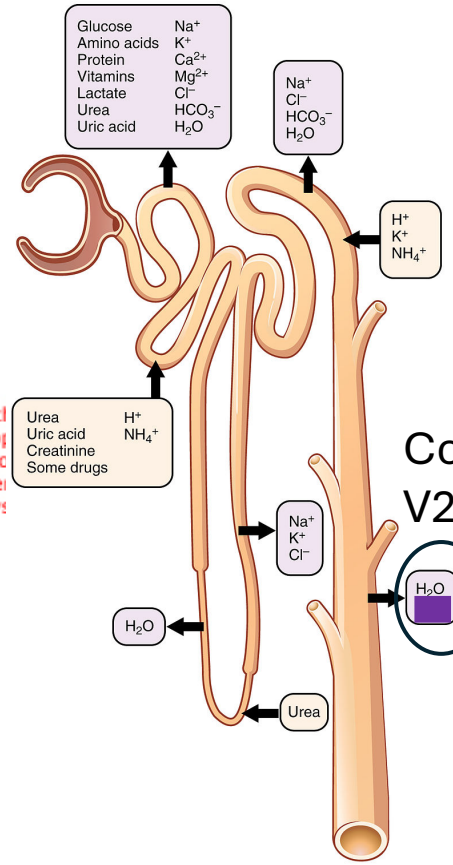






Collecting tubule
V2 receptors

Water reabsorption via AQP channels down the gradient

https://commons.wikimedia.org/wiki/File:2618_Nephron_Secretion_Reabsorption.jpg#/media/File:2618_Nephron_Secretion_Reabsorption

ADH: Clinical Pearls

💡 ADH saves water… even when you don't need it:

💡 In the presence of ADH, when water is reabsorbed from the urine, urine becomes **more concentrated**.

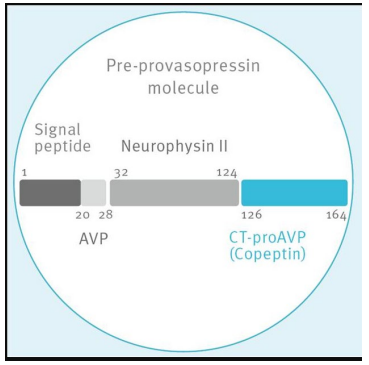
💡 As the particles (osmoles) in the urine become concentrated, urine osmolality (concentration of stuff) >> 300 mOsm/kg (typically ranging from 600 to 1200 mOsm/kg).

💡 Without ADH, urine is dilute, with urine osmolality less than 100 mOsm/kg.

💡 Without an increased interstitial gradient, even in the presence of ADH, water cannot be adequately reabsorbed (as seen in conditions such as ATN/AKI or during the use of loop diuretics).

ADH

- Made in hypothalamus as *pre-pro-AVP (*Arginine vasopressin):
  - Cleaved into:
    1. **Vasopressin (ADH)**
       - Cannot measure
    2. **Neurophysin II**
       - Cannot measure
    3. **Copeptin**
       - (serves as surrogate for ADH)
         - ❖Measurable (in research)



💡 Because ADH is **not easily measured**, we rely on **urine osmolality** to **infer its presence**. If urine osmolality is greater than 100-200 mOsm/kg, it usually indicates that ADH is being produced. However, determining the **degree and cause** of ADH production can be challenging.

Triggers for ADH Release

- **Osmotic**
  - ↑Plasma osmolality → ADH release
- **Non-Osmotic**
  - Volume depletion, pain, nausea

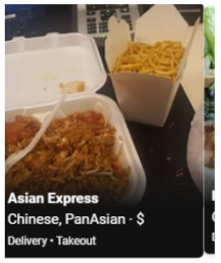
Osmotic stimulus for ADH release

Remember: major component of plasma osmolality is sodium

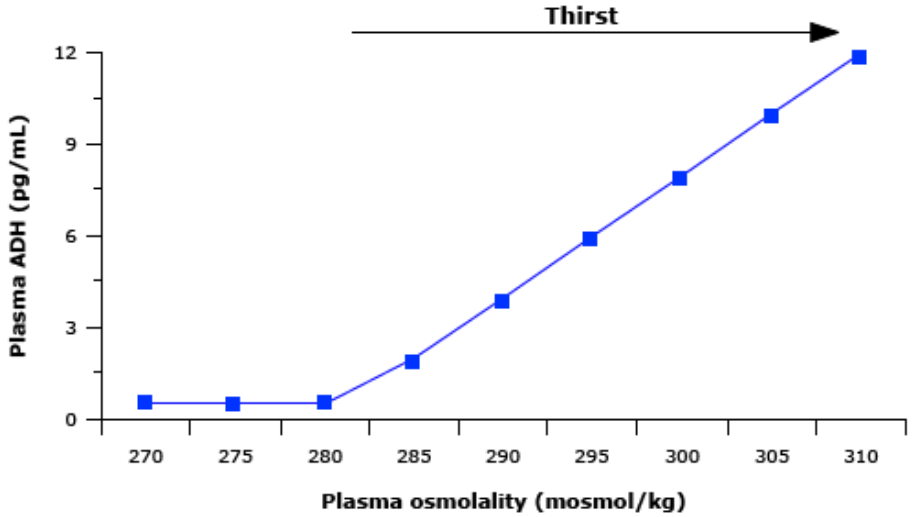
Salt Loading

Condensed soup 1600mg per can

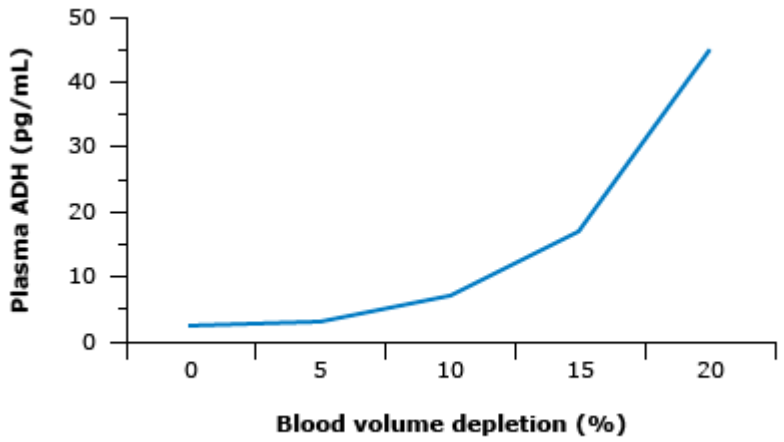
Asian take out: chow main- **980**, kang pau chicken – **800**, egg roll **390**, hot and saur soup **– 930** , soy sauce table spoon - **1,000** mg per tablespoon



total daily sodium= 6000 – 7000 or more ….



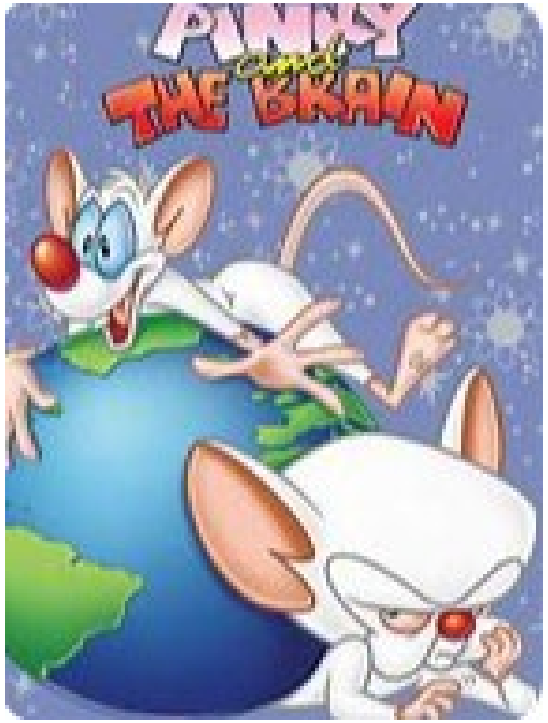
Non-Osmotic Stimuli for ADH Release



- Volume depletion
- Low effective circulating volume (e.g., CHF, HRS)
- Nausea
- Drugs (e.g., SSRIs)
- Pain

Why is Hyponatremia a Big Deal?

