DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 11 2000

TRANSMITTED VIA FACSIMILE

Nanette E. Holston
Manager, U.S. Regulatory Affairs
Wyeth-Ayerst
P.O. Box 8299
Philadelphia, PA 19101-8299

RE: NDA #20-699
Effexor XR (venlafaxine) Extended Release Capsules
MACMIS #8741

Dear Ms. Holston:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of a promotional campaign for Effexor XR (venlafaxine) Extended Release Capsules that is false, misleading, or otherwise in violation of the Federal Food, Drug, and Cosmetic Act and its regulations. Promotional materials that comprise this campaign include, but are not limited to, journal advertisements (ID#s 79347-00, 79396-00), sales aids, (ID#s 79368-00, 79457-00), mailers (ID#s 79524-00, 79364-00, 79520-00, 79521-00) and brochures (ID#s 79366-00, 79349-00, 79539-00).

More specifically, these materials are misleading because they directly claim or imply that Effexor XR can get patients "beyond better to well" and can "bring patients to true wellness." "Well" is a broad category that implies a cure or freedom from a disease or illness, not simply that its symptoms are alleviated. Control of one's disease or condition does not necessarily make one "well." "Beyond better" and "true wellness" implies the ultimate response that anyone who had the condition has been cured and is no different than a person who never had the condition. These claims further imply that it will be unlikely that the condition will return. DDMAC has reviewed Wyeth-Ayerst's (Wyeth) data to support these claims. The data fail to demonstrate that Effexor has cured depression (i.e., after treatment with Effexor, drug therapy can be terminated and depression will no longer occur). In addition, the data fail to demonstrate that Effexor has caused a "remission" of depression. Therefore, DDMAC has determined that there is no adequate substantiation for the claims in question.

In addition to the issues described above, the promotional materials that depict children are misleading because the disclaimer that the efficacy and safety of Effexor XR for pediatric use has not been established is not prominent.

Nanette E. Holston
Wyeth
NDA 20-699 (MACMIS 8741)

To address these objections, DDMAC recommends that Wyeth do the following:

1. Immediately discontinue the use of these materials and any other promotional materials with the same or similar issues.

2. Respond to this letter, in writing, within 10 days. Wyeth-Ayerst's response should include a statement of its intent to comply with the above, a list of all violative promotional materials with the same or similar issues, and Wyeth's methods for discontinuing the materials.

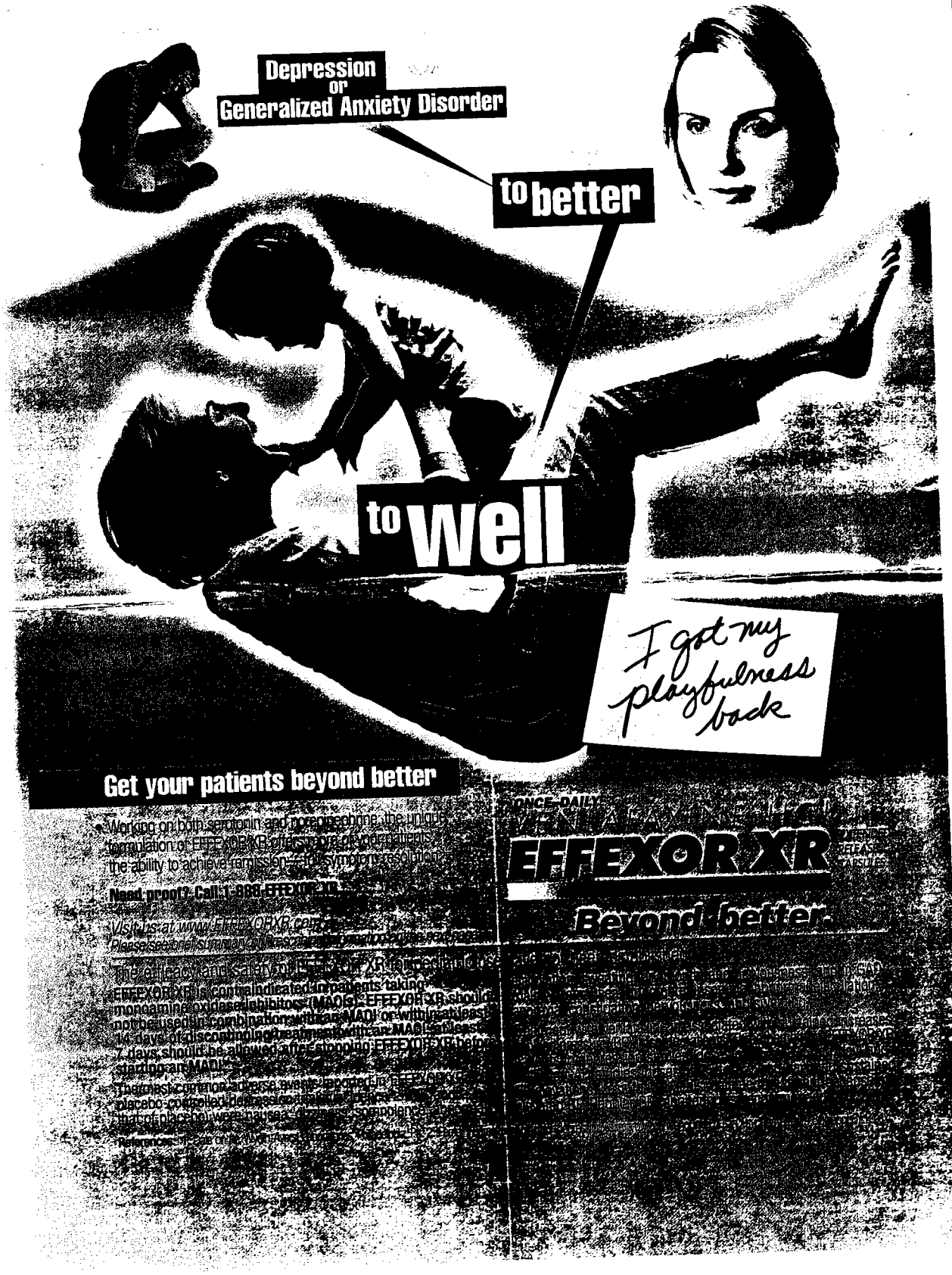
In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8741 in addition to the NDA number.

If you have any questions or comments, please contact Dr. Lisa L. Stockbridge by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

Sincerely,

/S/

Lisa L. Stockbridge, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications


Depression
or
Generalized Anxiety Disorder
to better
to well
I got my playfulness back
Get your patients beyond better
EFFEXOR XR
Beyond better.

VENLAFAXINE HCl

EFFEXOR® XR

EXTENDED RELEASE CAPSULES

Brief Summary

See package insert for full prescribing information.

Indications and Usage: Effexor XR is indicated for the treatment of depression and for the treatment of Generalized Anxiety Disorder (GAD).

Contraindications: Effexor XR is contraindicated in patients known to be hypersensitive to venlafaxine hydrochloride. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see "Warnings").

Warnings: POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS—Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. [illegible] reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. [illegible] These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.

SUSTAINED HYPERTENSION—Venlafaxine is associated with sustained increases in blood pressure in some patients. Among patients treated with 75-375 mg per day of Effexor XR in premarketing depression studies, 3% experienced sustained hypertension (defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits). Among patients treated with 75-225 mg per day of Effexor XR in premarketing GAD studies, 0.4% (2/476) experienced sustained hypertension. Experience with immediate release venlafaxine showed that sustained hypertension was dose related, increasing from 3-7% at 100-300 mg per day to 13% at doses above 300 mg per day. An insufficient number of patients received mean doses of Effexor XR [illegible]

[illegible]

In postmarketing experience, there have been reports of fatalities in patients taking overdoses of venlafaxine, predominantly in combination with alcohol and/or other drugs.

[illegible] Monitor cardiac rhythm and vital signs. [illegible] Induction of emesis is not recommended. [illegible] Activated charcoal should be administered. [illegible] In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference®* (PDR).

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (See "Contraindications" and "Warnings").

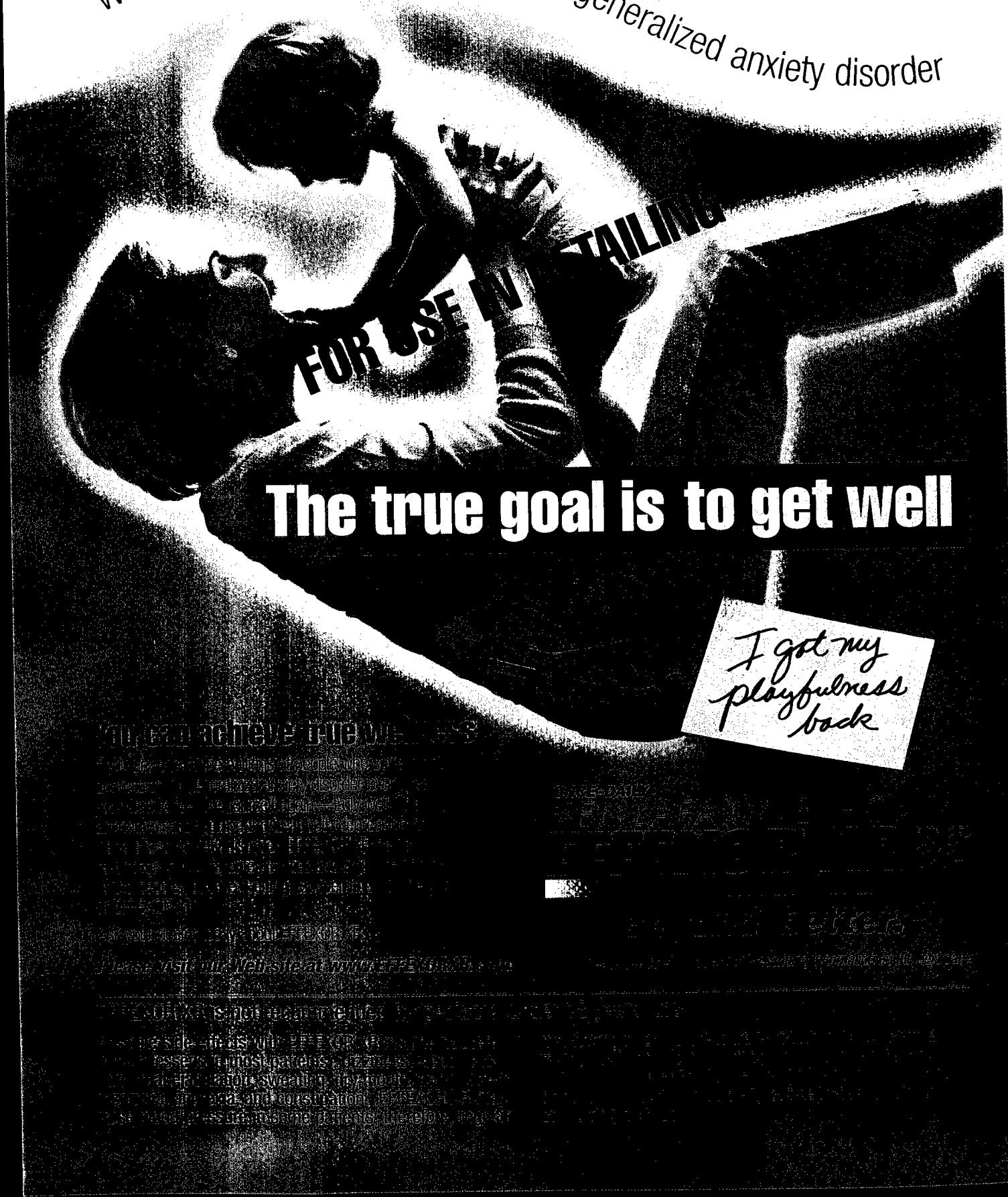
Please consult full prescribing information for detailed dosing instructions.

This brief summary is based on the circular 4876-4, issued March 22, 1999.

