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.

Tea Polyphenols Provide Some Parkinson's Relief

BY DAMIAN McNAMARA

FROM THE WORLD FEDERATION OF NEUROLOGY WORLD CONGRESS ON PARKINSON'S DISEASE AND RELATED DISORDERS

MIAMI BEACH — Green tea polyphenols taken daily provide minor symptomatic improvement for people with Parkinson's disease, particularly those with more severe disease at baseline, according to findings in a 12-month study. However, the green tea did not provide any disease-modifying effect.

The study lends some confirmation to observations in China of a dose-dependent protective effect of tea drinking against Parkinson's disease, Dr. Piu Chan reported at the congress.

The mechanism that could account for green tea's effects is unknown, but green tea is rich in flavonoids, which make up 30% of its dry weight. In addition, the most abundant compound in green tea, epigallocatechin gallate, protects against toxins in animal models and "may down-regulate expression of pro-apoptotic genes," Dr. Chan said.

To determine the efficacy of green tea polyphenols for slowing progression of Parkinson's disease, he and his colleagues conducted a randomized, double-blind, placebo-controlled, and delayed-start study. They enrolled 410 untreated people with Parkinson's disease at 32 Chinese Parkinson Study Group sites. Patients were randomized to 0.4, 0.8, or 1.2 g of green tea polyphenols daily, or placebo. At 6 months, the placebo group switched to 1.2 g of green tea polyphenols daily as well. Two cups of green tea typically contain about 300 mg of polyphenols, Dr. Chan noted.

Patients were assessed in-person at baseline and at 3, 6, 9, and 12 months. They also kept a tea consumption diary. Change in Unified Parkinson Disease Rating Scale (UPDRS) score was the main outcome. Although a significant improvement in UPDRS scores was observed at 6 months for patients in each dosage group, they were no longer significantly different at 12 months compared with placebo.

Although green tea abstract was safe and well tolerated, there was "no obvious disease-modifying effect seen," said Dr. Chan, director of the Beijing Institute of Geriatrics and Department of Neurology, Xuanwu Hospital of Capital University of Medical Sciences, Beijing. ■

Optimal Screen for Early Parkinson's Still Elusive

BY DAMIAN McNAMARA

FROM THE WORLD FEDERATION OF NEUROLOGY WORLD CONGRESS ON PARKINSON'S DISEASE AND RELATED DISORDERS

MIAMI BEACH – Widespread screening for early Parkinson's disease with olfactory testing followed by neurologic imaging holds promise but is not yet practical, based on studies that have revealed the limitations of each method.

Olfactory impairment is common enough in premotor Parkinson's that some researchers propose using it as an early predictor of risk (Ann. Neurol. 2008;63:167-73).

However, olfactory testing has not garnered widespread adoption because it lacks sufficient specificity for population-based screening, Dr. Henk W. Berendse said at the congress. He and others have proposed coupling olfactory testing with highly specific brain imaging, such as dopamine transporter single-photon emission computed tomography (DAT SPECT).

There is a catch, though. The imaging would have to be done in a large number of individuals, many of whom would not develop Parkinson's disease, said Dr. Berendse, head of the movement disorders service at the VU University Medical Centre in Amsterdam.

In a subsequent presentation at the meeting, Dr. Andrew D. Siderowf of the neurology department at Pennsylvania Hospital in Philadelphia called population screening for Parkinson's disease a "numbers game."

The incidence of Parkinson's disease is low, so the number of potentially identifiable cases in a population at any given time also is low, he said.

In 2005, the worldwide prevalence of the disease was estimated to be between 4.1 million and 4.6 million (Neurology 2007;68:384-6).

Dr. Berendse calculated that "if you expect to detect 125 patients in the premotor phase [of Parkinson's disease], somewhere between 1,000 and 7,000 individuals would have to undergo SPECT scans. Assuming a 10% prevalence of hyposmia, we would need to screen 70,000 individuals."

The 10% prevalence of hyposmia is based on a study that screened 361 asymptomatic, 50- to 75-year-old relatives of patients with idiopathic Parkinson's. All of the relatives had olfactory testing, and the 40 who tested positive also had serial ^{123}I-beta-CIT SPECT scanning. Hyposmia in first-degree relatives was associated with at least a 10% risk of developing Parkinson's disease within 2 years (Ann. Neurol. 2004;56:173-81).

Dr. Berendse and Dr. Siderowf had no relevant financial disclosures. ■