



Review Article

Drug-induced hyponatremia in clinical care

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ABSTRACT

Purpose: Over the last decades, advances in understanding of previously described associations have important implications for diagnosis and workup of hyponatremia. In addition, new drug groups potentially affecting sodium balance and water homeostasis have evolved. The aim of this review is to summarize current evidence on drug-induced hyponatremia in clinical care.

Methods: We searched PubMed using the string "Inappropriate ADH Syndrome/chemically induced"[Mesh] OR "Inappropriate ADH Syndrome/diagnosis"[Mesh] OR ("Hyponatremia/chemically induced"[Mesh] OR "Hyponatremia/diagnosis"[Mesh]), January 1st, 2008, to September 2nd 2024. In total 2003 articles were found and reviewed. Relevant articles referenced herein were subsequently traced backwards and also reviewed.

Results: Drugs associated with hyponatremia, including selective serotonin reuptake inhibitors, antipsychotics, antiepileptic drugs and proton pump inhibitors, typically cause hyponatremia shortly after initiation of treatment. For thiazide diuretics, the number one culprit in drug-induced hyponatremia, the risk for hyponatremia is highest the first weeks after initiation and then gradually decreases to a stable but still increased level after around 3 months. Several drugs that promote a negative water balance such as loop diuretics, lithium and of sodium-glucose cotransporter-2 inhibitors appear to decrease the risk for hyponatremia. Treatment with immune checkpoint inhibitors is associated with an increased risk of hypophysitis and adrenalitis resulting in hyponatremia due to secondary and primary cortisol deficiency.

Conclusion: For most drugs associated with hyponatremia, including thiazides, the cause-effect relationship is tightly linked to newly initiated treatment. Further research is warranted to characterize the association between hyponatremia and newly developed drugs such as sodium-glucose cotransporter-2 inhibitors and immune checkpoint inhibitors.

1. Background

Hyponatremia is a condition characterized by large symptom variability, ranging from fatigue and confusion to headache, nausea, and more rarely seizures [1]. The prevalence differs depending on population, but hyponatremia is estimated to affect between 10% and 30% of hospitalized patients [2]. Pharmaceutical drugs are a common cause of hyponatremia [3]. Thiazides is the number one culprit, alone accounting for up to 25% of hospitalizations due to hyponatremia [4]. In addition,

selective serotonin reuptake inhibitors (SSRIs), antiepileptic drugs, cardiovascular drugs, along with a long list of drugs used in various therapeutic areas, have been associated with hyponatremia [5]. Over the last decades, substantial evidence has emerged regarding the association between pharmaceutical drugs and hyponatremia, both in terms of new culprit drugs, and in terms of our understanding of the underlying pathophysiology. One important dimension concerns the chronology, in essence the interval between initiation of treatment with a suspected culprit drug and the occurrence of hyponatremia. This has

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important implications regarding the subsequent cause-effect assessment. Furthermore, new drugs potentially affecting water homeostasis such as immune checkpoint inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, deserve attention. The aim of this review is to summarize current evidence on drug-induced hyponatremia in clinical care.

2. Search strategy

We searched PubMed using the query "Inappropriate ADH Syndrome/chemically induced"[Mesh] OR "Inappropriate ADH Syndrome/diagnosis"[Mesh] OR ("Hyponatremia/chemically induced"[Mesh] OR "Hyponatremia/diagnosis"[Mesh]), January 1st 2008 to September 2nd 2024. In total 2003 articles were found and reviewed for possible relevance. Relevant articles referenced herein were subsequently traced backwards and also reviewed.

3. Pathogenesis of drug-induced hyponatremia

The most important mechanisms in sodium and water homeostasis are thirst and effects of arginine vasopressin (AVP), also referred to as anti-diuretic hormone [6]. Arginine vasopressin is a pleiotropic hormone synthesized in the hypothalamus but stored and released from the posterior pituitary in response to osmotic and non-osmotic stimuli. AVP is released in response to increased extracellular osmolality and exerts its effect on the vasopressin V2 receptor (V2R) on principal cells of renal collecting ducts. This leads to increased expression of aquaporin-2 (AQP2) water channels on the luminal membrane, increasing water permeability and electrolyte free water resorption, while concentrating urine. Most drugs that cause hyponatremia do so through activation of this system, resulting a relative, however not overt, fluid overload [2,6]. Increased release of AVP has generally been considered the primary mechanism of action in drug-induced hyponatremia [5], but more recent research suggests many drugs do not increase AVP concentrations

