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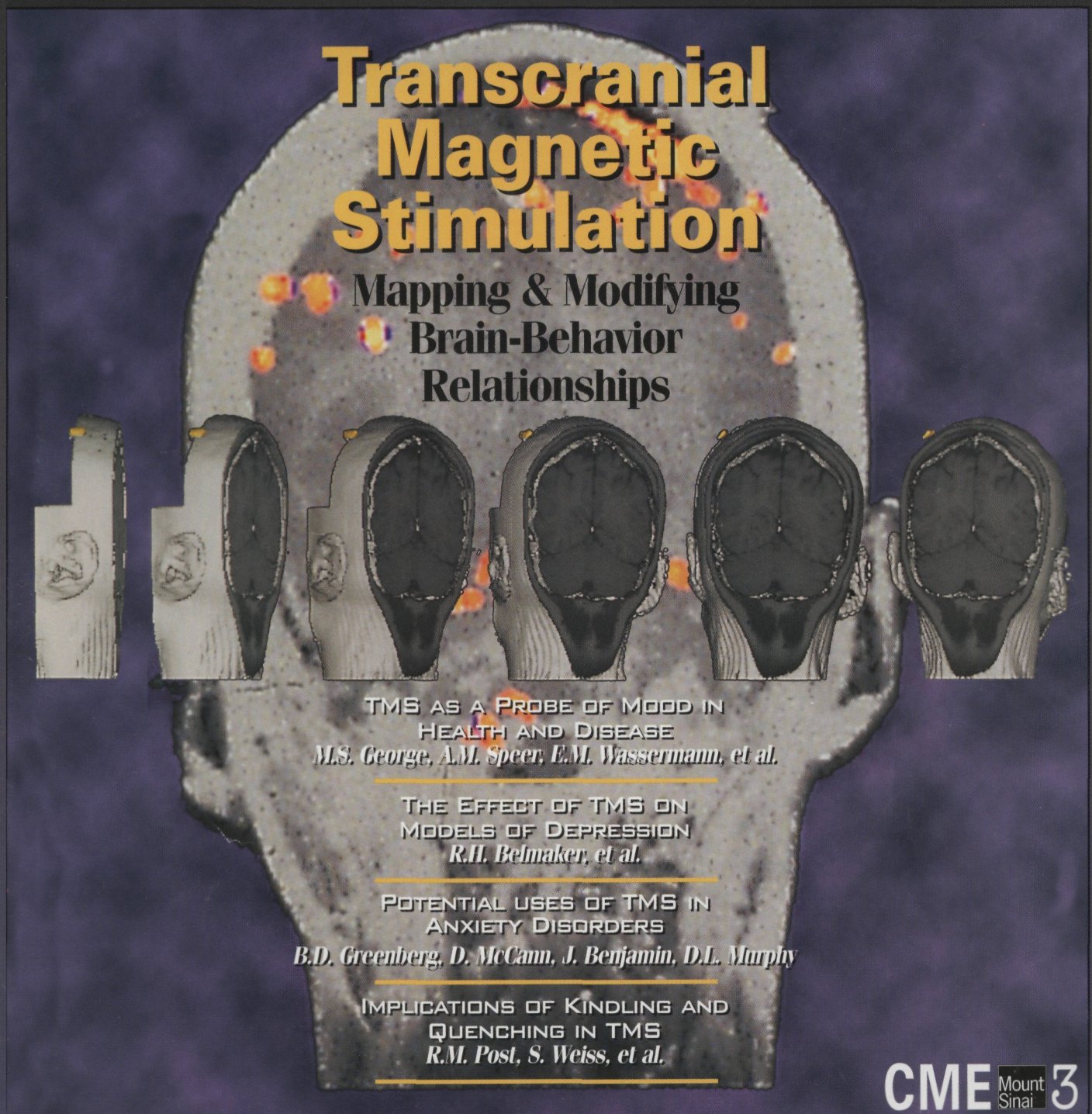
CNS SPECTRUMS™

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE



Transcranial Magnetic Stimulation

Mapping & Modifying Brain-Behavior Relationships

CME Mount Sinai 3

PHOTO ESSAY

Six Degrees of Separation: Recent advances in functional neuroimaging have improved several models of how the brain regulates emotion. TMS, with the ability to stimulate or temporarily impair brain regions, is a powerful tool for directly testing these theories of the brain basis of mood and anxiety brain regulation. ARTICLES INSIDE.

https://doi.org/10.1017/S1092852900004387 Published online by Cambridge University Press

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

EFFEXOR®

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 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 physicians if they develop a rash, hives, or related allergic phenomena.

