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**Approach to hyponatremia according to the clinical setting: Consensus statement from the Italian Society of Endocrinology (SIE), Italian Society of Nephrology (SIN), and Italian Association of Medical Oncology (AIOM)**

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1 **APPROACH TO HYPONATREMIA ACCORDING TO THE CLINICAL SETTING. CONSENSUS**  
 2 **STATEMENT FROM THE ITALIAN SOCIETY OF ENDOCRINOLOGY (SIE), ITALIAN SOCIETY OF**  
 3 **NEPHROLOGY (SIN) AND ITALIAN ASSOCIATION OF MEDICAL ONCOLOGY (AIOM)**

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5 *Emilia Sbardella<sup>1</sup>\*, Andrea M. Isidori<sup>1</sup>\*, Giorgio Arnaldi<sup>2</sup>, Maura Arosio<sup>3</sup>, Carlo Barone<sup>4</sup>, Andrea Benso<sup>5</sup>, Rossana*  
 6 *Berardi<sup>6</sup>, Gianni Capasso<sup>7</sup>, Massimiliano Caprio<sup>8</sup>, Filippo Ceccato<sup>9</sup>, Giovanni Corona<sup>10</sup>, Silvia Della Casa<sup>11</sup>, Luca De*  
 7 *Nicola<sup>12</sup>, Marco Faustini-Faustini<sup>13</sup>, Enrico Fiaccadori<sup>14</sup>, Loreto Gesualdo<sup>15</sup>, Stefania Gori<sup>16</sup>, Andrea Lania<sup>17</sup>, Giovanna*  
 8 *Mantovani<sup>3</sup>, Paolo Menè<sup>18</sup>, Gabriele Parenti<sup>19</sup>, Carmine Pinto<sup>20</sup>, Rosario Pivonello<sup>21</sup>, Paola Razzore<sup>22</sup>, Giuseppe*  
 9 *Regolisti<sup>14</sup>, Carla Scaroni<sup>9</sup>, Francesco Trepiccione<sup>7</sup>, Andrea Lenzi<sup>1</sup> and Alessandro Peri<sup>23</sup>,*

10 *on behalf of the: Fluid and Electrolytes Disorder Club of the Italian Society of Endocrinology; Italian Society of*  
 11 *Nephrology; and Italian Association of Medical Oncology*

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13

14 <sup>1</sup> Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

15 <sup>2</sup> Clinica di Endocrinologia e Malattie del Metabolismo, Ospedali Riuniti di Ancona, Ancona, Italy

16 <sup>3</sup> Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community  
 17 Health, University of Milan, Endocrinology and Diabetology Unit, Milan, Italy

18 <sup>4</sup> Divisione di Oncologia Medica, Università Cattolica del Sacro Cuore, Roma, Italy

19 <sup>5</sup> Division of Endocrinology, Diabetes and Metabolism, Department of Medical Sciences University of Turin, Turin,  
 20 Italy

21 <sup>6</sup> Clinica Oncologica; Università Politecnica delle Marche Azienda Ospedaliero-Universitaria; Ospedali Riuniti Umberto  
 22 I - GM Lancisi - G Salesi, Ancona, Italy

23 <sup>7</sup> Nephrology, 2<sup>nd</sup> Naples University Medical School, Naples, Italy

24 <sup>8</sup> Laboratory of Cardiovascular Endocrinology, IRCCS San Raffaele Pisana, Rome, Italy

25 <sup>8</sup> Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Roma Open University, Rome, Italy

26 <sup>9</sup> Endocrinology Unit, Department of Medicine DIMED, University-Hospital of Padova, Padova, Italy

27 <sup>10</sup> Endocrinology Unit, Medical Department, Azienda USI Bologna Maggiore-Bellaria Hospital, Bologna, Italy

28 <sup>11</sup> Endocrinology and Metabolic Diseases Unit, Catholic University of the Sacred Heart, Rome, Italy

29 <sup>12</sup> Nephrology, Naples University "Federico II" Medical School, Naples, Italy

30 <sup>13</sup> IRCCS Institute of Neurological Sciences Pituitary Unit Bellaria Hospital Bologna, Italy

31 <sup>14</sup> Renal Unit, Parma University Medical School, Parma, Italy

32 <sup>15</sup> Nephrology Dialysis and Transplantation, Bari University Medical School, Bari, Italy

33 <sup>16</sup> UOC Oncologia Medica, Ospedale Sacro Cuore-Don Calabria, Negrar (VR), Verona, Italy

34

35 <sup>17</sup> Endocrine Unit, Humanitas Research Hospital & Dept. of Biomedical Sciences, Humanitas University, Rozzano  
 36 (MI), Italy

37 <sup>18</sup> Nephrology, Sapienza University of Rome, Rome, Italy

38 <sup>19</sup> Endocrine Unit, Careggi Hospital, Florence, Italy

39 <sup>20</sup> Oncologia Medica IRCCS Arcispedale S. Maria Nuova, Reggio Emilia, Italy

40 <sup>21</sup> Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università "Federico II" di Napoli, Naples,  
41 Italy

42 <sup>22</sup> Endocrine Unit, AO Ordine Mauriziano, Turin, Italy

43 <sup>23</sup> Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

44

45

46 \* E.S. and A.M.I. contributed equally to this work

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60 Address all correspondence and requests for reprints to:

61 Alessandro Peri, MD. PhD.

62 Endocrine Unit

63 Department of Experimental and Clinical Biomedical Sciences "Mario Serio"

64 University of Florence

65 AOU Careggi

66 Viale Pieraccini, 6

67 50139 Florence

68 Italy

69 E mail: [alessandro.peri@unifi.it](mailto:alessandro.peri@unifi.it)

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## 72 INTRODUCTION

73 Hyponatremia (hypoNa, serum sodium levels  $<135$  mEq/L), is the most frequently observed electrolyte disorder in  
74 clinical practice, affecting up to 15-30% of hospitalized patients (1). HypoNa is characterized by an excess of water  
75 relative to exchangeable total body sodium, that can be normal, increased or decreased. As a consequence, hypoNa can  
76 be classified by the fluid volume status of the patient (euvoletic, hypovolemic and hypervolemic hypoNa), or by plasma  
77 tonicity, i.e., the effective osmolality, (isotonic, hypertonic and hypotonic hypoNa). Hypotonic hypoNa is the most  
78 commonly observed form in daily clinical practice (2). Severe hypoNa, especially if acutely developed (i.e. in less than  
79 48 hours), may determine major neurological symptoms due to brain edema, a potentially life-threatening complication  
80 if not promptly recognized and treated (3). However, even mild hypoNa (130-134 mEq/L) may also be associated with  
81 other strictly related clinical problems, often insidious and scarcely symptomatic, such as bone demineralization or gait  
82 instability and attention deficits, which may increase the risk of falls and bone fractures, especially in the elderly (4-8).  
83 Accordingly, recent meta-analyses have shown that even milder forms of hypoNa are associated with an increased risk  
84 of mortality in different clinical settings (9), along with prolonged hospital stay, increased readmission rates and higher  
85 hospital costs (10).

