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Hyponatremia and Psychotropic Drugs

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Abstract

Given the widespread use of psychotropic drugs in the population, it's important to consider hyponatremia as an avoidable and reversible adverse effect and include the detection of high-risk subjects to establish safer medications, as well as early detection measures in routine clinical practice. Although hyponatremia has been especially associated with serotonergic antidepressants (SSRIs), there is also an elevated risk with tricyclics, duals and heterocyclic antidepressants, due to the different mechanisms of action at the renal tubular level and the release of ADH. Hyponatremia secondary to tricyclics with slow CYP2D6 metabolizers have higher plasma concentrations of antidepressants metabolized by CYP2D6. Hyponatremia secondary to SSRIs appears in the first week of treatment, it is "not dose-dependent" and normalization of natremia occurs between 2 and 20 days after stopping the medication. Bupropion, trazodone, mianserin, reboxetine and agomelatine are a safe alternative. Also antiepileptics have been related to hyponatremia. Both typical and atypical antipsychotics have been exposed to an increased risk of hyponatremia, even after adjusted factors such as age, sex and comorbidity. Other factors that favor the onset of hyponatremia act synergistically with psychotropic drugs, such as: advanced age, female sex, concomitant diuretic intake, low body weight and low sodium levels; NSAID, ACEIs, and warm.

Keywords: hyponatremia, antipsychotic, antidepressant, antiepileptic, psychotropic drugs

1. Introduction

Hyponatremia is the most frequent hydroelectrolytic disorder in clinical practice, both in hospital and outpatient settings [1]. Defined as a serum sodium concentration or sodium level < 135 mmol/L, its frequency varies according to its intensity, with severe and more severe hyponatremia in hospitalized patients. Hyponatremia is present in 15–20% of urgent hospital

admissions and in up to 20% of critical patients. Although it estimates a daily incidence of 1% in hospitalized patients and a prevalence of 2.5%, its frequency is probably higher, since it is frequently underdiagnosed [2]. Some epidemiological studies report that only 30% of patients with hyponatremia are diagnosed, including the most serious ones [3]. Clinical manifestations of hyponatremia have a broad spectrum, from mild to severe or even potentially lethal. Hyponatremia is related to an increase in mortality, morbidity, duration of hospital stay and socio-health costs in patients with multiple pathologies. Some studies show that the presence of hyponatremia is an independent predictor of mortality rate, implying a relative risk of death between 1 and 2 times higher [4]; risk that is maintained per year and even 5 years after a hospital admission. Hyponatremia is related to a higher rate of hospitalization in Intensive Care Units and mechanical ventilation units.

Etiology of hyponatremia is multifactorial, highlighting the pharmacological origin. Some of the mechanisms involved in the development of pharmacological hyponatremia are the alteration of sodium and water homeostasis (diuretics), the increase in the production of the antidiuretic hormone (antidepressants, antipsychotics, antiepileptics, anticancer drugs, methotrexate, interferon alfa, opiates) and the potentiation of the effects of antidiuretic hormone (antiepileptic, hypoglycemic, nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme inhibitors [ACEIs] and anticancer drugs). Factors such as female sex, weight, advanced age, the presence of associated pathologies (cardiological, hepatic, neurological and endocrine), the concomitant use of drugs (especially thiazide diuretics, inhibitors of the reuptake of serotonin and carbamazepine) and basal sodium levels in the low threshold of normality have been related to the development of hyponatremia [5].

Prescription and use of psychotropic drugs is currently growing, both due to the increase in the incidence of mental illnesses and depression, which according to the WHO will be the second cause of disability in the world in 2020 [6]. Elderly patients have higher prevalences of mood disorders, which together with the greater frequency of polypathology and polypharmacy, makes them a risk group for presenting hyponatremia.

2. Hyponatremia

2.1. Definition of hyponatremia

2.1.1. Definition of hyponatremia based on biochemical severity

Mild (sodium between 130 and 135 mmol/L); moderate (sodium between 125 and 129 mmol/L); severe (sodium <125 mmol/L).

2.1.2. Definition of hyponatremia based on development time

Acute (<48 h) or chronic (greater or equal to 48 h). Current literature establishes the limit of 48 h to distinguish between acute and chronic hyponatremia, since cerebral edema appears

more frequently when hyponatremia is established in less than 48 h. Experimental studies suggest that the brain needs approximately 48 h to adapt to a hypotonic environment; there is a risk of cerebral edema before such adaptation. However, once the adaptation is completed, a rapid rise in the serum sodium level can cause lesions of the myelin sheath, which is known as osmotic demyelination syndrome. Hence, the importance in clinical practice to distinguish between acute and chronic hyponatremia, evaluating whether a subject is at greater risk of cerebral edema or osmotic demyelination. If there are doubts about the development time of hyponatremia [7], it should be considered chronic, unless there are reasons to think otherwise.

2.1.3. Definition of hyponatremia based on symptoms

Moderate: any degree of hyponatremia associated with moderately severe symptoms of hyponatremia: nausea without vomiting, confusion, and headache.

Severe: any biochemical degree of hyponatremia associated with severe symptoms of hyponatremia: vomiting, cardiorespiratory distress, abnormal and deep drowsiness, seizures, and coma.