WYETH-AYERST LABORATORIES

79347-00

When suffering from depression or generalized anxiety disorder



VENLAFAXINE HCl

EFFEXOR XR EXTENDED RELEASE CAPSULES

Brief Summary
See package insert for full prescribing information.
Indications and Usage: Effexor XR is indicated for the treatment of depression and for the treatment of Generalized Anxiety Disorder (GAD).
Contraindications: Effexor XR is contraindicated in patients known to be hypersensitive to venlafaxine hydrochloride. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **"Warnings"**).
Warnings: POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS—**Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.**
SUSTAINED HYPERTENSION—Venlafaxine is associated with sustained increases in blood pressure in some patients. Among patients treated with 75-375 mg per day of Effexor XR in premarketing depression studies, 3% experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 75-225 mg per day of Effexor XR in premarketing GAD studies, 0.4% (2/476) experienced sustained hypertension. Experience with immediate release venlafaxine showed that sustained hypertension was dose related, increasing from 3-7% at 100-300 mg per day to 13% at doses above 300 mg per day. An insufficient number of patients received mean doses of Effexor XR >300 mg/day to fully evaluate the incidence of sustained blood pressure at these higher doses. In premarketing depression and GAD studies, 0.7% and 0.4% of the Effexor XR-treated patients, respectively, discontinued treatment because of elevated blood pressure. It is recommended that patients receiving Effexor XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.
Precautions: GENERAL—*Insomnia and Nervousness*: Treatment-emergent insomnia and nervousness have been reported for patients treated with Effexor XR. Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in Phase 3 depression studies. In Phase 3 GAD trials, insomnia and nervousness led to drug discontinuation in 5% and 3%, respectively, of the patients treated with Effexor XR.
Changes in Appetite/Weight: Treatment-emergent anorexia has been reported in short-term depression and anxiety studies. A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in placebo-controlled depression trials. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-treated and 0% of the placebo-treated patients in placebo-controlled GAD trials.
Activation of Mania/Hypomania: Mania or hypomania has occurred during short-term depression studies. Effexor XR should be used cautiously in patients with a history of mania.
Seizures: No seizures occurred among Effexor XR-treated patients in short-term trials. In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine-treated patients. Use Effexor XR cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures.
Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Closely supervise high-risk patients during initial drug therapy. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose. The same precautions observed when treating patients with depression should be observed when treating patients with GAD.
Use in Patients With Concomitant Illness: Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. In short-term depression studies electrocardiographic changes in corrected QT interval (QTc) for Effexor XR-treated patients showed an increase of 4.7 msec. In these same trials, the mean change from baseline heart rate for Effexor XR-treated patients was 4 beats per minute. In short-term GAD studies, mean changes in QTc for Effexor XR-treated patients did not differ significantly from placebo. The mean change from baseline heart rate for Effexor XR-treated patients in anxiety studies was 3 beats per minute. The clinical significance of these changes is unknown. In patients with renal impairment (GFR=10-70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients.
INFORMATION FOR PATIENTS—Clinical studies in healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to 1) notify their physician if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) inform physician about other prescription or over the counter medications they are taking or plan to take; 3) avoid alcohol while taking Effexor XR; 4) notify their physician if they develop a rash, hives, or related allergic phenomena.
LABORATORY TESTS: There are no specific laboratory tests recommended.
DRUG INTERACTIONS—*Cimetidine*: Use with caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly.
Haloperidol: Venlafaxine (150 mg/day) decreased total oral-dose clearance (CL/F) of haloperidol which resulted in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life was unchanged.
Drugs Inhibiting Cytochrome P4502D6 Metabolism: Venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome P4502D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. However, since the composite plasma levels of venlafaxine and ODV are essentially unchanged in CYP2D6 poor metabolizers, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.
The concomitant use of venlafaxine with a drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems.
Drugs Metabolized by Cytochrome P450 Isoenzymes: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4 (*in vitro* and *in vivo*), CYP2C9 (*in vitro*), or CYP2C19 (*in vitro*).
Imipramine—Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by 2.5-4.5 fold. Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.
Risperidone—Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).
Monoamine Oxidase Inhibitors: See **"Contraindications"** and **"Warnings."**
CNS-Active Drugs: Use of venlafaxine with CNS-active drugs has not been systematically evaluated; use caution when administering Effexor XR with such drugs.
Postmarketing Spontaneous Drug Interaction Reports: See **"ADVERSE REACTIONS," "Postmarketing Reports."**
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY—*Carcinogenesis*: There was no increase in tumors in 18-month studies in mice given up to 120 mg/kg/day [1.7 times the maximum recommended human dose (MRHD) mg/m^2 basis] or in 24-month studies in rats given up to 120 mg/kg/day.
Mutagenesis: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.
Impairment of Fertility: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m^2 basis.
PREGNANCY—*Teratogenic Effects—Pregnancy Category C*. Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m^2 basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed.
LABOR, DELIVERY, NURSING—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
PEDIATRIC USE—Safety and effectiveness in pediatric patients have not been established.
GERIATRIC USE—Approximately 4% and 3% of Effexor XR-treated patients in placebo-controlled premarketing depression and GAD trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase depression studies, 12% were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.
Adverse Reactions: ASSOCIATED WITH DISCONTINUATION OF TREATMENT—Approximately 11% and 23% of Effexor XR patients in placebo-controlled clinical depression and GAD trials, respectively, discontinued treatment due to an adverse event. The most common events leading to discontinuation in at least 1% of patients and at least twice that of placebo in depression trials included: nausea, anorexia, dry mouth, dizziness, insomnia, and somnolence; in U.S. placebo-controlled depression trials included: hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, and abnormal (mostly delayed) ejaculation; in GAD trials included: headache, asthenia, vasodilation, nausea, anorexia, dry mouth, dizziness, insomnia, nervousness, somnolence, thinking abnormal, tremor, and abnormal vision.
INCIDENCE IN CONTROLLED TRIALS—*Commonly Observed Adverse Events in Controlled Clinical Trials*: The most commonly observed adverse events associated with the use of Effexor XR in placebo-controlled depression trials (incidence of 5% or greater and incidence for Effexor XR at least twice that for placebo): nausea (31% vs. 12%), dizziness (20% vs. 9%), somnolence (17% vs. 8%), abnormal ejaculation (16% vs. <1%), sweating (14% vs. 3%), dry mouth (12% vs. 6%), nervousness (10% vs. 5%), anorexia (8% vs. 4%), abnormal dreams (7% vs. 2%), and tremor (5% vs. 2%). In U.S. placebo-controlled depression trials, the following were also reported with an incidence of at least 5% and at least twice that for placebo: impotence, anorgasmia, decreased libido, constipation, flatulence, insomnia, nervousness, tremor, abnormal vision, hypertension, vasodilation, and yawning. The most commonly observed adverse events associated with the use of Effexor XR in placebo-controlled GAD trials (incidence of 5% or greater and incidence for Effexor XR at least twice that for placebo): nausea (43% vs. 11%), dry mouth (23% vs. 5%), insomnia (22% vs. 11%), abnormal ejaculation (17% vs. 0%), anorexia (13% vs. 2%), constipation (12% vs. 5%), nervousness (12% vs. 5%), sweating (11% vs. <1%), abnormal vision (8% vs. 0%), yawn (6% vs. <1%), impotence (6% vs. 1%), decreased libido (6% vs. 2%), vasodilation (6% vs. 2%), vomiting (6% vs. 2%).
Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients: The following occurred in short-term, placebo-controlled depression trials (up to 12 weeks) with doses of 75 to 225 mg/day, at a frequency of 2% or more and greater than placebo. **Body as a Whole:** asthenia. **Cardiovascular:** vasodilation, hypertension. **Digestive:** nausea, constipation, anorexia, vomiting, flatulence. **Metabolic/Nutritional:** weight loss. **Nervous System:** dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, paresthesia, decreased libido, agitation. **Respiratory System:** pharyngitis, yawn. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, anorgasmia (female). The following occurred in short-term, placebo-controlled GAD trials (up to 8 weeks), with doses of 75 to 225 mg/day, at a frequency of 2% or more and greater than placebo. **Body as a Whole:** asthenia, infection, abdominal pain, fever, neck pain, chills. **Cardiovascular:** vasodilation, tachycardia. **Digestive:** nausea, anorexia, diarrhea, constipation, vomiting, flatulence. **Musculoskeletal System:** myalgia. **Nervous System:** dry mouth, insomnia, dizziness, somnolence, nervousness, decreased libido, abnormal dreams, tremor, paresthesia, thinking abnormal, trismus, twitching. **Respiratory System:** rhinitis, yawn, cough increased. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, dysmenorrhea, orgasmic dysfunction (female), urinary frequency.
Vital Sign Changes: In clinical depression and GAD trials, Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min. (See the **"Sustained Hypertension"** section of **"Warnings"** for effects on blood pressure.)
Laboratory Changes: In clinical depression and GAD trials, Effexor XR was associated with a mean increase in serum cholesterol concentration of about 1.5 mg/dL and 2.5 mg/dL, respectively; clinical significance is unknown.
ECG Changes: (See the *"Use in Patients With Concomitant Illnesses"* section of **"Precautions"**.)
OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF EFFEXOR AND EFFEXOR XR—During premarketing assessment, multiple doses of Effexor XR or Effexor were administered to 4174 patients, and the following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = fewer than 1/1000 patients. It is important to emphasize that although the events occurred during treatment with venlafaxine, they were not necessarily caused by it.
Body as a whole - **Frequent:** chest pain substernal; **Infrequent:** face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; **Rare:** appendicitis, carcinoma, cellulitis, withdrawal syndrome. Cardiovascular system - **Frequent:** migraine, postural hypotension; **Infrequent:** angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, mitral valve disorder, mucocutaneous hemorrhage, myocardial infarct, pallor. Digestive system - **Frequent:** eructation, increased appetite; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, stomatitis, mouth ulceration; **Rare:** cheilitis, cholecystitis, cholelithiasis, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, oral moniliasis, proctitis, increased salivation, soft stools, tongue discoloration. Endocrine system - **Rare:** goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. Hemic and lymphatic system - **Frequent:** ecchymosis; **Infrequent:** anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; **Rare:** basophilia, cyanosis, eosinophilia, lymphocytosis. Metabolic and nutritional - **Frequent:** edema, weight gain; **Infrequent:** alkaline phosphatase increased, glycosuria, hypercholesteremia, hyperglycemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; **Rare:** alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, dehydration, gout, hemochromatosis, hypercalciuria, hyperkalemia, hyperlipemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia. Musculoskeletal system - **Frequent:** arthralgia; **Infrequent:** arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** pathological fracture, myopathy, osteoporosis, osteosclerosis, rheumatoid arthritis, tendon rupture. Nervous system - **Frequent:** amnesia, confusion, depersonalization, emotional lability, hypoesthesia, vertigo; **Infrequent:** apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, paranoid reaction, psychosis, seizure, abnormal speech, stupor; **Rare:** akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barré Syndrome, hypokinesia, neuritis, nystagmus, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis. Respiratory system - **Frequent:** dyspnea; **Infrequent:** asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare:** atelectasis, hemoptysis, hypoventilation, hypoxia, pleurisy, pulmonary embolus, sleep apnea. Skin and appendages - **Frequent:** rash, pruritus; **Infrequent:** acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare:** erythremia nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae. Special senses - **Frequent:** abnormality of accommodation, mydriasis, taste perversion; **Infrequent:** cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. Urogenital system - **Frequent:** metrorrhagia,* prostatitis,* urination impaired, vaginitis*; **Infrequent:** albuminuria, amenorrhea,* cystitis, dysuria, hematuria, female lactation,* leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; **Rare:** abortion,* anuria, breast engorgement, breast enlargement, fibrocystic breast, calcium crystalluria, cervicitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm.* (*Based on the number of men and women as appropriate.)
Postmarketing Reports: Voluntary reports of other adverse events temporally associated with the use of Effexor (the immediate release form of venlafaxine) that have been received since market introduction and that may have no causal relationship with the use of Effexor include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities (such as atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia), epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), pancreatitis, panic, prolactin increased, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of Effexor or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).
There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.
Drug Abuse and Dependence: Effexor® XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of venlafaxine misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).
OVERDOSAGE: In premarketing evaluation of Effexor XR for depression, there were 2 reports of acute overdosage (6 g of Effexor XR with 2.5 mg of lorazepam, and 2.85 g of Effexor XR). Both recovered without sequelae. In premarketing evaluation of Effexor, there were 14 reports of acute overdosage (highest dose was 6.75 g). All patients recovered without sequelae. Most patients reported no symptoms. Symptoms observed included somnolence, generalized convulsions, prolongation of QTc to 500 msec (compared with 405 msec at baseline) in one case, and mild sinus tachycardia. In premarketing evaluation of Effexor XR for GAD, there were 2 reports of acute overdosage (0.75 g of Effexor XR and 200 mg of paroxetine and 50 mg of zolpidem, and 1.2 g of Effexor XR). Both recovered without sequelae.
In postmarketing experience, there have been reports of fatalities in patients taking overdoses of venlafaxine, predominantly in combination with alcohol and/or other drugs.
Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference®* (PDR).
SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (See **"Contraindications"** and **"Warnings"**).
Please consult full prescribing information for detailed dosing instructions.
This brief summary is based on the circular 4876-4, issued March 22, 1999.

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

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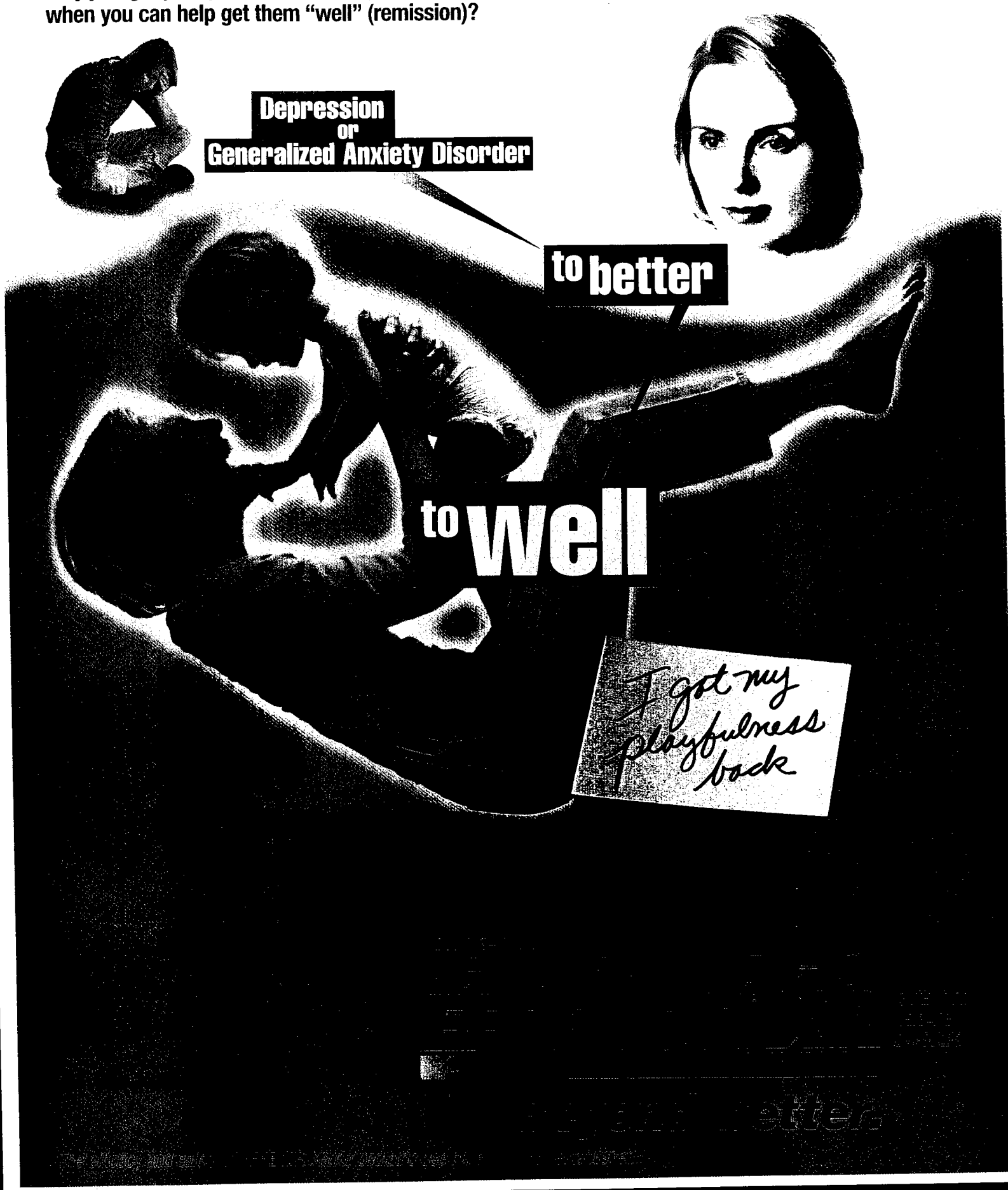
It has been estimated that up to 70% of patients can respond to antidepressant therapy[1]; less than 30% can achieve remission[2].

Why just get your patients "better" (response) when you can help get them "well" (remission)?



IN DEPRESSION AND GENERALIZED ANXIETY DISORDER

overlapping symptoms

Depressive disorders are estimated to coexist with GAD 8% to 39% of the time[4]

Up to 90% of depressed patients also have associated symptoms of anxiety[5]

EXPECT MORE FROM

antidepressant therapy

Effective reuptake inhibition of both serotonin and norepinephrine—two important neurotransmitters[6]

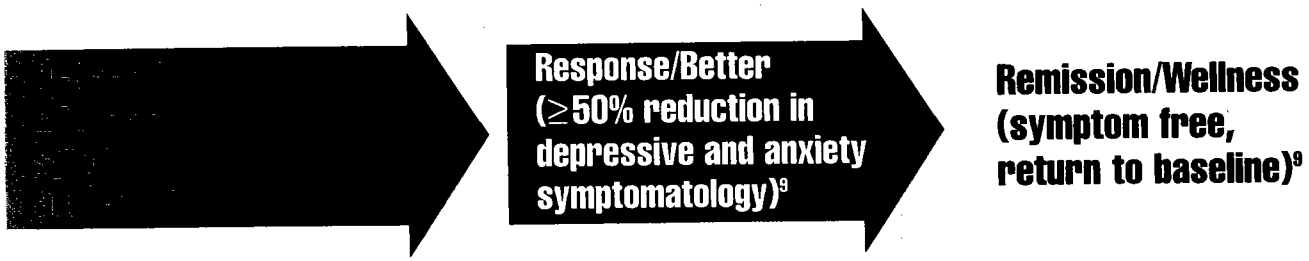
- Dual reuptake inhibition may produce a more robust response in a broader range of patients.[2]
- Antidepressants with two or more mechanisms of action may improve efficacy.[7]
- It may be best to treat with a dual-reuptake inhibitor first as opposed to serotonergic- or noradrenergic-only agents as it is unclear to which type of treatment a patient will respond best.[8]

IN YOUR PATIENTS

strive for wellness

Make remission the end point, not simply response

- Wellness is remission, rather than reduction, of symptoms.[8]



POWER TO

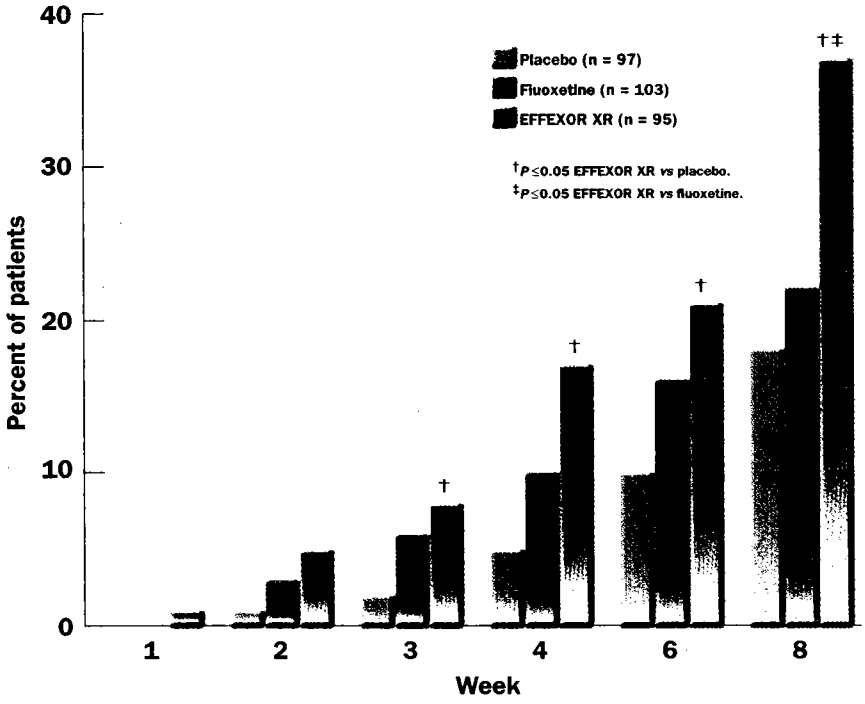
achieve remission

Remission *vs* response is a more complete and sustained improvement[9]

- Response is usually defined as a ≥50% reduction in depressive and anxiety symptomatology.[9]

Patients with remission of depression (HAM-D total ≤7*)[10]

Last-observation-carried-forward analysis



A randomized, double-blind, placebo-controlled study of outpatients with DSM-IV™ major depression. Doses ranged up to 225 mg/day of venlafaxine XR or 60 mg/day of fluoxetine. Mean doses were 175 mg/day for venlafaxine XR and 47 mg/day for fluoxetine during Weeks 4-8.[10] In this study, remission was defined as a score of 7 or less on the HAM-D, which indicates an absence of symptoms.[9]

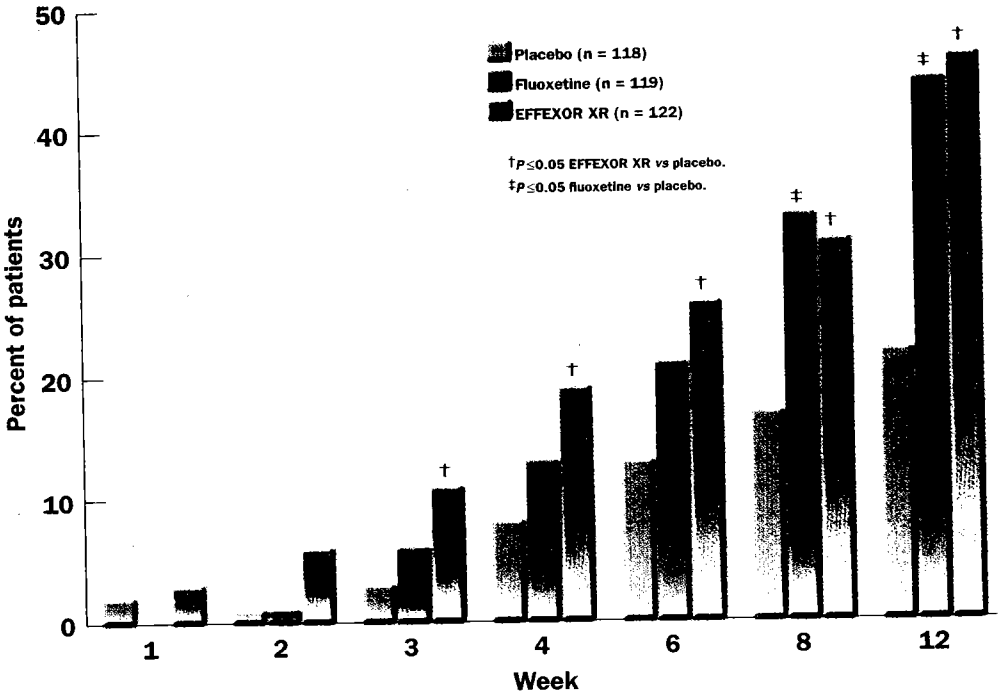
*Based on the first 21 items on the HAM-D.