86 Although the main mechanisms of renal sodium and water handling, especially for what concerns the fine regulation by  
87 the distal nephron, have been fully elucidated (11), several clinical issues make the approach to hypoNa a complex task.  
88 In fact, on one hand it should be timely diagnosed and appropriately managed according to the severity of the neurological  
89 status, but on the other hand an overly rapid correction may cause neurological damage possibly leading to the Osmotic  
90 Demyelination Syndrome (ODS) (12-14). Conditions that may be associated with a risk of hypercorrection of hypoNa  
91 and their related mechanisms are showed in Table 1.

92 Nevertheless, despite its high prevalence, especially among hospitalized patients, and its clinical impact, hypoNa is often  
93 neglected, or under- or mistreated (15). This is mainly due to both an empirical approach (i.e. not pathophysiology-driven)  
94 and to the high degree of heterogeneity of the clinical settings where hypoNa is encountered.

95 In recent years a new class of drugs, namely the vasopressin receptor antagonists or vaptans, has become available for the  
96 treatment of hypoNa secondary to the Syndrome of Inappropriate Antidiuresis (SIAD), one of the most frequent causes  
97 of hypoNa (16). Tolvaptan is the only licensed vaptan in Europe, so far (12). However, there is no agreement between  
98 the European Guidelines (17) and the recommendations of an US Expert Group (14) concerning the use of vaptans in  
99 clinical practice (18).

100 On this basis, a task force generated by the Fluid and Electrolytes Disorder Club of the Italian Society of Endocrinology,  
101 the Italian Society of Nephrology and the Italian Association of Medical Oncology has joined together, in order to prepare  
102 a practical guide to recognize and manage hypoNa in different clinical settings.

103 In the intention of the task-force the present paper should be considered nor as a formal Guideline nor as an all-inclusive  
104 in-depth review on the topic. Rather, this paper should be viewed as a pocket guide to support the practical approach to  
105 hyponatremic patients by different specialists.

106 We propose a simplified diagnostic algorithm for hypoNa (Figure 1, Table 2) and a treatment algorithm for hypoNa  
107 secondary to SIAD (Figure 2). The treatment strategies for hypovolemic (rehydration) or hypervolemic hypoNa (fluid  
108 restriction, hypertonic saline solution, furosemide) are very well established and for a detailed description we redirect  
109 the reader to the already mentioned recommendations/guidelines (14, 17). Here, we would like to remind that fluid  
110 restriction is not very effective and in several clinical situations this approach aiming to correct hypoNa is going to fail  
111 (19).

112

## 113 **HYPONATREMIA IN ONCOLOGY**

### 114 Prevalence and etiology:

115 HypoNa in patients with cancer is a common finding because three major pathogenetic factors may concur to its  
116 development: the tumor, through the ectopic secretion of the antidiuretic hormone (ADH), also named vasopressin, the  
117 anti-neoplastic treatments, and again the tumor itself, through non-hormonal mechanisms.

118 About 14% of all cases of hypoNa occurs in oncological patients (3). SIAD is one of the leading causes of hypoNa in  
119 inpatients with cancer, affecting 1 to 2% of the entire cancer population (20, 21). The likelihood that SIAD is the cause  
120 of hypoNa in cancer patients is >30% (22).

121 SIAD is commonly reported in small-cell lung cancer. However, hypoNa has been also reported in other tumors, such as  
122 gastrointestinal, genitourinary, breast, prostate or hematological malignancies. SIAD in these patients may also be caused  
123 by pharmacological treatments, e.g. by a number of chemotherapeutic agents, opioid analgesics, antidepressants,  
124 including tricyclics and selective serotonin reuptake inhibitors (SSRI), as well as phenothiazines used as antiemetic agents  
125 (Table 3) (23). Of notice, hypoNa in oncology patients may be secondary to other conditions besides SIAD (Table 4)  
126 (22), and for this reason a careful differential diagnosis is needed. Finally, hypoNa can be precipitated by fluid and salt  
127 losses due to emesis or diarrhea, with severely symptomatic acute hypoNa that can be superimposed to a relatively stable  
128 chronic electrolyte imbalance.

### 129 Mortality:

130 HypoNa significantly contributes to both morbidity and mortality in cancer patients, and it is an independent prognostic  
131 marker: in a large study, the hazard ratio risk of 90-day mortality for mild, moderate, and severe hypoNa was 2.04, 4.74  
132 and 3.46, respectively (24).

### 133 Notes on treatment:

134 In general, the treatment strategy of hypoNa in oncologic patients is not different from that suggested by the available  
135 recommendations (12-14).

136 However, specific situations may occur. For instance, in patients with mild hypoNa secondary to SIAD, fluid restriction  
137 may be problematic, because of the need of parenteral hydration used during chemotherapy.

138 The use of urea for the treatment of hypoNa, especially in cases of SIAD, has also been proposed since the '80s (25, 26).  
139 The rationale of this approach is based on the capability of urea to increase the free water clearance by the kidney. The  
140 urea dosages usually used in patients with SIAD to correct serum sodium range between 15–30 g/day taken orally after  
141 a meal in one or two doses (25).

142 While a few non controlled studies (27) (28) have reported that urea is effective in normalizing hypoNa, hypercorrection  
 143 with hypernatremia has also been reported in the same studies. In fact, the urea-induced increase in serum sodium  
 144 concentration is not easily predicted, as it depends on both hydration status and urine osmolality. Thus, while the European  
 145 Guidelines (13) recommend urea as the treatment of choice in patients with SIAD when water restriction is ineffective or  
 146 not feasible, poor palatability, scarce clinical experience and the risk of hypercorrection suggest that advantages and  
 147 disadvantages of urea should be balanced against the possible use of vasopressin receptor antagonists in this clinical  
 148 setting.

149 Therefore, a valuable option in cancer patients with SIAD could be represented by vaptans. In a recent prospective study  
 150 on small cell lung cancer patients with severe SIAD, tolvaptan led to an effective correction and stabilization of the serum  
 151 sodium levels, also enabling patients to receive chemotherapy without any delay (29). In addition, the use of vaptans may  
 152 avoid withdrawal of hypoNa-inducing chemotherapies.

