NEW APPROACHES OF THE HYPONATREMIA TREATMENT IN THE ELDERLY – AN UPDATE

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Abstract

Hyponatremia (hNa) is a frequently common imbalance in the elderly hospitalized patients. It is often correlated with elevated plasma quantities of arginine vasopressin (AVP, the antidiuretic hormone) and namely it depicts a water surplus in order to prevail sodium levels. It can conduct, in a comprehensive range, to detrimental changes that can affect the entire health status, especially the central nervous system, thus increasing the mortality and morbidity of hospitalized patients in care units. The inherent treatment of hNa, mainly of the chronic form, requires the correction of serum sodium concentrations at the appropriate rate, because, augmenting it at a warp speed, it can determine permanent or fatal neurologic sequelae. In this regard, the therapy for hNa may be enlightened by egressing therapies that include vasopressin V2 and V1a receptors antagonists, with the principal role of encouraging aquaresis and rise the serum sodium levels, alongside with the electrolyte-sparing discharge of free water.

Rezumat

Hiponatremia este o afecțiune frecvent întâlnită la pacienții vârstnici. Este asociată adesea cu un nivel plasmatic ridicat de arginină vasopresină (hormon antidiuretic) și adesea, definește excesul de apă în raport cu depozitele de sodiu predominante. Poate determina o serie largă de modificări periculoase, care implică în special sistemul nervos central, crescând mortalitatea și morbiditatea pacienților spitalizați. Tratamentul corespunzător al hiponatremiei, în special al formei cronice, implică corectarea concentrațiilor serice de sodiu la un nivel corespunzător, deoarece, în caz contrar, pot să apară sechele neurologice permanente sau fatale. Tratamentul hiponatremiei poate fi facilitat de terapii inovatoare care blochează acțiunile vasopresinei asupra receptorilor vasopresinei V2 și V1a pentru a favoriza excreția apei fără electroliți și a crește concentrațiile serice de sodiu.

Keywords: sodium, hyponatremia, vasopressin, vaptans

Introduction

Homeostatic mechanism involving renal control, craving, arginine vasopressin (AVP, the antidiuretic hormone) and water rendition [1] are responsible for maintaining the sodium concentration in plasma within a relatively narrow range [2]. When modifications occur in any of these essential segments, towards the control water balance, hyponatremia (hNa) becomes evident, revealing a commonly condition that pose many challenges [2], despite his apparent small clinical expression, by significantly amplifying the morbidity and mortality, alongside hindering the course of an accompanying disease [2, 3]. This review aims to express the theoretical aspects of the prevailing form of hNa, especially in elders, and to underline the great importance of a proper pharmacological treatment.

Hyponatremia – at a glance

We acknowledge three types of hNa: mild (serum sodium concentration is found between 130 and 134 mEq/L), moderate (serum sodium concentration average between 125 and 129 mEq/L) and severe (sodium concentration limit is < 125 mEq/L). In either case, it can embrace an acute (developed in less than 48 hours) or a chronic form (more or equal to 48 hours). With respect to an emerging cerebral oedema accompanying hNa stated in less than 48 h, current literature data underlines as a limit the time of 48 hours to perceive between acute and chronic hNa [4]. Experimental studies support the information according to which the brain requires almost 48 h to adapt to a hypotonic habitat, accomplished principally through the extrusion of sodium, chloride, potassium,

and organic osmoles from its cells [5]; in advance to such adjustment, within the brain, always a damage occurs, e.g. the risk of cerebral oedema. Yet, once the adaptation is performed, an injury of the myelin sheath enclosing individual neurons can trigger in the osmotic demyelination syndrome [6], which is a rare, but dramatic drawback in chronic hNa, mainly due to rapid correction [7] of the serum sodium level. This fact explains the relevance, in the clinical practice, of recognising the acute or the chronic form [5] of the hNa, judging whether the possible risk occurred entails cerebral oedema or osmotic demyelination. Unless there are reasons to think otherwise, if there are questions arising about the progress of the hNa [5-7], it should be assessed chronic. Also, whether moderate or severe, the most important based plasma osmolality [8-11] is the volume status, which leads to the main three forms of hNa. *The hypotonic hyponatremia* [4] is a condition

defined by water displacement from the extracellular area to the intracellular area, due to decreased extracellular sodium attended by extracellular fluid hypotonia and cellular oedema. Frequently, the inappropriate secretion of the antidiuretic hormone syndrome (SIADH) is incriminated (Figure 1) [12, 13]. *The non-hypotonic hyponatremia (isotonic or hypertonic)* [4], as a dilutional hNa [14], is generated by the accumulation of effective osmoles in the plasma concentration, replacing the water from the intracellular to the extracellular extent [14, 15]. According to the concentration of the plasma compounds, normal or enhanced values of the osmolality may be depicted (Figure 1). Hyperglycaemia is frequently the cause [16]. *The fictional hyponatremia or pseudohyponatremia* stands for a large gathering of lipids or proteins, in conditions of normal plasma osmolality, but with falsely diminished sodium plasma concentration [5, 17 - 19].

