

was largely attributable to reports of family members who were children of the participants and described their mothers as homemakers, while the mothers described themselves as having other professions. More than a third (38%) of responses from staff members indicating ignorance of the participant's occupation were for those whose family members described them as homemakers, Dr. Cohen-Mansfield reported.

In addition, although no significant gender differences were seen in role importance as assigned by participants and staff caregivers for each role group over time, family members reported significantly higher importance ranking for professional identi-

ty for males than for females in the past as well as present. "Family members generally estimated the importance of role identities in the past to be higher, and that in the present as lower, than did the participants," Dr. Cohen-Mansfield reported.

"Our results show that while general trends of a decline in importance of role-identity domains are the same between family informants and participants, the absolute ratings were significantly influenced by [which group were] informants." Understanding the changing self-identities of these people with dementia is a crucial first step toward providing tailored care and enhancing their life experience. ■

Hypertension Control May Preserve Cognition in Some

BY MARK S. LESNEY
Senior Editor

Elderly patients with mild to moderate hypertension and lowered cognitive function show greater cognitive decline, compared with equivalent hypertensive individuals with high cognitive function, a posthoc analysis shows.

The first Study on Cognition and Prognosis in the Elderly (SCOPE) analysis showed inconclusive results in demonstrating that antihypertensive treatment, primarily with candesartan, may preserve cognitive function and reduce the incidence of dementia, according to Ingmar Skoog, M.D., of Sahlgrenska University Hospital, Göteborg, Sweden, and colleagues in the international SCOPE study group.

The post hoc analysis was performed to compare cognitive and cardiovascular outcomes between 2,070 patients with slightly lower baseline cognitive function (LCF) as defined by Mini-Mental State Examination (MMSE) scores of 24-28, and 2,867 patients with higher cognitive function (HCF), defined by MMSE scores of 29-30 (Am. J. Hypertens. 2005;18:1052-9).

Additionally, the analysis separately compared cognitive and cardiovascular

outcomes in the candesartan control groups for LCF and HCF patients.

Significant cognitive decline was nearly twice as common in patients with LCF (6.6%), compared with patients with HCF (3.6%).

Cognitive decline did not differ significantly between candesartan and control groups. (For ethical reasons in the SCOPE trial, control patients also were given off-label active hypertensive therapy when deemed necessary, primarily with hydrochlorothiazide, significantly lowering blood pressure in both treatment groups).

Dementia onset during the study was found to be over four times as common in patients with LCF (4.4%) as in patients with HCF (1.0%). Here, too, no difference was seen between the candesartan and control groups, Dr. Skoog and colleagues reported.

Contrary to perceived fears by many physicians that lowering blood pressure in the elderly would cause cognitive decline because of reduction in cerebral blood flow, cognitive function changed very little, even in patients with LCF, the authors reported. In addition, dementia incidence in the study was found to be in the lower range of expectation for this age group. Thus, there appeared to be no negative effect of blood pressure control, according to the report.

Such evidence, coupled with the observation that mild to moderate hypertension and slightly impaired cognitive function in the elderly at baseline were associated with increased risk of significant cognitive decline and dementia, indicate that effective antihypertensive therapy may reduce cognitive decline in these patients, Dr. Skoog and colleagues concluded. ■



SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)

For Oral Inhalation Only
Brief Summary of Prescribing Information
INDICATIONS AND USAGE

SPIRIVA HandiHaler is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

CONTRAINDICATIONS

SPIRIVA HandiHaler is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product.

WARNINGS

SPIRIVA HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including angioedema, may occur after administration of SPIRIVA. If such a reaction occurs, therapy with SPIRIVA should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including SPIRIVA, may cause paradoxical bronchospasm. If this occurs, treatment with SPIRIVA should be stopped and other treatments considered.

PRECAUTIONS

General

As an anticholinergic drug, SPIRIVA may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) treated with SPIRIVA should be monitored closely.

Information for Patients

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler inhalation device. SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications.

Capsules should always be stored in sealed blisters and only removed immediately before use. The blister strip should be carefully opened to expose only one capsule at a time. Open the blister foil as far as the STOP line to remove only one capsule at a time. The drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced. Capsules that are inadvertently exposed to air (i.e., not intended for immediate use) should be discarded.

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Should any of these signs and symptoms develop, consult a physician immediately. Miotic eye drops alone are not considered to be effective treatment.

Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

SPIRIVA HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, i.e., as a rescue medication.

Drug Interactions

SPIRIVA has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions. These include sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids. However, the co-administration of SPIRIVA with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the Recommended Human Daily Dose (RHDD) on a mg/m² basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies. Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD on a mg/m² basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times the RHDD on a mg/m² basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m² basis). These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

Pregnancy

Pregnancy Category C

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m² basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥ 0.078 mg/kg (approximately 35 times the RHDD on a mg/m² basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m² basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m² basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

The safety and effectiveness of SPIRIVA has not been studied during labor and delivery.

Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA is administered to a nursing woman.

Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of SPIRIVA in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received SPIRIVA in the 1-year clinical trials, 426 were < 65 years, 375 were 65-74 years and 105 were ≥ 75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were -0.6%, 4.6% and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA dosage in geriatric patients is warranted.

ADVERSE REACTIONS

Of the 2,663 patients in the four 1-year and two 6-month controlled clinical trials, 1,308 were treated with SPIRIVA at the recommended dose of 18 mcg once a day. Patients with narrow angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.

Four multicenter, 1-year, controlled studies evaluated SPIRIVA in patients with COPD. Table 1 shows all adverse events that occurred with a frequency of $\geq 3\%$ in the SPIRIVA group in the 1-year placebo-controlled trials where the rates in the SPIRIVA group exceeded placebo by $\geq 1\%$. The frequency of corresponding events in the ipratropium-controlled trials is included for comparison.

Table 1: Adverse Experience Incidence (% Patients) in One-Year-COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n=550)	Placebo (n=371)	SPIRIVA (n=356)	Ipratropium (n=179)
Body as a Whole				
Accidents	13	11	5	8
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Sinusitis	11	9	3	2
Upper Respiratory Tract Infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the SPIRIVA treatment group, but were $< 1\%$ in excess of the placebo group.

Other events that occurred in the SPIRIVA group at a frequency of 1-3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole*: allergic reaction, leg pain; *Central and Peripheral Nervous System*: dysphonia, paresthesia; *Gastrointestinal System Disorders*: gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders*: hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders*: skeletal pain; *Cardiac Events*: angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder*: depression; *Infections*: herpes zoster; *Respiratory System Disorder (Upper)*: laryngitis; *Vision Disorder*: cataract. In addition, among the adverse events observed in the clinical trials with an incidence of $< 1\%$ were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age. Two multicenter, 6-month, controlled studies evaluated SPIRIVA in patients with COPD. The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

In addition to adverse events identified during clinical trials, the following adverse reactions have been reported in the worldwide post-marketing experience: epistaxis, palpitations, pruritus, and urticaria.

DOSE AND ADMINISTRATION

The recommended dosage of SPIRIVA HandiHaler is the inhalation of the contents of one SPIRIVA capsule, once-daily, with the HandiHaler inhalation device.

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA should be monitored closely. SPIRIVA capsules are for inhalation only and must not be swallowed.

HOW SUPPLIED

The following packages are available:

carton containing 6 SPIRIVA capsules (1 blister card) and 1 HandiHaler inhalation device (NDC 0597-0075-06)
carton containing 30 SPIRIVA capsules (5 blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-37)

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Rx only



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