



REVIEW

Psychotropic-Induced Hyponatremia: A Review

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ABSTRACT

Psychotropic-induced hyponatremia is the most common electrolyte imbalance experienced in the psychiatric clinical practice. It is commonly seen in geriatric patients and it is always overlooked and untreated in psychiatric patients and this would explain why it leads to increased mortality. Psychotropic drugs such as antidepressants, antipsychotics, mood stabilizers, and sedative-hypnotics can lead to hyponatremia, while it commonly occurs in antidepressant use. In this review, a thorough search was performed using the databases of ResearchGate, PubMed, Scopus, PsycInfo, ScienceDirect, and Google Scholar. This review aimed to shed light on the probable psychopathology, evaluation of hyponatremia, a closer look at different types of hyponatremia, and its incidence with various psychotropic medications. We also summarized the clinical presentations of hyponatremia, the identified risk factors with various psychotropic, and concluded by discussing the mainstay management of hyponatremia.

Keywords: Antipsychotics, hyponatremia, selective serotonin reuptake inhibitors, syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

INTRODUCTION

Sodium is an electrolyte, and it helps to regulate the amount of water that's in and around the cells. It is a most common electrolyte abnormality seen in psychiatric as well as other clinical practices and is associated with multiple poor clinical after effects including falls, fractures, long hospital stay and mortality.

Hyponatremia, is defined as the serum sodium level below 135 mmol/L (1, 2). The condition is rarely symptomatic until serum sodium level falls below 120 mmol/L and become symptomatic if it is 110 mmol/L. It is especially seen in patients with alcohol use disorder and it has the mortality rate over 50 percent. Among beer drinkers and malnourished patients always have reduced ability to excrete free water based on low intake and such patients develop hyponatremia with low urine osmolality.

The primary symptoms of hyponatremia are restlessness, drowsiness, myoclonic jerks, and generalized convulsions followed by confusion, coma and death if not treated properly. It occurs in the hospitalized patients as well as in routine (outpatient) psychiatric clinical practice (3). It also exacerbates psychotic symptoms. Some studies said that hyponatremia evolve in a general hospital population as it occurs in about 1 percent of patients (4). In psychiatric patients the frequency of hyponatremia has been reported to range from 3.3 percent to 12.2 percent (5). It commonly occurs in old age patients, those who are hospitalized or living in long-term care facilities because of the higher rate of comorbid conditions such as cardiac, hepatic, or renal failure which could lead to hyponatremia. Even though it is estimated that nearly 7% of healthy elderly persons have serum sodium concentrations of 137 mEq/L or less (6). However, in some studies it was reported that hyponatremia may have been present in 15 to 18 percent of patients in chronic care facilities (7).

Hyponatremia resulting from inappropriate secretion of antidiuretic hormone and renal sodium loss referred SIADH (syndrome of inappropriate secretion of

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antidiuretic hormone). It is thought to be most important mechanism lying in drug-induced hyponatremia. It was first described by Schwartz and colleagues in 1957 as a manifestation of dilutional hyponatremia. It is caused by water retention in euvolaemic patients with normal renal, liver, adrenal and thyroid function (8). The most common cause of SIADH is due to drugs like nicotine, barbiturates, opiates, carbamazepine, chlorpropamide, cytotoxic, and psychotropic. Some studies also suggested that aggravated psychosis in psychiatric patient might be because of hyponatremia independent of drug therapy (9).

There are many risk factors in psychiatric patients such as old age, history of prior hyponatremia, smoking, polydipsia and schizophrenia (10), as well as early onset of the psychiatric disorder below the age 20 years, longer duration of psychiatric disease more than 10 years and longer duration of hospital stay (5). An important risk factor is neuroleptic malignant syndrome (11). If hyponatremia is overlooked or left untreated, it can lead to fatal complications and serious clinical consequences such as delirium, seizures or rhabdomyolysis.

