

CNS SPECTRUMS™

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

SCHIZOPHRENIA & OCD: **Issue 1** Convergence

Editorial by
J. Zohar

**Obsessions and Delusions:
Separate and Distinct,
or Overlapping?**

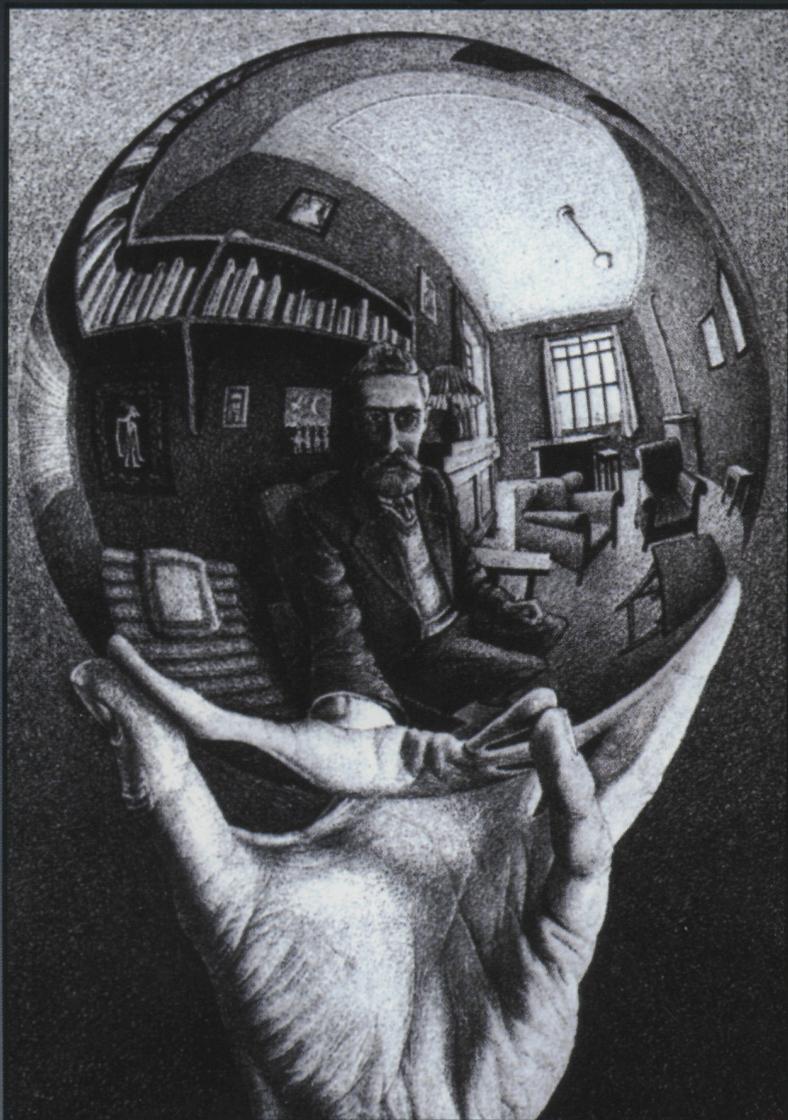
P.C. Bermanzohn • L. Porto
S.G. Siris • et al

**OC Symptoms in
Schizophrenia:
Are They Manifestations
of a Distinct Subclass
of Schizophrenia?**

I. Berman • D. Pappas
S.M. Berman

**Obsessions,
Compulsions, Clozapine,
and Risperidone**

R.W. Baker • D.A. Wirshing
K.N.R. Chengappa



CME Mount Sinai **3**

PHOTO ESSAY

Few thinkers were able to express the construction of the images of a human mind more systematically than the Dutch graphic artist, M.C. Escher (1898-1972), whose *Self-Portrait in Spherical Mirror* (January 1935) is reproduced above, left. This period in the artist's life dealt with the regular division of the plane, stressing how forms both interweave and separate—a fitting analogy for this first of two issues to address both convergent and divergent views of the relationship between Schizophrenia and OCD.

