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The Use of Vaptans in Clinical Endocrinology

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Context: Hyponatremia is the most common electrolyte disorder encountered in clinical practice and represents a clinical, social, and economic burden. Conventional treatments of hyponatremia present some pitfalls, such as suboptimal efficacy, risk of overly rapid correction, and adverse effects. Vasopressin receptor antagonists, known as vaptans, represent a new and interesting class of drugs for the treatment of the euvolemic and hypervolemic forms of hyponatremia.

Evidence Acquisition: This review is based on a PubMed search with the following terms: "vaptans," "vasopressin receptor antagonists," "tolvaptan," "conivaptan," "vasopressin receptor antagonists and SIADH," "vasopressin receptor antagonists and congestive heart failure," "vasopressin receptor antagonists and cirrhosis," and "vasopressin receptor antagonists and polycystic kidney disease."

Evidence Synthesis: Overall, the studies reported in this review indicate that vaptans effectively correct hyponatremia in euvolemic and hypervolemic patients. In the latter group, vaptans generally had favorable effects on fluid balance also. To date two vaptans, ie, conivaptan and tolvaptan, have been marketed in the United States for the treatment of euvolemic and hypervolemic hyponatremia, whereas tolvaptan has been marketed in Europe with the limitation of euvolemic hyponatremia. Although these drugs have a good safety profile, caution should be used, and treatment should be initiated in a hospital setting in order to closely monitor patients and avoid overly rapid correction or overcorrection.

Conclusions: Vaptans can be considered a new effective tool for the treatment of euvolemic and hypervolemic hyponatremia. Nevertheless, more comparative research of vaptans vs other therapies on clinical grounds is needed to more accurately assess the value of these drugs in the treatment of hyponatremia. **(*J Clin Endocrinol Metab* 98: 0000–0000, 2013)**

Hyponatremia is the most common electrolyte disorder encountered in clinical practice. Mild hyponatremia (serum [Na^+] between 130 and 135 mmol/L) occurs in about 20% of hospitalized patients, whereas moderate to severe hyponatremia (serum [Na^+] <130 mmol/L) occurs in up to 7% of hospitalized patients (1, 2).

Hyponatremia, which is an independent predictor of in-hospital mortality (3–5), represents a clinical and social burden. This is demonstrated by several studies published in the last few years that showed that mild, chronic hyponatremia may also lead to negative consequences on health status, such as altered gait and increased fall risk (6), attention deficits (7), fractures (8), and bone loss (9, 10). More recently, sustained hyponatremia has been shown to cause multiple manifestations of senescence in a rat model of the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH), including cardiomyopathy, skeletal muscle sarcopenia, decreased body fat, and hypogonadism (11). This electrolyte disorder has been linked to increased healthcare resource consumption and longer hospital stay, thus causing increased healthcare costs (12).

Hyponatremia is the consequence of an excess of water relative to total body sodium and can be associated with

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Abbreviations: ADH, antidiuretic hormone; CHF, congestive heart failure; LOS, length of stay; PKD, polycystic kidney disease; SIAD, syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate ADH secretion; V_1 receptor, vasopressin type 1 receptor; V_2 receptor, vasopressin type 2 receptor.

increased, normal, or reduced plasma osmolality. Hypotonic hyponatremia is the most frequent form encountered in clinical practice and can be classified based on extracellular volume status into hypovolemic, euvolemic, and hypervolemic forms (13). Patients with hypovolemic hyponatremia are effectively treated with isotonic saline (0.9% NaCl) infusion. In patients with euvolemic or hypervolemic hyponatremia, conventional therapeutic options include fluid restriction, hypertonic saline (3% NaCl) infusion, and loop diuretics (13–15). Hypertonic saline infusion has been classically considered the treatment of choice in the presence of acute symptomatic hyponatremia. This approach requires great caution because an overly rapid correction of hyponatremia may cause brain damage, ultimately leading to the osmotic demyelination syndrome (13–15). Fluid restriction represents the safe mainstay of management of asymptomatic euvolemic or hypervolemic hyponatremia. However, the efficacy of this approach is negatively affected by the modest improvement of serum [Na^+] and the poor compliance of the patients because of increased thirst (13, 14). In addition, fluid restriction will not work in patients who are not excreting free water (16). Other options for the treatment of euvolemic or hypervolemic hyponatremia (eg, demeclocycline, urea, lithium) are considered suboptimal for several reasons, including variable efficacy, slow responses, and serious toxicities (13, 14) (Table 1).

Vaptans represent a new class of drugs developed for the treatment of euvolemic or hypervolemic hyponatremia. These drugs are nonpeptide vasopressin receptor antagonists and, by binding vasopressin type 2 (V_2) receptors expressed in renal collecting duct cells, cause water diuresis, namely aquaresis, thus increasing serum [Na^+]. This review will address the development and mechanism of action of vaptans, clinical trials, and current use in clinical practice, as well as future perspectives.

Table 1. Advantages and Problems of Conventional Treatments for Hypotonic Euvolemic or Hypervolemic Hyponatremia

Therapy	Advantages	Problems
Fluid restriction	Inexpensive	Modest efficacy, poor compliance
Hypertonic saline	Effective	Possible overly rapid correction
Loop diuretics	Effective in correcting volume overload	Electrolyte imbalance
Demeclocycline	Generally effective	Slow onset of action, nephrotoxicity
Lithium	Sometimes effective	Inconsistent efficacy, adverse effects
Urea	Generally effective	Unpleasant taste, limited experience

The Development of Vasopressin Receptor Antagonists

The vasopressor and antidiuretic activity of hypophyseal extracts was first described between the end of the 19th century and the beginning of the 20th century (17–20). Only after the isolation and synthesis of vasopressin was it clear that the same hormone is responsible for both vasopressor and antidiuretic effects (21, 22).

The early studies on the effects of neurohypophysial peptide analogs on water diuresis were performed at Cornell University (New York, New York) by the Nobel laureate Vincent du Vigneaud, who reported the antivasopressin activity of two analogs of oxytocin, [4-leucine]-oxytocin and [2,4-diisoleucine]-oxytocin, in rats (23, 24). In the 1980s, a number of studies reported the identification of competitive V_2 receptor antagonists, which induced aquaresis in different animal models, such as rats, dogs, and monkeys (25). However, none of them emerged as a useful clinical antidiuretic antagonist because of low oral bioavailability, species differences, and mostly, agonistic effects when administered to humans (26–29).

A new era for the development of vasopressin receptor antagonists was started in 1991, when the first nonpeptide vasopressin type 1 (V_1) receptor antagonist was identified (30). This compound (OPC-21268) selectively and competitively antagonized the binding to the V_1 receptor and counteracted vasopressin-induced vasoconstriction after oral administration in rats. One year later, the discovery of a nonpeptide V_2 receptor antagonist (OPC-31260), which caused aquaresis in rats, was reported (31). The first successful use of a nonpeptide V_2 receptor antagonist in humans was reported in 1993 (32). Several nonpeptide vasopressin receptor antagonists were developed in the following years, including OPC-41061 and YM087, which subsequently became familiar to clinicians with the names "tolvaptan" and "conivaptan," respectively (33–36).

