

Donepezil Makes Difference in Severe Alzheimer's

BY PATRICE WENDLING

Chicago Bureau

CHICAGO — Patients with severe Alzheimer's disease showed improved cognition and function when treated with donepezil in a 24-week, placebo-controlled trial, Dr. Sandra Black and her associates reported in a poster at the annual meeting of the American Geriatrics Society.

The results are consistent with a Swedish nursing home study in a similar,

institutionalized population (Lancet 2006;367:1262-70), suggesting that even patients with severe disease can benefit from treatment with donepezil.

"The two studies taken together suggest that this stage of disease can show measurable benefits of treatment with donepezil," Dr. Black, professor of medicine and head of neurology at Sunnybrook Health Sciences Centre, University of Toronto, said in an interview. "They give a new evidence-based option for treat-

ment, which gives hope for a better quality of life in the final phase of this devastating disease."

Currently, donepezil (Aricept) is approved for mild to moderate Alzheimer's disease. In February 2006, the U.S. Food and Drug Administration accepted a supplemental new drug application for donepezil in severe Alzheimer's disease.

Doses of 5 mg and 10 mg of donepezil are typically administered once daily, although the higher 10-mg dose did not pro-

vide significantly greater clinical benefit in previous clinical trials.

In their study, Dr. Black and her colleagues randomized 343 patients with severe Alzheimer's disease to an initial dose of donepezil of 5 mg/day for 6 weeks and then 10 mg/day of donepezil (176 patients) or placebo (167 patients) for 24 weeks. Patients resided in the community or in assisted-living facilities. Baseline characteristics were similar in both groups. Their mean age was 78 years, mean Mini-Mental State Exam score was 7.5, and the majority (86.3%) had Functional Assessment Staging scores of 6.a-6.e.

Overall, 117 of the 176 donepezil-treated patients and 127 of the 167 placebo patients completed the study, which was supported by Eisai Inc. and Pfizer Inc.

Dr. Black holds no financial interest in either firm, but has been a study investigator for both. She is an ad hoc consultant and speaker, and has received honoraria from Pfizer.

The primary end points were change

from baseline in Severe Impairment Battery (SIB) total score and Clinician's Interview-Based Impression of Change-Plus (CIBIC-plus) at 24 weeks.

The primary analysis was based on the intent-to-treat population using a last observation carried forward

analysis at 24 weeks. The intent-to-treat population consisted of all patients who were randomized, received at least one dose of either donepezil or placebo, and had a baseline and at least one postbaseline efficacy value.

Categories in the CIBIC-plus analysis were collapsed (1-3 equals improved; 4 equals no change; and 5-7 equals worsened) because the distribution of values was sparse in categories 1, 2, and 7.

Donepezil was significantly superior to placebo on the SIB score at week 24 in the intent-to-treat population (mean difference 5.3), and at weeks 8, 16, and 24 in patients who completed the study, Dr. Black reported.

The collapsed category CIBIC-plus analysis significantly favored donepezil at week 24 in the intent-to-treat population and in patients who completed the study. Among donepezil-treated patients, 28% improved, 38% had no change, and 34% worsened, compared with 23%, 29%, and 48% of placebo patients, respectively.

Most reported adverse events were mild to moderate (74%), the most common of which were diarrhea, nausea, and insomnia. Placebo patients reported more serious and severe adverse events than donepezil-treated patients. However, more patients discontinued treatment because of adverse events in the donepezil group than in the placebo group (18.3% vs. 10.8%, respectively), Dr. Black reported.

Vivitrol™

(naltrexone for extended-release injectable suspension)

BRIEF SUMMARY See package insert for full Prescribing Information.

INDICATIONS AND USAGE: VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration. Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support. **CONTRAINDICATIONS:** VIVITROL is contraindicated in: • Patients receiving opioid analgesics (see PRECAUTIONS). • Patients with current physiologic opioid dependence (see WARNINGS). • Patients in acute opiate withdrawal (see WARNINGS). • Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids. • Patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent.

WARNINGS: Hepatotoxicity

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses.

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis.

Eosinophilic pneumonia In clinical trials with VIVITROL, there was one diagnosed case and one suspected case of eosinophilic pneumonia. Both cases required hospitalization, and resolved after treatment with antibiotics and corticosteroids. Should a person receiving VIVITROL develop progressive dyspnea and hypoxemia, the diagnosis of eosinophilic pneumonia should be considered (see ADVERSE REACTIONS). Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia. Clinicians should consider the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics. **Unintended Precipitation of Opioid Withdrawal—To prevent occurrence of an acute abstinence syndrome (withdrawal) in patients dependent on opioids, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting VIVITROL treatment. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge test should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of VIVITROL. Opioid Overdose Following an Attempt to Overcome Opiate Blockade** VIVITROL is not indicated for the purpose of opioid blockade or the treatment of opiate dependence. Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life-endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade (see INFORMATION FOR PATIENTS). There is also the possibility that a patient who had been treated with VIVITROL will respond to lower doses of opioids than previously used. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after VIVITROL treatment is discontinued (see INFORMATION FOR PATIENTS). **PRECAUTIONS: General—When Reversal of VIVITROL Blockade is Required for Pain Management** In an emergency situation in patients receiving VIVITROL, a suggested plan for pain management is regional analgesia, conscious sedation with a benzodiazepine, and use of non-opioid analgesics or general anesthesia. In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction), presumably due to histamine release. Irrespective of the drug chosen to reverse VIVITROL blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation. **Depression and Suicidality** In controlled clinical trials of VIVITROL, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in patients treated with VIVITROL than in patients treated with placebo (1% vs. 0). In some cases, the suicidal thoughts or behavior occurred after study discontinuation, but were in the context of an episode of depression which began while the patient was on study drug. Two completed suicides occurred, both involving patients treated with VIVITROL. Depression-related events associated with premature discontinuation of study drug were also more common in patients treated with VIVITROL (~1%) than in placebo-treated patients (0). In the 24-week, placebo-controlled pivotal trial, adverse events involving depressed mood were reported by