2.1.4. Definition of hyponatremia based on plasma osmolality

- **Hypotonic hyponatremia:** the decrease in extracellular sodium is accompanied by hypotonia of the extracellular fluid and displacement of water from the extracellular space to the intracellular space, causing cellular edema. The most frequent cause is a syndrome of inappropriate secretion of antidiuretic hormone (SIADH). There are three types according to the volume status:
 - a. *hypotonic hyponatremia with hypovolemia:* occurs when there are losses of sodium and water, with partial supplementation of fluid losses without electrolytes. Losses can occur through the skin, digestive tract, renal pathway or leakage of fluids into a third space.
 - b. *hypotonic hyponatremia with isovolemia:* SIADH is the most common cause of hyponatremia.
 - c. *hypotonic hyponatremia with hypervolemia:* it occurs both in situations of increased vasopressin secretion in states of a relative decrease in effective intravascular volume (chronic heart failure, liver cirrhosis with ascites, nephrotic edema); excessive fluid intake without electrolytes and an altered excretion of free water (acute kidney injury, advanced chronic kidney disease).
- **Nonhypotonic hyponatremia (isotonic or hypertonic):** increase in the plasma concentration of effective osmoles displaces the water from the intracellular to the extracellular space and generates a dilutional hyponatremia. Depending on the concentration of these compounds the plasma osmolality may be normal or increased. The most frequent cause is hyperglycemia.
- **Fictional hyponatremia or pseudohyponatremia** occurs when a plasma concentration of sodium falsely decreases as a result of a high concentration of lipids or paraproteins, with normal plasma osmolality.

2.2. Etiology

2.2.1. Acute hyponatremia

Primary polydipsia, intensive physical exercise, thiazide diuretics, postoperative state, vasopressin analogs, colonoscopy preparations, 3,4-methylenedioxymethamphetamine intake.

2.2.2. Nonhypotonic hyponatremia

- *Isotonic or hypertonic*: secondary to the presence of effective osmoles (glucose, mannitol, glycine, hyperosmolar radiological contrast, maltose).
- *Isotonic or hyperosmolar*: secondary to presence of ineffective osmoles that elevate measured serum osmolality but do not cause hyponatremia because they do not change effective osmolality and does not attract water to extracellular compartment (urea, alcohol).
- *Isotonic*: presence of endogenous solutes that cause pseudohyponatremia (triglycerides, cholesterol, proteins, intravenous immunoglobulins, monoclonal gammopathies).

2.2.3. Hypotonic hyponatremia

- *Hypovolemic*: excessive sweating, vomiting, diarrhea, digestive tract fistulas, diuretics, tubulopathies, mineralocorticoid deficiency.
- *Hypervolemic*: chronic heart failure, liver cirrhosis, nephrotic edema, ascites, acute and chronic renal failure.
- *Isovolemia*: syndrome of inappropriate secretion of antidiuretic hormone (SIADH) which can be secondary to tumors (lung, oropharynx, stomach, duodenum, pancreas, ureter, bladder, prostate, endometrium, Ewing sarcoma, lymphomas, neuroblastoma), nervous system disorder (encephalitis, meningitis, abscess, infection by Rickettsia and Plasmodium, HIV, subdural hemorrhage, stroke, hydrocephalus, multiple sclerosis, Guillain-Barré syndrome, delirium tremens, acute porphyria), drugs (antidepressants, anticonvulsants, antipsychotics, anticancer drugs, antidiabetics, vasopressin analogs, opioids, interferon, NSAIDs, clofibrate, nicotine, proton pump inhibitors, amiodarone) [7].

2.2.4. Hyponatremia and psychotropic drugs

As we have previously described, in case of psychotropic drugs, hyponatremia is mediated by the inappropriate release of ADH. ADH or vasopressin is a hypothalamic hormone that is stored and released through the neurohypophysis in response to osmotic and nonosmotic stimuli:

1. Osmotic stimulus: the ADH is released or inhibited depending on the concentration of effective osmoles in the extracellular compartment. Osmotic threshold for ADH release is 280 – 290 mOsm/kg.
2. Nonosmotic stimulus:

- Hemodynamics. In the presence of low effective circulating volume, the baroreceptors are activated. For example: hypovolemia, liver cirrhosis, arterial hypotension, congestive heart failure, nephrotic syndrome, primary adrenal insufficiency.
- Nonhemodynamic: mediated by the release of corticotropin-releasing hormone (CRH, neurotransmitter involved in the response to stress and responsible for activating the pituitary secretion of ACTH) and angiotensin II. For example: pain, stress, nausea and vomiting, hypoglycemia, drugs, cancer, postoperative state, pulmonary or central nervous system pathology.

Vasopressin has three receptors coupled to G proteins: V1 (presents vasopressor effect), V2 (responsible for the reabsorption of water in the collecting tubule of the nephron) and V3 (responsible for the release of ACTH). Vasopressin or ADH has several functions:

1. Renal. ADH acts on V2 receptors on collecting duct in the nephron. Its action increases the reabsorption of water, but not of solute, through the increased expression of aquaporin 2 channels (AQP2). Aquaporins are proteins that are part of the water channel. AQP2 is expressed exclusively in collecting duct principal cells and is responsible for the apical water permeability of this region of the nephron. Its activity is dependent on ADH, which is released in response to hyperosmolar and hypovolemic stimuli. There is a type of inherited nephrogenic diabetes insipidus associated with mutations in AQP2 [8].
2. Vascular smooth muscle. It produces vasoconstriction and increases peripheral vascular resistance.

2.3. Symptomatology

The symptomatology of hyponatremia varies depending on the biochemical severity and the speed of the establishment. It can be classified as mild, moderate and severe.

2.3.1. Mild symptoms

(Na 130–135 mEq/L): headache, attention deficit, memory alterations, irritability, depression.

2.3.2. Moderate symptoms

(Na 120–130 mEq/L): nausea, vomiting, bradypsychia, confusion, disorientation.