- In this study, significance *vs* placebo in rates of remission was achieved with EFFEXOR XR at Week 3 and maintained through Week 8 (study end point).[10]
- Nearly twice as many patients receiving EFFEXOR XR achieved remission as did patients receiving fluoxetine.[10]

Rates of discontinuation in both studies were comparable between EFFEXOR XR-treated and fluoxetine-treated patients[10]

Patients with remission of depression (HAM-D total ≤7*)[10]

Last-observation-carried-forward analysis



A randomized, double-blind, placebo-controlled study of outpatients with DSM-IV™ major depression as well as predefined levels of concomitant anxiety. For venlafaxine XR, doses ranged up to 225 mg/day, and for fluoxetine the maximum was 60 mg/day. Mean doses at Week 12 were 141 mg/day for venlafaxine XR and 40 mg/day for fluoxetine.[10]

*Based on the first 17 items on the HAM-D.

- Significance *vs* placebo in rates of remission was achieved with EFFEXOR XR at Week 3 and maintained through Week 12.[10]
- While not statistically significant, the number of patients achieving remission with EFFEXOR XR was higher than

POWER TO RELIEVE

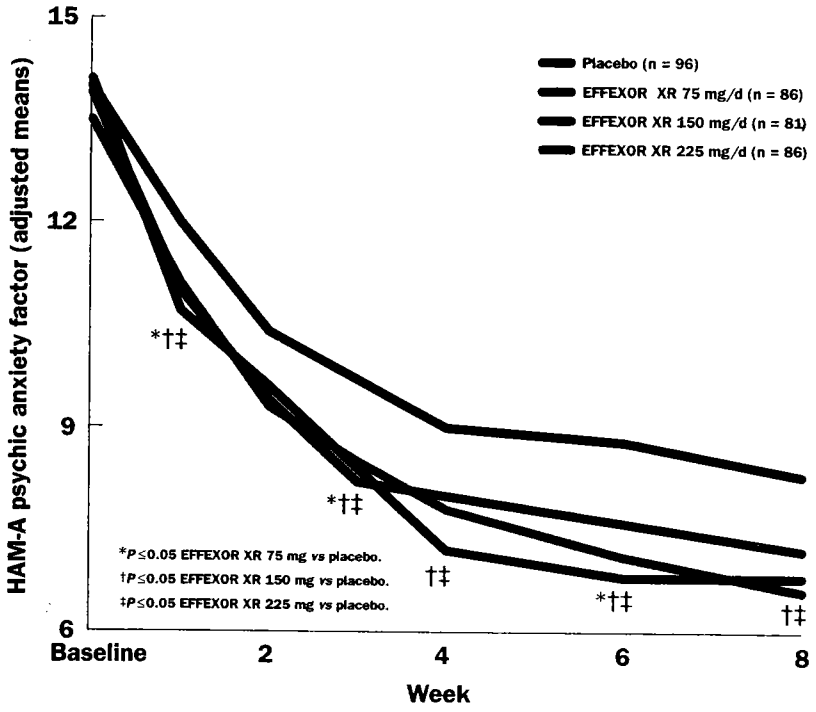
generalized anxiety disorder (GAD)

Worry and stress are prominent symptoms of GAD[3]

- Patients may present with distress due to constant worry and may experience related impairment in social, occupational, or other areas of functioning including everyday, routine life circumstances.[3]

Reduction of psychic anxiety in patients with generalized anxiety disorder[10]

Last-observation-carried-forward analysis



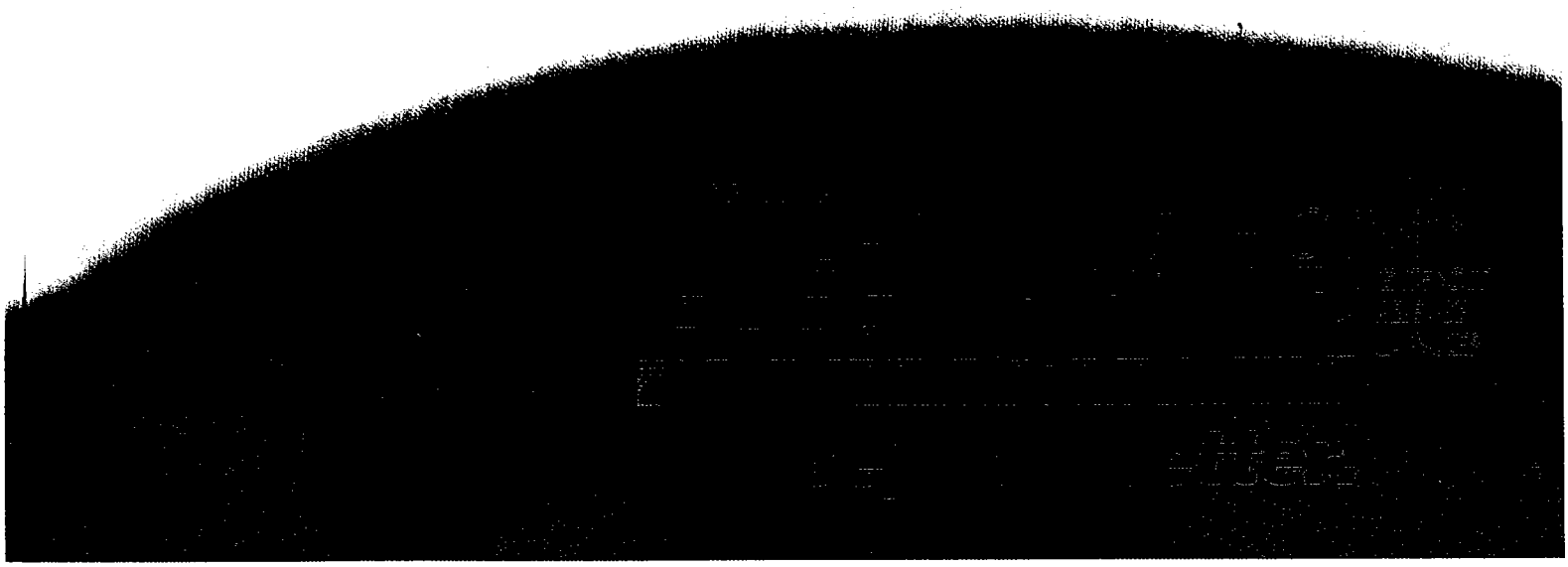
An 8-week, randomized, fixed-dose, double-blind, placebo-controlled study of outpatients with DSM-IV™ GAD. Patients with major depression were excluded. All EFFEXOR XR-treated groups were started at 75 mg/day, with dosage increases administered in weekly increments of 75 mg/day, up to a maximum of 225 mg/day.[10]

- All doses of EFFEXOR XR achieved statistical significance *vs* placebo at Weeks 1, 3, and 6.[10]
- EFFEXOR XR demonstrated efficacy *vs* placebo on the HAM-A psychic anxiety factor, which is based on the clinician's evaluation of anxious mood, tension, fears, insomnia, cognitive impairment, depression, and outward behavior at interview.[5]

IMPORTANT TREATMENT
considerations

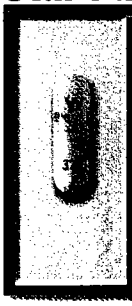
- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI because of potential for serious adverse reactions. Based on the half-life of EFFEXOR XR, at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevations. The incidence of sustained increases in blood pressure at doses greater than 300 mg/day has not been fully evaluated. Less than 1% discontinued treatment because of elevated BP. Experience with immediate release venlafaxine in depression studies showed that sustained hypertension was dose related, increasing from 3% to 7% at doses of 100 mg/day to 300 mg/day, to 13% at doses above 300 mg/day. Regular BP monitoring is recommended.
- The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.
- As with any psychotropic drug, EFFEXOR XR may impair judgment, thinking, or motor skills; patients should be advised to exercise caution until they have adapted to therapy.

References: 1. Thase ME, Rush JA. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress.* New York, NY: Raven Press; 1995:1081. **2.** Ferrier IN. Treatment of major depression: is improvement enough? *J Clin Psychiatry.* 1999;60(suppl 6):10-14. **3.** *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994:327, 432-436. **4.** Brawman-Mintzer O, Lydiard RB. Generalized anxiety disorder: issues in epidemiology. *J Clin Psychiatry.* 1996;57(suppl 7):3-8. **5.** Kaplan HI, Sadock BJ. *Kaplan and Sadock's Synopsis of Psychiatry. Behavioral Sciences/Clinical Psychiatry.* 8th ed. Baltimore, Md: Williams & Wilkins; 1998:309, 553. **6.** EFFEXOR® (venlafaxine HCl) Extended Release and Immediate Release Prescribing Information, Wyeth-Ayerst Laboratories, Philadelphia, Pa. **7.** Stahl SM. Are two antidepressant mechanisms better than one? *J Clin Psychiatry.* 1997;58:339-340. **8.** Stahl SM. Why settle for silver, when you can go for gold? Response vs. recovery as the goal of antidepressant therapy. *J Clin Psychiatry.* 1999;60:213-214. **9.** Thase ME. Relapse and recurrence in unipolar major depression: short-term and long-term approaches. *J Clin Psychiatry.* 1990;51 (suppl 6):51-57. **10.** Data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa.



simple once-daily dosing

Start at



37.5 mg once daily
Initial dosing option
For 4 to 7 days.
Minimizes potential for transient nausea.

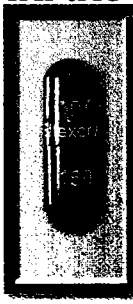
Treat with

75 mg once daily
Usual starting dose
75 mg/day has demonstrated significant response rates in clinical trials.[6]

Assess for

Patient's response to determine whether upward titration can be beneficial

Titrate to



150 mg* once daily
Additional dosing option
Upward titration to a maximum of 225 mg/day† of EFFEXOR XR can be beneficial in patients who do not respond fully to 75 mg/day.[6]

*Increase dose by up to 75 mg/day, at intervals of no less than 4 days.

†Experience with EFFEXOR XR at doses higher than 225 mg/day is very limited.

Note: Absorption is unaffected by food; however, dosing with meals is recomme

Pictured capsules are actual size.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories.

Please visit us at www.EFFEXORXR.com

Call 1-888-EFFEXOR XR for more proof.

getting patients well with

Please see Important Treatment ... page 7

· SWEATING ·

· FREQUENT URINATION ·

· PALPITATIONS ·

· IRRITABLE BOWEL SYNDROME ·

A simple solution to a complex of somatic symptoms in GAD[1,2]

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VENLAFAXINE HCl

EFFEXOR® XR

EXTENDED RELEASE CAPSULES

Beyond better.™

Remove the anxiety symptoms

44% of patients with generalized anxiety disorder sought general medical treatment for associated somatic symptoms[3]

Worry is a key feature

- Worry associated with generalized anxiety disorder is more pervasive and distressing, less realistic, and of longer duration than normal worry[4]
- More patients with generalized anxiety disorder experience greater life interference due to worry than patients with other anxiety disorders[5]

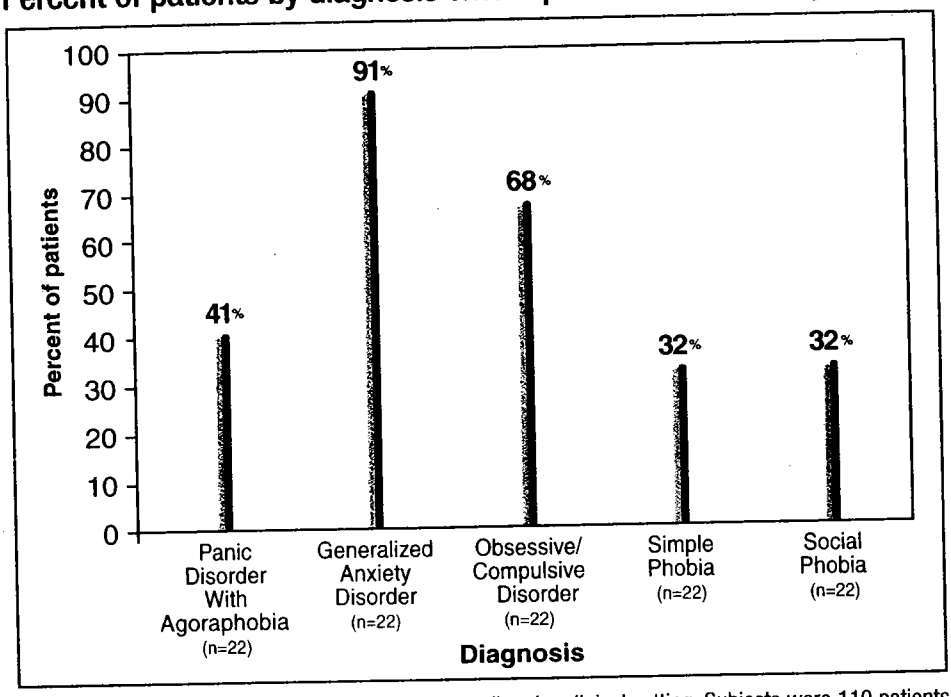
Diagnostic criteria for generalized anxiety disorder[4]:

- Difficult-to-control anxiety or worry
- Three or more of the following somatic symptoms: restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep problems

Please see Important Treatment Considerations on back cover.

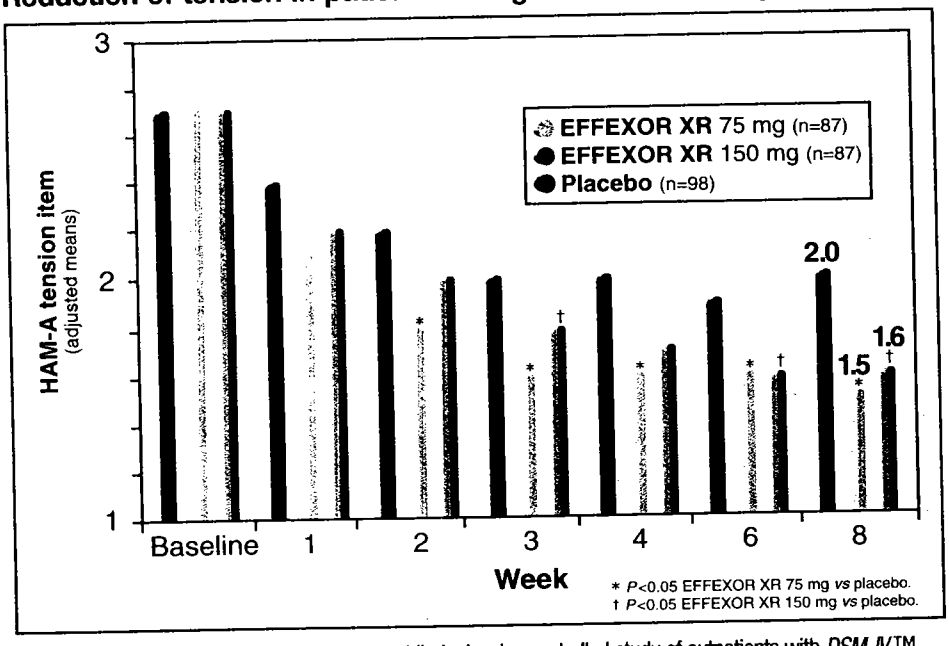
Please see accompanying Prescribing Information inside the pocket.

Percent of patients by diagnosis who report excessive worry*



Results from a structured interview in an anxiety disorder clinical setting. Subjects were 110 patients with anxiety disorders consecutively diagnosed upon presentation at the clinic.[6] Patients with a primary diagnosis of another anxiety disorder with a secondary diagnosis of generalized anxiety disorder were excluded from this sample. *Adapted from Sanderson et al.[6]

Reduction of tension in patients with generalized anxiety disorder[7]



An 8-week, randomized, fixed-dose, double-blind, placebo-controlled study of outpatients with *DSM-IV*™ generalized anxiety disorder. All EFFEXOR XR-treated groups were started at 75 mg/day, with dosage increases administered in weekly increments of 75 mg/day, up to a maximum of 225 mg/day.[7] Last observation-carried-forward analysis.

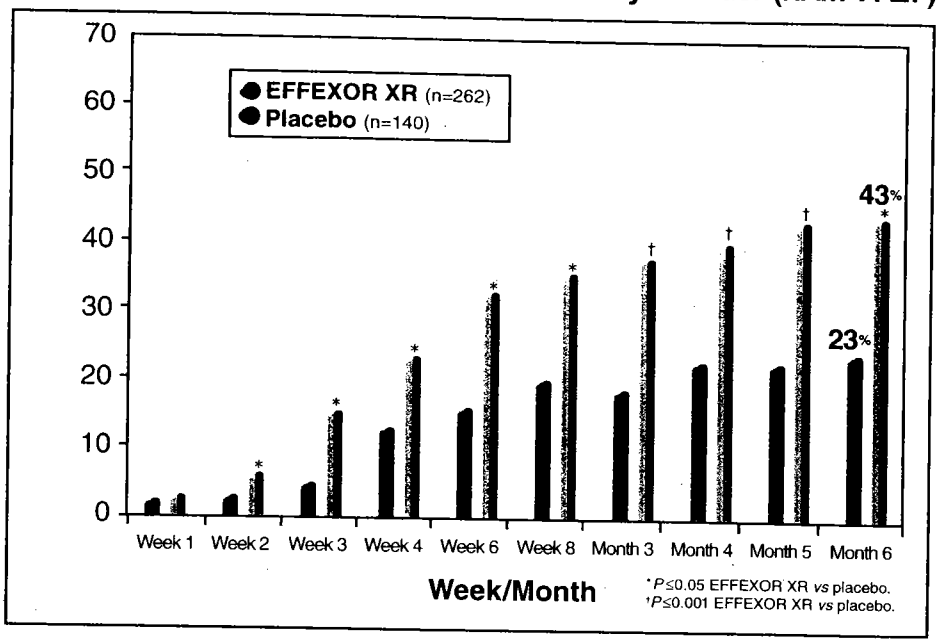
Patients with major depression were excluded.

