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The Reply

We appreciate the thoughtful points raised by Gross to our Expert Panel Recommendations, and offer the following responses to the issues he raises:

We agree that most patients with chronic hyponatremia have serum sodium concentrations that are only slightly below the normal range. We do not believe that there are sufficient data to inform recommendations for this important and large group of patients unless such patients are felt to be symptomatic, in which case correction of hyponatremia is recommended. Our review clearly addresses the shortcomings of our current knowledge: "Most studies in hyponatremic patients to date have been of relatively short duration. Thus, the following factors are unknown at present and will require additional studies of long-term therapies of hyponatremia: the most appropriate way to use more effective therapies for chronic treatment of hyponatremia; the long-term response rates associated with hyponatremic therapies; whether the role of water restriction will remain important during chronic use; and whether correction of chronic hyponatremia will result in improved cognitive function, quality of life, or functional status as suggested by 30-day studies of tolvaptan."[1] We consider future studies to assess the impact of more effective chronic treatment of hyponatremia in patients with mild hyponatremia to be a high priority.

We agree that an association between hyponatremia and increased mortality does not prove a cause-and-effect relationship. This point is reiterated throughout our article, and is highlighted in our recommendations for future studies: "Hyponatremia has a strong and independent association with a variety of serious adverse clinical outcomes such as hospitalization rate and mortality. This makes randomized controlled trials of the impact of more effective treatment of chronic hyponatremia a high priority for the many diseases in which chronic hyponatremia is strongly associated with adverse outcomes."[1]

Our article quoted an article that extracted data from the hyponatremic patients who were included in the EVEREST trial.[2] We agree that these results are limited and clearly say so in our article.

We agree, which is why we stated: "Failure to suppress AVP [arginine vasopressin] secretion at osmolalities below the osmotic threshold results in water retention and hyponatremia if the intake of hypotonic fluids is sufficient."[1] However, the volumes of fluid ingested by most hyponatremic patients are not greater than normal daily intakes, as was nicely shown by Gross previously.[3] In the absence of nonosmotic AVP secretion, these volumes can be easily excreted by normal kidneys without producing hyponatremia. Therefore, it can be reasonably argued that nonosmotic AVP secretion is, in fact, the primary cause of most cases of hyponatremia despite "normal" fluid intakes.

We agree that many hyponatremic patients have mixed etiologies, making it difficult in some cases to ascertain the primary cause of the low serum [Na^+]. For this reason, one of us (RHS) routinely treats severely hyponatremic patients with a combined infusion of desmopressin and hypertonic saline, making an assessment of volume status less compelling. However, because this approach has limited data to support it, we recommend both clinical and laboratory evaluations to guide initial therapy. Specifically, in the example provided, a patient with syndrome of inappropriate antidiuretic hormone (SIADH) who develops secondary volume depletion due to vomiting should be initially treated as a hypovolemic patient with appropriate strategies for correcting volume depletion. If this fails, or reaches a plateau in the correction of serum [Na^+], then reassessment should be done at that time to see if the patient is now manifesting a clinical picture that is more consistent with SIADH, with an appropriate modification of therapy. In cases where one is simply uncertain despite careful evaluation, we recommend a short trial of volume repletion with isotonic saline.

The evidence-based data available from clinical trials indicates that the doses of tolvaptan recommended in the Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved labels are both effective and safe, with rates of overly rapid correction $<3\%$. We know of no published data demonstrating the efficacy of

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lower doses as recommended by Gross; if subsequent clinical trials prove lower doses of tolvaptan to be consistently effective, then we would welcome these data. Unlike Gross, all of the authors of our review know of few, if any, colleagues in the US who routinely start initial therapy of SIADH with a lower dose of tolvaptan. The letter by Otsuka in cooperation with the EMA dated May 20, 2013 referred to by Gross and cited in our review warns of the possibility of liver damage at tolvaptan doses used in the clinical trials of polycystic kidney disease. There is no mention of problems with doses of tolvaptan approved for SIADH being "too large."

We could not agree more with Gross that recommendations of experts should not replace well-controlled clinical trials, and clearly state the need for more randomized controlled trials of hyponatremia to answer many of the currently unanswered questions in this area (second point above). In that regard we find it curious that he recommends employing lower doses of tolvaptan when placebo-controlled clinical trials support the doses recommended by the FDA and EMA in the absence of evidence-based data to support his recommendation. Until such data exist, we feel compelled to base our recommendations on the best published evidence available.

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