

Integrative Management of Anxiety

by James Lake, MD

Almost one third of US mental health care costs (approximately \$50 billion) go toward the treatment of anxiety disorders.¹ Conventional pharmacological treatments for anxiety are often beneficial but have limited efficacy. A meta-analysis of high-quality studies concluded that the efficacy of conventional drug treatments for anxiety disorders varies widely depending on the core symptom being treated.² Frequency and severity of panic attacks tend to improve and remain improved in response to benzodiazepines; however, patients who regularly use these drugs are at significant risk for dependence and withdrawal symptoms. Elderly patients who use benzodiazepines are especially at risk for falling.

Phobias, obsessions and compulsions, and symptoms of posttraumatic stress are often poorly responsive to conventional drugs.² In the context of efficacy and safety issues associated with conventional treatments for anxiety, psychiatrists should know about the evidence for nonconventional therapy. In Part 1 of this article, I review research findings on the most substantiated non-pharmacological and integrative treatments for anxiety. In Part 2, I will discuss less substantiated but promising nonconventional approaches.

OVERVIEW

Positive research findings consistently support the use of kava and L-theanine in the treatment of persons with generalized anxiety. Regular relaxation, meditation, and mindfulness practices improve symptoms of generalized anxiety, and these nonpharmacological therapies may be safely combined with conventional drugs. Virtual reality graded exposure therapy (VRGET) will play a significant role in the treatment of many anxiety disorders that respond poorly to currently available treatments, such as drugs and cognitive-behavioral therapy (CBT). Numerous studies show that electroencephalographic (EEG) and electromyographic (EMG) biofeedback are as effective as regular relaxation training or mind-body practices for the treatment of moderately severe symptoms of generalized anxiety. A growing body of evidence supports the use of microcurrent stimulation of the CNS for the management of generalized anxiety.

Less-substantiated treatments for anxiety will be reviewed in Part 2 of this column and include dietary changes, supplementation with L-tryptophan or 5-hydroxytryptophan, regular exercise, massage, acupuncture (including electro-acupuncture), healing touch, and Reiki.

VITAMINS AND SUPPLEMENTS Kava (*Piper methysticum*)

When kava is used at recommended dosages (typically 60 to 300 mg/d), patients do not experience the mental slowing or impaired cognitive functioning that is typical of many conventional anti-anxiety medications.³ Animal studies suggest that the mechanism of action involves serotonin blockade in the amygdala by alpha-pyrones, a principal bioactive constituent of kava.

ated with menopause.⁸

Kava compares favorably with benzodiazepines and other conventional anti-anxiety drugs. The findings of a small, double-blind, controlled trial suggest that patients who have generalized anxiety who gradually increased their daily dose of kava (up to 300 mg) while tapering off a benzodiazepine did not experience worsening anxiety or benzodiazepine withdrawal.⁹

A randomized, placebo-controlled, multicenter study of 129 outpatients concluded that a standardized kava preparation (LI 150) was as effective as 2 commonly prescribed anti-anxiety agents (buspirone [BuSpar] and opi-pramol [Insidon], which is commonly prescribed in Germany) for the treatment of generalized anxiety.¹⁰ Three

Part 1

fourths of patients in both the kava group and the conventional drug group experienced 50% or greater reductions in Hamilton Anxiety Scale scores and were classified as "treatment responders."

Kava is generally well tolerated, even at doses significantly above typical therapeutic doses. Uncommon ad-

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Kava also interferes with norepinephrine reuptake and has a high binding affinity with γ -aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) receptors. Kava may also modulate vagal heart tone in patients with generalized anxiety.⁴