2.3.3. Severe symptoms

(Na < 120 mEq/L): stupor, seizures, coma, respiratory depression.

2.3.4. Hyponatremic encephalopathy

In hyponatremia, low serum osmolarity causes an osmotic gradient between the extracellular space and the intracellular space, with the consequent passage of free water into the interior of the cell. This accumulation of water in the brain cells causes cerebral edema. The cellular

edema produces an increase in the size of the various organs, however in the case of brain, expansion is not possible due to the limitation of the cranial cavity. Thus, increases in brain volume of 8–10% can cause coma and compromise the condition of the individual due to intracranial hypertension and transtentorial herniation. However, hyponatremia activates a series of compensatory mechanisms to decrease the volume of intracellular fluid, to reduce the risk of cerebral edema and the risks derived from it [9]. Adequate regulation of brain volume is an essential factor in the prognosis of hyponatremic encephalopathy. Some of these compensatory mechanisms are:

1. The increase in intracranial pressure favors the increase of hydrostatic pressure and subsequent passage of water to the ventricular and venous system.
2. After an initial osmotic edema, the cells quickly expel electrolytes (potassium, chloride and sodium) into the extracellular space, with the subsequent release of water by osmotic gradient, restoring brain volume. This phenomenon allows to restore cell volume in hours but is energy dependent and requires the operation of sodium-potassium ATPase system.
3. Role of the astrocytes. Act as regulators of brain water content, its swelling in hyposmolar situations protect and spare neurons. Its extensions form the blood-brain barrier and they have high number of pores called aquaporins (AQP) particularly AQP1 and AQP4, allowing the passage of water into astrocytes in hyposmolar situations which selectively swell, whereas neurons are relatively spared.
4. Studies in animals have shown that brain osmolytes (glycine, taurine, creatine myo-inositol) leave the cell in hypoosmolar states and accumulate in the hyperosmolar states. Studies in humans with magnetic resonance imaging show that the osmolytes output is parallel to the changes in sodium concentration, which takes approximately 48 h.

Brain adaptation to hyponatremia is related to the speed of its establishment. In chronic hyponatremia (that lasts more than 48 h) the slow and progressive decrease of sodium allows a compensatory regulation of the whole volume, limiting the degree of cerebral edema and being asymptomatic or slightly symptomatic. However, in cases of acute hyponatremia, adaptive mechanisms are exceeded and symptoms are more likely to occur even with mild hyponatremia.

There are some risk factors for the development of hyponatremic cerebral edema:

- Menstruating women. Estrogens inhibit the sodium-potassium ATPase, making intracellular sodium leakage difficult; and affect the expression of AQP4 channels. In this patient profile, cases of hyponatremic encephalopathy with cerebral herniation have been documented even with serum sodium of 128 mEq/L.
- Children. They are a risk group for unfavorable evolution in hyponatremic encephalopathy. It is postulated that the high ratio of brain size to that of the skull after the closure of the fontanelles, as well as the lower activity of the sodium-potassium ATPase pump than in adults can limit the adaptation to cerebral edema.

- Hypoxia It has been postulated that hypoxia is a factor for death and brain damage in patients with hyponatremia, after adjustment for other comorbidities. It alters the regulation of the energy-dependent astrocyte volume, since the active transport of sodium requires oxygen. In addition, in patients with hyponatremic encephalopathy, cranial hypertension and incipient brain herniation may favor the development of a neurogenic pulmonary edema and hypercapnic respiratory failure that worsens hypoxia.
- Hormonal factors: vasopressin and estrogen make it difficult to adapt to cellular edema. On the one hand, vasopressin acts by decreasing brain flow and oxygen consumption through arterial vasoconstriction, as well as facilitating the displacement of water in brain cells through AQP4. On the other hand, estrogens increase the secretion of vasopressin.
- Risk factors to develop hyponatremia: as we have previously commented, the establishment of the hyponatremia and the severity of it is associated with multiple factors such as polyopathy and polymedication, among others. For this reason, literature recommends the identification of those risk factors to perform an adequate prevention and early detection of those cases of hyponatremia.

2.3.5. Age

Elderly patients are a vulnerable population and at risk of developing hyponatremia due to various causes. In the first place, the physiological changes characteristic of aging, such as the decrease in volume and body weight, pose a risk to develop hyponatremia. On the other hand, they are a population often with multi co-morbidities, exposed to diets without salt, to forced hydration (oral or intravenous) and with the use of polytherapy, which makes them candidates for risk.

2.3.6. Institutionalization

Some studies have shown a higher incidence of hyponatremia in subjects older than 60 years institutionalized in residences than in patients of the same age living at home (18 versus 8%) [10].

2.3.7. Female sex

Female sex has been associated with an increased risk of hyponatremia and the development of hyponatremic encephalopathy [11]. Some hypothesis proposed for this difference are based on hormonal factors and cellular transport of sodium and volume of distribution of body water different from men.

2.3.8. Comorbidity

Hyponatremia has been associated with multiple pathologies (infectious, oncological, neurological, renal, metabolic, etc.).

2.3.9. Polytherapy

Multiple drugs have been associated with an increased risk of hyponatremia, especially antipsychotics, antidepressants and antiepileptic [12], diuretics (mainly thiazides), ACEIs and NSAIDs. Other drugs have been related to hyponatremia, such as vasopressin analogs, interferon, antidiabetics, anticancer drugs, proton pump inhibitors and monoclonal antibodies, among others.