- A big problem for the brain, not as much for other organs



Hyponatremia: A Review of Physiology

- Brain cell :

More particles, more concentrated

- Interstitial space:

More water= hyponatremia; “less concentrated, less particles”

H2O

Brain cell

Acute Hyponatremia: Bad News for the Brain

- Brain cell :

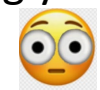
More particles, more concentrated

- Interstitial space:

More water= hyponatremia; “less concentrated, less particles”

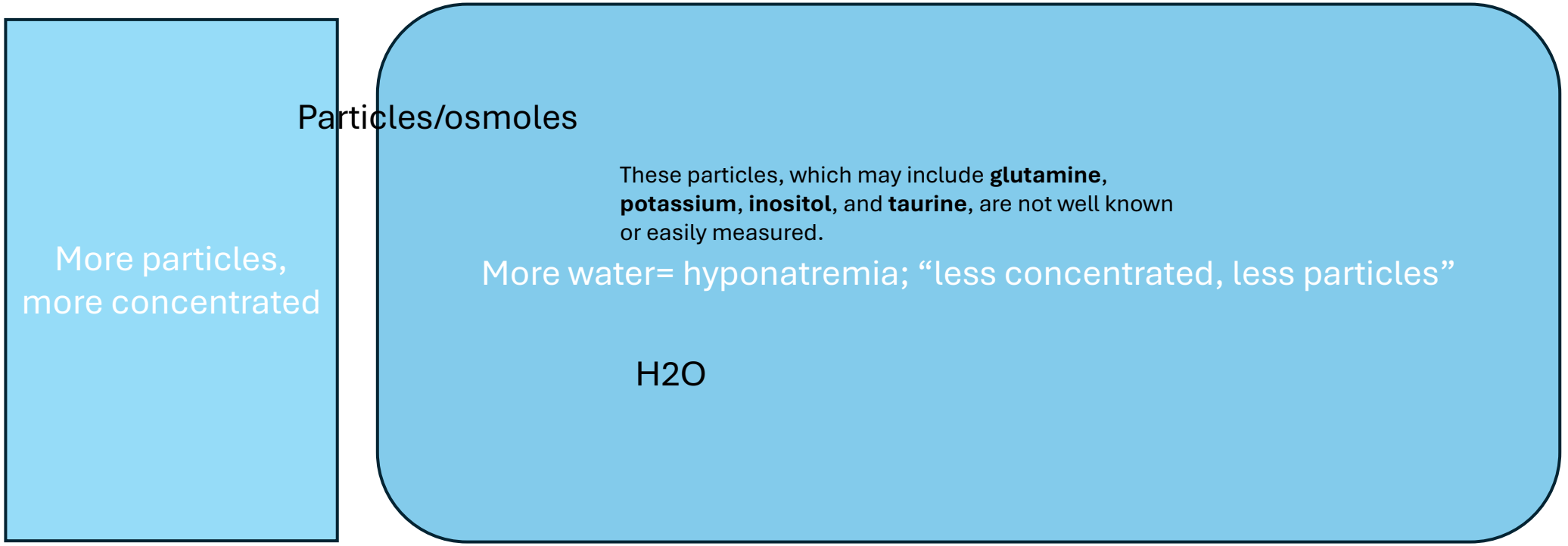
H2O

BUT the brain won’t allow the cells to expand – because the brain is inside a **solid/bony calvarium**, so as the brain edema ensues there is increasingly higher and higher **<u>pressure</u>** inside the brain- **seizures, AMS, herniation**



Brain Compensation in *Chronic Hyponatremia: Occurs by 48 Hours

- Brain cell :
- Interstitial space:



💡 *Note: While 'chronic' usually implies a long period of time, in the context of hyponatremia, it is defined as **48 hours**.*

HYPONATREMIA , SNA < 135 meq/L

Hypovolemic

ADH release:
triggered by low body volume

Euvolemic (SIADH)

ADH release:
Persistent, regardless of osm/volume

Hypervolemic

ADH Release:
Due to low "effective" circulating volume (e.g., CHF, cirrhosis)

You rely on history and physical exam to determine cause of hyponatremia NOT urine studies; urine sodium and osmolality alone **cannot clinch the diagnosis**

HYPONATREMIA , SNA < 135 meq/L

Hypovolemic

ADH release: triggered by low body volume

Urine Na (UNA) <10
Urine Cl (UCl) <10
Urine Osmolality >100

•**Mechanism**: ADH conserves water, concentrating urine

Euvolemic (SIADH)

ADH release:
Persistent, regardless of osm/volume

UNA>20
UCl > 20
Urine Osm > 100

•**Mechanism**: ADH conserves water, concentrating urine

Hypervolemic

ADH Release:
Due to low "effective" circulating volume (e.g., CHF, cirrhosis)

UNA < 10
UCl < 10
Urine Osm > 100

•**Mechanism**: ADH conserves water, concentrating urine

Because water is removed from the urine, urine is more concentrated and is such thru action of ADH in all three cases urine osm >> 100 (600-1200)

Pearls & Exceptions

- When Low Urine Osmolality (<100 mOsm/kg):

    1. **Primary (Psychogenic) Polydipsia**:
        - Excess water intake **suppresses ADH**, resulting in dilute urine. You pee how much you drink. Suppressing ADH protects you from developing hyponatremia - Less ADH, less water retention—sodium dilution avoided

Other tests to get for hyponatremia evaluation

- ☑ Serum Osmolality (Serum Osm)
- Thyroid-Stimulating Hormone (TSH)
- Random Cortisol / Cortisol Stimulation Test
- Uric Acid (low in SIADH)
- Echocardiogram (Echo)
- Liver Ultrasound (Liver US)
- Abdominal Imaging (to evaluate for cirrhosis)
- Chest X-ray
- Strict Urine Output Records
- Daily Weights

Serum Sodium and Serum Osmolality

- Serum Osmolality ↔ Serum Sodium correlate **directly**

$$\text{Calculated serum osmolality} = 2 \times [Na^+] + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8} \text{ (units: mOsm/kg)}$$

- This is called hypotonic hyponatremia

Low [Na] ≠ Low Serum Osmolality

- Low [sodium] -> but high/normal serum osm

1. **Pseudohyponatremia**
    - **Lab error** due to **indirect** potentiometry which estimates [NA]
    - *calculation error* based on incorrect *assumption* of plasma volume (usually 93% water, but wrong when plasma volume displacement by lipids/proteins
        - → **Consider:** 1) hyperTGs 2) MM 3) IVIG
- *Action*
    - → **Confirm with**> '**whole blood sodium**' 'point-of-care devices'
    - Direct ion-selective electrode doesn't dilute the sample and measures sodium in plasma water **directly**, so it isn't affected by abnormal fats or proteins.

HYPONATREMIA

Determine the volume status FIRST

Hypovolemic

Low BP
Tachy
Orthostatic

ADH release d/t low volume

History
1. Vomiting
2. Diarrhea

UNA < 10
UCl < 10
Urine Osm > 100

Treatment:
1. Isotonic saline

Euvolemic (SIADH)

Constant ADH release without osm or volume stimulus

Hypervolemic

ADH release due to low “effective” circulating volume

A 61-year-old woman is hospitalized with 5 days of nausea, vomiting, and poor oral intake. For the past 2 days, she has had dizziness when standing. Past history includes hypertension and type 2 diabetes mellitus. Current medications are aspirin, glipizide, enalapril, and chlorthalidone.

