Current PSYCHIATRY

Tx for pseudobulbar affect

The article "Dextromethorphan/quinidine for pseudobulbar affect" (Out of the Pipeline, CURRENT PSYCHIATRY, February 2011, p. 60-67) was of great interest. For the past 5 years I have led the clinical development of Nuedexta™ (dextromethorphan hydrobromide and quinidine sulfate; DMQ) and I found the review extraordinarily comprehensive and applaud the authors for their exhaustive research. I would, however, like to take the opportunity to provide some additional insight into a few areas covered by the article.

The authors, in describing the control groups in an earlier phase III study of DMQ for the treatment of patients with pseudobulbar affect (PBA), state, "However, the control conditions may not have been adequate. Quinidine alone would not be expected to have an effect on PBA, and the DM dose, which was the same in combination and monotherapy, may have been too low to be effective by itself. In support of this hypothesis, the DM plasma level was 18 times higher in patients taking DMQ 30-30 than those taking DM monotherapy." Although their observations regarding the effectiveness of higher doses may be true, the study was designed to meet the FDA standards for combination products—that a combination product's efficacy needs to exceed that which is appreciated by either of the components administered alone. As the authors correctly pointed out, even high doses of DM, when administered alone, are rapidly metabolized and cannot reach substantial bioavailability in order to exert a therapeutic effect.

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Having been involved in clinical drug development for nearly 20 years, I cannot agree with the authors conclusions that: "Although DMQ is convenient, its advantage over starting with DM alone and adding a small dose of a nonserotonergic 2D6 inhibitor if DM is not effective remains to be demonstrated." The statement implies that a reasonable approach is to consider testing DM combined with a series of arbitrary CYP2D6 inhibitors. These combinations have not been tested and there is no evidence on which to base the efficacy or safety of this approach. As clinical researchers, we have an obligation to make recommendations that are based on available data and that ensure patient safety. In our own exhaustive research, we believe there is no other CYP2D6 inhibitor, other than low-dose quinidine, 10 mg/d (1% to 3% of a typical antiarrhythmic dose), that can provide a safe and predictable pharmacologic profile when used in combination with DM. Lastly, I am disappointed with the assertion that "it would seem prudent to consider using an SSRI (selective serotonin reuptake inhibitor) or a TCA (tricyclic antidepressant) first." These drugs have not been extensively studied for the treatment of PBA, and have their own (not benign) risks. Moreover, these antidepressants have not met the standard of substantial clinical evidence required by the FDA and thus, are not approved for treating patients with PBA.

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The authors respond

We appreciate Dr. Kaye's letter, but would like to point out that registration trials designed to get FDA approval are designed to demonstrate superiority of the product to placebo and not to answer the question "under what circumstances and compared with what alternatives is this product more likely to be effective and safe?" We would not necessarily agree that this particular product is superior because it was approved by the FDA in placebo-controlled research designed to maximize the apparent benefit of the combination, when only clinical experience supports the use of alternatives. Perhaps the manufacturer would care to design head-to-head comparisons to support Dr. Kaye's contention that his product should be the first choice in the treatment of PBA, which has been done with cancer and human immunodeficiency virus products, among others. Such comparison trials should include patients with complex and comorbid disorders to reflect real-life clinical practice rather than efficacy in patients selected for their likelihood to respond to the product. In the meantime, clinicians have the task of evaluating marketing of products and ideas, which is inherent in many clini-

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Send letters in care of Christina Thomas, CURRENT PSYCHIATRY, 7 Century Drive, Suite 302, Parsippany, NJ 07054, christina.thomas@qhc.com or visit CurrentPsychiatry.com and click on the "Send Letters" link. All letters are subject to editing for brevity and clarity.

be considered in elderly patients for whom orthostatic hypotension is of concern *[see Warnings and Precautions (5.7) in full PI]*. Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with oral placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of oral risperidone regardless of concomitant use with furosemide. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis. *[See Boxed Warning and Warnings and Precautions]*

DRUG ABUSE AND DEPENDENCE: Controlled Substance: RISPERDAL® CONSTA® (risperidone) is not a controlled substance.

