

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

PATHOPHYSIOLOGY & COMORBIDITY: A WINDOW INTO PSYCHIATRY AND NEUROLOGY

MIGRAINE: A BORDER BETWEEN PSYCHIATRY AND NEUROLOGY D. Marazziti

SEROTONIN FUNCTION AND GENDER EFFECTS IN MIGRAINE PRODUCTION AND OCD C.M. Wong, E. Hollander

CONSENSUS STATEMENT ON THE UNDERTREATMENT OF DEPRESSION *R.M.A. Hirschfeld, M.B. Keller, et al.*

CATATONIC SYNDROME IN AN ADOLESCENT MALE IMMIGRANT: A CASE REPORT G. P. Panikkar, D. Mayerhoff CME Mount 3

https://dei.org/10.1017/S1092852900001711 Published online by Cambridge University Press

PHOTO ESSAY

The late Frank Netter's peerless medical illustrations have informed generations of physicians on the particulars of cerebrovascular anatomy. These drawings illustrate and describe the normal arteries and veins of the brain, showing the relationship of the many arterial and venous branches to the adjacent neuroanatomy. This computer-enhanced rendition of a Netter drawing is being used to illustrate some of the biological causes of migraine headaches.



Broken hearts require special care.

ny dad bac

When depressed patients are also suffering from cardiovascular disease, drug-drug interaction is a critical concern.^{2,3} Antidepressants that compete with cardiovascular agents utilizing the CYP2D6 and/or the CYP3A4 isoenzymes may cause potentially harmful drug interactions.^{2,3} EFFEXOR, while effectively treating depression, has a low potential to interact with other agents utilizing these CYP isoenzymes.³ By relieving depression, EFFEXOR can help bring patients and families together again.



Please see brief summary of Prescribing Information accompanying this advertisement.



Brief Summary

Brief Summary Effexor⁹ (veniafaxine hydrochloride) Tablets See package insert for full prescribing information. Clinical Pharmacology: The antidepressant action of veniafaxine is believed to be associated with potentiation of neurotransmitter activity in the CNS. In preclinical studies, veniafaxine and its active metabolite, O-desmethylveniafaxine (ODV), were potent inhibitors of neuronal serotonin and nor-epinephrine reuptake and weak inhibitors of dopamine reuptake. Veniafaxine and ODV have no sig-nificant affinity for muscarinic, histaminergic, or α -1 adrenergic receptors *in vitro*. Pharmacologic othibits at the granetare is hundheding to be documented by the various activity in the document. activity at these receptors is hypothesized to be associated with the various antichoninergic, sectative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity. Indications and Usage: Effector is indicated for the treatment of depression.

Indications and Usage: Effexor is indicated for the treatment of depression. Contraindications: Contraindicated in patients with known hypersensitivity. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see "Warnings"). Warnings: POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS (MAOIs)— Adverse reactions, some serious, have been reported when venlafaxine therapy is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of ven-lafaxine. Reactions have included tremor, mycolonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Given these reactions as well as the serious, sometimes fatal interactions reported with hornexclosured prometies similar to Effexor in combination with an with concomitant or immediately consecutive administration of MAOIs and other antidepressants with pharmacological properties similar to Effexor, do not use Effexor in combination with an MAOI or within at least 14 days of discontinuing MAOI treatment. Allow at least 7 days after stop-ping Effexor before starting an MAOI. Hyperthermia, rigidity, mycclonus, autonomic instability, mental status changes including extreme agitation progressing to delirium and coma, and fea-tures resembling neuroleptic malignant syndrome have been reported with concomitant selec-tive serotonin reuptake inhibitor/MAOI therapy. Severe hyperthermia and selzures, sometimes fatal, have been reported with concomitant tricyclic antidepressants/MAOI therapy. SUSTAINED HYPERTENSION—Effexor treatment is associated with dose-related sustained increas-es in supine diastolic blood pressure. Regular monitoring of blood pressure is recommended, and, when approvirate, consider dose reduction or discontinuation.

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-depen-

dent 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,

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: 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 suicide attempt is inherent in depression and may persist until significant remission occurs. Closely supervise high-risk patients during initial drug therapy. Write Effexor pre-scriptions 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 concomi-tent wetering Illness is unitight. Lies autitude the reduce the could develop to a conditione, the could be autited by the conditione that a could be autitude to a conditione the to could be autited by the conditione that a conditione that a conditione the conditione that a conditione that a conditione that a conditione the conditione that a c tant 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

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 psy-chomotor, 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 physician about other medications they are taking or plan to take; 3) avoid alcohol while taking ffavor. (I) outfit, their obviolance if they develop a cab, bixeo car cellet d alignein phonomene.

