

Psychotropic-induced hyponatremia

David J. Butterfield, PharmD, BCPS, BCPP, Shannon Eaves, PharmD, BCPS, BCPP, and Carol Ott, PharmD, BCPP



Vicki L. Ellingrod,
PharmD, FCCP
Department Editor

Hyponatremia is a common, multifactorial clinical condition. Hyponatremia is usually defined as a plasma sodium level <135 mmol/L; however, some studies define it as a level <130 mmol/L. Hyponatremia results from the inability of the kidney to excrete a sufficient amount of fluid, or is due to excessive fluid intake. Increases in osmolality stimulate thirst and result in increased fluid intake. This increase in osmolality is recognized by the osmoreceptors located in the hypothalamus, which release antidiuretic hormone (ADH). Antidiuretic hormone works on the collecting ducts within the kidneys, triggering increased fluid reabsorption resulting in decreased fluid loss and a reduction in thirst.

The syndrome of inappropriate antidiuretic hormone (SIADH) occurs when there is persistent ADH stimulation resulting in hyponatremia. SIADH commonly presents as euvolemic hyponatremia. Common diagnostic criteria for SIADH are listed in *Table 1*¹ (page 37).

Medications are a major cause of SIADH, and psychotropics are a primary offender. Most of the data for drug-induced SIADH come from case reports and small case series, such as those described in *Table 2*²⁻⁴ (page 37). The extent to which each psychotropic class

causes SIADH remains unknown. In this article, we focus on 3 classes of psychotropics, and their role in causing SIADH.

Antidepressants

There is a fair amount of data associating antidepressants with SIADH. The incidence of SIADH with selective serotonin reuptake inhibitors (SSRIs) varies greatly among studies, from .06% to 40%.⁵⁻¹² This wide variation is due to the way each study defined hyponatremia. A higher incidence was found when hyponatremia was defined as <135 mmol/L as opposed to <130 mmol/L. A large cohort study of SSRIs found that there was an increased risk with fluoxetine, escitalopram, and

Practice Points

- **Syndrome of inappropriate antidiuretic hormone (SIADH) is a drug-induced complication;** psychotropics are primary causative agents.
- **Serum sodium concentrations should be monitored in patients receiving psychotropic medications,** especially those at risk of hyponatremia (ie, age >65).
- **If SIADH is suspected, discontinue the offending agent and treat by restricting fluids or administering hypertonic saline,** based on the patient's clinical presentation.
- Once hyponatremia has resolved, **prescribe a medication from a different class** to minimize the risk of SIADH recurrence.

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists
cpnp.org
mhc.cpnp.org (journal)



Dr. Butterfield is Psychiatric Clinical Pharmacist, Pharmacy, Community Health Network, Indianapolis, Indiana. Dr. Eaves is Psychiatric Clinical Pharmacist, Pharmacy, Midtown/Eskenazi Health, and Dr. Ott is Psychiatric Clinical Pharmacist/Clinical Professor, Pharmacy, Eskenazi Health/Purdue University College of Pharmacy, Indianapolis, Indiana.

Disclosures

The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

Table 1

Common diagnostic criteria for SIADH

Common diagnostic criteria for SIADH	Criteria indicating likely not SIADH
Decreased serum osmolality (<275 mOsm/kg)	Urine osmolality <100 mOsm/kg
Euvolemia	Increased or decreased volume status
Urine osmolality >100 mOsm/kg	Hyperglycemia
Urinary sodium excretion >40 mmol/L	Polydipsia/polyuria
Normal renal function	Severe hyperlipidemia
Hyponatremia (sodium <135 mmol/L)	

