

# Vaptans: A Potential New Approach for Treating Chronic Hyponatremia in Psychotic Patients

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## Abstract

**Objective:** Hyponatremia (serum sodium concentration [Na<sup>+</sup>] <136 mEq/L) is a potentially life-threatening condition often found chronically in patients with psychotic disorders. Vasopressin antagonists have recently been shown in short-term studies to correct hyponatremia in diverse patient populations, including individuals with both psychosis and idiopathic hyponatremia. However, the safety and efficacy of long-term administration of vaptans is only beginning to be investigated. The objective of this study was to assess whether one of the vaptans, specifically tolvaptan, maintained its safety and efficacy over a prolonged period in patients with psychosis and chronic idiopathic hyponatremia. **Methods:** SALTWATER was a multicenter, open-label extension of the Study of Ascending Levels of Tolvaptan in Hyponatremia. Of the 111 patients enrolled in SALTWATER, eight were patients with both psychosis and idiopathic hyponatremia. These eight subjects provided a total of 7,406 patient days of exposure to oral tolvaptan. **Results:** Mean serum [Na<sup>+</sup>] in the eight psychotic patients increased from 131.6 mEq/L at baseline to >135 mEq/L throughout the observation period ( $p < 0.05$  versus baseline at most points). No drug-related adverse events led to study discontinuation. **Conclusions:** Chronic hyponatremia is known to have deleterious effects on the quality of life for many patient groups. These preliminary results suggest that oral tolvaptan provides rapid, effective, and safe treatment of chronic hyponatremia in patients with psychotic disorders and that the effect is safely sustained over long periods of time. These findings represent an important step forward in treating a significant unmet need in psychotic populations.

**Key Words:** Hyponatremia, Schizophrenia, Vaptans, Vasopressin Antagonists, Tolvaptan

## Introduction

Chronic hyponatremia (serum sodium concentration [Na<sup>+</sup>] <136 mEq/L) is a common electrolyte disorder observed in patients with psychotic illnesses (1, 2). The reported prevalence rates from long-term psychiatric institutions range from 1 to 7.9% depending on the clinical setting, definition of hyponatremia and, most importantly, the methods used to diagnose hyponatremia (3). Most likely, the prevalence rates are somewhat lower among community-based samples; however, the actual rate is unknown as no prevalence data have been published on psychotic outpatient samples. Early manifestations of the disorder (e.g., headache, nausea, lethargy, restlessness, confusion) are nonspecific and can be mistaken for aspects of the primary

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### Clinical Implications

Hyponatremia is not uncommon in patients with psychotic disorders (3, 21). It is associated with increased rates of morbidity and mortality in this population, and accumulating data suggest that it confers increased risk for cognitive dysfunction and falls (5, 6), as well as for osteoporosis and fractures (7, 8). It may be the case that vaptans will provide an effective and safe way to increase serum  $[Na^+]$  in this population over the long-term. However, most of the vaptan studies to date have been of relatively short duration and focused on disorders other than psychosis. Thus, there are many questions that remain unexplored, such as the most appropriate way to use this new class of drugs in psychotic patients with hyponatremia, their long-term response rates, and whether correction of chronic hyponatremia will result in improved cognition, functional status, and quality of life. As reported here, our preliminary results suggest that oral tolvaptan provides rapid, effective, and safe treatment of chronic hyponatremia in patients with psychotic disorders and that the effect is safely sustained over long periods of time. These findings represent an important step forward in treating a significant unmet need in psychotic populations.

psychotic disorder itself (2). As a result, chronic hyponatremia in the psychiatric context often goes unrecognized and unmanaged until the patient becomes severely agitated or has a seizure secondary to a precipitous drop in serum  $[Na^+]$ . Fluid restriction has been the treatment of choice for chronic hyponatremia to avoid worsening of the clinical condition (4, 5), but the potential therapeutic benefits of this approach are often undermined by poor patient compliance in psychotic populations. Moreover, the approach is slow to work and difficult to fine-tune. Others have suggested treatment with oral sodium chloride tablets (6) or electrolyte-containing beverages (7). Oral sodium chloride tablets transiently appear to improve hyponatremia, but there is little evidence of the efficacy of electrolyte-containing drinks. Sodium supplementation is usually suboptimal because the essential pathophysiology is water retention rather than salt depletion. When fluid restriction or sodium supplementation fails to normalize serum  $[Na^+]$ , most psychiatrists do not initiate further treatment (e.g., sodium supplementation, loop diuretics, demeclocycline) due to the prevailing view that mild to moderate chronic hyponatremia is benign.