1. Basal levels of sodium in low range of normality
2. Low weight
3. Exposure to high temperatures

2.4. Treatment

It is important to remember that despite of the severity of the neurological signs and symptoms of acute hyponatremia, the correction of hyponatremia in a rapid and uncontrolled way can generate chronic neurological lesions due to osmotic demyelination. When there is a decrease in sodium, cells excrete organic solutes and other molecules to maintain homeostasis, in a process that can last between 48 and 72 h, so hyponatremia can be classified as acute or chronic if the duration is shorter or greater than 48 h, respectively.

It is recommended that sodium correction rate does not exceed 8 mmol/L in any 24-h period, being even lower in those patients susceptible to osmotic demyelination (as in the case of advanced cirrhosis, alcoholism or severe malnutrition). Even in patients with severe hyponatremia that are accompanied by severe neurological symptoms, 4 – 6 mEq/L rise in serum sodium is sufficient in the first 24-h (this target can be achieved in first few hours in severely symptomatic patients and then maintained at that level for the first 24-h). Three percent sodium chloride solution can be used to achieve this. It is important to remember that the recommended correction rates of 24 h should not be exceeded.

There is a series of formulas that allow to calculate in a quantitative way the effect of the prescribed fluid therapy on patient's serum sodium.

The **Adroque-Madias Formula (AMF)** [13] helps to estimate the effect of a given fluid on serum sodium. It takes into account the sodium concentration and the total body weight (TBW) adjusted by a correction factor that varies according to age and sex. However, the AMF does not take into account the losses and the pathophysiology that underlies them and requires that sodium levels be monitored frequently during the infusion of the fluid.

Infusate formula: Adroque-Madias formula.

$$\Delta[\text{Na}^+]_s = \frac{[\text{Na}^+ + \text{K}^+]_{\text{inf}} - [\text{Na}^+]_s}{\text{TBW} + 1} \quad (1)$$

However, this formula has the limitation of being approximate as rise in sodium level is often greater than that predicted by the formula.

Fluid restriction should be the first therapeutic measure in cases of euvolemic or hypervolemic hyponatremia. Depending on the severity of the hyponatremia and symptomatic severity, the fluid should be restricted to provide a negative fluid balance of approximately 500 ml per day.

There are several therapeutic options for the treatment of hyponatremia secondary to SIADH:

Demeclocycline. It is a tetracyclic antibiotic whose mechanism of action is the inhibition of ADH receptors in the renal distal tubule, inducing nephrogenic diabetes insipidus. It is administered in doses of (300 – 600 mg twice a day). Side effects include photosensitivity, nephrotoxicity and nausea.

Antagonists of the vasopressin receptor (“vaptans”). ADH or vasopressin acts at the level of various receptors: V1a (causes vasoconstriction), V1b (secretion of ACTH) and V2 (water reabsorption and release of von Willebrand factor and factor VIII). Drugs that act on V2 receptors at the tubular level increase the excretion of water (aquaresis).

- Tolvaptan: It has an action as a selective antagonist of the V2 receptors of vasopressin at the level of the renal tubule, increasing the free elimination of water. It has been used in patients with congestive heart failure, cirrhosis and SIADH. Although it has not shown a reduction in the rates of rehospitalization or death due to congestive heart failure, it improves sodium levels, fluid balance and symptoms of congestion. It is approved for the treatment of hypervolemic and euvolemic hyponatremia.
- Conivaptan: Antagonist of the V1a-V2 receptors with approval for the treatment of euvolemic and hypervolemic hyponatremia. Its use is limited to intravenous use at the hospital level.
- Lixivaptan: V2 receptor antagonist of vasopressin, used in euvolemic and hypervolemic hyponatremia.

3. Hyponatremia and antipsychotics

Antipsychotics are a family of drugs used primarily in the treatment of schizophrenia, bipolar disorder and other affective psychoses, but also in other neuropsychiatric disorders (such as dementia and autism), symptomatic treatment of acute confusional symptoms and other conditions not psychiatric (nausea, hiccups, migraine). Some studies show stability in the prevalence (2.05%) and incidence (0.66%) in the use of antipsychotics in the last decade, although showing an increase in its use in the infant-juvenile population and higher employment of second generation antipsychotics (SGAPs) [14]. Its mechanism of action is dopaminergic blocking. They are classified into two main groups: the classic or typical antipsychotics, which present a blockade of the D2 dopaminergic receptor and are effective in the positive symptoms of schizophrenia (hallucinations and delusions) but show extrapyramidal symptoms as the most notable side effects; and the atypical or second generation antipsychotics, in addition to blocking the D2 receptor, exhibit muscarinic, adrenergic, serotonergic and histamergic receptor activity, showing a broader spectrum of action (including positive and

negative symptoms) and a different side effect profile of the typical ones (minor extrapyramidal symptoms, but weight gain, dry mouth, orthostatic hypotension, constipation, urinary retention, narrow-angle glaucoma, sedation).

Hyponatremia is an adverse effect described both in the case of classical and atypical antipsychotics. It is postulated that the etiopathogenesis of hyponatremia in atypical antipsychotics is mediated by the action of serotonin, both by the release of ADH induced by the stimulation of central receptors 5-HT₂ and 5-HT_{1c} and by the increase in the effects of ADH at the renal medullary level [15]. In the case of typical antipsychotics, prolonged blockade of dopamine D₂ receptors stimulates the release of ADH and increases its peripheral response [16]. The occurrence of hyponatremia occurs in the first 3 weeks of treatment in up to 50% of cases, although cases have also been reported in patients undergoing long-term chronic treatments. On the other hand, in the case of antipsychotics, neither age nor female sex are risk factors. The chemical structure and receptor affinity profiles of the dopamine D₂ receptor and serotonin 5-HT_{2A} have not shown a variation with respect to the risk of hyponatremia [17]. Several studies describe that hyponatremia at admission is associated with greater medical deterioration in hospitalized psychiatric patients [18], therefore adequate clinical monitoring should be performed to identify and treat somatic pathologies and concomitant use of drugs. Also, it is recommended to measure serum sodium in those patients on antipsychotic treatment who present with seizures.

