

Integrative Management of Anxiety

by James Lake, MD



In part 1 of this column (*Psychiatric Times*, November 2007, page 13), I reviewed research findings of the most substantiated nonpharmacological and integrative treatments for anxiety, such as kava-kava, L-theanine, applied relaxation, yoga, meditation and mindfulness training, virtual reality graded exposure therapy, and biofeedback training. In this part, I discuss less substantiated but promising nonconventional approaches, including dietary changes, supplementation with L-tryptophan or 5-hydroxytryptophan (5-HTP), regular exercise, massage, acupuncture and electroacupuncture, healing touch, and Reiki.

Dietary changes

Symptoms of generalized anxiety are frequently associated with a common condition known as reactive hypoglycemia, in which blood glucose drops to abnormally low levels following a glucose challenge. Persons who experience anxiety related to this condition benefit from dietary changes such as low carbohydrate and high protein intake, consumption of foods with different glycemic indices, and avoidance of caffeine.¹

Caffeine use is associated with an increased risk of anxiety. Caffeine consumption increases serum epinephrine, norepinephrine, and cortisol levels, and can result in feelings of “nervousness” in healthy adults or, in persons who are predisposed, increased feelings of generalized anxiety or panic episodes.^{2,3} Patients who have chronic anxiety report that symptoms diminish when they abstain from caffeine.⁴

A dietary deficiency of the amino acid tryptophan leads to reductions in brain serotonin levels. Persons who experience generalized anxiety or panic episodes reported more severe symptoms when they were being treated with an amino acid formula that excludes tryptophan.⁵

Ayurvedic herbs

Ayurvedic herbal preparations such as *Bacopa monnieri* and *Centella asiatica* have been used for thousands of years to treat symptom patterns that resemble generalized anxiety. Double-blind controlled trials suggest that both herbs effectively reduce general anxiety symptoms.^{6,7} Emerging evidence suggests that an Ayurvedic herbal compound formula called “Geriforte” may also alleviate symptoms of generalized anxiety.⁸ No serious adverse effects have been reported when the above preparations are used

at recommended dosages.

Ayurveda is an advanced, highly integrated system of medicine that employs diverse herbal, mind-body, and energetic treatment modalities. Patients who use Ayurvedic herbal preparations should be supervised by a trained Ayurvedic physician.

Amino acids and amino acid precursors

L-tryptophan and 5-HTP are widely used nonconventional treatments for generalized anxiety; however, to date, few double-blind studies have examined their efficacy. Both amino acids are essential precursors for synthesis of serotonin, a neurotransmitter that plays a central role in the regulation of

mood and anxiety. More extensive research literature is available for the treatment of anxiety with 5-HTP than with L-tryptophan.

In a double-blind study, 58% of patients with general anxiety ($n = 79$) who were randomized to L-tryptophan 3 g/d reported significantly greater reductions in baseline anxiety symptoms compared with placebo.⁹ Animal studies and human clinical trials show that 5-HTP has consistent antianxiety effects.^{10,11} 5-HTP may inhibit panic episodes that are induced by carbon dioxide.¹² Patients who were randomized to receive a combination of 5-HTP and carbidopa (a drug inhibiting

the enzyme that breaks down 5-HTP in the peripheral blood supply, thus increasing the amount of 5-HTP that crosses the blood-brain barrier) reported significant reductions in anxiety that were comparable to those seen with clomipramine (Anafranil), a conventional antianxiety medication. Patients taking placebo did not improve.¹¹

5-HTP may be safely combined with conventional antianxiety drugs when patients are monitored for adverse effects related to excessive brain serotonin, including insomnia, agitation, and nervousness. The risk of adverse effects is minimized when 5-

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HTP is started at dosages of 25 mg/d and gradually is increased over several weeks, to a daily regimen that is well tolerated and produces therapeutic antianxiety effects.