The diagnosis of hyponatremia can prove to be a challenging task since initial symptomatology may mimic psychiatric illness. Subsequent treatment and accurate diagnosis is essential as this disorder can progress to seizures, coma and death if not treated appropriately. Neither the true incidence nor the etiology of hyponatremia in patients with schizophrenia has been established, but a definite association has been shown to exist. Most of the times hyponatremia highlights the difficulties in identifying the illness in patients with schizophrenia. A discussion of the etiology, differential diagnosis and treatment follows, with the aim of increasing awareness of this potentially serious disorder.

Pathophysiology of hyponatremia

The mechanism behind antipsychotic-induced hyponatremia is development of SIADH. It has been proved from animal studies that psychotropic such as typical and atypical antipsychotics stimulate and facilitate ADH release in the brain.

Atypical antipsychotics such as aripiprazole, quetiapine, clozapine cause hyponatremia due to their

serotonin-mediated effects on central 5-HT₂ and 5-HT_{1c} receptors which lead to release of ADH. Moreover, serotonin is reset the osmostat and thereby it lowers the threshold for ADH secretion. Typical antipsychotics like chlorpromazine, haloperidol, fluphenazine, trifluoperazine, and thioridazine on the other hand have been hypothesized to cause hyponatremia by inducing severe polydipsia by stimulating the thirst center.

Carbamazepine or oxcarbazepine is supposed to induce hyponatremia either by increasing ADH release centrally or by the potentiation of ADH effect. Sodium valproate leads to hyponatremia through the mechanism of development of SIADH, whereas lithium has been associated with the development of paradoxical hyponatremia secondary to lithium-induced diabetes insipidus. On the other hand, lamotrigine has been found to induce hyponatremia by potentiating the renal tubule effects of ADH. Benzodiazepines have also been reported to cause hyponatremia by causing SIADH.

How to evaluate hyponatremia?

Important and necessary criteria for diagnosing hyponatremia are plasma osmolality or tonicity, urinary electrolytes, volume status, fractional excretion of sodium (FeNa), and the ability to rule out hypothyroidism and glucocorticoid deficiency. Hyponatremic patients always asymptomatic and the symptoms often do not occur until the serum sodium concentration drops below 125 mEq per L (125 mmol per L). Psychogenic polydipsia associated with polyuria and polydipsia is commonly seen in psychiatric inpatients and these patients may present with impaired mental status and further exacerbation of psychiatric symptoms. The most common manifestations of hyponatremia are neurological symptoms, due to swelling of brain cells secondary to intracellular movement of water. The symptoms of severe type of hyponatremia may present with nausea, headache, lethargy, confusion, coma or respiratory arrest. If hyponatremia develops suddenly, muscular twitches, irritability, and convulsions can occur. The clinical symptoms of chronic hyponatremia may be lethargy, confusion, and malaise. The first step is to determine the plasma and urine osmolality and to perform a clinical assessment of volume status. If the urine

osmolality is less than 100 mOsm per kg (100 mmol per kg) then psychogenic polydipsia should be evaluated and if the urine osmolality is 100 mOsm per kg or greater, then the renal function should be assessed.

Types of hyponatremia

Hyponatremia can be sub-classified according to tonicity and effective osmolality status namely hypertonic hyponatremia, isotonic hyponatremia and hypotonic hyponatremia.