Efficacy sustained over the long term[7]

- Remission was defined as a HAM-A score ≤7
- EFFEXOR XR showed statistical significance *vs* placebo starting at Week 2 through Month 6 (study end point)

Get your patients beyond better... to well

Remission in patients with generalized anxiety disorder (HAM-A ≤7)[7]



Results were obtained from a pooled analysis of two 6-month, placebo-controlled studies of 402 outpatients with *DSM-IV*™ generalized anxiety disorder. One was a fixed-dose study and the other was a flexible-dose study. Doses of EFFEXOR XR ranged from 37.5 mg/day to 225 mg/day.[7] Results shown from patients with moderate levels of anxiety. Last-observation-carried-forward analysis.

Patients with major depression were excluded.[7]

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Important treatment considerations

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI because of potential for serious adverse reactions. Based on the half-life of EFFEXOR XR, at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevations. The incidence of sustained increases in blood pressure at doses greater than 300 mg/day has not been fully evaluated. Less than 1% discontinued treatment because of elevated BP. Experience with immediate release venlafaxine in depression studies showed that sustained hypertension was dose related, increasing from 3% to 7% at doses of 100 mg/day to 300 mg/day, to 13% at doses above 300 mg/day. Regular BP monitoring is recommended.
- The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.
- As with any psychotropic drug, EFFEXOR XR may impair judgment, thinking, or motor skills; patients should be advised to exercise caution until they have adapted to therapy.

References: **1.** Roerig JL. Diagnosis and management of generalized anxiety disorder. *J Am Pharm Assoc.* 1999;39:811-821. Available at: http://www.medscape.com/APhA/JAPhA/1999/jap3906.03.roer/pnt-jap3906.03.roer.html. Accessed March 7, 2000. **2.** Woodman CL, Breen K, Noyes R Jr, et al. The relationship between irritable bowel syndrome and psychiatric illness: a family study. *Psychosomatics.* 1998;39:45-54. **3.** Anderson DJ, Noyes R Jr, Crowe RR. A comparison of panic disorder and generalized anxiety disorder. *Am J Psychiatry.* 1984;141:572-575. **4.** *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994:432-436. **5.** Brown TA, Barlow DH, Liebowitz MR. The empirical basis of generalized anxiety disorder. *Am J Psychiatry.* 1994;151:1272-1280. **6.** Sanderson WC, Barlow DH. A description of patients diagnosed with DSM-III-R generalized anxiety disorder. *J Nerv Ment Dis.* 1990;178:588-591. **7.** Data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa.

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Please see accompanying Prescribing Information inside the pocket

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(venlafaxine hydrochloride)
Extended-Release Capsules
CI 5044-5

Renal adjustment and equivalent.

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

Special Populations

Age and Gender: A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaffected by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see "DOSAGE AND ADMINISTRATION").

Extensive/Poor Metabolizers: Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different venlafaxine dosing regimens for these two groups.

Liver Disease: In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. Dosage adjustment is necessary in these patients (see "DOSAGE AND ADMINISTRATION").

Renal Disease: In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR=10-70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients

venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord*. 1999;56:171-181.

IMPORTANT TREATMENT CONSIDERATIONS

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- The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2x that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and anorexia; adverse events reported in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.

- As with any psychotropic drug, EFFEXOR XR should be prescribed with caution in patients who have had

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June 2000

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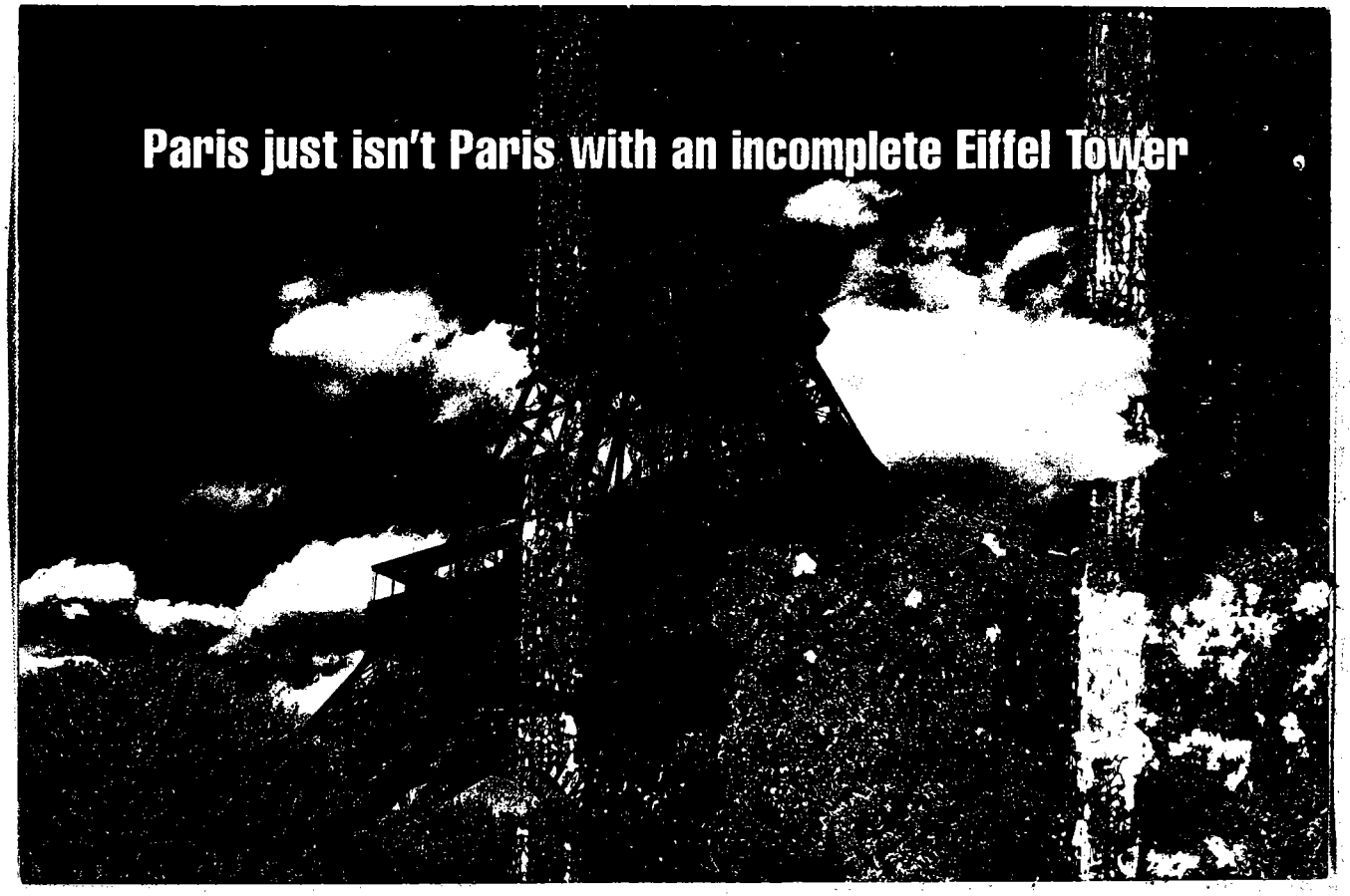
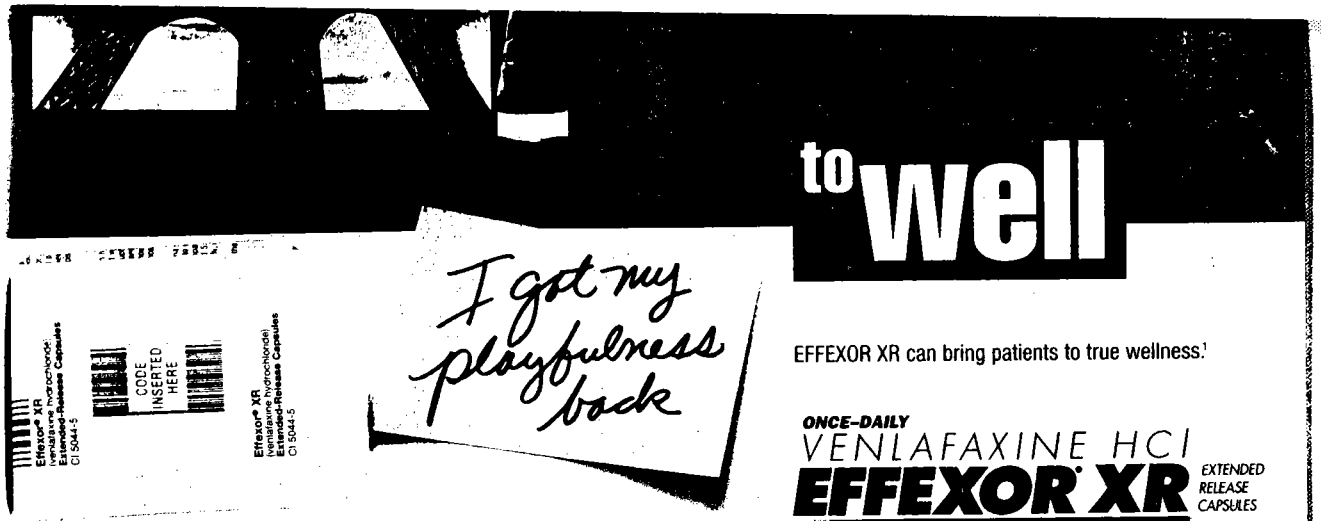

Paris just isn't Paris with an incomplete Eiffel Tower


Antidepressant therapy feels incomplete without a full return to wellness
Get your patients with...
depression or generalized anxiety disorder
beyond better
to well
I got my



EFFEXOR XR can bring patients to true wellness.[1]

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Reference: 1. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord.* 1999;56:171-181.

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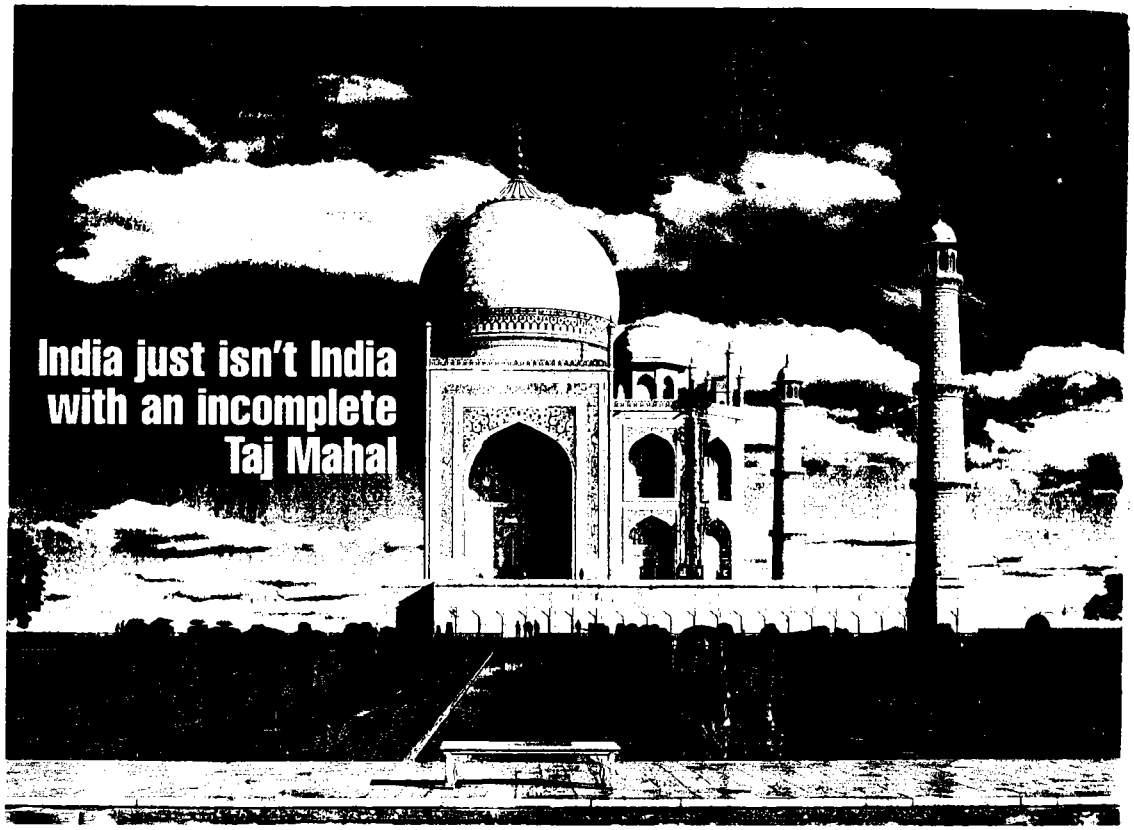
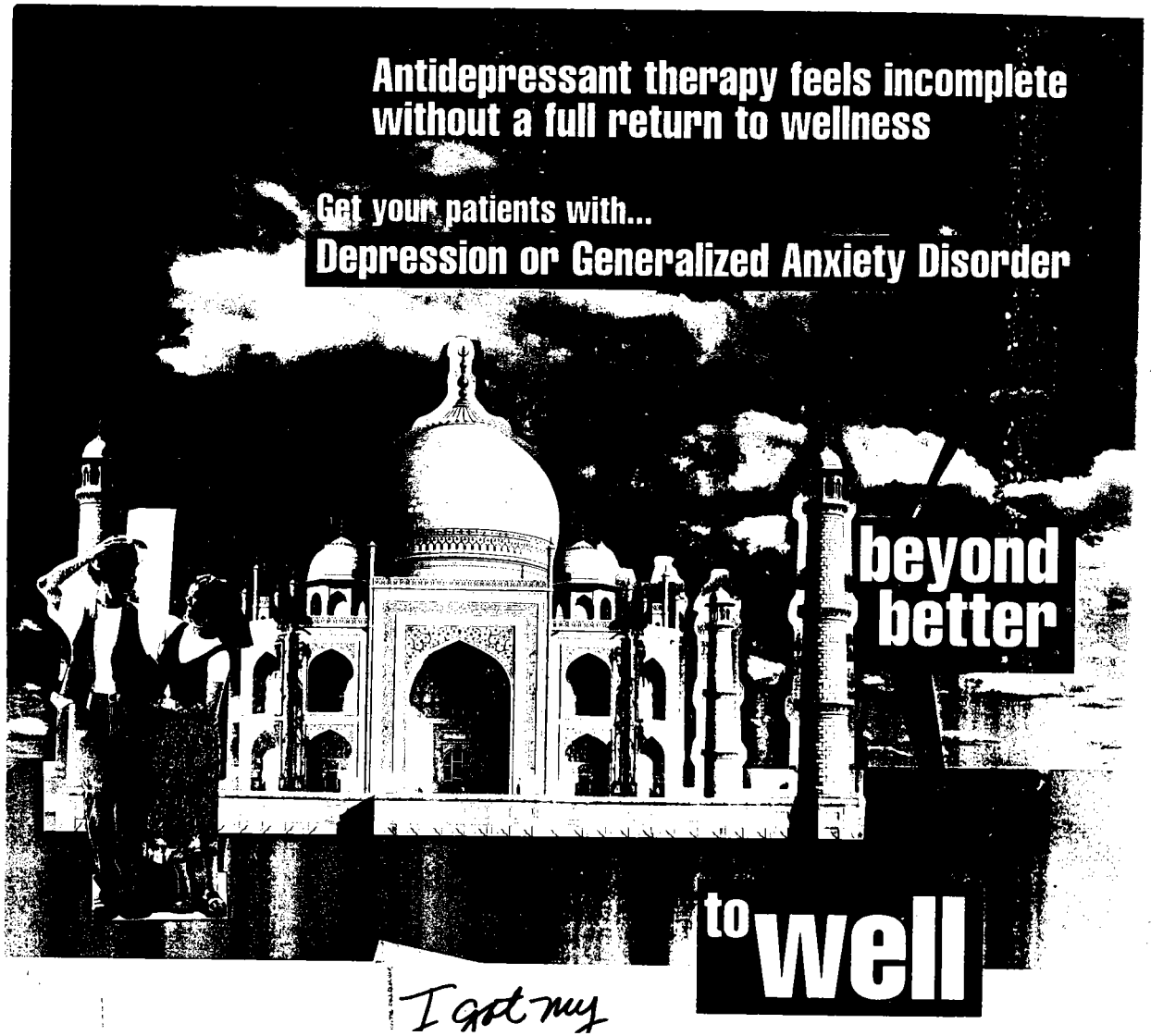
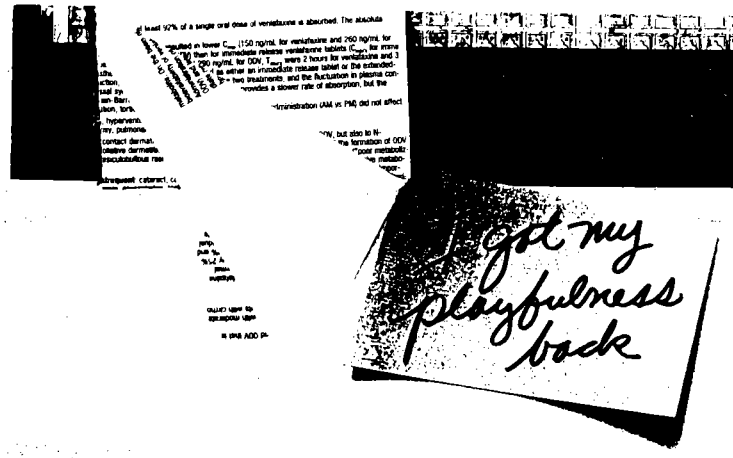

India just isn't India
with an incomplete
Taj Mahal


Antidepressant therapy feels incomplete without a full return to wellness
Get your patients with...
Depression or Generalized Anxiety Disorder
beyond better
to well

I got my



to well

EFFEXOR XR can bring patients to true wellness.[1]

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Reference: 1. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord* 1999;56:171-181.