In my clinical experience, 5-HTP 50 to 100 mg 3 times daily is well tolerated without excessive daytime sedation, and it is an effective approach for many patients with chronic anxiety when used alone or in combination with SSRIs or other conventional antianxiety drugs. Gradually increasing a bedtime dose of 5-HTP from 200 to 400 mg often reduces daytime anxiety and improves quality of sleep in patients with chronic anxiety who complain of insomnia.

duce many anxiety symptoms that respond to SSRIs, including panic episodes, agoraphobia, obsessions, and compulsions.¹³ Available conventional drugs are effective in only two thirds of patients who experience panic episodes.¹⁴ Inositol in dosages up to 20 g/d reduces the severity and frequency of panic episodes by interfering with one of the physiological causes of panic (metachlorophenylpiperazine).¹⁵

A 4-week, double-blind crossover study concluded that inositol 12 g/d and imipramine (Tofranil), a conventional medication, are equally effective in reducing the frequency and severity of panic episodes and agoraphobia.¹⁶ A 1-month, double-blind, placebo-controlled study of 20 patients concluded that inositol, up to 18 g/d, and fluvoxamine (Luvox, Faverin, Dumyrox), up to 150 mg/d, were similarly effective in reducing the frequency of panic episodes.¹⁴ The average number of weekly panic episodes in the inositol group decreased by 4, compared with an average decrease of 2 in the fluvoxamine group. Patients taking therapeutic doses of inositol have not reported serious adverse effects.

Somatic and mind-body approaches

Patients who are anxious frequently engage in strenuous physical activity in efforts to alleviate symptoms. Open studies suggest that regular aerobic exercise or strength training reduces anxiety.¹⁷ A daily exercise program of at least 20 to 30 minutes can significantly reduce symptoms of generalized anxiety.¹⁸ Findings of a prospective, 10-week study of exercise in persons who experience panic episodes suggest that regular walking or jogging (4 miles, 3 times per week) reduces the severity and frequency of panic episodes.¹⁹

In my clinical practice, I have observed that patients with anxiety who follow a regular exercise program pay more attention to their health in general and tend to respond more rapidly to both conventional and integrative treatments compared with patients who are not physically active. Persons with heart disease, chronic pain, or

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I encourage patients with anxiety to listen to soothing music as often as possible without distractions, especially at the start of their day.

Greater research evidence supporting the use of 5-HTP for anxiety treatment, together with smaller effective doses and increased CNS availability, generally makes 5-HTP the preferred choice over L-tryptophan.

Inositol

Inositol has been the focus of renewed research interest because of its role as a precursor of an important second messenger in the brain, phosphatidylinositol, which is an integral part of serotonin, norepinephrine, and other neurotransmitter receptors. Findings from several double-blind studies suggest that high doses of inositol re-

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other serious medical problems should consult their physician before starting an exercise program.

Massage

Massage is widely used to evoke feelings of deep relaxation and to reduce anxiety. The anxiety-reducing effects of massage are probably mediated by decreased cortisol and increased parasympathetic tone.^{20,21} Few controlled trials on massage have been done; however, a critical review of published studies concluded that there is no strong medical evidence supporting most of its therapeutic claims.²² Despite these criticisms, regular massage to treat chronic stress and anxiety is worthy of serious attention.

The subjective physical and psychological benefits of massage are difficult to quantify in controlled trials. Few massage therapists are trained in biomedical research methods or work in institutional settings where sham-controlled trials can be conducted. Consistent anecdotal evidence, a long-standing history of widespread use for stress reduction, and the findings of many open trials support the view that regular massage therapy reduces the severity of chronic, moderate anxiety in general, and specifically, in anxiety related to test-taking or problem-solving, work stress, or the anticipation of invasive medical procedures.²³⁻²⁷ In my clinical experience, regular massage therapy effectively reduces anxiety, improves emotional resilience, and enhances feelings of general well-being in anxious patients.