1. Hypertonic hyponatremia is by (or diagnosed when) plasma osmolality is more than 295 mOsm/kg, and it is, believed that it has artificial etiology.
2. Isotonic hyponatremia is diagnosed if plasma osmolality is in the range of 280–295 mOsm/kg and it is also called pseudo-hyponatremia.
3. Hypotonic hyponatremia, which is the most commonly seen in the clinical settings, and it is characterized by plasma osmolality of less than 280 mOsm/kg. Hypotonic hyponatremia is classified according to volume status, and again sub-classified to; hypervolemic, euvoletic, and hypovolemic hyponatremia.
 - a. Hypervolemic hyponatremia: It is when there is an increase in total body sodium with greater increase in total body water and have expansion of both intracellular and extracellular fluid, but there is reduced effective arterial blood volume. This is frequently associated with azotemia and is seen in patients experiencing advanced renal failure, cirrhosis, heart failure, and nephrotic syndrome.
 - b. Euvoletic hyponatremia: When the values show normal body sodium with increase in total body water. It is characterized by expansion of both intracellular and extracellular fluid; however, is characterized by the absence of edema and is seen in conditions such as psychogenic polydipsia, drug-induced hyponatremia, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion and in endocrinopathies such as hypothyroidism and hypocortisolism.
 - c. Hypovolemic hyponatremia: It is when there is a decrease in total body water with greater decrease in

total body sodium and is characterized by reduced extracellular fluid and occurs when there is primary natriuresis in conditions such as metabolic alkalosis, use of diuretics, and clinical conditions such as diarrhea, pancreatitis, and burns in which there are extrarenal sodium losses (12).

Among the all above causes of hyponatremia, drug-induced hyponatremia is very common. A medications such as diuretics, anticancer drugs, antihypertensives, antidiabetics, anti-inflammatory drugs, antiepileptics, and psychotropics have been reported to be associated with hyponatremia (13).

Hyponatremia with psychotropics

Psychotropic medications have been always associated with hyponatremia, because psychotropic may exhibit the sensation of a dry mouth, which may contribute to increased water intake. According to many studies hyponatremia is reported mostly with antidepressants such as SSRIs, and followed by carbamazepine, antipsychotic, but rarely, reported with benzodiazepine or anxiolytic (14-18). The mechanism of action for development of hyponatremia is thought to be due to SIADH. The most common cause of hyponatremia in this population is the underlying psychosis itself and the compulsive water drinking. Psychotropic drugs like phenothiazines causes anti-cholinergic side effect such as dry mouth and it may contribute to increase in water intake (16).

Antidepressants

There are many studies reported hyponatremia in association with antidepressants, and large amount of data available demonstrating the link between antidepressants and hyponatremia. Among psychotropics antidepressant medications commonly associated with hyponatremia mainly with SSRIs (Selective serotonin reuptake inhibitors), which is thought to causes hyponatremia more frequently than other antidepressant drugs. The incidence of hyponatremia caused by SSRIs varies widely from 0.5 percent to 32 percent. In most of the cases, hyponatremia occurs within the first few weeks of drug therapy, and it subsided within 2 weeks after drug

withdrawal. Geriatric patients and concomitant use of diuretics are the most important risk factors for the development of hyponatremia associated with antidepressant like SSRIs (15, 19). According to some studies, the incidence of hyponatremia is higher with SSRIs compared to TCAs (tricyclic antidepressants) of antidepressant-associated hyponatremia as it ranges from as low as 0.06 percent to as high as 40 percent. A drug surveillance study and population-based cohort study found almost similar results with a significantly increased risk of hyponatremia with fluoxetine, citalopram, and escitalopram and fewer risk with paroxetine and sertraline (20, 21). In other studies between SNRIs and SSRIs which have compared the incidence of hyponatremia, it was found that the incidence was equal or higher with venlafaxine (22, 23). Some studies on geriatric patients found that the incidence of hyponatremia in venlafaxine 17.2 percent and it developed within a few days of starting venlafaxine. Also some case reports of hyponatremia associated with the use of mirtazapine and bupropion, have been described the same among the elderly patients aged more than 60 years patients (24, 25, 26). Even though the data are limited and exact incidence rates are not as clear for antidepressants such as monoamine oxidase inhibitors (MAOIs) and noradrenergic reuptake inhibitors (NARIs), for example reboxetine, have also been associated with hyponatremia (27).