DRUG INTERACTIONS—*Cimetidine*: Use caution when administering Effexor with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. *Drugs Inhibiting Cytochrome $P_{450}IID_6$ Metabolism*: *In vitro,* venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome $P_{450}IID_6$. Therefore drugs inhibiting this isoenzyme could potentially increase plasma concentrations of venlafaxine and decrease concentrations of ODV. *Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro,* venlafaxine is a relatively weak inhibitor of this isoenzyme; clinical significance is unknown. *Monoamine Oxidase Inhibitors*: See **"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, vesiculobullous rash. **Special senses** - *Frequent*: abnormal vision, ear pain; *Infrequent*: cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, otitis media, parosmia, photophobia, subconjunctival hemorrhage, taste loss, visual field defect; *Rare*: blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, scleritis. **Urogenital system** - *Frequent*: anorgasmia, dysuria, hematuria, metrorrhagia*, urination impaired, vaginitis*; *Infrequent*: albuminuria, amenorrhea*, kidney calculus, cystitis, leukorrhea, menorrhagia*, nocturia, bladder pain, breast pain, kidney pain, polyuria, prostatitis*, pyelonephritis, pyuria, urinary incontinence, urinary urgency, uterine fibroids enlarged*, uterine hemorrhage*, vaginal hemorrhage*, vaginal moniliasis*; *Rare*: abortion*, breast engorgement, breast enlargement, calcium crystalluria, female lactation*, hypomenorrhea*, menopause*, prolonged erection*, uterine spasm*. (*Based on the number of male or female patients as appropriate.)

Drug Abuse and Dependence: CONTROLLED SUBSTANCE CLASS—Effexor is not a controlled substance. In a retrospective survey of new events occurring during taper or following discontinuation, the following occurred at an incidence of ≥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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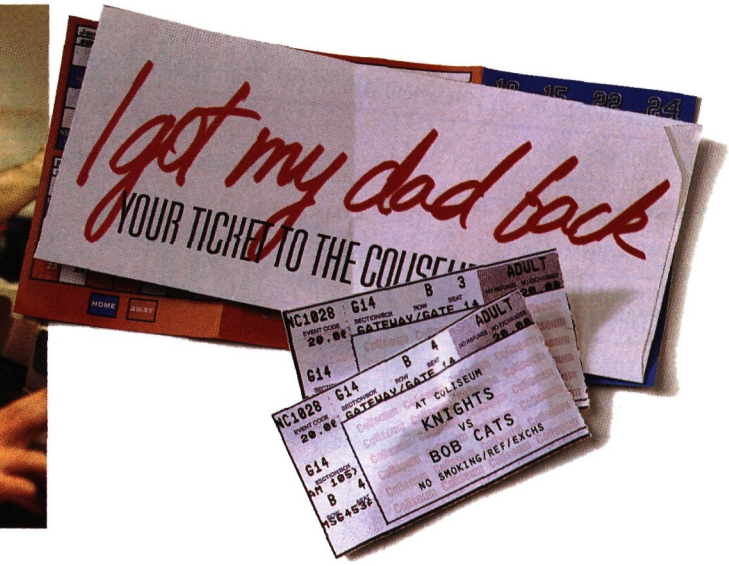

- Efficacy clearly demonstrated in depressed outpatients[6]
- Effective treatment in hospitalized depressed patients with major depressive disorder and melancholia meeting DSM-III-R™ criteria[7]