directly, but have downstream effects, either through activation of the V2R, or through increased expression of AQP2, resulting in AVP-independent syndrome of inappropriate antidiuresis (SIAD) [7]. For example, SSRIs has been demonstrated to increase collecting duct permeability in the absence of AVP in animal models [8,9] and carbamazepine and oxcarbazepine are thought to stimulate the V2R independent of AVP (Fig. 1) [10]. Thiazides are the most common cause of hyponatremia mediated by drugs. Thiazide-associated hyponatremia (TAH), should be distinguished from thiazide-induced hyponatremia (TIH) as the former refers to an event of hyponatremia and co-incident treatment with a thiazide diuretic but without proven causality, possibly reflecting a multifactorial aetiology. By contrast, a diagnosis of TIH demands a rigorous causality assessment. Consequently, TIH is an unlikely event after an extended duration of treatment. The pathogenesis is only partially understood. What is known, but sometimes overlooked in clinical practice is that patients with TAH are most often not volume depleted, but generally present slightly volume expanded [11–13] with features similar to those observed in patients with SIAD. Excess AVP secretion relative to serum osmolality is not a consistent finding in patients with TAH and does not provide a comprehensive explanation of hyponatremia. Other mechanisms, including increased water intake, solute depletion and decreased urea excretion have been suggested to contribute to TAH [14]. A high frequency of an allele of *SLCO2A1*, a gene which encodes a prostaglandin transporter in the distal nephron, has been reported among patients with TIH [11]. The proposed impairment in protein function from this allelic variant would result in increased concentrations of prostaglandin E2 (PGE2), which mediates expression of AQP2 in renal collecting ducts, promoting free water reabsorption. More recent research has not been able to replicate the allelic imbalance of *SLCO2A1* in patients with TIH but does support a role for PGE2-mediated water reabsorption in the pathogenesis (Fig. 2) [15]. Other mechanisms of drug-induced hyponatremia include autoimmune primary or secondary adrenal insufficiency precipitated by immune checkpoint inhibitors, where the former leads to hyponatremia

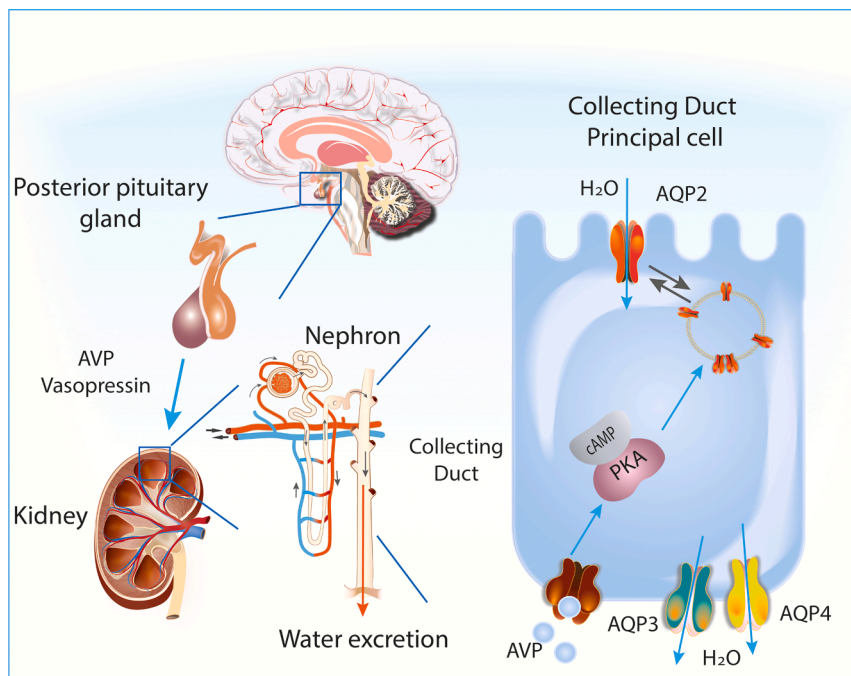


Fig. 1. Mechanisms of drug induced hyponatremia

Most mechanisms through which drugs cause hyponatremia is mediated by directly increasing ADH in the pituitary, or by downstream effects independent of ADH. For example, carbamazepine and oxcarbazepine are thought to stimulate the V2R and SSRIs has been demonstrated to upregulate aquaporin-2 via vasopressin-2 receptor/cAMP/protein kinase A signalling in the principal cell in the inner medulla of the collecting duct. In addition, immune checkpoint inhibitors may cause adrenalitis and hypophysitis causing hyponatremia on the basis of primary or secondary adrenal failure. Platinum compounds may occasionally cause salt-wasting nephropathies leading to hyponatremia.