However, mild chronic hyponatremia may not be benign. A small, but growing body of recent research suggests that mild hyponatremia is associated with gait and attentional impairment contributing to an increased rate of falls (8, 9), decreased bone mineral density and increased bone fragility (10, 11), and elevated risk for subsequent development of “acute” hyponatremia (5, 12). Thus, if not effectively treated, chronic hyponatremia can have a negative impact on therapeutic outcomes and long-term quality of life in this population (1, 2). For example, a recently published 20-year mortality study found that, on average, the life expectancy of schizophrenic patients with polydipsia and accompanying hyponatremia is a decade shorter than that of schizophrenic patients with normal fluid regulation (13). These mortality findings in schizophrenia are in line with results from a much larger prospective study ( $n=98,411$  adult medical patients), which showed that patients with hyponatremia are

at increased risk of death in hospital, at 1 year and at 5 years, even in cases with mild hyponatremia (14).

In light of these findings, the recent demonstrations that short-term use of vasopressin antagonists (known as “vaptans”) effectively treats hyponatremia are a very hopeful development. Several members of the “vaptan” drug family (conivaptan, satavaptan, tolvaptan, and lixivaptan) have now been reported to increase serum  $[Na^+]$  in patients with hyponatremia (15). Two have received FDA approval for the treatment of hyponatremia: conivaptan (brand name Vaprisol) was approved in 2004 for intravenous (IV) use for just four days maximum; tolvaptan (brand name Samsca) was approved in 2009 for use as an oral tablet. Of particular interest are findings from the pivotal Study of Ascending Levels of Tolvaptan (SALT) trial that established the short-term (30 days) efficacy of oral tolvaptan in raising and maintaining serum  $[Na^+]$  in patients with hyponatremia from various causes, including congestive heart failure, liver failure, and the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) (16). Also included in the SALT study were 19 subjects with schizophrenia or schizoaffective disorder as well as idiopathic hyponatremia. A separate analysis of this subgroup of psychotic patients confirmed that short-term treatment with tolvaptan was effective in this population (17). These short-term findings are encouraging, but unfortunately little information has been available about long-term efficacy and safety of tolvaptan in treating chronic hyponatremia. This is the more pressing treatment concern among psychotic patients, as most cases of hyponatremia in this population are chronic.

At the conclusion of SALT, a four-year open-label study (SALTWATER) was launched. The objective was to determine whether tolvaptan maintained its efficacy and safety profile over a prolonged period of time in hyponatremic patients who had previously participated in the SALT study. Recently published results from this study reveal that improvements in serum  $[Na^+]$  were well maintained over longer periods of time with an acceptable adverse event (AE)

profile (18). This initial SALTWATER report did not specify results from each participating subgroup. Therefore, this report specifically examines whether long-term treatment with tolvaptan maintained its safety and efficacy in the sample of psychotic patients with idiopathic hyponatremia.

## Methods

### Study Population

Of the 111 subjects enrolled in the SALTWATER study, eight had a psychotic disorder with idiopathic hyponatremia and were otherwise medically healthy (see Table 1). All eight subjects were male and recruited as inpatients from two long-term psychiatric hospitals where each had received a Research Diagnostic Criteria (RDC) psychiatric diagnosis. All eight had evidence of impaired water excretion demonstrated either by persistent hyponatremia ( $\leq 135$  mEq/L) despite fluid restriction or standard evidence of SI-ADH (i.e., urine osmolality  $>100$  mOsmoles/Kg with  $[\text{Na}^+] < 130$  mEq/L). The length of time between completion of the SALT study and enrollment in SALTWATER ranged from a minimum of seven days to a maximum of 386 days, with no vaptan treatment during this intervening time period.

