

Bipolar Patients at Risk for Alcohol Dependence

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PITTSBURGH — Patients with bipolar II disorder are at high risk for alcohol abuse and dependence, based on findings from a 20-year, longitudinal study with about 600 patients.

The study’s findings also suggest that bipolar II disorder can be more broadly defined than current DSM-IV criteria, Kathleen R. Merikangas, Ph.D., said at the

Sixth International Conference on Bipolar Disorder.

Men and women in this study who developed bipolar II disorder using DMS-IV criteria were 4.6-fold more likely also to develop alcohol abuse, compared with people in the study who did not develop mood disorders.

The bipolar patients were also 8.2-fold more likely to be alcohol dependent, compared with those without a mood disorder. Those rates of alcohol abuse and depen-

dence were substantially higher than for people in the study who had major depression of symptoms or mania but no bipolar disorder.

“It looks like alcohol is the drug that patients with bipolar disorder use,” said Dr. Merikangas, chief of the section on developmental genetic epidemiology at the National Institute of Mental Health.

She hypothesized that “bipolar patients drink when they’re manic. Mania is not a pleasant state. It’s marked by agitation and

restlessness. Alcohol calms them down.” But she stressed that that explanation for the high rate of alcohol use by bipolar patients needs confirmation.

The substance abuse and dependence in the bipolar patients appeared to be specific for alcohol, she said at the conference, which was sponsored by the University of Pittsburgh. A similar analysis found no increased risk for cannabis use or dependence in bipolar patients.

The study has been a collaboration between researchers at the National Institute of Mental Health and the University of Zurich. In 1978, more than 4,500 men aged 19 years and women aged 20 years were screened for the Zurich cohort study.

The men had registered for the Swiss draft, and the women had registered for work permits. The group was screened for risk factors for bipolar disorder, and two groups were selected for ongoing assessment over the following 20 years. One group had high symptom scores that showed they faced an increased risk of eventually developing bipolar disorder. A second group with low scores was also included to serve as controls.

A total of 591 people was selected for long-term follow-up, which involved periodic interviews. By 1999, after 20 years of follow-up, 367 people remained in the study.

Three different criteria were used to identify people with bipolar disorder. DSM-IV criteria were the most restrictive, requiring people to have at least three symptoms of bipolar disorder that each lasted at least 4 days. After 20 years of follow-up, 12 people had developed bipolar II disorder based on the DSM-IV criteria.

The Zurich strict criteria also required three symptoms, but they could last 1 day or longer to count toward a diagnosis. Also, the symptoms had to have consequences, such as impairment of life activities. By the Zurich strict criteria, 33 people from the group were diagnosed with bipolar disorder.

The Zurich broad criteria required that people have only two symptoms that each lasted for at least 1 day, and consequences of the symptoms were not necessary. By the broad criteria, 44 people eventually developed bipolar disorder during 20 years of follow-up.

In addition, 96 people were diagnosed with monopolar major depression using DSM-IV criteria.

Several analyses that compared the three definitions of bipolar disorder and monopolar depression confirmed that the broad Zurich definition was a reasonable way to identify patients with bipolar disorder. For example, the percentage of patients with a family history of mania was 25% among those who met the DSM-IV criteria for bipolar disorder, 6% of those who met the strict Zurich criteria, 18% of those who met the broad Zurich criteria, and 4% of those who were diagnosed with monopolar depression.

The broad definition of bipolar disorder appeared valid, because people who met the broad criteria showed consistent similarities with patients who met the DSM-IV criteria, Dr. Merikangas said. ■

ALLEGRA-D® 24 HOUR
(fexofenadine HCl 180 mg and
pseudoephedrine HCl 240 mg)
Extended-Release Tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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INDICATIONS AND USAGE

ALLEGRA-D 24 HOUR Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate and/or throat, itchy/watery/red eyes, and nasal congestion.

ALLEGRA-D 24 HOUR should be administered when both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

ALLEGRA-D 24 HOUR is contraindicated in patients with known hypersensitivity to any of its ingredients. Due to its pseudoephedrine component, ALLEGRA-D 24 HOUR is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (see Drug Interactions section). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Sympathomimetic amines should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see CONTRAINDICATIONS). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension.