Music and binaural sound

Music and sound are used in many cultures and healing traditions for anxiety-reducing benefits. In a randomized study, 40 adult patients with anxiety were assigned to cognitive therapy or music-assisted reframing. Patients in the music group experienced greater reductions in overall anxiety, based on standardized measures.²⁸

A unique auditory experience occurs when headphones are used to route slightly different frequencies of sound binaurally to the right and left hemispheres of the brain. The brainstem “constructs” binaural beats based on the frequency difference between the sounds processed in each hemisphere. Functional brain imaging studies suggest that interhemispheric synchronization of information is enhanced by this experience. Certain binaural beats consistently induce a calm, relaxed state, while others facilitate increased attention or arousal.²⁹ In this way, the therapeutic use of certain sound fre-

quency patterns to achieve different therapeutic goals is analogous to the use of different electroencephalographic biofeedback protocols.

I encourage patients with anxiety to listen to soothing music as often as possible without distractions, especially at the start of their day. I have observed that patients with general anxiety frequently experience both reduced anxiety and improved mental clarity after listening to binaural sounds of appropriate frequencies. Patients often report significantly reduced anxiety, increased feelings of peace, and a more hopeful outlook after becoming absorbed in a relaxing musical experience.

Biofeedback training using heart rate variability

In contrast to the documented efficacy of galvanic skin response and electromyographic and electroencephalographic biofeedback, few research studies have examined the efficacy of heart rate variability (HRV) biofeedback as a treatment for anxiety. Findings from case reports and controlled trials suggest that HRV biofeedback training significantly reduces stress and improves general feelings of emotional well-being in persons with acute job-related stress.³⁰ Beneficial changes in baseline anxiety following HRV biofeedback are associated with decreased serum cortisol levels and increased serum dehydroepiandrosterone levels.

Police officers are often subjected to unexpected severe stress. In a 4-month controlled trial, a majority of 29 police officers who were trained in biofeedback techniques based on HRV (HeartMath) reported significant improvements in baseline anxiety, while 36 officers who were assigned to a wait-list group did not report significant improvements.³¹ Patients with chronic anxiety who underwent HRV biofeedback training reported improvements in general emotional well-being and reduced baseline anxiety.³²

Acupuncture and electro-acupuncture

Acupuncture and acupressure are widely used to treat anxiety. Extensive case reports from Chinese medical literature suggest that different acupuncture protocols are beneficial in the management of anxiety symptom patterns that resemble generalized anxiety and panic episodes.³³ However, at present, only a few small, prospective controlled studies support the use of these traditional energy therapies; most studies on the anxiety-reducing effects of acupuncture have examined the general benefits of acupuncture on

diverse cognitive, affective, and behavioral symptoms, including anxiety.

A narrative review of controlled studies, outcome studies, and published case reports on acupuncture as a treatment for anxiety and depressed mood was published in 2002 by the British Acupuncture Council.³⁴ Sham-controlled studies yielded consistent improvements in anxiety using both regular acupuncture and electroacupuncture treatments. The reviewers noted that significant differences existed between the protocols used in regular acupuncture and electroacupuncture, pointing to the unresolved issue of a general beneficial or possible placebo effect. Positive findings from most controlled studies were suggestive of a general anxiety-reducing effect of acupuncture but were regarded by the reviewers as inconclusive because of study design problems, including the absence of standardized symptom rating scales in most studies, limited follow-up, and poorly defined differences between protocols used in different studies.

In 1 double-blind study, 36 patients with mild depression or anxiety were randomized to an acupuncture protocol that was believed to reduce anxiety or a sham acupuncture protocol.³⁵ Patients participated in 3 sessions. HRV and mean heart rate were measured 5 and 15 minutes after treatment. Resting heart rate was significantly lower in the treatment group but not in the sham group, and changes in HRV indices suggested that acupuncture had modulated autonomic activity and reduced overall anxiety. The significance of these findings is limited by the absence of comments on baseline anxiety before and after treatment.