Mechanism of Action of V_2 Receptor Antagonists

V_2 receptor antagonists, collectively known as vaptans, were thought to be therapeutically useful for the treatment of diseases characterized by fluid retention. They competitively block the binding of vasopressin to V_2 receptors, which are located on renal collecting duct cells. This prevents vasopressin-mediated activation of these receptors. As a consequence of receptor inactivation, the synthesis and transport of aquaporin-2 water channel proteins into the apical membrane of the collecting duct cells is inhibited (13, 37) (Figure 1). This prevents free water reabsorption

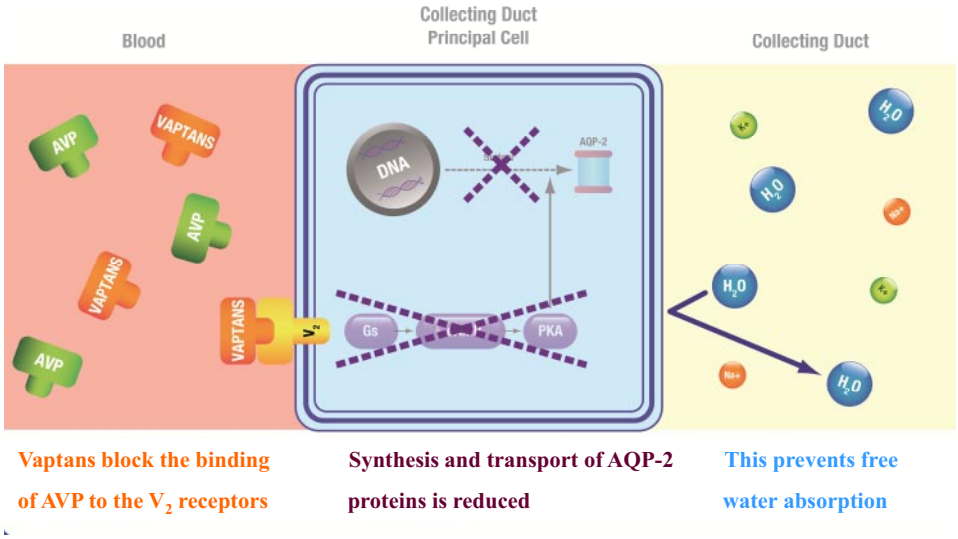


Figure 1. Schematic representation of the mechanism of action of vaptans. [Reproduced from A. Peri et al.: Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Endocrinol Invest*. 33:671–682, 2010 (14), with permission. © Editrice Kurtis.]. AVP, arginine vasopressin; AQP-2, aquaporin-2.

and causes increased urine volume. Noteworthy, the increased diuresis produced by V_2 receptor antagonists is quantitatively similar to diuretics such as furosemide, but it is qualitatively different because there is not a significant increase in the excretion of urine solutes, such as sodium and potassium. Therefore, V_2 receptor antagonists produce aquaresis, which is characterized by a decrease in urine osmolality and an increase in serum $[Na^+]$. The aquaretic effect is therefore the hallmark of these compounds and distinguishes them from traditional diuretics.

Vaptans: Clinical Trials

Several vaptans have been developed and tested in humans. Besides tolvaptan and conivaptan, this list includes lixivaptan, mozavaptan, satavaptan, and RWJ351647 (38) (Figure 2). These molecules bind V_2 receptors with a relative specificity, with the exception of conivaptan, which shows affinity for both V_{1a} and V_2 receptors. All vaptans can be administered orally, but conivaptan can also be administered iv. The pharmacological properties of the most investigated vaptans are shown in Table 2. Because of their mechanism of action, vaptans are not to be used in hypovolemic hyponatremia, whereas positive effects on fluid balance and on natremia can be predicted in patients with euvolemic or hypervolemic hyponatremia.

Vaptans in euvolemic hyponatremia

Patients with euvolemic hyponatremia were included with patients with hypervolemic hyponatremia in several clinical trials of treatment with vaptans, and the results were pooled together in most cases.

In two placebo-controlled, randomized, double-blind studies, 74 and 83 patients, respectively, with euvolemic or hypervolemic hyponatremia received oral conivaptan or placebo for 5 days (39, 40). In both trials, conivaptan (40 or 80 mg/d) caused a significantly greater increase in the area under the curve for serum $[Na^+]$ from baseline than placebo. In addition, patients treated with conivaptan had a faster and more prolonged increase of serum $[Na^+]$ compared to patients treated with placebo. Conivaptan was generally well tolerated; headache, hypotension, nausea, postural hypotension, urinary tract infections, pyrexia, and hypokalemia were among the most frequent adverse events. Similar results were obtained

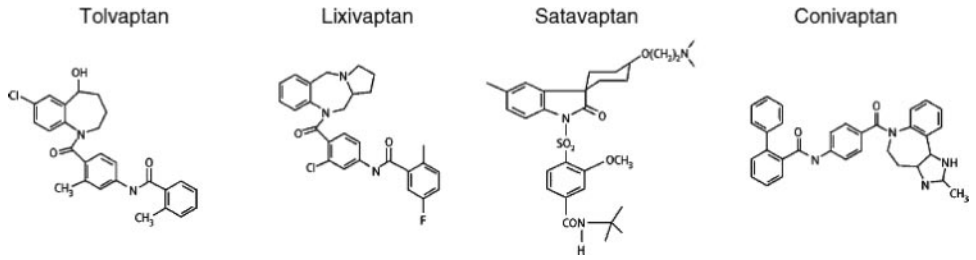


Figure 2. Chemical structure of the most investigated vaptans.

Table 2. Pharmacological Properties of the Most Investigated Vaptans

Pharmacological Properties	Tolvaptan	Lixivaptan	Satavaptan	Conivaptan
Receptor specificity	V_2	V_2	V_2	V_{1a}/V_2
Route of administration	Oral	Oral	Oral	Intravenous[a]
Elimination half-life, h	6–8	7–10	14–17	3–8
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Dosage, mg/d	15–60	10–400[b]	5–50[b]	20–40

[a] An oral formulation has been evaluated in clinical studies but is not currently approved for use.

[b] Doses used in clinical trials.

with iv administration of conivaptan (41) and with oral lixivaptan (42). Two multicenter, randomized, double-blind, placebo-controlled trials, the Study of Ascending Levels of Sodium in Hyponatremia 1 and 2 (SALT-1 and SALT-2), evaluated the efficacy of tolvaptan in patients with euvolemic or hypervolemic hyponatremia (43). Patients were randomly assigned to receive oral tolvaptan (n = 225; 15–60 mg/d) or placebo (n = 223). Serum [Na^+] increased to a greater extent in the tolvaptan group than in the placebo group during the first 4 days and at the completion of the treatment period (30 d). This difference was also maintained when patients were stratified into subgroups according to whether hyponatremia was defined as mild (130–135 mmol/L) or marked (<130 mmol/L) at baseline. Hyponatremia recurred soon after discontinuation of tolvaptan. Commonly observed side effects included increased thirst and dry mouth, in agreement with the aquaretic effect of the drug. In only 4 patients in the tolvaptan group, serum [Na^+] correction exceeded the desirable rate of 0.5 mmol/L·h during the first 24 h of the study, and in only 4 patients serum [Na^+] increased beyond 146 mmol/L. Interestingly, a combined analysis of the two trials showed a significant increase in the score of the mental component of the SF-12 health survey from baseline to day 30 in the tolvaptan group. The subsequent SALTWATER trial was a multicenter, open-label extension of the SALT-1 and SALT-2 trials (44). A total of 111 hyponatremic patients received tolvaptan for a mean follow-up of almost 2 years. Serum [Na^+] normalization occurred rapidly and was maintained throughout the observation period. Patients with euvolemic hyponatremia and those with congestive heart failure (CHF) showed similar responses, whereas the efficacy of tolvaptan appeared less evident in patients with cirrhosis. Similar to the results of the SALT-1 and SALT-2 trials, an excessive rate of serum [Na^+] increase or hypernatremia was also rarely observed in the SALTWATER trial. Another interesting study evaluated the effect of tolvaptan (10–60 mg/d) vs fluid restriction (1200 ml/d) on serum [Na^+] in hospitalized patients with euvolemic (36%) or hypervolemic (64%) hyponatremia (45). At the last inpatient visit (about 2 wk after the initiation of treatment), the mean increase in serum [Na^+] was close to 6 mmol/L in the tolvaptan group and ≤1 mmol/L in the fluid restriction group, whereas no difference in adverse events was observed.