Figure 1.
Aetiology of hyponatremia

By surveilling the literature date, it can be disclosed a relation encountered with the psychotropic drugs, especially on account of the inadequate discharge of the antidiuretic hormone, ADH, that mediates the hNa [20, 21]. ADH, the hypothalamic peptide, is hold and released through the neurohypophysis [4], playing a key role in the management of the total body water, as an osmotic and non-osmotic stimuli-response [22]. The vasopressin effects are mediated by stimulating the

tissue-specific G protein-coupled receptors (GPCRs) also named the vasopressin receptors: V1 (exhibits vasopressor effect), V2 (reliable for the reabsorption of the water in the nephron collecting tubules) and V3 (accountable for the ACTH release). ADH has two principal functions [4]. Firstly, *renal* – after its release from the posterior pituitary gland, it binds to the type-2 receptor (V2) in the collecting duct principal cells. Following an intracellular cyclic adenosine mono-

phosphate (cAMP) pathway after binding to the receptor, the phosphorylation of the aquaporin-2 (AQP2) occurs. The result is the decrease of the ADH levels, alongside with the water homeostasis, and AQP2 is internalized from the plasma membrane, leaving it watertight again [23]. In the nephron, AQP2 controls the apical water permeability and it is expressed exclusively in the collecting duct principal cells [4].

Due to the ADH-dependent activity, the response is released to hyperosmolar and hypovolemic stimuli (Table I). In this direction, a kind of passed-on nephrogenic diabetes insipidus correlated with some genetic AQP2 disorders is investigated [4, 22]. Secondly, in the *vascular smooth muscle*, it is responsible for vaso-constriction and enlarges peripheral vascular endurance [4, 23, 24].

Table I

Vasopressin receptors subtype, location, functions, and non-peptide antagonists

Receptor subtype		Location	Physiological effect	Non-peptide antagonist	Clinical progress	Signalling pathways
IUPHAR	alternate					
V1a	V1	vascular smooth muscle	vasoconstriction, myocardial hypertrophy	Relcovaptan	Raynaud's syndrome	G protein-coupled, phosphatidylinositol/calcium
		hepatocyte	glycogenolysis			
		platelet	platelet aggregation			
		myometrium	uterine contraction	Relcovaptan	dysmenorrhoea	
		renal	prostaglandin synthesis stimulation, decrease in inner renal blood flow, glomerular mesangial contraction			
		adrenal	stimulation of aldosterone and cortisol secretion	OPC-21268 (Fuscoside)	ACTH-independent macronodular adrenal hyperplasia	
V1b	V3	corticotrophin cells and anterior pituitary	releases ACTH, endorphins	Nelivaptan		G protein-coupled, phosphatidylinositol/calcium
		brain	stress adaptation	SSR-149415 (Nelivaptan)	depressive disorders	
V2	V2	cells membrane of the collecting ducts	intromission of AQP-2 water channels into apical membrane and thus water reabsorption, grounding the AQP-2 synthesis	Mozavaptan	only SIADH	Adenylyl cyclase/cAMP
				Lixivaptan	SIADH, cirrhosis, CHF	
				Conivaptan	hyponatraemia, CHF	
				Satavaptan	hyponatraemia, CHF, ascites formation prophylaxis	
				Tolvaptan	hyponatraemia, CHF, polycystic kidney disease	
		vascular endothelium	releases vWF and factor VIII			
		vascular smooth muscle cell	vasodilation			

IUPHAR – International Union of Basic and Clinical Pharmacology; cAMP – cyclic adenosine monophosphate;

ACTH – adrenocorticotrophic hormone; AQP-2 – aquaporine-2; CHF – chronic heart failure; vWF – von Willebrand factor.

Dispersion of hyponatraemia in the elderly

hNa in the elderly, similar to the general population, presents different variations, mainly depending on both the risk population and sodium concentration used to ascertain [3, 12, 24] this disorder and the frameworks in which the analysis is performed. Although there is a common used “normal range” for the serum sodium levels (135 - 142 mEq/L), regarding the U-shaped correlation between serum sodium concentration and mortality, other exact types of hNa have been suggested [3, 25, 26]. In this context, the dispersion of hNa was pronounced in the 75 years of age subjects, comprising 11.6% of subjects in a population-based Rotterdam

study [3]. In health care settings, the reduced serum sodium levels [3] are retrieved. For example, Miller *et al.* [27], in a nursing home population study, underlined that 18% of subjects aged 60 encountered hNa (defined by serum sodium concentrations, under the value of 130 mmol/L). Additionally, in a 12 months period of performing serum sodium multiple analyses, at any rate, one event of hNa was observed in almost a moiety of patients [3]. Likewise, in another prospective study, aiming hospitalized patients aged 65 years and more, the percentage of encountering low serum sodium levels, under 135 mEq/L, covered a third of the subjects [3, 28].

When observing the orthostatic hypotension risk factors in a healthy cohort, Caird *et al.* noticed that almost 7% of subjects [25] in the age of 65 years and older presented serum sodium levels under 137 mEq/L [29]. By contrary, among a long-term care facility subjects, the spreading of hNa was approximatively 20%, setting for the serum sodium concentration an endpoint value beneath 135 mEq/L [30, 31].

Not for the least, researchers included, in a recent study, patients with lower respiratory tract infection (LRTI), intending to disclose the occurrence of hNa in elderly. The study took into account the three encountered types of decrements for serum sodium concentration: mild (131 - 135 mmol/L), moderate (126 - 130 mmol/L) and severe decrements (< 126 mEq/L) [32]. The prevalence of hNa among elderly raised to the considerable percent of 45% patients [25] with associated pathologies, regardless the age, sex, and type of LRTI [32]. More than 300,000 samples were collected from more than 120,000 patients. Even though the reference group comprised a ≤ 30 -year-old cohort and the principal end-point was the serum sodium value < 136 mEq/L, the prevalence of hNa in subjects over 60 years was significantly higher at

admission and also as a hospital-acquired disease [25, 33-36].