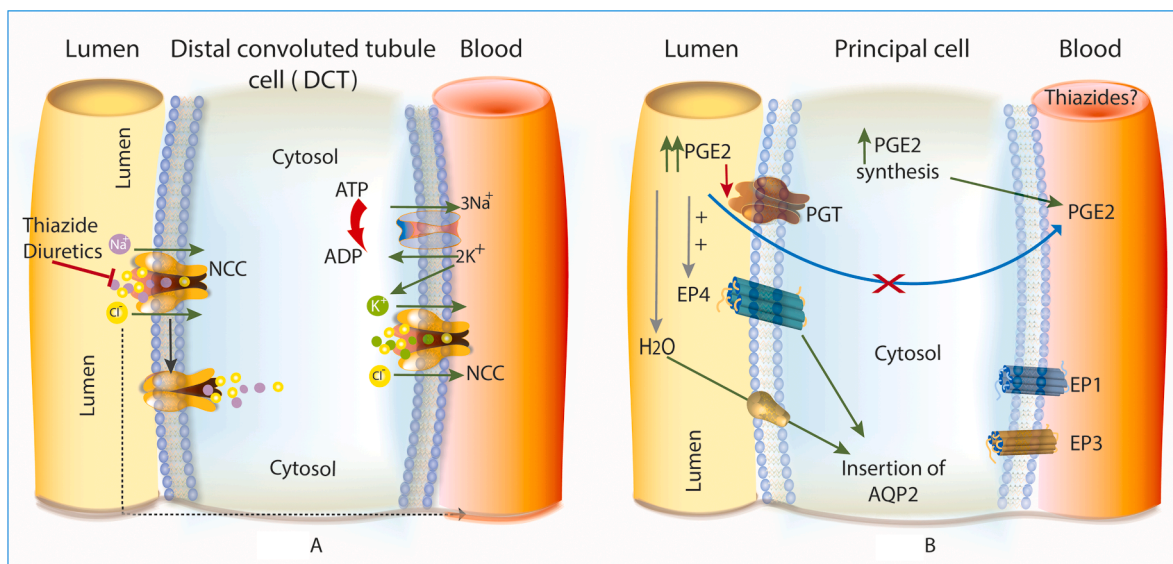


Fig. 2. Illustration of proposed molecular mechanisms of thiazide induced hyponatremia a) Site of action of thiazide diuretics that inhibit the sodium-chloride cotransporter (NCC) in the distal convoluted tubule (DCT). Tubular fluid entering the DCT has osmolarity of approximately 100 mOsm/L. NCC activity results in further dilution to 50 mOsm/L by reabsorbing sodium and chloride. Thiazide diuretic inhibition of NCC results in a tripled urine osmolarity (eg, 150 vs 50 mOsm/L). b) Reduction of PGE2 in the principal cell further downstream in the collecting duct: In the presence of thiazides PGT is inactivated which activates luminal EP4 receptors. This causes insertion of AQP2, directly reducing urine dilution and free-water excretion.

through mineralocorticoid deficiency, and the latter through loss of inhibition of AVP secretion due to cortisol deficiency [16]. Hyponatremia may also develop secondary to drug-induced nephropathies, with platinum based chemotherapies a recurring culprit [17]. Table 1 summarizes the mechanisms of actions regarding drugs that may affect sodium concentrations that will be discussed in the following.

4. Drugs associated with hyponatremia

4.1. Desmopressin and analogues

Desmopressin, a synthetic AVP analogue used for treating diabetes insipidus and nocturnal polyuria entails an obvious risk for water retention if overdosed [18]. This is well known in the paediatric setting [19,20] and among adults, especially elderly individuals [21]. From a pharmacokinetic perspective Chin et al. reviewed risk factors for deleterious water retention and their pharmacodynamic implications. Extremes of age (high and low), comorbidities, drug interactions, intranasal desmopressin formulations, predispose for an increased risk of severe hyponatremia, sometimes with severe consequences, and prompts for increased alertness [22].

Terlipressin, an AVP analogue that is intravenously administered in patients with bleeding oesophagus varices to lower the portal venous pressure. Hyponatremia, on the basis of water retention, is a common adverse effect that may limit its use [23]. Oxytocin is chemically similar to AVP and also secreted from the neurohypophysis. Synthetically produced oxytocin stimulates uterine contraction and is commonly used to promote labour. Its use is strongly associated with severe hyponatremia. It is therefore important to monitor the input output balance in laboring women receiving oxytocin to identify substantial fluid retention [24].

4.2. Antihypertensive drugs

4.2.1. Thiazides

Since their introduction in 1957, thiazides have been among the most commonly prescribed drugs used for the treatment of arterial hypertension [25]. Studies indicate that approximately 3 in 10 patients treated with thiazides, at some point, develop hyponatremia [26], sometimes with severe or even fatal consequences [27].

Risk factors for TAH includes old age, female sex, and low body weight [28,29]. Danish data show that patients treatment-naïve with regards to antihypertensive drugs initiating bendroflumethiazide or hydrochlorothiazide faced additional 2-year cumulative incidences of 3.8% and 3.5% as compared with individuals starting CCBs or ACEIs alone, corresponding to hazard ratios of 3.6 and 4.2 [30]. Although previous data on dose-response-relationship has been inconclusive [28, 29,31], the Danish study clearly indicated an increased risk associated with higher doses with regard to treatment with bendroflumethiazide as well as hydrochlorothiazide. Susceptible individuals may experience hyponatremia within 24 hours of initiation of treatment [12], but onset can occur after months or years [28]. A nationwide Swedish study based on health registers reported a 50-fold increase in risk of hospitalization due to hyponatremia during the first week of treatment, followed by a gradually decline in risk. The adjusted odds ratio (aOR) for individuals treated for longer than 13 weeks was 2.9 compared to unexposed individuals [4]. A large Korean study based on insurance claims data reported similar findings, with an aOR of 2.4 for hyponatremia (<130 mmol/L) within the first four weeks of treatment with thiazides, compared to ongoing treatment [32]. In accordance, the more recent Danish register-based cohort study reported high risk of hyponatremia (<130 mmol/L) in the first months of treatment among patients prescribed thiazides compared to patients commencing non-thiazide antihypertensive treatment [30].

