Effexor advertisement.

[s.l.]: [s.n.], 1992

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NEW FOR DEPRESSION

EFFEXOR® Tablets

VENLAFAXINE HCl

New...
A serotonin and norepinephrine reuptake inhibitor

Current hypotheses suggest that EFFEXOR may work by two potential mechanisms of action, inhibiting the reuptake of both serotonin and norepinephrine—with virtually no affinity for muscarinic, histaminergic, or adrenergic receptors.[1]

Pharmacologic activity

	Uptake Inhibition		Receptor Affinities		
Compound	**NE**	**5HT**	**Muscarinic**	**Histaminergic**	**Adrenergic**
TCAs[2,3]	✓	✓*	✓	✓	✓
SSRIs[4]		✓			
EFFEXOR[1]	✓	✓			

✓ = strong affinity.

NE = norepinephrine; **5HT** = serotonin; **TCA** = tricyclic antidepressant; **SSRI** = selective serotonin reuptake inhibitor.

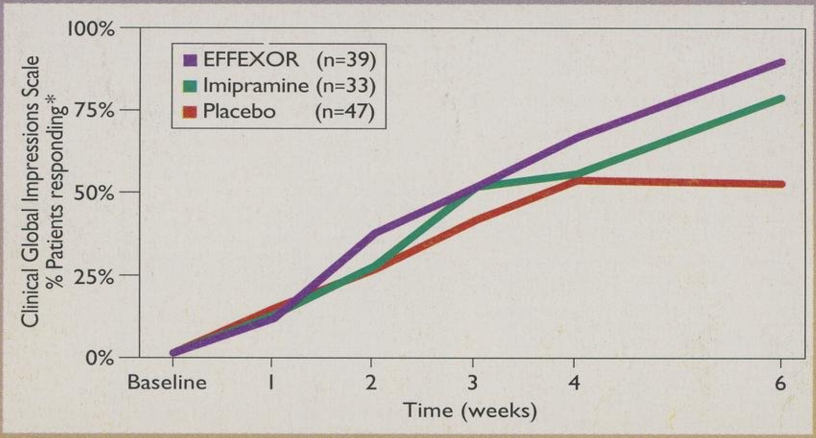
The clinical significance of these *in vitro* data is unknown.
*Serotonin reuptake inhibition varies among TCAs.

- Like SSRIs and TCAs, EFFEXOR is a weak inhibitor of dopamine reuptake
- As with SSRIs, anticholinergic-like side effects may occur with EFFEXOR
- EFFEXOR is a structurally novel antidepressant, and is chemically unrelated to any other available antidepressant[1]

EXPAND YOUR TREATMENT POSSIBILITIES

An effective first-line therapy for depressed patients

Response in depressed outpatients[5]



No significant difference between EFFEXOR and imipramine was observed.

Significant difference ($P < 0.05$); venlafaxine and imipramine > placebo at week 6.

*Response to treatment was defined as CGI improvement score of 1 (very much improved) or 2 (much improved).

In one randomized, double-blind, placebo-controlled study of depressed patients initiated/maintained on venlafaxine or imipramine at 75 mg to 225 mg daily in divided doses (observed cases at week 6).[5]

The effectiveness of EFFEXOR in long-term use (>6 weeks) has not been systematically evaluated in controlled trials.

Treatment with EFFEXOR is associated with sustained increases in blood pressure in some patients. These increases appear to be dose-dependent and occurred with an incidence of >5% at dosages above 200 mg/day. Regular monitoring of blood pressure is recommended.

EFFEXOR, as with other antidepressants, should not be used in patients receiving monoamine oxidase inhibitor (MAOI) therapy.

As with any psychotropic drug, EFFEXOR may impair judgment, thinking, or motor skills, and patients should be advised to exercise caution until they have adapted to therapy.

The most common adverse events reported in EFFEXOR clinical trials (>10% and ≥ 2x that of placebo) include nausea, somnolence, dry mouth, dizziness, constipation, nervousness, sweating, asthenia, abnormal ejaculation/orgasm, and anorexia.[1]

Please see brief summary of prescribing information on last page of this advertisement.