Mechanisms of a rising sensitiveness of the elderly to enhance hyponatremia

The main presumption of the elderly to evolve in a hNa condition is correlated with the weakened water-excretory capacity due to age, and the associated hNa diseases [3] and other pathologies linked medications. In elderly patients, a large scale of factors is commonly involved in the headway of hNa. This water-excretory capacity particularly assigned to the reduction of the glomerular filtration rate (GFR) age-correlated is more popular in elders developing hNa [3, 25, 36]. Additionally, it could be involved a mechanism which implies a lowest intrarenal prostaglandins generation production encountered in advanced age [3, 37]. Nevertheless, the total body water content age-related reduction is conducting to abnormal variations of serum sodium levels, because the serum sodium concentration is formed of the total exchangeable sodium and potassium, reported to the total body water, as the Edelman equation [36, 38] depicts (Figure 2).

Figure 2.

Hyponatremia pathogenesis following the water excess in relation with the body's sodium and potassium concentrations (TBW – total body water; K_e^+ – exchangeable potassium; Na_e^+ – exchangeable sodium)

Moreover, in geriatric population [3] it is more often assessed as relatively rare the idiopathic SIAD [12, 13]. But, regarding the elderly population, there is acknowledged a preserved urinary diluting ability [3], even with a low GFR, and the factors involving an emerging hNa are in agreement with a high amount of water consumption, along with other ardent or/and

overlying factors [3], among which some are below presented.

Drugs

In the discussed context, elderly persons frequently take drugs, among which stand out non-steroidal anti-inflammatory drugs (NSAIDs) [3], serotonin-nor-

epinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs) [35], thiazide diuretics and/or undergo different associated pathologies (e.g., endocrinopathies, diabetes mellitus (DM), liver diseases, heart failure, tumours, infections) [39] that support today the hNa causes. Among these present additional low serum sodium levels risk factors [39], the hNa incidence induced by thiazides has not yet distinctly fulfilled the blanks. Besides, within a population of patients with thiazide medication [3], approximatively 14% had hNa, whereas patients aged more than 65 years were linked with a fourfold rising of the hNa risk [41]. In the neurological field, in patients aged 60 years and older, receiving SSRIs, SNRIs and mirtazapine, the hNa cases have an ascending slope. Drugs like bupropion, trazodone and tricyclic antidepressants are less incriminated in the hNa aetiology [40]. Moreover, many elderly have cardiac pathologies or low-salt diet due to heart failure [3, 39-42], along with a reduced protein intake diet (customised or due to overlapped disorders) that hinders water elimination and translates into low serum sodium concentrations, leading to another clue for the evolution of hNa [43, 44]. Also, it is valuable the observation regarding the seasonal variation of hNa (with a higher occurrence during the summer) because of more obvious increased water ingestion, distortion of renal function, increased sodium chloride deprivation, reduced sodium chloride intake [3, 25, 45]. Low body mass index, female gender, concomitant non-psychiatric medication administration, such as NSAIDs, PPIs (proton-pump inhibitors), diuretics, angiotensin-converting enzyme inhibitors [41], likewise as the attendance of heart injury, adrenal insufficiency or liver disorders are encouraging features that explain the associated hNa in the elders treated with psychotropic medications [42]. Antiepileptic drugs (AEDs), e.g. carbamazepine and oxcarbazepine acetate are prevailing hNa [46, 47]. Lately, other AEDs, such as lamotrigine, gabapentin, eslicarbazepine, levetiracetam and sodium valproate, have also been claimed to render hNa. Properly, phenytoin, topiramate and valproic acid have been incriminated with a pronounced threat of producing hNa in patients being hospitalized in comparison with those who did not pursue an AEDs treatment [3, 25-27, 47, 48].

SIADH

Expanded plasma vasopressin concentrations acts like an escort for aging [3, 7, 12, 49]. Researchers were preoccupied to enlist patients at the age of 65 years and even older in clinical trials and mostly found SIADH in half of subjects [3, 50] with hNa. This syndrome was the leadership reason that entails severe hyponatremia in elderly hospitalized patients. It is to note that the relatively rare idiopathic SIADH discloses a high percentage among the elderly, related to pain,

mild hypovolemia, and orthostatic hypotension. Also, several types of cancers cause excessive production of ADH leading to SIADH [51].

Endocrine dysfunctions

With regard to patients over 65 years of age or older, hypopituitarism it should not be evaluated as a scare source of developing hNa [3]. Ishikawa *et al.* described that 40% of this hyponatraemic patients, with signals like weakness or fatigability, have pituitary adrenal dysfunction [3, 49, 52]. Nevertheless, diabetes mellitus (DM) ranks between the first positions among the seniors. During marked episodes of hyperglycaemia, considering glucose as an osmotic active substance, able to take out the water from cells and afterwards to diminish serum sodium levels by dilution, serum osmolality (Posm) is increased. In the case of uncontrolled DM, assessed hypovolemia is nearly an invariable exposure due to hypotonic liquid losing, in excess of electrolytes, and osmotic diuresis. This, followed by an extensive ingestion of hypotonic solutions or water (without solutes), may be a possible cause for hNa [3, 52, 53]. Noticeable, there is a correlation between DM and hNa regardless of the attendance of hyperglycaemia [51, 54].

“Tea and toast” hyponatremia

A salt and protein poor diet, but linked with a large volume of water, transpose this type of hNa into an accountable condition in elders with a low GFR [3, 33, 36]. In these cases, it follows an increased water reabsorption and a low filtrate distal transportation (due to modest GFR and presumably persistent sodium loss), suitable for a low rate of osmoles excretion. Also, when renal water excretion capacity is surpassed by the water consumption, hNa occurs [33, 55, 57].

