

NSAID Pair Fails Alzheimer's Prevention Test

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Naproxen and celecoxib failed to prevent Alzheimer's disease in the first clinical trial to test the agents as preventives in older subjects who had no cognitive impairment, wrote Barbara K. Martin, Ph.D., of Johns Hopkins Bloomberg School of Public Health, Baltimore, and her associates.

Epidemiologic data suggest that pro-

longed NSAID use might protect against age-related cognitive decline, a possible forerunner of Alzheimer's disease, but small observational studies have yielded conflicting results.

The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), sponsored by the National Institute on Aging, was a placebo-controlled clinical trial designed to assess naproxen and celecoxib in 2,528 cognitively normal men and women aged 70 or older. A total of 726 were allo-

cated to celecoxib, 719 to naproxen, and 1,083 to placebo. The study was halted early "after increased cardiovascular risk was observed with celecoxib in another prevention trial," the investigators said (Arch. Neurol. 2008 May 12 [doi:10.1001/archneur.2008.65.7.nct70006]).

A total of 2,117 subjects contributed follow-up cognitive measures for at least 6 months after discontinuing the study medications.

Subjects' scores on the Modified Mini-

Mental State Examination, a measure of global cognitive function, were significantly lower for both treatment groups than for the placebo group (-0.32 points for celecoxib and -0.36 points for naproxen), Dr. Martin and her associates said.

To put their findings in a clinical context, the researchers noted that the differences in cognitive scores between the treatment groups and the placebo group are equivalent to the average yearly decline among normal elderly subjects. ■