Antipsychotics

Limited studies have tried to evaluate the incidence of hyponatremia with antipsychotics. Available data are mainly in the form of case reports and few observational studies, and this data has been reviewed by some of the researchers (28). Among the atypical antipsychotics, there are case reports of hyponatremia with risperidone, (29) olanzapine, (30) aripiprazole, (31) clozapine, (32) and quetiapine (33). Among typical antipsychotics, phenothiazines are at increased risk of hyponatremia (34). Other neuroleptics like thioridazine, haloperidol, fluphenazine, thiothixene and trifluoperazine, but not molindone reported as the prescribed treatment in a patient with hyponatremia (35). Interestingly enough, data also suggest that atypical antipsychotics help in treating

hyponatremia associated with psychogenic polydipsia. Among those with reported benefit is, clozapine has been reported to be better than other antipsychotics (18, 36) although some case reports suggest that risperidone and olanzapine are also effective (37, 38).

Mood stabilizers

Mood stabilizers like, carbamazepine (CBZ) or oxcarbazepine, valproate, and lamotrigine have been found to cause hyponatremia in several studies (39-43). The above three classical mood stabilizers carbamazepine is medication most commonly to cause hyponatremia. Most of the patient with CBZ-induced hyponatremia is asymptomatic. CBZ has antidiuretic properties, which was responsible for water intoxication and dilutional hyponatremia. The incidence rate of hyponatremia with carbamazepine varies from 4.8% to 41.5% depending on the patient population studied (43-44). These studies have included patients with affective or psychotic disorders, mental retardation or intellectual disability. Data are limited for lamotrigine-induced hyponatremia. (45).

Sedatives or hypnotics

There are few reports of hyponatremia associated with anxiolytics and hypnotics. However, there are some isolated case reports of benzodiazepine or hypnotic-induced hyponatremia. Several benzodiazepines such as alprazolam, lorazepam, clonazepam, oxazepam, triazolam, temazepam, clorazepate, and zolpidem such as nonbenzodiazepine hypnotic have also, been reported to have a link with development of hyponatremia (46, 47).

Clinical features of hyponatremia

Initially hyponatremia is asymptomatic; if the serum sodium level start decreasing in patients start complaining headache, muscle weakness, spasms and cramps, lethargy, confusion and can have severe agitation. Table 1 displays the classification associated with clinical manifestation of hyponatremia. Severe signs and symptoms include seizures, stupor, Cheyne–Stokes breathing, diminished deep tendon reflexes and may lead to coma, if the serum sodium level drops below 120 mmol/L (48). Chronic untreated mild hyponatremia in elderly patient has been

Table 1: Clinical manifestations of hyponatremia

Classification	Serum sodium level	Clinical features
Mild hyponatremia	130–134 mmol/L	Initially asymptomatic, later patients present with headache, nausea, muscle cramps, vomiting, fatigue, anorexia, confusion
Moderate hyponatremia	125–129 mmol/L	Disturbances in gait, headache, vomiting, fatigue, confusion, muscle weakness, spasms and cramps, depressed deep tendon reflexes
Severe hyponatremia	Less than 125	Restlessness, agitation or lethargy, delirium, seizures, brainstem herniation, respiratory arrest, coma, death

found to be associated with recurrent falls (49), bone demineralization or osteoporosis (50), hip fractures (51) and cognitive impairment (52). Improved quality of life and decrease mortality is seen if careful correction of the hyponatremia was done (52), all these abnormalities are reversible.

Risk factor of hyponatremia

There are several risk factors for developing hyponatremia secondary to psychotropics use. Table 2 shows the risk factors for development of hyponatremia with psychotropics. Age is one of the important risk factor for the development of hyponatremia associated with antidepressants. Other risk factors for psychotropic-induced hyponatremia such as polypharmacy, gender, duration of psychotropic drug use, type of psychotropic drug. Literature in many studies showed that older age is at significant risk factor for development of drug-induced hyponatremia, though it has also been reported in young patients rarely (53). The higher risk of hyponatremia is closely associated with the age-related physiology. Elderly patients are always prone to dehydrated, and used to frequent falls and they suffer multiple comorbidities, and