IMPORTANT TREATMENT CONSIDERATIONS

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI because of potential for serious adverse reactions. Based on the half-life of EFFEXOR XR, at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevations. The incidence of sustained increases in blood pressure at doses greater than 300 mg/day has not been fully evaluated. Less than 1% discontinued treatment because of elevated BP. Experience with immediate release venlafaxine in depression studies showed that sustained hypertension was dose related, increasing from 3% to 7% at doses of 100 mg/day to 300 mg/day, to 13% at doses above 300 mg/day. Regular BP monitoring is recommended.
- The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.
- As with any psychotropic drug, EFFEXOR XR may impair judgment, thinking, or motor skills; patients should be advised to exercise caution until they have adapted to therapy.

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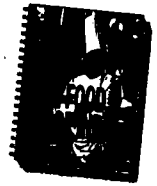

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Effexor® XR
(venlafaxine hydrochloride)
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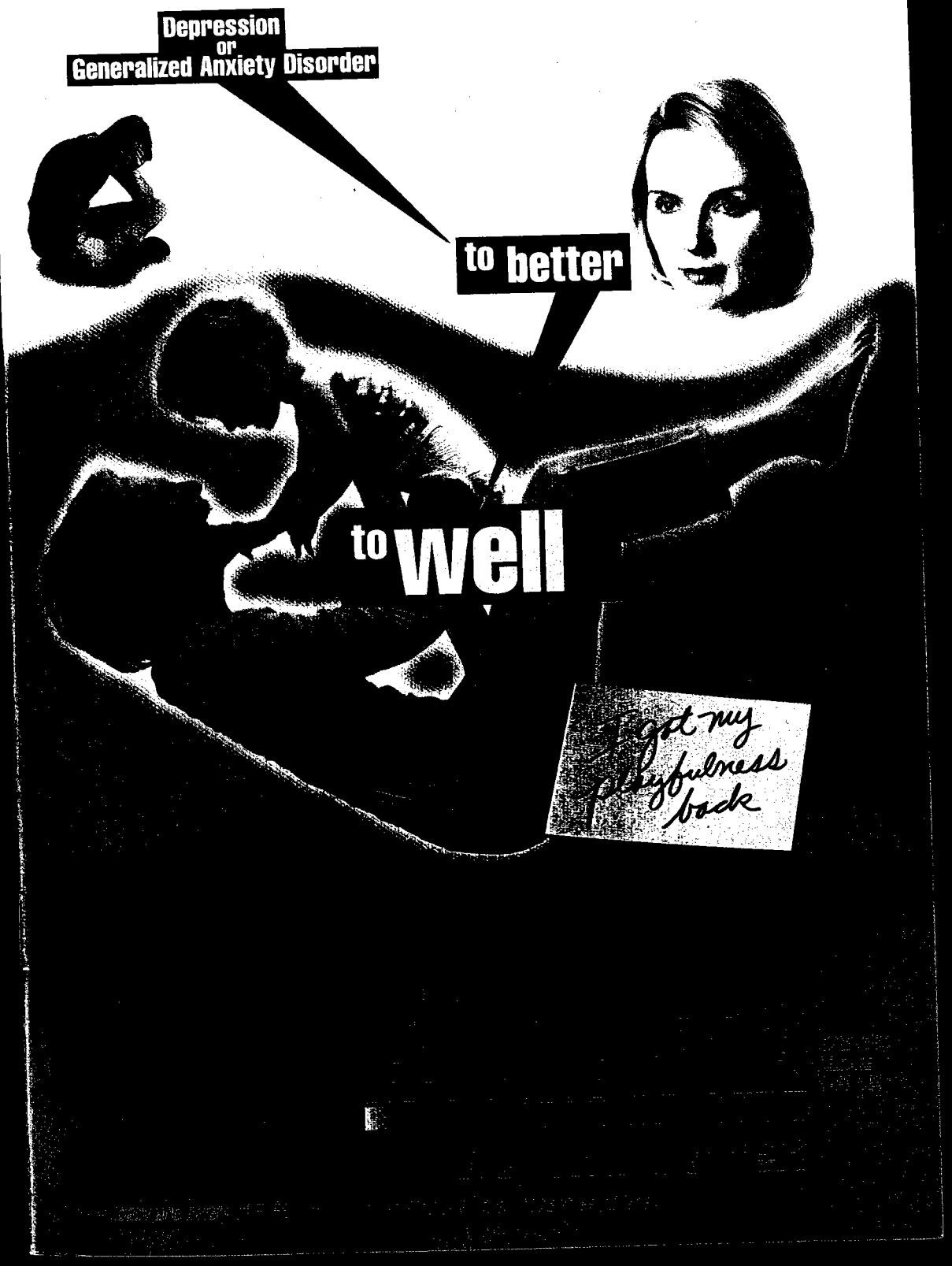
There are flowers and then there are... flowers

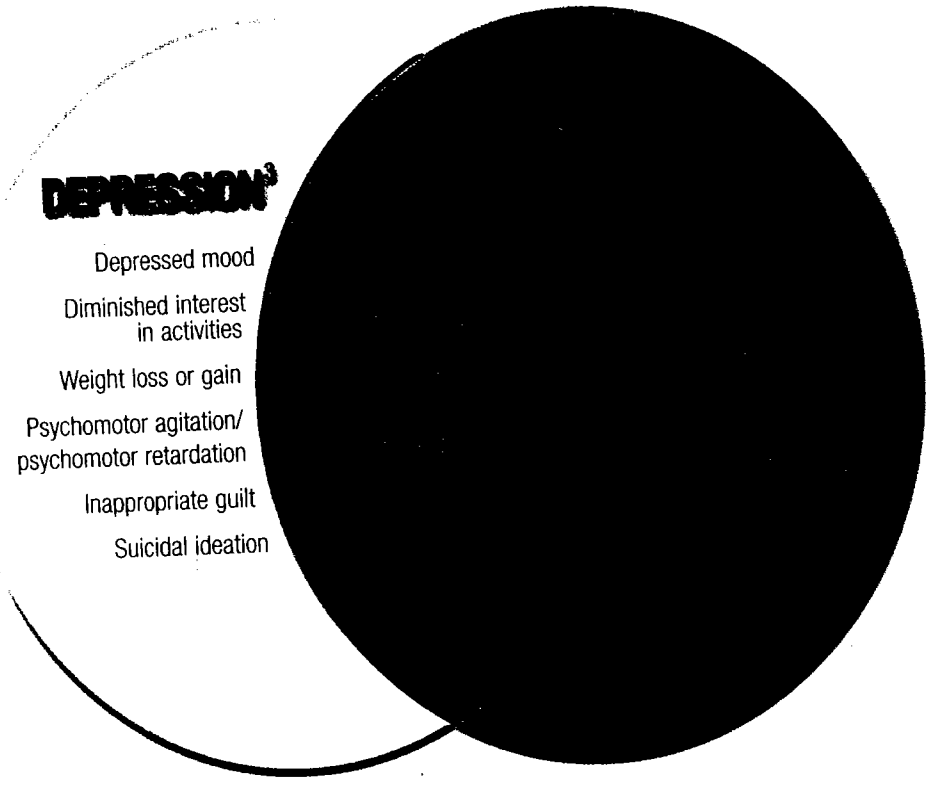
It has been estimated that up to 70% of patients can respond to antidepressant therapy[1]; less than 30% can achieve remission[2]

Why just get your patients "better" (response) when you can help get them "well" (remission)?



IN DEPRESSION AND GENERALIZED ANXIETY DISORDER

overlapping symptoms



Depressive disorders are estimated to coexist with GAD 8% to 39% of the time[4]

Up to 90% of depressed patients also have associated symptoms of anxiety[5]

with

sociated

EXPECT MORE FROM
antidepressant therapy

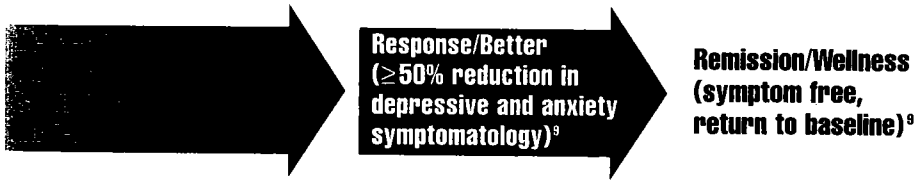
Effective reuptake inhibition of both serotonin and norepinephrine—two important neurotransmitters[6]

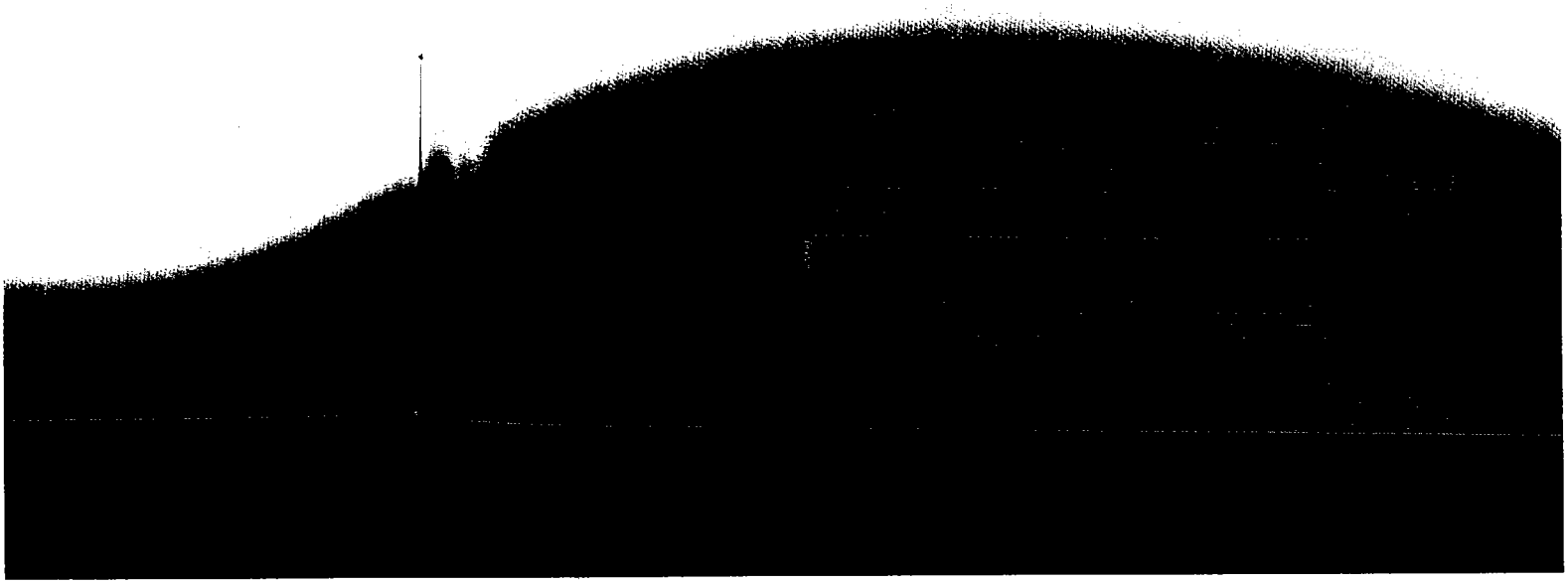
- Dual reuptake inhibition may produce a more robust response in a broader range of patients.[2]
- Antidepressants with two or more mechanisms of action may improve efficacy.[7]
- It may be best to treat with a dual-reuptake inhibitor first as opposed to serotonergic- or noradrenergic-only agents as it is unclear to which type of treatment a patient will respond best.[8]

IN YOUR PATIENTS
strive for wellness

Make remission the end point, not simply response

- Wellness is remission, rather than reduction, of symptoms.[8]





POWER TO

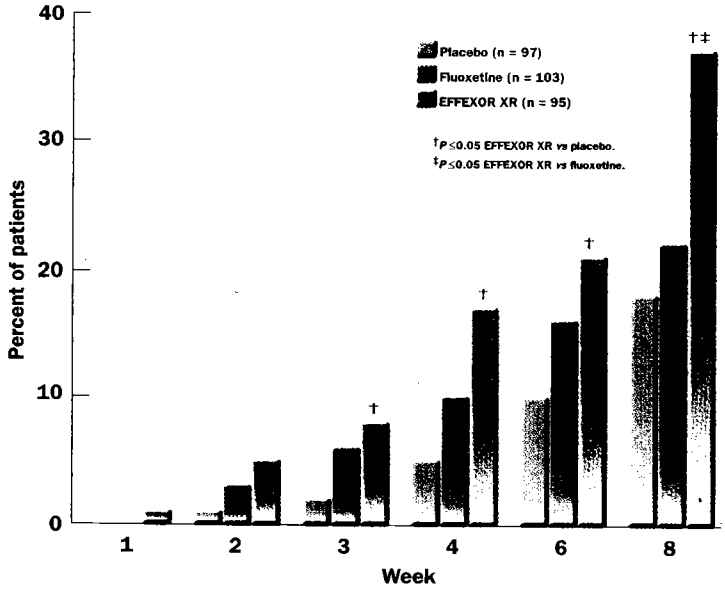
achieve remission

Remission *vs* response is a more complete and sustained improvement[9]

- Response is usually defined as a ≥50% reduction in depressive and anxiety symptomatology.[9]

Patients with remission of depression (HAM-D total ≤7*)[10]

Last-observation-carried-forward analysis



A randomized, double-blind, placebo-controlled study of outpatients with DSM-IV™ major depression. Doses ranged up to 225 mg/day of venlafaxine XR or 60 mg/day of fluoxetine. Mean doses were 175 mg/day for venlafaxine XR and 47 mg/day for fluoxetine during Weeks 4-8.[10] In this study, remission was defined as a score of 7 or less on the HAM-D, which indicates an absence of symptoms.[9]

*Based on the first 21 items on the HAM-D.

- In this study, significance *vs* placebo in rates of remission was achieved with EFFEXOR XR at Week 3 and maintained through Week 8 (study end point).[10]
- Nearly twice as many patients receiving EFFEXOR XR achieved remission as did patients receiving fluoxetine.[10]

*)[10]

M-IV™ major depression.
ne. Mean doses were
4-8.[10] In this study,
dicates an absence of symptoms.[9]

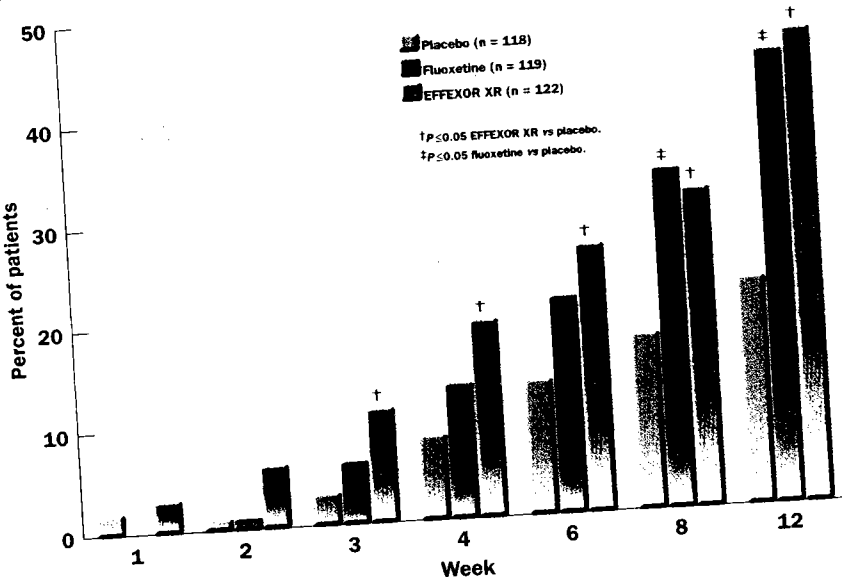
on was achieved with
8 (study end point).[10]

chieved

Rates of discontinuation in both studies were comparable between EFFEXOR XR-treated and fluoxetine-treated patients[10]

Patients with remission of depression (HAM-D total ≤7*)[10]

Last-observation-carried-forward analysis



A randomized, double-blind, placebo-controlled study of outpatients with DSM-IV™ major depression as well as predefined levels of concomitant anxiety. For venlafaxine XR, doses ranged up to 225 mg/day, and for fluoxetine the maximum was 60 mg/day. Mean doses at Week 12 were 141 mg/day for venlafaxine XR and 40 mg/day for fluoxetine.[10]

*Based on the first 17 items on the HAM-D.