General recommendations for treatment

Water Restriction

Although this pathogenesis involves water retention and the kidney's remissive capacity to eliminate it, the headstone of the chronic hNa treatment has been the water intake restriction [25]. However, such restriction is barely endured over time and the compliance with significant water restriction is problematic. The fluid intake [2, 7] is not driven by thirst, but rather is appointed by habits or other facets. Water intake restriction is often strongly supported [25], in the absence of any scientific support. Furthermore, when it is present a severe diluting defect, water restriction is not always a solution, particularly. As presented by Furst *et al.* [44], when the total amount of urinary potassium and sodium concentrations overruns the serum sodium concentration, the water without electrolytes is not excreted and that explains why none of the

water restriction volume [25] will determine an enhancement in the serum sodium concentration.

Demeclocycline

After vasopressin binds to the V2 receptor, inhibiting the adenylate cyclase activity [27], this drug aims the mechanism fulfilling the enquiring water-retaining pathogenesis states. In case of water restriction or not-treatable cause of hNa, the usual range dose is between 900 and 1200 mg/day. The response rate is extremely variable [25]. This agent acknowledges severe gastro-intestinal side effects, photosensitivity, nephrotoxicity, augmented by co-pathologies like liver diseases [58]. Demeclocycline is not officially authorised by Food and Drug Administration (FDA) for the treatment of hNa [25], mainly due to the nephrotoxic effect.

High ceiling diuretics and NaCl

Dietary intake is supplemented with the administration of 2 - 3 g daily of NaCl, in order to prevent concomitant unwanted sodium depletion. The scientific explanation for the loop/high ceiling diuretics therapy and NaCl supplementation binds with the capacity of these drugs to encourage the electrolyte-free water excretion. The NaCl intake and excretion will rise the solute delivery which translates into an enhancement of the electrolyte free water clearance. Additionally, potassium repletion [5, 36, 38, 44] or potassium-saving diuretic medication is also often required for escaping from the clinically considerable hypokalaemia. Although this pharmaceutical manner has been widely used in the symptomatic hNa treatment, the literature data arise one case treated successfully for 6 months [59].

Urea

Administering urea in a dose range of 30 - 50 g/day can achieve the goal of augmenting serum sodium concentration in chronic hNa patients [25], by lowering the urinary sodium and potassium concentrations and consequently rising the elimination of water without electrolytes, by increasing urine flow rate [59-61]. Although a recent study by Soupart *et al.* [62] described that urea has been effective in increasing serum sodium levels with a high degree of tolerability, as the vasopressin antagonist tolvaptan, in 13 patients with SIADH [61], the main reason the for not using urea is because of his poor palatability connected with his own poor adherence. Although urea [25] has two main advantages,

that is a low cost and is potentially effective, patients do not tolerate this drug because of its taste. So, we can assume it can be considered a second line treatment option.

Vaptans (Vasopressin Receptor Antagonists) – regulating water excretion drugs

Vaptans bind to the V2 receptor and therefore block ADH, leading to aquaresis electrolyte [37] or free diuresis. In hyponatraemic patients, the serum sodium concentrations are elevated because of the aquaresis (acquired nephrogenic diabetes insipidus). In this regard, vasopressin has not the appearance to unfold important physiologic or pathophysiologic effects *via* the V1 receptors. Tolvaptan, mozavaptan, lixivaptan and satavaptan are drugs that specifically block the V2 receptor, while conivaptan is a non-specific blocker of both the V2 and the V1a [37] receptors. In the United States, only tolvaptan and conivaptan are available for clinical use, instead, satavaptan has been withdrawn for further research (it was correlated with a higher mortality, especially in patients with cirrhosis, that is when diuretics are a must and the treatment is for long term [63]) and lixivaptan has not been discharged for clinical use [64]; in Japan, mozavaptan has been authorized for the treatment of SIADH. Taking into consideration the administration pathways, conivaptan is available only as an intravenous drug, recorded as a benefit for the hospitalised critically ill patients [49, 65]. The oral preparations are included in therapy, but it is acknowledged their potency as inhibitors of the cytochrome P450 3A4 [37] system, leading to many drug-drug interactions [24, 47, 48, 61-64]. As earlier recalled, only conivaptan binds likewise to V1a and V2 receptors, whereas the other vaptans develop a higher specificity for the V2 receptors (Table II). Although, the pharmacokinetic and pharmacodynamic profiles are still limited, these agents are rather different in the backgrounds of bioavailability, peak urinary effect, time to peak plasma concentration and clearance halftime after oral [66] administration. In hospitalized patients, in the treatment scheme of the clinically significant euvoletic and hypervolemic hNa, the intravenous conivaptan and oral tolvaptan have been stated [67].

