REVIEW

Hyponatraemia and the syndrome of inappropriate antidiuresis (SIAD) in cancer

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Abstract

Hyponatraemia is a common electrolyte abnormality seen in a wide range of oncological and haematological malignancies and confers poor performance status, prolonged hospital admission and reduced overall survival, in patients with cancer. Syndrome of inappropriate antidiuresis (SIAD) is the commonest cause of hyponatraemia in malignancy and is characterised by clinical euvolaemia, low plasma osmolality and concentrated urine, with normal renal, adrenal and thyroid function. Causes of SIAD include ectopic production of vasopressin (AVP) from an underlying tumour, cancer treatments, nausea and pain. Cortisol deficiency is an important differential in the assessment of hyponatraemia, as it has an identical biochemical pattern to SIAD and is easily treatable. This is particularly relevant with the increasing use of immune checkpoint inhibitors, which can cause hypophysitis and adrenalitis, leading to cortisol deficiency. Guidelines on the management of acute, symptomatic hyponatraemia recommend 100 mL bolus of 3% saline with careful monitoring of the serum sodium to prevent overcorrection. In cases of chronic hyponatraemia, fluid restriction is recommended as first-line treatment; however, this is frequently not feasible in patients with cancer and has been shown to have limited efficacy. Vasopressin-2 receptor antagonists (vaptans) may be preferable, as they effectively increase sodium levels in SIAD and do not require fluid restriction. Active management of hyponatraemia is increasingly recognised as an important component of oncological management; correction of hyponatraemia is associated with shorter hospital stay and prolonged survival. The awareness of the impact of hyponatraemia and the positive benefits of active restoration of normonatraemia remain challenging in oncology.

Key Words

- syndrome of inappropiate antidiuresis (SIAD)
- hyponatraemia
- cancer
- lung cancer
- immune checkpoint inhibitors
- tolvaptan
- fluid restriction

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Introduction

Hyponatraemia is an extremely common complication of malignancy, which may arise as a complication of the tumour or as a side effect of therapy. Although the management of hyponatraemia has not traditionally been regarded as an important aspect of oncological treatment, there is a growing awareness of the detrimental effects of hyponatraemia in cancer patients. Numerous studies have demonstrated that hyponatraemia confers poorer prognosis in patients with malignancy, and as survival in cancer improves, the negative effects of hyponatraemia on quality of life are also assumed importance.

The role of ectopic secretion of the antidiuretic hormone, arginine vasopressin (AVP), in causing hyponatraemia due to the syndrome of inappropriate antidiuresis (SIAD), is well established, as has hyponatraemia in association with cytotoxic therapy. New treatments, such as stem cell transplant, are also now recognised to be responsible for the development

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of hyponatraemia, and the widespread use of immune checkpoint inhibitors has revealed hyponatraemia either from the development of SIAD or from hypophysitis and ACTH deficiency, which may present with a SIAD-like syndrome and primary adrenal failure secondary to an adrenalitis. Hyponatraemia has well-described and widely accepted effects on cognitive function and quality of life in patients with cancer. Hyponatraemia is clearly also a predictor of poorer outcome and shortened survival in a wide spectrum of cancers; however, it is not clear whether the shortened survival is due directly to the electrolyte imbalance or whether hyponatraemia is a manifestation of more widespread or aggressive disease.

In this review, we will summarise the data on SIAD in malignant disease and discuss the emerging evidence that treatment of hyponatraemia due to SIAD can improve quality of life and positively influence survival outcome.

Hyponatraemia in malignancy

Background

The original description of syndrome of inappropriate antidiuretic hormone secretion (SIADH), in 1957, arose from a series of careful and sophisticated studies of water balance conducted in two hyponatraemic patients with bronchogenic carcinoma (Schwartz *et al.* 1957). Although both patients had post-mortem evidence of adrenal metastases, corticosteroid secretion was considered normal prior to death. The patients had clear evidence of antidiuresis, with concentrated urine despite serum hypoosmolality, and in elegant, carefully supervised in-patient studies, the authors were able to demonstrate that water restriction led to a rise in plasma sodium concentration, and liberalisation of fluid intake led to hyponatraemia worsening. The authors concluded that the presence of an antidiuretic hormone, which they termed ADH, was causing water retention, and dilutional hyponatraemia (Schwartz *et al.* 1957). The authors hypothesised that direct pressure from the mediastinal tumour masses had exerted compressive effects on a neural structure such as the vagus nerve and stimulated non-osmotic secretion from the brain or that cerebral secondaries had mediated secretion; ectopic hormone secretion from the tumour was not considered (Schwartz *et al.* 1957). The syndrome of SIADH, characterised by euvolaemic hyponatraemia in the presence of inappropriate urine concentration and natriuresis, was developed from this classical description. Since then, the term 'syndrome of inappropriate antidiuresis' (SIAD) has superseded SIADH as the preferred terminology (Verbalis *et al.* 2013).

