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CNS SPECTRUMS™

The International Journal of Neuropsychiatric Medicine

New Research: Functional Imaging, Phylogenetic Models, and Pharmacoeconomics

In This Issue

Photo Essay This microscope illustrates the current presentation of original research on quality-of-life and economic costs of psychiatric illnesses, how functional imaging correlates with facial emotion recognition, the phylogenetic considerations of contrasting theoretical models of OCD, and the novel uses of anticonvulsant medications.

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LUVOX® (fluvoxamine maleate) 25 mg TABLETS, 50 mg and 100 mg SCORED TABLETS

Brief Summary of prescribing information (based on 8E1252 Rev 3/97)

INDICATIONS AND USAGE

LUVOX Tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R. Obsessive Compulsive Disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

CONTRAINDICATIONS

Co-administration of terfenadine, astemizole, or cisapride with LUVOX Tablets is contraindicated (see WARNINGS and PRECAUTIONS).

LUVOX Tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOIs), there have been reports of serious, sometimes fatal, reactions. Therefore, it is recommended that LUVOX® Tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. In addition, after stopping LUVOX® Tablets, at least 2 weeks should be allowed before starting a MAOI.

Terfenadine, astemizole and cisapride are all metabolized by the cytochrome P450IIIA4 isoenzyme. Increased plasma concentrations of terfenadine, astemizole and cisapride cause QT prolongation and have been associated with torsades de points-type ventricular tachycardia, sometimes fatal. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine, astemizole, or cisapride.

Other Potentially Important Drug Interactions

(Also see PRECAUTIONS - Drug Interactions) ***Benzodiazepines:*** Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine. ***Alprazolam-*** When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{ss}, T-) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX Tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX Tablets. ***Diazepam-*** The co-administration of LUVOX Tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration. Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam is derived from a study in which healthy volunteers taking 150 mg/day of fluvoxamine were administered a single oral dose of 10 mg of diazepam. In these subjects (n=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level that was too low to measure over the course of the 2 week long study. It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses. Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered. ***Theophylline:*** The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately 3-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX Tablets. ***Warfarin:*** When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX Tablets.

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX Tablets should be used cautiously in patients with a history of mania. ***Seizures:*** During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. LUVOX Tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures. ***Suicide:*** The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for LUVOX Tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. ***Use in Patients with Concomitant Illness:*** Closely monitored clinical experience with LUVOX Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism. LUVOX Tablets have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes. In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. LUVOX Tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe LUVOX Tablets: ***Interference with Cognitive or Motor Performance:*** Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX Tablets therapy does not adversely affect their ability to engage in such activities. ***Pregnancy:*** Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with LUVOX Tablets. ***Nursing:*** Patients receiving LUVOX Tablets should be advised to notify their physicians if they are breast feeding an infant. (See PRECAUTIONS - Nursing Mothers.) ***Concomitant Medication:*** Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX Tablets. ***Alcohol:*** As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX Tablets. ***Allergic Reactions:*** Patients should be advised to notify their physicians if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX Tablets.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised. ***Potential interactions with drugs that inhibit or are Metabolized by Cytochrome P450 Isozymes:*** Based on a finding of substantial interactions of fluvoxamine with certain drugs and limited *in vitro* data for the IIIA4 isoenzyme, *it appears that fluvoxamine inhibits isoenzymes that are known to be involved in the metabolism of drugs such as warfarin, theophylline and* propranolol. A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine, astemizole cisapride, warfarin, theophylline, certain benzodiazepines and phenytoin. If LUVOX® Tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady state conditions are reached. Please see complete prescribing information for recommendations regarding CNS drugs such as monoamine oxidase inhibitors, alprazolam, diazepam, lorazepam, lithium, tryptophan, clozapine, alcohol, tricyclic antidepressants, carbamazepine, methadone; and other drugs such as theophylline, propranolol and other beta-blockers, warfarin, digoxin, and diltiazem. ***Effects of Smoking on Fluvoxamine Metabolism:*** Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers. ***Electroconvulsive Therapy (ECT):*** There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine maleate.There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis. ***Mutagenesis:*** No evidence of mutagenic potential was observed in a mouse micronucleus test, an in vitro chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation. ***Impairment of Fertility:*** In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate, (approximately 2 times the maximum human daily dose on a mg/m^2 basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

Pregnancy

Teratogenic Effects - Pregnancy Category C: In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m^2 basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m^2 basis.) While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of fluvoxamine on labor and delivery in humans is unknown.