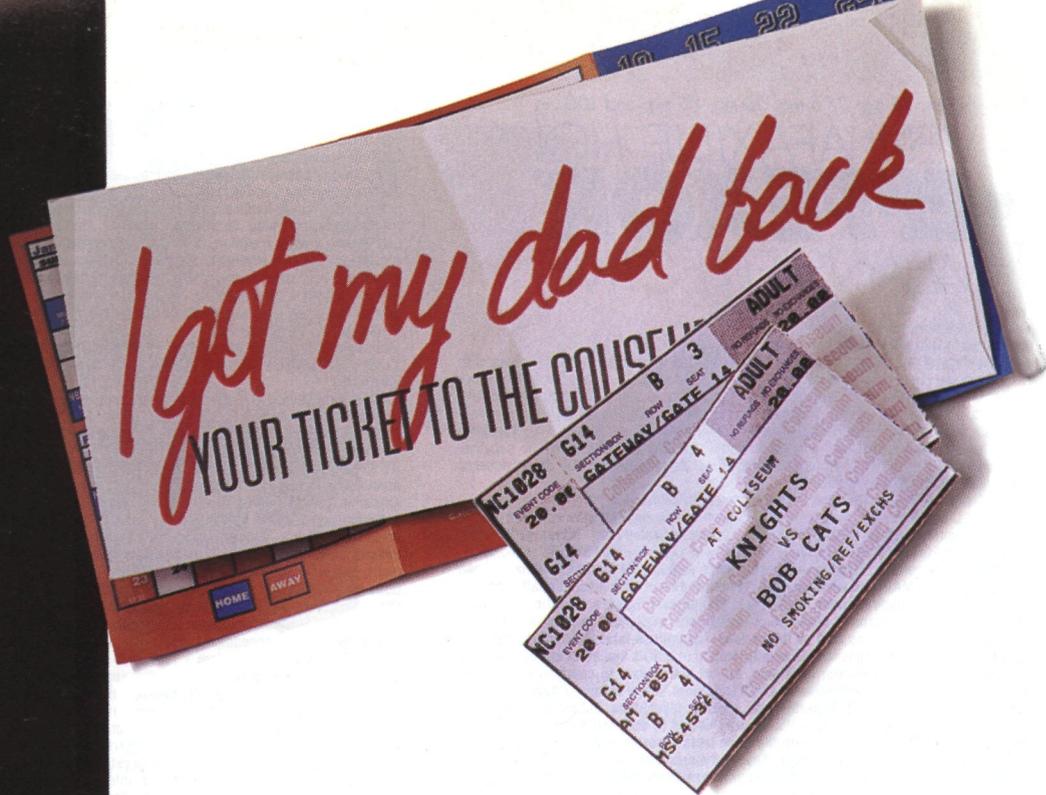
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Broken hearts require special care.

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.

VENLAFAXINE HCl
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MEANS EFFECTIVE

Please see brief summary of Prescribing Information accompanying this advertisement.

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

VENLAFAXINE HCl EFFEXOR® MEANS EFFECTIVE

Brief Summary

Effexor® (venlafaxine hydrochloride) Tablets

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: 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 venlafaxine. Reactions have included tremor, myoclonus, 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 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 stopping Effexor before starting an 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 antidepressant/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 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=10–70 mL/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 physician 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 P₂U₂ Metabolism:** *In vitro*, venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome P₂U₂. Therefore drugs inhibiting this isoenzyme could potentially increase plasma concentrations of venlafaxine and decrease concentrations of ODV. **Drugs Metabolized by Cytochrome P₂U₂:** *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 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 120 mg/kg/day [16 times the maximum recommended human dose (MRHD)]. In 24-month studies, there was no evidence of carcinogenicity 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 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 ≥ 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 fol-

lowing 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, hypotonia, 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 mmHg.

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 ache, 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, thrombocytopenia, 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, hypercholesterolemia, 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, manic reaction, 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, seizures. **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, ichthyoid 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 defects; **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 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 less than 4 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 discontinuation of an MAOI and 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, CI 4193-3, Revised July 17, 1995, which is the same text as CI 4268-4 with a revision date of July 17, 1995.

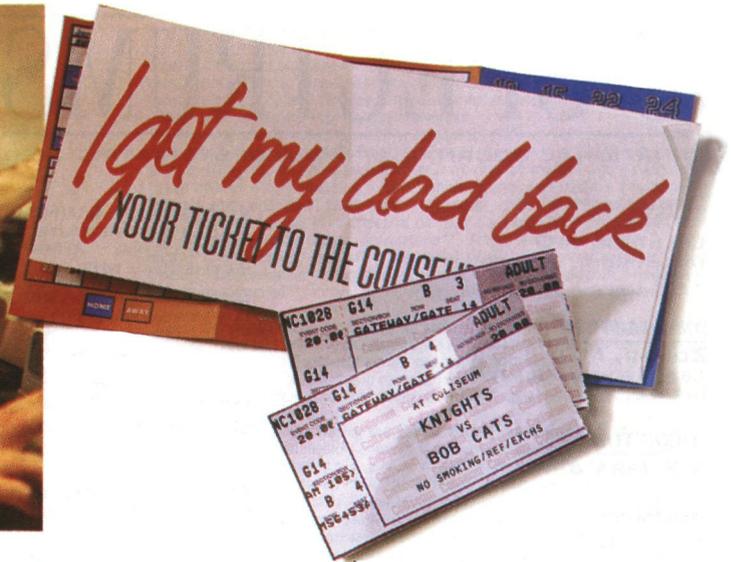
References: 1. Shader RI, von Mollke LL, Schmitter J, et al. The clinician and drug interactions—an update. *J Clin Psychopharmacol.* 1996;16:197-201. 2. Krishnan KRR, Stefens DC, Doraiswamy PM. Psychotropic drug interactions. *Primary Psychiatry.* 1996;3:21-45. 3. Ereshtsky L. Drug interactions of antidepressants. *Psychiatric Annals.* 1996;26:342-350. 4. EFFEXOR® (venlafaxine HCl) Prescribing Information, Wyeth-Ayerst Laboratories, Philadelphia, Pa. 5. Ereshtsky 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. Guelif JD, White C, Hackett D, et al. Effectiveness of venlafaxine in patients hospitalized for major depression and melancholia. *J Clin Psychiatry.* 1995;56:450-458.