On exam, BP is 85/60 mm Hg, HR 98/min, mucous membranes are dry, skin turgor is decreased. Cardiac and lung exams are normal, no edema. She is alert and oriented.

Labs:
- Na^+: 120 mEq/L
- K^+: 3.7 mEq/L
- Cl^-: 86 mEq/L
- HCO_3^-: 26 mEq/L
- BUN: 85 mg/dL
- Creatinine: 8 mg/dL (baseline 1 mg/dL 1 month ago)
- Urinalysis: several hyaline casts
- Urine sodium: 4 mEq/L

Which of the following is the next best step in this patient's management?

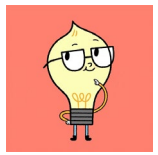
(A) Dialysis

(B) Fluid restriction

(C) Intravenous normal

(D) (0.9%) saline

(E) Intravenous 3% sodium chloride



Low Na< a hallmark of prerenal AKI from volume depletion. *(FeNa can confirm but is not required when urine sodium is already low.)*

Why does hyponatremia correct with 0.9% NS?

A. We gave saline, so we replaced sodium losses

✅ B. The kidneys start to release retained water (producing dilute urine) (“auto-correction”)

Administration of 0.9 % saline restores intravascular volume

↓

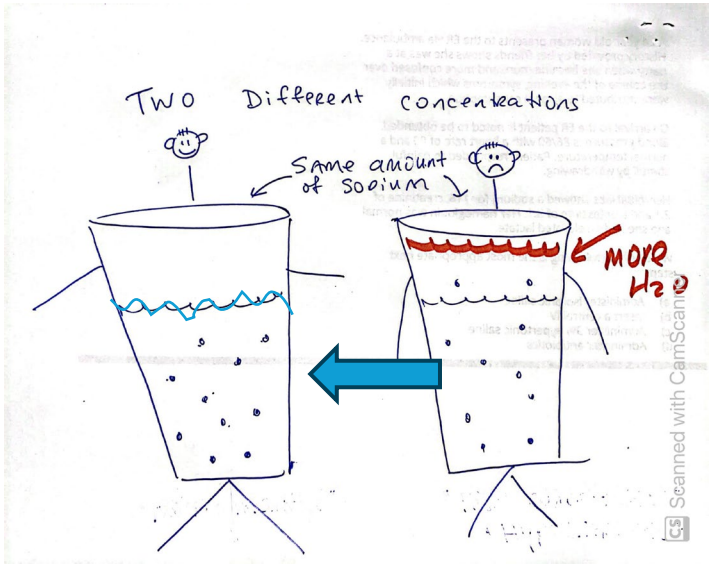
Non-osmotic ADH release is suppressed

↓

Kidneys excrete dilute urine (free water loss)

↓

Serum sodium concentration risec back to normal



HYPONATREMIA

Hypovolemic

ADH release d/t low volume

Euvolemic (SIADH)

NL BP
No edema
No history of volume losses

Constant ADH release without osm or volume stimulus

1. Drugs:
    1. SSRI
    2. diuretics: thiazide (HCTZ)
2. Pain
3. Nausea
4. Cancer

Hypervolemic

ADH release due to low “effective” circulating volume

A 35-year-old woman presents for follow-up 8 days after hospitalization for *E. coli* pyelonephritis
treated successfully with trimethoprim-sulfamethoxazole. She takes an oral contraceptive and no other medications. She feels well and has no new complaints. Vitals are normal, and examination shows a thin woman in no distress, with normal heart, lung, and neurologic findings; no peripheral edema.

Laboratory studies reveal:

- sodium 124 mEq/L
- potassium 3.6 mEq/L
- glucose 122 mg/dL
- BUN 12 mg/dL
- creatinine 0.7 mg/dL
- serum osmolality 266 mOsm/kg
- urine sodium 110 mEq/L
- urine osmolality 407 mOsm/kg.

Question:

Which of the following is the most likely cause of this patient's hyponatremia?

A. Adrenal insufficiency

B. Primary polydipsia

C. SIADH

D. Thiazide diuretic use

HYPONATREMIA

Hypovolemic

ADH release d/t low volume

Euvolemic (SIADH)

Constant ADH release without osm or volume stimulus

Hypervolemic

ADH release due to low "effective" circulating volume

Low normal BP
++ edema
++ history no volume losses
Cirrhosis, jaundice

1. CHF
2. Cirrhosis
3. Nephrotic syndrome

A 65-year-old man with a history of CAD) with previous PCI, CHF with low EF presents with shortness of breath and 10 lbs weight gain over the past few days. Physical examination reveals 3+ bilateral lower extremity edema. He reports compliance with his diuretic regimen but admits to eating takeout food daily. Blood pressure is 90/60 mmHg.

Laboratory findings:

- Glucose: 122 mg/dL
- Blood urea nitrogen: 35 mg/dL
- Creatinine: 1.7 mg/dL
- Sodium: 124 mEq/L
- Potassium: 3.6 mEq/L
- Serum osmolality: 266 mOsm/kg H_2O
- Urine sodium: <10 mEq/L
- Urine osmolality: 407 mOsm/kg H_2O

Which of the following is the most best treatment for the patient's hyponatremia?

A) Give IVFs b/c Cr is up and blood pressure is low

B) Hold diuretics and ACEI b/c Cr is up

C) Give IVFs b/p is low

D) Start diuretics

HYPONATREMIA **TREATMENT**

Goals: 1) turn off ADH,2)excrete the water, 3) prevent water retention

Hypovolemic

ADH release d/t low volume

Shut off ADH

Vomiting

Isotonic saline

Euvolemic (SIADH)

ADH release for reason other than volume or osmolality

Drugs: SSRI, HCTZ

1. Stop meds, treat pain, treat nausea, treat hypothyroid – to shut off ADH
2. Fluid restriction

Prevent H2O retentio n

3. Other:
   - ❑ Loop diuretic
   - ❑ Salt tabs
   - ❑ Urea
   - ❑ Tolvaptan

Excrete water

Hypervolemic

ADH release due to low "effective" circulating volume

1. CHF, cirrhosis

Fluid restriction
Loop diuretic +

Prevent H2O retention & excrete water + salt

To shut off ADH treat underlying condition management- inotropes, chf afterload reduction therapies, liver transplant, heart transplant , etc

Commonly **Confusing** Treatment Strategies for **SIADH**: **Clarifying** the Options

- Fluid Restriction
- Loop Diuretics (e.g., Furosemide)
- Tolvaptan (V2 Receptor Antagonist)
- Salt Tablets / Increased Solute Intake
- Urea
- Hypertonic Saline (3% NaCl)

Loop Diuretics in SIADH and Hyponatremia Correction

- Myth: “**all *diuretics*** *cause hyponatremia*.”

- Reality: **Thiazides** often cause hyponatremia by impairing urine dilution in the distal tubule.

    - Loop diuretics (e.g., furosemide) do not typically cause hyponatremia and can be used to *treat* it in SIADH.

Loop Diuretics

- Loop diuretic (e.g., furosemide)
  - ↓ Blocks **$Na^+/K^+/2Cl^-$ symporter** in thick ascending limb
  - ↓ Abolishes medullary **osmotic gradient** needed for urine concentration
  - ↓ Kidney **cannot concentrate** urine even with high ADH
  - ↓ Increased free **water excretion** (water diuresis)
  - ↓ Reduced water retention → **dilution resolves**
  - ↑ Serum [sodium] → **correction** of hyponatremia

"protects" patients from developing hyponatremia despite increased ADH

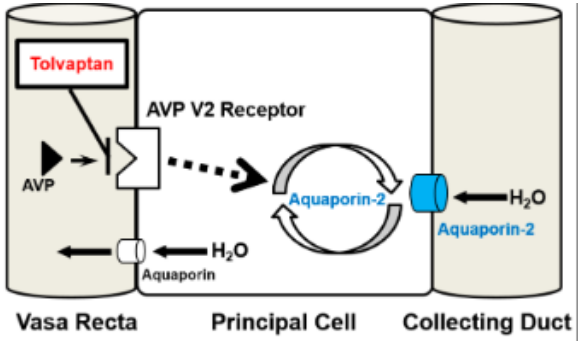
V2 Receptor Blocker in SIADH – Mechanism of Action

- Tolvaptan is a selective vasopressin **V2 receptor antagonist** acting on the renal collecting ducts.