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 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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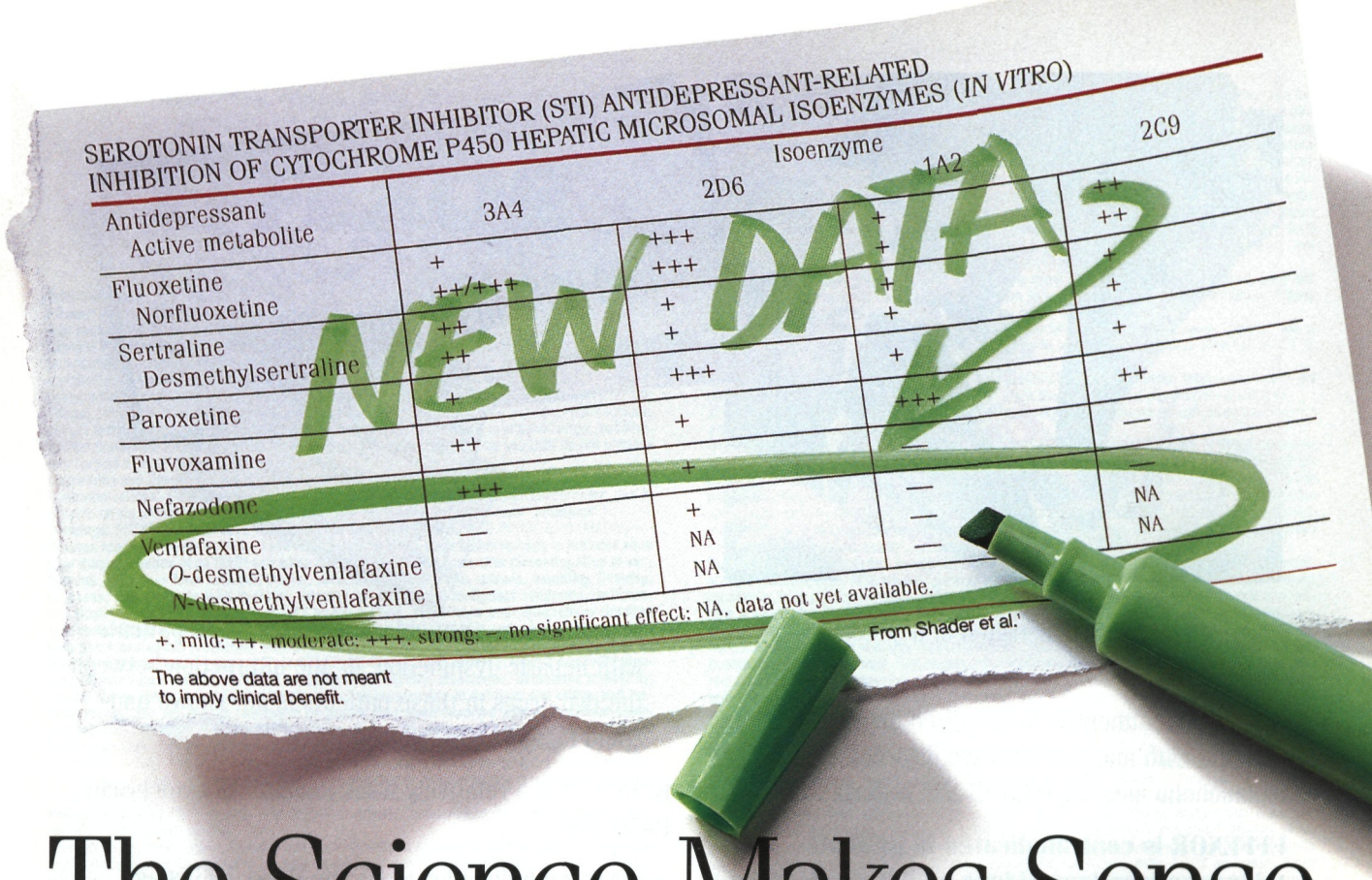

The Science Makes Sense

Drug-drug interactions are a concern in the treatment of depression.

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

Consider the cytochrome P450 (CYP) system

The cytochrome P450 system present in the liver is involved in the oxidative metabolism of numerous drugs.[2] Among the more than 30 enzymes currently recognized, the following systems—CYP2D6, CYP3A4, CYP1A2, CYP2C9, and CYP2C19—have been identified as important in the metabolism of psychoactive and other commonly prescribed drugs.[2,3] *In vitro* studies have demonstrated that venlafaxine is a relatively weak inhibitor of CYP2D6 as compared to the SSRIs and has very weak or no inhibitory potentials at CYP3A4, CYP1A2, and CYP2C9.[2,4,5] The clinical significance of these *in vitro* data is unknown.