Since this classic index description, hyponatraemia became well recognised as a complication of malignancy and, in particular, small cell cancer of the lung. Early demonstration of elevated plasma AVP concentrations in the plasma of lung cancer patients (Vorherr *et al.* 1968) implicated the role of the hormone in the pathogenesis of SIAD. In their classical paper, George *et al.* showed that AVP could be detected by RIA in the tissue of a bronchogenic tumour removed surgically from a patient with hyponatraemia (George *et al.* 1972). This description raised the likelihood of ectopic AVP secretion from tumour tissue as the basis for SIAD in some cancer patients. The development of sensitive RIAs allowed for further characterisation of the control of AVP secretion in patients with lung cancer and hyponatraemia (Robertson *et al.* 1982, Maurer *et al.* 1983, Smith *et al.* 2004) and molecular biology techniques were able to demonstrate AVP gene expression in tissues derived from small cell lung cancers (Friedmann *et al.* 1994). A compelling case had therefore emerged for ectopic synthesis of AVP in lung tumour tissue, leading to elevated plasma hormone levels, and the development of hyponatraemia as a result of the antidiuretic effects of AVP.

Since then, hyponatraemia has been described in a wide variety of malignant processes. The association has been documented most often and most comprehensively in bronchogenic carcinoma (Alamoudi 2010, Hansen *et al.* 2010, Castillo *et al.* 2012, Sengupta *et al.* 2013, Tiseo *et al.* 2014, Fiordoliva *et al.* 2017, Chan *et al.* 2020, Bartalis *et al.* 2021, Sandfeld-Paulsen *et al.* 2021). A meta-analysis published in 2021, of 31 articles, showed the mean prevalence of hyponatraemia in lung cancer was 25%; however, the findings were highly discordant, ranging from 3 to 95% due to heterogeneity in patient characteristics, evaluation of hyponatraemia and the cut-off points used (Bartalis *et al.* 2021). Although no study has compared the incidence of SIAD in lung cancer by histological type, it is widely accepted that SIAD due to ectopic production of vasopressin is significantly more common in small cell lung cancer than non-small cell (Cuesta & Thompson 2016). Hyponatraemia has been reported in association with almost all forms of cancer; one review, of over 2000 patients treated in Dubai, reported that hyponatraemia occurred in 57% of cases of prostate cancer, 57% of pancreatic cancer, 49% of liver cancer and 24% of liver cancer, compared with 40% of lung cancer (Abu Zeinah *et al.* 2014); 4% of patients with head and neck cancer develop hyponatraemia in one large series (Talmi

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et al. 1992). Hyponatraemia has therefore been implicated in a wide range of solid organ and also haematological malignancies (Koumpis *et al.* 2020) and is associated with significant morbidity and mortality (Castillo *et al.* 2016, Workeneh *et al.* 2020).

It is important to recognise that most publications do not distinguish between the various pathophysiologies which lead to hyponatraemia. Hyponatraemia is not synonymous with SIAD, which is the focus of this review and which is characterised by euvolaemic hyponatraemia. SIAD is caused by different pathologies, requires different diagnostic criteria and has an entirely different therapeutic approach (Martin-Grace *et al.* 2022 in press) to hypovolaemic or hypervolaemic hyponatraemia. SIAD also has lower associated mortality than other forms of hyponatraemia (Cuesta *et al.* 2017, Kutz *et al.* 2020). Although hyponatraemia has been attributed to SIAD in lung cancer in 60% of cases (Grohé *et al.* 2015), and in 30% of all-cause cancers (Berghmans *et al.* 2000, Cuesta *et al.* 2017), the criteria used to diagnose SIAD in many studies are incomplete (Burst *et al.* 2017)). In this review, we will distinguish as far as possible between the data related to SIAD in cancer and that related to all-cause hyponatraemia.

Pathogenesis of hyponatraemia in malignancy

It is recommended that the diagnostic approach to hyponatraemia should incorporate an assessment of blood volume status (Verbalis *et al.* 2013), partly because the management of hyponatraemia differs widely depending upon whether the patient is hypovolaemic, euvolaemic or hypervolaemic (Verbalis *et al.* 2013) and partly because mortality varies significantly between the groups, being higher in hypovolaemic and euvolaemic hyponatraemia than in SIAD (Cuesta *et al.* 2017, Kutz et al 2020). Although it has been claimed that SIAD is the commonest cause of hyponatraemia in oncology patients (Berardi *et al.* 2019), the spectrum of hyponatraemia pathogenesis in malignancy is wide (Table 1).