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 Resoll & Metabolism: In vitro*, venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome *Resoll De*. Therefore drugs inhibiting this isoenzyme could potentially increase plasma concentrations of venlafaxine and decrease concentrations of ODV. could potentially increase plasma concentrations of venlafaxine and decrease concentrations of ODV. *Drugs Metabolized by Cytochrome P₄₅₀IID₆: In vitro*, venlafaxine is a relatively weak inhibitor of this isoenzyme; clinical significance is unknown. *Monoamine Oxidase Inhibitors:* See "Contraindications" and "Warnings." *CNS-Active Drugs*: Use of venlafaxine with CNS-active drugs has not been system-atically 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 120 mg/kg/day [16 times the maxi-mum recommended human dose (MRHD)]. In 24-month studies, there was no evidence of carcino-englishtu in the disen 270 times (on a mg/kg/day).

genicity in rats given 120 mg/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

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 off-spring. 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 Effector 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 Effector or Its metabolites are excreted in human milk; exercise caution when admin-istering to a nursing woman.

Stering 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 <u>s</u>65 years of <u>age</u>. Overall differences in efficacy or safety in the elderly have not been demonstrated, however, greater sensi-tivity of older patients should not be ruled out. **Adverse Reactions:** ASSOCIATED WITH DISCONTINUATION OF TREATMENT—Nineteen percent

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 (21%) 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%), thry nouth (22% vs. 11%), dizziness (19% vs. 7%), nervousness (13% vs. 6%), anxiety (6% vs. 3%), threm of (5% vs. 11%), burred 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 fol-

lowing occurred in 4- to 8- week placebo-controlled trials, with doses of 75 to 375 mg/day, at a fre-Idving occurred in 4 to 8-week placebo-controlled thats, with obses of 75 to 375 ing/value, 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, puritus. Gastrointestinal: nausea, constipation, anorexia, diarrhea, vomiting, dyspepsia, flatulence. Metabolic: weight loss. Nervous System: some loss of the strengt abaretime in pervension and strengt abaretime in the strengt abaretime in anoroxa, darmad, volning, oyopola, nationae mediator region oso, rentos, reporter sen nolence, dry mouth, dizzines, insomnia, nervousness, anxiety, remor, abnormal dreams, hyperto-nia, paresthesia, libido decreased, agitation, confusion, thinking abnormal, depression, depression, urinary retention, twitching Respiration; yawn. Special Senses: blurred vision, taste perversion, tinnitus, mydriasis. **Urogenital System**: abnormal ejaculation/orgasm, impotence, uristructure of the structure of the struct

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 mmHa

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

4 beats per limite from desemine. 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 def-initions above. It is important to emphasize that although the events occurred during Effexor treatment, they were not necessarily caused by it.