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

Completed *in vivo* studies confirm the *in vitro* data stated previously. One study, using dextromethorphan as a clinical marker, indicated that there is a decrease in the relative risk of clinically significant interactions between EFFEXOR and drugs metabolized by CYP2D6.[6] The isoenzyme CYP2D6 is involved in the metabolism of many drugs, such as codeine, propranolol, other beta-blockers, and certain antiarrhythmic agents.[3] Other *in vivo* studies confirm that EFFEXOR has little or no potential to inhibit CYP3A4. EFFEXOR does not significantly inhibit the metabolism of alprazolam, diazepam, terfenadine, and carbamazepine, all substrates for CYP3A4.[2,4]

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

EFFEXOR is effective therapy for depressed outpatients. EFFEXOR is effective even in severely depressed patients. When considering the needs of your depressed patients who are on concomitant therapies, the science makes sense in selecting EFFEXOR as proven treatment for depression.

VENLAFAXINE HCl
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MEANS EFFECTIVE

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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.

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

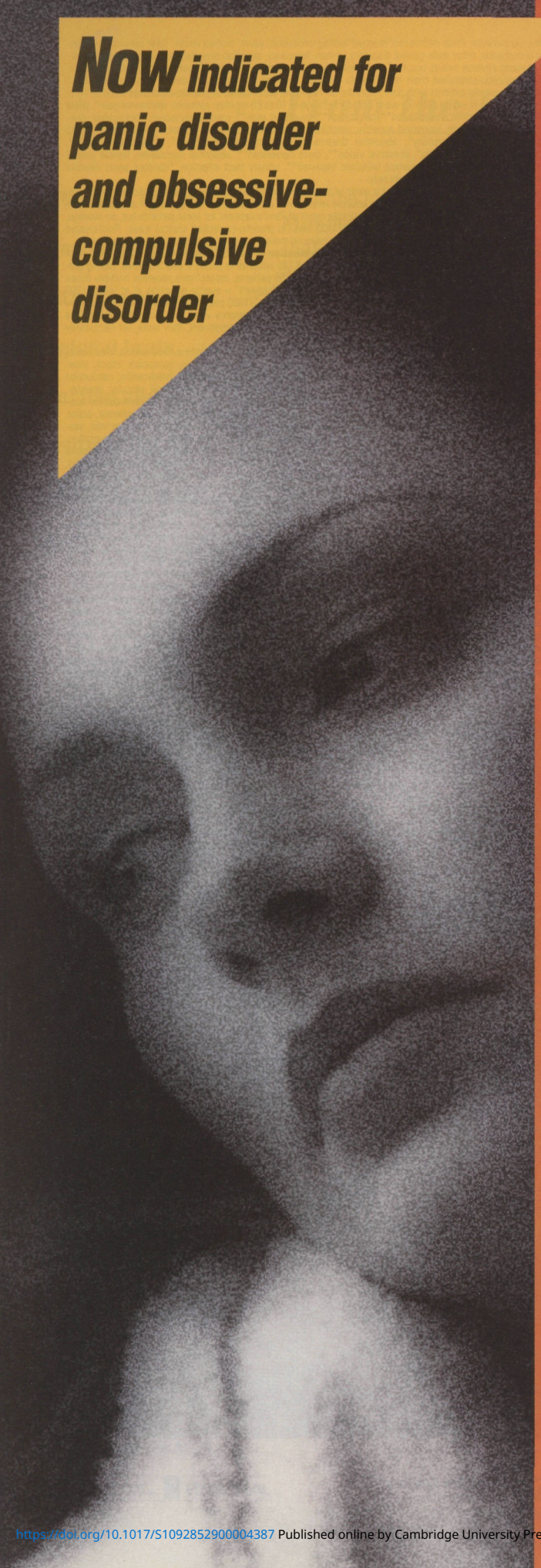
Voluntary reports of adverse events that have been received since market introduction and not listed above that may have no causal relationship with *Paxil* include–acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases 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:L11

SB SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

JANSSEN PHARMACEUTICA RESEARCH FOUNDATION



Now indicated for panic disorder and obsessive-compulsive disorder

She's anxious.

She's agitated.

She can't sleep.

She's depressed.

