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CNS SPECTRUMS™

The International Journal of Neuropsychiatric Medicine

Reflections on the Future of Neuroscience

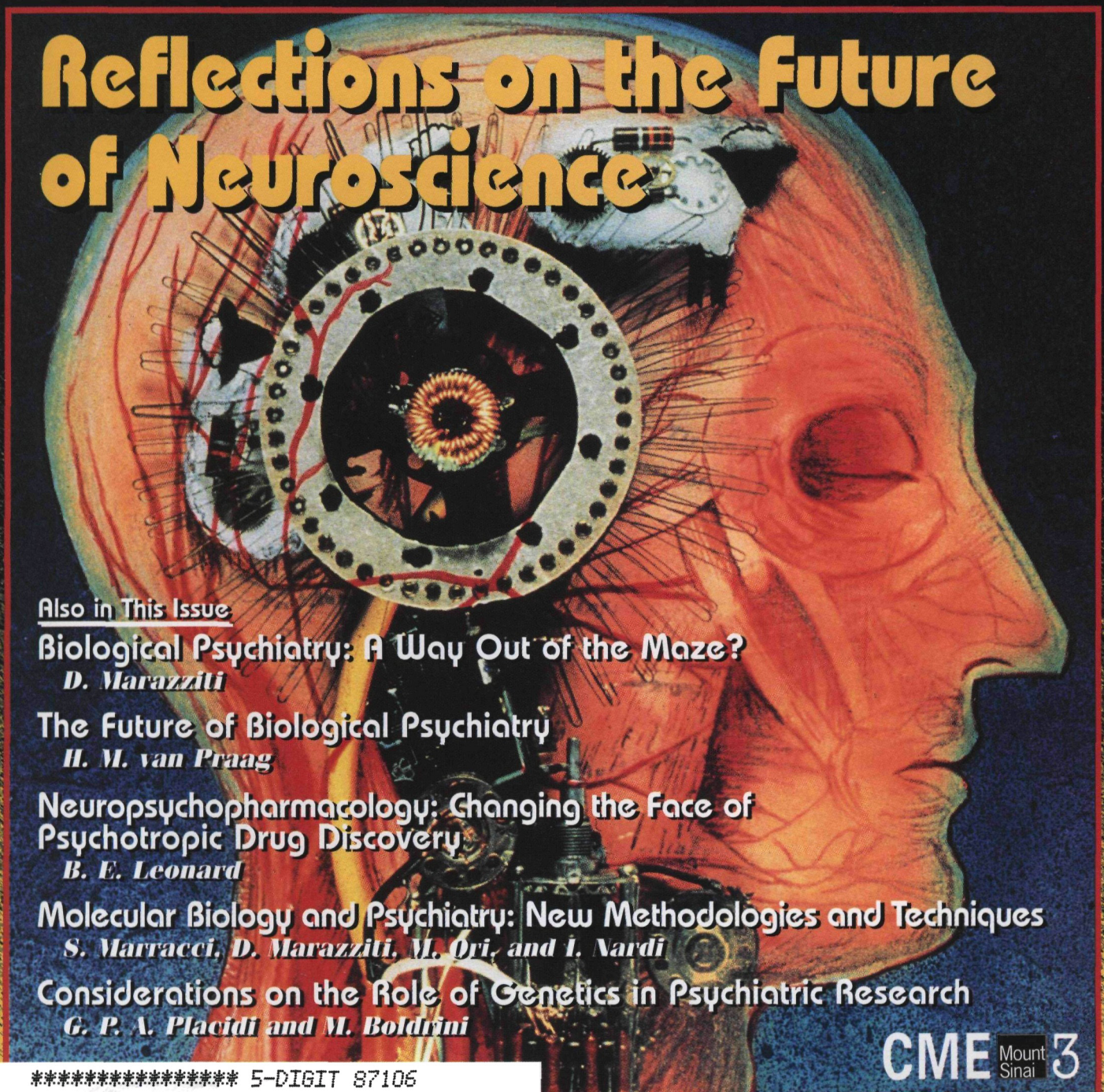

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Photo Essay Is it or is it not tenable to hold the viewpoint that it is possible to discover fully how the brain functions and dysfunctions? This issue of *CNS Spectrums* deals with some of the approaches used in biological psychiatry, which can provide state-of-the-art perspectives on the various disciplines, and give an idea of future developments.