they use of multiple medications, which increases the risk of hyponatremia (54). Comorbid medical conditions such as; diabetes mellitus, hypertension, heart failure, liver cirrhosis, hypothyroidism, COPD (chronic obstructive pulmonary disease), head injury, stroke and malignancies and decreased glomerular filtration rate each is on its own for independent risk factor for development of hyponatremia (55, 56). It is also found that the incidence of hyponatremia is seen in elderly female patient and more among low body weight or those weighing less than 60 kg. Past history of hyponatremia, are also one of the risk factor of developing antidepressant-associated hyponatremia (57). Antidepressant-induced hyponatremia has been reported to be during the summer season (58) which means that we must consider also the environmental risk factor. Hyponatremia has also been reported in psychiatric patients with the following diagnosis; schizophrenia, psychotic depression, bipolar disorder, substance use disorders, anorexia nervosa, mental retardation, and other neuropsychiatric conditions such as epilepsy, psychogenic polydipsia is seen in 6–20% of psychiatric patients. Psychotropic-associated hyponatremia increases with concomitant use of other

Table 2: Risk factors for development of hyponatremia with psychotropics

Prevalence: Elderly and female patient
Physical appearance of patient: Decrease body weight
History: Past history of hyponatremia
Baseline serum sodium levels: Low baseline serum sodium levels
Climate: Summer season
Character of condition: Longer duration of psychiatric illness, early-onset psychiatric illnesses long stay in hospital
Co-morbid medical conditions: Hypertension, diabetes mellitus, heart failure, liver cirrhosis, hypothyroidism, COPD, head Injury, stroke and malignancies
Medications: Antidepressants, antihypertensive, diuretics, cytochrome P450 inhibitors
Psychotropic dosage: Higher dose in case of carbamazepine, antidepressants, and antipsychotics dosage; not conclusive
Duration of treatment: During the initial phase of treatment
Polypharmacy

Table 3: Management of psychotropic-induced hyponatremia

Mild hyponatremia (130–134 mmol/L)	Moderate hyponatremia (125–129 mmol/L)	Severe hyponatremia (less than 125 mmol/L)
<ul style="list-style-type: none"> • First; wait and watch then addition of extra salt in diet. • Discontinuation of the drug may be considered, if worsening of serum sodium level. • If discontinuation does not affect to an increase in the serum sodium level, water restriction should be apply, around (0.5 to 1 L/day) may be used. 	<ul style="list-style-type: none"> • Discontinuation of causative agent associated with water restriction (0.5 to 1 L/day) may be used. • Correction of hyponatremia with hypertonic saline if patient is having neurological signs and symptoms of hyponatremia. • To follow medicine consultation, Vaptan therapy is last-line treatment of hyponatremia. 	
<ul style="list-style-type: none"> • Avoid the medications from the same group and switch to another group of psychotropics 		

medications needed to treat comorbid medical illness including; antihypertensives, antidiabetics, diuretics, proton pump inhibitors, antibiotics, antiepileptics, and nonsteroidal anti-inflammatory drugs (59). Psychotropic-induced hyponatremia usually develop during the initial phase of treatment.

Diet style and other electrolyte abnormalities associated with hyponatremia

There is a relation between hyponatremia and diet style and other electrolyte abnormalities, different types of foods and drinks can be consumed to support an increase in sodium levels. Consuming electrolyte drinks is an easy way to supplement your body and support building the electrolyte balance of sodium, calcium, potassium, chlorine, magnesium, and bicarbonate. Wakame, kelp, Swiss chard, beet greens and oysters are foods that are naturally very rich in sodium, with over 65 milligrams of sodium per serving. Using average table salt is another easy way to support increasing the sodium levels of your body.

Before managing hyponatremic patient we should consult other clinicians for, patients with high-risk factors for developing severe hyponatremia after starting psychotropics. The clinicians should consider informing patients about the risk of hyponatremia, preventive fluid moderation or restriction, and following serum sodium at 1 or 2 weeks. The clinicians should take a detailed history of psychotropic use, especially for the duration of new psychotropic use for inpatients with serious hyponatremia.