In the diagnosis of SIAD in malignant disease, it is therefore important to exclude hypovolaemic and hypervolemic causes (Thompson *et al.* 2012). It can be difficult clinically to distinguish between mild hypovolaemia and SIAD, where clinical signs may be subtle. However, the distinction is important as the first-line treatment recommended by guidelines is so different (Verbalis *et al.* 2013, Spasovski *et al.* 2014). In cases where the urine sodium is low, or where there is a history of vomiting, it would be usual to assume a diagnosis of hypovolaemic hyponatraemia, even in the absence of typical clinical signs and to treat empirically with i.v. sodium chloride solution. In our clinical practice, we administered 1 L of sodium chloride intravenously over 8–12 h, while monitoring the serum sodium, typically every 2–4 h. Further treatment is dependent on the initial response to i.v. fluids.

SIAD in malignancy

SIAD has been reported in association with a wide variety of malignancies (Verbalis *et al.* 2013), which have been summarised in Table 2. In many instances, AVP is synthesised in tumour tissue (George *et al.* 1972), causing ectopic hormone secretion. Primary intracerebral tumours and brain metastases induce SIAD by physically interfering with the osmoregulatory pathways within the hypothalamus and neurohypophysis, causing the non-osmotic release of vasopressin (Esposito *et al.* 2011). Postoperative SIAD can also occur following neurosurgical resection of intracranial tumours (Sherlock *et al.* 2009) and is particularly common with suprasellar, thalamic and hypothalamic lesions (Madden *et al.* 2010). In addition, a number of treatments, particularly chemotherapy, can cause SIAD. Vinca alkaloids such as vincristine and vinblastine, platinum compounds such as cisplatin and carboplatin and alkylating agents, particularly cyclophosphamide and

Table 1 Causes of hyponatraemia in malignancy.

	Clinical signs	Urine sodium < 20 mmol/L	Urine sodium > 20 mmol/L	Treatment
Hypovolaemia	Dry mouth, skin Tachycardia Low BP/CVP	Vomiting Diarrhoea	Adrenal insufficiency Diuretics	i.v. saline
Euvolaemia		Hypothyroid	SIAD Glucocorticoid deficiency	Fluid restriction Vaptans
Hypervolaemia	Ankle/sacral oedema Raised JVP Ascites	Ascites Nephrotic syndrome Cardiac failure	Renal failure	i.v. diuretics Albumin treatment in ascites

BP, blood pressure; CVP, central venous pressure; JVP, jugular venous pressure; SIAD, syndrome of inappropriate anti-diuresis.

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Table 2 Causes of SIAD in malignancy.

Malignancy	Lung – small cell, non-small cell, mesothelioma, secondaries GI – oesophagus, stomach, colon, pancreas, duodenum Haematological – lymphoma, myeloma, leukaemia Brain – glioma, meningioma, medulloblastoma, pinealoma, neurofibroma, secondaries Miscellaneous – renal, prostate, breast, urological, melanoma
Treatment	Cytotoxics – vincristine, vinblastine, cisplatin, carboplatin, melphalan, levamisole, cyclophosphamide methotrexate, interferon (increased hypothalamic AVP secretion) and cyclophosphamide (potentiation of AVP action) Immune checkpoint inhibitors – nivolumab, pembrolizumab, ipilimumab Adjunctive therapy – opiates, anti-emetics, antidepressants, carbamazepine, haloperidol, phenothiazines Stem cell transplantation Radiotherapy
Miscellaneous	Nausea Associated infections – pneumonia, sepsis, covid-19

melphalan, all potentiate the secretion of AVP from the hypothalamus, while cyclophosphamide also augments the antidiuretic actions of AVP on the collecting ducts of the kidney (Castillo *et al.* 2012). Cisplatin is particularly liable to cause hyponatremia, which occurs in 40–60% of patients prescribed the drug during clinical trials (Verzicco *et al.* 2020), whereas if high-dose cyclophosphamide is included in the regimen, up to 90% of patients develop hyponatraemia (Lee *et al.* 2010). It should be emphasised that these figures are for all-cause hyponatraemia, rather than SIAD. They will therefore include a substantial number of patients who develop hyponatraemia due to vomiting, for instance, and have hypovolaemia, or secondary to i.v. fluids, and have increased blood volume.