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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 ≥2× 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.

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PAXIL® (brand of paroxetine hydrochloride)

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or PDR. The following is a brief summary.

INDICATIONS AND USAGE: Paxil is 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 agoraphobia, as defined in DSM-IV.

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. (See WARNINGS and PRECAUTIONS.)

WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use Paxil in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping Paxil before starting a MAOI.

PRECAUTIONS: As with all antidepressants, use Paxil cautiously in patients with a history 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 inherent in depression and may persist until significant remission occurs. Close 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 hyponatremia has been reported, mainly in elderly patients, patients taking diuretics or those who were otherwise volume depleted. Abnormal bleeding (mostly ecchymosis and purpura), including a case of impaired platelet aggregation, has been reported; the relationship to paroxetine is unclear.

Clinical experience with Paxil in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic 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 their ability to engage in such activities. Tell patients 1) to continue therapy as directed; 2) to inform physicians about other medications they are taking or plan to take; 3) to avoid alcohol while taking Paxil; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy, or if they're nursing.

Weakness, hyperreflexia, and incoordination following use of an SSRI and sumatriptan have been rarely reported.

Concomitant use of Paxil with tryptophan is not recommended. Use cautiously with warfarin. When administering Paxil with cimetidine, dosage adjustment of Paxil after the 20 mg starting dose should be guided by clinical effect. When co-administering Paxil with phenobarbital or phenytoin, no initial Paxil dosage adjustment is needed; base subsequent changes on clinical effect. Concomitant use of Paxil with drugs metabolized by cytochrome P₄₅₀2D₆ (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines such as thioridazine, Type 1C antiarrhythmics such as propafenone, flecainide and encainide) or with drugs that inhibit this enzyme (e.g., quinidine) may require lower doses than usually prescribed for either Paxil or the other drug; approach concomitant use cautiously. An *in vivo* interaction study revealed that paroxetine had no effect on terfenadine pharmacokinetics. Additional *in vitro* studies showed that the inhibitory effects of paroxetine on other IIIA₂ substrates (astemizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent than ketocozazole, a potent IIIA₂ inhibitor. Assuming that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other IIIA₂ substrates, paroxetine's inhibition of IIIA₂ activity should have little clinical significance. Use caution when co-administering Paxil with tricyclic antidepressants (TCAs). TCA plasma concentrations may need monitoring and the TCA dose may need to be reduced. Administration of Paxil with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug. Concomitant use of Paxil and alcohol in depressed patients is not advised. Undertake concomitant use of Paxil and lithium or digoxin cautiously. If adverse effects are seen when co-administering Paxil with procyclidine, reduce the procyclidine dose. Elevated theophylline levels have been reported with Paxil co-administration; monitoring theophylline levels is recommended.

In 2-year studies, a significantly greater number of male rats in the 20 mg/kg/day group developed reticular cell sarcomas vs. animals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with Paxil.

Rats receiving paroxetine at 15 mg/kg/day (2.4 times the MRHD on a mg/m² basis) showed a reduced pregnancy 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 selective toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester 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 fetus. The effect of Paxil on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when administering Paxil to a nursing woman.

Safety and effectiveness in the pediatric population have not been established.

In worldwide premarketing Paxil clinical trials, 17% of Paxil-treated patients were ≥65 years of age. Pharmacokinetic 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 in Controlled Trials—Commonly Observed Adverse Events in Controlled Clinical Trials: The most commonly observed adverse events associated with the use of Paxil in the treatment of depression (incidence of 5% or greater and incidence for Paxil at least twice that for placebo): asthenia (15% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs. 2%), somnolence (23% vs. 9%), dizziness (13% vs. 6%), insomnia (13% vs. 6%), tremor (8% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (13% vs. 0%) and other male genital disorders (10% vs. 0%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of obsessive compulsive disorder (incidence of 5% or greater and incidence for Paxil at least twice that of placebo) were: nausea (23% vs. 10%), dry mouth (18% vs. 9%), decreased appetite (9% vs. 3%), constipation (18% vs. 6%), dizziness (12% vs. 6%), somnolence (24% vs. 7%), tremor (11% vs. 1%), sweating (9% vs. 3%), impotence (8% vs. 1%) and abnormal ejaculation (23% vs. 1%).