Articles Inside.

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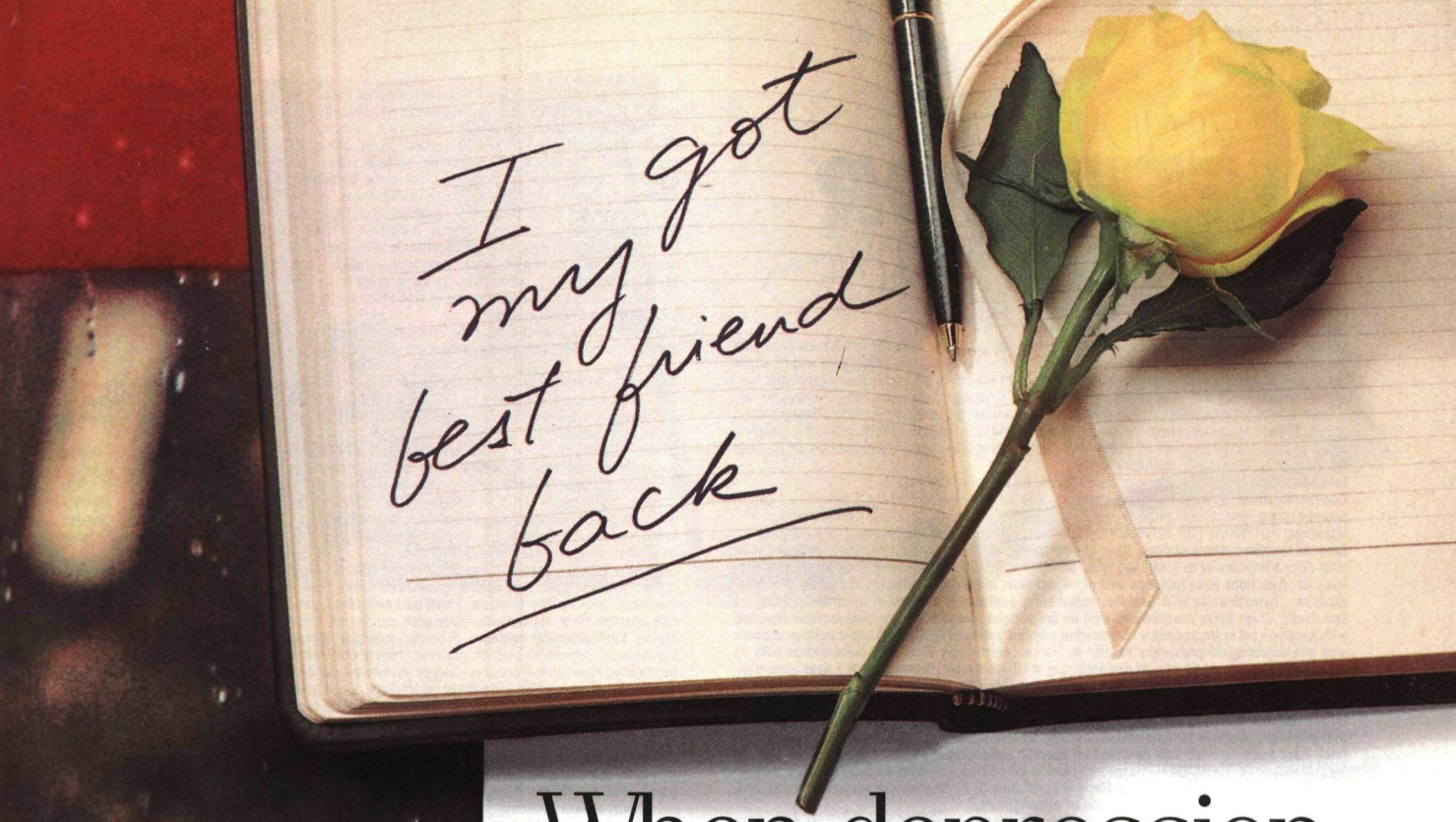

When depression is complicated by fear,

drug-drug interaction can be a treatment concern. Antidepressants that compete with benzodiazepines or other anxiolytics 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 back together again and help restore the days without sadness.