**Table 1** Demographic and Baseline Characteristics of SALTWATER Subjects

Variable	Mean (SD)
Age (years)	48.5 (6.7)
Baseline weight (kg)	85.3 (12.2)
Baseline CPZ equivalent (mg)*	1,275 (732.9)
Baseline $[\text{Na}^+]$ (mEq/L)	131.6 (3.6)
Baseline creatinine (mg/dL)	0.92 (0.3)
Baseline urea nitrogen (mg/dL)	8.20 (4.4)
Baseline potassium (mEq/L)	4.43 (0.3)
Baseline glucose (mg/dL)	93.83 (25.7)

\*At baseline, the 8 subjects were receiving antipsychotic medications: risperidone (3 subjects), quetiapine (1), fluphenazine HCL (1), quetiapine & haloperidol (1), olanzapine & fluphenazine decanoate (1), quetiapine, fluphenazine HCL & fluphenazine decanoate (1). CPZ equivalents based on the method of Gardner et al. (19).

For the duration of SALTWATER, all eight subjects remained either hospitalized in a long-term facility or were transferred to highly supervised and locked community-based treatment facilities; in both settings, study medication was administered daily by nursing staff. All eight enrolled subjects completed at least 106 weeks of the study. Two completed the entire 214-week study. Of the six subjects who did not complete the entire study, five were enrolled a year or more after SALTWATER was initiated, and the study was discontinued before the four years could be completed. One subject was withdrawn from the study after he was admitted to a community medical hospital for treatment following a serious fall that resulted in facial lacerations. Because tolvaptan was not yet FDA approved, the hospital did not permit administration of the drug.

The study was conducted in accordance with the generally accepted standards for the protection of patient safety and welfare. All subjects provided consent to participate by signing and dating the informed consent prior to the performance of any protocol procedures.

### Study Design

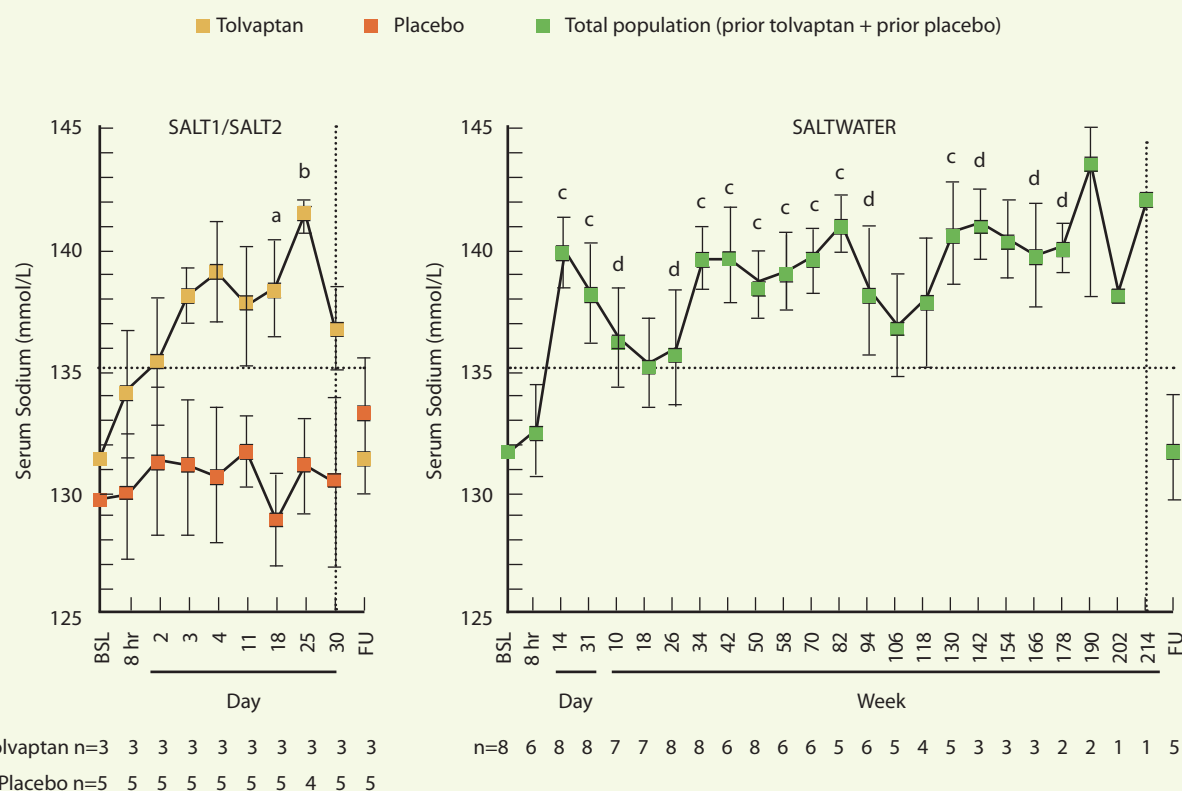
The study procedure has been previously published (18). Briefly, patients were eligible when they participated successfully in the original SALT trial and evidenced a continued need and desire for further therapy with tolvaptan. Subjects were not eligible for SALTWATER if they presented a current medical condition for which long-term treatment with an aquaretic agent posed an undue risk (e.g., pregnancy, urinary flow obstruction); hyponatremia that was acute and reversible (e.g., polydipsia, hypothyroidism), artifactual, or due to conditions not associated with arginine vasopressin excess and, therefore, unlikely to respond to aquaretic therapy; severe renal impairment (e.g., creatinine  $>3.5$  mg/dL); or, a clinical condition with potential to confound results (e.g., poorly controlled diabetes). Initially, subjects were enrolled to receive oral tolvaptan tablets once daily for up to 58 weeks. The study was later extended to a maximum of 214 weeks. The initial tolvaptan dosage was 15 mg, which was increased to 30 mg or 60 mg when the patient continued to be hyponatremic and the change in serum  $[\text{Na}^+]$  was  $<5$  mEq/L relative to a measurement 22 to 24 hours earlier.