Other clinical studies exclusively addressed the effect of vaptans in patients with euvolemic hyponatremia and therefore included only patients with SIADH. This syndrome has been recently referred to also with the acronym SIAD, for syndrome of inappropriate antidiuresis. The new terminology has been proposed after the first description of infants with clinical and laboratory features consistent with the presence of SIADH, but with undetectable ADH levels. Gain-of-function mutations in the V_2 receptor gene were identified in these patients (46). The new term SIAD also includes this type of patients, and in the opinion of the author of this review it should be preferred to the traditional acronym SIADH, although there has been no formal renaming of the syndrome so far.

The effects of oral satavaptan in patients with SIAD were evaluated in 34 patients enrolled in a randomized, double-blind study. Both 25 and 50 mg/d of satavaptan caused a greater increase in serum [Na^+] (mean basal concentration was 127 mmol/L) than placebo starting from day 2. Mean serum [Na^+] continued to rise gradually, and the persistent effect of satavaptan was also evident in an open-label follow-up treatment for up to 12 months (47). In another study, 56 patients with hyponatremia (serum [Na^+] from 115 to 129 mmol/L) due to SIAD received conivaptan (40 or 80 mg/d via continuous iv infusion) or placebo for 4 days. Both doses of the drug significantly increased serum [Na^+] more than placebo after 2 and 4 days of treatment; on day 4, the mean increase from baseline was 8.4 and 6.1 mmol/L with conivaptan (80 and 40 mg/d, respectively) and 2.8 mmol/L with placebo (48). Similar results were obtained with mozavaptan, administered for 7 days to patients with paraneoplastic SIAD caused by ectopic ADH secretion (49).

The efficacy of vaptans in correcting hyponatremia associated with paraneoplastic SIAD was confirmed in 13 hyponatremic patients, 7 of whom were affected by small-cell lung cancer, treated with tolvaptan. In some patients, overcorrection occurred (in one case, serum [Na^+] in-

creased from 114 to 131 mmol/L within 24 h after a single dose of 15 mg), and the authors hypothesized a higher sensitivity to tolvaptan in paraneoplastic SIAD (50). A subgroup analysis of patients with SIAD (n = 110) in the SALT-1 and SALT-2 trials revealed that the change in the average daily area under the curve for serum [Na^+] from baseline to day 4 and from baseline to day 30 was significantly greater in the tolvaptan group compared to the placebo group (on d 4, 5.28 ± 3.35 vs 0.47 ± 2.81 mmol/L, respectively; on d 30, 8.07 ± 4.55 vs 1.89 ± 4.13 mmol/L, respectively) (51). The SF-12 Health Survey revealed a significant positive effect of tolvaptan on the physical component and a near-significant trend on the mental component in SIAD patients. With regard to safety, no serious adverse event in patients treated with tolvaptan was considered to be related to the medication; similarly, the 1 death occurring in the tolvaptan group was not considered treatment-related. Finally, a long-term Belgian trial in patients with chronic SIAD compared the efficacy, tolerability, and safety of vaptans vs urea. Twelve patients were treated with satavaptan or tolvaptan for 1 year, followed by a 1-year treatment with urea (52). The conclusions of the study were that urea has efficacy similar to vaptans in increasing serum [Na^+] and it is generally well tolerated. Human studies have shown the efficacy of long-term treatment with urea (53). Anyway, it has to be said that not many centers have experience in the use of urea, which is not available in many countries, and that its unpleasant taste has limited its use. Data regarding trials with vaptans specifically in patients with SIAD are summarized in Table 3.

Vaptans in hypervolemic hyponatremia: CHF

Several studies specifically addressed the use of vaptans in patients with CHF (54–61). These studies reported primarily the effects of different vaptans (ie, tolvaptan, lixivaptan, or conivaptan) on hemodynamic parameters, whereas only a minority of patients had hyponatremia. Overall, these studies showed that vaptans caused favorable changes in hemodynamics and water balance and also serum [Na^+] increase in patients with CHF. No serious adverse events were observed as a consequence of the treatment. Two of these studies also addressed the effects of tolvaptan on survival. In one study (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure [ACTIV in CHF]), patients who were treated with tolvaptan (30–90 mg) and who had an increase in serum [Na^+] of at least 2 mmol/L had half the mortality rate (11%) 2 months after discharge compared to patients with no serum [Na^+] improvement (56). On the contrary, in the other study (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan [EVEREST]), treatment with tolvaptan (30 mg/d) for 2 months raised serum [Na^+] levels and improved some hemodynamic indexes, but it did not affect mortality or morbidity compared to placebo (57). However, further beneficial effects of tolvaptan on signs and symptoms were confirmed in the EVEREST trial by subsequent post hoc or subset analyses (60, 61). Similarly, the Dilutional Hyponatremia (DILIPO) trial, which included mostly CHF patients, demonstrated the long-term (up to 343 d of treatment) efficacy of satavaptan on serum [Na^+] correction and weight loss (62). However, higher rates of adverse events, including overly rapid correction of hyponatremia, were reported in patients treated with satavaptan compared to placebo.

Other recent studies showed that the use of vaptans (tolvaptan or conivaptan) as an add-on treatment to conventional diuretics (mostly furosemide) in patients with CHF was tolerable and effective in reducing volume overload (63–66) and caused a greater increase of serum [Na^+] compared to furosemide alone (67). Altogether, these studies indicate that in patients with CHF and signs of volume overload despite using conventional diuretics, vaptans can be a valuable option in order to improve congestive symptoms and signs and spare electrolyte loss.