Management of hyponatremia

The basics of the treatment of hyponatremia are to focus on the removal of free water, treatment of underlying causes, and use of saline infusion to replace the lost

sodium (60). Treatment is further categorized on the basis of the severity of the symptoms, which depends on the sodium level, time to development, and patient symptoms. In mild-to-moderate hyponatremia treatment should be focus on treating the underlying cause, and further therapy considerations are dependent on the etiology. Whereas in severe hyponatremia patient should be in critical care setting with isotonic or hypertonic fluids and frequent monitoring of serum sodium in order to ensure a safe rate of sodium correction. Table 3 shows management of psychotropic-induced hyponatremia.

The following step-wise procedure should be followed:

Step-1: Attention on all possible precipitating factors.

If hyponatremia is detected in patient receiving psychotropic medication, then for the possible etiology of hyponatremia should be done to rule out all other possible or precipitating causes of hyponatremia such as heart failure, dehydration, and cirrhosis before attributing the same to psychotropic medication only.

Step-2: Look and review the prescription. Medications known to cause hyponatremia should preferably be discontinued after reviewing the medications. For example, concurrent use of diuretics and SSRIs can both lead to low serum sodium. Nonsteroidal anti-inflammatory and thiazide diuretics drugs increase the risk of developing hyponatremia in elderly patient (61).

Step-3: Stop the medications including the psychotropic agent causing hyponatremia after making sure that hyponatremia or SIADH is due to psychotropic medications, then stop the medications.

Step-4: Mild, moderate and severe hyponatremia. It should be managed according to serum sodium level. If

the hyponatremia is mild and discontinuation of the drug does not lead to an increment in the serum sodium level, water restriction (0.5-1 L/day) may be used.

If the hyponatremia is moderate to severe, then discontinuation of causative agent along with water restriction (0.5-1 L/day) may be used, if the patient has neurological signs and symptoms of hyponatremia, then correction with hypertonic saline is indicated.

If the serum sodium level is less than 125 mmol/L and or there is worsening of neurological signs and symptoms irrespective of serum sodium level, then hyponatremia should be considered as a medical emergency. Firstly do proper evaluation followed by furosemide administration to prevent the kidney from concentrating urine even in the presence of high levels of ADH (anti-diuretic hormones) (54) then hypertonic saline infusion is required.

Step-5: other measures. Treat the patient of hyponatremia with other medications, but there is minimal evidence supporting with this medications. Some studies have been suggested the beneficial effect of medications such as phenytoin, (61) demeclocycline, (62) lithium, (63) and vasopressin receptor antagonists (vaptan therapy) such as conivaptan or tolvaptan (64), these medications are relatively expensive and require strict monitoring due to side effect profile of liver injury. Vaptans play a critical role in last-line treatment of hyponatremia.

CONCLUSIONS

Hyponatremia is a life threatening condition occurs frequently in psychiatric patients, particularly in geriatric age group patients taking various psychotropic drugs. This harmful medical comorbidity always overlooked, frequently undiagnosed and untreated in psychiatric patients. Careful monitoring of patient's sign and symptoms and serum sodium levels is therefore essential to minimize the risk to patients. The causality between psychotropic agents and hyponatremia has been shown more persuasively with antidepressants and mainly with SSRIs, other psychotropic drugs should also be considered to have the potential to cause hyponatremia. It's our duty to evaluate the potential risk factors for the development of

hyponatremia in an elderly patient before prescribing a psychotropic medications and one must be cautious enough to monitor the sodium serum level during the initial phase of treatment. If psychotropic--induced hyponatremia does occur, the causative drug should be withdrawn and to correct the hyponatremia with hypertonic saline and other measures. In management of hyponatremia patient it is imperative to consult other clinicians for high risk patients and consider the possibility of development of severe hyponatremia following psychotropic medications.

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