- It **blocks ADH** from binding to V2 receptors on collecting duct cells.

- This prevents insertion of **aquaporin-2 water channels** into the membrane.

- Result: **Reduced water reabsorption** without significant sodium loss → increased free **water diuresis** → **raises** serum **[NA]**



Vaptans vs. Loop Diuretics

- **Both** promote **water loss** and improve hyponatremia in SIADH, but by distinct renal mechanisms:
  - Loop diuretics **disrupt urine concentrating ability** indirectly by abolishing the medullary osmotic gradient.
  - Tolvaptan directly **blocks ADH signaling at V2** receptors preventing aquaporin insertion.
  - Both: **Increase free water excretion** (water diuresis) and lead to correction of dilutional hyponatremia

*tolvaptan should not be used in any patient for longer than 30 days and should not be given to patients with **liver disease (including cirrhosis)**

Salt Tablets in Hyponatremia Management: Mechanism & Clinical Use

- Mechanism of Action:
  - Salt Intake ↑→ Osmotic Diuresis ↑ → Water Loss ↑
- Clinical Use:
  - Often used *alongside loop diuretics and/or when fluid restriction isn't sufficient*
- Salt tab **Dose**:
  - Comparable to salt intake from a typical American diet
    - Or **equivalent to 1L of 0.9% NS** (NS=salt or NaCL)
  - Example: 3g TID totaling ~9g NaCl/day (same salt as in 1 liter NS)
  - *Oral salt tablets should NOT be given to patients with edema or hypervolemic states*

Urea Therapy in SIADH: Mechanism and Challenges

- Urea mechanism: **Increases osmoles** → promotes **osmotic diuresis** → enhanced free **water excretion** → correction of hyponatremia

- Adverse events :
  - **distaste** or mild **GI discomfort** rather than toxicity.
  - Tastes and **smells like urine**, although our fellows tried it **“not that bad”**

A 60-year-old male presents to the clinic to review labs. He has a history of hypertension, diabetes, and lung cancer for which he is undergoing treatment. He voices no complaints at this time. He underwent a colonoscopy two years ago that did not identify any lesions or polyps. He is up to date with his eye exams. He says his appetite has been great and denies any weight loss. He also denies vomiting or diarrhea. His only medications are metformin and lisinopril.

His blood pressure is 124/82mmHg Standing and 120/80mmHg sitting. His physical exam does not reveal any jugular venous distention (JVD) or lower extremity edema.

Labs show:
HgbA1c 6.4%
CBC normal
LDL 58mg/dL
CMP is normal except for a sodium level of 123mg/dL
Serum osmolarity 250mOsm/L

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His blood pressure is **124/82mm**Hg Standing and **120/80mmHg sitting**. His physical exam does **not reveal any jugular venous distention (JVD) nor lower extremity edema.**

Labs show:
HgbA1c 6.4%
CBC normal
LDL 58mg/dL
CMP is normal except for a sodium level **of 123mmol/l**
Serum osmolarity **250mOsm/L**

Which of the following is the best solution for his hyponatremia at this time?

A. Furosemide

B. 3% normal saline

C. 0.9% normal saline

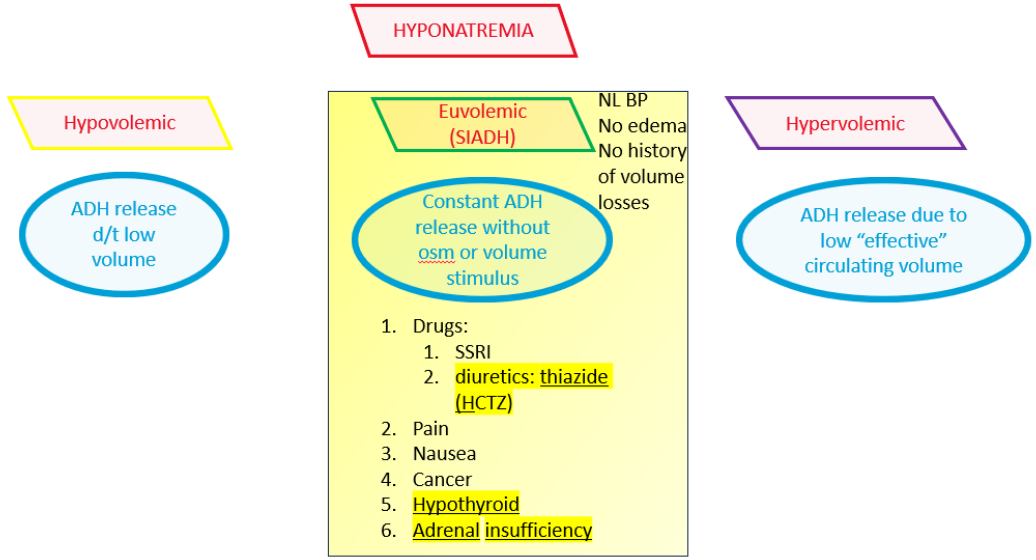
D. Fluid restriction

E. 5% dextrose in water (D5W solution)

How much fluid restriction? 800ml of all liquids

Unusual causes of hyponatremia

- Focus on (in the middle section , SIADH category) :
  1. Adrenal insufficiency
  2. Hypothyroid
  3. Thiazides



Mechanisms of AI

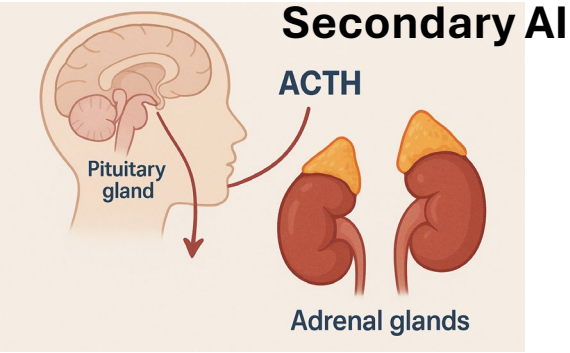
- *Why?*
  - b/c ↑ cortisol normally provides negative feedback on ADH through CRH

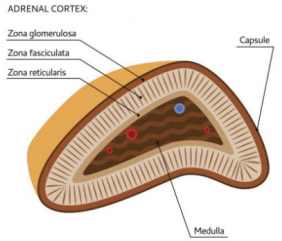
- *Low cortisol → ↑ CRH (hypothalamus)→* CRH leads to nonosmotic stimulus for *↑ ADH → water retention → dilutional hyponatremia*

💡 **Clinical Pearl: Urinary sodium is usually normal or high in AI. Why shows up in the "siadh" category, because urine sodium is not 'low' but patients may still present "hypovolemic" due to low BP from AI**

Adrenal Insufficiency Hyponatremia: **Clinical Pearls —**

- **Primary AI (levels of adrenals)**
  - **Na^+ down + K^+ ↑** → aldosterone + cortisol deficiency
- **Secondary AI** (**level of pituitary**); spares aldosterone b/c aldo is mediated through RAAS →
  - Usually **no** hyperkalemia — due to isolated cortisol deficiency (aldosterone intact)
- **Causes of primary:**
  - TB remains a leading cause in developing regions
  - Surgical resection
  - Autoimmune Addison's dominates in developed countries.
  - Meningococcal sepsis → Waterhouse–Friderichsen syndrome → acute adrenal crisis.