Vaptans in hypervolemic hyponatremia: cirrhosis

Clinical trials have assessed the efficacy of different vaptans exclusively in patients, mostly normonatremic, with liver cirrhosis. The oldest of them demonstrated that a single oral dose of mozavaptan increased diuresis and

Table 3. Trials with Vaptans That Included Patients with SIAD Exclusively

First Author (Ref.)	Trial Type and Length	Patients (n)	Drug	Dose, mg/d	Route	Efficacy	Overcorrection (n)
Soupart (47)	R, DB + OL, PC, 12 months	34	Satavaptan	25–50	Oral	Yes	7
Verbalis (48)	MC, R, DB, PC, 4 d	56	Conivaptan	40–80	Intravenous	Yes	1
Yamaguchi (49)	MC, OL, 7 d	16	Mozavaptan	30	Oral	Yes	None
Kenz (50)	OL, up to 4 mo	13	Tolvaptan	7.5–30	Oral	Yes	2
Verbalis (51)	MC, R, DB, PC, 30 d	110	Tolvaptan	15–60	Oral	Yes	3
Soupart (52)	OL, 12 mo	10	Satavaptan	5–50	Oral	Yes	Not specified
		2	Tolvaptan	30–60	Oral	Yes	

Abbreviations: R, randomized; DB, double-blind; OL, open-label; PC, placebo-controlled; MC, multicenter.

reduced urine osmolality in patients with cirrhosis to a lesser extent than in healthy individuals (68). This observation is in agreement with the idea that impaired water excretion in cirrhosis is partially due to a vasopressin-independent mechanism, such as reduced distal delivery of filtrate. However, subsequent studies showed favorable effects of lixivaptan, satavaptan, and tolvaptan on fluid balance in cirrhosis (69–72). In a recent study, 1200 patients were included in 3 randomized double-blind trials comparing satavaptan (5–10 mg/d) with placebo in uncomplicated or difficult-to-treat ascites, with or without concomitant diuretic treatment (73). Satavaptan appeared to confer a slight advantage in delaying ascites formation and increased serum [Na^+] in patients with hyponatremia more effectively than placebo. In patients receiving satavaptan and diuretics, an increased mortality was observed compared to placebo, and this caused an early termination of the study. Specific causes for this finding were not identified, and the authors reported that most deaths were associated with complications of cirrhosis.

One trial specifically investigated the effects of vaptans in cirrhotic patients with hyponatremia. Patients (n = 110) were treated with satavaptan (5–25 mg/d for 14 d) together with spironolactone (100 mg/d) (74). Satavaptan treatment confirmed the favorable effect in controlling ascites and caused a significantly greater increase in serum [Na^+] than placebo at all the doses that were used. This finding was confirmed by a subanalysis of the SALT-1 and SALT-2 trials, which showed that in the subgroup of cirrhotic patients with hyponatremia treated with tolvaptan, the increase in serum [Na^+] was significantly greater than in patients treated with placebo, whereas adverse event rates and deaths were similar in both groups (75).

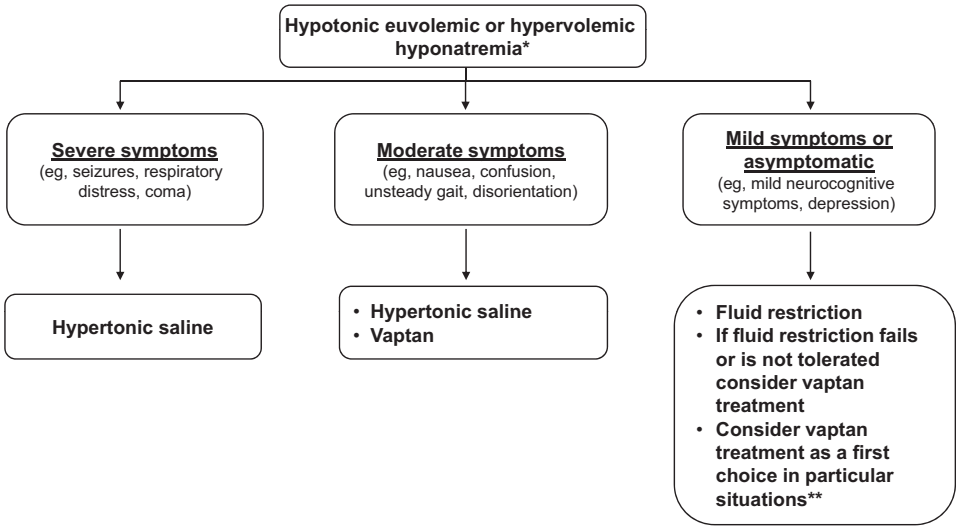
Vaptans: From Clinical Trials to Clinical Grounds

Currently, in the United States and Europe there are two vasopressin receptor antagonists available on the market, conivaptan (injection formulation) and tolvaptan (oral tablet). Conivaptan was approved by the US Food and Drug Administration (FDA) on December 29, 2005, and is marketed in the United States with the indication of "treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients". Tolvaptan was approved by the FDA on May 29, 2009, and is marketed in the United States with the indication of "treatment of clinically significant hypervolemic and euvolemic hyponatremia", thus including patients with heart failure, cirrhosis, and SIAD. In Europe, tolvaptan was approved by the European Medicines Agency (EMA) on August 9, 2009, but the indication was restricted to the "treatment of adult patients with hyponatremia secondary to SIADH". Tolvaptan treatment should be initiated in a hospital setting but can be continued after discharge once the optimal dose has been established. The availability of an oral formulation undoubtedly represented an important achievement for the management of hyponatremia. As mentioned earlier, it has to be remembered that vaptans are not to be used in hypovolemic hyponatremia; therefore, a thorough clinical and diagnostic evaluation should always precede the use of these drugs. Data summarizing the main practical issues regarding the use of conivaptan or tolvaptan are reported in Table 4.

Table 4. Summary of the Main Practical Issues Regarding the Use of Marketed Vaptans

	Conivaptan	Tolvaptan
Dosage forms and strengths	Intravenous injection solution: conivaptan hydrochloride 20 mg/100 ml premixed in 5% dextrose	Tablets, 15 and 30 mg
Starting dose	Loading dose: 20 mg administered over 30 min, followed by continuous infusion, 20 mg/d	15 mg once daily
Dose titration	After initial day of treatment, dosage can be increased to 40 mg/d (continuous infusion)	Dosage may be increased at intervals ≥24 h to 30 mg once daily, and to a maximum of 60 mg once daily
Treatment schedule	Up to 4 d	Variable
Serum [Na^+] monitoring	At least every 6 h during initiation and dose titration	At least every 6 h during initiation and dose titration

In clinical practice, whereas hypertonic saline remains the mainstay of treatment in hypervolemic or euvolemic patients with severe hyponatremia-related symptoms, such as respiratory distress, seizures, and coma, vaptan treatment can be considered a valuable option in: 1) hyponatremic patients with moderate symptoms (eg, confusion, disorientation, nausea, unsteady gait), as an alternative to hypertonic saline infusion; or 2) patients with mild symptoms (eg, mild neurocognitive alterations, depression) or asymptomatic, if fluid restriction fails or is not tolerated (76) (Figure 3). Vaptans can be reasonably taken into consideration as the first-choice treatment instead of fluid restriction when the kidneys are not excreting solute-free water, according to the urine/serum electrolyte ratio



* Other treatment options, including loop diuretics, demeclocycline, urea, lithium, and removal of drugs that are known to cause hyponatremia, may be considered on a case-by-case basis. Specific treatment of the underlying disease should be started, when possible.

** For instance in hyponatremic patients before surgery or chemotherapy, in patients who are not expected to excrete solute free water, as a trial to treat symptoms likely related to hyponatremia.

Figure 3. Treatment algorithm for the correction of hypotonic euvolemic or hypervolemic hyponatremia. For specific approvals and indications in the United States and in Europe see the text.