SIADH: syndrome of inappropriate antidiuretic hormone
Source: Reference 1

Table 2

Syndrome of inappropriate antidiuretic hormone: 3 Case reports

Reference	Patient	Synopsis
Kenes et al ² (2016)	Man, age 27, with no psychiatric history was admitted with a traumatic brain injury after pedestrian vs car accident	Due to agitation, patient received haloperidol, 10 mg IV, every 2 hours as needed and quetiapine, 200 mg, every 6 hours as needed. The patient's sodium level was 140 mmol/L on admission, decreased to 126 mmol/L after 7 days, and eventually reached 123 mmol/L on hospital Day 8. His serum osmolality was 271 mOsm/kg. The patient was diagnosed with SIADH, and haloperidol and quetiapine were discontinued. Serum sodium was corrected by hospital Day 9 to 133 mmol/L. Later in hospital course, patient was rechallenged with quetiapine, 100 mg, every 6 hours as needed for agitation, and his serum sodium decreased again from 134 to 127 mmol/L
Twardowsky et al ³ (2006)	Woman, age 53, was started on fluoxetine, 20 mg/d, for treatment of depression	Nine days after initiation of fluoxetine, the patient presented with weakness, nausea, confusion, and vomiting. Three hours later, she became unresponsive and had a seizure. Her sodium level was 105 mmol/L, and she was diagnosed with SIADH induced by fluoxetine. Fluoxetine was discontinued, and the patient was treated successfully; her symptoms resolved after 5 days
Patel et al ⁴ (2010)	Man, age 54, with history of schizophrenia was admitted to an inpatient psychiatry unit	Baseline laboratory tests revealed a sodium level of 139 mmol/L. He was started on risperidone but was later found to have a mood component to his illness and the diagnosis was revised to schizoaffective disorder. He was started on valproate sodium. The dose was titrated up to 2,000 mg/d at bedtime after 1 week. After titration, his sodium level decreased to 126 mmol/L. Plasma osmolality was drawn and found to be 259 mOsm/kg. His serum sodium valproate level at this time was 57 mg/L. Sodium valproate was tapered off, and his sodium level increased to 137 mmol/L. A presumptive diagnosis of SIADH was made

SIADH: syndrome of inappropriate antidiuretic hormone

Clinical Point

SIADH commonly presents as euvolemic hyponatremia



Discuss this article at www.facebook.com/MDedgePsychiatry

citalopram (.078% to .085%) vs paroxetine and sertraline (.033% to .053%).¹³ Studies comparing the incidence of SIADH with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) found that the rates were equal or

slightly higher with the SNRI venlafaxine.¹³ SNRIs as a group have an estimated incidence of .08% to 4%, based on studies that defined hyponatremia as <130 mmol/L.^{13,14} Tricyclic antidepressants have an estimated incidence of .005%

Clinical Point

Compared with antidepressants, there's less evidence linking SIADH with antipsychotics

Table 3

Studies evaluating the incidence of SIADH with antidepressants

Study	Serum sodium cutoff	Design	Sample size (N)	Age	Drug(s) studied	Incidence rate (%)
Letmaier et al ¹² (2012)	130 mmol/L	Drug surveillance	263,864	≥65 years	SSRIs	.06%
					Venlafaxine	.08%
Coupland et al ¹³ (2011)	130 mmol/L	Cohort	60,746	≥65 years	SSRIs	.44%
Leah-Møller et al ¹⁴ (2016)	130 mmol/L	Register-based population study	638,352	33 years	SSRIs SNRIs TCAs MAOIs	8.9%
Bouman et al ⁷ (1998)	135 mmol/L	Retrospective	32	66 to 87 years	SSRIs	25%
Kirby et al ⁹ (2002)	135 mmol/L	Retrospective	199	74.2 years; range 60 to 100 years	Venlafaxine	71%
					Paroxetine	32%
					Sertraline	29%
					Fluoxetine	60%
De Picker et al ¹⁵ (2014)	135 mmol/L	Retrospective review of 15 studies	8 to 256	49 to 80 years	SSRIs	.06% to 40%
					Venlafaxine	.08% to 71%
					TCAs	.005% to 16.7%

MAOIs: monoamine oxidase inhibitors; SIADH: syndrome of inappropriate antidiuretic hormone; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Table 4

