Letters to the Editor

Oxcarbazepine-Induced Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Sir: The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a relatively rare syndrome that occurs in various circumstances such as central nervous system diseases, cancers, and infections. SIADH is also reported to be associated with use of some psychotropic drugs, e.g., carbamazepine, neuroleptics, tricyclic antidepressants, and, more recently, selective serotonin reuptake inhibitors.[1–4] Common symptoms of SIADH include weakness, lethargy, headache, anorexia, and weight gain. These symptoms may be followed by confusion, convulsions, coma, and death. The early symptoms are vague and nonspecific and may mimic the symptoms of the psychiatric disorder itself.

Case report. Mr. A, a 70-year-old man, was hospitalized for bipolar disorder, manic state (DSM-IV criteria). He had a previous history of prostate hypertrophy and cataract. At admission, there were no pathologic findings on physical examination, serum hematologic and biochemical values, and computerized brain tomography. He was given oxcarbazepine, 150 mg/day (gradually raised to 600 mg/day at the third week). At the sixth week, the patient developed weakness, lethargy, dizziness, nausea, and hiccups. There was no hypotension, dehydration, or edema. Measurements of serum electrolytes revealed significant hyponatremia (sodium, 106 mEq/L; potassium, 4.4 mEq/L), but renal and thyroid functions were normal. Despite the hyponatremia and the patient's adherence to a low-sodium diet, urine sodium was 40 mEq/L. Oxcarbazepine was stopped, and he was given furosemide, 20 mg t.i.d. intravenously, and isotonic saline infusion. He was begun on a normal-sodium diet and fluid restriction.

The diagnosis of SIADH was based on the following data: (1) Serum sodium concentration was 106 mEq/L, and serum osmolality was calculated as 230 mOsm/kg H_2O. (2) Despite the hyponatremia and low-sodium diet, urinary excretion of sodium was 40 mEq/day. (3) There was no hypotension, dehydration, or clinical edema. The clinical condition improved with fluid restriction and a normal-sodium diet.

Serum sodium levels gradually increased to normal values within a week. The patient was begun on lithium, 600 mg/day. During the follow-up period of 4 months, the hyponatremia was not seen again.

Because of its pharmacokinetic advantages and efficacy, oxcarbazepine is suggested to be superior to carbamazepine and considered as the first choice for conditions in which carbamazepine is currently indicated. Oxcarbazepine has similar hyponatremic effects to those of carbamazepine, but whether hyponatremia occurs more often with oxcarbazepine than with carbamazepine is not clear yet.[5] Pendlebury and colleagues[6] showed that the mean plasma sodium level fell from 137.5 to 128.5 mEq/L in patients taking oxcarbazepine. Hyponatremia after the use of oxcarbazepine is usually benign, as long as the acute water intoxication is effectively treated.[7]

Imposed restriction of fluid intake might minimize the degree of hyponatremia.[6] It becomes more important for psychiatric patients because primary polydipsia can be seen in 6% to 17% of hospitalized patients in psychiatry units; 25% to 50% of these patients with polydipsia develop hyponatremia.[8]

Elderly people especially are at increased risk for hyponatremia associated with oxcarbazepine and some of the other psychotropic drugs. Physicians caring for elderly patients should be aware of this potentially serious but reversible adverse effect.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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The Role of Micronutrients as Possible Mood-Stabilizing Agents

Sir: The study by Kaplan et al.[1] and the accompanying commentary by Popper[2] raise intriguing questions regarding the role of micronutrients as possible mood-stabilizing agents. Both the article and the commentary raise appropriate caveats regarding

the limitations of existing research and potential concerns about the use of these nonprescription supplements. Importantly, Dr. Popper notes that, in his clinical experience, "introducing micronutrients too quickly can increase the adverse effects of medications, including agitation…."[2(p934)] Two of the ingredients listed in Appendix 1 of the Kaplan et al. article—chromium and inositol—merit additional comments with respect to their use in bipolar patients. As Kaplan et al. note, chromium has been used as adjunctive treatment in depressed patients,[3] as has inositol.[4] Although some findings have been encouraging, chromium supplementation has been associated, in 1 case, with abnormalities in thinking and concentration,[4] while inositol has been implicated in the induction of mania or hypomania.[5]

Since the E.M.Power+ formulation as described by Kaplan et al. does not specify the *amount* of inositol provided by this supplement, it is impossible for clinicians to calculate what degree of risk is entailed with respect to inducing mania in susceptible patients. (This complication was not reported in the study subjects.). Since the popular media are likely to report the favorable findings of the Kaplan et al. study without reporting potential risks,[6] clinicians must be particularly cautious (as Dr. Popper's comments suggest) in both recommending micronutrients and inquiring as to whether their patients are already using them. Nevertheless, further controlled research is certainly warranted in this promising area.

Dr. Pies reports no financial or other relationship relevant to the subject matter of this letter.

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Drs. Kaplan and Simpson Reply

Sir: We are pleased to respond to the thoughtful questions raised by Dr. Pies regarding the safety of chromium and inositol in E.M.Power+, a nutrient supplement that we found effective in open trials for the treatment of bipolar disorder.[1] This supplement contains 36 ingredients, most of which are micronutrients such as vitamins and minerals. His questions draw attention to reports of adverse effects of micronutrients.