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

60% to 90% of depressed patients exhibit associated symptoms of anxiety such as agitation, sleep disorders, weight loss and gastrointestinal problems[5,6]

Incidence of agitation with *Paxil* is comparable to placebo (2.1% vs 1.9%); incidence of nervousness and of anxiety vs placebo is 5.2% vs 2.6% and 5.0% vs 2.9%, respectively[7]

Most common adverse events include: nausea, somnolence, asthenia, dizziness, insomnia, sweating, ejaculatory disturbance and other male genital disorders.*[7] Concomitant use of *Paxil* in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

*Incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo.

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

ONCE-DAILY

PAXIL®

PAROXETINE HCl

LIFTS DEPRESSION. LOWERS ASSOCIATED ANXIETY SYMPTOMS.

SB SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

PX7221

JANSSEN PHARMACEUTICA RESEARCH FOUNDATION

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CNS SPECTRUMS
THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE
VOL•2 – NO•1
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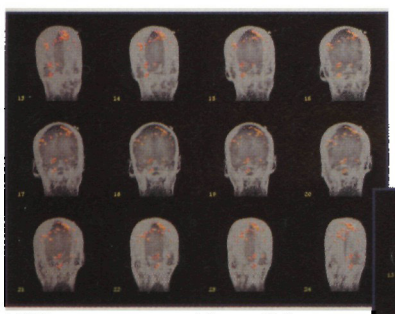
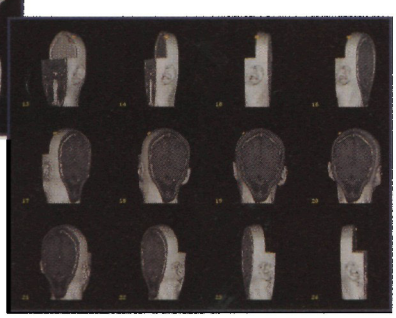
FEATURE ARTICLES





MRI images courtesy of Donna Roberts, MUSCV Functional Imaging Division, Charleston, SC.

PHOTO ESSAY:

The orange color areas on the large coronal translucent MRI scan (journal cover and images, left, this page) represent regions activated in the right motor cortex in one subject when they move their left hand. Note the activity in the motor cortex on the right side as well as areas on the same side of the movement (ipsilateral) and in the cerebellum. Thus, using echopolar Blood Oxygen Level Dependent (BOLD) fMRI, one can determine the neutral network associated with a task, in this case, moving the left hand. The small round sphere outside of the skull represents the point where, in this subject, one can place a transcranial magnetic stimulation (TMS) coil and cause the left thumb to move. These images thus show the overlap and general concordance of these two ways of determining brain-behavior relationships – conventional imaging or actually non-invasively stimulating brain regions with TMS. The solid brain renditions rotating across the middle of the cover figure show the same information in a different way.

TMS is thus a powerful new way of mapping brain-behavior relationships, and unlike conventional imaging, may even have therapeutic potential.

CNS SPECTRUMS
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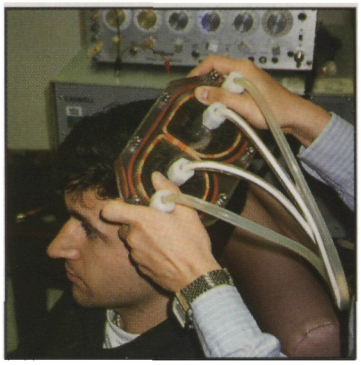
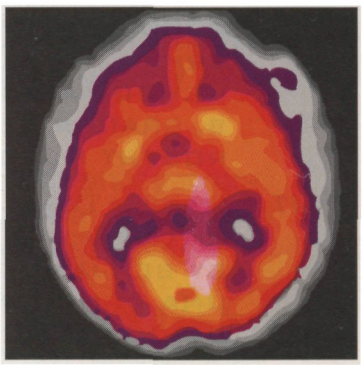
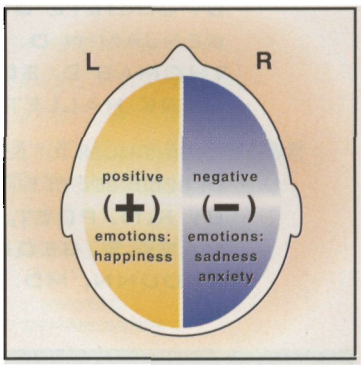
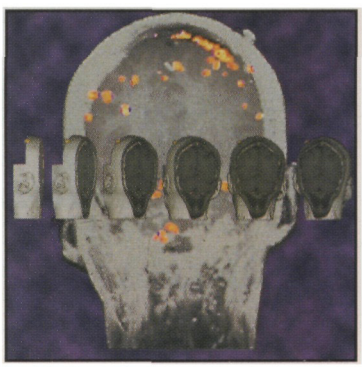
DEPARTMENTS/MONTHLY COLUMNS



