

Target Patient's Physical Symptoms of Depression

BY DAMIAN McNAMARA

Miami Bureau

BOCA RATON, FLA. — Targeting physical symptoms of depression in a primary care setting increases the likelihood of treatment response and remission, according to a multicenter study.

Somatic symptoms of depression are getting increased attention as part of a drive to achieve asymptomatic remission, said Sidney H. Kennedy, M.D. He and his

associates hypothesized that alleviation of physical symptoms of depression would improve response and remission rates.

They assessed 205 patients undergoing open-label antidepressant treatment for 8 weeks in 47 primary care settings. Patients were being treated with venlafaxine, citalopram, fluoxetine, paroxetine, sertraline, bupropion, or mirtazapine. Mean patient age was 43 years, and 64% were female. A total of 157 patients completed the study.

At baseline, and every 2 weeks there-

after, researchers compiled an aggregate somatic score for each patient based on eight items culled from the Hamilton Depression Rating Scale (HAMD). This shorter instrument (HAMD-S) assessed gastrointestinal somatic symptoms; weight loss; early, middle, and late insomnia; general somatic symptoms; somatic anxiety; and hypochondriasis.

Two other scales—the Montgomery Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression Scale

for Improvement and Severity of Illness—were used to measure depression severity.

Results were presented during a poster session at a meeting of the New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health.

HAMD-S scores decreased from a mean of 10 at baseline to 3 at week 8, a statistically significant difference. There was a significant correlation between improvements on the HAMD-S and overall reductions in MADRS total score, response score, and remission score. Both HAMD-S and MADRS findings correlated with Clinical Global Impression Scale findings.

“The bottom line is we showed that physical symptoms responded comparably with the other symptoms,” said Dr. Kennedy, a psychiatrist with the University Health Network, Toronto.

The HAMD-S and MADRS scales, however, have not been validated as somatic subscales, Dr. Kennedy cautioned. This is a possible limitation of the study.

The study was funded by Wyeth Pharmaceuticals. Dr. Kennedy is a consultant and speaker for the company. ■

Depression Common in Teen Mothers

LOS ANGELES — Half of adolescent mothers experience significant depression in the first year after giving birth, according to a study of 417 young mothers followed for 48 months.

The study included roughly equal numbers of Mexican American, African American, and Caucasian mothers who were enrolled within 48 hours of giving birth and then surveyed with a Beck Depression Inventory at 3, 12, 24, and 48 months. Each returned at least three of the four surveys, R. Michelle Schmidt, M.D., said at the annual meeting of the Society for Adolescent Medicine.

The prevalence of depression, defined as moderate to severe symptoms on the inventory, was highest at 3 months (37%), said Dr. Schmidt of Baylor College of Medicine, Houston. After that, the prevalence steadily declined to 21% at 48 months.

Overall, 50% of the subjects had depression in the first year, and 57% had depression at some point during the study.

Depression, when it was present, appeared to persist. Eighty percent of those with depression at 3 months were also depressed at two or more other reporting periods. Moreover, 88% of those depressed at 48 months had been depressed at 12 months, and 15% had depression at every follow-up.

African American subjects had a prevalence of depression only half that of the two other groups at 3 months, and the prevalence among the African American subjects at 48 months was higher than it was at 24 months (20% vs. 16%).

—Timothy F. Kirn

Non-steroidal Anti-inflammatory Drugs: in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when AVALIDE (irbesartan-hydrochlorothiazide) Tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Irbesartan-Hydrochlorothiazide

No carcinogenicity studies have been conducted with the irbesartan-hydrochlorothiazide combination. Irbesartan-hydrochlorothiazide was not mutagenic in standard *in vitro* tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay). Irbesartan-hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (*in vitro*—human lymphocyte assay; *in vivo*—mouse micronucleus study).

The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

Irbesartan

No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to two years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC_{0-24hours}, bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) of 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan was not mutagenic in a battery of *in vitro* tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (*in vitro*-human lymphocyte assay; *in vivo*-mouse micronucleus study).

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC_{0-24hours}, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters)

(See WARNINGS: Fetal/Neonatal Morbidity and Mortality.)

