

Asthma Admissions Drop After Smoking Ban

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FROM THE NEW ENGLAND
JOURNAL OF MEDICINE

Pediatric asthma hospitalizations decreased by about 20% per year after a ban on smoking in enclosed public spaces was enacted in Scotland, said Daniel Mackay, Ph.D., of the University of Glasgow and his associates.

Before the legislation was imple-

mented, there was concern that people might transfer their smoking from public areas to their homes, “leading paradoxically to an increase in exposure ... among children,” they said (N. Engl. J. Med. 2010;363:1139-45).

Such displacement of smoking activity has not occurred. Instead, the results support the conclusion of another study that found that the public ban on smoking was followed by an increase in vol-

untary smoking restrictions in homes as well, the investigators said.

They used government databases to identify all 21,415 asthma admissions across Scotland from January 2000 through October 2009 for children younger than 15 years.

In the period from 2000 until implementation of the smoking ban in 2006, hospital admissions for asthma rose an adjusted average of 4.4% per year.

In the period after the smoking ban was enacted, the risk-adjusted annual rate of pediatric asthma admissions declined 19.5%, a statistically significant difference. The rate of asthma hospitalizations decreased both in preschool and school-age children, Dr. Mackay and his colleagues said.

NHS Health Scotland funded the study. The investigators had no relevant conflicts of interest. ■

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, moderate, and severe Alzheimer's Disease. **DOSAGE AND ADMINISTRATION** ARICEPT should be taken in the evening, just prior to retiring. ARICEPT can be taken with or without food and should be swallowed whole with water. ARICEPT should not be split or crushed. The 23 mg tablet should not be crushed or chewed because this may increase its rate of absorption. Allow ARICEPT ODT tablet to dissolve on the tongue and follow with water. **Mild to Moderate Alzheimer's Disease:** 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.

Moderate to Severe Alzheimer's Disease: ARICEPT has been shown to be effective in controlled clinical trials at doses of 10 mg and 23 mg administered once daily. Results of a controlled clinical trial in moderate to severe Alzheimer's Disease that compared ARICEPT 23 mg once daily to 10 mg once daily suggest that a 23 mg dose of ARICEPT provided additional benefit. **Titration:** The recommended starting dose of ARICEPT is 5 mg once daily. Evidence from the controlled trials in mild to moderate Alzheimer's disease indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events compared to the 5 mg dose. In open-label trials using a 6 week titration, the type and frequency of these same adverse events were similar between the 5 mg and 10 mg dose groups. Therefore, because ARICEPT steady state is achieved about 15 days after it is started and because the incidence of untoward effects may be influenced by the rate of dose escalation, a dose of 10 mg should not be administered until patients have been on a daily dose of 5 mg for 4 to 6 weeks. A dose of 23 mg once daily can be administered once patients have been on a dose of 10 mg once daily for at least 3 months.

CONTRAINDICATIONS ARICEPT is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS AND PRECAUTIONS** **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. Syncope episodes have been reported in association with the use of ARICEPT. **Nausea and Vomiting:** 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, and more frequently with the 23 mg dose than with the 10 mg dose. Specifically, in a controlled trial that compared a dose of 23 mg/day to 10 mg/day in patients who had been treated with donepezil 10 mg/day for at least three months, the incidence of nausea in the 23 mg group was markedly greater than in the patients who continued on 10 mg/day (11.8% vs 3.4%, respectively), and the incidence of vomiting in the 23 mg group was markedly greater than in the 10 mg group (9.2% vs 2.5%, respectively). The percent of patients who discontinued treatment due to vomiting in the 23 mg group was markedly higher than in the 10 mg group (2.9% vs 0.4%, respectively). Although in most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT, patients should be observed closely at the initiation of treatment and after dose increases. **Peptic Ulcer Disease and GI Bleeding:** 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 in a dose of 5 mg/day to 10 mg/day have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Results of a controlled clinical study with 23 mg/day showed an increase, relative to 10 mg/day, in the incidence of peptic ulcer disease (0.4% vs. 0.2%) and gastrointestinal bleeding from any site (1.1% vs. 0.6%). **Weight Loss:** Weight loss was reported as an adverse event in 4.7% of patients assigned to ARICEPT in a dose of 23 mg/day compared to 2.5% of patients assigned to 10 mg/day. Compared to their baseline weights, 8.4% of patients taking 23 mg/day were found to have a weight decrease of $\geq 7\%$ by the end of the study, while 4.9% of patients taking 10 mg/day were found to have weight loss of $\geq 7\%$ at the end of the study. **Genitourinary Conditions:** 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.

ADVERSE REACTIONS Clinical Studies Experience: ARICEPT 5 mg/day and 10 mg/day **Mild to Moderate 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 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 or more the incidence seen in placebo patients, are shown in Table 1. **Table 1. Most Frequent Adverse Events Leading to Discontinuation from Controlled Clinical Trials by Dose Group (Placebo, 5 mg/day ARICEPT, and 10 mg/day ARICEPT, respectively); Patients Randomized (355, 350, 315); Event/% Discontinuing:** Nausea (1%, 1%, 3%); Diarrhea (0%, <1%, 3%); Vomiting (<1%, <1%, 2%). **Most Frequent Adverse 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 Mild to Moderate 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%, 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 patients treated with ARICEPT than with placebo. 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% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo Treated Patients (Body System/ Adverse Event: Placebo [n=355], ARICEPT [n=747], 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); Diarrhea (5, 10); Vomiting (3, 5); Anorexia (2, 4). **Hemic and Lymphatic System:** Echinymosis (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 three 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 related. 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, thrombocytopenia, 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. **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 or more the incidence seen in placebo, were anorexia (2% vs. 1% placebo), nausea (2% vs. <1% placebo), diarrhea (2% vs. 0% placebo) and urinary tract infection (2% vs. 1% placebo). **Most Frequent Adverse 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 at twice or more the placebo rate, are largely predicted by ARICEPT's cholinomimetic effects. These include diarrhea, anorexia, vomiting, nausea, and ecchymosis. 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 adverse events that were