Thus, the markedly elevated risk immediately after initiation warrants an increased awareness of symptoms indicative of severe hyponatremia. This is especially important in high-risk groups. In case of hyponatremia the most important therapy is cessation of thiazide use, and oral fluid restriction. In case of severe symptoms, infusion with 3% saline solution may be indicated.

4.2.2. Potassium sparing diuretics

Some data indicate that mineralocorticoid receptor antagonists and other potassium-sparing diuretics impose an increased risk for the development of hyponatremia. In one large observational study, aOR for newly initiated and ongoing use of spironolactone, was 3.6 and 1.8 compared to unexposed individuals. The corresponding risk associated with amiloride was 2.7 and 1.6 [33]. In addition, some trials have assessed the risk for hyponatremia in specific treatment groups. Two

Table 1

Strength mechanism and brief characterization of associations between drugs and potential hyponatremia. Mild, moderate and marked effect defined by a relative risk increase of a magnitude of up to two, between two and five and over five times, is illustrated by +, ++ and +++. An inverse association is illustrated by -.

Drugs	Risk of hyponatremia	Proposed mechanism by which sodium levels are affected	Characterization of association between drug and hyponatremia
Analgesics			
Non-steroidal anti-inflammatory drugs	+	Nephrogenic SIAD* through reduction of renal prostaglandin synthesis [147]	Weak association [93]
Opioids	+	SIAD [88,148]	Moderate association, uncertain temporal association [32, 89,90]
Antibiotics			
Aminoglycosides	+	Unknown	Weak association [115]
Linezolid	+++	SIAD[112, 149].	Marked association [110–114]
Quinolones	+	SIAD[150, 151]	Weak association [116]
Trimethoprim-sulfamethoxazole	+++	Renal salt wasting[152]	Marked dose-dependent association[108]
Antidepressants			
Noradrenergic and specific serotonergic antidepressants	++	SIAD[153]	Moderate association substantially lower than that of SSRIs[50,52, 53]
Selective serotonin reuptake inhibitors	+++	Nephrogenic SIAD[8,9]	Marked association primarily associated with newly initiated treatment[49,50, 52–56]
Serotonin–norepinephrine reuptake inhibitors	+++	SIAD[154]	Marked association primarily associated with newly initiated treatment[53]
Tricyclic antidepressants	+	SIAD[155]	Mild effect substantially lower than that of SSRIs[49,53]
Antihypertensives			
Angiotensin-converting enzyme inhibitors	+	SIAD[41]	Mild effect with uncertain causal association[38, 40–42]
Angiotensin II receptor blockers	+	Unknown	Mild effect with uncertain causal association[38, 43]
Beta blockers	+	Unknown	Mild effect with uncertain causal association[38]
Calcium channel blockers	+	SIAD[156, 157]	Mild effect with uncertain causal association [37–39]

Table 1 (continued)

Drugs	Risk of hyponatremia	Proposed mechanism by which sodium levels are affected	Characterization of association between drug and hyponatremia
Loop diuretics	-	Inhibits electrolyte free water reabsorption [126]	Data indicate an inverse effect regarding the development of hyponatremia [33]
Potassium sparing diuretics	+	Unknown	Mild effect with uncertain causal association [33–36]
Thiazides	+++	Multiple mechanisms leading to water retention and weight gain similar to that in SIAD[158]	Marked immediate effect that to some extent persists over time[4,12, 26,30]
Antipsychotics			
First generation	+	Nephrogenic SIAD[7,9]	Mildly elevated risk[51,80–83, 85,86]
Second generation	+	Nephrogenic SIAD[7]	Association about half that of first-generation antipsychotics [51,83,85,86]
Antiepileptic drugs			
Carbamazepine	+++	Nephrogenic SIAD[9,159]	Strong association[58, 59,61,63,68,69]
Gabapentin	+	Unknown	Weak association [69]
Lamotrigine	+	SIAD[160, 161]	Weak association [69]
Levetiracetam	(+)	SIAD[162]	Conflicting results[69, 163–167]
Oxcarbazepine	+++	Nephrogenic SIAD[168]	Marked association [59–63,69]
Phenytoin	++	Unknown	Moderate association[68, 69]
Valproate	++	SIAD[169, 170]	Moderate association[68, 69]
Desmopressin			
Lithium			
	+++	AVP-analog [22]	Marked association[22]
	-	Blunted response to AVP. Exact mechanism unknown . [135]	Data indicate an inverse effect regarding the development of hyponatremia [136]
Lipid lowering agents			
Ezetimib	-	Unknown	Data indicate an inverse effect regarding the development of hyponatremia [138,140]
Statins	-	Unknown	Data indicate an inverse effect regarding the development of hyponatremia [138–140,171]
Proton pump inhibitors			
	++	SIAD[74–76]	Moderate association with newly initiated. use. Causality of