In a follow-up study over 15 years with a sample of 2051 patients diagnosed with schizophrenia [19] from 1998 to 2013, an incidence of hyponatremia of 6.7% was observed. The study showed that the use of antipsychotics, both typical and atypical, was associated with an elevated risk of hyponatremia with respect to the nonuse of antipsychotics, even after adjusting for age, sex and physical comorbidity. Age of diagnosis of the disease, low income, physical comorbidity, psychiatric admissions and concomitant treatment with carbamazepine were also associated with an increased risk of hyponatremia. Another retrospective study showed that treatment with atypical antipsychotics in the elderly was associated with a modest but statistically significant increase in the risk of hospitalization for hyponatremia in 30 days, an association that was smaller than other psychotropic drugs [20]. A systematic review on hyponatremia and the use of antipsychotics, published in 2010 [16], which includes 4 studies and 91 cases and series of cases, showed that the diagnosis of schizophrenia and male sex were more frequently associated with hyponatremia. Using the Naranjo Scale of Adverse Drug Reaction Probability Scale, in 80% of the cases possible causality was determined, in 19% probable causality and in 1% impossible causality. No significant association was found between daily doses of drugs and serum sodium or time to onset of hyponatremia. Currently, tolvaptan is positioned as a drug approved by the FDA in the treatment of euvolemic and hypervolemic hyponatremia, and useful in the management of hyponatremia associated with the use of antipsychotics [21].

3.1. First generation antipsychotics (FGAS)

In recent decades the use of typical antipsychotics has been progressively replaced by atypical ones, by the receptor profile and side effects. Nonetheless, haloperidol continues to be the

drug of choice in the management of agitation and acute confusional syndrome. Haloperidol-related hyponatremia has been reported for decades [22, 27], but also with other first-generation antipsychotics such as chlorpromazine, perphenazine, and fluphenazine [23–25]. In the majority of cases there were other intercurrent factors involved in the development of hyponatremia (concomitant treatment with ACE inhibitors, diuretics and other psychotropic drugs).

3.2. Second generation antipsychotics (SGAS)

3.2.1. Aripiprazole

Aripiprazole is a partial agonist of dopamine, frequently used for its efficacy in cognitive and affective symptoms in psychosis. There are currently presentations for oral, parenteral and prolonged release treatment. Literature collects cases of aripiprazole-induced hyponatremia both in patients who developed the symptoms at the start of treatment [15] and in increasing the dose [26], improving in all of them the clinical symptoms with interruption of treatment and water restriction.

3.2.2. Olanzapine

It is an atypical antipsychotic, antagonist of D2 and 5HT2A receptor. It is commonly used in clinical practice to control agitation and positive symptoms. Cases of olanzapine-induced hyponatremia have been reported together with the concomitant use of other psychoactive drugs [5, 27]. In 2014, a case of death was described in a young schizophrenic male who presented with hyponatremia secondary to excessive water intake and which was related to the increase in the dose of olanzapine, which could have acted aggravating the intoxication itself [28].

3.2.3. Quetiapine

Synthesized in 1985, it is used in the treatment of schizophrenia, bipolar disorder, Alzheimer's disorder and major depression. There are few cases of SIADH induced by quetiapine, something that could be related to underdiagnosis and underreporting of this situation. Nonetheless, some cases are collected where quetiapine, together with other factors such as advanced age and polytherapy, is involved in the development of hyponatremia [29–31].

3.2.4. Risperidone

Approved by the FDA in 1993 for the use of schizophrenia, exists in oral presentation and depot. Like the other antipsychotics, risperidone has also been associated with the risk of developing hyponatremia, although some cases have been described in which the use of risperidone improved polydipsia in the schizophrenic patient [32, 33]. However, the results in the literature are inconclusive and controversial regarding the improvement of certain atypical antipsychotics (olanzapine and risperidone) on primary polydipsia.

3.2.5. *Paliperidone*

Paliperidone is an active metabolite of risperidone, indicated in the management of schizophrenia and schizoaffective disorder. In 2016, a case of rhabdomyolysis, malignant neuroleptic syndrome and SIADH associated with paliperidone prolonged release in a 35-year-old man hospitalized for psychotic decompensation was described. Two days after the administration of the treatment, the patient presented with a tonic-clonic seizure that was attributed to hyposmolar hyponatremia [34]. It is important to remember that in all patients receiving antipsychotic treatment, serum sodium should be measured in the presence of epileptic seizures.

3.2.6. *Ziprasidone*

Ziprasidone is an atypical antipsychotic indicated in psychotic agitation, schizophrenia and manic and mixed episodes in bipolar disorder. The literature includes a series of cases in which hyponatremia is observed in the context of the use of ziprasidone, concomitantly with other psychopharmaceuticals such as duloxetine [35] and with comitial symptoms in the debut of the hyponatremia [36], as a neurological symptom present in cases of hyponatremia.

3.2.7. *Clozapine*

Synthesized in the late 1950s, clozapine is considered the first atypical antipsychotic. It emphasizes its low rate of extrapyramidal effects and its antipsychotic potency, being currently indicated in the management of resistant psychosis and psychotic symptoms in Parkinson's disease. Literature collects controversial data on its relationship with hyponatremia, although some authors defend its use in Syndrome of Psychosis, Intermittent Hyponatremia and Polydipsia (PIP syndrome) [37].