153 The duration of treatment for hypoNa is largely dependent on the cause. In drug-induced hypoNa, the electrolyte  
 154 alteration is usually reverted within days after the cessation of the involved drug. Conversely, in ADH secreting tumors,  
 155 hypoNa usually requires a longer and somewhat unpredictable duration of therapy, which is also dependent on the  
 156 response to anti-tumoral treatments (30).

157 In summary, we suggest that hypoNa should be carefully taken into account and timely corrected in oncology patients,  
 158 preferably avoiding severe fluid restriction or agents that may increase nausea (urea), taking into account that the  
 159 normalization of sodium levels has been found to have a positive effect on the prognosis and length of in-hospital stay  
 160 (31).

161

## 162 **HYPONATREMIA IN THE ELDERLY**

### 163 *Prevalence and etiology:*

164 The prevalence of hypoNa is increased in elderly patients compared with that in the general population, reaching almost  
 165 50% of all acute geriatric admissions (32, 33).

166 In the elderly, the etiology of hypoNa is multifactorial in 50–75% of cases (34, 35). SIAD is the most common cause,  
 167 even if a risk of over-diagnosis has been claimed (34). Other frequent causes are congestive heart failure, water and  
 168 sodium homeostasis alterations, renal and hepatic dysfunction, and especially drug-induced hypoNa, because older people  
 169 often receive multiple pharmacological treatments (Table 5) (35) .

170 In elderly patients alterations of electrolyte and water balance are favoured by age-related reduction in total body water,  
 171 reduced renal function (36), decreased cortical blood flow and glomerular filtration rate, impaired responsiveness to  
 172 sodium balance changes (37), osmoreceptors hypersensitivity, and higher ADH release (38). Additionally, the ability to  
 173 excrete free water is reduced (39).

### 174 *Mortality:*

175 HypoNa is associated with increased all-cause mortality in elderly subjects: a recent study showed that the adjusted  
 176 hazards ratio (95%CI) in hyponatremic men without chronic kidney disease (CKD), stroke or heart failure was 1.30  
 177 (confidence interval 1.02 to 1.66) (40).

### 178 *Notes on clinical features and diagnosis:*

179 HypoNa in the elderly is mostly mild, chronic and apparently asymptomatic, but it often associated with bone  
180 demineralization and cognitive impairment, increased risk of falls and fractures (7, 34).

181 Conversely, acute hypoNa in the elderly is characterized by confusion, irritability, lethargy, anorexia and nausea, but pre-  
182 existing cognitive and sensory impairment might interfere with timely identification of symptoms (34, 38).

183 The diagnosis in older people may be challenging, due to polypharmacy, difficult assessment of fluid volume status by  
184 clinical examination, presence of several confounding co-morbidities, and difficulties in obtaining a reliable clinical  
185 history (34, 41).

#### 186 Notes on treatment:

187 Treatment of both acute and chronic hypoNa in the elderly does not differ from that of younger patients (14, 34). Vaptans  
188 could represent an option in hypoNa secondary to SIAD also in the elderly. The use of low doses - at least initially - may  
189 reduce the risk of overtreatment. Appropriate hydration should be strictly monitored. In the case of hypovolemic hypoNa,  
190 rehydration should be provided with special caution, especially when cardiac function is reduced and/or chronic kidney  
191 disease coexist (36).

192

### 193 **HYPONATREMIA IN CONGESTIVE HEART FAILURE**

#### 194 Prevalence and etiology

195 The prevalence of hypoNa among patients with heart failure (HF) is about 20-25% (42) (43) (44) (45) (46), however, it  
196 may be higher in patients admitted for acutely decompensated HF (ADHF): 38% at hospital admission and 28% as new-  
197 onset hyponatremia during hospital stay (47).

198 In this clinical setting, effective arterial blood volume (EABV) is decreased, due to low cardiac output and systemic  
199 venous congestion. The decreased EABV releases the tonic baroreceptor-dependent inhibition on efferent sympathetic  
200 tone and vasopressin release. The ensuing hyperactivation of the sympathetic nervous system, together with renal  
201 hypoperfusion, is associated with decreased glomerular filtration rate, increased proximal sodium reabsorption and  
202 reduced sodium delivery to distal nephron segments. These latter mechanisms and the high circulating vasopressin levels  
203 – always disproportionate to the reduced plasma tonicity - are mainly responsible for decreased free water clearance and  
204 development of HypoNa. On the other hand, secondary hyperaldosteronism due to increased renin release and elevated  
205 circulating angiotensin II favors increased sodium reabsorption at the distal nephron, increased total body sodium balance,  
206 edema formation and hypervolemic hypoNa (48).

#### 207 Mortality

208 A correlation between hypoNa and overall mortality was first documented 30 years ago in HF. Moreover, in patients with  
209 ADHF hypoNa is associated with an increased mortality and risk of re-hospitalization (47) (49). In particular, a recent  
210 meta-analysis of the available data documented that hypoNa doubled the risk of mortality in patients with HF (9). In  
211 addition, patients admitted for ADHF and normal serum sodium values at admission, it has also been shown that the  
212 development and worsening of hypoNa during hospital stay are strongly correlated with an increase in overall and  
213 cardiovascular mortality (50).

214 Finally, a recent retrospective study in patients admitted for ADHF with hypoNa at admission reported that even persistent  
215 hypoNa at the time of hospital discharge is associated with a significant increase re-hospitalization or mortality at 30 days  
216 (51).