How psychotropics cause SIADH

Psychotropic class	Mechanism
Mood stabilizers	Increases secretion of ADH by the hypothalamus
Antipsychotics	Serotonin effects on 5-HT ₂ and 5-HT _{1C} lead to an increase in ADH Psychogenic polydipsia leads to excessive consumption of water resulting in hyponatremia
Antidepressants	Increases secretion of ADH from the hypothalamus Potentiates the effect of ADH in the kidneys Lowers the threshold for the release of ADH

ADH: antidiuretic hormone; SIADH: syndrome of inappropriate antidiuretic hormone
Source: Adapted from reference 24

to 16.7%, based on a retrospective study that reviewed 15 studies and 100 case reports.¹⁵ Mirtazapine and bupropion do not have enough evidence to obtain a true definition of incidence; case reports for these drugs suggest a causal link for hyponatremia. *Table 3*^{7,9,12-15} provides an

overview of the incidence rate of hyponatremia for select antidepressants. It is clear that a more stringent cutoff for hyponatremia (<130 mmol/L) reduces the incidence rates. More evidence is needed to identify the true incidence and prevalence of SIADH with these agents.

continued on page 40

continued from page 38

Table 5

Diagnosis of SIADH vs psychogenic polydipsia

Disease	Signs/symptoms	Lab values/notes
Hyponatremia from polydipsia	Lethargy Confusion Seizures Ataxia	Serum osmolality: <280 mOsm/kg Urine osmolality: <100 mOsm/kg Urine sodium: ≤20 mmol/L Serum sodium: <135 mmol/L
SIADH	Lethargy Confusion Seizures Ataxia	Serum osmolality: <280 mOsm/kg Urine sodium: >40 mmol/L Patient is receiving a medication that can cause SIADH (antidepressants, antipsychotics, mood stabilizers)

SIADH: syndrome of inappropriate antidiuretic hormone
Source: Adapted from reference 25

Clinical Point

SIADH and psychogenic polydipsia both result in hyponatremia, and can be hard to differentiate

Table 6

Causes of hyponatremia other than SIADH

Cause	Diagnostic marker	Treatment
Diuretic use	Urine sodium >20 mmol/L	Discontinue diuretic
Gastrointestinal losses	Urine sodium <20 mmol/L	IV fluids
Hypothyroidism	Elevated thyroid-stimulating hormone value	Thyroid replacement therapy (levothyroxine)
Renal failure	Elevated BUN-to-creatinine ratio Urine sodium >20 mmol/L	Correct underlying disease
Chronic hyponatremia	Sodium <135 mmol/L	Reduce free water intake (<1 L/d)
Low BMI or female sex	N/A	Monitor sodium more closely (every 3 to 4 weeks) while patient is receiving a medication that can cause hyponatremia

BMI: body mass index; BUN: blood urea nitrogen; SIADH: syndrome of inappropriate antidiuretic hormone
Source: Adapted from reference 26

Antipsychotics

Compared with antidepressants, there's less evidence linking SIADH with antipsychotics; this data come mainly from case reports and observational studies. Serrano et al¹⁶ reported on a cross-sectional study that included 88 patients receiving clozapine, 61 patients receiving other atypical antipsychotics, 23 patients receiving typical antipsychotics, and 11 patients receiving both typical and atypical antipsychotics. They reported incidence rates of 3.4% for clozapine, 4.9% for atypical antipsychotics, 26.1% for typical antipsychotics, and 9.1% for the group receiving both typical and atypical antipsychotics.¹⁶ The primary

theory for the decreased incidence of SIADH with use of atypical antipsychotics is related to decreased rates of psychogenic polydipsia leading to lower incidence of hyponatremia.

Mood stabilizers

Several studies have associated carbamazepine/oxcarbazepine, valproic acid, and lamotrigine with SIADH.¹⁷⁻²³ Studies show incidence rates ranging from 4.8% to 41.5% for these medications. Carbamazepine appears to have the highest incidence of SIADH. A limitation of these studies is the small sample sizes, which ranged from 12 to 60 participants.