THE ADRENAL GLAND

Primary AI

Treatment for Adrenal Insufficiency

- ✓Hyponatremia in AI **does not correct with fluid restriction alone** — steroid replacement is needed.
  - ✓Cortisol administration (hydrocortisone, fludrocortisone)
  - ✓Volume repletion (Isotonic saline)

A 22-year-old woman presents to the emergency department with **severe dizziness, weakness, nausea, and vomiting** for 1 week. She has experienced fatigue and moderate weight loss over the past 2 months. Her history is notable for hypothyroidism treated with levothyroxine.

On examination, she is **168 cm** tall, weighs **53 kg**, and has **BP 90/60 mm Hg supine, 80/50 mm Hg standing**; **pulse 84/min supine, 96/min standing**. Skin is tanned with **marked hyperpigmentation of the gums and palmar creases**.

Laboratory studies show:
Na^+: 124 mEq/L
K^+: 5.8 mEq/L
Glucose: 61 mg/dL
BUN: 39 mg/dL
Creatinine: 1.2 mg/dL

What is the most likely underlying cause of the hyponatremia?

(A) Acute adrenal hemorrhage

(B) Autoimmune adrenalitis (Addison's disease)

(C) Fulminant meningococcemia

(D) Pituitary apoplexy

(E) Tuberculosis

Mnemonic: *"**P**rimary = **P**igment + **P**otassium up"*

Primary = Pigment 🟤 + Potassium ⬆️

- Focus on :
  - Adrenal insufficiency
  - **Hypothyroid**
  - Thiazides

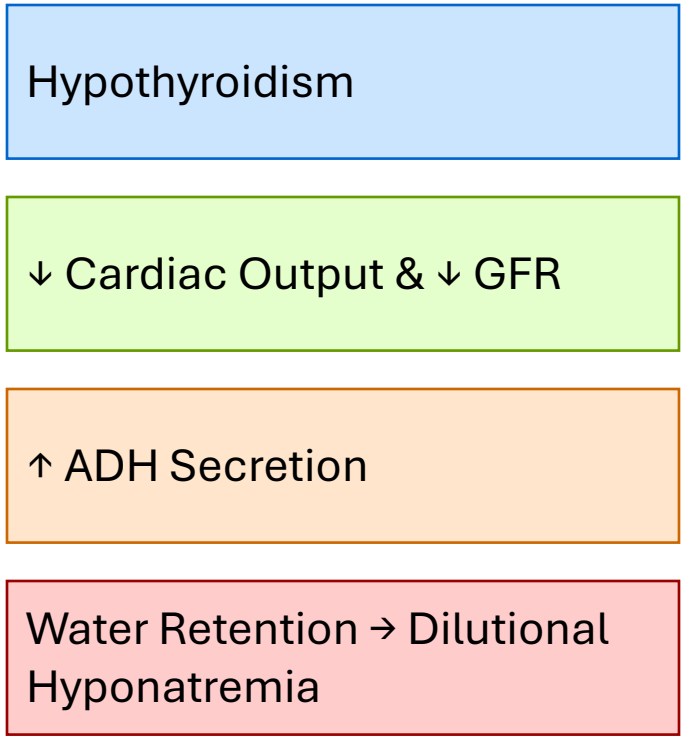
Hyponatremia in Hypothyroidism

Mechanisms:

- ↓ Cardiac output → ↓ effective arterial blood volume → ↑ ADH → water retention.
- ↓ GFR & impaired free water clearance → dilutional hyponatremia.

Presentation:

- *Severe* hypothyroidism (myxedema) → most pronounced effect.
- Usually mild; corrects with thyroid hormone replacement (Synthroid) .

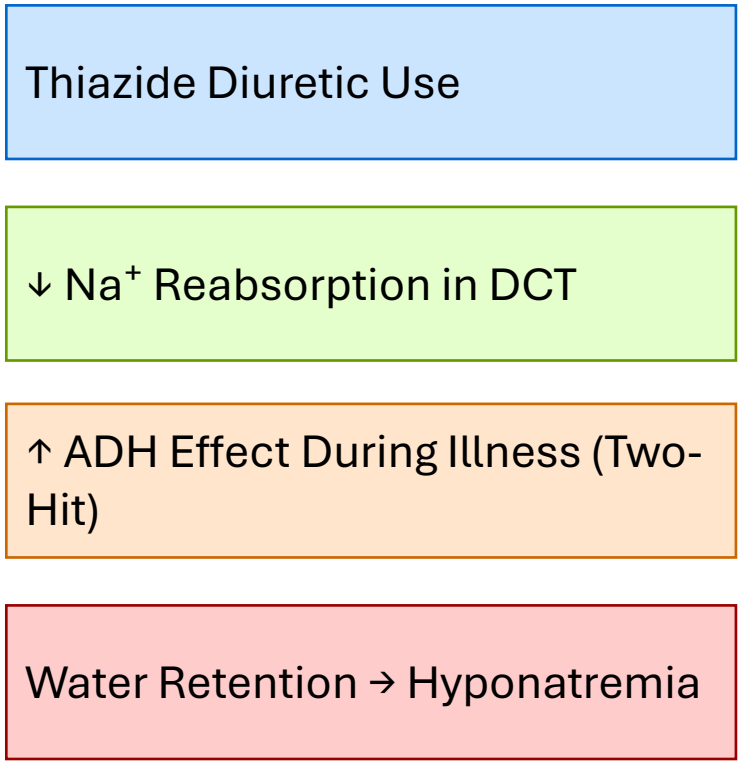


💡 **Clinical Pearl: Urinary sodium is usually normal or high in hypothyroid hyponatremia — it's a water clearance problem, not sodium loss. Why shows up in the "siadh" category. Patients appear euvolemic**

- Focus on :
  - Adrenal insufficiency
  - Hypothyroid
  - **Thiazides**

Hyponatremia & Thiazide Diuretics

- One of the **most common** causes of hyponatremia requiring hospitalization.
- Usually occurs within **1–2 weeks** after starting, but can appear months–years later.
- Often triggered during intercurrent illness causing inappropriate ADH secretion (**'two-hit'** hypothesis).
- May **recur** upon rechallenge with thiazide.
- Clinically: **often euvolemic** (like SIADH) or mildly volume expanded.



Thiazide Induced Hyponatremia

Risk factors:

- Older women with low body weight are most susceptible
- low dietary solute intake

Frenkel Thiazide-induced hyponatraemia is associated with increased water intake and impaired urea-mediated water excretion at low plasma antidiuretic hormone and urine aquaporin-2. J Hypertens. 2015 Mar;33(3):627-33.

Thiazide Hyponatremia: Mechanisms (complicated!)

- An underlying tendency to *increased water intake (aka polydipsia)*
  - 2543 versus 1828 mL/day

↑

- *Volume depletion* stimulates the release of ADH

Frenkel Thiazide-induced hyponatraemia is associated with increased water intake and impaired urea-mediated water excretion at low plasma antidiuretic hormone and urine aquaporin-2. J Hypertens. 2015 Mar;33(3):627-33.

Thiazide Hyponatremia: Mechanisms

- ~50% of TIH patients carry a **variant in SLCO2A1** (prostaglandin transporter, PGT)

- Variant → **↓ PGT function** → ↑ luminal prostaglandin E_2 (PGE_2) in collecting duct

- ↑ PGE_2 activates EP4 receptor → **↑ AQP2 channels** → ↑ water reabsorption (independent of ADH)

    - Effect occurs even with suppressed ADH
    - Result: Hyponatremia due to ADH-independent water retention

A **73-year-old woman** is brought to the emergency department after **falling** at home. Her family states that she has been very **confused and disoriented** over the **past 2 days** and that she began a new medication **4 days ago.** She has type 2 diabetes mellitus, hypertension, and glaucoma. A bag containing the patient's medications includes glyburide, metformin, **hydrochlorothiazide**, acetazolamide, and enalapril.