A systematic review of 11 controlled, double-blind studies that included more than 600 patients concluded that kava was superior to placebo for the short-term management of generalized anxiety.⁵ Randomized, controlled, double-blind studies support the use of kava preparations that are standardized to 70% kava lactones in divided doses of 70 to 240 mg/d for the treatment of "stress" and moderate anxiety but not for severe anxiety or agitation.^{6,7} Daily use of standardized kava preparations of 100 to 200 mg was found to effectively reduce anxiety symptoms associ-

verse effects include GI upset, rash, headache, and dizziness.¹¹ In recent decades, there have been reports of kava inebriation,¹² although this social phenomenon has not been observed in Europe, where kava preparations are used medicinally to treat anxiety. Kava does not potentiate the effects of alcohol consumption in humans. Rare case reports suggest that kava may cross-react with benzodiazepines, increasing their sedating effects.¹³ Reports of hepatitis¹⁴ and fulminant liver failure have led to restrictions in the sale of kava products in many European countries and to a warning issued by the FDA.¹⁵ These cases were rare, however, and independent experts have concluded that most reported cases of liver failure were associated with a processing error that resulted in toxic levels of alkaloids in a single batch of kava.^{16,17}

In view of these safety issues, patients should be advised against taking kava¹⁸ when there is a question of alcohol abuse or concurrent use of conventional sedative-hypnotics.

One case report suggests that kava may interfere with anti-parkinsonian drugs.¹⁹



L-Theanine (gamma-ethyl-amino-L-glutamic acid)

Green tea is used as a restorative in traditional Chinese medicine and contains many bioactive constituents, including the amino acid L-theanine. The anti-anxiety effect of L-theanine is achieved through enhanced alpha brain wave activity and increased synthesis of GABA.^{20,21} Greater GABA levels, in turn, increase the brain's levels of dopamine and reduce serotonin levels, resulting in general feelings of calm and well-being.²² Changes in brain electrical activity, as measured with EEG, are dose-dependent and are similar to the beneficial EEG changes observed in meditation, including increased alpha waves in the occipital and parietal regions.²³ A calming effect is usually noted within 30 to 40 minutes after L-theanine is taken at doses of 50 to 200 mg, and typically lasts 8 to 10 hours. Moderate anxiety symptoms often improve in patients taking 200 mg once or twice daily. More severe anxiety symptoms may require dosages of 600 to 800 mg/d, taken in divided doses of 100 to 200 mg.

Unlike benzodiazepines and other conventional anti-anxiety treatments, L-theanine does not result in increased drowsiness, slowed reflexes, or impaired concentration. There is no risk of tolerance or dependence developing, and there have been no reports of serious adverse effects or interactions with other natural products or conventional drugs.

SOMATIC AND MIND-BODY APPROACHES

Applied relaxation comparable to cognitive therapy

Applied relaxation is a generic term for somatic or mind-body exercises used to diminish generalized anxiety. Relaxation techniques include sustained deep breathing,²⁴ progressive muscle relaxation, guided imagery, and systematic desensitization. Several models have

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been proposed to explain the anxiety-reducing effects of mind-body practices, including Benson's relaxation response and Selye's general adaptation syndrome. One model posits that anxiety is associated with muscle tension and is reduced by behaviors or cognitions that diminish tension and autonomic arousal. The effectiveness of relaxation as a treatment of various anxiety symptoms has been extensively reviewed.²⁵

Guided imagery is widely used as a self-directed treatment of generalized anxiety. Applied relaxation techniques are often practiced together with mental imagery, meditation, or mindfulness training. Imagery can be individualized to the specific anxiety symptoms of each patient and is known to have beneficial effects on the immune system, physiological stress responses, and cognitive-emotional functioning in general.²⁶ The consistent practice of mental imagery effectively reduces many kinds of anxiety symptoms, including generalized anxiety, feelings of panic, and traumatic memories.^{27,28} Imagery and relaxation techniques are often used together to induce hypnotic trance states, resulting in a dramatic reduction in symptoms of generalized anxiety.²⁹

In a 5-month prospective study, patients with general anxiety randomized to a relaxation group versus a group treated with conventional antidepressants and relaxation experienced equivalent and significant improvements in state anxiety levels by the end of the trial.³⁰ In a small controlled trial, 36 anxious adult outpatients randomized to 12 weekly sessions of applied relaxation or conventional cognitive therapy experienced significant and comparable reductions in anxiety.³¹