In another double-blind study, 55 adults (in whom an anxiety disorder had not been diagnosed) were randomized to a bilateral auricular acupuncture protocol called the “shenmen” point—a protocol believed to be effective against anxiety (the so-called relaxation point)—versus a sham acupuncture point.³⁶ Acupuncture needles remained in place for 48 hours. The “relaxation” group was significantly less anxious at 30 minutes and at 24 and 48 hours compared with the other 2 groups; however, there were no significant intergroup differences in blood pressure, heart rate, or electrodermal activity. A small, double-blind, sham-controlled trial involving patients who were anxious with mixed symptoms of moderate depressed mood obtained a response rate of 85% following 10 acupuncture treatment sessions that used specific acupuncture points (Du.20, Ex.6, He.7, PC.6, Bl.62).³⁷ Uncommon transient adverse effects associated with acupuncture

include bruising, fatigue, and nausea. Very rare cases of pneumothorax have been reported.

Regular Reiki treatments

The findings from 2 studies suggest that regular Reiki treatments reduce the severity of anxiety symptoms in persons who are chronically stressed.^{38,39} Patients with mixed anxious-depressed mood experienced significant relief following weekly treatments with contact or non-contact Reiki.⁴⁰ Reiki treatments may improve state anxiety in patients with chronic pain. A total of 120 patients with chronic illnesses were randomized to receive Reiki, sham Reiki, progressive muscle relaxation, or no treatment.⁴¹ Improvements in state anxiety (and pain) in patients receiving Reiki were significantly greater than in the other 3 groups. Findings of this study are limited because possible differences in the use of anxiety-reducing medications between the active treatment groups and the control groups were not taken into account in the study design.

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References

1. Bell SJ, Forse RA. Nutritional management of hypoglycemia. *Diabetes Educ.* 1999;25:41-47.
2. Uhde TW, Boulenger JP, Jimerson DC, Post RM. Caffeine: relationship to human anxiety, plasma MHPG and cortisol. *Psychopharmacol Bull.* 1984;20:426-430.
3. Charney DS, Heninger GR, Jatlow PI. Increased anxiogenic effects of caffeine in panic disorders. *Arch Gen Psychiatry.* 1985;42:233-243.
4. Bruce MS, Lader M. Caffeine abstinence in the management of anxiety disorders. *Psychol Med.* 1989;19:211-214.
5. Klaassen T, Klumperbeek J, Deutz NE, et al. Effects of tryptophan depletion on anxiety and on panic provoked by carbon dioxide challenge. *Psychiatry Res.* 1998;77:167-174.
6. Stough C, Lloyd J, Clarke J, et al. The chronic effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy human subjects. *Psychopharmacology (Berl).* 2001;156:481-484.
7. Bradwejn J, Zhou Y, Koszycki D, Shlik J. A double-blind, placebo-controlled study on the effects of Gotu Kola (*Centella asiatica*) on acoustic startle response in healthy subjects. *J Clin Psychopharmacol.* 2000;20:680-684.
8. Shah LP, Nayak PR, Sethi A. A comparative study of Geriforte in anxiety neurosis and mixed anxiety-depressive disorders. *Probe.* 1993;32:195-201.
9. Zang DX. A self body double blind clinical study of L-tryptophan and placebo in treated neurosis [in Chinese]. *Zhonghua Shen Jing Jing Shen Ke Za Zhi.* 1991;24:77-80,123-124.
10. Soderpalm B, Engel JA. Serotonergic involvement in conflict behavior. *Eur Neuropsychopharmacol.* 1990;1:7-13.
11. Kahn RS, Westenberg HG, Verhoeven WM, et al. Effect of a serotonin precursor and uptake inhibitor in

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anxiety disorders; a double-blind comparison of 5-hydroxytryptophan, clomipramine and placebo. *Int Clin Psychopharmacol.* 1987;2:33-45.