Immune checkpoint inhibitors such as nivolumab, pembrolizumab and ipilimumab have transformed the outlook of many cancers but carry a substantial collateral burden of hyponatraemia. A recent large retrospective study of over 2000 patients reported that 62% developed hyponatraemia in the first year of therapy (Seethapathy *et al.* 2021). Hyponatraemia reported with immune checkpoint inhibitors may arise from a number of different mechanisms. Low plasma sodium concentrations may reflect SIAD due to drug treatment, the underlying malignant process, cortisol deficiency secondary to hypophysitis or adrenalitis, or it may be due to nausea; in some cases, it may be multifactorial. Published data suggest that most cases are due to SIAD (Verzicco *et al.* 2020). Although immune checkpoint inhibitors are associated with significant endocrinopathies, including hypophysitis, hypothyroidism and adrenalitis (Chang *et al.* 2019), they account for less than 0.3% of cases of hyponatraemia (Seethapathy *et al.* 2021). Targeted therapies such as cetuximab, an EGF receptor inhibitor, are associated with high rates of severe hyponatraemia (up to 35%), with even higher rates seen when used in combination with other therapies (Berardi *et al.* 2016). Bortezomib, a proteosome inhibitor, used in the treatment of multiple myeloma can induce SIAD. Hyponatraemia in multiple myeloma has been successfully reversed with the AVP-receptor antagonist tolvaptan, indicating an AVP-dependent mechanism (O'Connor-Byrne *et al.* 2019). Stem cell therapy has been documented to cause SIAD, though in practice, it is difficult to tease out the effects of stem cell therapy itself, and the contribution of associated chemotherapy, such as cyclophosphamide and melphalan. Although there are multiple causes of SIAD in cancer patients, it is important to consider that hyponatraemia is often multifactorial. A patient with small cell lung cancer may have ectopic AVP synthesis and secretion but may also be on chemotherapy, anti-epileptics and diuretics and have a superimposed pneumonia. The full diagnosis of the cause of hyponatraemia may therefore be more nuanced and multifactorial than suggested by algorithms. Expert endocrine or renal opinion is often needed to tease out the precise causation.

Diagnosis of SAID

The basic criteria for the diagnosis of SIAD (Verbalis *et al.* 2013) have changed little from those originally proposed after the initial physiological studies were published (Schwartz *et al.* 1957) and are summarised in Table 3. It is essential that the patient is demonstrated to be clinically euvolaemic and to have inappropriate urine concentration, reflecting AVP action on the kidney, and manifested by urine osmolality in excess of 100 mOsm/kg. Elevated urine sodium must be present and a crucial diagnostic step is to exclude glucocorticoid deficiency. Studies have shown poor documentation of the basic diagnostic criteria for SIAD in clinical practice (Tzoulis & Bouloux 2015, Berkman *et al.* 2018) and even in international registries (Greenberg *et al.*

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Table 3 Diagnostic criteria for the diagnosis of SIAD.

Parameter	Explanatory notes
Hyponatraemia	pNa < 132 mmol/L or pOsm < 275 mOsm/kg
Euvolaemia	No evidence of dehydration or fluid overload
Inappropriate urine concentration	Urine osmolality >100 mOsm/kg indicates inappropriate presence of AVP in a hyponatraemic patient
Elevated urine sodium	uNa > 20–30 mmol/L, with a normal salt intake
Exclusion of confounding conditions	Glucocorticoid deficiency, most important confounder Severe hypothyroidism Normal renal function and absence of diuretic therapy

pNa, plasma sodium concentration; pOsm, plasma osmolality; uNa, urine sodium concentration.

2015), which were set up to document clinical practice, the ascertainment of essential investigations was poor.

Of the various diagnostic criteria, the exclusion of cortisol (glucocorticoid) deficiency is particularly important. The electrolyte abnormalities in glucocorticoid deficiency are indistinguishable from those of SIAD (Thompson *et al.* 2012) and are principally related to the requirement for cortisol in order to excrete water from the kidneys. In a prospective study of over 500 patients admitted to hospital with euvolaemic hyponatraemia, with a presumptive diagnosis of SIAD, 4% had evidence of undiagnosed cortisol deficiency on formal testing (Cuesta & Thompson 2016). Despite this, the possibility of cortisol deficiency is often ignored, with testing performed in only 33–45% of hyponatraemic patients in routine clinical practice (Tzoulis & Bouloux 2015, Berkman *et al.* 2018) and in 33% of euvolaemic patients entered into the international hyponatraemia registry (Greenberg *et al.* 2015). Clearly, basic diagnostic standards are not routinely fulfilled in clinical practice, and equally clearly, cases of treatable cortisol deficiency are being missed.

The wide range of malignant complications can impair cortisol secretion and make it crucial to test the integrity of glucocorticoid secretion in patients with malignancy. Missing a diagnosis of cortisol deficiency can impair quality of life and render the cancer patient vulnerable to adrenal crisis during intercurrent illness or infection. The causes of cortisol deficiency in malignancy are summarised in Table 4. It has recently become apparent that 20–40% of patients treated with immune checkpoint inhibitors develop hypophysitis – higher rates are seen with combination therapy – most of whom require steroid replacement therapy (Chang *et al.* 2019, Garon-Czmil *et al.* 2019). These patients may all present with biochemical features indistinguishable from SIAD.