- Significance *vs* placebo in rates of remission was achieved with EFFEXOR XR at Week 3 and maintained through Week 12.[10]
- While not statistically significant, the number of patients achieving remission with EFFEXOR XR was higher than with fluoxetine.[10]

POWER TO RELIEVE

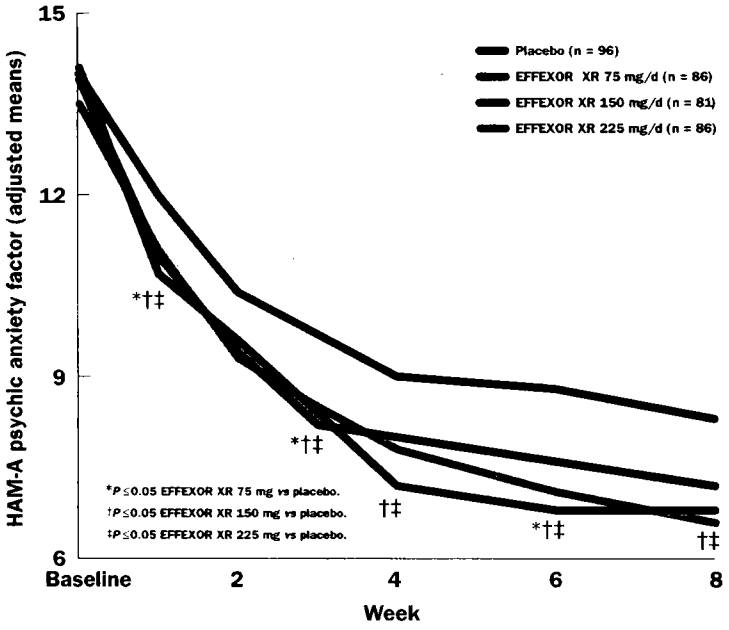
generalized anxiety disorder (GAD)

Worry and stress are prominent symptoms of GAD[3]

- Patients may present with distress due to constant worry and may experience related impairment in social, occupational, or other areas of functioning including everyday, routine life circumstances.[3]

Reduction of psychic anxiety in patients with generalized anxiety disorder[10]

Last-observation-carried-forward analysis



An 8-week, randomized, fixed-dose, double-blind, placebo-controlled study of outpatients with DSM-IV™ GAD. Patients with major depression were excluded. All EFFEXOR XR-treated groups were started at 75 mg/day, with dosage increases administered in weekly increments of 75 mg/day, up to a maximum of 225 mg/day.[10]

- All doses of EFFEXOR XR achieved statistical significance *vs* placebo at Weeks 1, 3, and 6.[10]
- EFFEXOR XR demonstrated efficacy *vs* placebo on the HAM-A psychic anxiety factor, which is based on the clinician's evaluation of anxious mood, tension, fears, insomnia, cognitive impairment, depression, and outward behavior at interview.[5]

AD)

GAD[3]

ınd may
ther areas
s.[3]

ized anxiety disorder[10]

(n = 86)
(n = 81)
(n = 86)

†‡

8

ients with DSM-IV™ GAD.
started at 75 mg/day, with
n of 225 mg/day.[10]

placebo at

A psychic anxiety factor,
, tension, fears, insomnia,
ıterview.[5]

IMPORTANT TREATMENT considerations

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References: 1. Thase ME, Rush JA. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress.* New York, NY: Raven Press; 1995:1081. **2.** Ferrier IN. Treatment of major depression: is improvement enough? *J Clin Psychiatry.* 1999;60(suppl 6):10-14. **3.** *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994:327, 432-436. **4.** Brawman-Mintzer O, Lydiard RB. Generalized anxiety disorder: issues in epidemiology. *J Clin Psychiatry.* 1996;57(suppl 7):3-8. **5.** Kaplan HI, Sadock BJ. *Kaplan and Sadock's Synopsis of Psychiatry. Behavioral Sciences/Clinical Psychiatry.* 8th ed. Baltimore, Md: Williams & Wilkins; 1998:309, 553. **6.** EFFEXOR® (venlafaxine HCl) Extended Release and Immediate Release Prescribing Information, Wyeth-Ayerst Laboratories, Philadelphia, Pa. **7.** Stahl SM. Are two antidepressant mechanisms better than one? *J Clin Psychiatry.* 1997;58:339-340. **8.** Stahl SM. Why settle for silver, when you can go for gold? Response vs. recovery as the goal of antidepressant therapy. *J Clin Psychiatry.* 1999;60:213-214. **9.** Thase ME. Relapse and recurrence in unipolar major depression: short-term and long-term approaches. *J Clin Psychiatry.* 1990;51(suppl 6):51-57. **10.** Data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa.

simple once-daily dosing

Start at

37.5 mg once daily
Initial dosing option
For 4 to 7 days.
Minimizes potential for transient nausea.

Treat with

75 mg once daily
Usual starting dose
75 mg/day has demonstrated significant response rates in clinical trials.[3]

Assess for

Patient's response to determine whether upward titration can be beneficial

Titrate to

150 mg* once daily
Additional dosing option
Upward titration to a maximum of 225 mg/day† of EFFEXOR XR can be beneficial in patients who do not respond fully to 75 mg/day.[6]

* Increase dose by up to 75 mg/day, at intervals of no less than 4 days.

† Experience with EFFEXOR XR at doses higher than 225 mg/day is very limited.

Note: Absorption is unaffected by food; however, dosing with meals is recommended.

Pictured capsules are actual size.

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Please see accompanying Prescribing Information inside the pocket.

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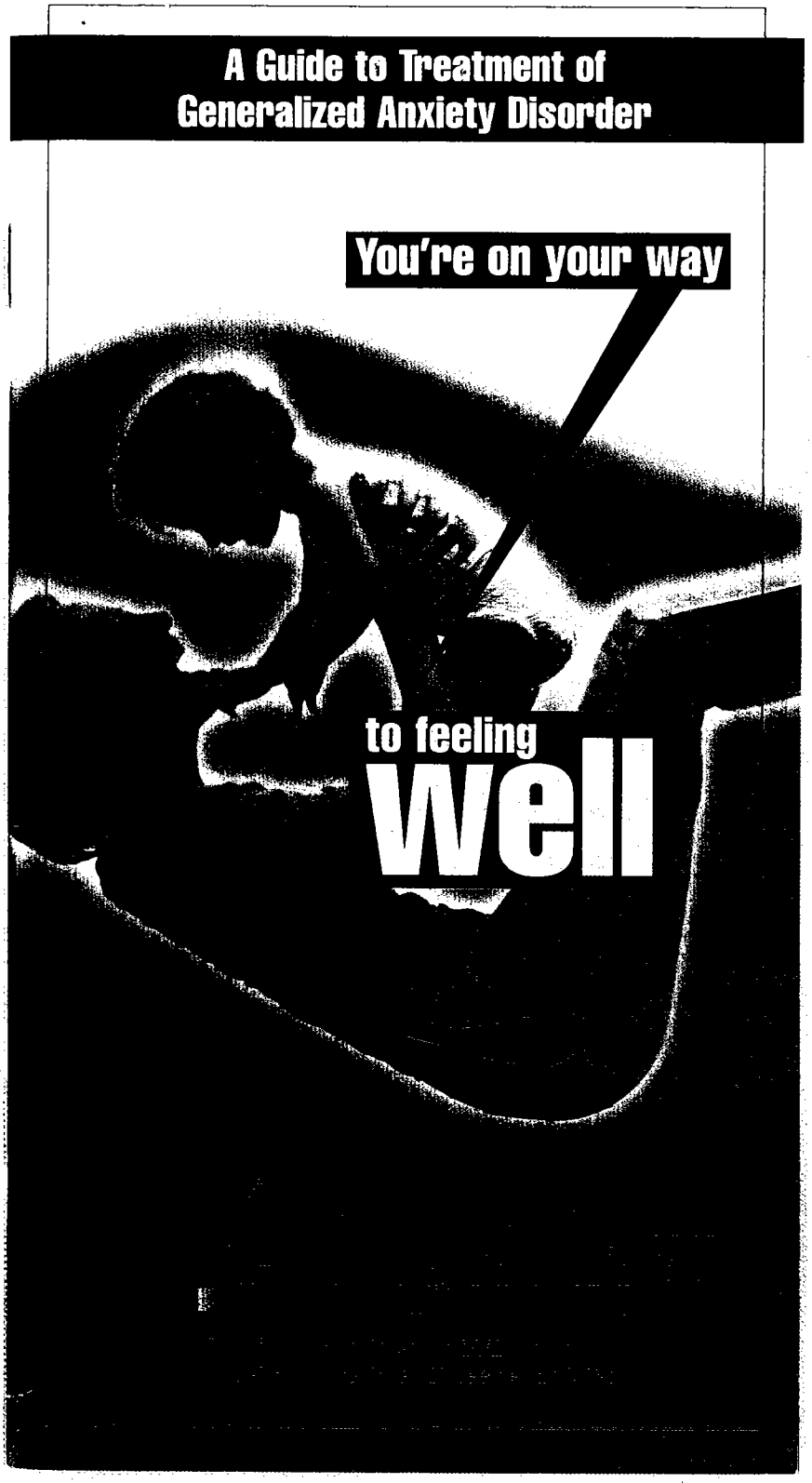
A Guide to Treatment of Generalized Anxiety Disorder



Now that you're being treated for
generalized anxiety disorder...

This booklet is designed to answer your questions about generalized anxiety disorder—commonly referred to as GAD—and about the medication your doctor has prescribed for you: EFFEXOR XR.® Talking to your doctor is the first step toward getting well; and now that you've done this, and have received a prescription for EFFEXOR XR, you're headed on the road to recovery. While EFFEXOR XR works extremely well in people who have GAD, it is actually an antidepressant. It was originally, and still is, used to treat people with depression. However, in one national study it was found that over 62% of people who have suffered from GAD in their lifetime have suffered from depression at some point as well.[1] The fact that EFFEXOR XR works for GAD and depression is a big plus in many ways, especially for people who have both of these disorders.

Anxiety and worry: A big part of generalized anxiety disorder

By now, you're undoubtedly aware of the key signs of GAD: difficult-to-control anxiety and worry that have lasted for at least 6 months. In addition, people with GAD have at least three of the following symptoms[2]:

- Restlessness or feeling on edge
- Being easily fatigued
- Difficulty concentrating
- Irritability
- Muscle tension
- Sleep disturbance

Your doctor has determined that you have GAD. Most likely, your distress makes it difficult for you to function comfortably in everyday situations at work or home, school or play. You may have told your doctor that you have felt anxious and nervous all your life. This is very common in people with GAD.

Some other features associated with GAD include the following[2]:

- Symptoms associated with muscle tension, including trembling, twitching, feeling shaky, and muscle aches and soreness
- Physical symptoms such as clammy hands, dry mouth, sweating, nausea or an increased need to urinate, and an exaggerated

People with generalized anxiety disorder often have depression as well

Many people who have GAD also suffer from depression. People with depression feel sad and lose interest in partaking in normall enjoyable activities. These symptoms must have lasted for at leas 2 weeks in a row for the person to be diagnosed with depression While many antidepressants can cause the symptoms of depress to improve, EFFEXOR XR is an antidepressant that has been shov to get patients beyond better and actually get them well.

Symptoms of depression include the following[2]:

- Difficulty thinking, concentrating, and making decisions
- Change in appetite, weight loss, or weight gain
- Sleeping much more than usual or being unable to sleep
- Observably slowed or agitated physical and/or spoken respo
- Feeling worthless or guilty
- Lacking energy or feeling tired all the time
- Thoughts of killing oneself

EFFEXOR® XR (venlafaxine HCl) will help you feel well again

With the help of EFFEXOR XR, it is possible for you to feel well aga As you feel better, you're likely to become more sociable and confident, and you're likely to get more pleasure from life. The proc of getting well can take time, and during the time you are taking EFFEXOR XR, you may also find that psychotherapy (talk therapy) n help you. Many people find that medication such as EFFEXOR XR a talk therapy help more in combination than either one alone does. is a subject for you to discuss with your doctor.

Wyeth-Ayerst CONNEXIONS: A program for families

Having a family member with GAD or depression may add stress tc family relationships and often may create barriers among family members. The Wyeth-Ayerst CONNEXIONS program was created tc help families

CA

Getting started on EFFEXOR XR

You may be wondering what the "XR" stands for in EFFEXOR XR. It refers to "extended release." This means that when you take EFFEXOR XR, its active ingredients are released in your body over an extended period of time. This makes it possible for EFFEXOR XR to be given once a day instead of two or three times a day.

As shown in the patient starter kit you received from your physician, you can start with a dose of 37.5 mg once a day for 4 to 7 days. This dose allows your body to get used to the drug. After 4 to 7 days, you can start taking 75 mg once a day. Your physician may decide to increase your dose to 150 mg once a day at a later time, after assessing your progress. Be sure to communicate to your physician how the medication is working.

Why did my doctor prescribe EFFEXOR XR?

A shortage of two chemicals in the brain—serotonin and norepinephrine—is thought to play an important role in GAD as well as in depression. EFFEXOR XR acts on serotonin and norepinephrine in such a way that their levels in the brain are increased. This may explain how EFFEXOR XR works to relieve symptoms of anxiety. The way in which medications like EFFEXOR XR work is an area that scientists continue to study.

How do I start taking EFFEXOR XR?

EFFEXOR XR should be taken at about the same time every day, either in the morning or evening, and always after a meal. Swallow the capsules whole; do not try to cut them in half, crush them, chew them, or dissolve them in water. It is extremely important that you take EFFEXOR XR every single day. That is how the medication will best work, and your chances of feeling relief quickly will be greater.

How quickly does EFFEXOR XR work?

Most people who take EFFEXOR XR begin to feel better in 4 to 6 weeks. EFFEXOR XR works more quickly for some people and more slowly for others. The best way to assure that your symptoms improve sooner rather than later is to take your medication every day, as instructed by your doctor.

In what way will I experience improvement after taking EFFEXOR XR?

Since you are taking EFFEXOR XR for GAD, you will notice that your symptoms of GAD will start to disappear. Specifically, you may worry less, feel more relaxed and less keyed up, sleep better, and have improved concentration.

While you may not notice a change in yourself right away, your friends and family may see the signs of improvement before you do. It may be a good idea to discuss with them how you're feeling. Often, friends and family can offer lots of encouragement to a person being treated for GAD. Remember that taking your medication every day, at the dose your doctor has prescribed for you and on the time schedule you have set for yourself, will increase your chance of getting better sooner.

For people who take EFFEXOR XR for depression, they will notice improvement in their symptoms of depression. They may have more energy, sleep more soundly, and feel less irritable. Their appetites may return to normal, and everyday activities such as having dinner with family and friends may become enjoyable again.

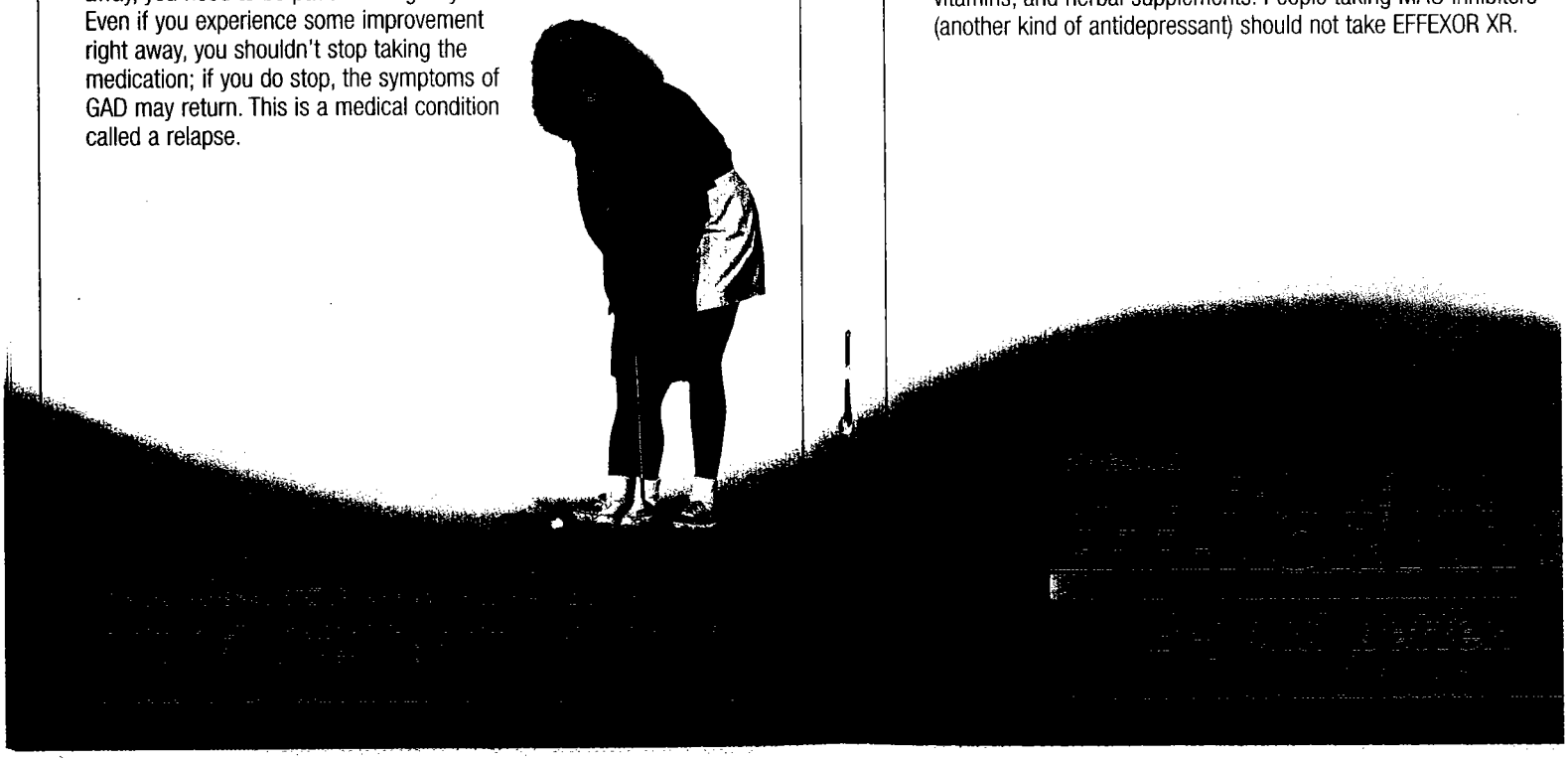
How long does it usually take to feel well again?

Different people respond to the same medication differently, so you should expect that the time it takes to feel well again may differ from that of other people taking EFFEXOR XR. Don't be surprised if you have a bad day after a good one. You may find it helpful to keep a diary of your feelings, sleep patterns, and other activities. This will make it easier to keep track of how you're responding to the medication. Family members can also point out changes in your behavior that may be signs of progress. Of course, you will want to share this information with your doctor.

If your symptoms of anxiety have not changed in 6 weeks, talk to your doctor. Sometimes a higher dosage of EFFEXOR XR is necessary, or a different medication may be more appropriate for you. **Remember, never stop taking your medication without first talking to your doctor.** Even if the medication does not seem to be working as fast as you think it should, you should continue to take it until you have the chance to discuss the best course of action with your doctor.

Why is it important that I keep taking the medication?

A medication for a condition such as GAD needs time to work. If you stop taking the medication, you minimize your chance for treatment success. If you aren't feeling any improvement right away, you need to be patient and give yourself 4 to 6 weeks. Even if you experience some improvement right away, you shouldn't stop taking the medication; if you do stop, the symptoms of GAD may return. This is a medical condition called a relapse.



Will I have side effects with EFFEXOR XR? What should I expect?

Usually, when you start taking any new medication, it takes a little while for your body to get used to it. If you have some initial proble adjusting to EFFEXOR XR, remember that some side effects go aw within 2 weeks of starting treatment. If they do not, or if serious si effects occur, talk to your doctor.