Pathophysiology

The kidneys are responsible for maintaining homeostasis between bodily fluids and serum sodium levels. ADH, which is produced by the hypothalamus, plays a significant role in fluid balance, thirst, and fluid retention. Inappropriate and continuous secretion of ADH, despite normal or high fluid status, results in hyposmolality and hyponatremia. The specific mechanisms by which psychotropic medications cause SIADH are listed in *Table 4*²⁴ (page 38).

Diagnosis

Diagnosis of SIADH can be complex because there are many clinical reasons a patient may have hyponatremia. For example, SIADH and psychogenic polydipsia both result in hyponatremia, and sometimes the 2 conditions can be difficult to distinguish. Hyponatremia is typically discovered by routine blood testing if the patient is asymptomatic. *Table 5*²⁵ (page 40) highlights the major laboratory markers that distinguish SIADH and psychogenic polydipsia.

Treatment

The primary treatment for SIADH is cessation of the offending agent. Based on the patient's clinical presentation, free water restriction (.5 to 1 L/d) can be implemented to increase serum sodium levels. If the patient is having neurologic complications due to the severity of hyponatremia, correction with hypertonic saline is indicated. Upon resolution, the recommended course of action is to switch to a medication in a different class. Re-challenging the patient with the same medication is not recommended unless there is no other alternative class of medication.²⁴ *Table 6*²⁶ (page 40) highlights other causes of hyponatremia, what laboratory markers to assess, and how to treat high-risk individuals.

Hyponatremia is a complex medical complication that can be life-threatening. Psychotropics are a relatively common cause of hyponatremia, specifically SIADH. Older adults appear to be at highest risk, as most

Related Resources

- Spasovski G, Vanholder R, Alolio B, et al. Clinical practice guidelines on diagnosis and treatment of hyponatremia. *Eur J Endocrinol.* 2014;170(3):G1-G47.
- Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126(10 Suppl 1):S1-S42.

Drug Brand Names

Bupropion • Wellbutrin	Mirtazapine • Remeron
Carbamazepine • Tegretol	Oxcarbazepine • Trileptal
Citalopram • Celexa	Paroxetine • Paxil
Clozapine • Clozaril	Quetiapine • Seroquel
Escitalopram • Lexapro	Risperidone • Risperdal
Fluoxetine • Prozac	Sertraline • Zoloft
Haloperidol • Haldol	Valproic acid • Depakote
Lamotrigine • Lamictal	Venlafaxine • Effexor
Levathroxine • Levotiroid	

case reports are in patients age ≥ 65 . Patients who are prescribed psychotropics should be treated with the lowest effective dose and monitored for signs and symptoms of hyponatremia throughout therapy.

References

1. Sahay M, Sahay R. Hyponatremia: a practical approach. *Indian J Endocrinol Metab.* 2014;18(6):760-771.
2. Kenes MT, Hamblin S, Tumuluri SS, et al. Syndrome of inappropriate antidiuretic hormone in a patient receiving high-dose haloperidol and quetiapine therapy. *J Neuropsychiatry Clin Neurosci.* 2016;28(2):e29-e30. doi: 10.1176/appi.neuropsych.15110392.
3. Twardowsky CA, Bertolucci CB, Gracia Cde M, et al. Severe hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with fluoxetine: case report. *Arq Neuropsiquiatr.* 2006;64(1):142-145.
4. Patel KR, Meesala A, Stanilla JK. Sodium valproate-induced hyponatremia: a case report. *Prim Care Companion J Clin Psychiatry.* 2010;12(5):PCC.09100941. doi: 10.4088/PCC.09100941.
5. Pillans PI, Coulter DM. Fluoxetine and hyponatraemia—a potential hazard in the elderly. *N Z Med J.* 1994;107(973):85-86.
6. Strachan J, Shepherd J. Hyponatraemia associated with the use of selective serotonin reuptake inhibitors. *Aust N Z J Psychiatry.* 1998;32(2):295-298.
7. Bouman WP, Pinner G, Johnson H. Incidence of selective serotonin reuptake inhibitor (SSRI) induced hyponatraemia due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion in the elderly. *Int J Geriatr Psychiatry.* 1998;13(1):12-15.
8. Wilkinson TJ, Begg EJ, Winter AC, et al. Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol.* 1999;47(2):211-217.
9. Kirby D, Harrigan S, Ames D. Hyponatraemia in elderly psychiatric patients treated with selective serotonin reuptake inhibitors and venlafaxine: a retrospective controlled study in an inpatient unit. *Int J Geriatr Psychiatry.* 2002;17(3):231-237.
10. Wee R, Lim WK. Selective serotonin re-uptake inhibitors (SSRIs) and hyponatraemia in the elderly. *Int J Geriatr Psychiatry.* 2004;19(6):590-591.