A largely unexplored field of oncology is the potential for high-dose corticosteroid therapy, used to supplement chemotherapy, to cause adrenal suppression. Immunosuppressive steroids have been reported to cause adrenal suppression in a spectrum of clinical conditions (Dineen *et al.* 2019, Tomkins *et al.* 2022), which is often unrecognised. Patients prescribed immunosuppressive steroids for inflammatory conditions are also much less likely than endocrine patients to be made aware of sick day rules or to carry steroid warning cards (Salehmohamed *et al.* 2018), so the potential vulnerability to adrenal crisis in this situation is considerable (Dineen *et al.* 2019). Although synacthen testing is the gold standard to establish the presence of adrenal insufficiency, data in euvolaemic hyponatraemia have shown that a 09:00 h plasma cortisol of >300 nmol/L (>10.9 ng/mL) is sufficient to exclude glucocorticoid deficiency in SIAD (Cuesta & Thompson 2016).

Table 4 Causes of adrenal insufficiency manifesting as SIAD.

Cause	Notes
Withdrawal of adjuvant steroid therapy	Following high-dose steroids as adjuvant to chemotherapy. Usually transient but may complicate post chemo infections
Immune checkpoint inhibitors	Hypophysitis in 9–17%, higher with combined therapy; 90% need steroid replacement, of whom 60% present with hyponatraemia Adrenalitis is more likely to cause Addison's disease picture
Adrenal secondaries	Rarely cause glucocorticoid insufficiency alone – more likely to cause Addison's disease picture
Pituitary metastases	Usually do not affect anterior pituitary function. Diabetes insipidus more likely. Isolated reports of ACTH deficiency causing SIAD-like syndrome
Treatment for adrenal carcinoma	Mitotane particularly – usually needs higher maintenance doses of steroid replacement.
Cerebral irradiation	ACTH deficiency. More common with long-term follow-up

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Effects of SAID in malignancy

Hyponatraemia has numerous detrimental effects in patients with cancer. It can interfere with the conduct of anti-tumour therapy, and it leads to impaired quality of life and an excess of hospital admissions (Burst *et al.* 2017). There is a considerable accumulation of evidence to show that in hospitalised patients with cancer, all-cause hyponatraemia is associated with increased mortality, prolonged duration of in-patient stay and amplification of health care costs (Hansen *et al.* 2010, Jeppesen *et al.* 2010, Petereit *et al.* 2011, Doshi *et al.* 2012, Abu Zeinah *et al.* 2014, Schutz *et al.* 2014, Berardi *et al.* 2015*a*,*b*). Hyponatraemia has been associated with lower performance status using the Eastern Cooperative Group Performance Status (ECOG-PS) in patients with non-small cell lung cancer (Chan *et al.* 2020) and has been associated in two meta-analyses, with shorter overall survival in non-small cell lung cancer (Sandfeld-Paulsen *et al.* 2021) and all-cause lung cancer (Bartalis *et al.* 2021). It is important to emphasise that these are associations with hyponatraemia. The figures have been extrapolated in past publications to be readily translatable to SIAD, on the basis of a largely unproven assumption that hyponatraemia in cancer is nearly always due to SIAD (Burst *et al.* 2017), but confirmatory data are lacking. One of the few papers which analysed SIAD separately had no non-hyponatreamic control group for comparison (Burst *et al.* 2017). At present, therefore, we can comment on the effect of hyponatraemia on outcomes in cancer but not SIAD *per se*.

Treatment of SAID in malignancy

Acute hyponatraemia

Acute hyponatraemia is a medical emergency that requires immediate treatment, irrespective of the underlying condition, to prevent neurological damage and to reduce mortality (Sterns 2018*b*). Conventionally, acute hyponatraemia is defined as occurring in less than 48 h (Verbalis *et al.* 2013). When hyponatraemia develops as quickly as this, there is no time for cerebral adaptation to occur, and water moves osmotically across the blood–brain–barrier into the brain, which expands, causing cerebral oedema (Sterns & Silver 2016, Verbalis 2019). If intracerebral pressure rises sufficiently, seizures and brain herniation may occur.