(continued on next page)

Table 1 (continued)

Drugs	Risk of hyponatremia	Proposed mechanism by which sodium levels are affected	Characterization of association between drug and hyponatremia
			effect uncertain [77–79]

* SIAD, syndrome of inappropriate antidiuresis

studies focusing on heart failure showed that 31% and 6%, respectively, of patients initiating spironolactone developed hyponatremia [34,35]. In a randomized controlled trial on patients with treatment-resistant hypertension, the introduction of spironolactone resulted in hyponatremia in 1.35% of study participants. However, no serious adverse drug reactions due to hyponatremia were reported [36].

4.2.3. Non-diuretic antihypertensives

Although TAH is well-established, the question whether hyponatremia can be induced by the other four major drug classes, i.e., in calcium channel blockers (CCBs), beta-receptor blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs), is more controversial [5].

Most evidence of CCB-induced severe hyponatremia is restricted to case reports, concerning the vascular CCB amlodipine [37,38]. Increased risk of moderate hyponatremia in psychiatric patients using CCBs has also been reported [39].

Similarly, BBs have rarely been linked to hyponatremia. However, taking advantage of a prospective pharmacovigilance program, Ramirez et al. linked atenolol (n=4), bisoprolol (n=1) and propranolol (n=1) to the occurrence of severe hyponatremia [38].

Inhibiting the renin-angiotensin-aldosterone system, it seems plausible that ACEIs and ARBs would result in increased risk of hyponatremia. However, the evidence is weak and mostly based on case reports [40–44]. One exception is the study by Ramirez et al. that linked between 4% and 9% of patients suffering from severe hyponatremia to the treatment with ARBs or ACEIs [38].

These results are partly contradicted by a Swedish nationwide register-based study. The risk of severe hyponatremia among individuals with newly initiated CCBs, BBs, ACEIs, and ARBs, was moderately elevated, about twice that of controls. However, when analyzing individuals with treatment that had been ongoing for at least three months, there was no association [45].

4.3. Antidepressants

Antidepressants are important for the treatment of depression and anxiety, with a widespread and increasing use that in the USA amounts to 13% of the population [46,47]. Antidepressants as a group has been associated with the development of hyponatremia [46,48]. Increasing evidence from large population-based trials associate SSRIs with the occurrence of SIAD. Studies indicate that the risk may not be dose-dependent in the therapeutic range [49–51]. Studies show that the association is related to recently initiated treatment [32,49,50,52–55]. One retrospective detailed investigation of the time-course of SSRI-associated hyponatremia revealed an immediate markedly elevated risk of severe hyponatremia sustained over the first four weeks (aOR 29) that then gradually declined. After three months of treatment the risk was the same as for patients that did not take SSRIs [56].

The corresponding risk associated with serotonin–norepinephrine reuptake (SNRI) inhibitors, i.e., venlafaxine appears to be comparable [32,49,53] or slightly larger [57], with an effect closely associated with newly initiated treatment [32,49,52,53].

Atypical antidepressants (e.g., mirtazapine) and tricyclic antidepressants have also been consistently linked to hyponatremia, but the

risk seems substantially lower with hazard ratios about half those of SSRI and venlafaxine. Mirtazapine, or possibly TCAs may therefore be an option for individuals predisposed for hyponatremia in need of antidepressant treatment [32,49,53,57].

Due to the strong association between newly initiated treatment with SSRIs or venlafaxine and severe hyponatremia, a heightened vigilance for the occurrence of hyponatremia is warranted after initiating SSRIs or venlafaxine. This is particularly important in the elderly. However, for patients who have been on SSRIs or venlafaxine for a longer period, the likelihood of hyponatremia being directly caused by these medications is low and other potential contributing factors should be investigated.

4.4. Antiepileptic drugs

A large proportion of individuals starting carbamazepine and oxcarbazepine are known to develop hyponatremia (4.8–31.3% and 0.14–73.3%, respectively) [58–64]. For carbamazepine, some studies indicate a dose-dependent relationship [65,66] although the data is not conclusive [67]. Regarding oxcarbazepine one study showed no dose dependent relationship [60].