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%), tremor (9% vs. 1%), abnormal ejaculation (21% vs. 1%), female genital disorders (9% vs. 1%) and impotence (5% vs. 0%).

Twenty percent (1,199/6,145) of Paxil patients in worldwide clinical trials in depression and 11.8% (64/542) and 9.4% (44/469) of Paxil patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related include the following: depression—somnolence, agitation, tremor, nausea, diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating;

OCD—insomnia, dizziness, constipation, nausea, asthenia, abnormal ejaculation, impotence; panic disorder—somnolence, insomnia, nausea.

The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequency of 1% or more, in patients dosed (20 to 50 mg/day) for the treatment of depression: headache, asthenia, palpitation; vasodilation; sweating, rash; nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, oropharynx disorder, dyspepsia; myopathy, myalgia, myasthenia; somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesia, libido decreased, drugged feeling, confusion; yawn; blurred vision, taste perversion; ejaculatory 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 participated 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, diarrhea, decreased appetite, increased appetite; insomnia, somnolence, dizziness, tremor, nervousness**, libido decreased, agitation**, anxiety**: abnormal dreams**, concentration impaired**, depersonalization**, myoclonus, amnesia**, rhinitis**, abnormal vision**, taste perversion**: abnormal ejaculation, female 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. There was evidence of adaptation to some adverse events with continued Paxil therapy (e.g., nausea and dizziness). 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) loss. 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 Evaluation of Paxil: During premarketing assessment in depression multiple doses of Paxil were administered to 6,145 patients in phase 2 and 3 studies. During premarketing clinical trials in OCD and panic disorder, 542 and 469 patients, respectively, received multiple doses of Paxil. 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 above definitions. It is important to emphasize that although the events occurred during Paxil treatment, they were not necessarily caused by it.

Body as a Whole: frequent: chills, malaise; infrequent: allergic reaction, carcinoma, face edema, moniliasis, 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 disorder; rare: angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral infarct, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

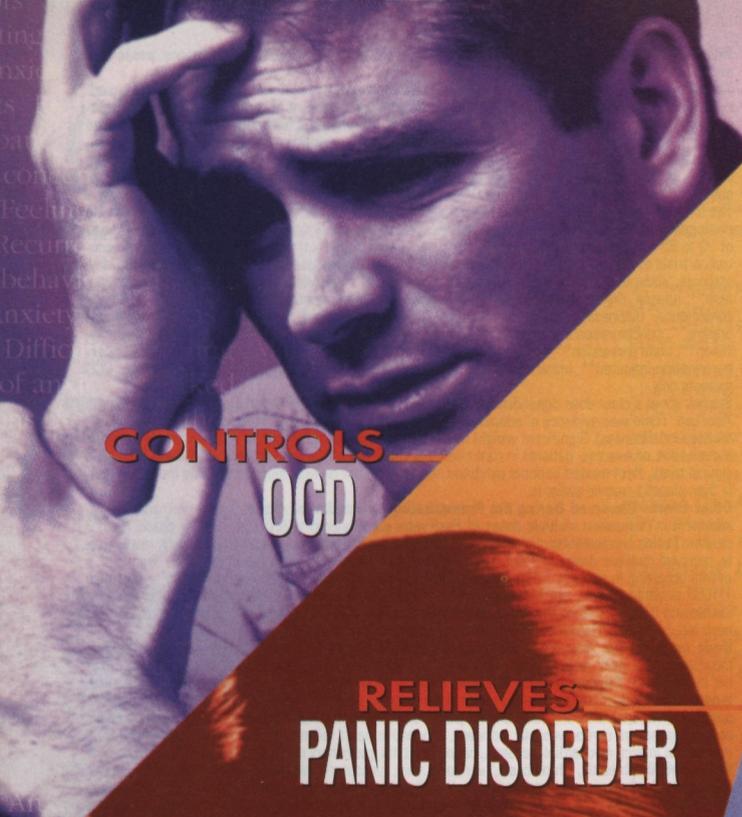
Digestive System: frequent: bruxism, colitis, dysphagia, eructation, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage, ulcerative stomatitis; rare: aphthous stomatitis, bloody diarrhea, bulimia, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries, tooth malformation. **Endocrine System:** rare: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** frequent: anemia, leukopenia, lymphadenopathy, purpura; rare: abnormal erythrocytes, basophilia, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocytopenia.