The treatment of choice is i.v. infusion of 3% NaCl solution, as this offers the opportunity to reverse hyponatraemia promptly and reliably (Verbalis *et al.* 2013). Traditionally, a continuous infusion of i.v. 3% NaCl has been used, though recent expert consensus guidelines have recommended 100 mL i.v. boluses of 3% NaCl, aimed at elevating plasma sodium concentration by 4–6 mmol/L over 4–6 h (Verbalis *et al.* 2013). A subsequent observational study reported that changing from i.v. infusion of 3% NaCl to bolus correction was associated with a more rapid early rise in plasma sodium concentration, over the first 6 h, but similarly, plasma sodium rises at 24 h; crucially, the bolus treatment was associated with a quicker return of neurological disability, as measured by the Glasgow Coma Scale, in the first 6 h, with no recorded instance of osmotic demyelination (Garrahy *et al.* 2019). However, the need for intervention to address overcorrection of hyponatraemia was higher in the bolus group. In contrast, the SALSA trial, a large prospective randomised comparison of intermittent bolus therapy with continuous infusion, showed no difference in the rates of overcorrection, which were significant in both groups (17% of bolus-treated vs 24% of infusion-treated), though the data also showed a treatment advantage for bolus therapy in terms of achieving early plasma sodium targets (Baek *et al.* 2021). The authors concluded with their recommendation that bolus therapy could become the treatment of choice for acute severe symptomatic hyponatraemia. Some authors have recommended a further sophistication of 'clamping' renal-free water clearance with dDAVP (Achinger & Ayus 2017), in order to avoid the occasional, very rapid overcorrection seen when a sudden aquaresis accompanies the hypertonic infusate; the authors contend that this diminishes the need to treat for overcorrection of hyponatraemia and will further reduce the risk of osmotic demyelination.

In malignant disease, acute symptomatic hyponatraemia is seen most often in association with the administration of i.v. fluids, administered at the same time as chemotherapeutic agents which stimulate drug-induced SIAD. If a patient on chemotherapy and i.v. fluids develops disorientation, or neurological symptoms, urgent electrolytes should be ordered, and if hyponatraemia has developed, emergency endocrine consultation to supervise hypertonic saline is advisable.

Chronic hyponatreamia

Evidence has accumulated that active management of hyponatraemia is associated with improved patient outcomes (Garrahy *et al.* 2021). There are data to show that this is true in the oncology population. Patients with neurocognitive symptoms due to symptomatic SIAD in small cell lung cancer have been shown to

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have improved symptom scores on the restoration of normonatraemia (Petereit *et al.* 2013, Ren & Yang 2021), though a recent meta-analysis reported that this was not a consistent finding across all studies in non-small cell lung cancer (Sandfeld-Paulsen *et al.* 2021). Chronic, mild hyponatraemia can exacerbate common cancer-related symptoms including anorexia, nausea and lethargy; active treatment can reduce these symptoms and potentially improve overall quality of life. In addition, treatment of hyponatraemia has been shown to improve gait stability in the non-oncology population, which can reduce falls and the risk of pathological fractures (Renneboog *et al.* 2006). As long-term survivorship from cancer continues to improve, the deleterious effects of untreated chronic hyponatraemia on bone mineral density should also be considered (Upala & Sanguankeo 2016). Treatment of SIAD to improve hyponatraemia in lung cancer has also been shown to improve overall survival at 10 but not 20 months, in a meta-analysis, though it should be acknowledged that longer follow-up will document diminishing returns on survival with a malignant process (Bartalis *et al.* 2021). The reason for the positive effect of active treatment of SIAD is not known. Hyponatraemia treatment may improve cancer survival, improving patient well-being and performance status, thus allowing early and more intensive cancer treatment regimens. Several studies have found that hyponatraemia is associated with poorer chemotherapy responses; correction of hyponatraemia could therefore potentially improve treatment outcomes (Schutz *et al.* 2014, Svaton *et al.* 2014, Berardi *et al.* 2015).

The decision to treat hyponatraemia will remain individualised. A composite analysis of severity of hyponatraemia symptoms, likely overall survival, and appropriateness of treatment options available should inform the decision to treat in any clinical circumstance. There are a number of options available for the treatment of chronic SIAD, many of which have been used in patients with cancer. This was reflected in an analysis of treatments used in the hyponatraemia registry. In SIAD associated with malignancy, 12% of patients received no active treatment, while the most frequently used therapies – fluid restriction and isotonic saline – had very modest effects on plasma sodium concentration (Burst *et al.* 2017). Tolvaptan was the most effective therapy and the only treatment for SIAD that was as effective in cancer patients, as in non-cancer SIAD.

Fluid restriction

Both the US and European guidelines recommend fluid restriction (FR) as first-line treatment for chronic SIAD (Verbalis *et al.* 2013, Spasovski *et al.* 2014). The data to support this recommendation are limited. A randomised prospective trial of FR vs no therapy showed a modest rise in plasma sodium concentration of 3 vs 1 mmol/L after 3 days of FR, with minimal further rise in plasma sodium concentration at 30 days (Garrahy *et al.* 2020). Results from the hyponatraemia registry showed that FR produced an even less impressive rise in plasma sodium in a mixed aetiology group of patients with SIAD, with no statistical difference in the rise in plasma osmolality, when compared with no therapy at all (Greenberg *et al.* 2015). The SIAD cohorts in both of these studies were of mixed aetiology, but each contained patients with malignant causes of SIAD. If a presumption is made that patients with malignant SIAD respond in a similar way to SIAD from other causes, FR may not be effective for long-term treatment of SIAD.