On physical examination, temperature is 37 °C (98.6 °F), heart rate is 68/min, respiration rate is 12/min, and blood pressure is **115/65 m**m Hg. She **is confused** and unable to answer questions appropriately. Cardiac examination is nor mal. The lungs are clear. There is **no edema**.

Laboratory studies:

Blood urea nitrogen 17 mg/dL
Creatinine 1.1 mg/dL.
Sodium 107 meq/L
Potassium 2.9 meq/L
Chloride 76 meq/L
Bicarbonate 24 meq/L

Which of the following drugs was most likely recently started in this patient?

(A) Acetazolamide

(B) Enalapril

(C) Glyburide

(D) Hydrochlorothiazide

(E) Metformin

When to Use 3% Saline?

Indicated only in Symptomatic Hyponatremia

📍 Symptoms more likely in:

1. Acute hyponatremia **(<48 hrs)** – brain has not adapted to low Na^+.
2. Severe chronic hyponatremia **(>48 hrs)** – usually when Na^+ <120 mEq/L.

ℹ️ Most patients, even with severe hyponatremia, may be asymptomatic.

⚠️ Symptoms:

- Altered mental status
- Seizures
- Tremors
- Brainstem herniation
- Coma
- Death

How to Administer 3% Saline?

📍 **Administer ONLY in ICU with close monitoring of serum sodium every 2–4 hours.**

- 3% saline contains 513–554 mEq of Na^+ per liter (≈0.5 mEq/ml).
    - ❖ 🌊 Average ocean water ≈ **3.5% salt**
        - ❖ **peripheral IV** access ok (central line not needed).

Severe Hyponatremia Treatment

Presumed Chronic (>48 hours)

🚫 LIMIT rate of sodium correction — this is a safety cap, not a goal.

- **Maximum: 6–8 mEq/**L increase in serum Na^+ per 24 hours.
  - regardless of how low the initial sodium is
    - e.g. presenting w/ 107 -> **limit (not a goal)** to 112 at 24 hours (less is ok esp w/out symptoms)
  - **correct** note=>"**limit** sodium correction to 112
  - **incorrect** note => "**goal** sodium correction 112

⚠️ Exceeding this limit increases risk of osmotic demyelination syndrome (ODS).

A 24-year-old woman is brought to the emergency department by ambulance after becoming progressively confused at a party. Her friends initially attributed her symptoms to alcohol consumption. On arrival, she is obtunded, with:

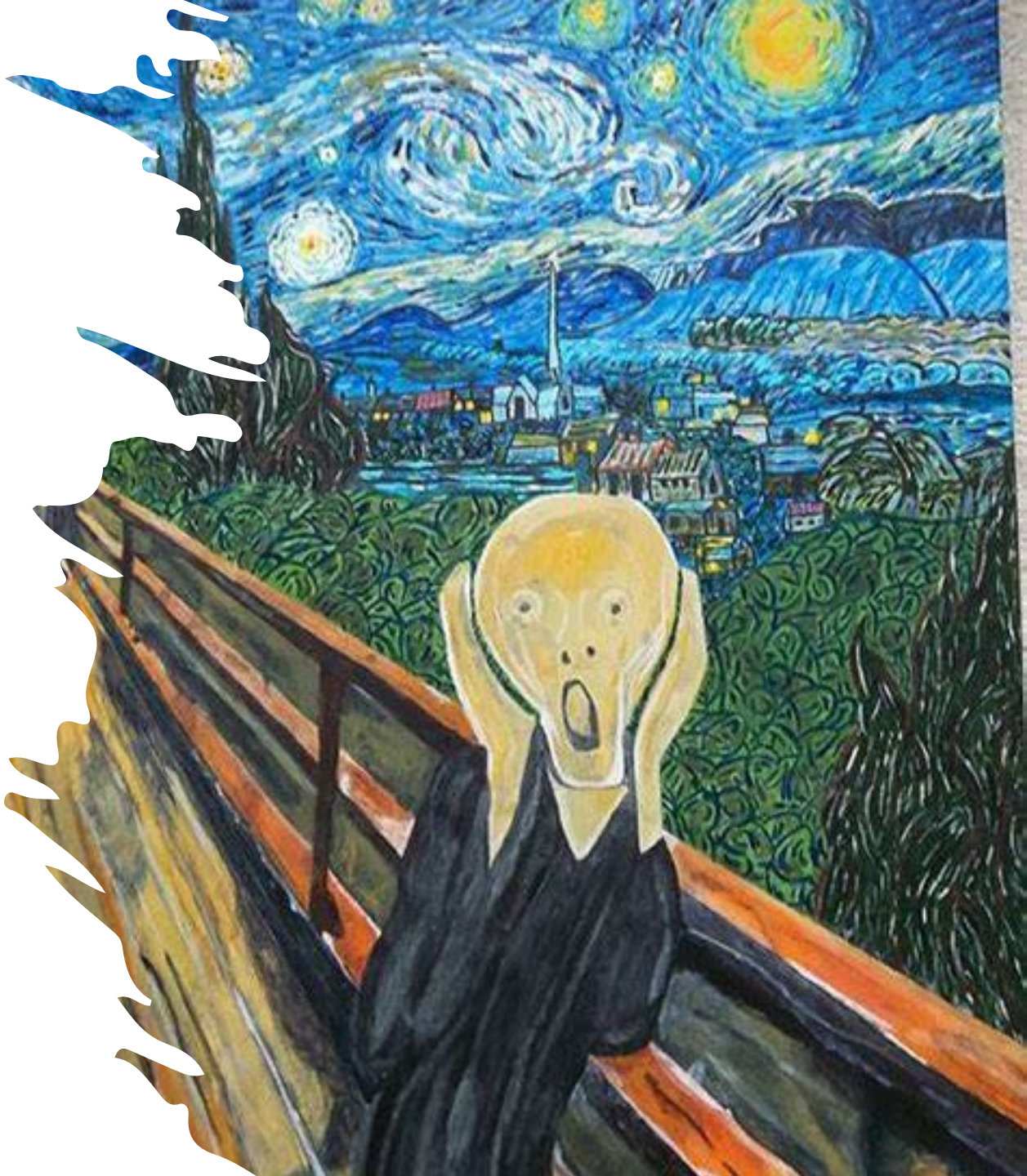
BP: 86/60 mm Hg
HR: 80/min
Temp: Normal
Withdraws to painful stimuli
Laboratory results:
Na^+: 116 mEq/L
K^+: 3.1 mEq/L
Creatinine: 2.1 mg/dL
Hemoglobin: Normal
Lactate: Elevated

Which of the following is the most appropriate next step:

a) Administer isotonic saline
b) Insert a central IV
c) Administer 100ml 3% hypertonic saline
d) Administer antibiotics

Why slow is better?