ment, they were not necessarily caused by it. **Body as a Whole** - *Frequent* accidental injury, malaise, neck pain; *Infrequent* abdomen enlarged, allergic reaction, cyst, tace edema, generalized edema, hangover effect, hernia, intentional injury, moniliasis, neck rigidity, overdose, chest pain substernal, pelvic pain, photosensitivity reaction, sui-cide attempt; *Rare* appredicitis, body odor, carcinoma, cellultits, haltiosis, ucler, withdrawal syn-drome. **Cardiovascular system** - *Frequent*: migraine; *Infrequent*: angina pectoris, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, throm-bophiebitis; *Rare*: anythima, first-degree atrioventricular block, bradycardia, bundle branch block, miral valve disorder, muccutaneous hemorrhage, sinus bradycardia, varicose vein. **Digstive sys**mitral valve disorder, mucocutaneous hemorrhage, sinus bradycardia, varicose vein. Digestive system - Frequent: dysphagia, eructation; Infrequent: colitis, tongue edema, esophagitis, gastritis, gastritis, gastritis, gingivitis, glossitis, rectal hemorrhage, hemorrholds, melena, stomatitis, stomach ulcer, mouth ulceration; Rare: cheilitis, cholecystitis, choleithiasis, hematemesis, gum hemorrhage, hepatitis, lietis, laudice, 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, lymphatenopathy, lymphocytosis, thrombocythemia, Metabolic and nutritional - Frequent: peripheral edema, weight gair, Infrequent: alkaline phosphatese increased created diphetes mellitus, edema, ulycosulia, hypotholesteremia Metabolić and nutritional - Frequent, peripheral edema, weight gair; Intrequent; ikikaline phos-phatase increased, creatinine increased, diabetes mellitus, edema, glycosuria, hypercholesteremia, hyperglycemia, hyperipemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, gout, hemochromatosis, hyperkalemia, SGPT increased, uremia. Musculoskeletal system - Infrequent: anthritis, arthrosis, bone pain, bone spurs, bursitis, joint disorder, myasithenia, tenosynovitis; Rare: osteoporosis. Nerrouus system - Frequent: emotional lability, trismus, vertigo, Infrequent; apata, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperinosa, hyperotoined, hypotino incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, paranoid reac-tion, psychosis, psychotic depression, sleep disturbance, abnormal speech, stupor, toricolilis, Rare akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, cerebrovascular accident, loss of con-sciousness, elusions, deumentia, dvisonia, hypotkinesia, neuropathy, paranoid reac-tion, psychosis, gelusions, dementia, dvisonia, hypotkinesia, neuropathy, series of con-sciousness, elusions, deumentia, dvisonia, hypotkinesia, neuropathy, series of con-sciousness, elusions, deumentia, dvisonia, hypotkinesia, neuropathy, series of consciousness, delusions, dementia, dystonia, hypokinesia, neuritis, nystagmus, reflexes increased, seizures. Respiratory system - Frequent: bronchitis, dyspnea; Infrequent: asthma, chest congestion, seizures. Respiratory system - Frequent: bronchittis, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyporxia, 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, uricaria; Rare: skin atrophy, exfolative dermatitis, fungal der-matitis, lichenoid dermatitis, hair discoloration, eczema, furunculosis, hirsutism, skin hypertrophy, leukoderma, psoriasis, pustular rash, vesiculobullous rash. Special senses - Frequent: ahnormal vision, ear pairi, Infrequent: cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, ofitis media, parosmia, photophobia, subconjunctival hemorrhage, taste loss, visual field defect; Rare: blepharitis, chormatopsia, conjunctival edema, deafness, glaucoma, hyperacusis, ker-atitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, scleritis. Urogenital system Frequent: amerorhagi, kinder ucluus, cystilis, leukorrhea, menorrhagia*, intrequent; albuminuria, menorhae*, kidney calculus, cystilis, leukorhae, menorhagia*, nocturia, bladder

Frequent: anorgasmia, dysuria, hematuria, metrorrhagia*, urination impalred, vaginitis*; Infrequent: albuminuria, amenorrhea*, kidney calculus, cystitis, leukorrhea, menorrhagia*, nocturia, bladder pain, breast pain, kidney pain, polyuria, porstattis*, pyelonephritis, pyuria, urinary incontinence, urinary urgency, uterine fibroids enlarged*, uterine hemorrhage*, vaginal hemorrhage*, vaginal moniliasis*; Rare: abortion*, breast engorgement, breast enlargement, calcium crystalluria, temale 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 sub-stance. In a ertorspective survey of new events occurring during taper or following discontinuation, the following occurred at an incidence of 5%, with incidence for Effexor at least twice that for place-bo: 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 closeking behavior). Dosage and Administration: The recommended starting dose is 75 mg/day in 2 or 3 divided doses,

Dosage and Administration: The recommended starting dose is 75 mg/day in 2 or 3 divided doses, taken with food. If needed, dose increments of up to 75 mg/day should be made at intervals of no Last in the days. Maximum recommended dose, for use in severely depressed patients, is 375 mg/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. SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinue onlose twinorun initiation of therapy with Effexor. In addition, at least 7 days should be allowed after stopping Effexor before starting an MAOI (see "Contraindications" and "Warnings"). Please consult full prescribing information for detailed dosing instructions.

This brief summary is based on the current direction circulars, Cl 4193-3, Revised July 17, 1995, which is the same text as Cl 4268-4 with a revision date of July 17, 1995.

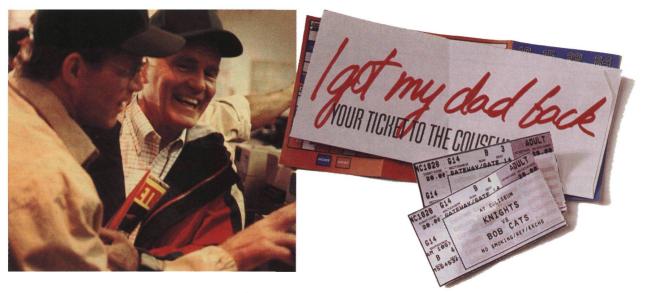
References: 1. Shader RI, von Moltke LL, Schmider J, et al. The clinician and drug interactions-an update J Clin Psychopharmacol. 1996;16:197-201. 2. Krishnan KRR, Steffens DC, Doraiswamy PM. Psychotropic drug interactions. Primary Psychiatry. 1996;3:21-45. 3. Ereshefsky L. Drug interactions of antidepressants. Psychiatric Anals. 1962;66:342-350. 4. EFFEXOR[®] (ventataxine HC) Prescribing Information, Wyeth-Ayerst Laboratories, Philadelphia, Pa. 5. Ereshefsky L. Treating depression: potential drug-drug interactions: commentary. J Clin Psychopharmacol. 1996;16(suppl 2):50S-53S. 6. Data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa. 7. Guelfi JD, White C, Hackett D, et al. Effectiveness of venlafaxine in patients hospitalized for major depression

Printed in U.S.A.