There are also significant reasons why FR would not be an ideal choice for malignant SIAD. For FR to be effective, intake must usually be restricted to 800 mL daily, which includes fluids contained in fruit, yoghurt, etc. This is rarely compatible with long-term care, especially if there is a requirement to take fluids with medications, or to maintain fluid intake when on chemotherapy. In addition, when a balanced diet is required to replace weight or muscle loss, it is difficult to restrict fluid intake. Most importantly, hospitalised patients may be on i.v. antibiotics or antiemetics, as well as i.v. fluids associated with administration of chemotherapy. For this reason, FR is rarely of practical value in SIAD associated with malignancy.

Vaptans

Vaptans are vasopressin receptor antagonists with specificity for the renal V2 receptors. The SALT studies showed the effectiveness of tolvaptan in elevating plasma sodium concentration in a mixed cohort of patients with either SIAD or hypervolaemic hyponatraemia (Schrier *et al.* 2006). The rise in plasma sodium was accompanied by an improvement in quality of life parameters. A post-study subgroup analysis confirmed the effectiveness of vaptans in the cohort with SIAD (Verbalis *et al.* 2011). A further *post hoc* analysis in patients with cancer in the SALT study confirmed that tolvaptan was a safe and effective therapy in this group (Gralla *et al.* 2017); side effects, such as thirst and dry mouth, were mild and predictable given the mechanism of action of tolvaptan. The results were strongly suggestive of treatment benefit. However, in common with all *post hoc* analyses, the conclusions require confirmatory prospective evaluation. A comparison of tolvaptan treatment with

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supportive care in SIAD in oncology patients showed that tolvaptan therapy was associated with quicker reversal of hyponatraemia, decreased hospital stay and decreased symptoms and complications (Bilgetekin *et al.* 2021) and also showed that if plasma sodium concentration was normalised, overall survival improved. A small retrospective review, of 23 patients with small cell lung cancer treated with tolvaptan, confirmed that improved performance status resulted from elevation in plasma sodium concentration (Ren & Yang 2021). Interestingly, this study showed that smaller doses of tolvaptan than those utilised in the SALT studies (Schrier *et al.* 2006) were equally efficacious in reversing hyponatraemia. This reflects a sense that the doses of tolvaptan used in the early SALT studies may have been higher than needed for clinical effects and that better dosing studies are needed in SIAD (Sterns 2018*a*). Although tolvaptan may be efficacious in reversing hyponatraemia associated with the SIAD of cancer, a loss of effect has been reported, associated with rising plasma AVP concentrations, as small cell lung cancer tumour mass progresses and cancer becomes more active (Garrahy *et al.* 2018). In the patients reported, escalating doses of tolvaptan were needed to maintain normonatreamia as plasma AVP concentrations increased, with eventual loss of drug effect.

Tolvaptan is an effective treatment for SIAD but is an expensive therapy for long-term use. A recent Italian study did suggest however that the use of tolvaptan was associated with reduced length of hospital stay in patients with cancer; it was argued that savings from reduced in-patient bed days could offset the cost of therapy (Berardi *et al.* 2019). Vaptans can be useful for short-term interventions which allow i.v. fluid replacement during chemotherapy (O'Connor-Byrne *et al.* 2019) or for longer-term therapy to reverse hyponatraemic symptoms (Bilgetekin *et al.* 2021). Side effects are reflective of the aquaretic effects of the drug and include polyuria and thirst. Overcorrection has been reported (Schrier *et al.* 2006), particularly when the starting plasma sodium is very low, but osmotic demyelination has not been a significant issue. Although tolvaptan is marketed at doses of 15–30 mg, in practice, many clinicians initiate therapy with lower doses, to diminish the risk of overcorrection of sodium. A reversible transaminitis has been reported with tolvaptan therapy in autosomal dominant polycystic kidney disease (Torres *et al.* 2012) but not in hyponatraemia, where lower doses of tolvaptan are typically used (Schrier *et al.* 2006). It is recommended that liver function tests be monitored at baseline, 2 and 4 weeks and monthly thereafter. Tolvaptan should be held if aspartate aminotransferase (AST) or alanine transaminase (ALT) increases to two times the upper limit of normal (ULN) and permanently discontinued if the increase exceeds three times the ULN (Chebib *et al.* 2018).