(77), or as a trial to treat symptoms likely due to hyponatremia. A prompt use of these drugs can be also recommended in surgical and neoplastic patients with euvolemic or hypervolemic hyponatremia, in order to obtain a rapid correction and avoid any treatment delay. Noticeably, pretreatment hyponatremia has been independently associated with a shorter survival time in neoplastic patients (78), and failure to normalize serum [Na^+] has been identified as a negative prognostic factor in these patients (79). Hyponatremia appears to be a particularly important issue in those patients who have to start chemotherapy with drugs that can worsen hyponatremia, such as platinum-based antineoplastic agents, cyclophosphamide, vincristine, vinblastine, melphalan (80), ifosfamide (81), or etoposide (82). It is worth mentioning that mozavaptan was specifically approved in 2006 in Japan for the treatment of patients with paraneoplastic SIAD, although it is neither approved nor under development in other countries (49).

Critical care patients represent another category of patients who may effectively benefit from vaptan treatment. In fact, hyponatremia is a common problem in patients in intensive care units (prevalence, 30–40%), where it is frequently caused by SIAD and is associated with increased duration of hospital stay and increased morbidity and mortality (83). In these patients, vaptan treatment can be used to correct hyponatremia, which is associated with many disease states seen in critically ill patients that are direct causes of SIAD, including serious infections, pneumonia or other lung injuries, and pain. The iv agent conivaptan may be used in patients (in the United States) who cannot tolerate oral medications.

The general rules that should be strictly followed in the correction of hyponatremia with active therapies apply also to patients treated with vaptans. Therefore, serum [Na^+] should be monitored frequently (every 4–6 h) to prevent overly rapid correction of hyponatremia and reduce the risk of osmotic demyelination syndrome. Active therapy should be stopped if the rate of correction exceeds 12 mmol/L within 24 h or 18 mmol/L within 48 h. These limits should be reduced to 8 mmol/L within 12 h and 12 mmol/L within 48 h in patients with risk factors for developing central pontine myelinosis (eg, malnutrition, alcoholism, very low serum [Na^+], and hypokalemia) (84). The risks associated with overly rapid correction have been brilliantly highlighted by Thomas Berl in his article appropriately titled "Treating hyponatremia: damned if we do and damned if we don't" (85). Marketed vaptans have a <12-h half-life, and daily or continuous administration is required to maintain activity. Therefore, the increase in serum [Na^+] can be limited by stopping the drug or reducing the dose; when necessary, hypotonic fluid should be infused to counteract an excessive serum [Na^+] increase (13). Although the safety data regarding vaptans are rather reassuring, some variability in the magnitude of the response has been observed, and in patients with serum [Na^+] ≤120 mmol/L greater responses have been documented, thus suggesting the possibility to use lower doses compared to those that have been officially approved (Table 4). In one study reporting data on patients with SIAD

treated with iv conivaptan, for instance, lower serum [Na^+] was associated with a greater increase 24 h after initiation of therapy (86). In addition, baseline blood urea nitrogen, glomerular filtration rate, and creatinine clearance also showed a significant correlation with the absolute increase in serum [Na^+] at 24 h, and low blood urea nitrogen and hyperfiltration were predictors of a greater response. With regard to safety, recently both the FDA and the EMA have reinforced recommendations about fluid and electrolyte monitoring in patients treated with tolvaptan (FDA and EMA) or conivaptan (FDA), together with warnings on concomitant use of other treatments for hyponatremia, in order to avoid overly rapid and/or excessive corrections. These recommendations followed the acknowledgment of the occurrence of osmotic demyelination syndrome in association with tolvaptan treatment by the FDA. However, a causal relationship to drug exposure has not been clearly established, and the neurological sequelae might have been caused by improper treatment strategies.

Another practical issue to be considered is the interaction between vaptans and other drugs. Vaptans are metabolized by cytochrome CYP_3A_4, and therefore caution should be exercised in case of coadministration of CYP_3A_4 inhibitors (eg, ketoconazole, macrolide antibiotics, diltiazem) or inducers (eg, rifampicin, barbiturates), which increase or reduce serum concentrations of vaptans, respectively (87). Grapefruit is a potent inhibitor of CYP_3A_4, and it has been demonstrated that grapefruit juice increases the bioavailability of tolvaptan (mean maximal concentration: 1.86-fold increase) (88). Thus, patients taking these drugs should avoid ingesting grapefruit or grapefruit juice. Tolvaptan treatment did not have any effect on serum concentrations of other CYP_3A_4 substrates, such as warfarin or amiodarone (89). Serum digoxin concentrations have been found to be increased (mean maximal concentration: 1.27-fold increase) during coadministration of multiple (16 d) once daily 60-mg doses of tolvaptan (90). Patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with vaptans.

The duration of treatment with tolvaptan, which is currently the only V_2 receptor antagonist available also for chronic use, may vary based on several issues, including the etiology of hyponatremia, the chronicity of the underlying disease, the response to the drug, its tolerability, and the coadministration of other drugs with lowering effects on serum [Na^+]. In patients with SIAD, for instance, the underlying etiology may predict the duration of tolvaptan requirement. In fact, in patients with paraneoplastic, drug-induced (without discontinuation of the offending drug), or idiopathic SIAD, the likely duration of this condition is indefinite. In other situations, SIAD may be a temporary condition, limited to a few weeks (eg, after subarachnoid hemorrhage, stroke) or even a few days (eg, in postoperative hyponatremia, pneumonia), and a temporary treatment with tolvaptan may be foreseen.

An important issue about the use of drugs, particularly newly marketed drugs, is the cost/effectiveness analysis. A retrospective cohort analysis showed that the length of stay (LOS) in the hospital was 2 days longer for patients admitted with hyponatremia, and admittance to the intensive care unit was 10% higher for patients with moderate-to-severe hyponatremia compared with normonatremic patients (91). Another large retrospective analysis reported that patients with hyponatremia had an 18% increase in total healthcare costs compared to patients without hyponatremia (3). An analysis of the impact of hyponatremia on 1-year direct medical costs using longitudinal data from a large managed care claims database in the United States (National Managed Care Benchmark Database) showed a 45.7% increase in hyponatremic vs normonatremic patients (92). Another study reported that in a high-risk population of patients hospitalized for CHF, the hospitalization costs attributed to hyponatremia were increased up to more than $1000 in patients with severe hyponatremia (93). The post hoc analysis of the LOS in the hospital in patients with hyponatremia secondary to SIAD enrolled in the SALT-1 and SALT-2 trials revealed a trend toward a reduced LOS in the tolvaptan group (mean, 4.98 d) compared to the placebo group (mean, 6.19 d) (51). The post hoc analysis of the EVEREST trial showed that patients with hyponatremia treated with tolvaptan had a 15% decreased LOS in comparison with patients given placebo (94). Admittedly, the crucial question remains whether treatment with vaptans may be associated with hospital cost savings. To this purpose, two economic models based on the results of the SALT-1/SALT-2 and EVEREST trials have been constructed. The LOS reduction revealed by the post hoc analyses of these trials was applied to the associated costs and resource usage of a US study population from the Nationwide Inpatient Sample database. These models predicted an estimated cost offset associated with tolvaptan treatment of $694 per admission and $15 million/year for patients with SIAD, based on the SALT-1/SALT-2 trials (95), and of $265 per admission and $21 million/year for hyponatremic patients with CHF, based on the EVEREST trial (96).