Table II

Vaptans used in clinical trials

	OPC-41061	YM-087	VA-985	SR-121463-B	OPC-31260
Drug name	Tolvaptan	Conivaptan	Lixivaptan	Satavaptan	Mozavaptan
Trade name	Samsca®	Vaprisol®	-----	Aquilda®	Physuline®
Drug status	Approved by FDA for SIADH, CHF, cirrhosis; Approved by EMEA for SIADH	Approved by FDA for hypovolemic and euvoletic hNa	Phase III Clinical trial	Withdrawn in 2008 by the manufacturer	Approved in Japan for SIADH secondary to malignancy
Development laboratory	Otsuka	Yamanouchi Astellas	Wyeth-Ayerst (Pfizer) Cardiokine	Sanofi Aventis	Otsuka
Core	Benzazepine	Benzazepine	Benzazepine	N-arylsulfonyl-oxindole	Benzazepine

	OPC-41061	YM-087	VA-985	SR-121463-B	OPC-31260
Administration route	Oral	iv	Oral	Oral/iv	Oral
Dose	7.5 - 15 - 60 mg/day	40 - 80 mg/day	50 - 100 mg twice/day	5 - 25 mg/day	30 - 60 mg/day
Protein binding	> 98%	98%	> 98%	< 90%	
Half-life (hours)	6 - 8	3 - 8	7 - 10	15 - 17	
Receptors blocked	V2	V1 + V2	V2	V2	V2
Metabolism	CYP3A4	CYP3A4	CYP3A4	CYP3A4 CYP2D6	CYP3A4
Elimination	Faeces				

The safety profile of the vaptans acknowledge as primary adverse effect thirst. Every so often, vaptans have been noticed to increase the sodium levels in plasma in a faster manner than it is registered to shun the osmotic demyelination [6], a possible complication that was not reported in any clinical trial [68] performed on vaptans. Nevertheless, clinicians have pursued the vaptan therapy with the use of fluid restriction [62-64], leastways during the initial 24 h, although the most common described adverse effect is thirst and also because the increased liquid consumption may counterbalance the wished effect regarding the plasma sodium levels. These should be closely observed during treatment and in the same manner used to conduct any decision regarding the fluid intake and continued dosing. Mild chronic hNa [37] (average serum sodium around 130 mEq/L) was the main inclusion criteria for enrolling subjects in the randomized controlled trials (Table III) conducted with vaptans. The possible explanation for not including symptomatic severe chronic hNa patients in these trials [37] entail the ethical requirements, meaning the patients from the placebo arm would be injured. A placebo-controlled randomized trial performed with intravenous conivaptan [37], on hospitalized asymptomatic patients with euvoletic and hypervolemic hyponatremia, revealed the safety and efficacy of this drug (serum sodium 115 to 0.5 mEq/L/h in the first day of research) [69]. Osmotic demyelination as a possible adverse event was not described. The efficacy and the safety of tolvaptan were demonstrated in the vasopressin antagonism in heart failure trial – EVEREST (“The Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure”) [70]. This vaptan was the drug administered to 2072 hospitalized patients [37] and diagnosed with decompensated heart failure, the result being a marked enhancement of serum sodium levels for the patients with hNa, even though that was not an inclusion criterion. Two osmotic demyelination post marketing reports [37] have been highlighted when tolvaptan was administered for correcting hNa with hypertonic saline. As revealed by the TEMPO trial (“Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes”) [37, 71], in which the focus was the prevention of gradual renal failure in patients with polycystic

kidney disease, FDA has expressed an advertisement not to administrate tolvaptan to liver associated pathology patients (the liver enzymes have evidenced an 2.5-fold increase reported to placebo) and has also restricted the employment time to 30 days [37]. It should be emphasised that the trial was conducted with significant higher doses (60 - 120 mg/ day, modal 90 mg/day) as against the most used doses in the hNa clinical trials (maximum 60 mg/day). On the other hand, in the SALT (“Study of Ascending Levels of Tolvaptan in Hyponatremia”) tolvaptan clinical trial [37, 72], in euvoletic patients, the increase in serum sodium concentration on the first 24 hours of drug administration [25], in the tolvaptan group, was 5.60 mEq/L, towards 7.45 mEq/L in a trial with conivaptan [25], and respectively 6.29 mEq/L in a comprehensive meta-analysis [73]. Going through this meta-analysis involving the hypervolemic patients, although the recorded response was unpretentious, at 4.09 mEq/L, there is to note the adverse effects, correlated particularly to the aquaretic involving drugs effects: polyuria, dry mouth, nocturia and thirst [25]. Nonetheless, the final goal would be the increase of serum sodium concentrations with 5 - 7 mEq/L in the first 24 hours, and free access to water should be permitted to patients in order to reduce excessive correction ratios [25, 27, 30-33]. Studying hyponatraemic subjects inside of larger ongoing placebo-controlled trials with tolvaptan, outwards the positive effect involving the physical component, the mental component pointed out a significant trend [19, 69, 72, 74]. The SALT-2 (“Study of Ascending Levels of Tolvaptan in Hyponatremia”) extensive randomized placebo-controlled trial was exhibited in a preliminary form. 243 hyponatraemic patients were permitted to receive 15 to 60 mg/day tolvaptan in a gradual manner for a 30-day period. Patients receiving tolvaptan compared to placebo were yield increased serum sodium levels as well as results of the lixivaptan trials [68, 69, 72, 74]. But, 25% of patients discard the study, and resistance (defined as the nonfulfillment of an enhancement in the serum sodium by ≥ 5 mEq/L) materialised for 37% of patients with congestive heart failure, 17% with cirrhosis, and 11% of patients with associated SIADH, respectively [67, 74].