Combining relaxation with guided imagery is probably more effective than either approach alone. In an open trial, 60 women who reported anxiety and postpartum depression experienced significant reductions in both anxiety and depressed mood using a combined relaxation-guided imagery protocol during the first 4 weeks after childbirth.³² In contrast to the largely beneficial effects of relaxation on general anxiety symptoms, panic attacks are sometimes reported during applied relaxation exercises by those who have panic disorder.³³

Yoga

Open studies and anecdotal evidence provide a strong argument for the therapeutic benefits of regular yoga practice among persons with generalized anxiety. The regular and skillful practice of specific yogic postures or breathing

methods results in sustained changes in brain activity and possibly in beneficial changes in neurotransmitter activity that manifest as a subjective state of alert calmness. Training in a particular style called Sudarshan Kriya yoga involves a specialized breathing technique that reportedly decreases serum cortisol levels, the major stress hormone in humans.³⁴ Patients with any anxiety disorder diagnosis improved significantly when they combined a daily yoga prac-

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tice with relaxation and mindfulness training.³⁵ Yoga reduces anxiety in patients with hypertension and epilepsy,^{36,37} and probably reduces test anxiety.³⁸ There is some evidence that regular yoga practice reduces the need for conventional drugs in generally anxious patients.³⁷ Findings of a small controlled study showed that the regular practice of a specific Kundalini yoga left-nostril breathing technique significantly reduced symptom severity in patients with obsessive-compulsive disorder.³⁹

Meditation and mindfulness training

Meditation practices are used in many cultures to reduce anxiety and maintain optimal psychological and spiritual health. Beneficial physiological effects of meditation include decreased oxygen consumption, respiratory rate, and blood pressure, as well as EEG changes associated with decreased autonomic arousal.⁴⁰ Mindfulness-based stress reduction (MBSR) is an integrative approach pioneered by Kabat-Zinn⁴¹ that has been validated as highly effective in reducing the physical, emotional, and cognitive consequences of chronic stress. MBSR incorporates elements of different Eastern meditation practices and Western psychology.

Research findings show that the consistent practice of mindfulness meditation, in which the patient practices detached self-observation, significantly reduces generalized anxiety and other anxiety symptoms.^{35,42} Ninety-three percent of patients (N = 322) who started a 10-week MBSR program successfully completed it, and the majority reported significantly decreased physical and emotional distress, improved quality of life, a greater sense of general well-being, increased optimism, and increased feelings of control.⁴³ Patients

with irritable bowel syndrome (IBS), a frequent concomitant of generalized anxiety, experienced significantly fewer symptoms of both IBS and anxiety when they engaged in 2 brief (15-minute) daily sessions of mindfulness meditation.⁴⁴ The cultivation of self-awareness through mindfulness training assists anxious patients in avoiding potentially stressful situations and engaging in more effective coping when stress is unavoidable.⁴⁵

Virtual reality graded exposure therapy

Controlled studies confirm that VRGET is more effective than conventional imaginal exposure therapy (ie, the use of mental imagery to provoke a feared object or situation) and has comparable efficacy to in vivo exposure therapy.^{46,47} Anxious or phobic patients are frequently unable to tolerate conventional exposure therapy and remain chronically impaired because they never become desensitized to a feared object or situation. As in imaginal exposure and in vivo therapy, VRGET has the goal of desensitizing the patient to a situation or object that would normally cause anxiety or panic.

