Young Patient With Chest Pain? Suspect Cocaine

BY SHERRY BOSCHERT

San Francisco Bureau

SAN FRANCISCO — Consider cocaine use as a cause of chest pain, especially in young patients, Dr. Priscilla Hsue advised at a meeting sponsored by the California chapter of the American College of Cardiology.

In 2004, 2 million Americans were cocaine users, and cocaine was the most frequently used illicit drug among patients seeking care in emergency departments. About 6% of patients with cocaine-associated chest pain who are seen in emergency departments develop MI, one study suggests.

"I was covering the cardiology service a couple of weeks ago, and almost every day 50% of our admissions were for some kind of side effect from cocaine," said Dr. Hsue of San Francisco General Hospital. "This is something we see so often.

Patients with cocaine-related chest pain,

unstable angina, or MI tend to be younger than 40 years old, male, and cigarette smokers who have no other risk factors for coronary artery disease.

Chronic and first-time cocaine users have the same risk for MI. Symptoms can appear within minutes or hours after exposure to any dose of cocaine via any route—smoking, snorting, or ingesting.

Cocaine increases the risk of MI 24-fold within 1 hour of use, with the risk decreasing over time after that. The overall likelihood of MI is seven times higher in chronic cocaine users, compared with nonusers. Combining cocaine with alcohol use increases the risk of sudden death by more than 20 times, compared with nonusers, studies suggest.

Cocaine use increases the risk for MI in three ways: by increasing the heart rate and blood pressure in a setting of limited oxygen supply; by vasoconstriction (which is a danger especially in patients who smoke cigarettes or who have preexisting cardiovascular disease), and by promoting inflammation (possibly due to increases in C-reactive protein and platelet levels), she said at the meeting, also sponsored by the University of California, San Francisco.

Ischemic chest discomfort from cocaine use can be indistinguishable from unstable angina or non-ST-segment elevation MI due to coronary atherosclerosis. Only 13% of the patients who presented with chest pain to an emergency department were assessed for cocaine use, one study found.

If cocaine use is suspected or known in a patient with chest pain who has ECG changes, treat with oral nitroglycerin and a calcium antagonist, in accordance with 2002 guidelines from the ACC and American Heart Association. If ST-segment elevations persist, perform coronary arteriography immediately. Give thrombolytic therapy if a thrombus is detected, and consider it if catheterization is not available, the guidelines state.

Those class I recommendations are backed by evidence for or general agreement about their effectiveness and usefulness. The guidelines include several class IIa recommendations based on conflicting evidence or opinions that tend to favor efficacy. These include giving β-blockers for patients with hypertension or sinus tachycardia, and giving intravenous calcium antagonists if the ECG changes suggest ischemia (J. Am. Coll. Cardiol. 2002;

Controversy over some of these treatment recommendations will be addressed in new guidelines for the management of patients with unstable angina and non-STsegment elevation MI to be released in 2007, said Dr. Hsue, who helped draft the document.

Thrombolytic therapy is controversial in these patients because of case reports of complications. There is no way clinically to differentiate cocaine-related MI from non-cocaine-related MI, and 50%-80% of cocaine users with chest pain have abnormal ECG results that can persist for weeks, complicating the diagnosis.

We tend not to recommend [thrombolytic therapy] in our cocaine users," she

Many clinicians believe that β-blockers should not be given to patients with cocaine-induced chest pain, but this view is based on one small study of normotensive patients with no prior cocaine use, she noted. The evidence for use of calcium channel blockers likewise comes from a few small studies of patients not representative of cocaine users.

These studies were small, and it's hard to base conclusions on them," she said.

Brief Summary—see package insert for full prescribing information.