3.3. Syndrome of psychosis, intermittent hyponatremia and polydipsia (PIP syndrome)

Hyponatremia in psychotic patients is a relatively frequent complication, both due to the osmotic dysregulation of the disease and the secondary effect of antipsychotics. The PIP syndrome is characterized clinically by the presence of acute confusional symptoms derived from symptomatic hyponatremia and water intoxication. Between 6 and 20% of psychotic patients presents with polydipsia. In psychotic patients, in addition to xerostomia and consequent compulsive water intake, the role of supra-optic and paraventricular hypothalamic nuclei, responsible for the regulation of thirst and secretion of antidiuretic hormone (ADH) in the pathophysiology of hyponatremia, is postulated, as well as dopamine and endogenous opioids as neurotransmitters involved in the ingestion of water. Neuroimaging studies in schizophrenic patients show a ventricular dilation in basal conditions, however under conditions of hyponatremia cerebral edema and ventricular contraction are observed. Some studies show that the MDR1 C3435T polymorphism may increase the susceptibility to polydipsia in schizophrenia [38].

Despite its prevalence, morbidity and mortality, it is an underestimated entity in its prevention and early diagnosis. One of the diagnostic challenges is the differentiation between hyponatremia induced by antipsychotics and PIP, since often the treatment of one of the entities worsens the other. Some studies show that urine concentration measurements are useful to differentiate both situations, detecting more frequently concentrated urine in pharmacological hyponatremia and dilute urine secondary to psychotic decompensation [39]. While some studies show that clozapine can generate polydipsia and hyponatremia, others show that it improves the symptoms of polydipsia, so clozapine is postulated as a therapeutic option [37], especially as an alternative to electroconvulsive therapy in cases of catatonia [40].

4. Antidepressants

The consumption of antidepressants has increased significantly in most Organization for Economic Co-operation and Development (OECD) countries since the year 2000. There is significant variation in consumption of antidepressants between countries. For example, in Germany, antidepressant use had risen 46% in just 4 years, in case of Spain and Portugal, it rose about 20% during the same period and Iceland led the pack in overall use with about one in 10 people taking a daily antidepressant [41]. The new generation of antidepressant drugs are widely used as the first line of treatment for major depressive disorders and are considered to be safer than tricyclic agents due to a profile of better tolerability and lower rate of side effects [42]. Several side effects are transient and may disappear after a few weeks following treatment initiation, but potentially serious adverse events may persist or ensue later.

Hyponatremia is the most common electrolyte disorder in ambulatory outpatients, especially in the elderly, and is one of the many well-known side effects of antidepressants [43]. Most of the evidence pointing toward an increased risk of hyponatremia with the use of antidepressant medications is based on multiple case reports and a few observational studies. It is important to remember that mild hyponatremia is associated with instability and falls, reduced cognitive function, osteoporosis and increased morbidity and mortality [44]. Most studies are small and observational and only few have had the power to examine whether specific antidepressants carry a higher or lower risk of hyponatremia.

Hyponatremia, usually, is not dose dependent and the patient recovers when treatment with antidepressant is interrupted. For this reason, early detection as well as the evaluation of concomitant risk factors in all patients starting antidepressant are important. Besides, it seems necessary to supervise sodium plasma levels periodically when patients are in treatment with antidepressants and to choose safe drugs between all possibilities [45].

The selective serotonin reuptake inhibitors (SSRIs) and venlafaxine appear to be the antidepressants most commonly associated with hyponatremia. Between the SSRIs, the incidence of hyponatremia varies based on the definition of hyponatremia used. On the one hand, studies which defined hyponatremia as serum sodium levels <135 mmol/l, the incidence ranged from 9 to 40%. On the other hand, the incidence decreased to 0.06–2.6% when

hyponatremia was defined as serum sodium levels <130 mmol/l. The number of case reports and small observational studies with hyponatremia concerning SSRI is substantially higher than the number of case reports and observational studies with other antidepressants, but it is not clear whether this is due to a true difference in incidence of hyponatremia. A review concluded that current evidence suggests a relatively higher risk of hyponatremia with SSRIs and venlafaxine compared to tricyclic antidepressants (TCA) and mirtazapine, but for several antidepressants, data were insufficient to determine the risk of hyponatremia [46]. We found that there were no consistent difference in the incidence of hyponatremia among different SSRI members, but available data indicate that the incidence could be slightly higher for citalopram, fluoxetine and escitalopram, whereas incidence rates may be lower for sertraline and paroxetine [47–49].

Nevertheless, according to national and international pharmacovigilance committees, 1/3 of the reports of drug induced hyponatremia are severe, with the greatest frequency involving paroxetine, fluoxetine, fluvoxamine, citalopram, venlafaxine, escitalopram and sertraline [50].

The data looking at the risk of hyponatremia associated with the use of serotonin–norepinephrine reuptake inhibitors (SNRIs) are even more limited. Most studies have found incidence rates of hyponatremia comparable to the ones reported for SSRIs. Incidence figures for mirtazapine and tricyclic antidepressants (TCAs) appear to be lower [46, 51].