### Assessments

Study assessments occurred on Day 1 (pre-dose baseline and 8 hours after first dose), Days 2 through 14 (to end of titration), and Day 31; every 8 weeks from Weeks 10 through 58; every 12 weeks from Weeks 70 through 214; and a follow-up visit 7 days after the last dose of tolvaptan (either after the final study visit or early termination). Safety of long-term tolvaptan was assessed at all visits by collecting AEs, vital signs, ECGs, and physical examinations.

### Results

In the prior SALT study, mean pre-dose baseline serum  $[\text{Na}^+]$  for these eight subjects was 130.3 mEq/L ( $\pm 3.7$ ); mean baseline serum  $[\text{Na}^+]$  for SALTWATER was 131.6 mEq/L ( $\pm 3.6$ ). A modest correction of serum  $[\text{Na}^+]$  was observed at 8 hours posttreatment in SALTWATER (131.6 to 132.5 mEq/L). Thereafter, as seen in Figure 1, improvements in serum  $[\text{Na}^+]$  were well-maintained (between 135–143 mEq/L) over longer periods. Previous treatment with tolvaptan ( $n=3$ ) or placebo ( $n=5$ ) during the SALT study did not appear to alter the long-term efficacy of tolvaptan in SALTWATER (see Table 2).

**Figure 1** Group Mean Serum [Na<sup>+</sup>] Levels for Patients with Psychotic Disorders Enrolled in Both the Double-Blind SALT and Open-Label SALTWATER Trials


BSL indicates group mean serum [Na<sup>+</sup>] on Day 1 prior to dosing, while 8 hr indicates group mean serum [Na<sup>+</sup>] 8 hours post dose on Day 1. The left-hand figure includes only those 8 subjects in the SALT studies with schizophrenia or schizoaffective disorder who continued on into SALTWATER. As previously mentioned, all 8 subjects completed at least 106 weeks of the study, and 2 completed the entire 214-week study. Inconsistent n's reflect subject refusal of blood collection at those time points. Error bars are  $\pm$ SE. BSL=baseline; FU=follow-up visit occurring 7 days after early withdrawal or trial completion.

<sup>a</sup> $p < 0.05$ , tolvaptan vs. placebo; <sup>b</sup> $p < 0.01$ , tolvaptan vs. placebo; <sup>c</sup> $p < 0.01$ , vs. baseline; <sup>d</sup> $p < 0.05$ , vs. baseline.