Metabolic and Nutritional: frequent: edema, weight gain, weight loss; infrequent: hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare: alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesterolemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased. **Musculoskeletal System:** frequent: arthralgia; infrequent: arthritis; rare: arthrosis, bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. **Nervous System:** frequent: amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; infrequent: abnormal thinking, akinesia, alcohol abuse, ataxia, convulsion, depersonalization, dystonia, hallucinations, hostility, hyperkinesia, hypertonica, hyposthesia, incoordination, lack of emotion, manic reaction, neurosis, paralysis, paranoid reaction; rare: abnormal electroencephalogram, abnormal gait, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus, withdrawal syndrome. **Respiratory System:** frequent: cough increased, rhinitis; infrequent: asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis, voice alteration; rare: emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased. **Skin and Appendages:** frequent: pruritus; infrequent: acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; rare: angioedema, contact dermatitis, erythema nodosum, erythema multiforme, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, maculopapular rash, photosensitization, seborrhea, skin discoloration, skin hypertrophy, skin melanoma, skin ulcer, vesiculobullous rash.

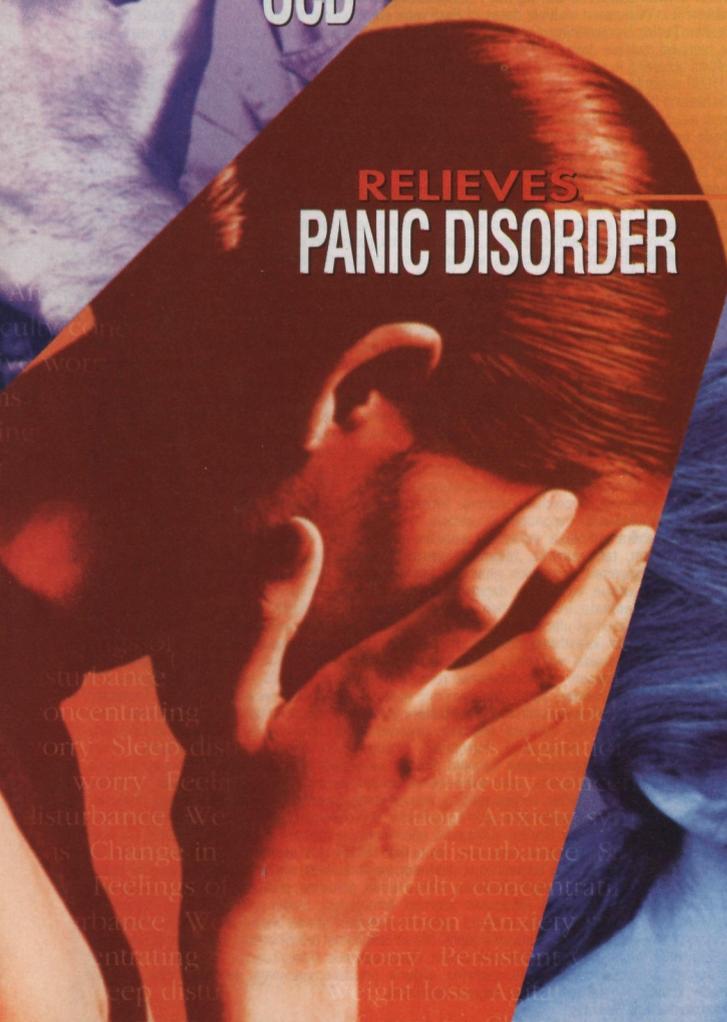
Special Senses: frequent: tinnitus; infrequent: abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, taste loss, visual field defect; rare: amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, keratoconjunctivitis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage. **Urogenital System:** infrequent: abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, hematuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; rare: breast atrophy, breast carcinoma, breast enlargement, breast neoplasm, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney function abnormal, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, prostatic carcinoma, pyuria, urethritis, uterine spasm, uterine prolapse, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports
Voluntary reports of adverse events that have been received since market introduction and not listed above that may have no causal relationship with Paxil include: acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis (which has been associated with concomitant use of pimozide), tremor and trismus; and serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired Paxil metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). There have been spontaneous reports that abrupt discontinuation may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. There has been a report of an elevated phenytoin level after 4 weeks of Paxil and phenytoin co-administration, and a report of severe hypotension when Paxil was added to chronic metoprolol treatment.