The mechanisms of antidepressants induced hyponatremia remain incompletely elucidated, but these agents can act by either increasing the release of antidiuretic hormone (ADH) or increasing the sensitivity to ADH resulting in a clinical picture similar to the syndrome of inappropriate secretion of ADH [12]. It must be clarified that the precise mechanism is not known but today it is known that antidepressants are thought to cause the syndrome of inappropriate antidiuretic hormone release (SIADH) by direct or indirect stimulation of vasopressin release from the posterior pituitary gland. SIADH can be produced by multiple causes (hyponatremia with plasma hyposmolality and increased urinary excretion of sodium, increase in urinary osmolality, hypotension, heart failure, nephropathy, liver disease...) and lead to retention of water and to hyponatremia [52]. The prevalence of SIADH in patients using antidepressants has been described in several case reports and a case series and is estimated to occur in five of every 1000 patients treated per year [44, 46, 53–54]. If we take into account the genetic factor, it is known that most antidepressants are metabolized by the hepatic enzyme cytochrome P450 2D6 (CYP2D6), which is highly polymorphic with >60 variant alleles (<http://www.cypalleles.ki.se>). In case of individuals carrying two functional CYP2D6 alleles (*1, *2) have “normal” enzyme activity and are classified as extensive metabolizers. However, 5–10% of the population lack enzyme activity due to inheritance of two nonfunctional alleles (*3, *4, *5, *6) and form the so-called poor metabolizers. CYP2D6*4 is the most common variant allele in Caucasians (allele frequency of 20%) [55]. Poor metabolizers have higher plasma concentrations of antidepressants metabolized by CYP2D6 and are therefore more likely to suffer from adverse drug events [56]. It has been hypothesized that hyponatraemia or low serum sodium concentration may be one of these adverse events [57]. This review evaluated the literature on association of hyponatremia and the different families of antidepressants.

4.1. SSRI: selective serotonin reuptake inhibitors

The phenomenon of recurrent hyponatremia induced by the use of SSRI has been described in the literature by some authors in subjects who were exposed to it.

Sertraline: In 2013 there were over 41 million prescriptions, making it the most prescribed antidepressant and second most prescribed psychiatric medication in the United States [58] and is used for a number of conditions. There are many publications with patient cases that take this treatment and suffer from hyponatremia [59, 60].

Paroxetine: Paroxetine is primarily used for many mental disorders, has a well-known discontinuation syndrome and shares many of the common adverse effects of SSRIs such as hyponatremia [61–63].

Fluoxetine: It is a widely used antidepressant, with a multitude of indications and has been assessed as the most effective and safe medicine needed in a health system [64]. There are many cases of patients with hyponatremia taking this treatment [65].

Citalopram: This antidepressant has a good anxiolytic profile but some cases of hyponatremia were recorded [66, 67].

Escitalopram: Is the (S)-stereoisomer of the earlier medication citalopram, used in clinical practice and is related with cases of hyponatremia [68, 69].

Fluvoxamine: Antidepressant with some uses and some analgesic properties. Many cases of hyponatremia were related [70, 71].

4.2. SNRI: serotonin-norepinephrine reuptake inhibitors

Data looking at the risk of hyponatremia associated with the use of SNRIs are even more limited but some cases were described.

Venlafaxine: Drug widely used in daily clinical practice, with indications for mental disorders and painful pathology. Cases of hyponatremia were registered [72–74].

Duloxetine: Recommended as a first line agent for the treatment of chemotherapy-induced neuropathy and for fibromyalgia in the presence of mood disorders, in addition to other disorders. There are patient cases that take this treatment and suffer from hyponatremia [75, 76].

Desvenlafaxine: Desvenlafaxine is a synthetic form of the major active metabolite of venlafaxine and some cases of hyponatremia were registered [77].

4.3. Mirtazapine

It has noradrenergic and specific serotonergic antidepressant effect and it is more likely to cause weight gain and sleepiness than other treatments. Some cases of hyponatremia were described [14, 53–55], however, this antidepressant has not been associated with hyponatremia in all cases or with less power of association to this side effect [46, 49, 53, 60, 76, 78].

4.4. Bupropion

Is a norepinephrine-dopamine reuptake inhibitor (NDRI) primarily used as an antidepressant and smoking cessation aid and related with cases of hyponatremia [79, 80], but less than other antidepressants and that does not happen in all cases [51, 61].

4.5. Tricyclic antidepressants

Discovered in the early 1950s, they have number of uses, many of their side effects may be related to the antimuscarinic properties and cases of hyponatremia were registered [81], but with fewer registered cases than with other antidepressants [47, 49, 82].

4.6. Vortioxetine

New antidepressant so-called serotonin modulator and stimulator and two cases of patients with hyponatremia were registered [83].

4.7. Trazodone

Is a serotonin antagonist and reuptake inhibitor that is widely used for the treatment of depression and insomnia. We found controversial results for relationship between trazodone and hyponatremia: case reports in patients on treatment [84], some cases were reported in overdose [85] or articles which describe less power of association to this side effect [51].

4.8. Agomelatine

Agomelatine is a potent agonist at melatonin receptors and an antagonist at serotonin-2C (5-HT_{2C}) receptors. Given the limited references of hyponatremia associated with agomelatine, it has been postulated as a therapeutic alternative in those patients with risk or a history of hyponatremia that require antidepressant treatment [5].

4.9. Mianserine

Mianserin is a tetracyclic antidepressant with serotonergic (5HT₂, 5HT_{1c}), histaminergic and adrenergic (α ₁, α ₂) inhibitory activity. Some studies report that the association of hyponatremia and mianserin is low [86].

5. Antiepileptics

Epilepsy is a group of neurological disorders characterized by epileptic seizures. It is estimated that nearly 40 million people have epilepsy [86], with differences between countries and age groups. The median incidence of epilepsy is around 50.4/100,000/year: 45.0 for high-income countries and 81.7 for low- and middle-income countries [87]. Incidence is highest in old age (>60 years of age), with an estimated 60–135 new cases per 100,000 older adults each year [87]. Antiepileptics are, usually, initiated as monotherapy for the treatment of epilepsy [88].

