

Brief Screen Finds Depression in Cardiac Patients

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NEW ORLEANS — A brief, two-question screening instrument is sensitive for identifying depression in patients with coronary heart disease, a study has shown.

Because major depression is associated with adverse outcomes in this patient population, the availability of a quick, effective tool for improving detection and referral rates could improve patient outcomes sub-

stantially, David D. McManus, M.D., reported at the annual meeting of the Society of General Internal Medicine.

Using data from the Heart and Soul Study out of the University of California, San Francisco, Dr. McManus and his colleagues compared the test characteristics of four depression case-finding instruments with those of the Diagnostic Interview for Depression in 1,024 adults with stable coronary heart disease (CHD) recruited from San Francisco-area outpatient clinics.

The instruments selected for comparison were the 10-item short form of the Center for Epidemiologic Studies Depression Scale (CES-D), the 9-item Patient Health Questionnaire (PHQ-9), the 2-item Patient Health Questionnaire (PHQ-2), and a brief screen that asks patients about depressed mood and anhedonia.

Specifically, the brief screen asks patients, "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "During the

past month, have you often been bothered by little interest or pleasure in doing things?" Dr. McManus said. An answer of "yes" to either of these questions was considered a positive screen.

Of the 1,024 study participants, 224 had major depression by standard measure (Diagnostic Interview for Depression). The brief, two-question screen was, at 90%, the most sensitive of the four test measures. The sensitivity of the CES-D, the PHQ-9, and the PHQ-2 was 76%, 54%, and 39%, respectively. The specificity of the brief screen was 69%, compared with 79%, 90%, and 92% for the CES-D, the PHQ-9, and the PHQ-2.

The instrument can be easily integrated into outpatient visits in the busiest practices, he said. "A negative response to both questions effectively rules out depression, and a positive response to either suggests the patient might benefit from referral or treatment."

The Heart and Soul Study is an ongoing, prospective cohort study designed to determine how psychosocial factors influence disease progression in patients with CHD. Study participants, whose mean age is 67, were recruited from the Veterans Affairs medical centers of San Francisco and Palo Alto, Calif., the University of California at San Francisco Medical Center, and nine public health clinics in the Community Health Network of San Francisco. ■



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 SPIRIVA (n=550)	Placebo (n=371)	Ipratropium-Controlled Trials 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)

Rx only

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Boehringer
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Low Body Temp Raises Mortality In Heart Failure

WASHINGTON — Body temperature below 36° C at hospital admission was independently associated with a lower survival rate in a study of 56,659 patients with advanced heart failure.

Disordered thermoregulation is common in patients with advanced heart failure, and body temperature measurements may improve risk assessment in these patients, Brahmajee K. Nallamothu, M.D., wrote in a poster presented at the Clinical Research 2005 meeting sponsored by the American Federation for Medical Research.

Dr. Nallamothu, a cardiologist at the University of Michigan, Ann Arbor, and his associates reviewed data on patients aged 65 years and older who were participating in the National Heart Care Project.

The mean body temperature upon hospital admission was 36.5° C, and most of the patients' admission temperatures were between 36° and 38° C. However, 10,754 (18.5%) of the patients had body temperatures below 36° C and 1,145 (1.9%) had body temperatures above 38° C.

After multivariate analysis, patients with body temperatures below 36° had significantly higher mortality, both in hospital (adjusted risk ratio, 1.28) and at 1 year after their hospitalizations (adjusted risk ratio, 1.14).

—Heidi Splete