Two population-based studies have been able to compare the risk between different antiepileptics. Firstly, Gandhi et al. investigated the 30-day risk of hospitalization after the initiation of carbamazepine or any of valproate/phenytoin/topiramate compared to non-exposed older adults. They found an adjusted relative risk (RR) of 8.2 for carbamazepine while for valproate/phenytoin/topiramate it was 2.6 [68]. Similarly, a register based Swedish study found a strong association between newly initiated treatment with carbamazepine (aOR 10), oxcarbazepine (only found in the hyponatremia group) and levetiracetam (aOR 10), and hospitalization due to hyponatremia. The corresponding association was moderate for phenytoin and valproate (aOR 5) and weaker for lamotrigine and gabapentin (aOR 1.7 and 1.6) [69]. Comparable findings were reported in a large retrospective review of Japanese patients followed at an epilepsy center, with the exception that levetiracetam was not associated with hyponatremia (OR 1.0) [64]. Thus, in patients experiencing clinically significant hyponatremia, i.e., symptomatic hyponatremia after recent initiation of carbamazepine, oxcarbazepine, phenytoin, valproate or levetiracetam, an alternative treatment could be lamotrigine or gabapentin.

4.5. Proton pump inhibitors

Proton pump inhibitors (PPIs), used as first-line treatment and prophylaxis of peptic ulcer and gastro-esophageal reflux, are among the most commonly prescribed drugs worldwide, with an estimated proportion of PPI users in the US population close to 7% [70]. There is some evidence that PPIs may precipitate hyponatremia due to SIAD [71–76]. Buon et al. found that the prevalence of moderate hyponatremia (123–134 mmol/L) was elevated in elderly individuals [77]. In a post-marketing safety data for PPIs from the United States Food and Drug Administration (FDA) Makunts et al. found that omeprazole was associated with hyponatremia [78]. A Swedish study reported a strong association between newly initiated omeprazole/esomeprazole treatment and hyponatremia (aOR 7). After ninety days drug use, the risk for hyponatremia equaled that of the general population [79]. The risk for hyponatremia appears to be similar between different PPIs [73]. The prompt temporal relationship between initiating PPI and hospitalization due to hyponatremia suggests a causal association. However, some of the association may be confounded by the condition for which the initiated PPI was prescribed such as a peptic ulcer. Consequently, newly initiated PPIs may be considered the culprit in any patient suffering from hyponatremia. However, if patients had this treatment a longer time, the PPI should be considered a less likely cause.

4.6. Antipsychotics

Antipsychotics have been linked to the development of hyponatremia in different settings [80–83]. The underlying mechanism is believed to be SIAD [7,84]. The effect results in a moderately elevated risk of hyponatremia (aOR 1.6 and 1.7, respectively) [81,85]. Consistently, the association attributed to typical antipsychotics have been about twice that of atypical antipsychotics [51,83,85,86]. In contrast to several other drug groups, data on a temporal association between initiation of antipsychotics and hyponatremia are inconsistent [32,85]. Due to the relatively modest association, alternative causes should be explored when hyponatremia develops in a patient treated with antipsychotic drugs. If a causal relation seems probable, a risk-benefit analysis should be performed in collaboration with the treating psychiatrist.

4.7. Analgesics

Up until recently, the signals of opioids as a culprit for hyponatremia had been restricted to case reports only. However, during the last decade additional evidence have emerged, most of which suggest an association with a mechanism mediated by SIAD [87,88]. In a population-based Canadian study, Fournier et al. investigated the risk of hyponatremia following the initiation of tramadol versus codeine in 332,880 patients. The use of tramadol was associated with a doubled risk of hyponatremia requiring hospitalization [89].

Using Swedish nationwide data and a similar population-based case control approach, Falhammar et al. found similar associations between hyponatremia and use of tramadol and codeine, [90] in contrast to the study by Fournier et al. With newly initiated treatment (<3 months), the risk associated with use of tramadol and codeine was doubled, compared to matched population controls. In contrast, no association was found for ongoing therapy. Taking advantage of hospital data using a propensity score based model, Lee et al. found that tramadol was associated with a moderately increased risk (OR 1.57) of hyponatremia (< 135 mEq/L) within 10 days of initiation when compared to treatment with paracetamol [91]. By contrast, Kwanghee et al., using Korean insurance data, reported a higher risk of hyponatremia (<130 mmol/L) with ongoing use of opioids than with newly initiated treatment [32], and a French pharmacovigilance study taking advantage of 225,575 individual case safety reports did not find an independent association for tramadol alone [92].

There are occasional signals that associate non-steroidal anti-inflammatory drugs (NSAIDs) with hyponatremia. In a retrospective analysis based on 273 geriatric patients the association between NSAIDs and hyponatremia was investigated [93]. Although the association was statistically significant, the confidence interval was large due to the rather small sample size (adjustedOR 3.61, 95% CI 1 - 12.99).

4.8. Antineoplastic drugs

Cancer per se can invoke hyponatremia most often on the basis of SIAD. This is especially common in head and neck cancers, malignancies of the brain and small-cell lung cancer but other types may also be involved. In addition, antineoplastic drugs may cause hyponatremia [94]. Thus, as evident by case reports, vinca alkaloids, e.g., vincristine [95,96], alkylating agents such as cyclophosphamide [97,98] and platinum compounds e.g. cisplatin [99,100] may increase the release of AVP invoking dilutional hyponatremia. An additional large number of case reports indicate that platinum compounds may occasionally cause salt-wasting nephropathies leading to hyponatremia [17].