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67332-01



- Efficacy clearly demonstrated in depressed outpatients⁶
- Effective treatment in hospitalized depressed patients with major depressive disorder and melancholia meeting DSM-III-R[™] criteria⁷

EFFEXOR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR 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, at least 7 days should be allowed after stopping EFFEXOR before starting an MAOI.

Treatment with EFFEXOR is associated with sustained increases in blood pressure (BP) in some patients. The incidence was seen at >5% at dosages above 200 mg/day and appears to be dose dependent. It is recommended that patients have regular BP monitoring. For patients experiencing a sustained increase in BP, dose reduction or treatment discontinuation should be considered.

Low potential exists for interaction in patients taking lithium, diazepam, or cimetidine.⁴

—In combination with cimetidine, EFFEXOR should be used with caution in patients with preexisting hypertension, or in elderly patients, or in patients with hepatic dysfunction, as the interaction between the two drugs in these patients is not known and could be more pronounced.⁶

EFFEXOR at steady state increased the AUC of a single dose of haloperidol by 70%. The mechanism explaining this finding is unknown.

EFFEXOR is a relatively weak inhibitor of cytochrome P450 2D6.⁴

- ---Weak inhibition of cytochrome P450 2D6 is an important characteristic when considering other drugs metabolized by this enzyme.⁴
- ---Potential exists for a drug interaction between EFFEXOR and drugs that inhibit cytochrome P450 2D6 metabolism.⁴

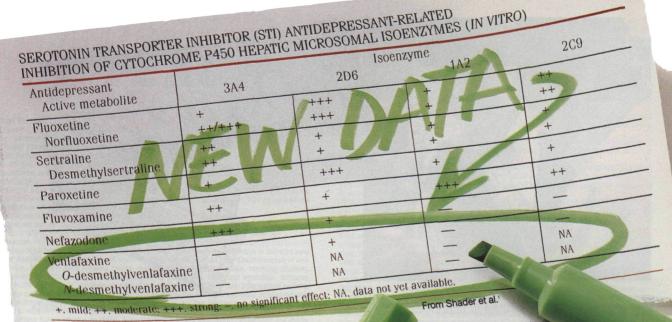
The most common adverse events reported in EFFEXOR clinical trials (incidence >10% and $\geq 2 \times$ that of placebo) were nausea, somnolence, dry mouth, dizziness, constipation, nervousness, sweating, asthenia, abnormal ejaculation/orgasm, and anorexia.

EFFEXOR has not demonstrated any clinically significant impairment of psychomotor, cognitive, or complex behavior performance in healthy volunteers. However, as with any psychotropic drug, EFFEXOR may impair judgment, thinking, or motor skills; patients should be advised to exercise caution until they have adapted to therapy.

Please see brief summary of Prescribing Information on previous page of this advertisement.



https://doi.org/10.1017/S1092852900001711 Published online by Cambridge University Press



The above data are not meant

to imply clinical benefit

The Science Makes Sense Drug-drug interactions are a concern in the treatment of depression.

Many people who seek treatment for depression are

often already receiving pharmacologic treatment for a physical or another emotional disorder. With this in mind, it is incumbent upon the physician treating the depressed patient to be cognizant of the metabolic pathways of prescribed pharmacologic treatment.

Consider the cytochrome P450 (CYP) system

The cytochrome P450 system present in the liver is involved in the oxidative metabolism of numerous drugs.² Among the more than 30 enzymes currently recognized, the following systems-CYP2D6, CYP3A4, CYP1A2, CYP2C9, and CYP2C19—have been identified as important in the metabolism of psychoactive and other commonly prescribed drugs.^{2,3} In vitro studies have demonstrated that venlafaxine is a relatively weak inhibitor of CYP2D6 as compared to the SSRIs and has very weak or

no inhibitory potentials at CYP3A4, CYP1A2, and CYP2C9.2.4.5 The clinical significance of these in vitro data is unknown.