12. Schruers K, Pols H, Overbeek T, et al. E5-hydroxytryptophan inhibits 35% CO₂ induced panic. Abstracts of the 22nd CINP Congress, Brussels, July 9-13, 2000. *Int J Neuropsychopharmacol.* 2000;3:S272.

13. Belmaker RH, Levine JA, Kofman O. Inositol—a novel augmentation for mood disorders. Presented at the 151st Annual Meeting of the American Psychiatric Association; May 30-June 4, 1998; Toronto.

14. Palatnik A, Frolov K, Fux M, Benjamin J. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *J Clin Psychopharmacol.* 2001;21:335-339.

15. Benjamin J, Nemetz H, Fux M, et al. Acute inositol does not attenuate m-CPP-induced anxiety, mydriasis and endocrine effects in panic disorder. *J Psychiatr Res.* 1997;31:489-495.

16. Benjamin J, Levine J, Fux M, et al. Double-blind placebo-controlled crossover trial of inositol treatment for panic disorder. *Am J Psychiatry.* 1995;152:1084-1086.

17. Paluska SA, Schwenk TL. Physical activity and mental health. *Sports Med.* 2000;29:167-180.

18. Osei-Tutu KE, Campagna PD. Psychological bene-

fits of continuous vs intermittent moderate intensity exercise. In: *Medicine and Science in Sports and Exercise.* Vol. 30; 1998:S117. Abstract.

19. Stevinson C. Exercise may help treat panic disorder. *Focus on Alternative & Complementary Therapies.* 1999;4:84-85.

20. Acolet D, Modi N, Giannakouloupolous X, et al. Changes in plasma and catecholamine concentrations in response to massage in preterm infants. *Arch Dis Child.* 1993;68:29-31.

21. Serepca B. Interview with Dr Tiffany Field, PhD, director of the Touch Research Institute. *Massage Magazine.* Sept 1996;No. 63.

22. Ernst E, Falck V. The clinical effectiveness of massage therapy—a critical review [in German]. *Forsch*

Komplementarmed. 1994;1:226-232.

23. McKechnie AA, Wilson F, Watson N, et al. Anxiety states: a preliminary report on the value of connective tissue massage. *J Psychosom Res.* 1983;27:125-129.

24. Shulman KR, Jones GE. The effectiveness of massage therapy intervention on reducing anxiety in the workplace. *J Applied Behav Science.* 1996;32:160-173.

25. Field T, Ironson G, Scafidi F, et al. Massage therapy reduces anxiety and enhances EEG pattern of alertness and math computations. *Int J Neurosci.* 1996;86:197-205.

26. Okvat HA, Oz MC, Ting W, et al. Massage therapy for patients undergoing cardiac catheterization. *Altern Ther Health Med.* 2002;8:68-65.

27. Kim MS, Cho KS, Woo H, et al. Effects of hand massage on anxiety in cataract surgery using local anesthesia. *J Cataract Refract Surg.* 2002;27:884-890.

28. Kerr T, Walsh J, Marshall A. Emotional change processes in music-assisted reframing. *J Music Ther.* 2001;38:193-211.

29. Le Scouarnec RP, Poirier RM, Owens JE, et al. Use of binaural beat tapes for treatment of anxiety: a pilot study of tape preference and outcomes. *Altern Ther Health Med.* 2001;7:58-63.

30. McCraty R, Atkinson M, Tomasio D. *Science of the Heart: Exploring the Role of the Heart in Human Performance—An Overview of Research Conducted by the Institute of HeartMath.* Boulder Creek, Calif: HeartMath Research Center, Institute of HeartMath; 2001. Publication 01-001.

31. McCraty R, Tomasio B, Atkinson M, Sundram J. *Impact of HeartMath Self-Management Skills Program on Physiological and Psychological Stress in Police Officers.* Boulder Creek, Calif: HeartMath Research Center, Institute of HeartMath; 1999. Publication 99-075.