Immune checkpoint inhibitors (ICIs) are increasingly being used in the treatment of various cancer types. Concerns have been raised regarding the increased risk of hypophysitis and adrenalitis [101–103] causing hyponatremia. The mechanism is similar to the effect of an untreated Addison's disease or the sudden withdrawal of glucocorticoid

replacement therapy disrupting the HPA-axis. One meta-analysis including 6 RCTs focusing on small cell lung cancer indicated that the incidence of hyponatremia was elevated by 4 percentage points in individuals receiving ICIs (alone or combined with chemotherapy) as compared to standard chemotherapy alone [104]. According to another meta-analysis including 5 clinical trials of PD-1 inhibitors (nivolumab or pembrolizumab) the risk ratio was not significantly elevated, suggesting intraclass differences in propensity for hyponatremia [105]. A retrospective observational study showed that 6% (136/2458) of patients starting treatment with ICIs developed severe hyponatremia within a year. In nine cases (reflecting a total incidence of 0.3%) the underlying cause was an endocrinopathy, while SIAD, volume depletion and terminal illness were more common etiologies [106].

4.9. Antibiotics

Infectious diseases are frequently associated with hyponatremia complicating assessment of the cause effect relationship regarding antibiotics used for its treatment. Nevertheless, substantial evidence indicates that trimethoprim-sulfamethoxazole (TMP-SMX) is linked to the development of hyponatremia in a dose-dependent manner, possibly by interfering with sodium reabsorption in the distal nephron [107]. In one single center study 72% (55/76) of individuals treated with high dose TMP-SMX (8 mg/kg/d) had a sodium concentration <136 mEq/L, on average 5.5 days after initiation of therapy [108,109].

Linezolid is an antibacterial agent used to treat complicated Gram-positive dermatologic and soft tissue infections. Case reports have indicated that linezolid may induce hyponatremia due to SIAD [110–113]. One recent well conducted propensity score matched study showed that linezolid-treated individuals (n=97) run an almost 4 times increased risk of developing hyponatremia compared with patients on vancomycin (n=353) [114].

Finally, as evident by case reports, other antibiotics such as aminoglycosides [115] and quinolones [116] have also been associated with hyponatremia.

4.10. Amiodarone

Amiodarone is a class III antiarrhythmic agent associated with a broad range of adverse effects including thyroid dysfunction and pulmonary toxicity [117]. In addition, case reports (n~20) suggest that amiodarone may induce hyponatremia based on water retention [118, 119].

5. Drugs with ambiguous associations to hyponatremia

5.1. Sodium-glucose cotransporter-2 inhibitors

The introduction of sodium-glucose cotransporter-2 (SGLT-2) inhibitors has had a large impact benefitting large populations of patients with diabetes mellitus, heart- and kidney-failure [120]. The pharmacodynamics of SGLT-2 inhibitors are consistent with both an increased and a decreased risk of hyponatremia. The blocking of the SGLT-2 in the proximal tubules of the kidney leads to a transient increase in urine sodium losses, with potential for hyponatremia, but within days, sodium losses taper off due to a compensatory increase in sodium reabsorption in distal segments of the nephron [120]. The persisting glycosuria and osmotic diuresis enable electrolyte free water clearance, reducing the risk of dilutional hyponatremia. One case report describes profound hyponatremia associated with the treatment with canagliflozin [121], and a retrospective cohort analysis found an increased prevalence of hyponatremia (<135 mmol/L) among hospitalized patients 5-8 days after initiation of dapagliflozin (17.5% vs. 10.2%, p=0.01) [122]. By contrast, two small prospective randomized trials have demonstrated modest benefit of empagliflozin in raising serum sodium (3-4 mmol/L) among patients with SAID [123,124]. The risk profile with SGLT2

inhibition is perhaps best demonstrated in a post-hoc analysis of the DAPA-HF trial by Yeoh et al. They found that hyponatremia within 14 days of study drug initiation was more common in patients exposed to dapagliflozin compared to placebo (11.3% vs 9.4%, $p=0.04$), but that this pattern then reversed and at 12 months hyponatremia was more common among patients exposed to placebo than dapagliflozin (4.6% vs 6.7%, $p=0.003$) [125].

6. Drugs reversely associated with hyponatremia

6.1. Loop-diuretics

Loop diuretics exert their effect by blocking the Na-K-Cl cotransporter in the loop of Henle, thus reducing the reabsorption of electrolytes. This leads to increased renal excretion of sodium, but also depletes the medullary osmotic gradient, reducing the capacity for water reabsorption in the collecting duct system through the influence of AVP [126]. The pharmacodynamic of furosemide is complex [127] and in subgroups, such as individuals also treated with spironolactone, the risk for hyponatremia may increase [128]. However, for most patients, the net loss of both sodium and water makes loop diuretics an unlikely cause of hyponatremia. This may seem counter-intuitive given that hyponatremia is a frequent finding among patients using loop diuretics. However, this is likely due to the underlying disease and not to the drug itself [129]. Instead, observational data adjusted for confounding co-morbidities indicate a reduced risk of severe hyponatremia [33] but an increased risk of hypernatremia [130,131] with loop-diuretics. Furthermore, loop diuretics has an important place in treatment of hypervolemic hyponatremia [1,132,133].