Vaptans: Future Perspectives

Vaptans appeared to hold their initial promises and have been generally recognized in the last few years as an ad-

ditional effective and safe tool for the correction of euvolemic or hypervolemic forms of hyponatremia. It may be true, as Peter Gross, Andrea Wagner, and Guy Decaux titled their review article on vaptans in 2011, that "vaptans are not the mainstay of treatment in hyponatremia: perhaps not yet" (97). However, the issues raised by these authors about the exact indications for vaptans, the effects on LOS in the hospital and on mortality, the cost/effectiveness analysis, and the optimal regimen have been at least partially solved or are being thoroughly investigated. Nevertheless, more comparative research of vaptans vs other therapies and analyses of patients treated with these drugs on clinical grounds are needed to better determine the benefits on patient outcome and more accurately assess the exact role and the value of vaptans in the treatment of hyponatremia. With regard to this point, real-life cost/benefit analyses will be also needed.

Although it is beyond the aim of this review, which is addressed to endocrinologists, it is worth mentioning finally that another possible area of application of vaptans may be polycystic kidney disease (PKD), which remains an unsolved medical problem. OPC-31260 and tolvaptan have been effective in reducing cAMP levels in kidney epithelial cells and cystogenesis in PKD models (98–100). Several clinical studies investigating the effects of tolvaptan in autosomal dominant PKD (ADPKD) have been performed under the Tolvaptan Efficacy and Safety in Management of ADPKD and Outcomes (TEMPO) program. Very recently, the results of a phase 3, multicenter, double-blind, placebo-controlled, 3-year trial within the TEMPO program were published (101). Tolvaptan (average dose, 95 mg/d) significantly slowed the increase in total kidney volume and the decline in kidney function, compared to placebo. However, a higher discontinuation rate was observed in patients receiving tolvaptan compared to the placebo group (23 vs 13.8%, respectively), mostly due to the effect on aquaresis and to elevation of liver-enzyme levels, which returned to baseline after discontinuation of the drug. Therefore, at this time the potential benefit of tolvaptan in patients with ADPKD needs to be further weighted against risks.

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References

1. **Hoorn EJ, Lindemans J, Zietse R.** Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. *Nephrol Dial Transplant*. 2006;21:70–76.
2. **Ellison DH, Berl T.** Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med*. 2007;356:2064–2072.
3. **Zilberberg MD, Exuzides A, Spalding J, et al.** Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. *Curr Med Res Opin*. 2008;24:1601–1608.
4. **Waikar SS, Mount DB, Curhan GC.** Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med*. 2009;122:857–865.
5. **Wald R, Jaber BR, Price LL, Upadhyay A, Madias NE.** Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med*. 2010;170:294–302.
6. **Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G.** Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med*. 2006;119:71.e1–e8.
7. **Miyazaki T, Ohmoto K, Hirose T, Fujiki H.** Chronic hyponatremia impairs memory in rats: effects of vasopressin antagonist tolvaptan. *J Endocrinol*. 2010;206:205–211.
8. **Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA.** Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clin J Am Soc Nephrol*. 2010;5:275–280.
9. **Verbalis JG, Barsony J, Sugimura Y, et al.** Hyponatremia-induced osteoporosis. *J Bone Miner Res*. 2010;25:554–563.
10. **Barsony J, Sugimura Y, Verbalis JG.** Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. *J Biol Chem*. 2011;25:10864–10875.
11. **Barsony J, Manigrasso MB, Xu Q, Tam H, Verbalis JG.** 2012 Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. Age (Dordr). Published Online: January 5, 2012 (doi:10.1007/s11357-011-9347-9).
12. **Dasta JF, Chiong JR, Christian R, et al.** Update on tolvaptan for the treatment of hyponatremia. *Expert Rev Pharmacoecon Outcomes Res*. 2012;12:399–410.
13. **Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH.** Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med*. 2007;120:S1–S21.
14. **Peri A, Pirozzi N, Parenti G, Festuccia F, Menè P.** Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Endocrinol Invest*. 2010;33:671–682.
15. **Peri A, Combe C.** Considerations regarding the management of hyponatraemia secondary to SIADH. *Best Pract Res Clin Endocrinol Metab*. 2012;26:S16–S26.
16. **Goldberg M.** Hyponatremia. *Med Clin North Am*. 1981;65:251–269.
17. **Oliver G, Schäfer EA.** On the physiological action of extracts of pituitary body and certain other glandular organs: preliminary communication. *J Physiol*. 1895;18:277–279.
18. **Howell WH.** The physiological effects of extracts of the hypophysis cerebri and infundibular body. *J Exp Med*. 1898;3:245–258.
19. **Farini F.** Diabete insipido ed opoterapia. *Gazz Osped Clin*. 1913;34:1135–1139.