32. McCraty R, Barrios-Chopin B, Rozman D, et al. The impact of a new emotional self-management program on stress, emotions, heart rate variability, DHEA and cortisol. *Integr Physiol Behav Sci.* 1998;33:151-170.

33. Flaws B, Lake J. *Chinese Medical Psychiatry: A Textbook and Clinical Manual.* Boulder, Colo: Blue Poppy Press; 2001.

34. British Acupuncture Council, Acupuncture Research Resource Council. Depression, anxiety and acupuncture: the evidence for effectiveness. Briefing paper No. 9; 2002.

35. Agelink MW, Sanner D, Eich H, et al. Does acupuncture influence the cardiac autonomic nervous system in patients with minor depression or anxiety disorders? [in German]. *Fortschr Neurol Psychiatr.* 2003;71:141-149.

36. Wang SM, Kain ZN. Auricular acupuncture: a potential treatment for anxiety [in German]. *Fortschr Neurol Psychiatr.* 2001;92:548-553.

37. Eich H, Agelink MW, Lehmann E, et al. Acupuncture in patients with minor depression or generalized anxiety disorders—results of a randomized study [in German]. *Fortschr Neurol Psychiatr.* 2000;68:137-144.

38. Heidt P. Effect of therapeutic touch on anxiety level of hospitalized patients [dissertation]. New York: New York University; 1979.

39. Kramer NA. Comparison of therapeutic touch and casual touch in stress reduction of hospitalized children. *Pediatr Nurs.* 1990;16:483-485.

40. Shore AG. Long-term effects of energetic healing on symptoms of psychological depression and self-perceived stress. *Altern Ther Health Med.* 2004;10:42-48.

41. Dressen L, Singg S. Effects of Reiki on pain and selected affective and personality variables of chronically ill patients. *Subtle Energies.* 1998;9:51-82. □

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Vyvanse™ (lisdexamfetamine dimesylate) CII Rx Only
BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

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 AMPHETAMINE 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, who met DSM-IV criteria for ADHD (see CLINICAL TRIALS). A diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD, DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment in social, academic, or occupational functioning, and be present in two or more settings, e.g., at school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met. **Special Diagnostic Considerations:** Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program: Vyvanse is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms. **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. Therefore, the physician who elects to use Vyvanse for extended periods 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 idiosyncrasy to the sympathomimetic amines, glaucoma.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

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 (see CONTRAINDICATIONS).

Adults

Sudden deaths, 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 also 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 (see CONTRAINDICATIONS).

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) 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 (see CONTRAINDICATIONS).

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 pre-existing psychiatric disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of 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 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) of 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 there is no systematic evidence that the postmarketing 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 for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth

Carbonyl follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months to the ages of 10 to 13 years, suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d to l enantiomer ratio of 3:1) in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and -2.8 lbs., respectively, for patients receiving 10 mg and 20 mg of amphetamine (d to l enantiomer ratio of 3:1). Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. In a controlled trial of lisdexamfetamine in children ages 6 to 12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.8, and -2.5 lb, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine, compared to a 1 lb weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Carbonyl follow-up for weight in children ages 6 to 12 years who received lisdexamfetamine 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 percentile at baseline and 12 months, were 80.6 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.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizure, 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.

PRECAUTIONS

General: The least amount of Vyvanse 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.

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

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should be cautioned accordingly. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with lisdexamfetamine and should counsel them in its appropriate use. A patient Medication Guide is available for Vyvanse. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Drug Interactions

Urinary acidifying agents—These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers—Adrenergic blockers are inhibited by amphetamines.

Anti-depressants, tricyclic—Amphetamines may enhance the activity of tricyclic anti-depressants or sympathomimetic agents: d-amphetamine with desipramine or protriptyline and possibly other tricyclic cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors—MAOI anti-depressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines—Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives—Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine—Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines and can be used to treat amphetamine poisoning.