6.2. Lithium

Lithium has a documented effect of inhibiting AVP-mediated resorption of electrolyte free water [134] and inducing nephrogenic diabetes insipidus in chronic users [135]. This propensity for volume depletion appears to reduce the risk of fluid overload, with a population-based case control study indicating that the risk for hospitalization due to hyponatremia was nearly halved in individuals prescribed lithium [136].

6.3. Lipid-lowering agents

Despite being the most prescribed drug-class worldwide, there is a paucity of data linking statins or other lipid-lowering agents to hyponatremia. In vitro, statins have been demonstrated to induce AVP-independent electrolyte-free water resorption [137] but observational data demonstrate an inverse association between use of lipid-lowering agents and risk of hyponatremia, indicating a potential protective effect [138–140].

7. Clinical considerations

7.1. The chronology of a suspected drug-induced hyponatremia

In the workup of a patient with suspected drug-induced hyponatremia, one important aspect is the chronology, in essence, the interval between the initiation of drug treatment and the adverse effect. For many drugs such as antiepileptic drugs [69], mild opioids [90], PPIs [79] and SSRIs [49,50,52–55], the association with hyponatremia is clearly linked with newly initiated treatment. For SSRIs the risk of hyponatremia seems to be closely, or even exclusively related to newly initiated treatment. This should prompt prescribing physicians to be attentive of symptoms consistent with hyponatremia when initiating SSRI treatment, particularly among patients at high risk, such as elderly females [141]. Here, analysis of sodium concentrations is warranted even with subtle symptoms consistent with hyponatremia.

The risk of TAH is high immediately after initiation. It has therefore been suggested to routinely monitor sodium concentrations 1–2 weeks after thiazide initiation [142,143]. However, due to a low baseline risk, the absolute risk of developing a clinically relevant hyponatremia may be, for most individuals, too modest to motivate this. Still, when prescribing thiazides to risk groups, in essence elderly women with low body weight, physicians should consider routinely measuring serum sodium concentrations as suggested above [28,29]. Unlike many other drug classes, some risk of hyponatremia persists over time with thiazide treatment. Nevertheless, when confronted with patients with low sodium concentrations, establishing a timeline of when hyponatremia developed in relation to drug initiation will improve the likelihood of identifying a culprit drug. With the exception of thiazides, treatments initiated months or years before onset of hyponatremia are unlikely to represent a causal link.

7.2. The risk of spurious associations

Hyponatremia is often multifactorial in origin, with diseases, drugs, behavioral factors, and environmental exposures either additively or through interactive mechanisms contributing to hyponatremia [32,64,144,145]. For commonly used drugs, even a rare adverse reaction may have considerable clinical implications. On the other hand, when the exposure is common, the risk of a false alarm due to spurious associations is equally elevated. This risk is especially high when the underlying condition motivating treatment is also linked to hyponatremia, i.e., confounding by indication. Examples of drug groups where this is the case are those used to treat cardiovascular diseases. Loop diuretics and spironolactone which are used to treat congestive heart failure, renal failure and liver failure, all important causes of hypervolemic hyponatremia, stand out in this regard. ACEIs and ARBs, both cornerstones in the treatment of heart failure provide equal methodological challenges. Consequently, indications of a moderately increased risk associated with any of these drugs may very well be mediated by the underlying disease rather than the drug per se. For anticancer agents and antibiotics, a causal link can also be difficult to establish in patients with hyponatremia. Similarly, the elevated risk associated with newly initiated PPIs should be interpreted with caution. From a clinical perspective, the importance of evaluating the effect of drug discontinuation, even if a causal link is highly likely, must be emphasised, as persistent hyponatremia could signal more sinister underlying causes [146].

8. Conclusion

Hyponatremia is common in clinical practice and drugs are often the cause. Thiazides are the number one culprit, alone accounting for up to 25% of hospitalizations due to hyponatremia. Several groups of drugs that promote a negative water balance such as loop diuretics, lithium and of sodium-glucose cotransporter-2 inhibitors appear to decrease the risk for hyponatremia. Treatment with immune checkpoint inhibitors used to treat various cancer types is associated with an increased risk of hypophysitis and adrenalitis resulting in hyponatremia based on cortisol deficiency. For SSRIs and several other groups of drugs as well, the chronology is crucial to differentiate a true casual effect from a spurious finding. For a patient with a clinically significant hyponatremia with newly initiated treatment an alternative treatment should be considered. However, for a patient with ongoing treatment, other causes should be explored.

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Declaration of competing interest

The authors have nothing to declare.

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