Research findings support the use of VRGET as a treatment for many anxiety disorders, including specific phobias, generalized anxiety, panic disorder with agoraphobia,⁴⁸ and posttraumatic stress disorder (PTSD).⁴⁹ In a controlled study, VRGET and conventional CBT were equally effective in the treatment of panic disorder with agoraphobia; however, patients who underwent VRGET required 33% fewer sessions.⁵⁰

Case reports and controlled studies have demonstrated the efficacy of VRGET for many specific phobias, including fear of flying,^{51,52} heights, animals, and driving.^{53,55} In one controlled study (N = 45), 65% of anxious adults who had a specific anxiety disorder according to *DSM-IV* criteria reported significant reductions in 4 of 5 anxiety measures.⁵⁶ VRGET is as effective as conventional exposure therapy for fear of flying, and is more cost-effective because both patient and therapist avoid the expense and time commitments required for in vivo desensitization.^{51,53,54} In a preliminary study, persons who overcame fear of flying using VRGET combined with biofeed-

back (including respirations, galvanic skin response [GSR], and heart rate) were able to fly without the use of conventional medications or alcohol 3 months posttreatment.⁵²

VRGET is also beneficial in traumatized patients in whom PTSD has been diagnosed. A virtual environment that simulates the devastation following the September 11, 2001, attacks on the World Trade Towers has been successfully used to treat individuals with severe PTSD.⁵⁷

Emerging evidence suggests that combining VRGET with D-cycloserine, a partial NMDA agonist, results in greater improvement in acrophobic symptoms compared with treatment with VRGET alone. Findings from animal studies and a randomized clinical trial suggest that D-cycloserine functions as a cognitive enhancer by stimulating NMDA receptors, and may facilitate extinction of conditioned fear in patients with phobia.⁵⁸ Twenty-eight patients with a *DSM-IV* diagnosis of acrophobia were randomized to receive either 500 mg of D-cycloserine or placebo in combination with 2 sessions of VRGET in a virtual glass elevator environment. Patients receiving D-cycloserine experienced significantly greater improvement in phobic symptoms than matched patients being treated with VRGET alone.⁵⁹ This difference was noticeable 1 week following treatment and was maintained at 3-month follow-up.

VRGET will become more available as technology costs continue to decrease, and it will probably become a widely used and cost-effective approach for outpatient treatment of panic attacks, PTSD, agoraphobia, social phobia, and other specific phobias. Several basic VRGET tools are available over the Internet, permitting mental health professionals to guide patients in the use of these computer-based advanced exposure protocols through real-time videoconferencing anywhere high-speed Internet access is available.⁶⁰ In the near future, the integrative management of phobias, panic attacks, and other severe anxiety syndromes will combine VRGET, biofeedback, and pharmacological treatment in outpatient settings. Patients with severe phobia will also have the option of gaining access to Web-based VRGET tools via high-speed Internet connections.

Patients who are considering using VRGET should be aware of infrequent but significant safety issues. Fewer than 4% of persons experience transient symptoms of disorientation, nausea, dizziness, headache, and blurred vision when in a virtual environment. "Simulator sleepiness" is a feeling of generalized fatigue that occurs infrequently. Intense sensory stimulation during

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VRGET can trigger migraine, seizures, or gait abnormalities in persons who are prone to these medical conditions, and VRGET is therefore contraindicated in these populations. Anxious patients who are actively abusing alcohol or narcotics should not use VRGET. Patients who have disorders of the vestibular

system should be advised against trying VRGET. Patients with psychosis should not use VRGET because immersion in a virtual environment can exacerbate delusions and potentially worsen reality testing.⁶¹

EMG, GSR, and EEG biofeedback training

Biofeedback has nonspecific beneficial effects on many anxiety symptoms. EMG, GSR, and EEG biofeedback

training are effective treatments for generalized anxiety.⁶²⁻⁶⁴ Patients with chronic anxiety trained in EEG or EMG biofeedback achieve symptom reduction similar to those taking conventional anti-anxiety medications.^{65,66} The long-term benefits of EEG biofeedback for anxious patients have not been clearly established. One study evaluated 2 EEG biofeedback machines on patients complaining of anxiety and "burnout" in an addiction treatment center.⁶⁷ Al-

though patients experienced immediate reductions in state anxiety during biofeedback training, long-term effects on burnout were not maintained following discontinuation of treatment.