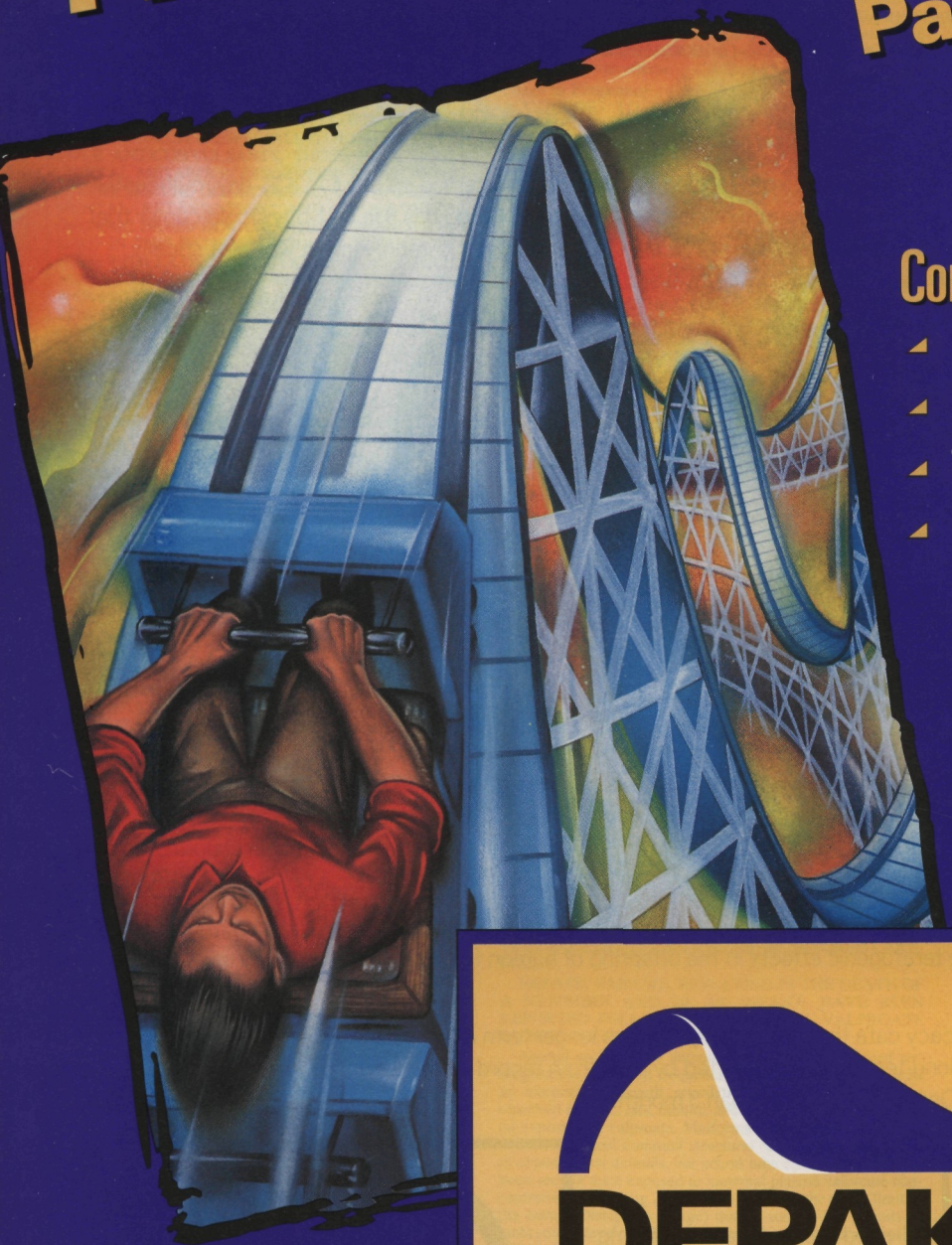






In mania associated with bipolar disorder...