EFFEXOR...New data demonstrate a favorable drug interaction profile

Completed in vivo studies confirm the in vitro data stated previously. One study, using dextromethorphan as a clinical marker, indicated that there is a decrease in the relative risk of clinically significant interactions between EFFEXOR and drugs metabolized by CYP2D6.⁶ The isoenzyme CYP2D6 is involved in the metabolism of many drugs, such as codeine, propranolol, other beta-blockers, and certain antiarrhythmic agents.³ Other in vivo studies confirm that EFFEXOR has little or no potential to inhibit CYP3A4. EFFEXOR does not significantly inhibit the metabolism of alprazolam, diazepam, terfenadine, and carbamazepine, all substrates for CYP3A4.2.4

Efficacy and safety profiles for the special needs of today's depressed patients

EFFEXOR is effective therapy for depressed outpatients. EFFEXOR is effective even in severely depressed patients.

When considering the needs of your depressed patients who are on concomitant therapies. the science makes sense in selecting EFFEXOR as proven treatment for depression.

Please see brief summary of Prescribing Information accompanying this advertisement.

CNS SPECTRUMS

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

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VOLUME 2, NUMBER 2

CNS SPECTRUMS IS PUBLISHED 10 TIMES A YEAR (JANUARY, FEBRUARY, MARCH, APRIL, MAY, JUNE, JULY/AUGUST, SEPTEMBER, OCTOBER, & NOVEMBER/DECEMBER) BY MBL COMMUNICATIONS, INC., 665 BRCAADWAY, NEW YORK, NY 10012-2302.

PERIODICALS POSTAGE RATES PENDING AT NEW YORK, NY, AND AT ADDITIONAL MAILING OFFICES.

ONE YEAR SUBSCRIPTION RATES: DOMESTIC \$90; FOREIGN \$145; IN-TRAINING \$50. FOR SUBSCRIPTIONS: 212-328-0800.

POSTMASTER: SEND ADDRESS CHANGES TO CNS SPECTRUMS 665 BROADWAY, NEW YORK, NY 10012-2302.

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References:

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Dunbar GC, Fuell DL. *Psychopharmacol Bull*. 1992;28:139-143. 6. Clayton PJ, Grove WM, Coryell W, et al. *Am J Psychiatry*. 1991;148: 1512-1517. 7. Paxil® (paroxetine HCI) Prescribing Information.

1512-1517. 7. Paxil[®] (paroxetine HCI) Prescribing Information. PAXIL[®] (brand of peroxetine hydrochloride) See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or PDR. The following is a brief summary. INDICATIONS AND USAGE: Paxil's indicated for the treatment of depression, obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in DSM-IV, and panic disorder, with or without agorapholia, as defined in DSM-IV. CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is con-traindicated, See WARNINGS and PRECAUTIONS: WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concom-tiant or immediately consecutive administration of MAOIs and other SSRIs, do not use Paxil' in com-bination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping Paxil before starting a MAOI. The possibility of suicide attempt is inhearts in a preservition of mania. Use Paxil cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures. The possibility of suicide attempt is inheart in depression and may perissi until significant remission occurs. Case supervision of high-risk patients should accompany initial drug therapy. Write Paxil prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. Reversible hyponatermia has been reported, mainty in elderly patients, patients taking diureits or those who were otherwise volume depleted. Abnormal bleeding (mostly ecchymosis and purpura), including a case of impaired platelita aggregation, has been reported, mainty in clearnoc <30 mL/min.) or severe hepat-ic impairment, a lower starting dose (10 mg) should be used. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that Paxil therapy does not affect metabilism including

or if they're nursing. "" with tryptophan is not recommended. Use cautiously with warfarin. When administer-ing Paxi/ with cimetidine, dosage adjustment of Paxi/ after the 20 mg starting dose should be guided by clinical effect. When co-administering Paxi/ with phenobarbial or phenytoin. no finitel Paxi/ dosage adjustment is need-ed; base subsequent changes on clinical effect. Concomitant use of Paxi/ with drugs metabolized by cychorhome Peollog (antidepressants such as notrriptyline, amitriptyline, imipramine, desipramine and fluoxethe; phenothia-zines such as thioridazine. Type 1 C antiarriytyline, imipramine, desipramine and fluoxethe; phenothia-the other drug; approach concomitant use culturely. A with or the paratele that paravetine had no effect on terfenadine phermacokinetics. Additional *in vitro* studies showed that the inhibitory effects of paroxe-tine on other IIIA, substrates (asternizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent han ketoconazole, a potent IIIA, inhibitor. Assuming that the relationship between paroxetine's *in witro* K i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other IIIA, substrates, garavetine is inhibit tricyclic antidepressants (TCAs). TCA plasma concentrations may need monitoring and the TCA dose may need to be reduced. Administration of *Paxi/* and lithium or digoxin cautiously. If *adverse* effects are seen when co-admin-istering *Paxi/* with throyclicline, reduce the procycline dose. Elevated theophylline levels have been cad-mating with the processed into the procycline rates in the 200 mg/kg/day group developed reticulum cell across dose groups for the occurrence of lwynphoreticular tumors in male rats. Although here was a desertel-ad increase in the number of thus erats in the 200 mg/kg/day group developed reticulum cell across dose groups for the occurrence of lwynphoreticular tumors in male rats need to be weed so effects on the reased linear trend across dose groups for the occurrence of