Nursing Mothers

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of LUVOX® (fluvoxamine maleate) Tablets therapy to the mother.

Pediatric Use

The efficacy of fluvoxamine maleate for the treatment of Obsessive Compulsive Disorder was demonstrated in a 10-week multicenter placebo controlled study with 120 outpatients ages 8-17. The adverse event profile observed in that study was generally similar to that observed in adult studies with fluvoxamine (see ADVERSE REACTIONS).

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

Geriatric Use

Approximately 230 patients participating in controlled premarketing studies with LUVOX Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see Pharmacokinetics under CLINICAL PHARMACOLOGY), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event.

Adverse events in OCD Pediatric Population

In pediatric patients (N=57) treated with LUVOX® Tablets, the overall profile of adverse events is similar to that seen in adult studies. Other reactions which have been reported in two or more of the pediatric patients, and were more frequent than in the placebo group (N=63) were: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

Events for which the incidence in fluvoxamine maleate was equal to or less than the incidence in placebo (N=63) and involved two or more of the pediatric study patients were: abdominal pain, abnormal dreams, fever, headache, nausea, nervousness, pain, pharyngitis and rhinitis.

Incidence in Controlled Trials - *Commonly Observed Adverse Events in Controlled Clinical Trials:* LUVOX Tablets have been studied in controlled trials of OCD (n=320) and depression (n=1350). In general, adverse event rates were similar in the two data sets. The most commonly observed adverse events associated with the use of LUVOX Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 2 were: *somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia,* and *sweating.* In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: *dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis* and *taste perversion.* ***Adverse Events Occurring at an Incidence of 1%:*** Table 2 enumerates adverse events that occurred at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with LUVOX Tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied. ***Adverse Events in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference) in Rate from the Pooled Event Rates in OCD and Depression Placebo Controlled Studies:*** The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea. The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia* and *urinary retention.* These events are listed in order of decreasing rates in the OCD trials.

Vital Sign Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

Table 2: TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN OCD AND DEPRESSION POPULATIONS COMBINED[1] (fluvoxamine [n=892] vs. placebo [n=778] by patients–percentage): **BODY AS WHOLE:** Headache (22 vs. 20); Asthenia (14 vs. 6); Flu Syndrome (3 vs. 2); Chills (2 vs. 1). **CARDIOVASCULAR:** Palpitations (3 vs. 2). **DIGESTIVE SYSTEM:** Nausea (40 vs. 14); Diarrhea (11 vs. 7); Constipation (10 vs. 8); Dyspepsia (10 vs. 5); Anorexia (6 vs. 2); Vomiting (5 vs. 2); Flatulence (4 vs. 3); Tooth Disorder[a] (3 vs. 1); Dysphagia (2 vs. 1). **NERVOUS SYSTEM:** Somnolence (22 vs. 8); Insomnia (21 vs. 10); Dry Mouth (14 vs. 10); Nervousness (12 vs. 5); Dizziness (11 vs. 6); Tremor (5 vs. 1); Anxiety (5 vs. 3); Vasodilatation[2] (3 vs. 1) Hypertonia (2 vs. 1) Agitation (2 vs. 1); Decreased Libido (2 vs. 1); Depression (2 vs. 1); CNS Stimulation (2 vs. 1). **RESPIRATORY SYSTEM:** Upper Respiratory Infection (9 vs. 5); Dyspnea (2 vs. 1); Yawn (2 vs. 0). **SKIN:** Sweating (7 vs. 3). **SPECIAL SENSES:** Taste Perversion (3 vs. 1); Amblyopia[a] (3 vs. 2). **UROGENITAL:** Abnormal Ejaculation[5,6] (8 vs. 1); Urinary Frequency (3 vs. 2); Impotence[6] (2 vs. 1); Anorgasmia (2 vs. 0); Urinary Retention (1 vs. 0).[3]