#### 217 Notes on treatment

218 Clearly, sodium and fluid restriction, diuretics, blockers of the renin-angiotensin-aldosterone system, and betablockers,  
219 are the mainstay of treatment in patients with HF. While hypoNa bears a clear negative prognostic impact, few data are  
220 currently available in the literature to clearly ascertain whether correction of hypoNa per se may ameliorate outcomes in  
221 patients with HF (13). As a matter of fact, long-term treatment with tolvaptan in patients with HF was not associated with  
222 decreased mortality or risk of re-hospitalization compared with placebo, notwithstanding greater weight loss, better  
223 dyspnea relief, and a significant increase in serum sodium values at discharge (52). However, a post-hoc analysis of the  
224 Acute and Chronic Therapeutic Impact of a Vasopressin antagonist (ACTIV) study (53) suggested a possible correlation  
225 between increased serum sodium levels and increased survival. Furthermore, a post-hoc analysis of the Efficacy of  
226 Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial showed decreased incidence  
227 of the combined endpoint of cardiovascular mortality and cardiovascular morbidity in tolvaptan-treated patients with  
228 serum sodium values  $\text{Na} < 130 \text{ mEq/L}$  (54). Thus, expert consensus by US investigators (14) suggested that vaptans  
229 (tolvaptan, and possibly conivaptan, not licensed in Europe, so far) may represent a useful therapeutic tool in patients  
230 with CHF and mild-to-moderate hyponatremia. On the other hand, based on the results of an extended meta-analysis  
231 indicating a non-significant trend towards increased mortality in hyponatremic patients with expanded extracellular fluid  
232 volume, European guidelines (13) are against the use of vaptans in conditions where hyponatremia is associated with  
233 expanded extracellular fluid volume. A faster decongestion with dyspnea relief represents a desirable goal in the treatment  
234 of patients with ADHF, and no cases of osmotic myelinolysis have been reported either in the ACTIV and EVEREST  
235 trials or in the subgroup of patients with CHF enrolled in the Study of Ascending Levels of Tolvaptan in Hyponatremia  
236 1 and 2 (SALT-1 and SALT-2) trials (55). For these reasons, the use of tolvaptan may be envisaged as a potentially useful  
237 add-on treatment strategy in patients with CHF and mild-to moderate hypoNa. However, very recently, the Targeting  
238 Acute Congestion with Tolvaptan in Congestive Heart Failure (TACTICS-HF) trial (56) reported no significant  
239 differences in dyspnea relief and in-hospital or post-discharge clinical outcomes in patients with ADHF treated with  
240 tolvaptan 30 mg given at 0, 24 and 48 hours on top of fixed-dose furosemide compared with patients receiving placebo,  
241 despite greater weight loss and net fluid loss in tolvaptan-treated patients. Thus, at the present time no firm  
242 recommendation about the use of vaptans in CHF can be supported by the available literature data.

243

## 244 **HYPONATREMIA IN DECOMPENSATED LIVER CIRRHOSIS**

### 245 Prevalence and etiology

246 The prevalence of hypoNa in patients admitted for decompensated liver cirrhosis reaches 57% (57). Between 21% and  
247 28% of patients have serum sodium values  $< 130 \text{ mEq/L}$  (57-59), whereas severe hypoNa (serum  $\text{Na} \leq 120 \text{ mEq/L}$ ) is  
248 relatively infrequent ( $< 1.2\%$ ) in this setting (57).

249 Post-sinusoidal capillary hypertension, hypoalbuminemia and splanchnic vasodilation play a pivotal role in ascites  
250 accumulation; specifically, overproduction of nitric oxide, mainly due to circulating endotoxin associated with bacterial

251 translocation, maintains splanchnic vasodilation (60). In this clinical setting, pathophysiological mechanisms triggered  
 252 by decreased EABV are essentially the same as in HF. Thus, while total body sodium balance is increased, the  
 253 development of hypoNa is facilitated by reduced sodium delivery to the distal nephron and high circulating vasopressin  
 254 levels (60).

### 255 Mortality

256 The negative prognostic role of hypoNa in patients with liver cirrhosis has been clearly documented (59, 60). In a study  
 257 performed in 6769 patients with liver failure waiting for liver transplantation, of whom 422 had deceased within 90 days  
 258 since entering the waiting list, the investigators found an increased risk of death associated with hypoNa, even independent  
 259 of the MELD score (61). Accordingly a recent meta-analysis of the available data documented that hypoNa was associated  
 260 with more than 3-fold increased risk of mortality in patients with cirrhosis (9).

### 261 Notes on treatment

262 In patients with liver failure, treatment with vaptans has been shown to ameliorate fluid balance in some studies (62-64).  
 263 Moreover, treatment with satavaptan was associated with greater increase in serum sodium values and decreased ascites  
 264 formation in cirrhotic patients receiving either diuretics (65) and spironolactone (59). However, one of those studies (65)  
 265 also found an increase in the risk of death due to complication of cirrhosis in patients treated with both satavaptan and  
 266 diuretics, which subsequently lead to drug withdrawal from commerce. Lixivaptan, on top of standard treatment with  
 267 spironolactone, proved to be effective in increasing free water clearance and serum sodium values in patients with  
 268 decompensated liver cirrhosis (66).

269 Tolvaptan, so far the only vaptan approved in Europe, so far, and allowed only in patient with hypoNa secondary to SIAD,  
 270 has been also tested on top of standard treatment with furosemide and spironolactone in patients with decompensated  
 271 liver cirrhosis. Although the drug proved to be effective, also at low doses (e.g., 3.5 and 7.5 mg/day), in reducing ascites  
 272 volume and body weight (67), as well as in increasing serum sodium values (68, 69), however both the European  
 273 guidelines (13) and the US expert consensus document (14) recommend against the use of vaptans in patients with liver  
 274 disease. Anyway, as hypoNa may complicate the use of high-dose loop diuretics in oliguric patients with refractory ascites  
 275 and may predispose them to hepatic encephalopathy, a cautious use of tolvaptan in combination with diuretics may  
 276 represent a treatment strategy that should be explored in future research (60). In any case, liver function should be closely  
 277 monitored, and the drug should be discontinued if worsening of it is detected.

278

## 279 **HYPONATREMIA IN CHRONIC KIDNEY DISEASE**

### 280 Prevalence and etiology

281 Prevalence and incidence values of hypoNa in chronic kidney disease (CKD) are respectively 13.5% and 26% (mean  
 282 follow-up 5.5 years) (70). HypoNa is especially common among patients with stage 5 CKD on dialysis (End-Stage Renal  
 283 Disease, ESRD): 29.3% prevalence in hemodialysis, 14.5% incidence in peritoneal dialysis (71).

284 Three main pathogenetic mechanisms may lead to hypoNa in renal patients (72):

- 285 • Direct renal sodium loss, such as in salt-losing nephropathies (chronic pyelonephritis, chronic drug-associated  
 286 or toxic tubule-interstitial), characterized by reduced renal sodium reabsorption, sodium and potassium  
 287 depletion, reduced concentration ability, hypovolemia and ADH stimulation (73). The consequence is hypoNa  
 288 with volume depletion.
- 289 • Reduced urinary dilution capacity due to severe impairment of glomerular filtration rate with ensuing lower  
 290 availability of preurine at the diluting segments of the distal nephron and reduced ability to generate free water.  
 291 In this case hypoNa will be euvolemic or hypervolemic (74) (72).
- 292 • Oligoanuria or anuria along with free water/hypotonic fluid intakes exceeding losses, such as the case of ESRD  
 293 on chronic dialysis or in acute kidney injury. These forms of hypoNa are usually hypervolemic (74).

