# Policy & Practice

## Carotid Stent Guidelines Released

A coalition of groups has released a set of guidelines for determining when physicians are qualified to perform carotid artery stenting. "This is a very rigorous set of standards," said Kenneth Rosenfield, M.D., director of cardiac and vascular invasive services at Massachusetts General Hospital in Boston. "This sets the bar very high." The standards call for physicians to first be proficient in other types of stenting, and then to perform a minimum of 30 diagnostic angiograms and 25 carotid stenting procedures under supervision. They also call for physicians to be skilled in risk assessment, diagnosis, and alternative therapies for the patients involved, and to report and analyze their outcomes. The document notes that physicians of many different subspecialties will seek the training; one of the issues in developing the guidelines had been whether to restrict training only to certain specialists.

## Neuroscience Partnership at NIH

The National Institutes of Health is breaking down barriers between 14 of its institutes and centers to better coordinate research done on the brain and nervous system. Neuroscience is "one of the most important and dynamic scientific frontiers for biomedical and behavioral research in this century," said NIH Director Elias A. Zerhouni, M.D. "Greater synergy and cross-fertilization across research disciplines will be needed for progress in our understanding of this complex system and new discoveries of benefit to our patients." The partnership blueprint will allow resources established by one institute or center to be open to scientists supported by other centers. The blueprint is available at http://neuroscienceblueprint.nih.gov.

## Site for Parkinson's Trials Launched

A consortium comprising patient groups, private foundations, government, and industry has launched a new Web site dedicated to clinical trials for Parkinson's disease. The site, www.pdtrials.org, is part of Advancing Parkinson's Therapies (APT), a project designed to accelerate the development of new treatments. Currently, about 5,000 Parkinson's patients particulate in clinical trials, "far short of the 10,000-15,000 participants researchers anticipate they will need to efficiently conduct clinical studies over the next 2-3 years," APT noted in a statement. The new site helps patients find trials by type of disease and geographic location and encourages visitors to sign up to receive e-mail updates when new trials are added.

## Health Care Spending by the Elderly

U.S. seniors spent an average of $11,089 on personal health care goods and services in 1999, but nearly half that amount was reimbursed by Medicare and another 15% was paid for by Medicaid, according to a report prepared by the Centers for Medicare and Medicaid Services' Office of the Actuary. The amount spent by seniors was almost four times the average of $2,793 for people under age 65. "What this report shows is the importance of our efforts to bring down the high cost of health care for America's seniors," CMS Administrator Mark B. McClellan, M.D., said in a statement. Although people 65 and over made up only 13% of the population in 1999, they accounted for 36% of personal health care spending, according to the report.

## Improper Payments Increase

Medicare made about $20 billion in improper payments in fiscal year 2004, a report from the Centers for Medicare and Medicaid Services found. The sum included $900 million in underpayments to providers due to errors made by insurers and $20.8 billion in overpayments to providers. CMS hopes to cut the rate of erroneous payments more than half, to 4%, in 2008 by conducting more extensive payment reviews and other quality controls. "We have made significant strides in how we measure the error rate in Medicare payments, and that will enable us to do even more to bring it down," said CMS Administrator Mark McClellan, M.D. A recent report from the Congressional Budget Office suggested that some of Medicaid's reimbursement policies may have contributed to increasing markups by pharmaceutical manufacturers.

## Patients Turn to CAM

Discouraged by costly conventional treatments, 6 million Americans turned to alternative medicines in 2002 for chronic pain and other conditions, the Center for Studying Health System Change reported. These alternatives "may be of questionable value," said HSC President Paul Ginsburg, Ph.D. About 63% of 31,000 adults said they used herbal remedies, yet two of the most popular remedies—St. John's wort and kava—can have serious side effects. The conventional medical professional was rarely aware of their patient using an alternative treatment.

—Joyce Frieden


**ARICEPT®** (Donepezil Hydrochloride Tablets)

Brief Summary—see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **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 muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial 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 at increased risk for developing ulcers, e.g., those with a 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 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 convulsions. 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 Metabolism of Other Drugs:*** No *in vivo* clinical trials 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 $K_i$ 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 ketoconazole. No effects of ARICEPT® on the pharmacokinetics of these drugs were observed. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, 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 ($AUC_{0-24}$ and $C_{max}$) by 36%. The clinical relevance of this increase in concentration is unknown. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, 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 Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with 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 up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m² 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/m² basis). Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, 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) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not 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 decrease 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. **Nursing 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 occurring in children. **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 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 ≥65 years old and <65 years old. **ADVERSE REACTIONS Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. 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**

| Dose Group | Placebo | 5 mg/day ARICEPT® | 10 mg/day ARICEPT® |
|---|---|---|---|
| **Patients Randomized** | 355 | 350 | 315 |
| **Event/% Discontinuing** | | | |
| Nausea | 1% | 1% | 3% |
| Diarrhea | 0% | <1% | 3% |
| Vomiting | <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 cholinomimetic effects. These include nausea, 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 common adverse events were lower than those seen in patients titrated to 10 mg/day over one week 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 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**

| Adverse Event | 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) |
|---|---|---|---|---|
| Nausea | 6% | 5% | 19% | 6% |
| Diarrhea | 5% | 8% | 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 cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical 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 at Least 2% of Patients Receiving ARICEPT® and at a Higher Frequency than Placebo-treated Patients**

| Body System/Adverse Event | Placebo (n=355) | ARICEPT® (n=747) |
|---|---|---|
| **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 |
| Diarrhea | 5 | 10 |
| Vomiting | 3 | 5 |
| Anorexia | 2 | 4 |
| **Hemic and Lymphatic System** | | |
| 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 |
| **Urogenital System** | | |
| Frequent Urination | 1 | 2 |

**Other Adverse Events Observed During Clinical Trials** ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated 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 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; *Infrequent:* 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 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:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, 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:* 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, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, 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, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry 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. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, 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 nausea, 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 antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. ARICEPT® should be taken in the evening, just prior to retiring. ARICEPT® can be taken with or without food. **HOW SUPPLIED** ARICEPT® is supplied as film-coated, round tablets containing either 5 mg or 10 mg of donepezil hydrochloride. The 5 mg tablets are white. The strength, in mg (5), is debossed on one side and ARICEPT is debossed on the other side. The 10 mg tablets are yellow. The strength, in mg (10), is debossed on one side and ARICEPT is debossed on the other side. 5 mg (White): Bottles of 30 (NDC# 62856-245-30), Bottles of 90 (NDC# 62856-245-90), Unit Dose Blister Package 100 (10x10) (NDC# 62856-245-41). 10 mg (Yellow): Bottles of 30 (NDC# 62856-246-30), Bottles of 90 (NDC# 62856-246-90), Unit Dose Blister Package 100 (10x10) (NDC# 62856-246-41). **Storage:** Store at controlled room temperature, 15°C to 30°C (59°F to 86°F).

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