Microcurrent electrical stimulation

Microcurrent electrical stimulation, also called "cranial-electrotherapy stimulation" (CES), is an effective treatment for generalized anxiety. Quantitative EEG studies have confirmed beneficial changes in brain electrical activity when this approach is used.⁶⁸ A meta-analysis of double-blind, controlled trials comparing CES with a sham treatment (ie, electrodes applied, but with no current) concluded that measures of generalized anxiety improved in 7 of 8 studies, and the magnitude of improvement reached statistical significance in 4 of these.⁶⁹ A larger review encompassing 34 sham-controlled trials conducted between 1963 and 1996 concluded that regular CES treatments resulted in short-term symptomatic relief of generalized anxiety symptoms mediated by direct effects on autonomic brain centers.⁷⁰

In a 10-week open trial of daily, self-administered CES therapy in 182 individuals with *DSM-III* anxiety disorders, 73% of patients reported significant reductions in anxiety that were maintained at 6-month follow-up.⁷¹ Significantly, conventional drugs had failed in 25% of patients in the study, and 58% had received no previous treatment of any kind for their anxiety symptoms. In general, patients who receive at least 4 to 6 CES treatments experience more sustained reductions in anxiety than patients who receive fewer treatments. The results of a small, double-blind, sham-controlled study (N = 20) suggest that a single CES treatment in patients who report generalized stress results in beneficial changes in autonomic arousal that are sustained at least 1 week following treatment, as measured by decreases in EMG and heart rate.⁷²

Patients with one or more phobias reported significant reductions in state anxiety when exposure to the anxiety-inducing stimulus was followed by 30 minutes of CES treatment.⁷³ Comparable anxiety reduction was achieved with CES and conventional anti-anxiety medications, suggesting that CES may be an effective approach for patients with phobia who wish to discontinue conventional drugs.

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BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information. Daytrana™ (methylphenidate transdermal system) **ClI Rx Only**

INDICATION AND USAGE
Attention Deficit Hyperactivity Disorder (ADHD): Daytrana™ (methylphenidate transdermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and is available in 10, 15, 20, and 30 mg dosing strengths. The efficacy of Daytrana™ was established in two controlled clinical trials in children with ADHD.
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-TR characteristics.
Need for Comprehensive Treatment Program: Daytrana™ 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 and psychological interventions are essential and 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 Daytrana™ for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Daytrana™ for extended periods should periodically re-evaluate the long-term usefulness of Daytrana™ for the individual patient.

CONTRAINDICATIONS
Agitation: Daytrana™ is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate: Daytrana™ is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester).

Glaucoma: Daytrana™ is contraindicated in patients with glaucoma.

Tics: Daytrana™ is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see **ADVERSE REACTIONS**).

Monamine Oxidase Inhibitors: Daytrana™ is contraindicated during treatment with monamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monamine oxidase inhibitor (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.

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.

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) (see **ADVERSE REACTIONS**), 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 with 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, 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.

Contact Sensitization: Use of Daytrana™ may lead to contact sensitization. Daytrana™ should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana™ and is not by itself an indication of sensitization. However, sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Diagnosis of allergic contact dermatitis should be corroborated by appropriate diagnostic testing.

Patients sensitized from use of Daytrana™, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting.

Patients who develop contact sensitization to Daytrana™ and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to Daytrana™ may not be able to take methylphenidate in any form.

A study designed to provoke skin sensitization revealed a signal for Daytrana™ to be an irritant and also a contact sensitizer. This study involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, followed by a 2 week rest period, and the challenge phase. Under conditions of the study, Daytrana™ was more irritating than both the placebo patch control and the negative control (saline). Of 133 subjects who participated in the challenge phase of the sensitization study, at least 18 (13.5%) were confirmed to have been sensitized to Daytrana™ based on the results of the challenge and/or rechallenge phases of the study.

Using Daytrana™ as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported. However, since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what the true incidence of sensitization is when Daytrana™ is used as directed.

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 3,482 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 has been reported in clinical trials and 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: Careful 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 6 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. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or 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 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.

Use in Children Under Six Years of Age: Daytrana™ should not be used in children under six years of age, since safety and efficacy in this age group have not been established.