[a]Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increase, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst and tinnitus. [b]Includes "toothache," "tooth extraction and abscess," and "caries." [2]Mostly feeling warm, hot, or flushed. [3]Mostly "blurred vision." [5]Mostly "delayed ejaculation." [6]Incidence based on number of male patients.

Other Events Observed During the Premarketing Evaluation of LUVOX Tablets

During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories.In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less than 1/1000 patients. ***Body as a Whole:*** *Frequent: accidental injury, malaise; Infrequent: allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; Rare:* cyst, pelvic pain, sudden death. ***Cardiovascular System:*** *Frequent:* hypertension, hypotension, syncope, tachycardia; *Infrequent:* angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; *Rare:* AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles. ***Digestive System:*** *Frequent:* elevated liver transaminases; *Infrequent:* colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, gingivitis, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; *Rare:* biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice. ***Endocrine System:*** *Infrequent:* hypothyroidism; *Rare:* goiter. ***Hemic and Lymphatic Systems:*** *Infrequent:* anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare:* leukopenia, purpura. ***Metabolic and Nutritional Systems:*** *Frequent:* edema, weight gain, weight loss; *Infrequent:* dehydration, hypercholesterolemia; *Rare:* diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased. ***Musculoskeletal System:*** *Infrequent:* arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; *Rare:* arthrosis, myopathy, pathological fracture. ***Nervous System:*** *Frequent:* amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; *Infrequent:* agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; *Rare:* akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome. ***Respiratory System:*** *Frequent:* cough increased, sinusitis; *Infrequent:* asthma, bronchitis, epistaxis, hoarseness, hyperventilation; *Rare:* apnea, congestion of upper airway, hemophysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia. ***Skin:*** *Infrequent:* acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria. ***Special Senses:*** *Infrequent:* accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; *Rare:* corneal ulcer, retinal detachment. ***Urogenital System:*** *Infrequent:* anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[2], hematuria, menopause[1], menorrhagia[1], metrorrhagia[1], nocturia, polyuria, premenstrual syndrome[1], urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; *Rare:* kidney calculus, hematospermia[2], oliguria.

[1]Based on the number of females. [2]Based on the number of males.

Non-US Postmarketing Reports

Voluntary reports of adverse events in patients taking LUVOX Tablets that have been received since market introduction and are of unknown causal relationship to LUVOX Tablets use include: toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, neuropathy, aplastic anemia, anaphylactic reaction, hyponatremia, acute renal failure, hepatitis, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

CAUTION: Federal law prohibits dispensing without prescription.

8E1252 Rev 3/97

Reference: 1. Data on file, Solvay Pharmaceuticals, Inc.

Pharmacia&Upjohn

Solvay Pharmaceuticals

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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

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•10
NOVEMBER/DECEMBER 1997

FEATURE ARTICLES

PHOTO ESSAY

This microscope illustrates the current presentation of original research on quality-of-life and economic costs of psychiatric illnesses, how functional imaging correlates with facial emotion recognition, the phylogenetic considerations of contrasting theoretical models of OCD, and the novel uses of anticonvulsant medications.