10% of patients treated with VIVITROL 380 mg, as compared to 5% of patients treated with placebo injections. Alcohol dependent patients, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking. Families and caregivers of patients being treated with VIVITROL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's healthcare provider. **Injection Site Reactions** VIVITROL injections may be followed by pain, tenderness, induration, or pruritus. In the clinical trials, one patient developed an area of induration that continued to enlarge after 4 weeks, with subsequent development of necrotic tissue that required surgical excision. Patients should be informed that any concerning injection site reactions should be brought to the attention of the physician (see INFORMATION FOR PATIENTS). **Renal Impairment** VIVITROL pharmacokinetics have not been evaluated in subjects with moderate and severe renal insufficiency. Because naltrexone and its primary metabolite are excreted primarily in the urine, caution is recommended in administering VIVITROL to patients with moderate to severe renal impairment. **Alcohol Withdrawal** Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms. **Intramuscular injections** As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (e.g., hemophilia and severe hepatic failure). **Information for Patients** Physicians are advised to consult Full Prescribing Information for information to be discussed with patients for whom they have prescribed VIVITROL. **Drug Interactions** Patients taking VIVITROL may not benefit from opioid-containing medicines (see PRECAUTIONS, Pain Management). Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of VIVITROL. No clinical drug interaction studies have been performed with VIVITROL to evaluate drug interactions, therefore prescribers should weigh the risks and benefits of concomitant drug use. The safety profile of patients treated with VIVITROL concomitantly with antidepressants was similar to that of patients taking VIVITROL without antidepressants. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies have not been conducted with VIVITROL. Carcinogenicity studies of oral naltrexone hydrochloride (administered via the diet) have been conducted in rats and mice. In rats, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The clinical significance of these findings is not known. Naltrexone was negative in the following in vitro genotoxicity studies: bacterial reverse mutation assay (Ames test), the heritable translocation assay, CHO cell sister chromatid exchange assay, and the mouse lymphoma gene mutation assay. Naltrexone was also negative in an in vivo mouse micronucleus assay. In contrast, naltrexone tested positive in the following assays: Drosophila recessive lethal frequency assay, non-specific DNA damage in repair tests with E. coli and WI-38 cells, and urinalysis for methylated histidine residues. Naltrexone given orally caused a significant increase in pseudopregnancy and a decrease in pregnancy rates in rats at 100 mg/kg/day (600 mg/m²/day). There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known. **Pregnancy Category C** Reproduction and developmental studies have not been conducted for VIVITROL. Studies with naltrexone administered via the oral route have been conducted in pregnant rats and rabbits. **Teratogenic Effects:** Oral naltrexone has been shown to increase the incidence of early fetal loss in rats administered ≥30 mg/kg/day (180 mg/m²/day) and rabbits administered ≥60 mg/kg/day (720 mg/m²/day). There are no adequate and well-controlled studies of either naltrexone or VIVITROL in pregnant women. VIVITROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The potential effect of VIVITROL on duration of labor and delivery in humans is unknown. **Nursing Mothers** Transfer of naltrexone and 6- α -naltrexol into human milk has been reported with oral naltrexone. Because of the potential for tumorigenicity shown for naltrexone in animal studies, and because of the potential for serious adverse reactions in nursing infants from VIVITROL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and efficacy of VIVITROL have not been established in the pediatric population. **Geriatric Use** In trials of alcohol dependent subjects, 2.6% (n=26) of subjects were >65 years of age, and one patient was >75 years of age. Clinical studies of VIVITROL did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. **ADVERSE REACTIONS** In all controlled and uncontrolled trials during the premarketing development of VIVITROL, more than 900 patients with alcohol and/or opioid dependence have been treated with VIVITROL. Approximately 400 patients have been treated for 6 months or more, and 230 for 1 year or longer. **Adverse Events Leading to Discontinuation of Treatment** In controlled trials of 6 months or less, 9% of patients treated with VIVITROL discontinued treatment due to an adverse event, as compared to 7% of the patients treated with placebo. Adverse events in the VIVITROL 380-mg group that led to more dropouts were injection site reactions (3%), nausea (2%), pregnancy (1%), headache (1%), and suicide-related events (0.3%). In the placebo group, 1% of patients withdrew due to injection site reactions, and 0% of patients withdrew due to the other adverse events. **Common Adverse Events** The most common adverse events associated with VIVITROL in clinical trials were nausea, vomiting, headache, dizziness, fatigue, and injection site reactions. For a complete list of adverse events, please refer to the VIVITROL package insert for full Prescribing Information. A majority of patients treated with VIVITROL in clinical studies had adverse events with a maximum intensity of "mild" or "moderate." **OVERDOSAGE:** There is limited experience with overdose of VIVITROL. Single doses up to 784 mg were administered to 5 healthy subjects. There were no serious or severe adverse events. The most common effects were injection site reactions, nausea, abdominal pain, somnolence, and dizziness. There were no significant increases in hepatic enzymes. In the event of an overdose, appropriate supportive treatment should be initiated. This brief summary is based on VIVITROL Prescribing Information (VIV 500 Apr 2006).

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