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VENLAFAXINE HCl
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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 antidepressants/MAOI therapy.**

SUSTAINED HYPERTENSION—Effexor treatment is associated with dose-related sustained increases in supine diastolic blood pressure. Regular monitoring of blood pressure is recommended, and, when appropriate, consider dose reduction or discontinuation.

Precautions: GENERAL—*Anxiety and Insomnia:* Anxiety, nervousness, and insomnia have been reported in short-term studies.

Changes in Appetite/Weight: Anorexia has been reported in short-term studies, and a dose-dependent weight loss has been reported in patients taking Effexor for several weeks.

Activation of Mania/Hypomania: Hypomania or mania has been reported; as with all antidepressants, use cautiously in patients with a history of mania.

Seizures: Seizures were reported in premarketing testing (0.26%). Use cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

Suicide: The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Closely supervise high-risk patients during initial drug therapy. Write Effexor prescriptions for the smallest quantity consistent with good patient management to reduce risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with Effexor in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. In patients with renal impairment (GFR=10-70mL/min) or liver cirrhosis, clearance of venlafaxine and its active metabolite were decreased, resulting in prolonged elimination half-lives. A lower dose may be necessary; use with caution in such patients.

INFORMATION FOR PATIENTS—Clinical studies revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that Effexor does not adversely affect their ability to engage in such activities. Tell patients to 1) notify their physician if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) inform physician about other medications they are taking or plan to take; 3) avoid alcohol while taking Effexor; 4) notify their physician if they develop a rash, hives, or related allergic phenomena.

DRUG INTERACTIONS—*Cimetidine*: Use caution when administering Effexor with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. *Drugs Inhibiting Cytochrome $P_{450}IID_6$ Metabolism*: *In vitro*, venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome $P_{450}IID_6$. Therefore drugs inhibiting this isoenzyme could potentially increase plasma concentrations of venlafaxine and decrease concentrations of ODV. *Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro*, venlafaxine is a relatively weak inhibitor of this isoenzyme; clinical significance is unknown. *Monoamine Oxidase Inhibitors*: See **"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 (≥1%) associated with discontinuation and considered to be drug-related included: somnolence, insomnia, dizziness, nervousness, dry mouth, anxiety, nausea, abnormal ejaculation (male), headache, asthenia, and sweating.

INCIDENCE IN CONTROLLED TRIALS—*Commonly Observed Adverse Events in Controlled Clinical Trials*: The most commonly observed adverse events associated with the use of Effexor (incidence of 5% or greater and incidence for Effexor at least twice that for placebo): asthenia (12% vs. 6%), sweating (12% vs. 3%), nausea (37% vs. 11%), constipation (15% vs. 7%), anorexia (11% vs. 2%), vomiting (6% vs. 2%), somnolence (23% vs. 9%), dry mouth (22% vs. 11%), dizziness (19% vs. 7%), nervousness (13% vs. 6%), anxiety (6% vs. 3%), tremor (5% vs. 1%), blurred vision (6% vs. 2%), abnormal ejaculation/orgasm male (12% vs. <1%), and male impotence (6% vs. <1%).

Adverse Events Occurring at an Incidence of 1% or More Among Effexor-Treated Patients: The following occurred in 4- to 8- week placebo-controlled trials, with doses of 75 to 375 mg/day, at a frequency of 1% or more. This includes patients with at least one episode of an event at some time during treatment. **Body as a Whole:** headache, asthenia, infection, chills, chest pain, trauma. **Cardiovascular:** vasodilatation, increased blood pressure/hypertension, tachycardia, postural hypotension. **Dermatological:** sweating, rash, pruritus. **Gastrointestinal:** nausea, constipation, anorexia, diarrhea, vomiting, dyspepsia, flatulence. **Metabolic:** weight loss. **Nervous System:** somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, tremor, abnormal dreams, hypertonia, paresthesia, libido decreased, agitation, confusion, thinking abnormal, depersonalization, depression, urinary retention, twitching. **Respiration:** yawn. **Special Senses:** blurred vision, taste perversion, tinnitus, mydriasis. **Urogenital System:** abnormal ejaculation/orgasm, impotence, urinary frequency, urination impaired, orgasm disturbance, menstrual disorder.

Studies indicate a dose dependency for some of the more common adverse events associated with Effexor use. There also was evidence of adaptation to some adverse events with continued Effexor therapy over a 6-week period.