Drug Dependence
Daytrana™ should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS
Patients Using External Heat: All patients should be advised to avoid exposing the Daytrana™ application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, etc., while wearing the patch. There is a potential for temperature-dependent increases in methylphenidate release of greater than 2-fold from the patch.

Hematologic Monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients: Patients should be informed to apply Daytrana™ to a clean, dry site on the hip, which is not oily, damaged, or irritated. The site of application must be alternated daily. The patch should not be applied to the waistline, or where tight clothing may rub it.

Daytrana™ should be applied 2 hours before the desired effect. Daytrana™ should be removed approximately 9 hours after it is applied, although the effects from the patch will last for several hours.

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana™ to monitor application and removal time, and method of disposal.

If there is an unacceptable duration of appetite loss or insomnia in the evening, taking the patch off earlier may be attempted before decreasing the patch size.

Skin redness or itching is common with Daytrana™, and small bumps on the skin may also occur in some patients. If any swelling or blistering occurs the patch should not be worn and the patient should be seen by the prescriber.

Drug Interactions: Daytrana™ should not be used in patients being treated (currently or within the preceding two weeks) with monamine oxidase inhibitors (see **CONTRAINDICATIONS-Monamine Oxidase Inhibitors**).

Because of a possible effect on blood pressure, Daytrana™ should be used cautiously with pressor agents.

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

Serious adverse events have been reported in concomitant use of methylphenidate with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity studies of transdermal methylphenidate have not been performed. In a lifetime carcinogenicity study of oral methylphenidate carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors and the significance of these results to humans is unknown.

Orally administered methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week oral carcinogenicity study in the transgenic mouse strain p53^{-/-}, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. In this study, male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese hamster ovary cells.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Contraception Breeding study. The study was conducted at doses up to 160 mg/kg/day.

Pregnancy Category C: Animal reproduction studies with transdermal methylphenidate have not been performed. In a study in which oral methylphenidate was given to pregnant rats during the period of organogenesis at doses up to 200 mg/kg/day, no teratogenic effects were seen, although an increase in the incidence of a variation, dilation of the lateral ventricles, was seen at 200 mg/kg/day; this dose also produced maternal toxicity. A previously conducted study in rabbits showed teratogenic effects of methylphenidate at an oral dose of 200 mg/kg/day. In a study in which oral methylphenidate was given to pregnant rats during the period of organogenesis at doses up to 100 mg/kg/day, no teratogenic effects were seen although a slight delay in fetal skeletal ossification was seen at doses of 60 mg/kg/day and above; these doses caused some maternal toxicity.

In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity. Adequate and well-controlled studies in pregnant women have not been conducted. Daytrana™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Daytrana™ is administered to a nursing woman.

Pediatric Use: The safety and efficacy of Daytrana™ in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see **WARNINGS**).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS
The pre-marketing clinical development program for Daytrana™ included exposures in a total of 1,158 participants in clinical trials (758 pediatric patients and 400 healthy adult subjects). These participants received Daytrana™ in patch sizes ranging from 6.25 cm² to 50 cm². The 758 pediatric patients (age 6 to 16 years) were evaluated in 9 controlled clinical studies, 2 open-label clinical studies, and 4 clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events data, the results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Refer to the Full Prescribing Information for details of adverse event data collection.

Adverse Findings in Clinical Trials With Daytrana™
Adverse Events Associated With Discontinuation of Treatment: In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana™ discontinued due to adverse events compared with 1.2% (1/82) receiving placebo. The reasons for discontinuation among the patients treated with Daytrana™ were application site erythema, application site reaction, confusional state, crying, lites, headaches, irritability, infectious mononucleosis, and viral infection.

Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated With Daytrana™: Table 1 enumerates the incidence of treatment-emergent adverse events reported in a 7 week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting.