PRECAUTIONS

General

Because ALLEGRA-D 24 HOUR is a once-daily, fixed-dose combination that cannot be titrated and renal insufficiency increases the bioavailability and prolongs the half-life of fexofenadine hydrochloride and pseudoephedrine hydrochloride, ALLEGRA-D 24 HOUR tablets should generally be avoided in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, and DOSAGE AND ADMINISTRATION).

Information for Patients

Patients taking ALLEGRA-D 24 HOUR tablets should receive the following information: ALLEGRA-D 24 HOUR tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be instructed to take ALLEGRA-D 24 HOUR tablets only as prescribed. **Do not exceed the recommended dose.** If nervousness, dizziness, or sleeplessness occur, discontinue use and consult the doctor. Patients should also be advised against the concurrent use of ALLEGRA-D 24 HOUR tablets with over-the-counter antihistamines and decongestants. The product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease. Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant. Patients should be advised to take the tablet on an empty stomach with water. Patients should be directed to swallow the tablet whole. Patients should be cautioned not to break or chew the tablet. Patients should also be instructed to store the medication in a tightly closed container in a cool, dry place, away from children.

Drug Interactions

Fexofenadine hydrochloride and pseudoephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly.

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co-administration of fexofenadine hydrochloride with either ketoconazole or erythromycin led to increased plasma concentrations of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of either erythromycin or ketoconazole. In 2 separate studies, fexofenadine hydrochloride 120 mg twice daily was co-administered with either erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with either erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on steady-state fexofenadine pharmacokinetics after 7 days of co-administration with fexofenadine hydrochloride 120 mg every 12 hours (two times the recommended twice daily dose) in healthy volunteers (n=24)		
Concomitant Drug	C _{max} SS (Peak plasma concentration) +82%	AUC _{SS(0-12h)} (Extent of systemic exposure) +109%
Erythromycin (500 mg every 8 hrs)		
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro*, *in situ*, and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion. Due to the pseudoephedrine component, ALLEGRA-D 24 HOUR is contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs which interfere with sympathetic activity (e.g., methyl dopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of ALLEGRA-D 24 HOUR concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

Drug Interactions with Antacids

Administration of 120 mg of fexofenadine hydrochloride (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox®) decreased fexofenadine AUC by 41% and C_{max} by 43%. ALLEGRA-D 24 HOUR should not be taken closely in time with aluminum and magnesium containing antacids.

Interactions with Fruit Juices

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine hydrochloride was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the bioequivalence study data, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that ALLEGRA-D 24 HOUR should be taken with water (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or *in vitro* studies on the combination product fexofenadine hydrochloride and pseudoephedrine hydrochloride to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (area-under-the plasma concentration versus time curve [AUC]). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses up to 150 mg/kg of terfenadine for 18 and 24 months, respectively. In both species, 150 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 2 and 3 times, respectively, the exposure from the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR.

Two-year feeding studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at doses up to 10 and 27 mg/kg, respectively (less than the maximum recommended human daily oral dose of pseudoephedrine hydrochloride on a mg/m² basis).

In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

Reproduction and fertility studies with terfenadine in rats produced no effect on male or female fertility at oral doses up to 300 mg/kg/day (approximately 3 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR based on comparison of the AUCs of fexofenadine). However, reduced implants and post-implantation losses were reported at 300 mg/kg. A reduction in implants was also observed at an oral dose of

150 mg/kg/day (approximately 3 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR based on comparison of the AUCs). In mice, fexofenadine produced no effect on male or female fertility at average dietary doses up to 4438 mg/kg (approximately 10 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR based on comparison of the AUCs).

Pregnancy

Teratogenic Effects: Category C. Terfenadine alone was not teratogenic in rats at oral doses up to 300 mg/kg (approximately 3 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR based on comparison of the AUCs of fexofenadine) and in rabbits at oral doses up to 300 mg/kg (approximately 25 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR based on comparison of the AUCs of fexofenadine).

In mice, no adverse effects and no teratogenic effects during gestation were observed with fexofenadine at dietary doses up to 3730 mg/kg (approximately 10 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR based on comparison of the AUCs).