Otsuka (Otsuka Pharmaceutical, Osaka, Japan), the pharmaceutical company that manufactures tolvaptan,

recommends the use of this drug in a dose range of 15 to 30 mg once daily p.o. for hNa [75]. In the United States, the price for a tablet is approximately USD 150. In Germany, a tablet's price (15 or 30 mg/tablet alike) is at the moment Euro 105, approximately equivalent to USD 115 [76]. In this regard, a vaptan treatment for a month – if that were evermore to be administered to a patient – rises to approximately Euro 4500 in Europe or USD 8300 in the United States [76]. These high prices are pertinent to be spent in the hypervolemic hNa. In euvolemic hNa, the vaptans treatments costs are similar to be dropped, because it is noticed an outstanding responsiveness to vaptan. The calculations exceed these numbers in the case of chronic haemodialysis for a month. In

the same class of drugs, the therapy expenditure is different, meaning tolvaptan therapy is even less expensive than conivaptan in Europe [64-66, 76]. Surveilling the literature data, we cannot find any published prospective study that should justify such costs in the benefit of the patient and also, further, to the healthcare system. Considering that the largest mass of hyponatraemic patients are clinically oligo-symptomatic or asymptomatic, the raised question is that urea has more sense for treating chronic hNa? In this regard, a comparative study involving urea and vaptan therapy, enrolling patients with mild hNa, would be more designated to exhibit the quality-of-life features, the efficacy, and the cost of both treatments [76].

Table III
Clinical trials with vaptans

Clinical trial or reference	Study design	Patient population	Treatment arms	Goal	Results	Adverse reactions
Hypervolemic or euvolemic hNa [3, 37, 77, 78]	Prospective, multicentre, open-label RCCT	28 Hospitalized patients ($s[Na^+] \leq 135$ mEq/L ≥ 2 consecutive days) + HF, liver cirrhosis, SIADH, and normovolemia or fluid overcharge	2:1 ratio Oral Tolvaptan (OPC-41061) alone ($n = 17$) - starting dose 10 mg/day, raised to 60 mg/day Fluid restriction ($n = 11$) (1200 mL/day) + Placebo , individualized to obtain normalized $s[Na^+]$ For 12 days or until the inpatient stay, whichever comes first	Normalization of $s[Na^+]$ achieved with tolvaptan	Significantly higher rate of subjects obtained normalization of $s[Na^+]$ in the tolvaptan group ($p = 0.007$) compared with the fluid-restriction group ($p = 0.049$)	No adverse events requiring discontinuation
SALT-1 and SALT-2 [3, 37, 72, 78, 79]	Multicentre, double-blind, placebo controlled RCCT	448 Patients aged ≥ 18 years with mild ($s[Na^+] = 130 - 135$ mEq/L) or pronounced hNa subordinate to chronic HF, cirrhosis, or SIADH	Oral Tolvaptan ($n = 225$) starting dose 15 mg/day, raised to a highest dose of 60 mg/day, according to $s[Na^+]$ Placebo ($n = 223$) For 30 days	Change from baseline and in the daily average AUC for $s[Na^+]$ to days 4 and 30		Placebo and Tolvaptan: thirst, dry mouth, increased urination, ascites, constipation, diarrhoea, nausea, vomiting,
SALT-1		205 Patients	Oral Tolvaptan ($n = 102$) Placebo ($n = 103$)		<i>Day 4</i> : 3.62 (2.68) with tolvaptan ($n = 95$) and 0.25 (2.08) mEq/L with placebo ($n = 89$), ($p < 0.001$). <i>Day 30</i> : 6.22 (4.10) with tolvaptan and 1.66 (3.59) mmol/L ($n = 95$) with placebo ($n = 89$) ($p < 0.001$)	weakness, fatigue, peripheral oedema, weakness, urinary tract infections, hyperglycaemia, hyperkalaemia, dizziness, headache
SALT-2		243 Patients	Oral Tolvaptan ($n = 123$) Placebo ($n = 120$)		<i>Day 4</i> : 4.33 (2.87) with tolvaptan and 0.42 (2.56) mEq/L ($n = 118$) with placebo ($n = 114$) ($p < 0.001$). <i>Day 30</i> : 6.20 (3.92) with tolvaptan and 1.84 (3.83) mEq/L ($n = 118$) with placebo ($n = 114$) ($p < 0.001$).	
EVEREST (clinical status trials) [37, 70, 78]	Prospective, multicentre, double-blind, placebo-RCCT	4118 Hospitalized patients aged ≥ 18 years with an EF $\leq 40\%$ + worsening HF symptoms/ minimal exertion + ≥ 2 signs of congestion (dyspnoea, peripheral oedema)	Oral Tolvaptan ($n=2063$) 30 mg/day Placebo ($n=2055$) initiated in no more than 48 hours of the admittance, for ≥ 7 inpatient days or until discharge	Mean (SD) changes in global health status and body weight at day 7 or discharge if earlier; improvement in dyspnoea and peripheral oedema and global clinical status	Global clinical status improvements were not different between groups. <i>Day 1</i> : improvement in dyspnoea for patients receiving tolvaptan (684 [76.7%] for trial A and 678 [72.1%] for trial B, respectively) vs patients receiving placebo (646 [70.6%] and 597 [65.3%], respectively) (both trials $p = 0.001$). <i>Day 7 or discharge</i> : significantly improvements for oedema with tolvaptan in trial B ($p = 0.02$) but lacking the significance in trial A ($p = 0.07$).	
TRIAL A		2042 Patients	Tolvaptan ($n = 1015$) Placebo ($n = 1027$)		Higher improvement with tolvaptan vs placebo (mean [SD], 1.06 [0.43] vs 0.99 [0.44]) <i>Day 1</i> : mean (SD) body weight decrease was major with tolvaptan (1.71 [1.80] vs 0.99 [1.83] kg; $p = 0.001$).	Thirst, dry mouth, constipation, hypernatremia, pollakiuria, and polyuria