EFFEXOR® Tablets

VENLAFAXINE HCl

25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg

EFFEXOR® Tablets
VENLAFAXINE HCl
25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg

See package insert for full prescribing information.
Clinical Pharmacology: The antidepressant action of venlafaxine is believed to be associated with potentiation of neurotransmitter activity in the CNS. In preclinical studies, venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), were potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α-1 adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.
Indications and Usage: Effexor is indicated for the treatment of depression.
Contraindications: None known.
Warnings: POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS (MAOIs)—**Given the serious, sometimes fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other antidepressants with pharmacological properties similar to Effexor, do not use Effexor in combination with a MAOI or within 14 days of discontinuing MAOI treatment. Allow at least 7 days after stopping Effexor before starting a MAOI. Hyperthermia, rigidity, myoclonus, autonomic instability, mental status changes including extreme agitation progressing to delirium and coma, and features resembling neuroleptic malignant syndrome have been reported with concomitant selective serotonin reuptake inhibitor/MAOI therapy. Severe hyperthermia and seizures, sometimes fatal, have been reported with concomitant tricyclic antidepressants/MAOI therapy.** SUSTAINED HYPERTENSION—Effexor treatment is associated with dose-related sustained increases in supine diastolic blood pressure. Regular monitoring of blood pressure is recommended, and, when appropriate, consider dose reduction or discontinuation.
Precautions: GENERAL—*Anxiety and Insomnia:* Anxiety, nervousness, and insomnia have been reported in short-term studies.
Changes in Appetite/Weight: Anorexia has been reported in short-term studies, and a dose-dependent weight loss has been reported in patients taking Effexor for several weeks.
Activation of Mania/Hypomania: Hypomania or mania has been reported; as with all antidepressants, use cautiously in patients with a history of mania.
Seizures: Seizures were reported in premarketing testing (0.26%). Use cautiously in patients with a history of seizures. Discontinue it 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. Write Effexor prescriptions for the smallest quantity consistent with good patient management to reduce risk of overdose.
Use in Patients with Concomitant Illness: Clinical experience with Effexor in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. In patients with renal impairment (GFR=10-70mL/min) or liver cirrhosis, clearance of venlafaxine and its active metabolite were decreased, resulting in prolonged elimination half-lives. A lower dose may be necessary; use with caution in such patients. INFORMATION FOR PATIENTS—Clinical studies 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 Effexor does not adversely affect their ability to engage in such activities. 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 physicians about other medications they are taking or plan to take; 3) avoid alcohol while taking Effexor; 4) notify their physicians if they develop a rash, hives, or related allergic phenomena.
DRUG INTERACTIONS—*Cimetidine:* Use caution when administering Effexor with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. *Drugs Inhibiting Cytochrome $P_{450}IID_6$ Metabolism: In vitro,* venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome $P_{450}IID_6$. Therefore drugs inhibiting this isoenzyme could potentially increase plasma concentrations of venlafaxine and decrease concentrations of ODV. *Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro,* venlafaxine is a relatively weak inhibitor of this isoenzyme; clinical significance is unknown. *Monoamine Oxidase Inhibitors:* See "**Warnings**." *CNS-Active Drugs:* Use of venlafaxine with CNS-active drugs has not been systematically evaluated; therefore, use caution when administering Effexor with such drugs.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY—*Carcinogenesis:* In 18 month studies, there was no evidence of carcinogenicity in mice given 120mg/kg/day [16 times the maximum recommended human dose (MRHD)]. In 24 month studies, there was no evidence of carcinogenicity in rats given 120mg/kg/day. *Mutagenicity:* In male rats receiving 200 times (on a mg/kg basis) the MRHD, chromosomal aberrations were found in the bone marrow in vivo. *Impairment of Fertility:* No impaired reproductive function was found in rats given 8 times (mg/kg) the MRHD.
PREGNANCY—*Teratogenic Effects—Pregnancy Category C.* Reproduction studies in rats given 11 times, and rabbits given 12 times the MRHD (on a mg/kg basis) revealed no malformations of offspring. However, in rats given 10 times the MRHD, there was a decrease in pup weight, 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 during pregnancy only if clearly needed.