Vital Sign Changes: In clinical trials, Effexor was associated with a mean increase in pulse rate of about 3 beats/min, and a dose-dependent increase in mean diastolic blood pressure of 0.7 to 2.5 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 ulcer, mouth ulceration; *Rare*: cheilitis, cholecystitis, cholelithiasis, hematemesis, gum hemorrhage, hepatitis, ileitis, jaundice, oral moniliasis, intestinal obstruction, proctitis, increased salivation, soft stools, tongue discoloration, esophageal ulcer, peptic ulcer syndrome. **Endocrine system** - *Rare*: goiter, hyperthyroidism, hypothyroidism. **Hemic and lymphatic system** - *Frequent*: ecchymosis; *Infrequent*: anemia, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, thrombocythemia, thrombocytopenia, WBC abnormal; *Rare*: basophilia, cyanosis, eosinophilia, erythrocytes abnormal. **Metabolic and nutritional** - *Frequent*: peripheral edema, weight gain; *Infrequent*: alkaline phosphatase increased, creatinine increased, diabetes mellitus, edema, glycosuria, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; *Rare*: alcohol intolerance, bilirubinemia, BUN increased, gout, hemochromatosis, hyperkalemia, hyperphosphatemia, hypoglycemic reaction, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia. **Musculoskeletal system** - *Infrequent*: arthritis, arthrosis, bone pain, bone spurs, bursitis, joint disorder, myasthenia, tenosynovitis; *Rare*: osteoporosis. **Nervous system** - *Frequent*: emotional lability, trismus, vertigo; *Infrequent*: apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypertonia, hypotonia, incoordination, libido increased, 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, lichenoid dermatitis, hair discoloration, eczema, furunculosis, hirsutism, skin hypertrophy, leukoderma, psoriasis, pustular rash, vesiculobullious rash. **Special senses** - *Frequent*: abnormal vision, ear pain; *Infrequent*: cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, otitis media, parosmia, photophobia, subconjunctival hemorrhage, taste loss, visual field defect; *Rare*: blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, scleritis. **Urogenital system** - *Frequent*: anorgasmia, dysuria, hematuria, metrorrhagia*, urination impaired, vaginitis*; *Infrequent*: albuminuria, amenorrhea*, kidney calculus, cystitis, leukorrhea, menorrhagia*, nocturia, bladder pain, breast pain, kidney pain, polyuria, prostatitis*, pyelonephritis, pyuria, urinary incontinence, urinary urgency, uterine fibroids enlarged*, uterine hemorrhage*, vaginal hemorrhage*, vaginal moniliasis*; *Rare*: abortion*, breast engorgement, breast enlargement, calcium crystalluria, female lactation*, hypomenorrhea*, menopause*, prolonged erection*, uterine spasm*. (*Based on the number of male or female patients as appropriate.)

Drug Abuse and Dependence: CONTROLLED SUBSTANCE CLASS—Effexor is not a controlled substance. In a retrospective survey of new events occurring during taper or following discontinuation, the following occurred at an incidence of ≥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 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 Annals.* 1996;26:342-350. **4.** EFFEXOR® (venlafaxine HCl) 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 and melancholia. *J Clin Psychiatry.* 1995;56:450-458.

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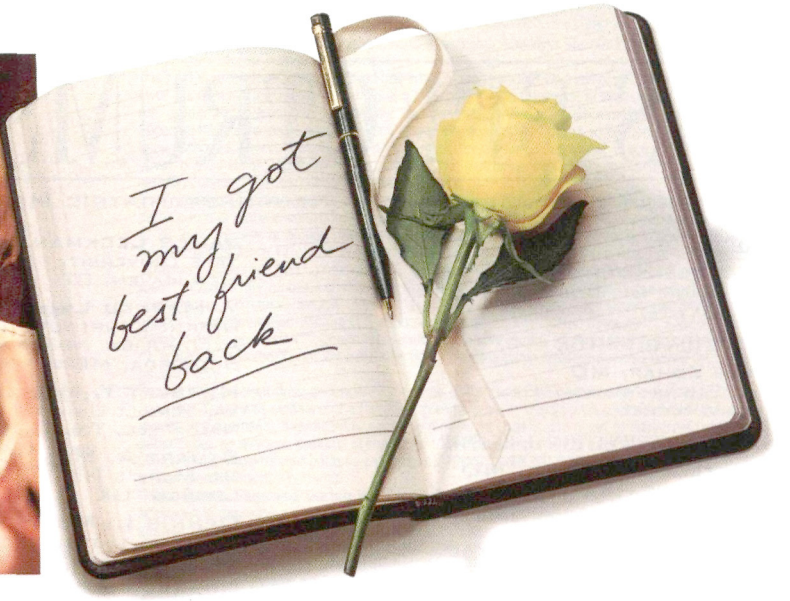