rate. **Pregnancy Category C.** Reproduction studies performed in rats and rabbits at doses up to 6 mg/kg/day, 8.1 (rat) and 1.9 (rabbit) times the MRHD on a mg/m² basis, have revealed no evidence of teratogenic effects or of selec-tive toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lectation when dosing occurred during the last timester of gestation and continued throughout lactation. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. *Paxil* should be used in pregnancy only if the potential benefit justifies the potential risk to the fatus. The effect of *Paxil* on labor and delivery in humans is unknown. Paroxetine is secreted in human miłk; exercise caution when administering *Paxil* to a nursing woman.

being in thinking is divinitively a tradective is secticated in homan mini, exercise caudion when administrating reach to a nursing woman. Safety and effectiveness in the pediatric population have not been established. In worldwide premarketing *Paxi*/ clinical trials, 17% of *Paxi*/treated patients were \geq 56 years of age. Pharmaco-kinetic studies revealed a decreased clearance in the elderly; however, there were no overall differences in the adverse event profile between older and younger patients. **ADVERSE REACTIONS: Incidence of Soft of Paxi/ End adverse events** associated with the use of *Paxil* in the treatment of depression (incidence of 5% or greater and incidence for *Paxi* at least twice that for placebol: asthenia (15% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs. 2%), somo-lence (23% vs. 9%), dizziness (13% vs. 6%), insomia (13% vs. 6%), thermor (8% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (13% vs. 0%) and other male genital disorders (10% vs. 0%). The most commonly observed daverse events associated with the use of paxiet neither twice that of placebol verse nausea (23% vs. 10%), dry mouth (18% vs. 9%), decreased appetite (6% vs. 3%), constipation (16% vs. 6%), vs. 1%) and abnormal ejaculation (23% vs. 1%). The most commonly observed daverse events associated with the use of parxetine in the treatment of bases vs. 1%) and abnormal ejaculation (23% vs. 1%). The most commonly observed daverse events associated with the use of parxetine in the treatment of panic disorder (incidence of 5% vs. 1%). The most commonly observed daverse events associated with the use of parxetine in the treatment of panic disorder (incidence of 5% vs. 1%). The most commonive observed daverse events associated with the use of parxetine in the treatment of panic disorder (incidence of 5% vs. 7%). The most commonly observed daverse events associated with the use of parxetine in the treatment of panic disorder (incidence of 5% vs. 7%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of panic disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: asthenia [14% vs. 5%), sweating [14% vs. 6%), decreased appetite [7% vs. 3%), libido decreased (9% vs. 1%), termor (9% vs. 1%), and importence [5% vs. 1%), bard more (1% vs. 1%), female genital disorders (9% vs. 1%) and importence [5% vs. 1%). Twenty percent (1.199/6.155) of *Paxil* patients in worldwide chinal trials in depression and 11.8% (64/542) and 9.4% (44/489) of *Paxil* patients in worldwide trials in OCD and panic disorder, respectively, discontinued treat-ment due to an adverse event. The most common events (21%) associated with discontinuation and considered to be drug related include the following: **depression**-somolence, agritation, tremor, nausea, diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating: **OCD**-insomnia, dizziness, constituation, and considered or more, in patients dosed (20 to 50 mg/day) for the treatment of depression headche, asthenia, patients, nausea, dry mouth, constipation, diarrhea, depression headche, asthenia, patients dosed (20 to 50 mg/day) for the treatment of depression headche, asthenia, patients dosed (20 to 50 mg/day) for the treatment of depression headche, asthenia, patients, nore, nervo, nerves, no patients dosed (20 to 50 mg/day) for the treatment of depression headche, asthenia, patientar, nervo, nervo, nerve, nerve, nervet, nerve nerve, nenve, nenve, nerve, nerve, nerve, n