**Table 2** Analysis of Serum [Na<sup>+</sup>] Change in SALTWATER by Prior Exposure

Treatment Group	Mean Baseline [Na <sup>+</sup> ] (mEq/L and SD)	Change from Baseline (mEq/L) ( $\Delta$ mEq/L and SD)			
		Post Dose 8 hours	Day 14	Day 31	Week 10
Placebo (n=5)	130.4 (3.0)	+3.0 (0.3)	+11.0 (1.8)	+7.6 (0.8)	+6.4 (0.8)
Tolvaptan (n=3)	133.7 (4.2)	+1.7 (0.5)	+7.0 (1.3)	+8.3 (0.9)	+6.7 (0.7)

During SALTWATER, the eight subjects were exposed to tolvaptan for a total of 7,406 patient days and experienced various adverse events (AEs). AEs that occurred with two or more subjects included hyponatremia (4 instances), diarrhea (2), toothache (2), chest pain (2), skin excoriation (2), hand fracture (2), skin laceration (3), and epistaxis (2). The four cases of hyponatremia were due to interruption or discontinuation of tolvaptan. One serious adverse event (SAE)

occurred in which one subject appeared to lose his balance and fell down several stairs. Later that same week he fell on a sidewalk and was admitted to a local community medical hospital for evaluation and treatment of facial lacerations. On admission, the hospital discontinued treatment with tolvaptan, and the subject experienced a precipitous drop in serum [Na<sup>+</sup>]. No subjects were withdrawn from the study due to drug-related adverse events.

## Discussion

Hyponatremia can produce a wide range of disturbances involving almost all body systems (4). If inadequately managed, the condition can negatively impact outcomes associated with chronic disease and have deleterious effects on the overall long-term quality of life. The long-term negative impact has been noted in several chronic diseases, most notably congestive heart failure (20); however, the degree of negative impact on patients with psychosis is also beginning to be appreciated (1, 2, 13). Therefore, the finding that treatment with one of the vaptans is both effective and safe in psychotic patients over long periods of time is a hopeful new development.

As there was no comparison group, treatment effects were assessed relative to baseline serum  $[Na^+]$ . With the exception of the 8-hour post-dose observation, all group mean serum  $[Na^+]$  values remained  $>135$  mEq/L for the duration of the observation period. Drug-related adverse events were minimal. Importantly, the return of serum  $[Na^+]$  to baseline 7 days after study discontinuation suggests that these patients have an irreversible defect in water excretion and that the requirement for treatment is long-term.

These are very interesting preliminary results with important clinical implications; however, they need to be understood within the context of several methodological limitations. First, the sample size is small ( $n=8$ ) and limited to male patients, leaving open the possibility that the treatment effects seen in this group are not representative of what might be observed in a larger, more varied population. Indeed, subject variables such as gender, age, duration of illness and others will need to be carefully explored in larger samples. Second, patients with significant comorbid conditions were excluded for this sample, although these excluded patients likely represent the majority of individuals with schizophrenia. The extent of medical comorbidity in this population and its potential impact on treatment will need to be carefully delineated in order to develop useful treatment guidelines. For example, one patient *not* included in this sample had hyponatremia *as well as* cirrhosis and, although treated with tolvaptan, this patient had serum  $[Na^+]$  values of 118 and 114 at Day 14 and Day 31 of SALTWATER, respectively. Third, interactions between psychotropic drugs and vasopressin antagonists will need thorough analysis.

Hyponatremia is not uncommon in patients with psychotic disorders (3, 21). It is associated with increased rates of morbidity and mortality in this population, and accumulating data suggest that it confers increased risk for cognitive dysfunction and falls (5, 6), as well as for osteoporosis and fractures (7, 8). It may be the case that vaptans will provide an effective and safe way to increase serum  $[Na^+]$  in this population over the long-term. However, most of the vap-

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Unfortunately, this new optimism for treatment is tempered by the current cost of the vaptans. The current average cost of conivaptan (IV only) is over \$500/day; oral tolvaptan costs over \$250/day. This level of expense raises significant cost-benefit considerations and will be a major obstacle to getting the vaptans approved on formularies of state psychiatric facilities. Are there clinical situations that justify the expense of these drugs? Would the availability of vaptans reduce medical costs associated with seizures and other medical complications in some cases? At present, the answers are unknown. Whether the correction of hyponatremia in patients with psychosis will lead to a decrease in length of hospitalization and an increase in long-term survival and chance of recovery awaits the completion of further large-scale studies. The answers will not come easily, but this new class of drugs appears to offer a fresh and hopeful line of clinical investigation aiming to treat this important unmet need in psychotic populations.

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