LABOR, DELIVERY, NURSING—The effect on labor and delivery in humans is unknown. It is also not known whether Effexor or its metabolites are excreted in human milk; exercise caution when administering to a nursing woman.
PEDIATRIC USE—Safety and effectiveness in children (<18 years) have not been established.
GERIATRIC USE—In clinical trials, 12% of Effexor-treated patients were $\geq$65 years of age. Overall differences in efficacy or safety in the elderly have not been demonstrated, however, greater sensitivity of older patients should not be ruled out.
Adverse Reactions: ASSOCIATED WITH DISCONTINUATION OF TREATMENT—Nineteen percent (537/2897) of Effexor patients in clinical trials discontinued treatment due to an adverse event. The more common events ($\geq$1% associated with discontinuation and considered to be drug-related included: somnolence, insomnia, dizziness, nervousness, dry mouth, anxiety, nausea, abnormal ejaculation (male), headache, asthenia, and sweating.
INCIDENCE IN CONTROLLED TRIALS—*Commonly Observed Adverse Events in Controlled Clinical Trials:* The most commonly observed adverse events associated with the use of Effexor (incidence of 5% or greater and incidence for Effexor at least twice that for placebo): asthenia (12% vs. 6%), sweating (12% vs. 3%), nausea (37% vs. 11%), constipation (15% vs. 7%), anorexia (11% vs. 2%), vomiting (6% vs. 2%), somnolence (23% vs. 9%), dry mouth (22% vs. 11%), dizziness (19% vs. 7%), nervousness (13% vs. 6%), anxiety (6% vs. 3%), tremor (5% vs. 1%), blurred vision (6% vs. 2%), abnormal ejaculation/orgasm male (12% vs. <1%), and male impotence (6% vs. <1%).
Adverse Events Occurring at an Incidence of 1% or More Among Effexor-Treated Patients: The following occurred in 4- to 8- week placebo-controlled trials, with doses of 75 to 375 mg/day, at a frequency of 1% or more. This includes patients with at least one episode of an event at some time during treatment. **Body as a Whole:** headache, asthenia, infection, chills, chest pain, trauma. **Cardiovascular:** vasodilatation, increased blood pressure/ hypertension, tachycardia, postural hypotension. **Dermatological:** sweating, rash, pruritus. **Gastrointestinal:** nausea, constipation, anorexia, diarrhea, vomiting, dyspepsia, flatulence. **Metabolic:** weight loss. **Nervous System:** somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, tremor, abnormal dreams, hypertonia, paresthesia, libido decreased, agitation, confusion, thinking abnormal, depersonalization, depression, urinary retention, twitching. **Respiration:** yawn. **Special Senses:** blurred vision, taste perversion, tinnitus, mydriasis. **Urogenital System:** abnormal ejaculation/orgasm, impotence, urinary frequency, urination impaired, orgasm disturbance, menstrual disorder.
Studies indicate a dose dependency for some of the more common adverse events associated with Effexor use. There also was evidence of adaptation to some adverse events with continued Effexor therapy over a 6-week period.
Vital Sign Changes: In clinical trials, Effexor was associated with a mean increase in pulse rate of about 3 beats/min, and a dose-dependent increase in mean diastolic blood pressure of 0.7 to 2.5 mm Hg.
Laboratory Changes: During clinical trials, only serum cholesterol exhibited statistically significant differences from placebo (increases of 3 mg/dL from baseline); clinical significance is unknown.
ECG Changes: Only heart rate exhibited a statistically significant difference, with mean increases of 4 beats per minute from baseline.
OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF EFFEXOR—During premarketing assessment, multiple doses of Effexor were administered to 2,181 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" = less than 1/1000 patients. Events are classified within body system categories and enumerated in order of decreasing frequency using the definitions above. It is important to emphasize that although the events occurred during Effexor treatment, they were not necessarily caused by it.
Body as a Whole - *Frequent:* accidental injury, malaise, neck pain; *Infrequent:* abdomen enlarged, allergic reaction, cyst, face edema, generalized edema, hangover effect, hernia, intentional injury, moniliasis, neck rigidity, overdose, chest pain substernal, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* appendicitis, body odor, carcinoma, cellulitis, halitosis, ulcer, withdrawal syndrome. **Cardiovascular system** - *Frequent:* migraine; *Infrequent:* angina pectoris, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; *Rare:* arrhythmia, first-degree atrioventricular block, bradycardia, bundle branch block, mitral valve disorder, mucocutaneous hemorrhage, sinus bradycardia, varicose vein. **Digestive system** - *Frequent:* dysphagia, eructation; *Infrequent:* colitis, tongue edema, esophagitis, gastritis, gastroenteritis, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, stomatitis, stomach