ARICEPT® (Donepezil Hydrochloride Tablets)

ARICEPT® ODT (Donepezil Hydrochloride) Orally Disintegrating Tablets

INDICATIONS AND USAGE ARICEPT® is indicated for the treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild to moderate Alzheimer's Disease, as well as in patients with severe Alzheimer's Disease. CONTRAINDICATIONS ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. WARNINGS Anesthesia: ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type piperdine derivatives. WARNINGS Anesthesia: ARICE*PI*, as a cholinesterase inhibitor, si kiely to exaggarate succinyicholine-type muscle relaxation during anesthesia. Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sincatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT*. Gastrointestinal Conditions: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those air increased risk for developing ulders, e.g., those with the propagation of the propagatio history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding, ARICEPT®, as have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. Genitourinary: Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction. Neurological Conditions: Seizures: Cholinomimetics are believed to have some potential to cause generalized comvulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. Pulmonary Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. PRECAUTIONS Drug-Drug Interactions (see Clinical Pharmacology: Clinical Pharmacokinetics: Drug-drug Interactions). Effect of ARICEPT® on the Netabolism of Other Drugs: No in vivo clinical trials have investigated the effect. ARICEPT® on the Netabolism of Control Pharmacology (2007) of the properties of the properties.) Interlations) Enect of ARICEPT* on the eleazonism of Unier Drugs: No in vivocialical trails have investigated the effect of ARICEPT* on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, in vitro studies show a low rate of binding to these enzymes (mean K, about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT* has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT* for interaction with theophylline, cimetidine, warfarin, digoxin and ketocorazole. No effects of ARICEPT* on the pharmacokinetics of these drugs were observed. Effect of Other Drugs on the Metabolism of ARICEPT*: Ketocorazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, this inhibit donepezil metabolism in with a Whether those is a clinical effect of ruinidinal is not known in a 7-chargers study in 18 health. inhibit donepezil metabolism in vitro. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy inhibit donepezil metabolism *in vitro* Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations (AUC₀₋₂₄ and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown. Inducers of CYP 206 and CYP 3A4 (e.g., phenytoin, carbarnazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine. *Use with Anticholinergis*: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfer the activity of anticholinergic medications. *Use with Cholinomimetics and Other Cholinesterase Inhibitors*: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. Carcinogenesis, *Mutagenesis*, *Impairment of Fertility* No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses unto 180 mo/kn/táxy (anorxximately 90 times the maximum ecommended human dose on a mo/m² basis). Or in a 104-week doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m² basis), or in a 104-week doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m* basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m* basis). Donepezil was not mulagenic in the Ames reverse mutation assay in baderia, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis). **Pregnancy Pregnancy Category C:** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis in the recensart rathis at doses up to 16 mg/kg/day (approximately 15 times the maximum recommended human dose on a mg/m² basis in the recensart rathis at doses up to 16 mg/kg/day (approximately 15 times the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² basis in the maximum recommended human dose on a mg/m² bas in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m basis) din of disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight docrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursting Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT* has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT* in any illness cocurring in childred. Geriatric Use Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of the patients enrolled in the clinical studies with ARICEPT® was 73 years; 80% of these patients were between 65 and 84 years old and 49% of the enrolled in the clinical studies with ARICEPT® was 73 years; 80% of these patients were between 65 and 84 years old and 49% of the patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups -86 years old and <65 years old. ADVERSE REACTIONS Mild To Moderate Atzheimer's Disease Adverse Events Leading to Discontinuation The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® mydday treatment groups were comparable to those of placebo-treatment groups at approximately 59%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1. Table 1.

Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group (Placebo), mm/day ABICEPT® and 10 mg/day ABICEPT® respectively. Patients Randomized (355, 356, 131). Event/%, and 10 mg/day ABICEPT® and 13 mg/day ABICEPT® respectively. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group (Placebo, 5 mg/day ARICEPT*, and 10 mg/day ARICEPT*, respectively); Patients Randomized (355, 350, 315); Eventry% Discontinuing: Naussa (1%, 1%, 3%); Diam'rea (0%, <1%, 3%); Domiting (<1%, <1%, 2%). Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT*. The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT*'s cholinominetic effects. These include naussa, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT* treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of rommon adverse events were lower than those seen in artistics titrated to 10 mg/day over one week over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one weel in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most in the controlled clinical traits and were comparable to those seen in patients on 5 mg/day. See table 210r a companson of the most common adverse events following one and six week titration regimens. Table 2. Comparison of rates of adverse events in patients titrated to 10 mg/day over 1 and 6 weeks (No titration: Placebo [n-315], No titration: 5 mg/day [n-311], One week titration: 10 mg/day [n-315], Six week titration: 10 mg/day [n-269], respectively): Nausea (6%, 5%, 19%, 6%); Diarrhea (5%, 6%, 15%, 9%); Insomnia (6%, 6%, 14%, 6%); Fatigue (3%, 4%, 8%, 3%); Vomiting (3%, 3%, 8%, 5%); Muscle cramps (2%, 6%, 8%, 3%); Anorexia (2%, 3%, 7%, 3%). Adverse Events Reported in Controlled Trials The events clied reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical trials reached in the conditions of clinical trials in a highly selected patient population. In actual clinical trials to the conditions of clinical trials in a highly selected patient population. In actual clinical trials are conditions of clinical trials in a highly selected patient longer on the patients are many or analyses the conditions of clinical trials in a highly selected patient longer or and the kinds. practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age. Table 3. Adverse Events Reported in Controlled Clinical Trials in Mild to Moderate Alzheimer's Disease in at Least 2% Patients Receiving ARICEPT® and at a Higher Frequency than Placebo-treated Patients (Body System/Adverse Event: Placebo In=355), ARICEPT® n=471, respectively): Percent of Patients with any Adverse Event: 72, 74. Body as a Whole: Headache (9, 10); Pain, various locations (8, 9); Accident (6, 7); Fatigue (3, 5). Cardiovascular System: Syncope (1, 2). Digestive System: Nausea (6, 11); Diarrhaa (5, 10); Vorniting (3, 5); Anorexia (2, 4). Hemic and Lymphatic Systems (Missale Carmos Maria Ecchymosis (3, 4). Metabolic and Nutritional Systems: Weight Decrease (1, 3). Musculoskeletal System: Muscle Cramps (2, 6): Arthritis (1, 2). **Nervous System:** Insomnia (6, 9): Dizziness (6, 8): Depression (<1, 3): Abnormal Dreams (0, 3): Somnolence 1, 2). Urugenital System: Frequent Urination (1, 2). Other Adverse Events Observed During Clinical Trials. ARICEPT[®] as been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been eated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials

in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced categores are used in the listing below. The frequencies represent the proportion of YWO patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events—those occurring in at least 1/100 patients; infrequent adverse events—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** Frequent: influenza, chest pain, toothache, finfrequents from preferring departments and in the controlled studies. The preferring the proportion of the propo fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. Cardiovascular System: Frequent: hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; Infrequent: angina Cardiovascular System: Frequent: hypertension, vascoliation, athal horilation, not hashes, hypotension; Infrequent: angine pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. Digestive System: Frequent: fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; Infrequent enclation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastrointestinals, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. Endocrine System: Infrequent: diabetes mellitus, goiter. Hemic and Lymphatic System: Infrequent: anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. Metabolic and Nutritional Disorders: Frequent: dehydration; Infrequent and though a programment of the programm gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. Musculoskeletal System: Frequent: bone fracture; Infrequent: muscle weakness, muscle fasciculation. Nervous System: Frequent: delusions, System: Prequent: one tracture; Intrequent muscie weardress, muscel teasciculation. Nervous System: Prequent: cellusor, termor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, ahonomal crying, nervousness, aphasia; Intrequent cerebrovascular accident, intracranial hemorthage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait ahonomality, typertonia, hypokinesia, neurodermatitis, numbness (localized), paranola, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. Respiratory System: Frequent: dyspnea, sore throat, bronchitis; Infrequent epistavis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. Skin and Appendages: Frequent: pruritus, diaphoresis, urticaria, Infrequent dermatitis, enythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, enythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herges zoste. Forecuert categoristic usiden blurget. Infraquent client infraquent (infraquent client fungales). hirsutism, skin striae, night sweats, skin ulcer. Special Senses: Frequent: cataract, eye irritation, vision blurred; Infrequent: dry nirsunsm, skin strae, night sweas, skin uicer. Special senses: requent: cataract, eye irritation, vision burred; imrequent only eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. Urogenital System: Frequent: urinary incontinence, nocturia; Infrequent: dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. Severe Alzheimer's Disease Adverse Events Leading to Discontinuation: The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® patients were approximately 12% compared to 7% for placebo patients. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of ARICEPT® patients and at twice the incidence seen in leaston and the leading to discontinuation, defined as those occurring in at least 2% of ARICEPT® patients and at twice the incidence seen in leaston and the leading to discontinuation, defined as those occurring in at least 2% of ARICEPT® patients and at twice the incidence seen in leaston and the leading to discontinuation; the retirement and the leading to discontinuation; the retirement and the leading to discontinuation of the leading to discontinuation of the leading to discontinuation; the retirement and the leading to discontinuation; the retirement and the leading to discontinuation of the leading to the leading to discontinuation; the retirement and the leading to the leading to discontinuation; the leading the leading the leading to the leading the leading to the leading to the leading to the leading to the le placebo patients, were anorexia (2% vs 1% placebo), nausea (2% vs <1% placebo), diarrhea (2% vs 0% placebo), and urinary trac infection (2% vs 1% placebo). Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT*
The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving ARICEPT* and twice the placebo rate, are largely predicted by ARICEPT* scholinornimetic effects. These include diarrhea, anorexia, vorniting, nause, and earlymosis. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT* treatment without the need for dose modification. Adverse Events Reported in Controlled Trials Table 4 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo -controlled trials who received ARICEPT* and for which the rate of occurrence was greater for ARICEPT* assigned than placebo -controlled trials who received ARICEPT* and for which the rate of cocurrence was greater for ARICEPT* assigned than placebo assigned patients. Table 4. Adverse Events Reported in Controlled Clinical Trials in Severe Alzheimer's Diseases in at Least 2% of Patients Receiving ARICEPT* and at a Higher Frequency than Placebo-treated Patients (Body System/Adverse Event: Placebo [n=392], ARICEPT* [n=501], respectively): Percent of Patients with any Adverse Event: 73, 81. Body as a Whole: Accident (12, 13) infection (9, 11); Headache (3, 4); Pain (2, 3); Back Pain (2, 3); Fever (1, 2); Chest Pain (-1, 2). Cardiovascular System: Hypertension (2, 3); Hemorrhage (1, 2), System: Ecchymosis (2, 5), Metabolic and Nutritional Systems: Creating Phosphokinase Increased (1, 3); Dehydration (1, 2); Hypertipernia (-1, 2). Nervous System: Insomnia (4, 5); Hostifie(2, 3); Parousness (2, 3); Hallucinations (1, 3); Somnolence (1, 2); Diziness (1, 2); Depression (1, 2); Confusion (1, 2); Enotional Lability (1, 2); Personality Disorder (1, 2). Skin and Appendages: Eczema (2, 3). Urogenital System: Urinary Incontinence (1, 2). Other infection (2% vs 1% placebo). Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT (1, 2); Personality Disorder (1, 2). Skin and Appendages: Eczema (2, 3). Urogenital System: Urinary Incontinence (1, 2). Other Adverse Events Observed During Clinical Trials ARICEPT® has been administered to over 600 patients with severe Alzheimer's Disease during clinical trials of at least 6 months duration, including 3 double blind placebo controlled trials, one of which had an open Disease during clinical finals of al least 6 months duration, including 3 double bind placebo controlled thats, one of which had an operate habel extension. All adverse events occurring at least twice are included, except for those already listed in Table 4, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system using the COSTART dictionary and listed using the following definitions. *requent adverse events—those occurring in at least 1/100 patients; interquent adverse events—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT* treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. **Body as a Whole:** *Frequent* abdominal pain, asthenia, fungal infection, flu syndrome; *Infrequent* allergic reaction, cellulitis, malaise, sepsis, face edema, hernia.