20. **Von Den Velden R.** Die Nierenvirkung von Hypophysenextracten beim Menschen. *Berl KlinWochenschr*. 1913;50:2083–2086.
21. **Turner RA, Pierce JG, du Vigneaud V.** The purification and the amino acid content of vasopressin preparations. *J Biol Chem*. 1951;191:21–28.
22. **du Vigneaud V, Gash DT, Katsoyannis PG.** A synthetic preparation possessing biological properties associated with arginine-vasopressin. *J Am Chem Soc*. 1954;76:4751–4752.
23. **Chan WY, Hruby VJ, Flouret G, du Vigneuad V.** 4-Leucine-oxytocin: natriuretic, diuretic, and antivasopressin polypeptide. *Science*. 1968;161:280–281.
24. **Chan WY, du Vigneaud V.** Natriuretic, diuretic and anti-arginine-vasopressin (ADH) effects of two analogs of oxytocin: [4-leucine]-oxytocin and [2,4-diisoleucine]-oxytocin. *J Pharmacol Exp Ther*. 1970;174:541–549.
25. **Kinter LB, Huffman WF, Stassen FL.** Antagonists of the antidiuretic activity of vasopressin. *Am J Physiol*. 1988;254:F165–F177.
26. **Allison NL, Albrightson-Winslow CR, Brooks DP, et al.** 1988 Species heterogeneity and antidiuretic hormone antagonists: what are the predictors? In: Cowley AW, Liard JF, Ausiello DA, eds. *Vasopressin: Cellular and Integrative Functions*. New York: Raven Press Ltd.; 207–214.
27. **Brooks DP, Koster PF, Albrightson-Winslow CR, Stassen FL, Huffman WF, Kinter LB.** SK&F 105494 is a potent antidiuretic hormone antagonist in the rhesus monkey (*Macaca mulatta*). *J Pharmacol Exp Ther*. 1988;245:211–215.
28. **Mah SC, Hofbauer KG.** Evaluation of the pharmacologic properties of a vasopressin antagonist in Brattleboro rats. *J Pharmacol Exp Ther*. 1988;245:1028–1032.
29. **Albrightson-Winslow CR, Caldwell N, Brooks DP, Huffman WF, Stassen FL, Kinter LB.** Cyclooxygenase inhibition unmasks the full antidiuretic agonist activity of the vasopressin antagonist, SK&F 101926, in dogs. *J Pharmacol Exp Ther*. 1989;249:366–371.
30. **Yamamura Y, Ogawa H, Chihara T, et al.** OPC-21268, an orally effective, nonpeptide vasopressin V1 receptor antagonist. *Science*. 1991;252:572–574.
31. **Yamamura Y, Ogawa H, Yamashita H, et al.** Characterization of a novel aquaretic agent, OPC-31260, as an orally effective, nonpeptide vasopressin V_2 receptor antagonist. *Br J Pharmacol*. 1992;105:787–791.
32. **Ohnishi A, Orita Y, Okahara R, et al.** Potent aquaretic agent. A novel nonpeptide selective vasopressin 2 antagonist (OPC-31260) in men. *J Clin Invest*. 1993;92:2653–2659.
33. **Serradeil-Le Gal C, Wagnon J, Garcia C, et al.** Biochemical and pharmacological properties of SR 49059, a new, potent, nonpeptide antagonist of rat and human vasopressin V1a receptors. *J Clin Invest*. 1993;92:224–231.
34. **Freidinger RM, Pettibone DJ.** Small molecule ligands for oxytocin and vasopressin receptors. *Med Res Rev*. 1997;17:1–16.
35. **Tahara A, Tomura Y, Wada KI, et al.** Pharmacological profile of YM087, a novel potent nonpeptide vasopressin V1A and V2 receptor antagonist, in vitro and in vivo. *J Pharmacol Exp Ther*. 1997;282:301–308.
36. **Yamamura Y, Nakamura S, Itoh S, et al.** OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. *J Pharmacol Exp Ther*. 1998;287:860–867.
37. **de Goma EM, Vagelos RH, Fowler MB, Ashley EA.** Emerging therapies for the management of decompensated heart failure: from bench to bedside. *J Am Coll Cardiol*. 2006;48:2397–2409.
38. **Robertson GL.** Vaptans for the treatment of hyponatremia. *Nat Rev Endocrinol*. 2011;7:151–161.
39. **Ghali JK, Koren MJ, Taylor JR, et al.** Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab*. 2006;91:2145–2152.
40. **Annane D, Decaux G, Smith N; Conivaptan Study Group.** Efficacy and safety of oral conivaptan, a vasopressin-receptor antagonist, evaluated in a randomized, controlled trial in patients with euvolemic or hypervolemic hyponatremia. *Am J Med Sci*. 2009;337:28–36.
41. **Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N; Conivaptan Study Group.** Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *Am J Nephrol*. 2007;27:447–457.
42. **Wong F, Blei AT, Blendis LM, Thuluvath PJA.** A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. *Hepatology*. 2003;37:182–191.
43. **Schrier RW, Gross P, Gheorghiade M, et al; SALT Investigators.** Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099–2112.
44. **Berl T, Quittnat-Pelletier F, Verbalis JG, et al; SALTWATER Investigators.** Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol*. 2010;21:705–712.
45. **Gheorghiade M, Gottlieb SS, Udelson JE, et al; Tolvaptan Investigators.** Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol*. 2006;97:1064–1067.
46. **Feldman BJ, Rosenthal SM, Vargas GA, et al.** Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med*. 2005;352:1884–1890.
47. **Soupart A, Gross P, Legros JJ, et al.** Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V2-receptor antagonist. *Clin J Am Soc Nephrol*. 2006;1:1154–1160.
48. **Verbalis JG, Zeltser D, Smith N, Barve A, Andoh M.** Assessment of the efficacy and safety of intravenous conivaptan in patients with euvolaemic hyponatraemia: subgroup analysis of a randomized, controlled study. *Clin Endocrinol (Oxf)*. 2008;69:159–168.
49. **Yamaguchi K, Shijubo N, Kodama T, et al; Ectopic ADH Syndrome Therapeutic Research Group.** Clinical implication of the antidiuretic hormone (ADH) receptor antagonist mozavaptan hydrochloride in patients with ectopic ADH syndrome. *Jpn J Clin Oncol*. 2011;41:148–152.
50. **Kenz S, Haas CS, Werth SC, Bohnet S, Brabant G.** High sensitivity to tolvaptan in paraneoplastic syndrome of inappropriate ADH secretion (SIADH). *Ann Oncol*. 2011;22:2696.
51. **Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS; SALT Investigators.** Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *Eur J Endocrinol*. 2011;164:725–732.
52. **Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G.** Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol*. 2012;7:742–747.
53. **Decaux G.** Long-term treatment of patients with inappropriate secretion of antidiuretic hormone by the vasopressin receptor antagonist conivaptan, urea, or furosemide. *Am J Med*. 2001;110:582–584.
54. **Gheorghiade M, Niazi I, Ouyang J, et al; Tolvaptan Investigators.** Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation*. 2003;107:2690–2696.
55. **Abraham WT, Shamshirsaz AA, McFann K, Oren RM, Schrier RW.** Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. *J Am Coll Cardiol*. 2006;47:1615–1621.
56. **Rossi J, Bayram M, Udelson JE, et al.** Improvement in hyponatremia during hospitalization for worsening heart failure is associated with improved outcomes: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. *Acute Card Care*. 2007;9:82–86.