#### 294 Mortality

295 Low sodium levels are associated with increased mortality risk, both in CKD patients on conservative treatment (70) and  
 296 in ESRD patients on dialysis (75) (76, 77).

#### 297 Notes on treatment

298 There is paucity of data in the literature concerning the treatment of hypoNa in patients with CKD on conservative therapy.  
 299 The oral vasopressin V<sub>2</sub>-receptor antagonist tolvaptan has been tested in small studies performed in CKD patients with or  
 300 without congestive heart failure (78). On the whole, a significant increase in urine volume was observed, together with  
 301 an increase in serum sodium concentration. Moreover, treatment with tolvaptan was not associated with deterioration of  
 302 kidney function in these patients.

303 The problems of the treatment of hypoNa during renal replacement therapy (RRT), and the inherent risks of overcorrection  
 304 and osmotic demyelization syndrome, have been addressed mainly in the critically ill patients. Specifically, reducing  
 305 serum sodium concentration in the substitution fluids has been advocated as the best approach to avoid the risk of  
 306 overcorrection during continuous veno-venous hemofiltration or continuous veno-venous hemodialysis (79). When  
 307 standard intermittent hemodialysis is chosen, sodium concentration in the dialysate should be reduced to a minimum of  
 308 130 mEq/L, and blood flow rate as low as 50 mL/min together with short duration (e.g., 3 hours) of dialysis session should  
 309 be prescribed (80).

310

### 311 **HYPONATREMIA IN NEUROLOGY**

#### 312 Prevalence and etiology:

313 HypoNa is a frequent complication of traumatic brain injury and meningitis (81).

314 Limited information is available for other neurological disorders. A large Swedish registry study documented that epilepsy  
 315 and stroke accounted for about 10% of all cases of hypoNa (82).

316 In subjects with stroke, many factors including dietary sodium restriction for hypertension control, use of thiazide  
 317 diuretics and infections might precipitate hypoNa (83).

318 Several antiepileptic drugs (AEDs) and in particular carbamazepine, oxcarbazepine, eslicarbazepine and levetiracetam  
 319 may cause asymptomatic or mildly symptomatic hypoNa secondary to SIAD, which in turn may exacerbate seizures  
 320 (Table 3) (81).

321 HypoNa can occur in Guillain–Barré syndrome (GBS) as a consequence of SIAD caused by the intravenous  
 322 immunoglobulin therapy, or of renal salt wasting syndrome as part of GBS-related dysautonomia (84).

323 Mortality:

324 HypoNa is associated with an increased risk of mortality in patients with neurological diseases: in a Danish cohort study,  
 325 the adjusted 30-day relative risk of death among hyponatremic patients compared to patients with normonatremia was 1.5  
 326 (0.9 –2.5) (85).

327 Serum sodium evaluation should be mandatory in the presence of neurological symptoms. Routine sodium monitoring  
 328 for patients receiving AEDs is not usually necessary, except in elderly subjects or in those receiving AED polytherapy or  
 329 sodium depleting drugs (81).

330 Notes on treatment:

331 HypoNa in neurological patients should be managed according to the general recommendations. Treatment mainly  
 332 depends on etiology; it has been shown for instance that in traumatic brain injury treatment usually lasts 0.5-2 years (30).  
 333 In SIAD caused by AEDs, the possibility to reduce the dose, switch to a different drug or stop treatment should be  
 334 evaluated together with the neurologist.

335

336 **HYPONATREMIA IN NEUROSURGERY**

337 Prevalence and etiology:

338 Hypotonic hypoNa is a frequent finding in the neurosurgical patients, with the highest rate (20-50%) in some series among  
 339 patients with subarachnoid hemorrhage (SAH) (86, 87). Observational studies have shown that brain tumors, during their  
 340 course, may be associated with hypoNa in about 15-20% of cases (86). The occurrence of hypoNa as a result of  
 341 transphenoidal surgery varies a lot in the different series, depending on the selection criteria. Symptomatic hypoNa was  
 342 much less frequent (4-7%) than asymptomatic hypoNa, which in some series occurred in up to 20-35% of patients,  
 343 according to serum sodium measured every day for at least 12 days after surgery (88-90).

344 Some neurosurgical disorders, such as acute and chronic SAH, subdural hematoma, hemorrhagic stroke, tumors, cysts,  
 345 metastases, and inflammatory diseases of the brain, pituitary, or hypothalamus, become harder to manage when hypoNa  
 346 develops (86, 87, 90-92). Such a complication may occur both before and after surgery. HypoNa may also be observed at  
 347 presentation in patients with pituitary apoplexy yet much less frequently than hypernatremia due to diabetes insipidus  
 348 (DI).

349 Mortality

350 Besides hypoNa, several other factors may contribute to increase the mortality risk in the neurosurgery setting. A recent  
 351 systematic review, aimed at characterizing the effect of hypoNa on morbidity and mortality after SAH, included thirteen  
 352 studies with a total number of 2387 patients and showed that hypoNa was associated with increased morbidity (especially  
 353 due to vasospasm), but it did not influence mortality (87). Interestingly, a recent retrospective observational study

354 reviewed 198 consecutive patients with SAH and indicated sodium fluctuation, rather than hypoNa per se, as a significant  
355 factor associated with worse neurologic outcome (91)

356 Specific notes on clinical features and diagnosis:

357 Most observational studies have shown that SIAD is the commonest cause of hypotonic hypoNa in neurosurgical patients  
358 (86). However, in this setting it is essential to differentiate SIAD and cerebral salt wasting syndrome (CSWS) as a possible  
359 cause of hypoNa, especially in pediatric series and in patients with SAH (86, 92, 93). The differential diagnosis between  
360 CSWS and SIAD may not be easy in clinical practice, the former having hypovolemia as a crucial point for the proper  
361 diagnosis (94).

362 In the evaluation of the hyponatremic patient after neurosurgery, it is essential to consider the possible occurrence of DI  
363 with a triphasic pattern (95) and the possible late occurrence of hypoNa due to SIAD, which can occur after the patient  
364 has been discharged (88-90)

365 In order to improve the outcome in neurosurgical patients, we suggest careful monitoring of serum sodium on admission  
366 and during the hospital stay. Whenever hypoNa is observed, a proper work-up has to be instructed to elucidate the  
367 underlying cause, bearing in mind that the evaluation of extracellular fluid volume status is mandatory. Also in case of  
368 early discharge the patients should receive clear instructions on what to do if hypoNa-compatible symptoms appear.