First Line Treatment for your Bipolar Patients



Consider

- Efficacy
- Onset of Action
- Tolerability and Safety
- Dosing Convenience

DEPAKOTE®

DIVALPROEX SODIUM

First Line For Mania

Please see brief summary of full prescribing information.

https://doi.org/10.1017/S1092852900004387 Published online by Cambridge University Press

In mania associated with bipolar disorder, DEPAKOTE
A First Line Mood Stabilizer

Proven Effective

- Proven effective in a 21-day, double-blind, multicenter, placebo-controlled, randomized clinical trial of 179 manic patients[1,2]
- Effective in patients who were previously intolerant of or not responsive to lithium in another 21-day, double-blind, single-center, placebo-controlled, randomized clinical trial[1,2]

Onset of Action

- Changes in manic symptoms among Depakote-treated patients were observed on day 5 in a 21-day multicenter trial (n=179; patients assessed at baseline, and on days 5, 10, 15, and 21) and day 8 in a 21-day single-center trial (n=43; patients assessed at baseline and on days 8, 15, and 22); symptomatic improvement was statistically significant ($P<0.05$) on study day 10 in multicenter trial and study day 15 in single-center trial[1,2]
- Significant symptomatic improvement was maintained through completion of both studies[1,2]

Well Tolerated in Clinical Trials

- Low rate of discontinuation due to intolerance in 21-day clinical trials[1,2]
- The only adverse event in 21-day clinical trials that was reported by significantly more patients receiving Depakote compared to placebo was vomiting ($P\leq0.05$)[1,2]
- Other common adverse events vs placebo were nausea (22% vs 15%), somnolence (19% vs 12%), and dizziness (12% vs 4%)[1]

Other Safety Considerations

- Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Hepatotoxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. Patients should be monitored closely for the appearance of such symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months. Depakote should not be administered to patients with hepatic disease or significant hepatic dysfunction.
- Valproic acid may produce teratogenic effects in the offspring of human females receiving the drug during pregnancy.
- Although there are no efficacy data that specifically address longer-term antimanic treatment with Depakote, the safety of Depakote in long-term use is supported by data from record reviews involving approximately 360 patients treated with Depakote for longer than 3 months.

Convenient Dosing

- Initiate dose at 750 mg/day in divided doses; titrate by 250 mg tablets every 2 - 3 days to a clinical response or desired range of plasma concentration (trough: 50 - 125 µg/mL)[1,2]
- Maximum recommended dosage is 60 mg/kg/day[1]

DEPAKOTE®
DIVALPROEX SODIUM
First Line For Mania

Please see brief summary of full prescribing information.

Abbott Laboratories
North Chicago, IL 60064
602-731-6028A • May 1996 • Printed in U.S.A.

References: 1. Depakote package insert, Abbott Laboratories. 2. Data on file, Abbott Laboratories.

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

DEPAKOTE® Tablets

DIVALPROEX SODIUM DELAYED-RELEASE TABLETS

BOX WARNING:
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF TWO YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DEPAKOTE IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

TERATOGENICITY:
VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA), ACCORDINGLY, THE USE OF DEPAKOTE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G., MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS.

AN INFORMATION SHEET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.

CONTRAINDICATIONS
DIVALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering DEPAKOTE products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When DEPAKOTE is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia [see **PRECAUTIONS**]) may be dose-related. In a clinical trial of DEPAKOTE as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 x 10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/mL (females) or ≥ 135 µg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage In Pregnancy
ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.

OTHER CONGENITAL ANOMALIES (EG, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 µg/mL (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater to pregnant rats during organogenesis produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 µg/mL or greater (3.4 times the upper limit of the human therapeutic range or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 µg/mL (2.8 times the upper limit of the human therapeutic range).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

Hepatic Dysfunction
See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS**.

General
Because of reports of thrombocytopenia (see **WARNINGS**), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of DEPAKOTE as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 x 10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/mL (females) or ≥ 135 µg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. Asymptomatic elevations of ammonia are more common and when present require more frequent monitoring. If clinically significant symptoms occur, DEPAKOTE therapy should be modified or discontinued.

