

Anxiety Plus Depression Boost Cardiac Deaths

BY BRUCE JANCIN

NEW ORLEANS — Persistent comorbid anxiety and depression are common in patients with coronary heart disease, and they carry a greater mortality risk than either mood disturbance alone.

"It's important to look for both anxiety and depression and really home in on patients who have symptoms of both," Lynn V. Doering, D.N.Sci., stressed in

presenting the study results at the annual scientific sessions of the American Heart Association.

Persistence of the dual comorbid forms of dysphoria in patients with coronary heart disease (CHD) appears to be a key factor in the associated increased risk of all-cause mortality, added Dr. Doering of the University of California, Los Angeles. "Anxiety and depression must be assessed periodically in patients

with CHD. While it is important to identify and treat new symptoms, it is perhaps even more important to attend to persistent symptoms that are unremitting, especially with treatment."

She presented a secondary analysis of data from the PROMOTION trial, a multicenter randomized study of an educational nursing intervention designed to reduce prehospital delay to treatment of acute coronary syndrome in patients

with known CHD. Her substudy focused on the 2,325 PROMOTION participants who completed mood evaluations at baseline and at 3 months, after which they were followed for a median of 22 months. Their mean age was 67 years, and 31% were women.

The brief mood assessment tools used were the Multiple Affect Adjective Checklist (MAACL) for depression and the six-item anxiety subscale of the Brief Symptom Inventory. Both are well validated, reliable instruments, Dr. Doering said.

Nineteen percent of participants were classified as persistently depressed on the basis of MAACL scores of 11 or more at both time points. Another 16% were deemed persistently anxious, with Brief Symptom Inventory scores below 0.33 at baseline and again at 3 months. Persistent comorbid anxiety and depression were

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more common than either condition alone, affecting 26% of subjects. Only 39% of the CHD patients were free of persistent anxiety and/or depression.

"In other words, almost two-thirds of the sample had a persistent mood disorder," Dr. Doering observed.

A total of 63 deaths occurred during follow-up, for a 2.7% mortality rate, including 23 deaths that were cardiac-related.

Persistently distressed CHD patients tended to be younger, female, sedentary, and current smokers. They also were more likely to have diabetes, angina, a history of MI, and to not have attended cardiac rehabilitation.

In a multivariate Cox regression analysis adjusted for clinical and demographic variables and assignment to the intervention or control arm in the parent study, only three variables emerged as independent predictors of all-cause mortality: age, a history of MI, and the presence of persistent comorbid anxiety and depression.

Persistent comorbid anxiety and depression was the strongest predictor of mortality, with a 2.35-fold increased risk, even greater than that conferred by a prior MI. Neither persistent anxiety nor persistent depression alone was associated with increased mortality.

Dr. Doering received an award for presenting what was judged the outstanding study in the cardiovascular nursing section of the AHA meeting.

Future studies, she said, will focus on such key issues as the biobehavioral mechanisms involved in the link between persistent anxiety/depression and mortality, identification of subgroups at particularly high risk, optimal treatment options, and how to make treatments more acceptable to patients. ■

Vyvanse® (lisdexamfetamine dimesylate)

CII Rx Only

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

WARNING: POTENTIAL FOR ABUSE

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY. MISUSE OF AMPHETAMINES MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

INDICATIONS AND USAGE

Vyvanse® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Vyvanse in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12 and one controlled trial in adults who met DSM-IV-TR® criteria for ADHD.

Vyvanse is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social).

Long-Term Use

The effectiveness of Vyvanse for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. The physician should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncratic reaction to sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS AND PRECAUTIONS

Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems: Children and Adolescents— Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults— Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions: Stimulant medications cause a modest increase in average blood pressure (about 2-4mm Hg) and average heart rate (about 3-6 bpm) and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g. those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications: Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g. electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-existing Psychosis: Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

Emergence of New Psychotic or Manic Symptoms: Treatment-emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) or stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression: Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment of ADHD should be monitored for the appearance of, or worsening of, aggressive behavior or hostility.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Tics

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome should precede use of stimulant medications.

Long-Term Suppression of Growth

Careful follow-up for weight in children ages 6 to 12 years who received Vyvanse over 12 months suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a slowing in growth rate, measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile, of -13.4 over 1 year (average percentiles at baseline and 12 months, were 60.6 and 47.2, respectively). Therefore growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Prescribing and Dispensing

The smallest amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose. Vyvanse should be used with caution in patients who use other sympathomimetic drugs.

ADVERSE REACTIONS

Clinical Studies Experience

The premarketing development program for Vyvanse included exposures in a total of 762 participants in clinical trials (348 pediatric patients, 358 adult patients and 56 healthy adult subjects).

In the controlled pediatric (aged 6 to 12) trial, 10% (21/218) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/72) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash (2/218 each; 1%). The most common adverse reactions (incidence $\geq 5\%$ and at a rate at least twice placebo) were decreased appetite, dizziness, dry mouth, irritability, insomnia, upper abdominal pain, nausea, vomiting and decreased weight.

In the controlled adult trial, 6% (21/358) of Vyvanse-treated patients discontinued due to adverse events compared to 2% (1/62) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%). The most common adverse reactions (incidence $\geq 5\%$ and at a rate at least twice placebo) were upper abdominal pain, diarrhea, nausea, fatigue, feeling jittery, irritability, anorexia, decreased appetite, headaches, anxiety, and insomnia.

Postmarketing Reports

The following adverse reactions have been identified during post approval use of Vyvanse.

Cardiac Disorders - Palpitation

Eye Disorders - Vision blurred, mydriasis, diplopia

Immune System Disorders - Hypersensitivity

Nervous System Disorders - Seizure, dyskinesia

Psychiatric Disorder - Psychotic episodes, mania, hallucination, depression, aggression, dysphoria, euphoria, logorrhea

Skin and Subcutaneous Tissue Disorder - Angioedema, urticaria

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: Vyvanse has not been studied in children under 6 years of age or adolescents. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: Vyvanse has not been studied in the geriatric population.

DRUG ABUSE AND DEPENDENCE

Vyvanse is classified as a Schedule II controlled substance.

OVERDOSAGE

Toxic symptoms may occur idiosyncratically at low doses. Treatment: Consult with a Certified Poison Control Center for up-to-date guidance and advice. The prolonged release of Vyvanse in the body should be considered when treating patients with overdose.

Manufactured for: Shire US Inc., Wayne, PA 19087

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