ulcer, mouth ulceration; *Rare:* cheilitis, cholecystitis, cholelithiasis, hematemesis, gum hemorrhage, hepatitis, ileitis, jaundice, oral moniliasis, intestinal obstruction, proctitis, increased salivation, soft stools, tongue discoloration, esophageal ulcer, peptic ulcer syndrome. **Endocrine system** - *Rare:* goiter, hyperthyroidism, hypothyroidism. **Hemic and lymphatic system** - *Frequent:* ecchymosis; *Infrequent:* anemia, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, thrombocythemia, thrombocytopenia, WBC abnormal; *Rare:* basophilia, cyanosis, eosinophilia, erythrocytes abnormal. **Metabolic and nutritional** - *Frequent:* peripheral edema, weight gain; *Infrequent:* alkaline phosphatase increased, creatinine increased, diabetes mellitus, edema, glycosuria, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; *Rare:* alcohol intolerance, bilirubinemia, BUN increased, gout, hemochromatosis, hyperkalemia, hyperphosphatemia, hypoglycemic reaction, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia. **Musculoskeletal system** - *Infrequent:* arthritis, arthrosis, bone pain, bone spurs, bursitis, joint disorder, myasthenia, tenosynovitis; *Rare:* osteoporosis. **Nervous system** - *Frequent:* emotional lability, trismus, vertigo; *Infrequent:* apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypertonia, hypotonia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, paranoid reaction, psychosis, psychotic depression, sleep disturbance, abnormal speech, stupor, torticollis; *Rare:* akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, hypokinesia, neuritis, nystagmus, reflexes increased. **Respiratory system** - *Frequent:* bronchitis, dyspnea; *Infrequent:* asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; *Rare:* atelectasis, hemoptysis, hypoxia, pleurisy, pulmonary embolus, sleep apnea, sputum increased. **Skin and appendages** - *Infrequent:* acne, alopecia, brittle nails, contact dermatitis, dry skin, herpes simplex, herpes zoster, maculopapular rash, urticaria; *Rare:* skin atrophy, exfoliative dermatitis, fungal dermatitis, lichenoid dermatitis, hair discoloration, eczema, furunculosis, hirsutism, skin hypertrophy, leukoderma, psoriasis, pustular rash, vesiculobullous rash. **Special senses** - *Frequent:* abnormal vision, ear pain; *Infrequent:* cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, otitis media, parosmia, photophobia, subconjunctival hemorrhage, taste loss, visual field defect; *Rare:* blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, scleritis. **Urogenital system** - *Frequent:* anorgasmia, dysuria, hematuria, metrorrhagia*, urination impaired, vaginitis*; *Infrequent:* albuminuria, amenorrhea*, kidney calculus, cystitis, leukorrhea, menorrhagia*, nocturia, bladder pain, breast pain, kidney pain, polyuria, prostatitis*, pyelonephritis, pyuria, urinary incontinence, urinary urgency, uterine fibroids enlarged*, uterine hemorrhage*, vaginal hemorrhage*, vaginal moniliasis*; *Rare:* abortion*, breast engorgement, breast enlargement, calcium crystalluria, female lactation*, hypomenorrhea*, menopause*, prolonged erection*, uterine spasm*. (*Based on the number of male or female patients as appropriate.)
Drug Abuse And Dependence: CONTROLLED SUBSTANCE CLASS—Effexor is not a controlled substance. In a retrospective survey of new events occurring during taper or following discontinuation, the following occurred at an incidence of $\geq$5%, with incidence for Effexor at least twice that for placebo: asthenia, dizziness, headache, insomnia, nausea, and nervousness. Taper the dose gradually and monitor the patient. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of Effexor misuse or abuse (e.g. development of tolerance, incrementations of dose, drug-seeking behavior).
Dosage and Administration: The recommended starting dose is 75mg/day in 2 or 3 divided doses, taken with food. If needed, dose increments of up to 75mg/day should be made at intervals of no less than 4 days. Maximum recommended dose, for use in severely depressed patients, is 375mg/day, in 3 divided doses. When discontinuing Effexor after more than 1 week of therapy, the dose should be tapered to minimize the risk of discontinuation symptoms. Please consult full prescribing information for detailed dosing instructions.

This brief summary is based on CI #4193-1, Issued December 29, 1993.

References: 1. EFFEXOR® prescribing information, Wyeth-Ayerst Laboratories, Philadelphia, PA. **2.** Preskorn SH, Burke M. Somatic therapy for major depressive disorder: selection of an antidepressant. *J Clin Psychiatry.* 1992;53(suppl):5-18. **3.** Richelson E. Synaptic pharmacology of antidepressants: an update. *McLean Hosp J.* 1988;8:67-88. **4.** *Physicians' Desk Reference®.* 48th ed. Montvale, NJ: Medical Economics Co Inc; 1994; Prozac®:877-880; Zoloft®:2000-2003; Paxil™:2267-2270. **5.** Data on file, Wyeth-Ayerst Laboratories.