- Efficacy clearly demonstrated in depressed outpatients[6]
- Effective treatment in hospitalized depressed patients with major depressive disorder and melancholia meeting DSM-III-R™ criteria[7]

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.

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

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ONCE-DAILY

PAXIL®

PAROXETINE HCl

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 $P_{450}IID_6$ (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines such as thioridazine; Type 1C antiarrhythmics such as propafenone, fecainide 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 $IIIA_4$ substrates (astemizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent than ketoconazole, a potent $IIIA_4$ 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 $IIIA_4$ substrates, paroxetine's inhibition of $IIIA_4$ 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 reticulum 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/m^2 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/m^2 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 (16% 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 ischemia, 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:** *infrequent:* 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:** *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia. **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, hypercholesteremia, 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, hypertonia, hypesthesia, 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, photosensitivity, seborrhea, skin discoloration, skin hypertrophy, skin melonoma, 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, urolith, 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, incrementations of dose, drug-seeking behavior).

BRS–PX:L12

SB SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

JANSSEN PHARMACEUTICA RESEARCH FOUNDATION
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CNS SPECTRUMS
THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE
VOL•2 – NO•9
OCTOBER 1997

FEATURE ARTICLES

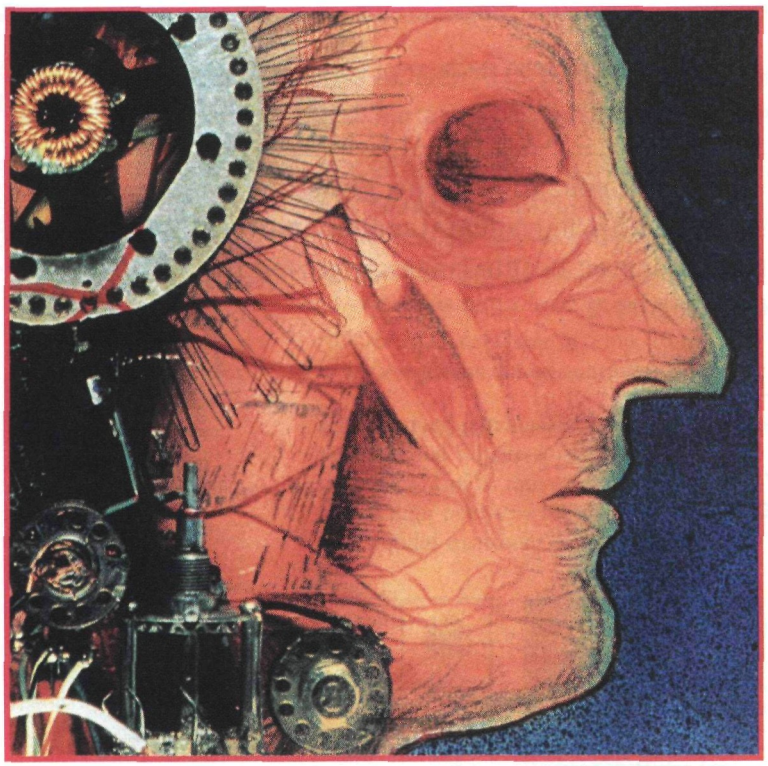

PHOTO ESSAY

Guest editor Donatella Marazziti asks, "is it or is it not tenable to hold the viewpoint that it is possible to discover fully how the brain functions and dysfunctions?"

In an attempt to address these questions, this issue of *CNS Spectrums* contains articles dealing with some of the approaches used in biological psychiatry, which can provide state-of-the-art perspectives on the various disciplines and give an idea of what can be predicted in terms of future developments.

