

**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, cardiopasm, 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 Olepro [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 C<sub>max</sub> 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-chlorophenylpiperazine (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 Olepro and the potential for serotonin syndrome, caution is advised when Olepro 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. Olepro 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 Olepro 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*]. Olepro should not be used in children or adolescents. **Geriatric Use** – Of 202 patients treated with Olepro 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 Olepro 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** – Olepro has not been studied in patients with renal impairment. Trazodone should be used with caution in this population. **Hepatic Impairment** – Olepro has not been studied in patients with hepatic impairment. Trazodone should be used with caution in this population.

**DRUG ABUSE AND DEPENDENCE: Controlled Substance** – Olepro 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 Olepro. 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 Olepro 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 Olepro 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.



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[February 2010]

# Amygdala, sACC Involved In Pathological Worry

BY ROXANNA GUILFORD-BLAKE

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR GERIATRIC PSYCHIATRY

SAVANNAH, GA. – Functional MRIs reveal neuroanatomical differences between normal worry and pathological worry in the elderly, and those differences might help explain why late-life anxiety often proves difficult to treat.

The amygdala and the subgenual anterior cingulate cortex (sACC) seem to be involved in the functional neuroanatomy of late-life anxiety disorders, Dr. Carmen Andreescu of the University of Pittsburgh reported at the meeting.

The findings, based on fMRIs of 10 nonanxious elderly people and 8 elderly people with anxiety, suggest a biological substrate for the persistent and uncontrollable characteristics of pathological worry, she said. The subjects were asked to worry while they were in the scanner, then they were asked to suppress the worry and think of “something nice” for a minute.

In the nonanxious subjects, worry induction increased activation of the amygdala and decreased activation of the sACC. During worry suppression,

the scans revealed decreased activation of the amygdala and increased activation of the sACC.

Not so for the elderly subjects with generalized anxiety disorder (GAD). The fMRI revealed increased activation of the amygdala and the subgenual ACC during worry suppression, suggesting a delayed yet sustained amygdala involvement and the unsuccessful attempts of the subgenual ACC to modulate the worry process, she explained.

That the amygdala stays active during worry suppression is “the most yummy part,” Dr. Andreescu reported, explaining it this way: Tell a friend without anxiety to stop worrying, and they will. Tell someone with pathological anxiety to stop worrying, and the result might be increased amygdala activity.

“There is a paucity of data regarding late-life anxiety, but based on my preliminary data, it seems that these regions are involved in late-life anxiety, just as they are in mid-life anxiety,” she said in an interview. Significantly, when someone tries to modulate his or her worry, “the interplay between these two regions is different in healthy people and in pathologically anxious people.”

Dr. Andreescu reported no conflicts relevant to the study. ■

# Latest Findings on Fish Oil, Cognition Disappointing

BY JENNIE SMITH

FROM THE AMERICAN JOURNAL OF CLINICAL NUTRITION

Consumption of omega-3 polyunsaturated fatty acid supplements has no measurable effect on cognition in older adults, according to U.K. researchers who sought to detect whether daily use of the supplements could prevent cognitive decline.

For their 2-year, blinded study, funded by U.K. health and nutrition agencies, a team of investigators led by Alan Dangour, Ph.D., of the London School of Hygiene & Tropical Medicine, randomly assigned 867 older adults in good cognitive health and who did not take fish-oil supplements to a daily dose of 200 mg eicosapentaenoic acid (EPA) plus 500 mg docosahexaenoic acid (DHA), or an olive-oil placebo.

The mean age of participants was 75 years; 55% were men, according to the study (doi: 10.3945/ajcn.2009.29121).

Though concentrations of EPA and DHA were significantly higher in blood samples from the treatment group, no decline in cognitive function was detected in either group. “After 2 years we can say definitively that there’s no benefit,” Dr. Dangour said in an interview. ■

“We’re disappointed, but we conducted the best possible study and certainly the largest to date.”

Standardized tests of memory and cognitive function and serum EPA and DHA levels were administered at baseline and after 24 months.

In the treatment arm, 376 subjects completed the study, compared with 368 in the control arm. Analysis was by intention to treat.

The findings appear in stark contrast to those of a 2006 study of 899 similar-age subjects from a large cohort (Arch. Neurol. 2006;63:1545-50). In that study, people in the top quartile of plasma DHA levels saw a 47% reduction in the risk of developing all-cause dementia after 9 years.

But cohort studies are difficult to compare with randomized, controlled trials, Dr. Dangour pointed out, and “there are loads of other studies that say there’s a benefit for people who eat more fish.”

The point of this study, specifically, was to detect a measurable benefit from a dietary change rather than the accumulated benefits of a lifelong habit.

Neither Dr. Dangour nor his coauthors declared any competing interests. Fish oil for the study was donated by Ocean Nutrition Canada Ltd. ■