Clinical trial or reference	Study design	Patient population	Treatment arms	Goal	Results	Adverse reactions
					Day 7 or discharge: (3.35 [3.27] vs 2.73 [3.34] kg; p = 0.001)	
TRIAL B		2076 Patients	Tolvaptan (<i>n</i> = 1048) Placebo (<i>n</i> = 1028)		Major improvement with tolvaptan vs placebo (1.07 [0.42] vs 0.97 [0.43]; p = 0.001) Day 1: mean (SD) body weight decrease was higher with tolvaptan (1.82 [2.01] vs 0.95 [1.85] kg; p = 0.001). Day 7 or discharge: (3.77 [3.59] vs 2.79 [3.46] kg; p = 0.001).	Thirst, dry mouth, constipation, polyuria, pollakiuria, and hyponatremia.
Vasopressin blockade with tolvaptan in chronic heart failure HF [4, 37, 76, 78, 80]	Multicentre, double blind, placebo-RCCT	254 Patients aged ≥ 18 years + HF symptoms for ≥ 30 days (irrespective of EF) + treatment with a fixed dose of oral FUR for ≥ 7 days before enrolment for signs of volume overload	Oral Tolvaptan (OPC-41061) 30 mg/day (<i>n</i> = 64) 45 mg/day (<i>n</i> = 62) 60 mg/day (<i>n</i> = 61) Placebo (<i>n</i> = 62) one dose daily 25 days	Change from baseline in the body weight	Reduction of the body weight by 0.84 kg in the tolvaptan group and improved hNa (p < 0.001) vs placebo between doses	Thirst, polyuria, dry mouth, dizziness, weakness
Tolvaptan in patients hospitalized with worsening heart failure [76, 78, 81, 82]	Multicentre, double-blind, placebo-RCT parallel-group, dose-ranging trial, phase 2	319 Hospitalized patients aged ≥ 18 years with decompensated systolic HF (EF < 40%), rales, or peripheral oedema after failure of initial in-hospital treatment of HF	Oral Tolvaptan 30 mg/day (<i>n</i> = 78) 60 mg/day (<i>n</i> = 84) 90 mg/day (<i>n</i> = 76) Placebo (<i>n</i> = 79) Within 96 hours of admission, for 60 days	<i>Part 1</i> (inpatient, ≤ 10 days)	In the first 24 h, body weight decreased by 1.4 kg vs placebo.	Dry mouth, thirst, nausea, dizziness, and hypotension
				Mean change in body weight at 24 hours after the first dose taken.		
				<i>Part 2</i> (outpatient, 60 days) Proportion with worsening HF (at 60 days after randomization).	No significant difference in worsening heart failure.	
Udelson et al. (2008) [3, 37, 78, 83]	Multicentre, double-blind, placebo-RCCT	181 Patients aged ≥ 18 years with an EF < 40% and NYHA functional class III – IV. HF treatment for ≥ 1 month and PCWP > 18 mm Hg on 2 readings ≥ 10 minutes apart 2 hrs before study drug administration	Oral tolvaptan (fixed dose) 15 mg/day 30 mg/day 60 mg/day Placebo	Mean (SD) change from baseline in PCWP 3 - 8 hrs after treatment administration	-6.38 (4.12) mm Hg with 15 mg/day (p < 0.01) -5.67 (4.58) mm Hg with 30 mg/day (p < 0.05) -5.71 (4.35) mm Hg with 60 mg/day (p < 0.05) -4.16 (4.57) mm Hg with placebo (p = NS between doses)	Patient-reported adverse events appeared in: 45.5% with 15 mg/day tolvaptan, 44.2% with 30 mg/day, 54.3%, with 60 mg/day, 33.3% with placebo, respectively
Ghali et al. [84]	Double-blind, placebo-controlled, multicentre study	51 hospitalized euvoletic and hyponatraemic patients aged > 18 years with s[Na ⁺] ≤ 130 mEq/L, serum osmolality < 290 mOsm/kg H ₂ O secondary to malignancy, CHF or idiopathic	Oral conivaptan initial dose 40 mg/day (<i>n</i> = 24) initial dose 80 mg/day in two divided doses (<i>n</i> = 27) Placebo (<i>n</i> = 23) 5 days Fluid restriction 2 L/day	Change from baseline for s[Na ⁺] and AUC to day 5	Both doses showed significant improvements over placebo 2.0-fold: higher for the 40 mg/day dose (p = 0.03) and 2.5-fold higher for the 80 mg/day dose (p < 0.001)	Headache, nausea, constipation, and postural hypotension
BALANCE study [85]	Double-blind, placebo-RCCT, phase 3	650 hospitalized patients aged > 18 years with worsening heart failure congestion and s[Na ⁺] ≤ 135 mEq/L	1:1 ratio Oral lixivaptan (<i>n</i> = 325) starting dose 50 mg/daily up to 100 mg twice daily based on s[Na ⁺] and volume status Fluid restriction Placebo (<i>n</i> = 325) 60 days with a 30 days follow-up	Change from baseline in s[Na ⁺] at day 7	Increased s[Na ⁺] and reduced body weight, without renal dysfunction or hypokalaemia	
Soupart et al. [86]	Double-blind, 1 st phase, multicentre, RCCT	34 patients aged > 62 years with hNa consecutive SIADH	Oral Satavaptan 25 mg/day (<i>n</i> = 14) 50 mg/day (<i>n</i> = 12) Placebo (<i>n</i> = 8) 7 to 30 days Fluid restriction < 1.5 L/day	Change from baseline in s[Na ⁺]	Increase of s[Na ⁺] following satavaptan 25 mg/day (p < 0.01) and 50 mg/day (p < 0.001) vs placebo.	
	Open label 2 nd phase, multicentre, CCT	22 patients with hNa consecutive SIADH	Oral Satavaptan (<i>n</i> = 22) increasing doses 12.5, 25, 50 mg/day 12 months Fluid restriction < 1.5 L/day	Change from baseline in s[Na ⁺]	15 of 18 enrolled subjects fulfilled 6 months and 10 fulfilled 12 months of treatment.	Urinary tract infection, vomiting, pruritus, stomatitis, vasculitis, cryoglobulinemia
Gines P et al. [87]	Double-blind, multicentric, RCCT	110 hyponatraemic patients with cirrhosis with ascites	Oral satavaptan 5 mg/day (<i>n</i> = 28) 12.5 mg/day (<i>n</i> = 26) 25 mg/day (<i>n</i> = 28)	Changes from baseline in s[Na ⁺] to day 5 and in body weight (day 1)	Improvements in s[Na ⁺] (p < 0.01 for all groups versus placebo). Improved management of	Thirst