Ethosuximide—Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol—Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate—The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meprobamate—Amphetamines potentiate the analgesic effect of meprobamate.

Methanamine therapy—Urinary excretion of amphetamines is increased, and efficacy is reduced by acidifying agents used in methanamine therapy.

Norepinephrine—Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital—Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenylethylamine—Amphetamines may delay intestinal absorption of phenylethylamine; co-administration of phenylethylamine may produce a synergistic anticonvulsant action.

Propoxyphene—In cases of propoxyphene overdose, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. **Veratrum alkaloids**—Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility: Carcinogenicity studies of lisdexamfetamine have not been performed.

No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK⁺ mouse lymphoma assay *in vitro*.

Amphetamine (d to l enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

Pregnancy: Pregnancy Category C. Reproduction studies of lisdexamfetamine have not been performed.

Amphetamine (d to l enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. Fetal malformations and death have been reported in mice following parental administration of dextroamphetamine doses of 50 mg/kg/day or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity. A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-) at doses similar to those used clinically can result in long term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with her mother during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamine have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

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

Pediatric Use: Vyvanse is indicated for use in children aged 6 to 12 years. A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m² basis. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four week drug-free recovery period bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose on a mg/m² basis). This effect partially or fully reversed during a four week drug-free recovery period.

Use in Children under Six Years of Age: Lisdexamfetamine dimesylate has not been studied in 3-5 year olds. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

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

ADVERSE EVENTS

The following development program for Vyvanse included exposures in a total of 404 participants in clinical trials (348 pediatric patients and 56 healthy adult subjects). Of these, 348 pediatric patients (ages 6 to 12) were evaluated in two controlled clinical studies (one parallel-group and one crossover), one open-label extension study, and one single-dose clinical pharmacology study. The information included in this section is based on data from the 4-week parallel-group controlled clinical trial in pediatric patients with ADHD. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MedRA terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment: Ten percent (21/218) of Vyvanse-treated patients discontinued due to adverse events during exposure. 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 (2/18 each; 1%).

Adverse events occurring in a controlled trial: Adverse events reported in a 4-week clinical trial in pediatric patients treated with Vyvanse or placebo are presented in the table below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following adverse events that occurred in at least 5% of the Vyvanse patients and at a rate twice that of the placebo group (Table 1): Upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.

The following additional adverse reactions have been associated with the use of amphetamine, amphetamine (d to l enantiomer ratio of 3:1), or Vyvanse:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation.

Allergic: Urticaria, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Vyvanse is classified as a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

Human Studies

In a human abuse liability study, when equivalent oral doses of 100 mg lisdexamfetamine dimesylate and 40 mg immediate release d-amphetamine sulfate were administered to individuals with a history of drug abuse, lisdexamfetamine 100 mg produced subjective responses on a scale of "Drug Liking Effects," "Amphetamine Effects," and "Stimulant Effects" that were significantly less than d-amphetamine immediate release 40 mg. However, oral administration of 150 mg lisdexamfetamine produced increases in positive subjective responses on these scales that were statistically indistinguishable from the positive subjective responses produced by 40 mg of oral immediate-release d-amphetamine and 200 mg of diethylpropion (C-IV).

Intravenous administration of 50 mg lisdexamfetamine to individuals with a history of drug abuse produced positive subjective responses on scales measuring "Drug Liking," "Euphoria," "Amphetamine Effects," and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

In animal studies, lisdexamfetamine produced behavioral effects qualitatively similar to those of the CNS stimulant d-amphetamine. In monkeys trained to self-administer cocaine, intravenous lisdexamfetamine maintained self-administration at a rate that was statistically less than that for cocaine, but greater than that of placebo.

OVERDOSAGE

Individual response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms: Manifestations of acute overdose with am