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DEPARTMENTS/MONTHLY COLUMNS

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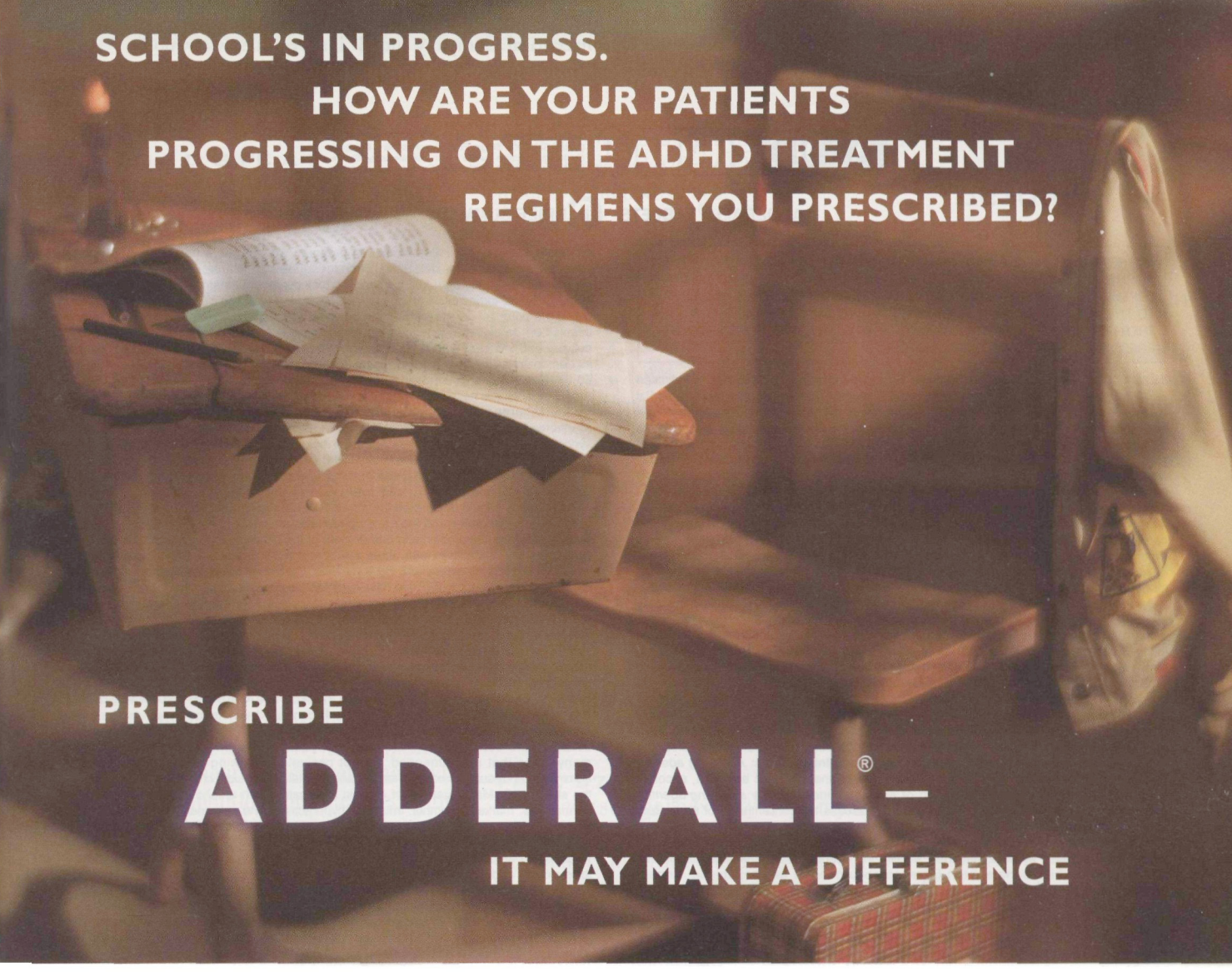


As children settle into the routine of a structured classroom environment and teachers become more familiar with individual capabilities and behavior patterns, potential problem behavior and academic underachievement may become more apparent. A change in medication may be warranted to optimize individual ADHD treatment plans.