Possible side effects with EFFEXOR XR include nausea (which less in most people), dizziness, sleepiness, abnormal ejaculation, swea dry mouth, nervousness, insomnia, anorexia, and constipation.

EFFEXOR XR may raise your blood pressure; therefore, regular monitoring of blood pressure is recommended.

EFFEXOR XR may impair judgment, thinking, or motor skills; you should exercise caution until you have adapted to therapy.

Can I take EFFEXOR XR when I'm pregnant?

No, pregnant or nursing women should not take any medication without consulting their doctor.

Can I take EFFEXOR XR with my other medications?

In most cases, yes. But be sure to tell *all* your healthcare provider about all medications you take, including over-the-counter drugs, vitamins, and herbal supplements. People taking MAO inhibitors (another kind of antidepressant) should not take EFFEXOR XR.

Can I drink alcohol when I'm taking EFFEXOR XR?

As with many medications, you should avoid alcohol while taking EFFEXOR XR.

What if I forget to take EFFEXOR XR one day?

You should take EFFEXOR XR at about the same time every day. However, if you miss a dose of EFFEXOR XR by more than several hours, you should skip the missed dose and wait to take the next dose as scheduled. Don't try to "make up" for the missed dose by taking two doses the next day.

Remember, in order to get the best effects from the medication, it is extremely important that you take it every day.

How long will I have to take EFFEXOR XR?

The amount of time that individuals should continue to take medication for GAD depends upon many factors, including how they respond to the medication. Your doctor will talk to you about how long you should take EFFEXOR XR.

If I have to take EFFEXOR XR for a long time, is it addictive?

No, medications like EFFEXOR XR are not addictive. EFFEXOR XR is not a narcotic or stimulant. EFFEXOR XR acts on specific sites in the brain (different from the sites where narcotics or stimulants work) to help restore your natural chemistry. That way, your brain chemistry can get back "in sync" and you'll feel like yourself again.

More questions?

If you have additional questions about EFFEXOR XR, ask your doctor and/or pharmacist.

Please visit our Web site at www.EFFEXORXR.com

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A support program for people with depression or generalized anxiety disorder and those who care about them

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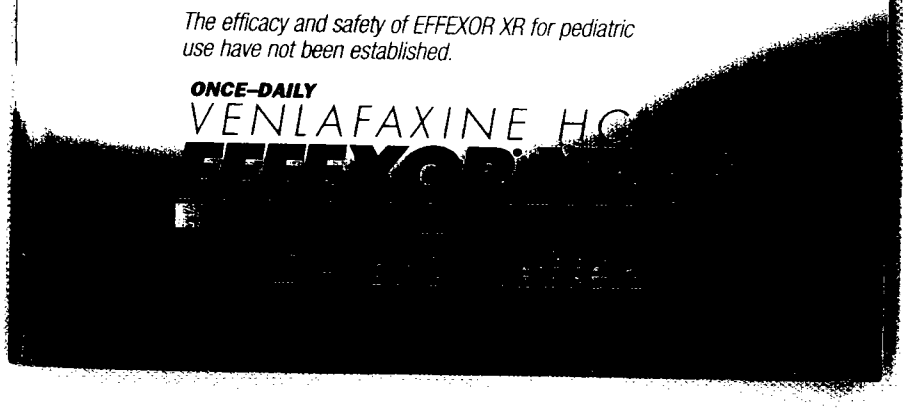
...d Statistical Manual of Mental Disorders: DSM IV™.* 4th ed. ... Psychiatric Association; 1994:327, 432-436.

KEY FACTS ABOUT EFFEXOR XR

The only antidepressant indicated for both depression and generalized anxiety disorder

The efficacy and safety of EFFEXOR XR for pediatric use have not been established.



What makes EFFEXOR XR stand out?

Introduction

EFFEXOR XR is the only antidepressant indicated for both depression and generalized anxiety disorder. Recent studies have shown that EFFEXOR XR effectively achieves remission of depression, getting patients beyond better to well.[1,2] EFFEXOR XR also eliminates excessive worry related to generalized anxiety disorder, the most "basic" anxiety disorder,[3] and has been shown to sustain efficacy over the long term in patients with generalized anxiety disorder.[4] Dosing is once daily with EFFEXOR XR, while dosing of immediate release EFFEXOR is BID.[5] Once-daily dosing may make EFFEXOR XR more acceptable to many patients with depression or generalized anxiety disorder who might benefit from it, including those taking multiple medications who might be at risk for drug interactions.

What is the mechanism of action of EFFEXOR XR?

EFFEXOR XR is a potent inhibitor of the reuptake of serotonin and norepinephrine[5]—two neurotransmitters thought to play important roles in the pathophysiology of depression.[6,7] However, it has virtually no affinity for other receptors which are hypothesized to be associated with the anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs, including the tricyclic antidepressants (TCAs).[5,8] As with SSRIs, anticholinergic-like side effects may occur with EFFEXOR XR.

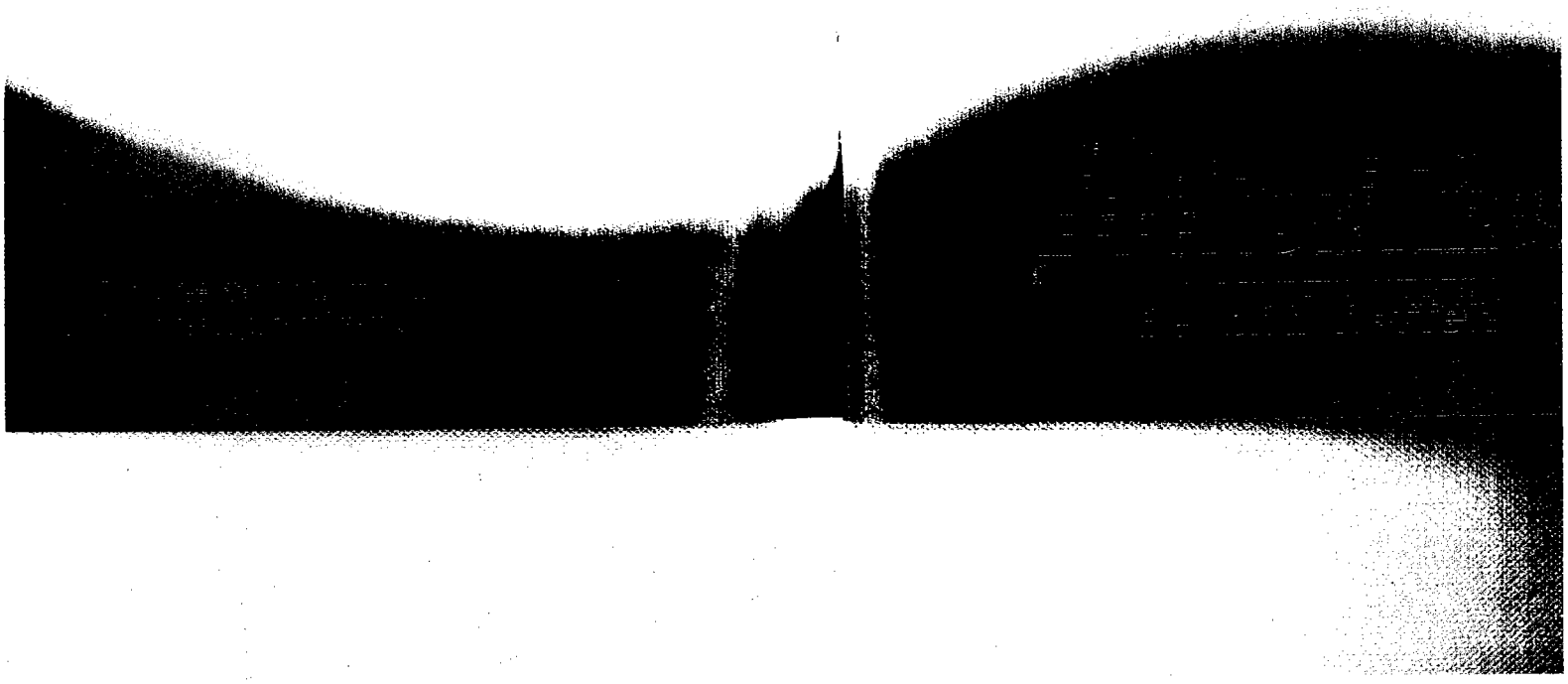
What are the benefits of combining reuptake inhibition of serotonin and norepinephrine?

Research suggests that changes in the serotonergic and noradrenergic systems have different effects on behavior and emotion. Serotonin (5HT) has been associated with the mood aspects of depression, especially anxiety and depressed mood while norepinephrine has been primarily associated with the psychomotor components, and only secondarily with mood.[9,10] Thus, an antidepressant with a combined mode of action shou be able to affect the actions of both neurotransmitters.

How does EFFEXOR XR differ from EFFEXOR?

EFFEXOR XR provides all the efficacy of immediate release venlafaxine with the additional benefit of once-daily convenience especially for patients on the go and those with complicated medication schedules.

In premarketing studies of EFFEXOR, the rate of discontinuation of treatment due to adverse events was 19%. In premarketing studies of EFFEXOR XR, the rate of discontinuation of treatment due to adverse events was approximately 11%.[5]



What is the pharmacokinetic profile of EFFEXOR XR?

EFFEXOR XR attains steady-state plasma concentrations of venlafaxine and its major active metabolite, O-desmethylvenlafaxine (ODV), within 3 days of oral multiple-dose administration. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg/day.

In equal daily doses, once-daily EFFEXOR XR capsules and BID immediate release EFFEXOR tablets have similar bioavailability as measured by areas under the curve (AUC) for both venlafaxine and ODV.[5] For venlafaxine and ODV, the approximate times to peak plasma concentration are 5.5 and 9 hours, respectively. The degrees of plasma protein binding are approximately 27% and 30%, respectively, at plasma concentrations ranging from 100 to 500 ng/mL. EFFEXOR XR had the same extent of absorption, but at a slower rate than immediate release EFFEXOR.[5]

Excretion

For venlafaxine and ODV, the approximate elimination half-lives are 5 and 11 hours, respectively. Venlafaxine and its metabolites are excreted primarily via the kidneys. After a single radiolabeled venlafaxine dose, 87% was recovered in the urine within 48 hours, mostly as conjugated and unconjugated ODV and other metabolites. The elimination half-life did not change between EFFEXOR and EFFEXOR XR.[5]

Special populations

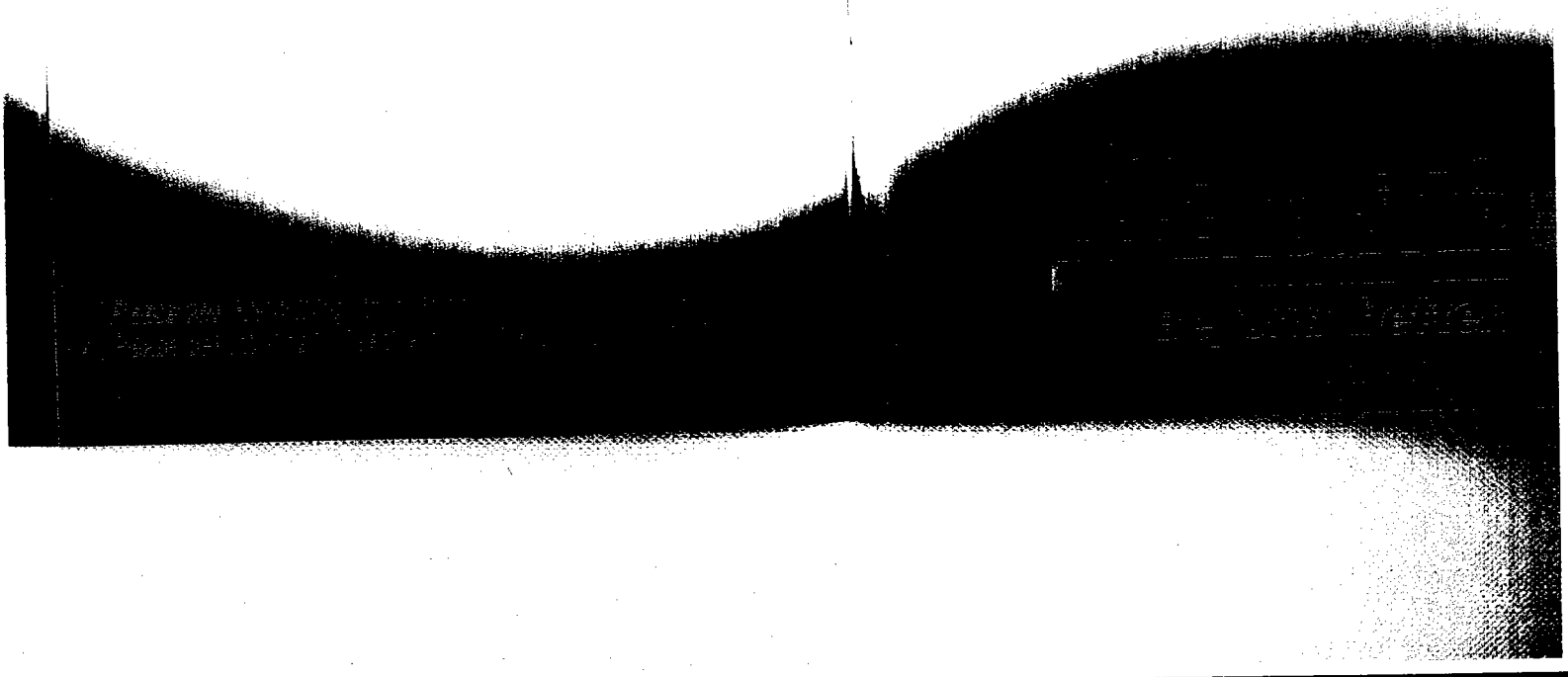
Venlafaxine and ODV pharmacokinetics appear to be unaffected by age, gender, or administration with or without food.[5] Please see section on Dosing.

What clinical trials have been conducted with EFFEXOR XR?

The efficacy and safety of EFFEXOR XR and fluoxetine in treating depression were assessed in two randomized, double-blind, placebo-controlled trials. EFFEXOR XR was significantly more effective than placebo at endpoint in both trials.[1,4] In a study in patients with generalized anxiety disorder, EFFEXOR XR was proven to eliminate excessive worry related to generalized anxiety disorder.[4] Excessive worry is the key feature of generali anxiety disorder.

Antidepressant response may be defined in many ways. For example, a 50% reduction in HAM-D scores compared to base is one of the research criteria used for measuring antidepressa efficacy.[11] In two comparative clinical trials, *remission* was defir as a reduction in the HAM-D 21-item total score, or in the HAI 17-item total score, to ≤7.[1,4] In one of these studies, remission was achieved in 37% of EFFEXOR XR-treated patients, 22% of fluoxetine-treated patients, and 18% of placebo-treated patien These results showed statistical significance between EFFEXOI and both fluoxetine and placebo.[1]

In one study, EFFEXOR XR achieved remission in nearly twice as many patients as fluoxetine.[1] In another study, data were pooled from eight double-blind, randomized trials to compare remission rates in patients with depression treated with EFFEXOR, EFFEXOR XR, or SSRIs. EFFEXOR and EFFEXOR XR achieved significantly higher remission rates than the SSRIs, and the remission was sustained.[2]



What are the dosage strengths of EFFEXOR XR?

EFFEXOR XR is available in three dosage strengths: 37.5 mg, 75 mg, and 150 mg, each designed for once-daily administration.

- For most patients, the recommended starting dose of EFFEXOR XR is 75 mg/day, administered in a single dose.
- For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow patients to adjust to the medication before increasing to 75 mg/day. The 37.5-mg capsule may be used in these patients or in patients with moderate hepatic or renal impairment. Some patients may require individualized dosage.[5]
- The 75-mg capsule, the usual starting dose, has demonstrated high response rates in clinical trials.[5]
- The 150-mg capsule may offer a benefit for patients who have not responded adequately to 75 mg/day.[5]

How should patients take EFFEXOR XR?

EFFEXOR XR should be taken in a single daily dose with food, either in the morning or in the evening, at approximately the same time each day.[5] Instruct patients to take each capsule whole with fluid, and not divide, crush, chew, or place in liquid prior to administration.

How can I dose EFFEXOR XR for optimum results in specific patients?

Patients with more severe depression

Patients not responding to the initial therapeutic dose of 75 mg/day may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady-state plasma levels of venlafaxine and its metabolite are achieved in most patients by 4 days.

It should be noted that in one study of the development program for EFFEXOR (the immediate release form of venlafaxine), more severely depressed inpatients responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day).[5] Whether or not higher doses of EFFEXOR XR are needed for more severely depressed patients is unknown; however, experience with EFFEXOR XR doses higher than 225 mg/day is very limited.

Are dosage adjustments needed for the elderly or renally or hepatically impaired patients?

Elderly:

No dosage adjustment is necessary based on age alone. As with any antidepressant, however, caution should be exercised in treating the elderly.

Renally impaired:

Reduce total daily dose by 25% in patients with mild-to-moderate impairment; 50% for dialysis patients (administer dose 4 hours after completion of dialysis).

Hepatically impaired:

Reduce dose by 50% in moderately impaired patients: a further reduction may be required in some patients with cirrhosis.

How do I switch patients to EFFEXOR XR?

From EFFEXOR to EFFEXOR XR:

Patients being treated with EFFEXOR may be switched to EFFEXOR XR at the nearest equivalent (mg/day) dose. For example, 75 mg of EFFEXOR is equivalent to 75 mg of EFFEXOR XR, so EFFEXOR XR 75 mg once daily would replace EFFEXOR 37.5 mg BID. Individual dosage adjustments may be necessary.[5]

From other antidepressants—general considerations:

There are no clinical trials to definitively answer questions about switching. Factors to bear in mind when evaluating the initial response to EFFEXOR XR include the half-life of the previous drug, the possibility of additive effects and drug-drug interactions, and the potential for tricyclic or SSRI discontinuation symptoms.