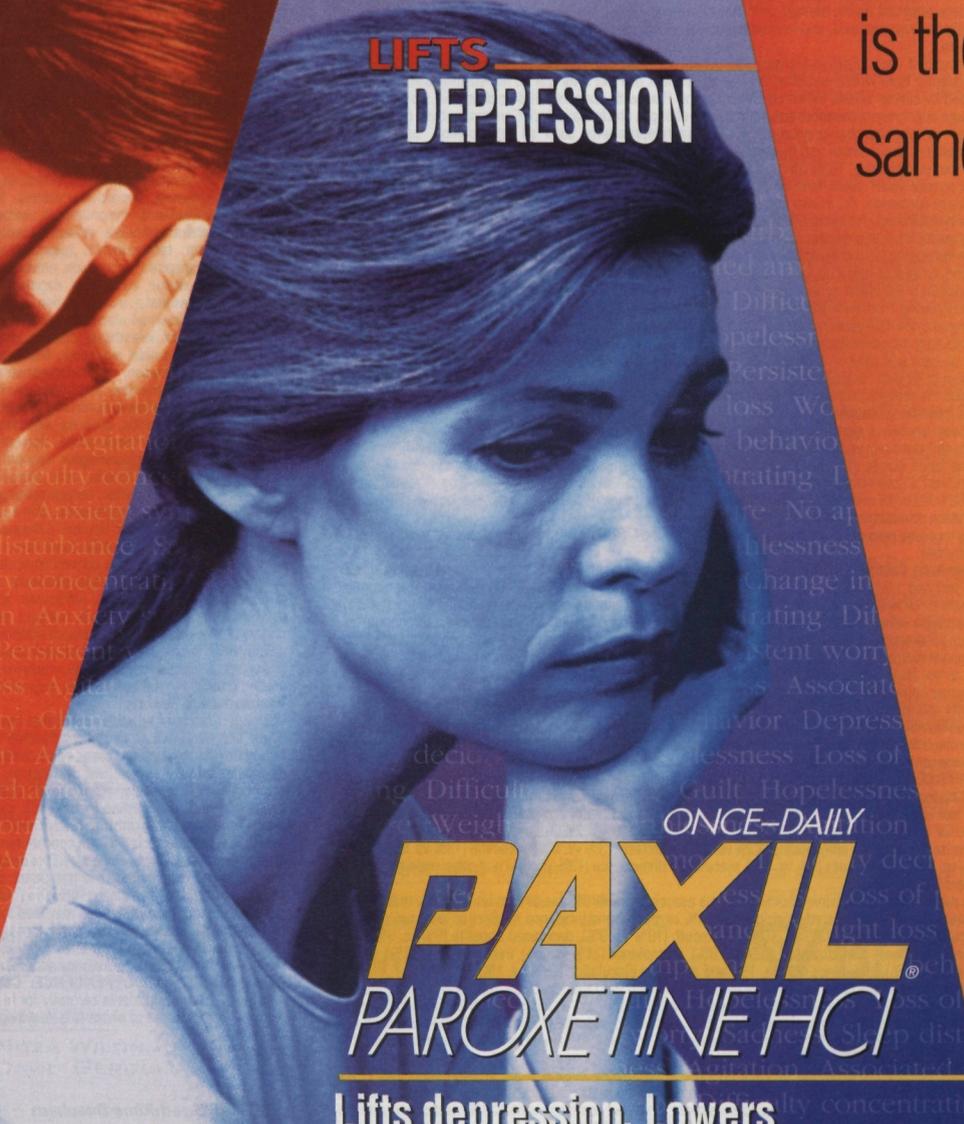
DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Paxil is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of Paxil misuse or abuse (e.g., development of tolerance, increments of doses, drug-seeking behavior).
BRX-PX-112



CONTROLS
OCD



RELIEVES
PANIC DISORDER



LIFTS
DEPRESSION

The symptoms may overlap... but the solution is the same

Most common adverse events (incidence of 5% or greater and incidence for Paxil at least twice that for placebo) in depression or OCD or panic disorder studies include nausea, somnolence, abnormal ejaculation, dry mouth, constipation, asthenia, sweating, dizziness, insomnia, tremor, female genital disorders, libido decreased, decreased appetite, impotence and nervousness. Concomitant use of Paxil in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

Please see brief summary of prescribing information at the end of this advertisement.

ONCE-DAILY

PAXIL
PAROXETINE HCl

Lifts depression. Lowers associated anxiety symptoms.

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CNS SPECTRUMS

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INTERNATIONAL
JOURNAL OF
NEUROPSYCHIATRIC
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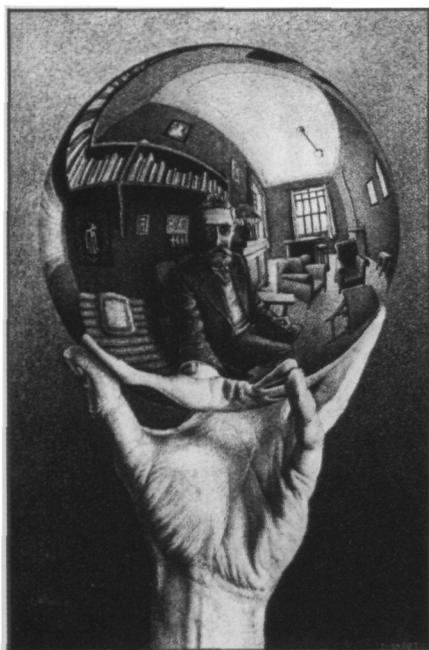


PHOTO ESSAY:

Few thinkers were able to express the construction of the images of a human mind more systematically than the Dutch graphic artist, M.C. Escher (1898-1972), whose *Self-Portrait in Spherical Mirror* (January 1935) is reproduced, left. This period in the artist's life dealt with the regular division of the plane, stressing how forms both interweave and separate—a fitting analogy for this first of two issues to address both convergent and divergent views of the relationship between Schizophrenia and OCD.