*Cardiovascular System: *Frequent* thypotension, bradycardia, ECG abnormal, heart failure, *Infrequent* myocardial infarction, acceptable bact failure expendituals reactivals reactivals reactivals are expendituals. angina pectoris, atrial fibrillation, congestive heart failure, peripheral vascular disorder, supraventricular extrasystoles, ventricular angina pectoris, atrial fibrillation, congestive heart failure, peripheral vascular disorder, supraventricular extrasystoles, ventricular extrasystoles, cardiomegaly. Digestive System: Frequent constipation, gastroenteritis, fecal incontinence, dyspepsia, infrequent: garma glutamy transpeptidase increase, gastritis, dysphagia, periodontitis, stomach ulcer, periodontal abscess; fathulence, liver function tests abnormal, eructation, esophagitis, rectal hemorrhage. Endocrine System: Infrequent: diabetes mellitus. Hemic and Lymphatic System: Frequent: ameria; Infrequent: leukocytosis. Metabolic and Nutritional Disorders: Frequent: weight loss, peripheral edema, edema, lactic dehydrogenase increased, alkaline phosphatase increased; Infrequent: hypercholestermia, hypokalemia, hypoglycemia, weight gain, bilirubinemia, BUN increased, B., deficiency anemia, cachexia, creatinine increased, gout, hyponatremia, hypoproteinemia, iron deficiency anemia, SGOT increased, SGPT increased. Musculoskeletal System: Frequent: arthritis; Infrequent: arthritis; Infrequent: arthritis; Infrequent: arthrosis, bone fracture, arthritis, Infrequent: anothy verification, delivisors, shormed Interess: Prequent: agitation, any long the proposed prop anxiety, tremor, convulsion, wandering, abnormal gait; I*nfrequent:* apathy, vertigo, delusions, abnormal dreams, cerebrovascular accident, increased salivation, ataxia, euphoria, vasodilatation, cerebral hemorrhage, cerebral infarction, cerebral ischemia, dementia, accident, increased salivation, ataxia, euriporia, vasocidiation, cerebral hemorrhage, cerebral infarction, cerebral ischemia, dementa, extrapyramidal syndrome, grand mal convulsion, hemiplegia, hypertonia, hypokinesia. Respiratory System: Frequent: phanyolitis, pneumonia, cough increased, bronchitis; Infrequent: dyspnea, rhinitis, asthma. Skin and Appendages: Frequent: phanyolitis, pneumonia, cough increased, bronchitis; Infrequent: dyspnea, thinitis, asthma. Skin and Appendages: Frequent: rash, skin ulcer, pruritus; Infrequent: psoriasis, skin discoloration, herpes zoster, dry skin, sweating, urticaria, vesiculobullous rash. Special Senses: Infrequent: conjunctivitis, glaucoma, abnormal vision, ear pain, lacrimation disorder. Urogenital System: Frequent: urinary tract infection, cystitis, hematuria, glycosuria; Infrequent: vaginitis, dysuria, urinary frequency, albuminuria. Postintroduction Reports Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that explored is producted to the discount of the caused relationship with the drug included the followings abdominal. not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdomina pain, agritation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia pain, agitation, cholecystists, conflusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyporatema, neuroleptic malignant syndrome, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe rausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an anticiote for ARICEPT® overdosage. Intravenous atropine sullate titrated to effect is recommended: an initial dose of 1.0 in 2.0 mpt / with subsequent drives beased unous chieful responses in blond prosessive and bease thas be been to 2.0 mg IV with subsequent doses based upon clinical response. Alvoical responses in blood pressure and heart rate have been to 2.0 mg iv with subsequent uses useau upon clinical response. Algorith responses in blood pressore and hear rate nave usen reported with other cholinomimetics when co-administered with quaterrary anticholinergics such as glycopyrrollate is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hernodialysis, peritoneal dialysis, or hernofilitation). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miceis, tremors, fasciculation and lower body surface temperature.