System Disorders – *Infrequent:* hypersensitivity; **Musculoskeletal and Connective Tissue Disorders –** *Frequent:* musculoskeletal complaints, myalgia; *Infrequent:* muscle twitching; **Nervous System Disorders –** *Frequent:* coordination abnormal, dysgeusia, memory impairment, migraine, paraesthesia, tremor; *Infrequent:* amnesia, aphasia, hypoesthesia, speech disorder; **Psychiatric Disorders –** *Frequent:* agitation, confusional state, disorientation; **Renal and Urinary Disorders –** *Frequent:* micturition urgency; *Infrequent:* bladder pain, urinary incontinence; **Respiratory, Thoracic and Mediastinal Disorders –** *Frequent:* dyspnea; **Skin and Subcutaneous Tissue Disorders –** *Frequent:* night sweats; *Infrequent:* acne, hyperhidrosis, photosensitivity reaction; **Vascular Disorders –** *Infrequent:* flushing. **Postmarketing Experience –** Spontaneous reports regarding trazodone hydrochloride received from postmarketing experience include the following: abnormal dreams, agitation, alopecia, anxiety, aphasia, apnea, ataxia, breast enlargement or engorgement, cardiospasm, cerebrovascular accident, chills, cholestasis, clitorism, congestive heart failure, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hirsutism, hyperbilirubinemia, increased amylase, increased salivation, insomnia, leukocytosis, leukonychia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/ vomiting (most frequently), paresthesia, paranoid reaction, priapism [***see Warnings and Precautions and Patient Counseling Information***], pruritus, psoriasis, psychosis, rash, stupor, inappropriate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo, and weakness. Cardiovascular system effects which have been reported include the following: conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, ventricular ectopic activity, including ventricular tachycardia and QT prolongation. In postmarketing surveillance, prolonged QT interval, Torsades de Pointes, and ventricular tachycardia have been reported with the immediate-release form of trazodone at doses of 100 mg per day or less [***see Warnings and Precautions***].

DRUG INTERACTIONS: MAOIs – MAOIs should not be used within 14 days of Oleptro [***see Warnings and Precautions***]. **Central Nervous System (CNS) Depressants –** Trazodone may enhance the response to alcohol, barbiturates, and other CNS depressants. **Cytochrome P450 3A4 Inhibitors –** In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with cytochrome P450 3A4 (CYP3A4) inhibitors. The effect of short-term administration of ritonavir (200 mg twice daily, 4 doses) on the pharmacokinetics of a single dose of trazodone (50 mg) has been studied in 10 healthy subjects. The Cmax of trazodone increased by 34%, the AUC increased 2.4-fold, the half-life increased by 2.2-fold, and the clearance decreased by 52%. Adverse effects including nausea, hypotension, and syncope were observed when ritonavir and trazodone were co-administered. It is likely that ketoconazole, indinavir, and other CYP3A4 inhibitors such as itraconazole may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. If trazodone is used with a potent CYP3A4 inhibitor, the risk of cardiac arrhythmia may be increased [***see Warnings and Precautions***] and a lower dose of trazodone should be considered. **Cytochrome P450 Inducers (e.g., carbamazepine) –** Carbamazepine induces CYP3A4. Following co-administration of carbamazepine 400 mg per day with trazodone 100 mg to 300 mg daily, carbamazepine reduced plasma concentrations of trazodone and m-chlorophenlypiperazine (an active metabolite) by 76% and 60% respectively, compared to pre-carbamazepine values. Patients should be closely monitored to see if there is a need for an increased dose of trazodone when taking both drugs. **Digoxin and Phenytoin –** Increased serum digoxin or phenytoin levels have been reported in patients receiving trazodone concurrently with either of these drugs. Monitor serum levels and adjust dosages as needed. **Serotonergic Drugs –** Based on the mechanism of action of Oleptro and the potential for serotonin syndrome, caution is advised when Oleptro is co-administered with other drugs that may affect the neurotransmitter systems [***see Warnings and Precautions***]. **NSAIDs, Aspirin, or Other Drugs Affecting Coagulation or Bleeding –** Due to a possible association between serotonin modulating drugs and gastrointestinal bleeding, patients should be monitored for and cautioned about the potential risk of bleeding associated with the concomitant use of trazodone and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding [***see Warnings and Precautions***]. **Warfarin –** There have been reports of altered (either increased or decreased) prothrombin times in taking both warfarin and trazodone.

USE IN SPECIFIC POPULATIONS: Pregnancy; Pregnancy Category C – Trazodone hydrochloride has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30 – 50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15 – 50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Oleptro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers –** Trazodone and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when Oleptro is administered to a nursing woman. **Pediatric Use –** Safety and effectiveness in the pediatric population have not been established [***see Boxed Warning and Warnings and Precautions***]. Oleptro should not be used in children or adolescents. **Geriatric Use –** Of 202 patients treated with Oleptro in the clinical trial, there were 9 patients older than 65. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical literature and experience with trazodone have not identified differences in responses between elderly and younger patients. However, as experience in the elderly with Oleptro is limited, it should be used with caution in geriatric patients. Antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients who may be at greater risk for this adverse reaction [***see Warnings and Precautions***]. **Renal Impairment –** Oleptro has not been studied in patients with renal impairment. Trazodone should be used with caution in this population. **Hepatic Impairment –** Oleptro has not been studied in patients with hepatic impairment. Trazodone should be used with caution in this population.