369  
370 **HYPONATREMIA IN THE PATIENT WITH TRAUMA AND POLYTRAUMA**

371 Prevalence and etiology

372 Little is known about hypoNa in patients with polytrauma (PT). In several studies, hypoNa has been reported in up to  
373 15% of patients after trauma or PT (96, 97). After PT, the occurrence of hypoNa can be related to the event *per se* (fluid  
374 depletion, hemorrhage), to the immediate treatment at the site of trauma or Emergency Department (hypotonic intravenous  
375 fluids), or to a pre-existing comorbidity disease, especially in the elderly.

376 Mortality

377 HypoNa is associated with poor prognosis and increased mortality in patients with crush syndrome: in a retrospective  
378 study conducted in Chinese reference hospitals during the Wenchuan earthquake the presence of hypoNa was common,  
379 up to 50% of patients were affected and 15% of them died. However, here the hypoNa was mainly correlated with the  
380 development of acute kidney failure (96).

381 Notes on clinical features and diagnosis

382 Hip fracture is the commonest cause of traumatic death in Europe: immediate surgery has been associated with higher  
383 rates of independent living, lower mortality rates, improved patient outcomes by reducing pain scores, and lowering the  
384 risk of decubitus ulcers. The occurrence of hypoNa ( $[\text{Na}]^+ < 135 \text{ mEq/L}$ ) in the course of the pre-surgical planning was  
385 the main medical pre-operative risk factor for surgery delay after 36 hours from trauma (98).

386 Rather than considering hypoNa always as a consequence of PT, this electrolyte disorder could be the cause of trauma:  
387 even mild hypoNa in fact has been associated with unsteady gait, falls, impaired concentration, and risk of fractures,  
388 especially hip and femur fractures (6, 99). In an extensive series of elderly adults, fracture risk incidence was higher in  
389 patients with hypoNa, also after adjusting for osteoporosis. Patients with moderate-severe hypoNa ( $[\text{Na}]^+ < 130 \text{ mEq/L}$ )

390 presented an 11-fold risk of fractures (100), and fragility fractures increased incrementally with a categorical decrease in  
391 median serum sodium levels in multivariate logistic regression models (101).

392 Notes on treatment

393 Specific consensus about the treatment of hypoNa targeted to PT patients has not been developed, yet. In general, we  
394 suggest to follow currently available guidelines and recommendations for the management of hypoNa.

395 HypoNa is common in PT patients without neurological involvement: however, larger studies are needed to investigate  
396 the relationship between trauma and serum sodium levels, and hypotonic intravenous fluids should be supplied carefully  
397 to patients with PT.

398 HypoNa is not always recognized in patients with PT: we suggest to pay attention to sodium balance in such patients.  
399 Population studies with a large number of participants have to be performed.

400

401 **HYPONATREMIA IN THE OUTPATIENT SETTING**

402 Prevalence and etiology:

403 The prevalence of hypoNa in this setting greatly depends on the age of the population considered (102-105). In a young  
404 and ethnically diverse population, the prevalence of hypoNa was 6.3% (105), but with aging the potential risk of  
405 developing hypoNa increases (103, 106).

406 In the outpatient setting, hyponatremic individuals are more likely to be smokers, to have black ethnicity, a history of  
407 diabetes mellitus, congestive HF or cirrhosis and to use thiazide diuretics, antiepileptic drugs or SSRI (103, 105).

408 However, in the Dallas Heart Study, among hyponatremic individuals with no predisposing medical conditions, 20% of  
409 them had criteria discriminators of the diagnosis of SIAD (105).

410 Mortality:

411 There are limited data in the literature regarding hypoNa in the outpatient setting, but similarly to hospitalized patients,  
412 also in the outpatient studies hypoNa has been reported to be an independent mortality risk factor (9, 102, 105, 107, 108).  
413 In a recent survey, hypoNa was found to be associated with a nearly two-fold increase in deaths, even after adjusting for  
414 major risk factors (105).

415 Specific notes on clinical features and diagnosis:

416 HypoNa in the outpatient is more likely to be mild, chronic and asymptomatic (103, 105, 107).

417 Actually, in clinical practice, hypoNa very often represents an incidental finding during an outpatient visit for another  
418 reason and it is difficult for the physician to formulate promptly a correct etiological diagnosis, which greatly depends on  
419 additional laboratory tests that may not be readily available.

420 Notes on treatment:

421 In the case of moderately or severely symptomatic hypoNa, hospitalization should be considered.

422 In the case of hypoNa secondary to SIAD, when vaptans use is indicated, patients should be hospitalized, because of the  
423 need of close initial monitoring, and to identify the appropriate dose (9, 109). A day-hospital admission may be suitable  
424 if there are no other serious concomitant disorders (110).

425 A regular outpatient follow-up is recommended, to evaluate the effectiveness of the therapy as well as the possibility of  
426 discontinuing it.

427 We suggest that hypoNa in this setting should be taken into consideration even if mild to moderate hypoNa to timely  
428 correct it, particularly in the elderly and in patients assuming drugs, thus likely limiting the consequences of persistent  
429 low sodium levels.

430

### 431 **LIFE-THREATENING HYPONATREMIA**

#### 432 Prevalence and etiology:

433 Acute and severely symptomatic hypoNa is rare. However, if not rapidly recognized and correctly treated, it may carry a  
434 high morbidity and mortality rate, even in previously healthy subjects, such as for example marathon runners, in which  
435 an incidence of 13% has been documented (111). Other causes can be represented by the rapid ingestion of large amounts  
436 of water, for example in psychiatric patients, or of other hypotonic liquids, such as in beer potomania or tea and toast diet.  
437 Other conditions associated with acute and potentially life-threatening hypoNa are the postoperative period, in particular  
438 after prostate transurethral resection or post uterine endoscopic surgery due to the use of hypotonic irrigant solutions,  
439 colonoscopy preparation, the use of some drugs such as oxytocin or cyclophosphamide, or a recent prescription of  
440 thiazides or desmopressin, and use of recreational drugs such as ecstasy (MDMA) (13, 112). The severity of the picture  
441 correlates both with the magnitude and the rate of sodium decrease.

442

#### 443 Mortality:

444 Mortality in this setting has been noted to be as high as 55% (113). However, the estimate from a broad-based literature  
445 survey gives much lower values (114).

#### 446 Specific notes on clinical features and diagnosis:

447 HypoNa may be itself the direct cause of death because of brain stem herniation due to cerebral edema for serum hypo-  
448 tonicity. Risk factors for brain edema are both the rate and the depth of sodium fall.