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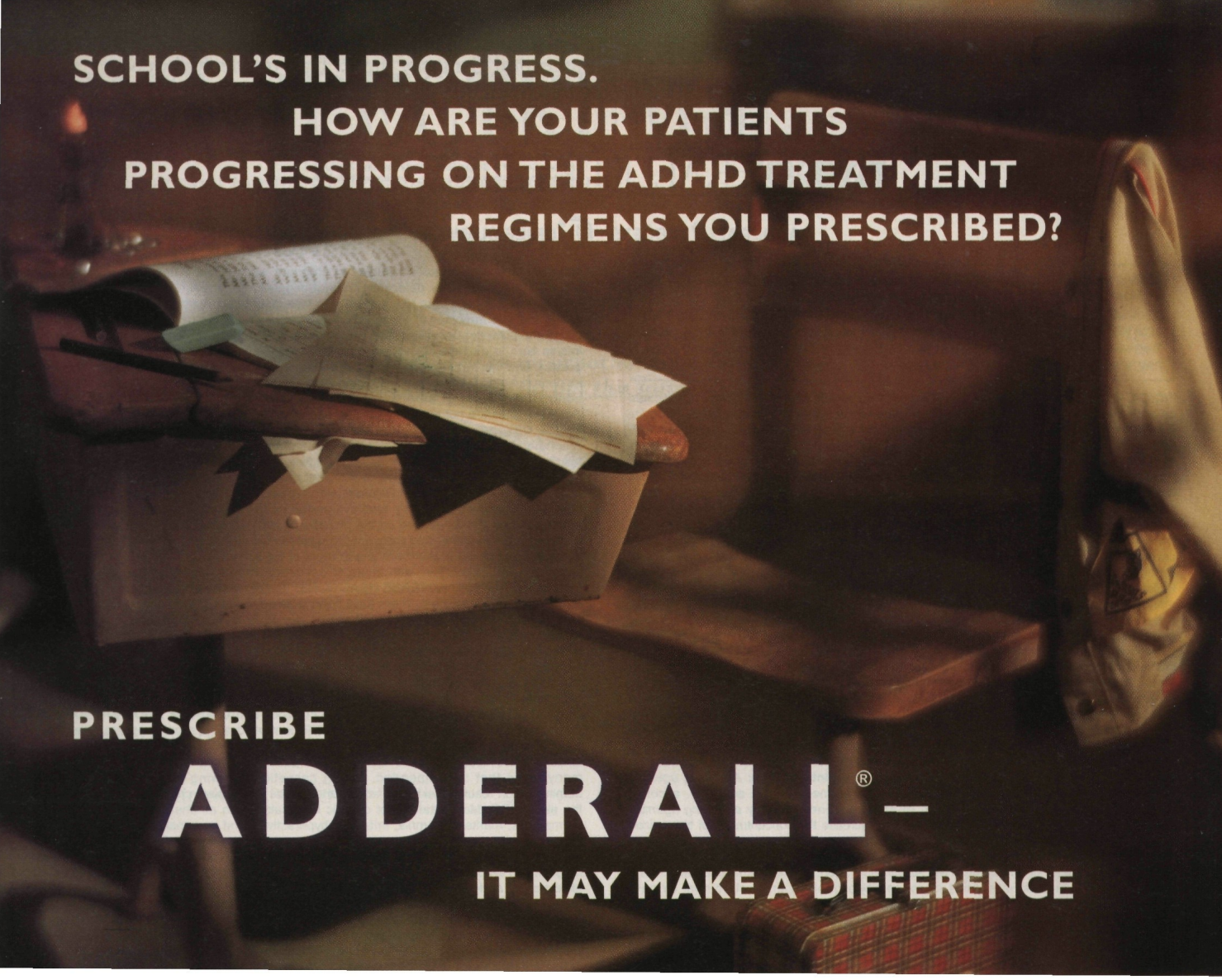
DEPARTMENTS/MONTHLY COLUMNS



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

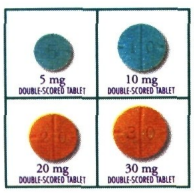
ADDERALL is the only ADHD product available to contain both dextro (*d*) and levo (*l*) amphetamine

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® 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

*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.

https://doi.org/10.1017/S1092852900011007 Published online by Cambridge University Press

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® 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

ADDERALL® TABLETS CII 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.

Richwood Pharmaceutical Company Inc.
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1-800-536-7878

...working to become your ADHD support company

Florence, KY 41042
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