Escher wrote about his work that "the ideas that are basic to [the art] often bear witness to my amazement and wonder at the laws of nature which operate in the world around us. He who wonders discovers that this is in itself a wonder. By keenly confronting the enigmas that surround us, and by considering and analyzing the observations that I had made, I ended up in the domain of mathematics. Although I am absolutely without training or knowledge in the exact sciences, I often seem to have more in common with mathematicians than with my fellow-artists."

Escher's self-portraits in spheres—of which a later version will highlight next month's cover—keenly summarizes his life and work. Interestingly, he compared himself to his own father when he wrote, "I'm very much like him. He too was a lonely man and sat in his room most of the time."

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**NEUROPSYCHIATRIC IMITATORS
OF EPILEPSY**

—Coming to **CNS SPECTRUMS** *this spring*—

On the high wire
of mania...



FOR A SAFE, SMOOTH RETURN TO A MORE NORMAL LIFE...

Smooth, slow release of lithium carbonate for initial or maintenance treatment of mania associated with bipolar disorder

- Smoother blood levels may reduce side effects^{1,2}
 - Helps minimize peak-to-trough variations in serum lithium concentrations
 - Common side effects that may occur during initial therapy include fine hand tremor, polyuria, mild thirst, and transient and mild nausea. These side effects usually subside with continued treatment, temporary reduction of dosage, or cessation.
- Interchangeable with immediate-release lithium preparations on a mg-to-mg basis¹⁻⁴
- Film-coated tablets eliminate metallic taste concerns
- B.I.D. convenience may enhance patient compliance

LITHOBID[®]
Slow-Release Tablets, 300 mg

WARNING: Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.

Please see brief summary of prescribing information on adjacent page.

LITHOBID®

(Lithium Carbonate, USP)
Slow-Release Tablets, 300 mg

Smooth, slow release of lithium carbonate for initial or maintenance treatment of mania associated with bipolar disorder

BRIEF SUMMARY:

The following is a brief summary only. Before prescribing, see complete prescribing information in LITHOBID® Slow-Release Tablets product labeling.

WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy (see DOSAGE AND ADMINISTRATION).

INDICATIONS:

Lithium is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

Typical symptoms: of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1 to 3 weeks.

WARNINGS:

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation, dehydration, sodium depletion, and to patients receiving diuretics, or angiotensin converting enzyme (ACE) inhibitors, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued. Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal function and morphologic changes and their association with lithium therapy have not been established.

Kidney function should be assessed prior to and during lithium therapy. Routine urinalysis and other tests may be used to evaluate tubular function (e.g., urine specific gravity or osmolality following a period of water deprivation, or 24-hour urine volume) and glomerular function (e.g., serum creatinine or creatinine clearance). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for reevaluation of treatment.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic, most notably haloperidol. In some instances, the syndrome was followed by irreversible brain damage. Because of possible causal relationship between these events and the concomitant administration of lithium and neuroleptic drugs, patients receiving such combined therapy or patients with organic brain syndrome or other CNS impairment should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as Neuroleptic Malignant Syndrome (NMS).

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to the therapeutic concentrations (see DOSAGE AND ADMINISTRATION).

Outpatients and their families should be warned that the patient must discontinue lithium therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

Usage in Pregnancy: Adverse effects on nidation in rats, embryo viability in mice, and metabolism in vitro of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palate in mice.

In humans, lithium may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised by their physician of the potential hazard to the fetus.

Usage in Nursing Mothers: Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazard to the child. Signs and symptoms of lithium toxicity such as hypertonia, hyperthermia, cyanosis and ECG changes have been reported in some infants.

Usage in Children: Since the safety and effectiveness of lithium in children under 12 years of age has not been established, its use in such patients is not recommended at this time.

There has been a report of transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.

PRECAUTIONS:

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see DOSAGE AND ADMINISTRATION).

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The elimination half-life of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2500-3500 mL) at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.

In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing thyroid disorders do not necessarily constitute a contraindication to lithium treatment. Where hypothyroidism preexists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters and/or adjustment of lithium doses, if any. If hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

In general, the concomitant use of diuretics or angiotensin converting enzyme (ACE) inhibitors with lithium carbonate should be avoided. In those cases where concomitant use is necessary extreme caution is advised since sodium loss from these drugs may reduce the renal clearance of lithium resulting in increased serum lithium concentrations with the risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium serum concentrations is recommended. See WARNINGS for additional caution information.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations and alkalinizing agents such as sodium bicarbonate.