449 The risk of death as a consequence of brain edema is increased in the presence of an intracranial disease, in the case of  
450 post-operative hypoNa or acute water intoxication.

#### 451 Notes on treatment:

452 Prompt infusion of hypertonic saline, independent of volume status, may save lives in life-threatening hypoNa.

453 In this emergency setting hypertonic 3% NaCl saline solution is administered as a 100/150 mL bolus (or 2 ml/Kg of body  
454 weight) given over 10-20 min, strictly monitoring sodium levels (every 20 min), and repeating the bolus administration,  
455 as needed, up to a maximum of 3 times. According to the European guidelines, this protocol is recommended until a  
456 serum sodium increase of 5 mEq/L is achieved (13).

457 In the case of symptoms improvement and/or after a 5-6 mEq/L increase in serum sodium (symptoms relief can take  
458 longer), 3% NaCl should be stopped, but the i.v. access kept. Meanwhile a diagnosis-specific process should be initiated,  
459 and appropriate management performed (13, 14).

460 In the absence of symptoms improvement after the first few hours, i.v. hypertonic 3% NaCl saline should be continued  
 461 aiming for an additional 1 mEq/L/h increase in serum sodium, limiting the overall 24 hours increase to 8-10 mEq/L and  
 462 stopping anyway the infusion upon reaching a serum sodium level of 130 mEq/L (13, 14). Therapy should be guided by  
 463 frequent monitoring of serum sodium concentration (possibly every 2 hours, but at least every 4 hours).

464

#### 465 **HYPONATREMIA OVERCORRECTION: CONDITIONS AT RISK, PREVENTION, TREATMENT**

466 Excessive correction of hypoNa (i.e. too much and/or too rapid increase of serum sodium levels) is associated with an  
 467 increased risk of negative neurologic outcomes (i.e. the ODS), especially in the chronic forms of hypoNa. On this regard,  
 468 specific attention is to be paid to the fact that during sodium correction an adequate renal response to hypotonicity (i.e.  
 469 an hypotonic polyuria) is often spontaneously (and rapidly) restored, even since the first 8-12 hours from treatment start.  
 470 This usually happens when pathogenetic factors responsible for the electrolyte derangement are promptly taken away,  
 471 such as for example by volume expansion with 0.9% saline in hypovolemic hypoNa, or by ceasing the trigger mechanism  
 472 for inappropriate secretion/response to ADH (i.e. drugs or inflammation). Thus, since the most frequent cause of hypoNa  
 473 overcorrection is actually the reactivation of the normal renal physiological response (increased free water clearance),  
 474 special attention should be paid to hypoNa settings characterized by rapidly reversible causes (Table 1) (18). A hypotonic  
 475 polyuria with maximally diluted urine output may in fact further increase the programmed/estimated rate of correction.

476 In such a circumstance, administration of a hypotonic solution should be started, as intravenous 5% dextrose or free water  
 477 by a nasogastric tube, initially at 10 ml/Kg/h over 1 h (13) or in repeated 3ml/kg infusions (14) and then matched to  
 478 urinary output in terms of rate and tonicity; desmopressin (i.v. or s.c.) at 2-4 µg every 8 hours can be associated, in order  
 479 to bring back the rate of correction to below 12 mEq/L/24 hours (or better to a target of 6-8 mEq/L in the first 24 hours)  
 480 (13). It is mandatory that specific measures to blunt overcorrection of hypoNa must be implemented by/or under the  
 481 direction of experienced medical personnel (13) .

482 Another possible (and underrated) cause of overcorrection of hypoNa is represented by the administration of potassium  
 483 salts along with NaCl, aiming at correcting coexisting hypokalemia/potassium depletion. Based on the original Edelman  
 484 equation, potassium and sodium salts are equivalent in terms of tonicity effects (115). In fact, in case of cellular potassium  
 485 depletion, the administered potassium enters the cells, with ensuing Na exit in order to maintain the electrical equilibrium.  
 486 Thus, serum sodium values increase (116).

487 The risk of overcorrection is not significantly reduced by the use of specific formulas aimed at estimating the rate and the  
 488 temporal trajectory of serum sodium during correction (117). Formulas may be useful to set the start of therapy, but they  
 489 do not completely avoid the risk of overcorrection due to their inherent limitations: they do not take into account the  
 490 possibility of a rapidly restored diluting capacity by the kidney, ongoing losses and other electrolyte supplements are  
 491 difficult to be integrated in the calculation, as it is the case of potassium administration in potassium depletion (117).  
 492 More conservatively, in these cases it is better to frequently check (at least every 4 hours in the first 24 hours) the actual  
 493 serum sodium levels.

494 Finally, it should kept in mind that some conditions are associated with a higher risk of ODS due to overly rapid correction  
 495 of hypoNa: serum sodium levels less than 105 mEq/L, alcoholism, malnutrition, advanced liver disease (14) Table 1.

496 These conditions must be recognized even before the start of treatment and a great caution should be used in these  
497 situations.

498

## 499 **CONCLUSIONS**

500 Despite being the most common electrolyte disorder encountered in clinical practice, hypoNa is frequently  
501 underdiagnosed and/or not appropriately treated. This may be due to a lack of awareness of the implications of this  
502 condition on patient outcomes, particularly when hospital-acquired and mildly or moderately symptomatic. Appropriate  
503 workup and treatment in the various clinical settings associated with hypoNa require a multidisciplinary approach. In  
504 such a need, this task force has provided the above-outlined suggestions and warnings. Ineffective management of hypoNa  
505 can negatively affect patient prognosis. New therapeutic options for the correction of hypoNa, particularly vaptans, the  
506 vasopressin receptor antagonists, represent an effective tool to safely treat this disorder and improve outcomes among a  
507 wide range of patients with hypoNa secondary to SIAD. However, the different clinical scenarios in which hypoNa may  
508 occur suggest that a thoughtful and personalized management should be individualized. This scenario is even more complex  
509 when we consider that not all the hospitals are properly equipped to perform an accurate differential diagnosis of hypoNa.  
510 As an example, the infrequent availability of osmometers in the medium/small hospital facilities is a limiting factor for  
511 the diagnosis of SIAD. Thus, we propose that clinicians may refer to calculated serum and/or urinary osmolality according  
512 to recently reviewed formulae (118).

513 A rapid recognition and optimal treatment of hypoNa can reduce the risk of death (119), also reducing the length of  
514 hospitalization and associated costs, and improving the quality of life.