In certain patients, clinical consideration should be given to:

- Those who have received high doses of the previous drug
- Those who have experienced adverse effects of the previous drug

From an SSRI to EFFEXOR XR:

The half-lives of antidepressants should be considered when switching from SSRIs to EFFEXOR XR. Keep in mind that SSRIs with longer half-lives have longer elimination periods during which the two drugs may interact pharmacokinetically or have additive serotonergic effects.[5,12,13]

From a TCA to EFFEXOR XR:

Since discontinuation symptoms may occur if the TCA is abruptly withdrawn,[14] clinicians should evaluate the washout period needed for the TCA before initiating EFFEXOR XR.

From an MAOI to EFFEXOR XR:

EFFEXOR XR should not be used within at least 14 days of discontinuing treatment with an MAOI (monoamine oxidase inhibitor) because of the potential for serious adverse reactions. Based on the half-life of EFFEXOR XR, at least 7 days should be allowed after stopping EFFEXOR XR before starting

How can I increase/augment the efficacy of EFFEXOR XR?

Increasing doses of immediate release venlafaxine may result in a progressively higher incidence of response. Data from two fixed-dose outpatient studies were suggestive of a dose-response relationship in the range of 75 to 225 mg/day. While the relationship between dose and antidepressant response for EFFEXOR XR has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. This positive dose response may reduce the need to switch agents, augment the regimen, or refer patients.[4,5]

Partial responders

Although the 75-mg capsule is the usual starting dose, some patients may benefit from increased doses up to 225 mg/day.[4,5] When increasing the dosage, increments of up to 75 mg/day should be made at intervals of no less than 4 days.

Are there patients for whom EFFEXOR XR is especially suitable?

Venlafaxine has demonstrated efficacy in a wide variety of patients:

- Depressed patients
- Patients with generalized anxiety disorder
- Elderly depressed patients and patients at risk for drug interactions

How prevalent is depression with associated anxiety symptoms?

It has been estimated that up to 90% of depressed patients also suffer from anxiety symptoms.[15]

Has EFFEXOR XR been proven effective for treating depression with associated anxiety symptoms?

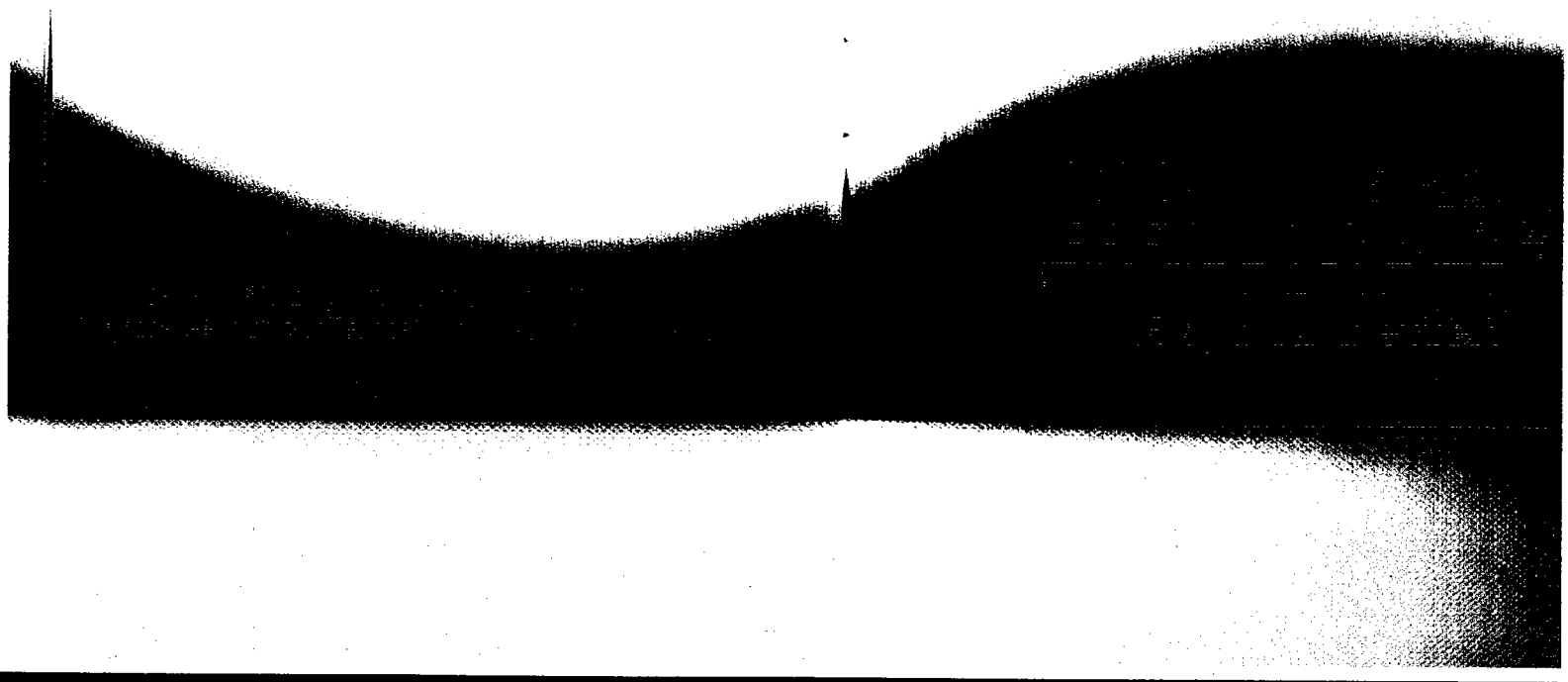
The results from several well-controlled clinical studies have demonstrated that EFFEXOR XR is effective in the treatment of depression with associated anxiety symptoms and is statistically superior to placebo.[16]

Can EFFEXOR XR be used in patients who consume alcohol?

EFFEXOR XR has not been shown to increase the alcohol-induc impairment of mental and motor skills. Nevertheless, advise patients taking EFFEXOR XR to avoid alcohol.

Are there patients for whom EFFEXOR XR is not recommended?

EFFEXOR XR is contraindicated in patients known to be hypersensitive to venlafaxine. It is contraindicated in those taking MAOIs. Do not use EFFEXOR XR in combination with a MAOI or within at least 14 days of discontinuing treatment w an MAOI because of the potential for serious adverse reactio Based on the half-life of EFFEXOR XR, allow at least 7 days after stopping EFFEXOR XR before starting an MAOI.[5]



What are the principal adverse events seen with EFFEXOR XR?

The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.

How can I help patients cope with side effects?

The 37.5-mg capsule is an initial dosing option to allow new patients to adjust to the medication before increasing to 75 mg/day. Counsel patients that certain adverse events, such as dizziness and nausea, usually diminish within the first 2 weeks.

What is the incidence of sexual dysfunction with EFFEXOR XR?

Abnormal ejaculation was reported in 16% of men. Impotence occurred in 4% of men. Anorgasmia occurred in 3% of women.[5]

How often do significant blood pressure (BP) increases occur?

Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevations. The incidence of sustained increases in blood pressure at doses greater than 300 mg/day has not been fully evaluated. Less than 1% discontinued treatment because of elevated BP. Experience with immediate release venlafaxine in depression studies showed that sustained hypertension was dose related, increasing from 3% to 7% at doses of 100 mg/day to 300 mg/day, to 13% at doses above 300 mg/day. Regular BP monitoring is recommended.

Can EFFEXOR XR be coadministered with other drugs that are metabolized by cytochrome P450?

...ine has only a minimal effect on the cytochrome P450 ...system—the enzyme system that promotes the ...merous drugs. Potential exists for a drug interaction between EFFEXOR XR and drugs that inhibit CYP2D6. Among the CYP450 isoenzymes, venlafaxine is unlikely to inhibit CYP3A4, as shown by *in vivo* effects on the pharmacokinetics of Valium®* (diazepam) C-IV or Xanax®* (alprazolam) C-IV, substrates for this isoenzyme.[5]

Other *in vivo* studies confirm that venlafaxine is also a relatively weak inhibitor of CYP2D6 and has little or no inhibitory potential for CYP3A4, CYP1A2, and CYP2C19.[17-19]

What should patients do if they miss a dose of EFFEXOR XR?

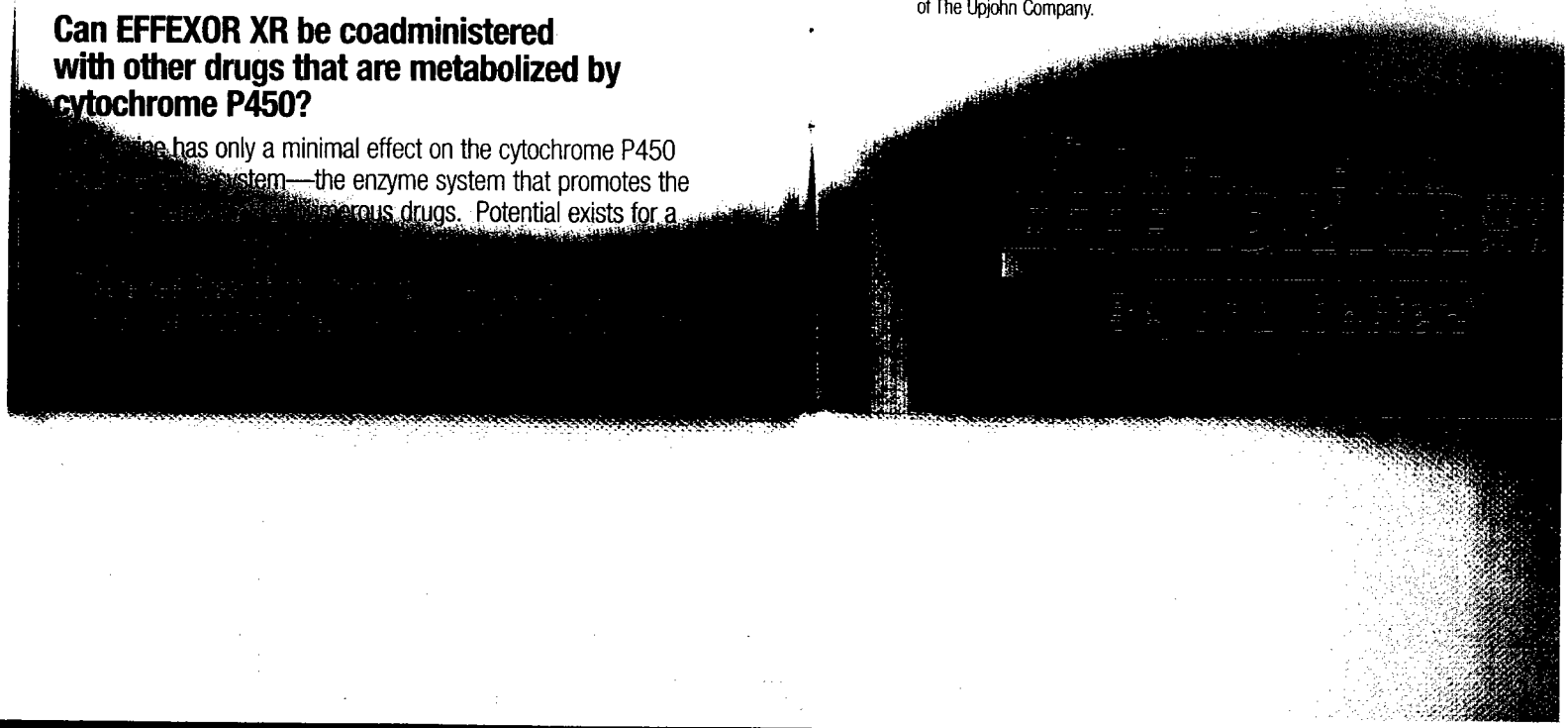
Patients should take EFFEXOR XR at about the same time every day. However, if they miss a dose by more than several hours, they should skip the missed dose and wait to take the next dose as scheduled.

Does EFFEXOR XR have a discontinuation syndrome after abrupt termination of therapy, like the tricyclics and SSRIs?

Adverse events have followed the discontinuation of EFFEXOR XR, like those seen with the tricyclics and SSRIs.[14,20] The most common events after discontinuation of EFFEXOR XR (at an incidence ≥3% and ≥2× that of placebo) were dizziness, dry mouth, insomnia, nausea, nervousness, and sweating.[5] It has been suggested that these phenomena may be attributed to serotonergic mechanisms in certain patients.[21]

Therefore, when discontinuing EFFEXOR XR after more than 1 week of therapy, taper the dose to minimize the risk of these symptoms. Patients discontinuing EFFEXOR XR after 6 weeks or more should have their dose tapered gradually over a 2-week period. In clinical trials, the dose was reduced by 75 mg at 1-week intervals. Individual patients may require different schedules for tapering.[5]

*Valium is a registered trademark of Hoffmann-LaRoche; Xanax is a registered trademark of The Upjohn Company.



What can I use to help explain depression or generalized anxiety disorder and their treatments to my patients, and to their friends and relatives?

Depression and generalized anxiety disorder affect not only the lives of those who suffer from these disorders, but also the lives of those closest to them. For this reason, Wyeth-Ayerst CONNEXIONS has been designed to serve the needs of the whole family—and friends as well. This unique program of support and education includes:

- A series of helpful booklets explaining key facts about depression and generalized anxiety disorder and how they impact relationships.
- A toll-free help line with suggestions on how to talk about depression or generalized anxiety disorder whether the caller or another person has the illness.
- A support group locator which enables a caller to find a mood or anxiety disorder support group in the caller's ZIP code.
- Referrals to the National Depressive and Manic-Depressive Association and local support groups.

For more information about Wyeth-Ayerst CONNEXIONS, contact your Wyeth-Ayerst sales representative, or call the toll-free number below.

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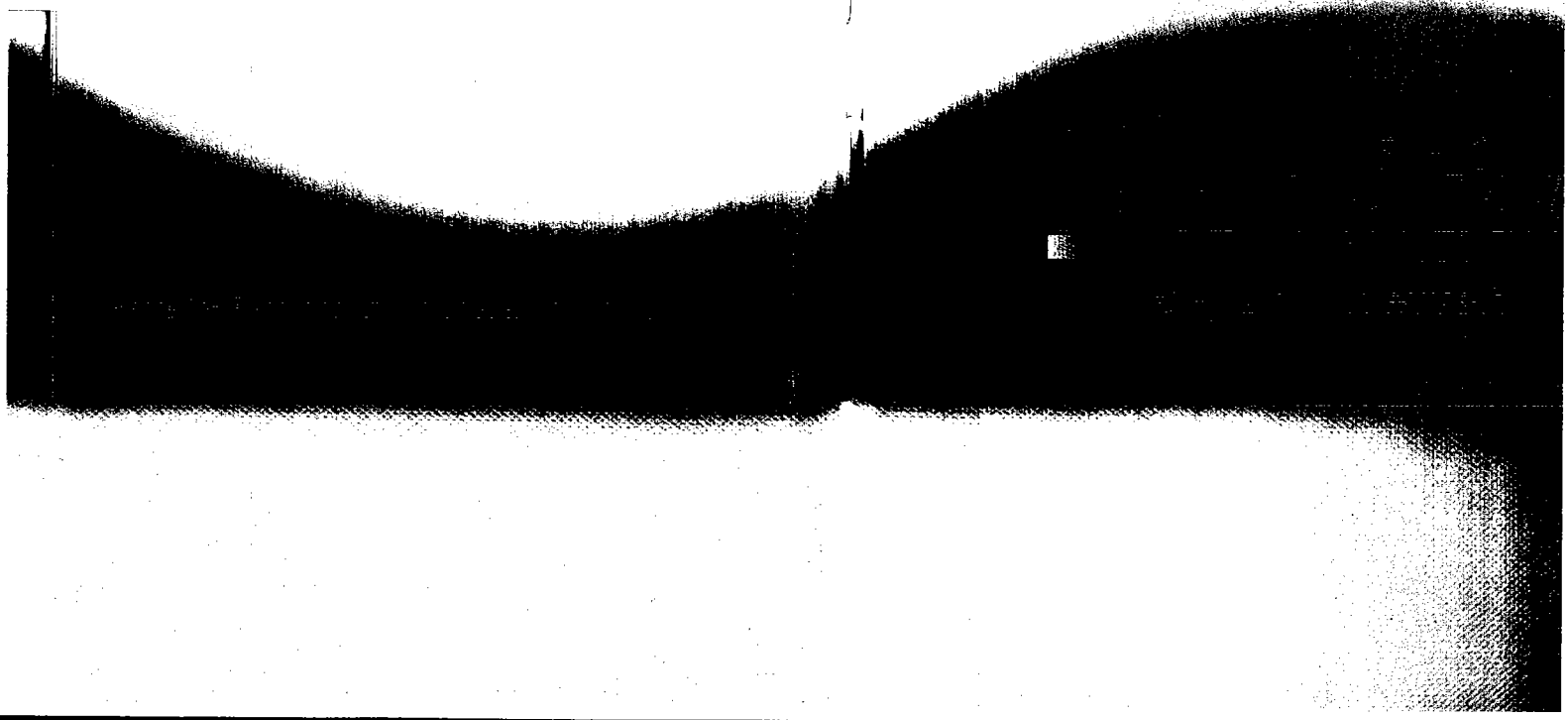
A support program for people with depression or generalized anxiety disorder and those who care about them

IMPORTANT TREATMENT CONSIDERATIONS

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XF should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI because of potential for serious adver reactions. Based on the half-life of EFFEXOR XR, at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevation The incidence of sustained increases in blood pressure at doses greater than 300 mg/day has not been fully evaluated. Less than 1% discontinued treatment becaus of elevated BP. Experience with immediate release venlafaxine in depression studies showed that sustained hypertension was dose related, increasing from 3% to 7% at doses of 100 mg/day to 300 mg/day, to 13% at doses above 300 mg/day. Regular BP monitoring is recommended.
- The most common adverse events reported in EFFEXOR XI placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence abnormal ejaculation, sweating, dry mouth, and nervousne and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.
- As with any psychotropic drug, EFFEXOR XR may impair judgment, thinking, or motor skills; patients should be advi to exercise caution until they have adapted to therapy.



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