Concomitant extended use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism. Indomethacin and piroxicam have been reported to significantly increase steady state serum lithium concentrations. In some cases lithium toxicity has resulted from such interactions. There is also some evidence that other nonsteroidal, anti-inflammatory agents may have a similar effect. When such combinations are used, increased serum lithium concentrations monitoring is recommended.

LITHOBID® (Lithium Carbonate, USP) Slow-Release Tablets, 300 mg

Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea and/or tinnitus. Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

Concurrent use of fluoxetine with lithium has resulted in both increased and decreased serum lithium concentrations. Patients receiving such combined therapy should be monitored closely.

Lithium may impair mental and/or physical abilities. Patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

Usage in Pregnancy: Pregnancy Category D (see WARNINGS).

Usage in Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from lithium, 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 (see WARNINGS).

Usage in Children: Safety and effectiveness in children below the age of 12 have not been established (see WARNINGS).

Usage in the Elderly: Elderly patients often require lower lithium dosages to achieve therapeutic serum concentrations. They may also exhibit adverse reactions at serum concentrations ordinarily tolerated by younger patients. Additionally, patients with renal impairment may also require lower lithium doses (see WARNINGS).

ADVERSE REACTIONS:

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations and to individual patient sensitivity to lithium. They generally occur more frequently and with greater severity at higher concentrations.

Adverse reactions may be encountered at serum lithium concentrations below 1.5 mEq/L. Mild to moderate adverse reactions may occur at concentrations from 1.5-2.5 mEq/L, and moderate to severe reactions may be seen at concentrations from 2.0 mEq/L and above.

Fine hand tremor, polyuria and mild thirst may occur during initial therapy for the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration.

These side effects usually subside with continued treatment or with a temporary reduction or cessation of dosage. If persistent, a cessation of lithium therapy may be required. Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium concentrations below 2.0 mEq/L. At higher concentrations giddiness, ataxia, blurred vision, tinnitus and a large output of dilute urine may be seen. Serum lithium concentrations above 3.0 mEq/L may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium concentrations should not be permitted to exceed 2.0 mEq/L during the acute treatment phase.

The following reactions have been reported and appear to be related to serum lithium concentrations, including concentrations within the therapeutic range:

Central Nervous System: tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreoathetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes. Cases of Pseudotumor Cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs. **Cardiovascular:** cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope); **Gastrointestinal:** anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion; **Genitourinary:** glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst and polydipsia; **Dermatologic:** drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angiodema; **Autonomic Nervous System:** blurred vision, dry mouth, impotence/sexual dysfunction; **Thyroid Abnormalities:** euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T₃ and T₄. ¹³¹Iodine uptake may be elevated (see PRECAUTIONS); Paradoxically, rare cases of hyperthyroidism have been reported. **EEG Changes:** diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm. **EKG Changes:** reversible flattening, isoelectricity or inversion of T-waves. **Miscellaneous:** Fatigue, lethargy, transient scototoma, exophthalmos, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, albuminuria, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, and dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypothyroidism which persist after lithium discontinuation have been received.

A few reports have been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of starting lithium treatment. The mechanism through which these symptoms (resembling Raynaud's Syndrome) developed is not known. Recovery followed discontinuance.

OVERDOSAGE:

The toxic concentrations for lithium (≥1.5 mEq/L) are close to the therapeutic concentrations (0.6-1.2 mEq/L). It is therefore important that patients and their families be cautioned to watch for early toxic symptoms and to discontinue the drug and inform the physician should they occur. (Toxic symptoms are listed in detail under ADVERSE REACTIONS).

Treatment: No specific antidote for lithium poisoning is known. Treatment is supportive. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient.

Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance and 3) regulation of kidney functioning. Urea, mannitol, and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. However, patient recovery may be slow.

Infection prophylaxis, regular chest X-rays, and preservation of adequate respiration are essential.

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References: 1. Grof P, MacCrimmon D, Saxena B, et al. Bioavailability and side effects of different lithium carbonate products. *Neuropsychobiology*. 1976;2:313-323. 2. Shaw DM, Hewland R, Johnson AL, et al. Comparison of serum levels of two sustained-release preparations of lithium carbonate. *Curr Med Res Opin*. 1974;2:90-94. 3. Kirkwood CK, Wilson SK, Hayes PE, et al. Single-dose bioavailability of two extended-release lithium carbonate products. *Am J Hosp Pharm*. 1994;51:486-489. 4. Cooper TB, Simpson GM, Lee JH, Bergner P-EE. Evaluation of a slow-release lithium carbonate formulation. *Am J Psychiatry*. 1978;135(8):917-922.