Dr. Pies cites Huszonek's letter[2] describing a patient who reported slowed cognitive processing within 2 hours of taking chromium picolinate on 3 separate occasions. In contrast, no significant adverse effects were reported in 5 patients treated successfully with adjunctive chromium picolinate or chromium polynicotinate combined with antidepressants.[3] We have now exposed approximately 80 adults and children to this supplement as part of ongoing studies and have not seen a single case of cognitive impairment. In general, chromium toxicity is associated with the hexavalent chromium compounds, whereas trivalent chromium (such as that used in E.M.Power+) is an essential mineral, appears to be safe for adults at doses up to 70 mg/day[4] (which is 70 times the amount in E.M.Power+), and is even potentially beneficial for certain health problems such as impaired glucose tolerance.[5] So few adverse effects have been associated with trivalent chromium that the Institute of Medicine did not even establish a Tolerable Upper Limit for it.[6]

Safety and toxicity of micronutrients must be considered with respect to the specific form under consideration, because different chemical forms have significantly different biological effects. For instance, the biological effects of phosphorus are quite different depending on whether it is delivered as phosphoric acid (potentially toxic when ingested) or as an essential element of all nucleic acids. The trivalent chromium in E.M.Power+ is an amino acid chelate, and so cannot be directly compared with the picolinate or polynicotinate forms. It appears that the patient in Huszonek's case report experienced an idiosyncratic reaction to a form of chromium that has little relevance for the nutrient supplement we are studying.

Dr. Pies was also concerned about the dose of inositol, whose psychotropic effects when used in monotherapy have been demonstrated at doses ranging from 6 to 18 g/day.[7,8] Although the inositol in E.M.Power+ is part of the proprietary portion of the blend whose amounts are unspecified, the manufacturer has given us permission to reveal that it is present at a level well below 500 mg/day. The cases described in Levine and colleagues' letter[9] involved 3 patients who took 27, 9, and 3 g daily. Two of the patients were taking concurrent antidepressants, and the third patient had just stopped antidepressant treatment (a maneuver that Levine et al. observe is known by itself to induce mania). Rather than demonstrating that inositol can induce mania, these 3 cases might instead illustrate the potentiation of the adverse effects of the psychiatric drugs by micronutrients, a phenomenon discussed by Popper.[10] It is not possible to conclude from the 3 cases described by Levine et al. that inositol itself was responsible for the induction of mania, a point that he and his colleagues acknowledged by ending the title of their letter with a question mark.

While inositol might interact with antidepressants to induce mania, it is unlikely that inositol at doses less than 500 mg daily (as in E.M.Power+) would have antidepressant or mania-inducing effects on its own. However, it is possible that interactions among the micronutrients might increase the chances that such low doses of inositol might have such psychotropic effects. Indeed, citing the possibility of micronutrient-medication interactions, Popper emphasized that it is important for clinicians to understand the risks of introducing micronutrient treatments to patients already receiving psychopharmacologic treatment.[10]

Dr. Pies's general point is that the safety of nutritional supplementation cannot be assumed. We would add that this is especially true when supplements are used in combination with psychiatric medications.[10] Initial assumptions about safety and toxicity of pharmaceuticals,[11,12] herbal preparations,[13] and micronutrient formulations should be questioned continuously and tested empirically. These issues need to be examined separately in children[14] as well as in other special medical populations. We concur with Dr. Pies's view that micronutrient treatment of psychiatric disorders is promising and deserves further controlled research.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Gabapentin and PTSD

Sir: The recent article "Open-Label Topiramate as Primary or Adjunctive Therapy in Chronic Civilian Posttraumatic Stress Disorder: A Preliminary Report" by Drs. Berlant and van Kammen is very well written and a welcome addition to the literature for clinicians treating this very debilitating illness.[1] In the authors' review of anticonvulsants used to treat posttraumatic stress disorder (PTSD), no mention of gabapentin is made. Although the literature on the topic is not voluminous, there are at least 3 references to the use of gabapentin in treating PTSD: two case reports[2,3] and a retrospective clinical series.[4] I agree fully with the authors that future research needs to be done and share the authors' enthusiasm about the promise topiramate shows in the treatment of PTSD.

Dr. Berigan reports no financial affiliation or other relationship relevant to the subject matter of this letter.

Drs. Berlant and van Kammen were shown this letter and declined to comment.

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Correction

In the article "Risk of Cardiovascular Disease and Sudden Death in Schizophrenia" (2002 Supplement 9, pages 5–11) by Michael Davidson, M.D., typographical errors appeared in 2 sentences in the right column on page 6 (lines 37–43). The gain in body weight should have been ≥ 7% in both sentences. The corrected sentences read:

> However, in premarketing studies, significantly more quetiapine-treated patients (23%) gained ≥ 7% of their body weight compared with placebo-treated patients (6%).[17] Ziprasidone appears to have a negligible effect on weight—in premarketing studies, only 10% of ziprasidone-treated patients gained ≥ 7% of their body weight compared with 4% of placebo-treated patients.[18]

The staff regrets these errors.