However, these drugs are also often used in treatment of nonepileptic conditions such as pain and psychiatric disorders, for this reason it is very common in clinical practice that we find antiepileptics associated with other drugs [89].

As with antidepressants, many cases of hyponatremia are associated with the use of antiepileptic drugs and have been reported and published. However, there are great differences between them [90]. Besides all this, it is important to differentiate cases of antiepileptic that induce asymptomatic hyponatremia and can be easily corrected [91] from cases of severe or symptomatic hyponatremia. Last ones are associated with various types of neurological damage: seizures, altered mentality, brain stem herniation, death, etc., [92]. Because hyponatremia frequently goes undiagnosed and untreated with associated risks, next we will talk about the effect of different antiepileptics in this electrolyte abnormality.

5.1. Phenytoin

This drug was approved by the FDA in 1953. It works by blocking voltage-sensitive sodium channels. It is one of the most used and affordable antiepileptics, with several presentations. Some cases of hyponatremia related to the use of this drug have been described [93], but with less intensity than with other antiepileptic drugs [94].

5.2. Carbamazepine

Is used primarily in the treatment of epilepsy, neuropathic pain, schizophrenia along with other medications and as a second line agent in bipolar disorder. Carbamazepine is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system World Health Organization [70]. It has sodium channel blocking effect. There are many publications with patient cases that take this treatment and suffer from hyponatremia, so it is one of the antiepileptics most frequently associated with this side effect [90, 93, 95–97].

5.3. Oxcarbazepine

Is a structural derivative of carbamazepine and acts by blocking voltage-sensitive sodium channels. Its use can reduce the occurrence of epileptic episodes, and in psychiatry, has been shown to improve mood (option for add-on therapy in the treatment of bipolar disorder) and reduce anxiety. There is approximately a 25–30% chance of cross-reactivity between carbamazepine and oxcarbazepine. Number of cases of hyponatremia have been recorded with this treatment and with greater strength of association [49, 84, 90, 92, 98, 99].

5.4. Eslicarbazepine acetate

The active component, eslicarbazepine, stabilizes the inactive state of voltage-gated sodium channels (same mechanism of action as oxcarbazepine). This new antiepileptic has potential uses for the treatment of trigeminal neuralgia and bipolar disorder. Cases of hyponatremia were recorded [91, 100, 101].

5.5. Topiramate

Its therapeutic activity and medical indications are very extensive, probably related to multiple receptorial effects: voltage-gated sodium channels, GABA-A, AMPA/kainate, high-voltage-activated calcium channels and carbonic anhydrase isoenzymes. Some cases of hyponatremia are related [85], but with less frequency than with other antiepileptic drugs [102].

5.6. Lamotrigine

Is a sodium channel blocking drug (inhibits voltage-sensitive sodium channels), suppress the release of glutamate and aspartate (two dominant excitatory neurotransmitters) and blocks L-, N-, and P- type calcium channels, among other receptor effects. It is used in several neurological and psychiatric disorders and patients with hyponatremia has been notified [90, 103].

5.7. Valproate

Acts through blockade of voltage-gated sodium channels and increased brain levels of gamma-aminobutyric acid (GABA). It is used as primary option to treat epilepsy, bipolar disorder and to prevent migraine headaches, and is included in the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system [64]. Many cases of hyponatremia with Valproate's treatment were identified [90, 93, 104–106].

5.8. Gabapentin

Is used primarily to treat seizures and neuropathic pain, and is commonly used to treat anxiety and other disorders. Gabapentin bind to the $\alpha 2\delta$ -1 subunit of voltage-gated calcium channels, interacts with NMDA receptors, protein kinase C and inflammatory cytokines. There is little relationship between hyponatremia and the use of this drug [90].

5.9. Levetiracetam

This antiepileptic is used to treat epilepsy and different types of seizures. It also associates a multitude of indications for its use: Tourette syndrome, anxiety disorder, neuropathic pain... It acts as a neuromodulator binding to a synaptic vesicle glycoprotein (SV2A) and by inhibiting presynaptic calcium channels. Association of some cases of hyponatremia and use of levetiracetam has been documented [90, 107].

5.10. Pregabalin

It is useful when added to other treatments for many indications. It is an analog of GABA and increases the density of GABA transporter proteins, the rate of functional GABA transport and the extracellular GABA concentrations. Few cases of hyponatremia with use of pregabalin were reported [108].

6. Conclusions

Hyponatremia is a frequent clinical situation in clinical practice, both in outpatient and inpatient settings. Clinical manifestations have a broad spectrum with effect on different indicators such as morbidity and mortality. Nevertheless, this side effect is avoidable and reversible. Given the wide use of psychotropic drugs (antidepressants, antipsychotics and antiepileptics) and its current growing use, it is important to know those pharmacological options with lower risk of hyponatremia such as bupropion, trazodone, mianserin, pregabalin or gabapentin.

We have seen that etiology of hyponatremia is multifactorial and involves pharmacological origin (increase in the production or potentiation of the effects of antidiuretic hormone, alteration of the homeostasis of sodium and water), but many other factors such as advanced age, associated pathologies, female sex, weight or use of concomitant drugs also contribute to the development of hyponatremia. It is important to identify vulnerable patients and to measure sodium levels frequently, especially in the first few days after initiating treatment to help prevent or correct hyponatremia and its undesirable effects.

Conflict of interest

The authors declare no conflict of interests.

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