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anxiety, paresthesia, libido decreased, drugged feeling, confusion; yawn; blurred vision, taste perversion; ejacu-latory disturbance, other male genital disorders, urinary frequency, urination disorder, female genital disorders. The following adverse events occurred at a frequency of 2% or more among OCD patients on *Paxil* who partic-ipated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on *Paxil* who participated in placebo-controlled trials of 10 to 12 weeks duration in which patients were dosed in a range of 10 to 60 mg/day; asthenia, abdominal pain^{*}, chest pain^{**}, back pain^{*}, chills; vasodilation^{**}, palpitation^{**}; sweating, rash^{**}; nausea, dry mouth, constipation, diar-rhea, decreased appetite, increased appetite, insomnia, somolence, diztiness, tremor, nervousness^{**}, libido decreased, agitation^{**}, anxiety^{*}; abnormal dreams^{**}, concentration impaired^{**}, depersonalization^{**}, myoclonus, amnesia^{**}, initis^{**}, abnormal vision^{**}; taste perversion^{**}; aborna ejaculation, fende genital disorder, impotence, urinary frequency, urination impaired^{***}, urinary tract infection. *denotes panic disorder patients only, **denotes OCD patients only. Studies show a clear dose dependency for some of the more common adverse events associated with *Paxil* use.

disorder, impotence, urinary frequency, urination impaired**, urinary tract infection. "Genotes period usioned patients only, **denotes OCD adaptation to some adverse events with continued *Paxil* therary (e.g., nausea and diziness). Significant weight loss may be an undesirable result of *Paxil* treatment for some patients but, on average, patients in controlled trials had minimal (about 1 lb) toss. In placebo-controlled clinical trials, *Paxil*-treated patients exhibited abnormal values on liver function tests no more frequently than placebo-treated patients. Other Events Observed During the **Premarketing Pavil** toring premarketing premarketing premarketing premarketing accurring in at least 1/1000 patients; *infrequent* = 1/100 to 1/1000 patients; *rare* = less than 1/1000 patients. Events are classified with in body system categories and enumerated in order of decreasing frequency using the above definitions. It is important to emphasize that although the events occurred during *Paxil* treatment, they were not necessarily caused by it.

In body system categories and enumerated in order of decreasing frequency using the above demintions. It is important to emphasize that although the events occurred during *Paxi* treatment, they were not necessarily caused by it. **Body as a Whole**: *frequent*: chills, malaise; *infrequent*: allergic reaction, carcinoma, face edema, monifilasis, neck pain; *rare*: abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, shock, ulcer. **Cardiovascular System**: *frequent*: hypertension, syncope, tachycardia, *infrequent*: bradycardia, conduction abnormalities, electrocardiogram abnormal, hematoma, hypotension, migraine, peripheral vascular dioorder; *rare*: angina pectoris, arrhythmia, atrail fibrillation, bundle branch block, cerebral ischemia, cerebrovascular acci-dent, congestive heart failure, heart block, low cardiac output, myocardial infact, myocardial ischemia, pallot, philebitis, pulmonary embolus, supraventricular extrasystoles, thrombophilebitis, thrombosis, variose vein, vas-cular headache, ventricular extrasystoles. **Digestive System**: *infrequent*: bruxism, colitis, dysphagia, eructation, reteritis, soppaditis, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, paptic ulcer, salivary gland enlargement, stomad lucer, stomati-tis, tongue discoloration, fougue edema, toth caries; tooth malformation. **Endocrine System**: *infrequent*: anemia, leukopenia, lymphadenopathy, pupurar; *rare*: abnormal erythrocytes, basophilia, eosinophilia, hypochromic anemia, monocytosis, normocytic anemia, thrombocythemia. **Metabolic and Nutritionel:** Frequent: edema, weight gain, weight loss; infrequent: threagine, hypokalemia, hyponatremia, BUN increased, SGP1 increased, SDF1 increased, theirt, *rare*: alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehir-tratic, unyelist, loss; momocytic, anemia, thronbocythemia, Metabolic and Nutritionel: Frequent: edema, hypos reflexes decreased, reflexes increased, stupor, trismus, withdrawal syndrome. Respiratory System: frequent: cough increased, thinitis: infrequent: asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respi-ratory flu, sinustis, voice alteration; rare: emphysema, hemotysis; hiccups, lung fibrosis, pulmonary edema, sputum increased. Skin and Appendages: frequent: pruritus; infrequent: ace, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; rare: angioedema, contact der: mittige ender and appecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; rare: angioedema, contact der: mittige ender and observations, with sporthea, skin discoloration, skin hypertrophy, skin melonoma, skin ulcer, vesiculobullous rash. Special Senses: frequent: tinnitus; infrequent: abnormalky of accommodation, conjunctivitis, sear pain, eve pain, mydriasis, otitis media, taste loss, visual field defect; rare: amblyopia, anisocoria, blepharitis, cataract, conjunctivitis, ebortien, agintis, mitis media, citiis externe, parosmia, photophobia; potosis, retrian hemorrhage. (Torgenital System: infrequent: abortion, amenorhea, breast pain, cystitis, dysmenorhea, dysuria, hematuria, menorhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis, rare: breast atrophy, breast carcinoma, breast enlargement, breast neoplasm, epididymitis, teatorin, fibrocystic breast, kindey calculus, kindey function abnormal, kidney pain, leukorhea, mastitis, metrorhagia, nephritis, oliguria, prostatic carcinoma, pyuria, urethritis, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis. Postmarketing Reporte