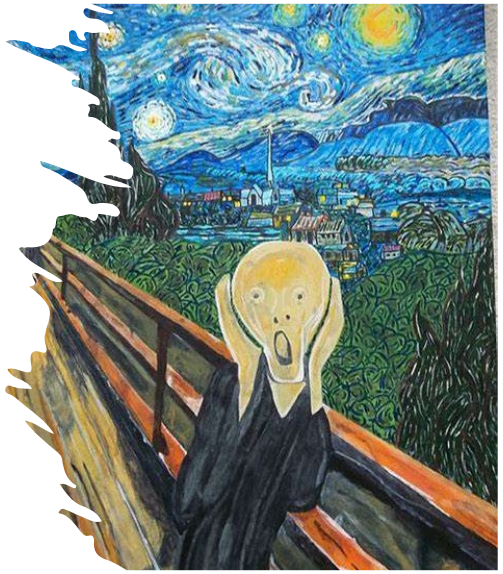
- Osmotic demyelination syndrome (ODS)
- The majority of ODS cases occur in patients whose sodium concentrations at presentation are **≤110 mEq** with correction rates > 6-8 meq /l per day (**over-correction**)
    - How the ODS occurs is not completely understood
    - In severe hyponatremia, the brain adapts to low sodium. Rapid correction pulls water out of brain cells → demyelination. Correct **slowly** to prevent irreversible neurologic damage
    - **Risk factors:**
        - liver disease, malnourished, risk of rapid over correction after stimulus for ADH has been removed



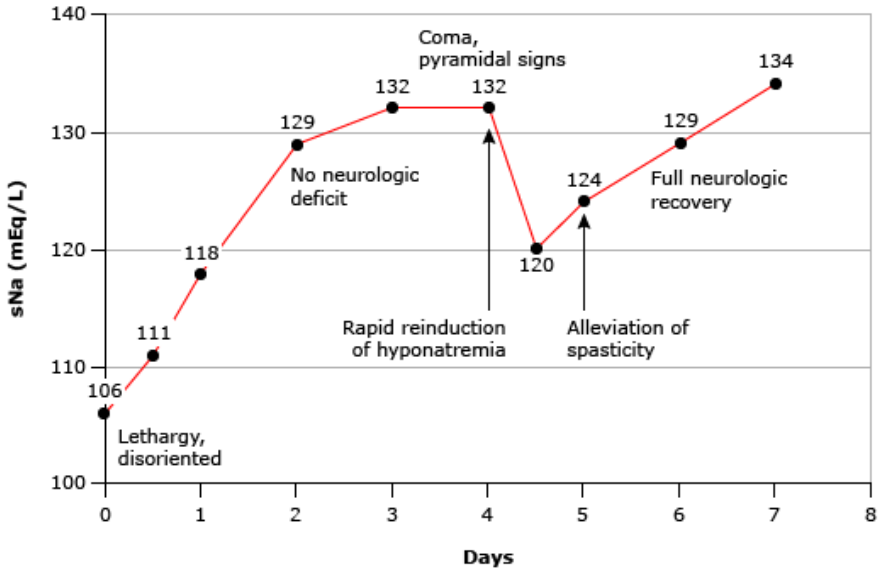
ODS Symptoms

- Dysarthria
- Dysphagia
- paraparesis
- **Quadriparesis**
- behavioral disturbances
- movement disorders
- **Seizures**

- Lethargy
- Confusion
- Disorientation
- Obtundation
- Coma
- **"locked in“**
- **Mute**
- Corticospinal signs



Delayed appearance of osmotic demyelination and relowering of the serum sodium

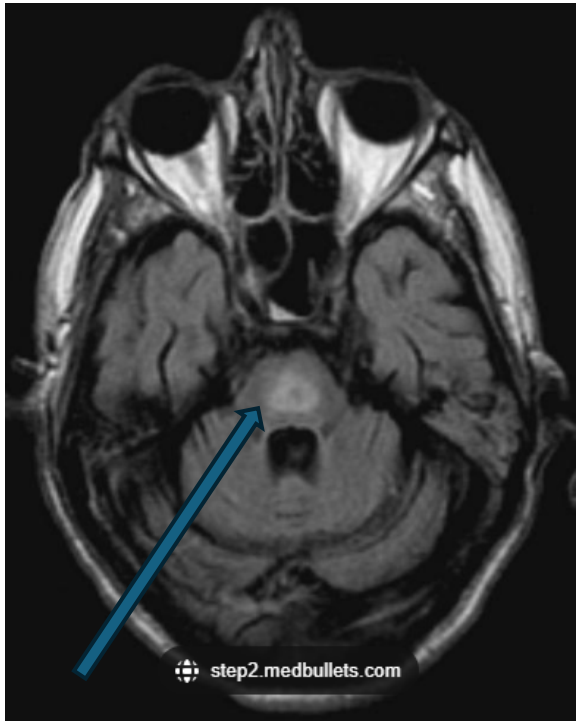


Neurologic symptoms of osmotic demyelination syndrome (ODS) typically occur 2 to 6 days after correction of the hyponatremia. In this patient, severe hyponatremia was corrected too quickly (23 mEq/L in 48 hours), and coma developed 2 days later. The serum sodium was quickly relowered and then slowly corrected. Neurologic symptoms improved, which may have been due to relowering of the serum sodium or may have represented spontaneous resolution.

sNa: serum sodium.

ODS Diagnosis: Clinical

- Imaging: brain MRI
  - Bright spot in pons



- central pontine demyelination **only**
- **both** central pontine and extrapontine demyelination
- **extrapontine** demyelination only

Other hyponatremias to be aware of: **Hyperglycemia → Hyponatremia**

- **Corrected Serum Sodium Formula:**
  - 📐 **Corrected Na^+=Measured Na^++2 mEq/L for every 100 mg/dL glucose > 100**
  - useful to assess whether hyponatremia can be fully explained by hyperglycemia.
- **Mechanism**:
  - 💧 High glucose pulls water out of cells → dilutes serum sodium.

- 🧪 **Extra Note for Severe Hyperglycemia (> 650 mg/dL):**
  - May also have **pseudohyponatremia** due to **lab artifact**.
  - High glucose interferes with **indirect** sodium measurement using ion-selective electrodes.
  - -> order **“whole blood sodium”**

Example calculation for pseudohyponatremia

Glucose: 400 mg/dL → 300 mg/dL above normal (100)

Measured Na^+: 130 mEq/L

Correction: Add 2 mEq/L for each 100 mg/dL glucose above normal

Corrected $Na^+ = 130 + (2 \times 3) = \mathbf{136\ mEq/L}$

Study Guide: click here

🙏 😄 THANK YOU!

Thanks for staying awake through this tough topic on hyponatremia!
I appreciate your focus and energy.
Looking forward to seeing you all on the wards! 👋🩺✨

Review questions

1. What is the main reason for ADH release in primary adrenal insufficiency?
2. What medications can be used to bind to V2 receptor that usually binds ADH?
3. What makes ADH ? – paraventricular neurons of hypothalamus as pre-pro-AVP
4. What stores ADH ? – posterior pituitary
5. What must be present in order for water reabsorption to occur once ADH binds to its receptor and increases number of AQP channels? – osmotic gradient
6. Which diuretic is likely to cause hyponatremia, loop or distal?
7. Which diuretic can be used to treat hyponatremia, loop or distal?
8. Hyperkalemia occurs w/ primary adrenal insufficiency or secondary and why?
9. Be able to interpret urine sodium without doing FENA
10. How much “salt” or NaCL is in 1 liter 0.9NS? 9 gm
11. How much “sodium” or Na is in 1 liter 0.9NS? ~ 3.5 gm
12. **to ponder on … do esrd or anephric patients have nephrons, how do they get hyponatremic**

- Thiazide mediated hyponatremia is purely d/t development of hypovolemia? T/F
- Name some non-osmotic stimuli for ADH release
- What is the most important treatment for SIADH? Fluid restriction 800ml to 1000ml
- Why do we have to rely on physical exam and history for assessment rather than just measure ADH? -- ADH is not measurable , copeptin is but not common in clinical practice
- Which molecule serves as a surrogate for ADH? – copeptin
- What is the major determinant of plasma osmolality? Potassium, sodium, urea, glucose ?? .. Sodium ; when you have hyponatremia serum osm should be also low
- T or F, Only factor to cause in thiazide hyponatremia is volume depletion
- How does tolvaptan treat hyponatremia?
- In which case you cannot administer tolvaptan?
- T or F, it safe to administer oral salt tab to patients with peripheral, pulmonary, or both edema
- T or F , a single cause can explain why hyponatremia may develop in primary adrenal insufficiency