Urea

Urea acts as an osmotic diuretic, which increases renal water loss, resulting in elevation of plasma sodium concentration. The European guidelines recommend it as an effective and inexpensive second-line treatment (Spasovski *et al.* 2014). Urea has been reported to be effective in a number of small non-randomised, retrospective European studies (Decaux & Genette 1981, Soupart *et al.* 2012) and in the data available suggest that it is safe and well-tolerated (Rondon-Berrios *et al.* 2018). A retrospective review of 36 non-randomised oncology patients, who were treated with urea for SIAD, concluded that it was safe and well-tolerated, although with the caveat that there was no control group or comparison with other treatments (Nervo *et al.* 2019). A significant advantage in the treatment of patients with cancer is that fluid restriction is not required with urea therapy. As with tolvaptan, the risk of overcorrection mandates the regular monitoring of plasma sodium concentrations after initiating therapy.

Demeclocycline

Demeclocycline is a tetracycline antibiotic which induces nephrogenic diabetes insipidus (Padfield *et al.* 1978) and causes a rise in plasma sodium concentration consequent upon an aquaresis. The onset of action is unpredictable and as a result of this, and side effects such as renal failure and photosensitivity rash, European guidelines have recommended against the use of demeclocycline in SIAD (Spasovski *et al.* 2014). A systemic literature review discovered no evidence based on the use of demeclocycline in SIAD (Miell *et al.* 2015), though two of the three authors were employed by Otsuka pharmaceuticals, which produces tolvaptan. There seems little to justify the side effects of demeclocycline given the toxicity, the lack of evidence and the availability of better agents.

Frusemide

Frusemide monotherapy for SIAD is not recommended, as the natriuresis leads to volume contraction, with the secondary stimulation of AVP secretion (Dineen *et al.* 2017). However, frusemide in combination with oral sodium chloride tablets, which are administered to replace urine sodium losses, has been endorsed by the European

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guidelines as second-line therapy (Spasovski *et al.* 2014) and is used extensively in the treatment of SIAD. There are little prospective data to support the use of frusemide/sodium chloride replacement, however. The available data have shown no advantage of frusemide/sodium chloride over fluid restriction alone with the disadvantage of higher rates of adverse events including hypokalaemia and acute kidney injury (Krisanapan *et al.* 2020). The hyponatraemia registry recorded that 4% of SIAD patients were treated with this form of therapy (Greenberg *et al.* 2015), with slightly higher usage, at 6.5%, in patients with cancer (Burst *et al.* 2017). Prospective randomised data are needed to support the recommendation for the use of this therapy in oncology with cancer.

Are patients with malignancy treated for hyponatraemia?

The evidence is compelling that hyponatraemia is common in malignancy and has negative effects on performance, survival and duration of hospital stay. There are little data from randomised, prospective trials that treatment of hyponatraemia improves outcomes, but there is enough evidence from the data available to strongly suggest symptomatic (Petereit *et al.* 2013, Bilgetekin *et al.* 2021, Ren & Yang 2021) and survival benefit (Tiseo *et al.* 2014, Yang *et al.* 2017, Wu *et al.* 2020, Bartalis *et al.* 2021, Sandfeld-Paulsen *et al.* 2021). Unpublished data from our own hospital (Murphy B., unpublished audit) suggest that other than renal medicine, where hyponatraemia is actively within-house, the lowest rate of endocrine referral is from patients who develop hyponatraemia on oncology/haematology services. As a consequence, the rate of active management of hyponatraemia is also lowest in oncology services. There is good evidence from the literature that active management of hyponatraemia reduces mortality (Garrahy *et al.* 2021), and the recommendations of a British expert panel have emphasised early referral to endocrinologists or renal physicians for symptomatic hyponatraemia (Grant *et al.* 2015). It has been recommended that SIAD is managed by specialised endocrinologists (Garrahy & Thompson 2017), though it is probably important that each hospital has a designated hyponatraemia specialist, irrespective of speciality, who can set protocols, audit standards and manage the most difficult cases. However, even after this system was introduced in our own hospital, referrals of oncology patients with hyponatraemia remained low and active management correspondingly remained low. It remains a challenge for endocrinologists to build partnerships with local oncology and haematology services, to ensure that patients with malignancy are properly assessed for causation of hyponatraemia and that management of SIAD is appropriate. Symptomatic outcomes, and perhaps even survival, of patients with malignancy and SIAD, may depend upon it.

Conclusion

Hyponatraemia confers significant morbidity to individuals with cancer, it is associated with impaired performance status, prolonged hospital admission, reduced treatment efficacy and overall survival. Thorough evaluation of the aetiology of hyponatraemia, in particular, differentiating between SIAD and cortisol deficiency is essential to ensure appropriate treatment. Active treatment of hyponatraemia, with specialist endocrinology input, is increasingly recognised as an important component of oncological management. Restoration of eunatraemia has been shown to improve hyponatraemia symptoms, reduce hospital stays and may improve overall survival. Tolvaptan is a safe and effective treatment of SIAD in the oncology setting.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review

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