have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of GI bleeding. Bleeding events related to use of SSRIs and SNRIs have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of LUVOX CR and NSAIDs, aspirin, or other drugs that affect coagulation. **Activation of Mania/Hypomania:** During premarketing studies of IR fluvoxamine maleate involving primarily depressed patients, hypomania or mania occurred in ~1% of patients treated with fluvoxamine. In a 10-week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63 placebo patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, LUVOX CR should be used cautiously in patients with a history of mania. **Seizures:** During premarketing studies with IR fluvoxamine maleate, seizures were reported in 0.2% of fluvoxamine-treated patients. Caution is recommended when the drug is administered to patients with a history of convulsive disorders. Fluvoxamine should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or seizure frequency increases. **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including LUVOX CR. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see **Geriatric Use**). Discontinuation of LUVOX CR should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Use in Patients with Concomitant Illness:** Closely monitored clinical experience with IR fluvoxamine maleate in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX CR to patients with diseases or conditions that could affect hemodynamic responses or metabolism. LUVOX CR or IR fluvoxamine maleate have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during premarket testing. Evaluation of the electrocardiograms (ECGs) for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes. In patients with liver dysfunction, following administration of IR fluvoxamine maleate, fluvoxamine clearance was decreased by ~30%. Patients with liver dysfunction should begin with a low dose of LUVOX CR and increase it slowly with careful monitoring. **Laboratory Tests:** There are no specific laboratory tests recommended. **Drug Interactions:** As with all drugs, the potential for interaction by a variety of mechanisms is a possibility. **Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes:** Multiple hepatic cytochrome P450 isoenzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the cytochrome P450 isoenzyme system has been obtained mostly from PK interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see **WARNINGS**) and limited *in vitro* data for CYP3A4, it appears that fluvoxamine inhibits several cytochrome P450 isoenzymes known to be involved in the metabolism of other drugs such as CYP1A2 (eg warfarin, theophylline, propranolol, tizanidine), CYP2C9 (eg warfarin), CYP3A4 (eg alprazolam), and CYP2C19 (eg omeprazole). *In vitro* data suggest that fluvoxamine is a relatively weak inhibitor of CYP2D6. Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as poor metabolizers (PMs) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the PK of fluvoxamine, an *in vivo* study of fluvoxamine single-dose PK in 13 PM subjects demonstrated altered PK properties compared to 16 extensive metabolizers (EMs): mean C_{max} , AUC, and $T_{1/2}$ were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity or receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (eg quinidine). The metabolism of fluvoxamine has not been fully characterized, and the effects of potent cytochrome P450 isoenzyme inhibition, such as the ketoconazole inhibition of CYP3A4, on fluvoxamine metabolism have not been studied. A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as warfarin or theophylline, certain benzodiazepines, and phenytoin. If LUVOX CR is to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or PD effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (see **CONTRAINDICATIONS** and **WARNINGS**). **CNS Active Drugs: Antipsychotics:** See **WARNINGS—Other Potentially Important Drug Interactions, NMS or NMS-Like Events, MAOIs:** See **CONTRAINDICATIONS** and **WARNINGS. Alprazolam and Diazepam:** See **WARNINGS. Alcohol:** Studies involving single 40 g doses of ethanol (oral administration in 1 study and intravenous in the other) and multiple dosing with IR fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the PK or PD of the other. **Carbamazepine:** Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of IR fluvoxamine maleate and carbamazepine. **Clozapine:** Elevated serum levels of clozapine have been reported in patients taking IR fluvoxamine maleate and clozapine. Since clozapine-related seizures and orthostatic hypotension appear to be dose related, the risk of these AEs may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when LUVOX CR and clozapine are used concurrently. **Lithium:** As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of IR fluvoxamine maleate and lithium. **Lorazepam:** A study of multiple doses of IR fluvoxamine maleate (50 mg bid) and a 4 mg single dose of lorazepam in healthy male volunteers (n=12) indicated no significant PK interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone. **Methadone:** Significantly increased methadone (plasma level:dose) ratios have been reported when IR fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in 1 patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient. **Ramelteon:** When IR fluvoxamine maleate 100 mg bid was administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and IR fluvoxamine maleate, the AUC for ramelteon increased ~190-fold and the C_{max} increased ~70-fold compared to ramelteon administered alone. Ramelteon should not be used in combination with LUVOX CR (see **WARNINGS**). **Serotonergic Drugs:** Based on the mechanism of action of LUVOX CR and the potential for serotonin syndrome, caution is advised when fluvoxamine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS—Serotonin Syndrome**). The concomitant use of LUVOX CR with other SSRIs, SNRIs, or tryptophan is not recommended. **Sumatriptan:** Rare postmarketing reports have described patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (eg fluoxetine, fluvoxamine, paroxetine, sertraline, etc.) is clinically warranted, appropriate observation of the patient is advised. **Tacrine:** In a study of 13 healthy male volunteers, a single 40 mg dose of tacrine added to IR fluvoxamine maleate 100 mg/day administered at steady state was associated with 5- and 8-fold increases in tacrine C_{max} and AUC, respectively, compared to the administration of tacrine alone. Five subjects experienced nausea, vomiting, sweating, and diarrhea following co-administration, consistent with the cholinergic effects of tacrine. **Thioridazine:** See **CONTRAINDICATIONS** and **WARNINGS. Triptans:** There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan.