Clinical Point

The primary treatment for SIADH is cessation of the offending agent

Clinical Point

Once SIADH has resolved, switch to a medication in a different class

11. Jung YE, Jun TY, Kim KS, et al. Hyponatremia associated with selective serotonin reuptake inhibitors, mirtazapine, and venlafaxine in Korean patients with major depressive disorder. *Int J Clin Pharmacol Ther*. 2011;49(7):437-443.
12. Letmaier M, Painold A, Holl AK, et al. Hyponatremia during psychopharmacological treatment: Results of a drug surveillance program. *Int J Neuropsychopharmacol*. 2012;15(6):739-748.
13. Coupland CA, Dhiman P, Barton G, et al. A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database. *Health Technol Assess*. 2011;15(28):1-202, iii-iv.
14. Leah-Møller KB, Hansen AH, Torstensson M, et al. Antidepressants and the risk of hyponatremia: a Danish register-based population study. *BMJ Open*. 2016;6(5):e011200. doi: 10.1136/bmjopen-2016-011200.
15. De Picker LD, Van Den Eede F, Dumont G, et al. Antidepressants and the risk of hyponatremia: a class by class review of literature. *Psychosomatics*. 2014;55(6):536-547.
16. Serrano A, Rangel N, Carrizo E, et al. Safety of long-term clozapine administration. Frequency of cardiomyopathy and hyponatremia: two cross-sectional, naturalistic studies. *Aust N Z J Psychiatry*. 2014;48(2):183-192.
17. Uhde TW, Post RM. Effects of carbamazepine on serum electrolytes: clinical and theoretical implications. *J Clin Psychopharmacol*. 1983;3(2):103-106.
18. Lahr MB. Hyponatremia during carbamazepine therapy. *Clin Pharmacol Ther*. 1985;37(6):693-696.
19. Joffe RT, Post RM, Uhde TW. Effects of carbamazepine on serum electrolytes in affectively ill patients. *Psychol Med*. 1986;16(2):331-335.
20. Vieweg V, Glick JL, Herring S, et al. Absence of carbamazepine-induced hyponatremia among patients also given lithium. *Am J Psychiatry*. 1987;144(7):943-947.
21. Yassa R, Iskandar H, Nastase C, et al. Carbamazepine and hyponatremia in patients with affective disorder. *Am J Psychiatry*. 1988;145(3):339-342.
22. Kastner T, Friedman DL, Pond WS. Carbamazepine-induced hyponatremia in patients with mental retardation. *Am J Ment Retard*. 1992;96(5):536-540.
23. Kelly BD, Hillery J. Hyponatremia during carbamazepine therapy in patients with intellectual disability. *J Intellect Disabil Res*. 2001;45(Pt 2):152-156.
24. Sahoo S, Grover S. Hyponatremia and psychotropics. *J Geriatr Ment Health*. 2016;3(2):108-122.
25. Siragy HM. Hyponatremia, fluid-electrolyte disorders and the syndrome of inappropriate antidiuretic hormone secretion: diagnosis and treatment options. *Endocr Pract*. 2006;12(4):446-457.
26. Braun M, Barstow CH, Pyzocha NJ. Diagnosis and management of sodium disorders: hyponatremia and hypernatremia. *Am Fam Physician*. 2015;91(5):299-307.