57. **Konstam MA, Gheorghiade M, Burnett JC Jr, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators.** Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297:1319–1331.
58. **Udelson JE, Smith WB, Hendrix GH, et al.** Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation*. 2001;104:2417–2423.
59. **Udelson JE, Orlandi C, Ouyang J, et al.** Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: an international, multicenter, randomized, placebo-controlled trial. *J Am Coll Cardiol*. 2008;52:1540–1545.
60. **Pang PS, Gheorghiade M, Dihu J, et al.** Effects of tolvaptan on physician-assessed symptoms and signs in patients hospitalized with acute heart failure syndromes: analysis from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) trials. *Am Heart J*. 2011;161:1067–1072.
61. **Vaduganathan M, Gheorghiade M, Pang PS, et al; EVEREST Investigators.** Efficacy of oral tolvaptan in acute heart failure patients with hypotension and renal impairment. *J Cardiovasc Med (Hagerstown)*. 2012;13:415–422.
62. **Aronson D, Verbalis JG, Mueller M, Krum H; DILIPO investigators.** Short- and long-term treatment of dilutional hyponatraemia with satavaptan, a selective arginine vasopressin V2-receptor antagonist: the DILIPO study. *Eur J Heart Fail*. 2011;13:327–336.
63. **Matsuzaki M, Hori M, Izumi T, Asanoi H, Tsutamoto T; Tolvaptan Investigators.** Effects of tolvaptan on volume overload in Japanese patients with heart failure: results of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Cardiovasc Drugs Ther*. 2011;25(suppl 1):S19–S31.
64. **Matsuzaki M, Hori M, Izumi T, Fukunami M; Tolvaptan Investigators.** Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST study). *Cardiovasc Drugs Ther*. 2011; 25(suppl 1):S33–S45.
65. **Inomata T, Izumi T, Matsuzaki M, Hori M, Hirayama A; Tolvaptan Investigators.** Phase III clinical pharmacology study of tolvaptan. *Cardiovasc Drugs Ther*. 2011;25(suppl 1):S57–S65.
66. **Goldsmith SR, Gilbertson DT, Mackedanz SA, Swan SK.** Renal effects of conivaptan, furosemide, and the combination in patients with chronic heart failure. *J Card Fail*. 2011;17:982–989.
67. **Udelson JE, Bilsker M, Hauptman PJ, et al.** A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. *J Card Fail*. 2011;17:973–981.
68. **Inoue T, Ohnishi A, Matsuo A, et al.** Therapeutic and diagnostic potential of a vasopressin-2 antagonist for impaired water handling in cirrhosis. *Clin Pharmacol Ther*. 1998;63:561–570.
69. **Guyader D, Patat A, Ellis-Grosse EJ, Orczyk GP.** Pharmacodynamic effects of a nonpeptide antidiuretic hormone V2 antagonist in cirrhotic patients with ascites. *Hepatology*. 2002;36:1197–1205.
70. **Ginès P, Wong F, Watson H, et al; NormoCAT Study Investigators.** Clinical trial: short-term effects of combination of satavaptan, a selective vasopressin V2 receptor antagonist, and diuretics on ascites in patients with cirrhosis without hyponatraemia—a randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2010;31:834–845.
71. **Wong F, Gines P, Watson H, et al.** Effects of a selective vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. *J Hepatol*. 2010;53:283–290.
72. **Okita K, Sakaida I, Okada M, et al.** A multicenter, open-label, dose-ranging study to exploratively evaluate the efficacy, safety, and dose-response of tolvaptan in patients with decompensated liver cirrhosis. *J Gastroenterol*. 2010;45:979–987.
73. **Wong F, Watson H, Gerbes A, et al; Satavaptan Investigators Group.** Satavaptan for the management of ascites in cirrhosis: efficacy and safety across the spectrum of ascites severity. *Gut*. 2012; 61:108–116.
74. **Ginès P, Wong F, Watson H, Milutinovic S, del Arbol LR, Olteanu D; HypoCAT Study Investigators.** Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: a randomized trial. *Hepatology*. 2008;48:204–213.
75. **Cárdenas A, Ginès P, Marotta P, et al.** Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. *J Hepatol*. 2012;56:571–578.
76. **Verbalis JG, Hoorn EJ.** The use of an algorithm to aid diagnosis and treatment of patients with hyponatraemia secondary to SIADH. In: Program of the 12th European Congress of Endocrinology; April 24–28, 2010; Prague, Czech Republic. Abstract P209.
77. **Furst H, Hallows KR, Post J, et al.** The urine/plasma electrolyte ratio: a predictive guide to water restriction. *Am J Med Sci*. 2000; 319:240–244.
78. **Castillo JJ, Vincent M, Justice E.** Diagnosis and management of hyponatremia in cancer patients. *Oncologist*. 2012;17:756–765.
79. **Hansen O, Sørensen P, Hansen KH.** The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. *Lung Cancer*. 2010;68:111–114.
80. **Sørensen JB, Andersen MK, Hansen HH.** Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. *J Intern Med*. 1995;238:97–110.
81. **Kirch C, Gachot B, Germann N, Blot F, Nitenberg G.** Recurrent ifosfamide-induced hyponatraemia. *Eur J Cancer*. 1997;33:2438–2439.
82. **Kleta R, Wagner A, Jürgens H.** Recurrence of SIADH after a high-dose regimen of thiotepa, carboplatin, and etoposide phosphate. *Med Pediatr Oncol*. 1998;31:129.
83. **Friedman B, Cirulli J.** Hyponatremia in critical care patients: frequency, outcome, characteristics, and treatment with the vasopressin V(2)-receptor antagonist tolvaptan. *J Crit Care*. Published Online: August 8, 2012 (doi:10.1016/j.jcrc.2012.06.001).
84. **Adrogué HJ, Madias NE.** Hyponatremia. *N Engl J Med*. 2000; 342:1581–1589.
85. **Berl T.** Treating hyponatremia: damned if we do and damned if we don't. *Kidney Int*. 1990;37:1006–1018.
86. **Velez JC, Dopson SJ, Sanders DS, Delay TA, Arthur JM.** Intravenous conivaptan for the treatment of hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone in hospitalized patients: a single-centre experience. *Nephrol Dial Transplant*. 2010;25:1524–1531.
87. **Shoaf SE, Bricmont P, Mallikaarjun S.** Effects of CYP3A4 inhibition and induction on the pharmacokinetics and pharmacodynamics of tolvaptan, a non-peptide AVP antagonist in healthy subjects. *Br J Clin Pharmacol*. 2012;73:579–587.
88. **Shoaf SE, Mallikaarjun S, Bricmont P.** Effect of grapefruit juice on the pharmacokinetics of tolvaptan, a non-peptide arginine vasopressin antagonist, in healthy subjects. *Eur J Clin Pharmacol*. 2012; 68:207–211.
89. **Shoaf SE, Elizari MV, Wang Z, et al.** Tolvaptan administration does not affect steady state amiodarone concentrations in patients with cardiac arrhythmias. *J Cardiovasc Pharmacol Ther*. 2005;10: 165–171.
90. **Shoaf SE, Ohzone Y, Ninomiya S, et al.** In vitro P-glycoprotein interactions and steady-state pharmacokinetic interactions between tolvaptan and digoxin in healthy subjects. *J Clin Pharmacol*. 2011;51:761–769.
91. **Callahan MA, Do HT, Caplan DW, Yoon-Flannery K.** Economic impact of hyponatremia in hospitalized patients: a retrospective cohort study. *Postgrad Med*. 2009;121:186–191.

92. **Shea AM, Hammill BG, Curtis LH, Szczech LA, Schulman KA.** Medical costs of abnormal serum sodium levels. *J Am Soc Nephrol*. 2008;19:764–770.
93. **Shorr AF, Tabak YP, Johannes RS, Gupta V, Saltzberg MT, Costanzo MR.** Burden of sodium abnormalities in patients hospitalized for heart failure. *Congest Heart Fail*. 2011;17:1–7.
94. **Cyr PL, Slawsky KA, Olchanski N, et al.** Effect of serum sodium concentration and tolvaptan treatment on length of hospitalization in patients with heart failure. *Am J Health Syst Pharm*. 2011;68:328–333.
95. **Dasta JF, Chiong JR, Christian R, Lin J.** Evaluation of costs associated with tolvaptan-mediated hospital length of stay reduction among US patients with the syndrome of inappropriate antidiuretic hormone secretion, based on SALT-1 and SALT-2 trials. *Hosp Pract (Minneap)*. 2012;40:7–14.
96. **Chiong JR, Kim S, Lin J, Christian R, Dasta JF.** Evaluation of costs associated with tolvaptan-mediated length-of-stay reduction among heart failure patients with hyponatremia in the US, based on the EVEREST trial. *J Med Econ*. 2012;15:276–284.
97. **Gross PA, Wagner A, Decaux G.** Vaptans are not the mainstay of treatment in hyponatremia: perhaps not yet. *Kidney Int*. 2011;80:594–600.
98. **Gattone VH II, Wang X, Harris PC, Torres VE.** Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med*. 2003;9:1323–1326.
99. **Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH II.** Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. *Nat Med*. 2004;10:363–364.
100. **Wang X, Wu Y, Ward CJ, Harris PC, Torres VE.** Vasopressin directly regulates cyst growth in polycystic kidney disease. *J Am Soc Nephrol*. 2008;19:102–108.
101. **Torres VE, Chapman AB, Devuyst O, et al; the TEMPO 3:4 Trial Investigators.** Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367:2407–2418.