If concomitant treatment of fluvoxamine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS—Serotonin Syndrome**). **Tizanidine:** See **CONTRAINDICATIONS** and **WARNINGS. Tricyclic Antidepressants (TCAs):** Significantly increased plasma TCA levels have been reported with co-administration of IR fluvoxamine maleate and amitriptyline, clomipramine, or imipramine. Caution is indicated with the co-administration of LUVOX CR and TCAs; plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced. **Tryptophan:** Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with co-administration of IR fluvoxamine maleate and tryptophan. **Other Drugs: Theophylline and Warfarin:** See **WARNINGS. Alosetron:** Because alosetron is metabolized by a variety of hepatic CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. Fluvoxamine is a known potent inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a PK study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 mg to 200 mg a day for 16 days, with co-administration of alosetron 1 mg on the last day. Fluvoxamine increased mean alosetron plasma concentration (AUC) ~6-fold and prolonged the half-life by ~3 fold (see **CONTRAINDICATIONS, PRECAUTIONS**, and Lotronex™ (alosetron) package insert). **Digoxin:** Administration of IR fluvoxamine maleate 100 mg daily for 18 days (n=8) did not significantly affect the PK of a 1.25 mg single intravenous dose of digoxin. **Diltiazem:** Bradycardia has been reported with the co-administration of IR fluvoxamine maleate and diltiazem. **Propranolol and Other Beta-Blockers:** Co-administration of IR fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean 5-fold increase (range 2- to 17-fold) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure. One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with co-administration of IR fluvoxamine maleate and metoprolol. If propranolol or metoprolol is co-administered with LUVOX CR, a reduction in the initial beta-blocker dose and more cautious dose titration are recommended. No dose adjustment is required for LUVOX CR. Co-administration of IR fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (n=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol, which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion. **Drugs that Interfere with Hemostasis (eg NSAIDs, Aspirin, and Warfarin):** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper GI bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when LUVOX CR is initiated or discontinued. **Effects of Smoking on Fluvoxamine Metabolism:** Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers. **Electroconvulsive Therapy (ECT):** No clinical studies have established the benefits or risks of combined use of ECT and fluvoxamine maleate. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 months (females) or 26 months (males). The daily doses in the high-dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is ~6 times the maximum human daily dose on a mg/m² basis. **Mutagenesis:** No evidence of genotoxic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation. **Impairment of Fertility:** In a study in which male and female rats were administered fluvoxamine (60, 120, or 240 mg/kg) orally prior to and during mating and gestation, fertility was impaired at oral doses ≥120 mg/kg, as evidenced by increased latency to mating, decreased sperm count, decreased epididymal weight, and decreased pregnancy rate. In addition, the numbers of implantations and embryos were decreased at the highest dose. The no effect dose for fertility impairment was 60 mg/kg (~2 times the maximum recommended human dose [MRHD] on a mg/m² basis). **Pregnancy—Teratogenic Effects—Pregnancy Category C:** When pregnant rats were given oral doses of fluvoxamine (60, 120, or 240 mg/kg) throughout the period of organogenesis, developmental toxicity in the form of increased embryofetal death and increased incidences of fetal eye abnormalities (folded retinas) was observed at doses ≥120 mg/kg. Decreased fetal body weight was seen at the high dose. The no effect dose for developmental toxicity in this study was 60 mg/kg (~2 times the MRHD on a mg/m² basis). In a study in which pregnant rabbits were administered oral doses of up to 40 mg/kg (~2 times the MRHD on a mg/m² basis) during organogenesis, no adverse effects on embryofetal development were observed. In other reproductive studies in which female rats were dosed orally during pregnancy and lactation (5, 20, 80, or 160 mg/kg), increased pup mortality at birth was seen at ≥80 mg/kg, and decreases in pup body weight and survival were observed at all doses (low effect dose ~0.1 times the MRHD on a mg/m² basis). **Nonteratogenic Effects:** Neonates exposed to IR fluvoxamine maleate and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on postmarketing reports. Complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs or SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**). Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN is associated with substantial neonatal morbidity and mortality. In a case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was ~6 fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. PPHN occurs in 1-2 per 1000 live births in the general population. When treating a pregnant woman with LUVOX CR during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery:** The effect of fluvoxamine on labor and delivery in humans is unknown. **Nursing Mothers:** Fluvoxamine is secreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** LUVOX CR has not been evaluated in pediatric patients (see **BOXED WARNING**). The efficacy of IR fluvoxamine maleate for the treatment of OCD was demonstrated in a 10-week multicenter placebo-controlled study with 120 outpatients ages 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another 1 to 3 years, equivalent to 94 patient years. The AE profile observed in that study was generally similar to that observed in adult studies with IR fluvoxamine maleate (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term. The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, no studies directly evaluated the effects of long-term fluvoxamine use on the growth, cognitive behavioral development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development, or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have