The ADDERALL® (mixed salts of a single-entity amphetamine product) Formulation and Starting Dosage Frequency of One to Two Times Per Day[1] May Make a Difference

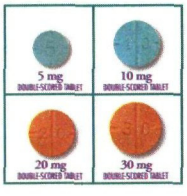
ADDERALL is the only ADHD product available to contain both dextro (*d*) and levo (*l*) amphetamine

ADDERALL usage data (n=611) indicate that **OVER 90% OF PATIENTS** can be maintained on a dosage frequency of one to two times per day[2]*

ADDERALL usage data (n=611) indicate that most patients, across a range of doses, do not experience adverse events with a frequency of more than 1%[2]*

ADDERALL is available in 5 mg, 10 mg, 20 mg, and **NEW 30 mg** double-scored tablets which allows you to achieve precise dosage correlation with individual therapeutic needs in a single prescription

As with most psychostimulants indicated for ADHD, the possibility of growth suppression and the potential for precipitating motor tics and Tourette's syndrome exists with ADDERALL treatment, and in rare cases exacerbations of psychosis have been reported. Since amphetamines have a high potential for abuse, ADDERALL should only be prescribed as part of an overall multimodal treatment program for ADHD with close physician supervision.



ADDERALL® C II

5 mg, 10 mg, 20 mg & 30 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

*Thirty-four patients receiving greater than 40 mg per day were excluded from this analysis.

Please see reverse side for references and brief summary of prescribing information.

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REFERENCES: 1. ADDERALL Package Insert, Richwood Pharmaceutical Company Inc. **2.** Data on file, Richwood Pharmaceutical Company Inc. Analysis of open-label data collected from March 1995 through February 1996.

ADDERALL® XR

5 mg, 10 mg, 20 mg & 30 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

ADDERALL® TABLETS ADDERALL® XR BRIEF SUMMARY

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

INDICATIONS: Attention Deficit Disorder with Hyperactivity: ADDERALL is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted. **In Narcolepsy: CONTRAINDICATIONS:** Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result). **WARNINGS:** Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment. **Usage in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing. **PRECAUTIONS: General:** Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. **Information for Patients:** Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly. **Drug Interactions:** *Acidifying agents* - Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines. *Urinary acidifying agents* - (ammonium chloride, sodium acid phosphate, etc.) Increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines. *Adrenergic blockers* - Adrenergic blockers are inhibited by amphetamines. *Alkalinizing agents* - Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines. *Antidepressants, tricyclic* - Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. *MAO inhibitors* - MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results. *Antihistamines* - Amphetamines may counteract the sedative effect of antihistamines. *Antihypertensives* - Amphetamines may antagonize the hypotensive effects of antihypertensives. *Chlorpromazine* - Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning. *Ethosuximide* - Amphetamines may delay intestinal absorption of ethosuximide. *Haloperidol* - Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines. *Lithium carbonate* - The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate. *Meperidine* - Amphetamines potentiate the analgesic effect of meperidine. *Methenamine therapy* - Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy. *Norepinephrine* - Amphetamines enhance the adrenergic effect of norepinephrine. *Phenobarbital* - Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action. *Phenytoin* - Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action. *Propoxyphene* - In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. *Veratrum alkaloids* - Amphetamines inhibit the hypotensive effect of veratrum alkaloids. **Drug/Laboratory Test Interactions:** • Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. • Amphetamines may interfere with urinary steroid determinations. **Carcinogenesis/Mutagenesis:** Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed. **Pregnancy - Teratogenic Effects:** Pregnancy Category C. Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude. **Pediatric Use:** Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE. Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications. Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated. **ADVERSE REACTIONS: Cardiovascular:** Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. **Central Nervous System:** Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome. **Gastrointestinal:** Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. **Allergic:** Urticaria. **Endocrine:** Impotence, changes in libido. **DRUG ABUSE AND DEPENDENCE:** Dextroamphetamine sulfate is a Schedule II controlled substance. Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines. **OVERDOSAGE:** Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal. In rats, the oral LD50 of dextroamphetamine sulfate is 96.8 mg/kg. **Symptoms:** Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomolysis. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma. **Treatment:** Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine (Regitine®, CIBA) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication. **DOSAGE AND ADMINISTRATION:** Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia. **Attention Deficit Disorder with Hyperactivity:** Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. **Narcolepsy:** Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response. Narcolepsy seldom occurs in children under 12 years of age; however, when it does dextroamphetamine sulfate, may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. **CAUTION:** Federal law prohibits dispensing without prescription.

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