The combination of terfenadine and pseudoephedrine hydrochloride in a ratio of 1:2 by weight was studied in rats and rabbits. In rats, an oral combination dose of 150/300 mg/kg produced reduced fetal weight and delayed ossification with a finding of wavy ribs. The dose of 150 mg/kg of terfenadine in rats produced an AUC value of fexofenadine that was approximately 3 times the AUC of the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR. The dose of 300 mg/kg of pseudoephedrine hydrochloride in rats was approximately 10 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR on a mg/m² basis. In rabbits, an oral combination dose of 100/200 mg/kg produced decreased fetal weight. By extrapolation, the AUC of fexofenadine for 100 mg/kg orally of terfenadine was approximately 8 times the human AUC of the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR. The dose of 200 mg/kg of pseudoephedrine hydrochloride was approximately 15 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR on a mg/m² basis.

There are no adequate and well-controlled studies in pregnant women. ALLEGRA-D 24 HOUR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine; this dose produced an AUC of fexofenadine that was approximately 3 times the human AUC of the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR.

Nursing Mothers

It is not known if fexofenadine is excreted in human milk. Because many drugs are excreted in human milk, caution should be used when fexofenadine hydrochloride is administered to a nursing woman. Pseudoephedrine hydrochloride administered alone distributes into breast milk of lactating human females. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by AUC is 2 to 3 times greater than the plasma AUC. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4% to 0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when ALLEGRA-D 24 HOUR is administered to nursing women.

Pediatric Use

Safety and effectiveness of ALLEGRA-D 24 HOUR in children below the age of 12 years have not been established. In addition, the doses of the individual components in ALLEGRA-D 24 HOUR exceed the recommended individual doses for pediatric patients under 12 years of age. ALLEGRA-D 24 HOUR is not recommended for pediatric patients under 12 years of age.

Geriatric Use

Clinical studies of ALLEGRA-D 24 HOUR did not include sufficient numbers of subjects aged 65 and older 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, although the elderly are more likely to have adverse reactions to sympathomimetic amines.

The pseudoephedrine component of ALLEGRA-D 24 HOUR is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

ADVERSE REACTIONS

Fexofenadine Hydrochloride

In a placebo-controlled clinical study in the United States, which included 570 subjects with seasonal allergic rhinitis aged 12 years and older receiving fexofenadine hydrochloride tablets at doses of 120 or 180 mg once daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated subjects. The following table lists adverse experiences that were reported by greater than 2% of subjects treated with fexofenadine hydrochloride tablets at doses of 180 mg once daily and that were more common with fexofenadine hydrochloride than placebo.

Once daily dosing with fexofenadine hydrochloride tablets at rates of greater than 2%		
Adverse experience	Fexofenadine 180 mg once daily (n=283)	Placebo (n=293)
Headache	10.6%	7.5%
Upper Respiratory Tract Infection	3.2%	3.1%
Back Pain	2.8%	1.4%

Events that have been reported during controlled clinical trials involving subjects with seasonal allergic rhinitis at incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or parosmia. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

Pseudoephedrine Hydrochloride

Pseudoephedrine hydrochloride may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

OVERDOSAGE

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. For the pseudoephedrine hydrochloride component of ALLEGRA-D 24 HOUR, information on acute overdose is limited to the marketing history of pseudoephedrine hydrochloride. Single doses of fexofenadine hydrochloride up to 800 mg (6 healthy volunteers at this dose level), and doses up to 690 mg twice daily for one month (3 healthy volunteers at this dose level), were administered without the development of clinically significant adverse events.

In large doses, sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma, and respiratory failure.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended. Following administration of terfenadine, hemodialysis did not effectively remove fexofenadine, the major active metabolite of terfenadine, from blood (up to 1.7% removed). The effect of hemodialysis on the removal of pseudoephedrine is unknown.

No deaths occurred in mature mice and rats at oral doses of fexofenadine hydrochloride up to 5000 mg/kg (approximately 110 and 230 times, respectively, the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR on a mg/m² basis.) The median oral lethal dose in newborn rats was 438 mg/kg (approximately 20 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR on a mg/m² basis). In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (approximately 300 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR on a mg/m² basis). The oral median lethal dose of pseudoephedrine hydrochloride in rats was 1674 mg/kg (approximately 55 times the maximum recommended human daily oral dose of ALLEGRA-D 24 HOUR on a mg/m² basis).

DOSAGE AND ADMINISTRATION

The recommended dose of ALLEGRA-D 24 HOUR Extended-Release Tablets is one tablet once daily administered on an empty stomach with water for adults and children 12 years of age and older. ALLEGRA-D 24 HOUR tablets should generally be avoided in patients with renal insufficiency. ALLEGRA-D 24 HOUR must be swallowed whole and never crushed or chewed.

Rx only

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