TABLE 1: Most Commonly Reported Treatment-Emergent Adverse Events (≥ 5% and 2x Placebo) in a 7-week Placebo-controlled Study

Adverse Event	Daytrana™ (N = 98)	Placebo (N = 85)
Number of Subjects With ≥ 1 Adverse Event	74 (76)	49 (58)
Nausea	12 (12)	2 (2)
Vomiting	10 (10)	4 (5)
Nasopharyngitis	5 (5)	2 (2)
Weight decreased	9 (9)	0 (0)
Anorexia	5 (5)	1 (1)
Decreased appetite	25 (26)	4 (5)
Affect lability*	6 (6)	0 (0)
Insomnia	13 (13)	4 (5)
Tic	7 (7)	0 (0)
Nasal congestion	6 (6)	1 (1)

* Six subjects had affect lability, all judged as mild and described as increased emotionality/sensitivity, emotional instability, emotional lability, and intermittent emotional lability.

emergent adverse events. The most common events leading to withdrawal were application site reaction (12 subjects, 6%), anorexia (7 subjects, 4%), and insomnia (7 subjects, 4%).

Adverse Events With Oral Methylphenidate Products: Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently, however, any of the other adverse reactions listed below may also occur.

Other adverse reactions: **Cardiac:** angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia; **Gastrointestinal:** abdominal pain, nausea; **Immune:** hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura; **Metabolism/Nutrition:** anorexia, weight loss during prolonged therapy; **Nervous System:** dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis; **Vascular:** blood pressure increased or decreased, cerebral aneurysm and/or occlusion.

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate: **Blood/Lymphatic:** leukopenia and/or anemia; **Hepatic/abnormal liver function:** ranging from transaminase elevation to hepatic coma; **Psychiatric:** transient depressed mood; **Skin/Subcutaneous:** scalp hair loss; **Neurologic Malignant Syndrome:** Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

Postmarketing Reports
Postmarketing reports of hypersensitivity reactions, including generalized erythematous and urticarial rashes, contact dermatitis, angioedema, and anaphylaxis, have been received. Because these reactions are reported voluntarily from a population of patients without a controlled study, they cannot be reliably estimated their frequency or establish a causal relationship to Daytrana™ exposure.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: Daytrana™ (methylphenidate transdermal system), like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance: See **WARNINGS-Drug Dependence** for boxed warning containing drug abuse and dependence information.

OVERDOSAGE
Signs and Symptoms: Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment: Remove all patches immediately and cleanse the area(s) to remove any remaining adhesive. The continuing absorption of methylphenidate from the skin, even after removal of the patch, should be considered when treating patients with overdose. Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia. Efficacy of peritoneal dialysis or extracorporeal hemodialysis for Daytrana™ overdose has not been established.

Poison Control Center: As with the management of all overdoses, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdose with methylphenidate.

Do not store patches unopened. Store at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F) [see USP Controlled Room Temperature]. Once the tray is opened, use contents within 2 months. Apply the patch immediately upon removal from the protective pouch. Do not store patches unopened. For transdermal use only.

REFERENCE: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association 1994. Manufactured for Shire US Inc., Wayne, PA 19087 by Noven Pharmaceuticals, Inc., Malvern, PA 19355. For more information call 1-800-928-2088 or visit www.daytrana.com

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LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia* (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). §Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* Lexapro (N=429) and Placebo (N=427): Autonomic Nervous System Disorders:** Dry Mouth (3% and 5%); Sweating Increased (4% and 1%); **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%); **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (3% and 2%); Toothache (2% and 0%); **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%); **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%); **Psychiatric Disorders:** Somnolence (3% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%); **Urogenital:** Ejaculation Disorder[†] (14% and 2%); Anorgasmia[‡] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). §Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of $\geq 5\%$ in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (80%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=255); Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%); *Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials** [In Males Only: **Lexapro (N=407) and Placebo (N=383):** Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%); [In Females Only: **Lexapro (N=737) and Placebo (N=636):** Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligam has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dys-equilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hematic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucinations, suicidal tendency. Reproductive Disorders/Female - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. N= 905 Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - *Frequent:* vision blurred, linnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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