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863 Table 1: Conditions at risk for hypoNa overcorrection

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CONDITION	MECHANISM OF HYPERCORRECTION
Hypovolemia	Elimination of the stimulus for ADH secretion due to baroreceptor activation by volume expansion by crystalloid
Low solute diet (Beer potomay, tea and toast diet etc.)	Diet correction increases dietary solute load → increased renal free water clearance
Thiazide diuretic therapy	Discontinuation of the drug directly restores renal diluting capacity
SSRI antidepressive drug therapy	Discontinuation of the drug reduces the serotonergic stimulus on ADH secretion
Hypopituitarism	Restoration of physiologic suppression of ADH secretion by cortisol replacement therapy
Hypoxemia	Elimination of non osmotic stimulus on ADH by normalization of blood gases
Stress, pain, nausea	Elimination of transient stimuli on ADH secretion
Hypokalemia, potassium depletion	With K administration, sodium leaves the cell in exchange with potassium entrance, in order to maintain electroneutrality

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Table 2 Diagnosis of SIAD [modified from (120)]

**Essential features**

Decreased effective osmolality ( $< 275$  mOsm/Kg of water)

Urine osmolality  $> 100$  mOsm/Kg of water

Clinical euvolemia

- No clinical signs of volume depletion of extracellular fluid (orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes)
- No clinical signs of excessive volume of extracellular fluid (edema or ascites)

Urinary sodium  $> 40$  mmol/liter with normal dietary salt intake

Normal thyroid and adrenal function

No recent use of diuretic agents

**Supplemental features**

Plasma acid uric  $< 4$  mg/dL

Blood urea nitrogen  $< 10$  ml/dL

Fractional sodium excretion  $> 1\%$ ; fractional urea excretion  $> 55\%$

Failure to correct hyponatremia after 0.9% saline infusion

Correction of hyponatremia through fluid restriction

Abnormal results on test of water load ( $< 80\%$  excretion of 20 ml of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution ( $< 100$  mOsm/Kg of water)

Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia

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924 Table 3 Drugs possibly used in oncological patients that may induce hyponatremia

DRUGS	INDICATION  for use	MECHANISM INVOLVED	REFERE NCES
<ul style="list-style-type: none"> <li>• Vinca alkaloids vincristine, vinblastine</li> <li>• Platinum compounds cisplatin, carboplatin</li> <li>• Alkylating agents ev cyclophosphamide, melphalan, ifosfamide</li> <li>• Anthracyclines</li> <li>• TK and monoclonal antibody inhibitor Afatinib Brivanib Cetuximab Gefinib Limifanib Pazopanib Sorafenib Vorinostat</li> <li>• Others Methotrexate IFN <math>\alpha</math>-<math>\gamma</math> Pentostatina IL2</li> </ul>	Chemotherapy	Increase AVP secretion Increase AVP secretion and renal waist syndrome Increase AVP secretion and increase renal sensitivity Ipervolemic hyponatremia  Direct natriuretic effect and interference in Na pathway and increase AVP secretion Possible role for iatrogenic hypotiroidism  Increase AVP secretion and possible fluid redistribution	(23), (121),(122) (123)  (122, 123)  (121, 122) (124)  (122, 125)  (23, 121- 123)
<ul style="list-style-type: none"> <li>• Opioid</li> <li>• Acetaminophen</li> <li>• Non-steroidal anti-inflammatory drugs</li> </ul>	Pain control	Increased renal sensitivity, indirect increase in ACP secretion secondary to nausea or hypotension	(23, 122, 123)
<ul style="list-style-type: none"> <li>• Tricyclic antidepressant Amitriptyline Protryptiline</li> </ul>	Antidepressant	Increase AVP secretion	(23, 122, 123)

<ul style="list-style-type: none"> <li>Desipramine</li> <li>SSRI</li> <li>MAO inhibitors</li> <li>Others</li> </ul> Duloxetine, Venlafaxine, Mitrazapina		Reset osmostat	(23)
<ul style="list-style-type: none"> <li>Carbamazepine, Oxcarbazepine</li> <li>Sodium valproate</li> <li>Lamotrigine</li> </ul>	Antiepileptic	Increase AVP secretion and potentiation AVP effect Reset osmostat	(23, 123, 126)
<ul style="list-style-type: none"> <li>Phenothiazine</li> </ul>	Antiemetic	Drug induced polydipsia	(122)
<ul style="list-style-type: none"> <li>Corticosteroid</li> </ul>	Anti-edema, nausea	Hyperglycemia – pseudo hyponatremia	(122, 123)
<ul style="list-style-type: none"> <li>First antidiabetic generation</li> </ul> Clorpropamide, Tolbutamide	Diabetes	Potentiation AVP effect	(123)
<ul style="list-style-type: none"> <li>Antibiotics</li> </ul> Ciprofloxacin Trimethoprim/sulphamethoxazole Linezolid Cefoperazone sulbactam	Infections	Increase AVP secretion  Hypovolemic hyponatremia	(23)  (127) (128)
<ul style="list-style-type: none"> <li>Proton pump inhibitor</li> </ul> Omeprazole, esomeprazole	Prevention gastric ulceration stress or or drug related	Increase AVP secretion	(23)
<ul style="list-style-type: none"> <li>Hypotensive drug</li> </ul> Diuretic loop furosemide ACE-I thiazide	Hypertension therapy	Hypovolemic hyponatremia Increase osmotic renal losses Increase AVP secretion Increase of thirst	(23)
<ul style="list-style-type: none"> <li>Mannitol</li> </ul>	Anti –edema	Pseudo hyponatremia	(122, 123)
<ul style="list-style-type: none"> <li>Hypotonic solution</li> <li>Isotonic solution</li> </ul>	Hydration	Dilutional	(122, 123)

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927 Table 4: Causes of HypoNa in cancer patients [modified from Ref. (22)].

CAUSES	%
SIAD	30.4
Dehydration	28.7
Diuretic use	14.0
Hypervolemia	7.8
Kidney failure	3.5
Hypotonic solutions	1.7
Miscellaneous	5.2
Not defined	1.7
False positive	7.0
Mixed causes	9.6
Total	100

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942 Table 5: Drugs commonly used in elderly patients that may cause or worsen hypoNa -(129)(130)(131)(132)(133)

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<b>DRUG CLASSES</b>	<b>Principal drugs involved in the class</b>
➤ <b>Diuretic drugs</b>	loop diuretics  thiazides
➤ <b>Second-generation antidepressants</b>	citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, venlafaxine, duloxetine, mirtazapine, or sertraline
➤ <b>Proton pump inhibitors</b>	omeprazole, esomeprazole
➤ <b>Hypotensive drugs</b>	Angiotensin-converting enzyme inhibitor

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