DRUG ABUSE AND DEPENDENCE: Controlled Substance – Oleptro is not a controlled substance. **Abuse –** Although trazodone hydrochloride has not been systematically studied in preclinical or clinical studies for its potential for abuse, no indication of drug-seeking behavior was seen in the clinical studies with Oleptro. However, it is difficult to predict the extent to which a CNS-active drug will be misused, diverted, and abused. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of trazodone hydrochloride (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience – It is expected that the health risks associated with overdose of Oleptro are most likely similar to those for trazodone immediate-release formulations. Death from overdose has occurred in patients ingesting trazodone and other CNS depressant drugs concurrently (alcohol; alcohol and chloral hydrate and diazepam; amobarbital; chlordiazepoxide; or meprobamate). The most severe reactions reported to have occurred with overdose of trazodone alone have been priapism, respiratory arrest, seizures, and ECG changes, including QT prolongation. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions. **Management of Overdose –** There is no specific antidote for Oleptro overdose. Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Forced diuresis may be useful in facilitating elimination of the drug. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

Sleep May Be Target In Treatment of PTSD

BY DIANA MAHONEY

ANALYSIS FROM THE MASSACHUSETTS GENERAL HOSPITAL PSYCHIATRY ACADEMY'S CONFERENCE ON COMPLEXITIES AND CHALLENGES OF PTSD AND TBI

BOSTON — Sleep disturbances may be an important target for treating posttraumatic stress disorder, according to Dr. R. Bruce Lydiard of the Medical University of South Carolina in Charleston.

Persistent, severe posttraumatic nightmares, REM sleep fragmentation, insomnia, excessive nocturnal periodic limb movements, and sleep-disordered breathing are frequently experienced by individuals with PTSD, Dr. Lydiard said. Although these sleep problems are often viewed as secondary symptoms of PTSD, "the evidence suggests that after a traumatic event, sleep disruption appears before the onset of PTSD and may be a risk factor for it," he proposed.

The alpha adrenergic antagonist prazosin has shown promise in multiple case and chart reviews, open-label trials, and placebo-controlled studies.

Polysomnographic data from 21 individuals with traumatic injuries showed that the number of REM periods and the (shorter) duration of REM periods within 1 month after the traumatic event were predictive of PTSD symptom severity 6 weeks later (Am. J. Psychiatry 2002;159:1696-701).

Neurobiologically, the association makes sense, Dr. Lydiard said. "Sleep is regulated in part by brain areas in which PTSD-related changes occur," which suggests that the stress response in PTSD and sleep dysfunction may be biologically linked.

Imaging studies suggest that exposure to trauma-related stimuli leads to hyperactivation in the amygdala and decreased activation in the medial prefrontal cortex/anterior cingulate cortex and hippocampus, with the magnitude of the activation correlating with the clinical severity of PTSD symptoms.

Polysomnographic investigations in patients with PTSD and sleep disturbances have revealed increased REM density, reduced REM duration, and increased motor activity, Dr. Lydiard said.

Together with clinical reports, "these data provide the basis for REM sleep dysregulation as a core feature in PTSD," whereby increased activity in the amygdala and decreased inhibitory input from the medial prefrontal cortex lead to a persistently overactive noradrenergic system. "As a result, the usual rhythm of REM-NREM sleep is disrupted, and REM sleep is fragmented," he said.

Based on this model, investigators have hypothesized that targeting noradrenergic signaling during or near REM episodes may normalize REM sleep, which in turn might improve PTSD sleep disturbances and, potentially, other PTSD symptoms, Dr. Lydiard said.

The alpha adrenergic antagonist prazosin has shown promise in multiple case and chart reviews, open-label trials, and placebo-controlled studies.

In one trial of 40 veterans with PTSD sleep disturbance, patients who were randomized to receive a nightly dose of prazosin—originally marketed as an antihypertensive agent—reported significant improvements in sleep quality and significant reductions in trauma nightmares, as well a better overall sense of well-being and improved daily functioning (Biol. Psychiatry 2007;61:928-34).

In another study, investigators evaluated the effect of prazosin vs. placebo on objective sleep parameters in 13 outpatients with chronic civilian trauma PTSD, frequent nightmares, and sleep disturbance. The prazosin group experienced significantly increased total sleep time as well as increased REM sleep time and mean REM period duration (Biol. Psychiatry 2008;63:629-32).

In the various studies, the therapeutic benefit of prazosin has been achieved within 1-2 weeks "with doses as low as 1 mg nightly," Dr. Lydiard said.

In addition to improving sleep measures, prazosin may be useful for other trauma-related symptoms. In a small study of PTSD subjects whose nightmares were well controlled with the drug, the addition of small daytime doses lessened patients' reactivity to trauma cues during the day, he said (Biol. Psychiatry 2006;59:577-81). This finding "adds to the growing body of evidence that targeting sleep in PTSD is clinically relevant."

Although some evidence exists to support the use of other antiadrenergic agents such as clonidine and guanfacine—as well as the anticonvulsant gabapentin—in PTSD, "large, randomized controlled trials are needed to clarify the role" of all of these agents, Dr. Lydiard said.

Additional studies also are warranted, he said, to investigate nonpharmacologic approaches to improving PTSD sleep disturbance, such as the use of imagery rehearsal therapy, which has demonstrated efficacy in small studies (J. Trauma Stress 2009;22:236-9).

Dr. Lydiard disclosed receiving honoraria from Reed Medical Education, the logistics collaborator for the Massachusetts General Hospital Psychiatry Academy. ■