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OVERDOSAGE: Human Experience: No cases of overdose were reported in premarketing studies with RISPERDAL® CONSTA®. Because RISPERDAL® CONSTA® is to be administered by health care professionals, the potential for overdosage by patients is low. In premarketing experience with oral RISPERDAL®, there were eight reports of acute RISPERDAL® overdosage, with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience with oral RISPERDAL® includes reports of acute overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to oral RISPERDAL® overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension. There is no specific antidote to risperidone. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

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cal recommendations, not only those for which the only controlled data come from industry-sponsored trials.

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More on hyperammonemia

The authors of the "The mysterious foreign accent" (Cases that Test Your Skills, Current Psychiatry, March 2011, p. 57-63) left us hanging by tantalizing us with an axis III diagnosis of asymptomatic hyperammonemia. They most likely did more work to come to that diagnostic conclusion but it's not evident in the article. I'm left with the feeling that a young person with delusions, psychosis, and average intelligence might have a metabolic source for those symptoms—particularly because she seems to have a high-achieving father, yet is a high school dropout. The discussion of foreign accent syndrome mentions structural cerebral lesions as a major source for the disorder. A quick Internet search failed to turn up an association with hyperammonemia but that would not necessarily rule out a connection in this case because both are rare disorders.

I also would think the presence of hyperammonemia would preclude use of valproate or certainly would need to be addressed during treatment. The response to risperidone and valproate would be in keeping with the standard response of a mild delirium to antipsychotic treatment. The his-

tory of physical and emotional abuse would be in keeping with the exploitation that mentally disordered people often are subjected to as Dr. Henry A. Nasrallah mentions in the Comments and Controversies section (Current Psychiatry, March 2011, p. 5,64).

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The authors respond

Hyperammonemia was an incidental finding. As a part of standard check-up, blood work was done. In the workup for the basic metabolic panel, ammonia level was found to be elevated above the normal range. But this lab finding was not correlated with other clinical findings. The liver panel was normal. The patient did not have any features of encephalopathy, nor did she have any clinical signs or symptoms. There have been reports of hyperammonemia associated with the use of valproate but unless the patient is clinically symptomatic, dose adjustment for valproate is not warranted. Periodic monitoring for ammonia level may be needed for high-risk patients on valproate if they have clinical signs and symptoms.

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TBI and growth hormone

In response to "Traumatic brain injury: Pharmacotherapy options for cognitive deficits" (Med/Psych Update, Current Psychiatry, February 2011, p. 21-37), traumatic brain injury (TBI) has been recognized as a risk factor for cognitive impairment, but TBI also has been shown to be a risk factor for hypopituitarism, presenting most frequently with growth hormone deficiency (GHD). GHD is associated not only with changes in body composition but also with impaired quality of life, cognitive dysfunctions, and psychiatric sequelae, usually classified as "depression."

In a case study we evaluated the impact of GH therapy on the mental status of TBI patients.[1] Psychiatric and cognitive functions were tested in 6 GHD patients at baseline (minimum 3 years after TBI) and reassessed after 6 months of GH therapy and 12 months after discontinuing GH therapy. Psychiatric and cognitive examinations included semi-structured interviews and 3 instruments: Symptom Checklist-90-Revised, Zung Depression Inventory, and a standard composite neuropsychological battery.

Our results showed that 6 months of GH therapy in GHD TBI patients improved cognitive abilities (particularly verbal and nonverbal memory) and significantly improved psychiatric functioning. Depression severity decreased, as did intensity of interpersonal sensitivity, hostility, paranoid ideation, anxiety, and psychoticism. Somatization, obsessive-compulsive symptoms, and phobic anxiety decreased in all but 1 patient. In 3 GHD patients who stopped GH therapy for 12 months, we observed worsening verbal and nonverbal memory, interpersonal sensitivity, anxiety, and paranoid ideation. Thus, GHD might be associated with affective and cognitive symptoms in TBI patients and GH replacement therapy could be beneficial. Screening for pituitary dysfunction in TBI patients is strongly recommended, particularly in presence of cognitive and affective symptoms.

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Reference

1. Maric N, Doknic M, Pavlovic D, et al. Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy. J Endocrinol Invest. 2010;33(11):770-775.