Nursing Mothers

It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of AVALIDE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Irbesartan-hydrochlorothiazide

AVALIDE has been evaluated for safety in 898 patients treated for essential hypertension. In clinical trials with AVALIDE, no adverse experiences peculiar to this combination drug product have been observed. Adverse experiences have been limited to those that were reported previously with irbesartan and/or hydrochlorothiazide (HCTZ). The overall incidence of adverse experiences reported with the combination was comparable to placebo. In general, treatment with AVALIDE was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of AVALIDE therapy due to clinical adverse experiences was required in only 3.6%. This incidence was significantly less ($p=0.023$) than the 6.8% of patients treated with placebo who discontinued therapy.

In these double-blind controlled clinical trials, the following adverse experiences reported with AVALIDE occurred in ≥1% of patients, and more often on the irbesartan-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

	Irbesartan/HCTZ (n=898) (%)	Placebo (n=236) (%)	Irbesartan (n=400) (%)	HCTZ (n=380) (%)
Body as a Whole				
Chest Pain	2	1	2	2
Fatigue	7	3	4	3
Influenza	3	1	2	2
Cardiovascular				
Edema	3	3	2	2
Tachycardia	1	0	1	1
Gastrointestinal				
Abdominal Pain	2	1	2	2
Dyspepsia/heartburn	2	1	0	2
Nausea/vomiting	3	0	2	0
Immunology				
Allergy	1	0	1	1
Musculoskeletal				
Musculoskeletal Pain	7	5	6	10
Nervous System				
Dizziness	8	4	6	5
Dizziness Orthostatic	1	0	1	1
Renal/Genitourinary				
Abnormality Urination	2	1	1	2

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group: headache, sinus abnormality, cough, URI, pharyngitis, diarrhea, rhinitis, urinary tract infection, rash, anxiety/nervousness, and muscle cramp.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Irbesartan

Other adverse experiences that have been reported with irbesartan, without regard to causality are listed below:

Body as a Whole: fever, chills, orthostatic effects, facial edema, upper extremity edema
Cardiovascular: flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, hypotension, syncope, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis

Dermatologic: pruritus, dermatitis, ecchymosis, erythema face, urticaria
Endocrine/Metabolic/Electrolyte Imbalances: sexual dysfunction, libido change, gout

Gastrointestinal: diarrhea, constipation, gastroenteritis, flatulence, abdominal distention
Musculoskeletal/Connective Tissue: musculoskeletal trauma, extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness

Nervous System: anxiety/nervousness, sleep disturbance, numbness, somnolence, vertigo, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident

Renal/Genitourinary: prostate disorder

Respiratory: cough, upper respiratory infection, epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing

Special Senses: vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: weakness

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

Metabolic: hyperglycemia, glycosuria, hyperuricemia

Musculoskeletal: muscle spasm

Nervous System/Psychiatric: restlessness

Renal: renal failure, renal dysfunction, interstitial nephritis

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

Special Senses: transient blurred vision, xanthopsia

Post-Marketing Experience

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue). Hyperkalemia has been rarely reported. Very rare cases of jaundice have been reported with irbesartan.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3 and 1.1 percent, respectively, of patients with essential hypertension treated with AVALIDE alone. No patient discontinued taking AVALIDE due to increased BUN. One patient discontinued taking AVALIDE due to a minor increase in serum creatinine.

Hemoglobin: Mean decreases of approximately 0.2 g/dL occurred in patients treated with AVALIDE alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dL in patients receiving placebo. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with AVALIDE alone, one patient was discontinued due to elevated liver enzymes.

Serum Electrolytes: (See PRECAUTIONS.)

OVERDOSAGE

Irbesartan

No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis.

To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the *Physicians' Desk Reference* (PDR). In managing overdose, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient.

Laboratory determinations of serum levels of irbesartan are not widely available, and such determinations have, in any event, no established role in the management of irbesartan overdose.

Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25- and 50-fold the maximum recommended human dose (300 mg) on a mg/m² basis, respectively.

Hydrochlorothiazide

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

DOSAGE AND ADMINISTRATION

A lower initial dose of irbesartan (75 mg) is recommended in patients with depletion of intravascular volume (e.g., patients treated vigorously with diuretics or on hemodialysis) (see WARNINGS: Hypotension in Volume- or Salt-depleted Patients).

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

Use in Patients with Renal Impairment

The usual regimens of therapy with AVALIDE may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so AVALIDE is not recommended.

Consult package insert before prescribing AVALIDE (irbesartan-hydrochlorothiazide) Tablets.

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