Since DEPAKOTE may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. (See **PRECAUTIONS-Drug Interactions**.)

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Suicidal ideation may be a manifestation of certain psychiatric disorders, and may persist until significant remission of symptoms occurs. Close supervision of high risk patients should accompany initial drug therapy.

Information for Patients
Since DEPAKOTE products may produce CNS depression, especially when combined with another CNS depressant (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions
Effects of Co-Administered Drugs on Valproate Clearance
Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyl transferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed:

Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The ß-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be co-administered.

Felbamate - A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 µg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to

133 µg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Rifampin - A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is co-administered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

Antacids - A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine - A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol - A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine - Cimetidine and ranitidine do not affect the clearance of valproate.

Effects of Valproate on Other Drugs

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyl transferases.

The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed:

Carbamazepine/carbamazepine-10,11-Epoxide - Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.

Clonazepam - The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam - Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide - Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine - In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate.

Phenobarbital - Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin - Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide - From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin - In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if DEPAKOTE therapy is instituted in patients taking anticoagulants.

Zidovudine - In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

Acetaminophen - Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.

Amitriptyline/Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline.

Clozapine - In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.

Lithium - Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam - Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids - Administration of a single-dose of ethinyloestradiol (50 µg)/levonorgestrel (250 µg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m^2 basis) for two years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of increase in SCE frequency is not known.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy

Pregnancy Category D: See **WARNINGS**.

Nursing Mothers

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when divalproex sodium is administered to a nursing woman.

Pediatric

The safety and effectiveness of DEPAKOTE for the treatment of acute mania has not been studied in individuals below the age of 18 years.

The basic toxicology and pathologic manifestions of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

Geriatric

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

ADVERSE REACTIONS

Mania

The incidence of treatment-emergent events has been ascertained based on combined data from two placebo-controlled clinical trials of DEPAKOTE in the treatment of manic episodes associated with bipolar disorder. The adverse events were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, DEPAKOTE, and lithium carbonate. A total of 4%, 8% and 11% of patients discontinued therapy due to intolerance in the placebo, DEPAKOTE, and lithium carbonate groups, respectively.

Table 1 summarizes those adverse events reported for patients in these trials where the incidence rate in the DEPAKOTE-treated group was greater than 5% and greater than the placebo incidence, or where the incidence in the DEPAKOTE-treated group was statistically significantly greater than the placebo group. Vomiting was the only event that was reported by significantly ($p \leq 0.05$) more patients receiving DEPAKOTE compared to placebo.

Table 1
Adverse Events Reported by > 5%
of DEPAKOTE-Treated Patients
During Placebo-Controlled Trials of Acute Mania[1]

Adverse Event	DEPAKOTE (n=89)	Placebo (n=97)
Nausea	22%	15%
Somnolence	19%	12%
Dizziness	12%	4%
Vomiting	12%	3%
Accidental injury	11%	5%
Asthenia	10%	7%
Abdominal pain	9%	8%
Dyspepsia	9%	8%
Rash	6%	3%

1 The following adverse events occurred at an equal or greater incidence for placebo than for DEPAKOTE: back pain, headache, constipation, diarrhea, tremor, and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 89 divalproex sodium-treated patients in controlled clinical trials:

Body as a Whole: Chest pain, chills, chills and fever, fever, neck pain, neck rigidity.

Cardiovascular System: Hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation.

Digestive System: Anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess.

Hemic and Lymphatic System: Ecchymosis.

Metabolic and Nutritional Disorders: Edema, peripheral edema.

Musculoskeletal System: Arthralgia, arthrosis, leg cramps, twitching.

Nervous System: Abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo.

Respiratory System: Dyspnea, rhinitis.

Skin and Appendages: Alopecia, discoid lupus erythematosis, dry skin, furunculosis, maculopapular rash, seborrhea.

Special Senses: Amblyopia, conjunctivitis, deafness, dry eyes, ear pain, eye pain, tinnitus.

Urogenital System: Dysmenorrhea, dysuria, urinary incontinence.

Other Patient Populations

Adverse events that have been reported with valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, and incoordination. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriate plasma levels; all patients recovered after the drug was withdrawn.

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see **PRECAUTIONS - General** and **Drug Interactions**). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate defi-