Performance in the provide a second sec Voluntary reports of adverse events that have been received since market introduction and not listed above that may have no causal relationship with *Paxii* include-acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossiy elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidemal necrolysis, priapism, thrombocytopenia, syndrome of inap-propriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syn-drome-like events; extrapyramidal symptoms which have included akathisia, bradytinesia, cogwheel rigidity, dys-tonia, hypertonia, oculogyric crisis (which has been associated with concomitant use of pimozide), tremor and drugs which may have impaired *Paxii* matabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hypereflexia, mycolonus, shivering, tachycardia and tremor). There have been spontaneous re-ports that abrupt discontinuation may lead to symptoms such as diziness, sensory disturbances, egitation or anx-iety, nausea and sweating; these events are generally self-limiting. There has been a report of an elevated phen *Paxii* was added to chronic metoprolol treatment. **DRUG ABUES LAND DEPENDENCE: Controlled Substance Class:** *Paxii* in not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxii* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

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She's agitated.

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Paxil effectively relieves depression and associated symptoms of anxiety.1-4

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Most common adverse events include: nausea, somnolence, asthenia, dizziness, insomnia, sweating, ejaculatory disturbance and other male genital disorders.*7 Concomitant use of Paxil in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. *Incidence of 5% or greater and incidence for Paxil at least twice that for placebo.

Please see brief summary of prescribing information on adjacent page of this advertisement



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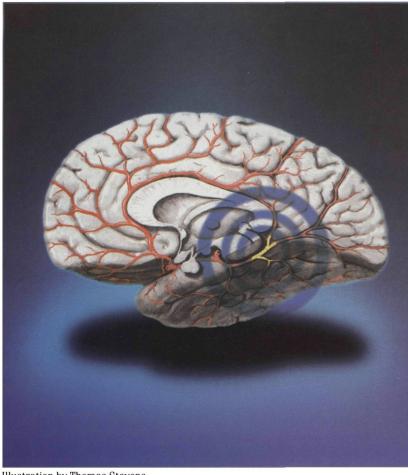
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CNS SPECTRUMS

INE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

> Vol•2 - No•2 February 1997

PHOTO ESSAY:

Dr. Frank Netter's peerless medical illustrations have informed generations of physicians on the particulars of cerebrovascular anatomy. For clinical practitioners of the neurosciences, knowledge of the cerebrovascular anatomy is especially helpful in evaluating patients with suspected cerebrovascular disease, infarct, intracerebral hemorrhage, vascular malformation, aneurysm, or tumor. In this issue, for example, Dr. Netter's drawings are being used to illustrate some of the biological and vascular causes of migraine headaches.

These drawings illustrate and describe the normal arteries and veins of the brain, showing the relationship of the many arterial and venous branches to the adjacent neuroanatomy. In addition, they identify the territories supplied and drained by these smaller vessels. In some patients, for whom computed tomography and angiography alone may not provide a definitive diagnosis, knowledge of the vascular anatomy involved enables the clinician to more effectively plan treatment.

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BY ERIC HOLLANDER, MD

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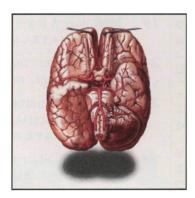
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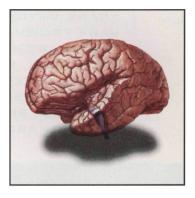
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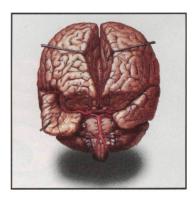
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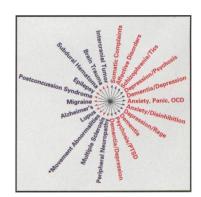
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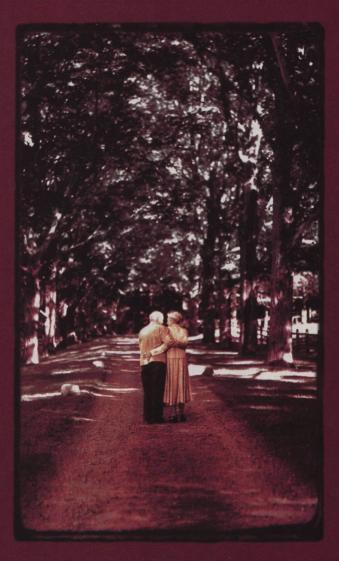








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