Clinical trial or reference	Study design	Patient population	Treatment arms	Goal	Results	Adverse reactions
			Placebo (<i>n</i> = 28) Fluid restriction < 1.5 L/day Spironolactone 100 mg/day For 14 days	to the end of treatment (day 14)	ascites, as prevailed by a reduction in body weight (<i>p</i> = 0.05 for a dose-effect relationship overall).	
Yamagouchi et al. [88]	Multicentred, open-labelled CT	16 patients aged > 48 years with malignancies	Oral Mozavaptan 30 mg/day for 7 days or for 3 days when it was allowed Fluid restriction was permitted throughout the study period only For participants in whom it had already begun	Change from baseline in s[Na ⁺]	s[Na ⁺] (mean + SD) significantly (<i>p</i> = 0.002) increased from 122.8 + 6.7 to 133.3 + 8.3 mEq/L	Dry mouth, increased blood K ⁺ and Ca ²⁺ levels

RCCT – randomized controlled clinical trial; s[Na⁺] – serum sodium concentration; AUC – area under curve; FUR – furosemide; EF – ejection fraction; HF – heart fraction; NYHA – New York Heart Association; PCWP – pulmonary capillary wedge pressure; NS – not-significant

Are vaptans safe for elders?

The safety profile is the first and foremost preoccupation in the treatment of older patients when new agents are developed. As the preclinical data disclose, these drugs are potent aquaretic agents, e.g., in the tolvaptan studies [82], the observed diuresis exceeded more than 4 liters *per* day [70]. However, the incidence of adverse effects occurrence after administering tolvaptan medication was alike to that noticed within the placebo group in the SALT trials [72]. In the first month of therapy, ordinary adverse effects comprised thirst (14%), dry mouth (13%), weakness (9%), constipation (9%) and nausea (8%) [82]. In the EVEREST study [70], with a median 9.9 months of treatment, tolvaptan evidenced a good safety profile, although this has to be rendered with precaution as only 10% of participants were suffering of hNa. In the framework of an open-label extension of the SATWATER trial [72], 6 out of 111 subjects in the study discontinued the treatment because of the drug adverse reactions [82]. Short follow-up was reported in the subsequent studies [50, 52, 82]. However, it is raised the uncertainty that tolvaptan would be as properly accepted in elderly patients, especially taking into account the dehydrated, misdiagnosed with SIADH patients [82] linked to the potential for inappropriate prescription. The mean ages of the clinical trials participants were solely 60 years in SALT-1, 62 years in SALT-2 and 65 years in SATWATER [67, 69, 82], although the oldest volunteer was 100 years old in SALT trials. The tolerability regarding the age group is not very clearly explained and needs further assessment in randomised controlled clinical trials with a large number of older participants. On a balance, at the present, vaptans are the solution where uncomplicated and low-priced resources collapsed. But, in very elderly patients, the reliance for their use might be undervalued [74], because in this type of age group, hNa is rather ordinary [82]. The postural balance and cognition refinements should be put in opposite with a younger population. The economic burden of uncorrected hNa on relapses [75, 84, 89] and cognitive impairment [76] embrace a large number, and the life expectation of hyponatraemic elders could provide an expectation of a potentially life-long treatment more sustainable

to healthcare funders [82]. Overall, vaptan therapy rise a question mark regarding the safe and cost-effective sections.

Conclusions

The capacity of vaptans to treat hyponatremia is still blurred. Their employment in patients with hypovolemic hNa, symptomatic hNa, and especially with damaged liver is labelled with a big question mark. Not so effective in cirrhosis, they also lead to a fortunate aquaresis in patients with chronic heart failure and the outliving was not astonishing. But, nevertheless, vaptans are a key solution in the management of SIADH even with an underneath starting dose of 7.5 mg. As emphasized in preliminary studies, the potential beneficial employment of vasopressin-receptor antagonists is found for treating Raynaud's syndrome, Meniere's disease, dysmenorrhoea, ACTH-independent macronodular adrenal hyperplasia, and depressive disorders. In the elderly population, subtracted serum sodium concentration is an ordinary condition in view of the extension factors leading to increased ADH and the perpetual prescribed medication associated with hNa, especially antidepressants, anti-psychotics, or antiepileptics. Both in outpatient and inpatient settings, the assessment, and the treatment of hNa in the elderly patients arise for any clinician many challenges. They should brief in themselves with the correct way of using vaptans, because recommending vaptans for treating hNa is the future goal for this disease, because of the additionally gathered experience with this class of agents.

Conflict of interest

The authors declare no conflict of interest.

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