From the perspective of salt: the lay of the land

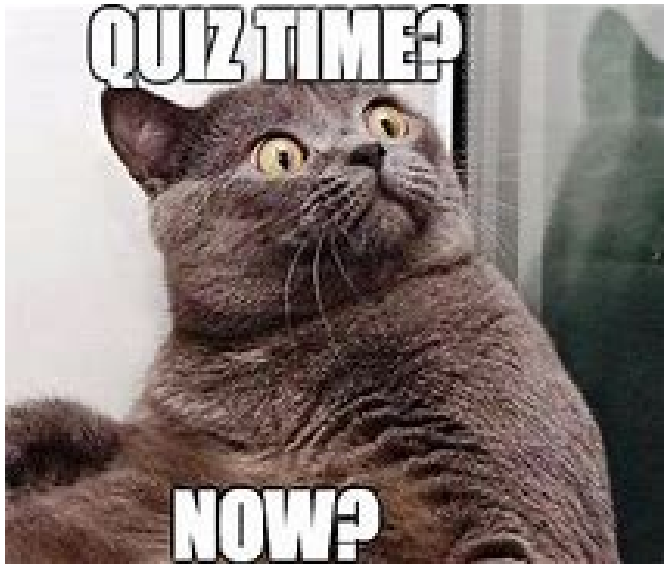
- Teaspoon of salt -> 2300mg of Na+ (NA+ vs NACL)
- 2000mg is typical total **daily** sodium restriction for patients with congestive heart failure, chronic kidney disease, hypertension, and cirrhosis

Type	Approximate amount of sodium in 1 teaspoon
Iodized table salt, fine	2,300 mg
Kosher salt, coarse	1,920 mg
Kosher salt, fine, Diamond Crystal®†	1,120 mg
Sea salt, fine	2,120 mg
Sea salt, coarse	1,560 mg
Pink (Himalayan) salt	2,200 mg
Black salt	1,150–2,200 mg
Fleur de sel	1,560–2,320 mg
Potassium salt (salt substitute)	0 mg (contains 2,760–3,180 mg potassium)

Salt and Sodium | The Nutrition Source | Harvard T.H. Chan School of Public Health

Trivia

- How much sodium is in sea water?
  - **Seawater** has a salinity of about 3.5% (35 g/L, 35 ppt, 600 mM)
  - * this is **equivalent** to **3% saline (IV)**
- How much sodium is in tablespoon soy sauce?
  - **1 tablespoon** of table salt contains ~ **1000 milligram**s of sodium.



Salt Comparisons

- Condensed soup 1600mg per

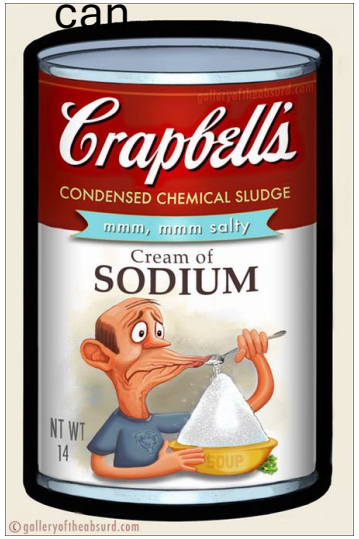
- 0.9% Saline (1L) 3500mg of Na

- 3% Saline (1L) (12,000mg)

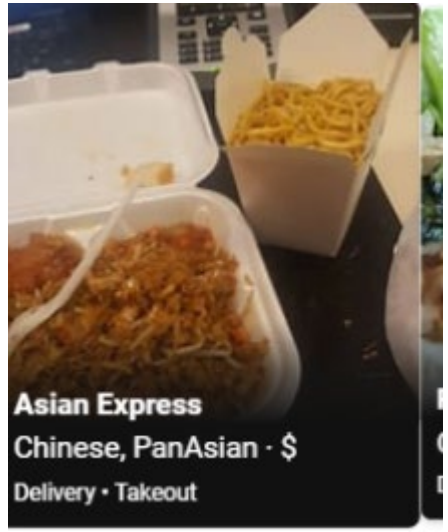
Salt Loading

1260

Condensed soup 1600mg per can



Asian take out: chow main- **980**, kang pau chicken – **800**, egg roll **390**, hot and saur soup **– 930** , soy sauce tablespoon - **1,000** mg per tablespoon



Average American total daily sodium intake = 6000 – 7000 or more ….

Should we advise someone with hyponatremia to drink Gatorade – an electrolyte rich fluid ?

How many teaspoons of sodium are in a liter of Gatorade?

Gatorade

Nutrition Facts

Serving Size 8 fl oz (240 mL)
Servings Per Container 4

Amount Per Serving	
Calories 50	
	% Daily Value*
Total Fat 0g	**0%**
Sodium 110mg	**5%**
Potassium 30mg	**1%**
Total Carbohydrate 14g	**5%**
Sugars 14g	
Protein 0g	

Not a significant source of Calories from Fat, Saturated Fat, Cholesterol, Dietary Fiber, Vitamin A, Vitamin C, Calcium, Iron.

* Percent Daily Values are based on a 2,000 calorie diet.

- One bottle 1 liter of Gatorade
  - 110mg of sodium per serving x 4 servings => 440mg per liter
  - 1/5th of teaspoon! (19meQ of NA)

Can you replace salt (rehydrate with electrolytes (AKA sodium) with Gatorade?NO

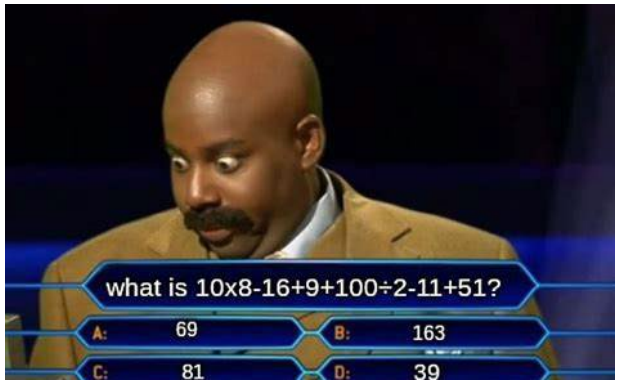
Can you replace salt (rehydrate with electrolytes (AKA sodium) with soy sauce? – YES
1.5 tablespoons and four cups of water

Thus you are adding 960ml of ‘free ‘ water (almost same as a liter of D5W) to your ECF and ICF (2/3, 1/3)

Gatorade Trivia

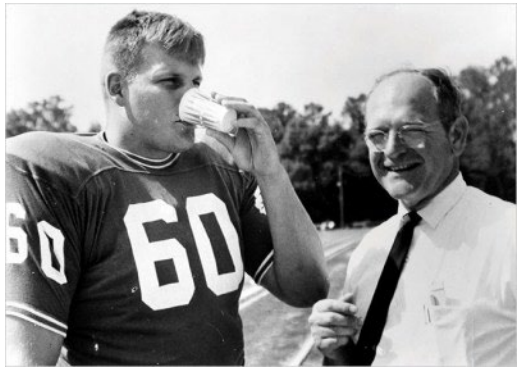
- Who is the lead inventor for Gatorade and it’s billion $$$ business?

“The test won’t even be that hard. It’s multiple choice.”



University of Florida **Nephrologist**

- Dr. J Robert Cade (1927-2007)



•Sodium 45 mEq (45x23=**1035mg**) in 1 liter

Oral Rehydration Therapy

PEDIALYTE (1 liter)

½ teaspoon of salt (same is in McD’s breakfast sandwich and less than in a can of soup)

Osmolality 250 mOsm/kg

Sodium 45 mEq (45x23=**1035mg**)

Potassium 20 mEq

Chloride 35 mEq