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CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

Women and the Mood Disorders Spectrum

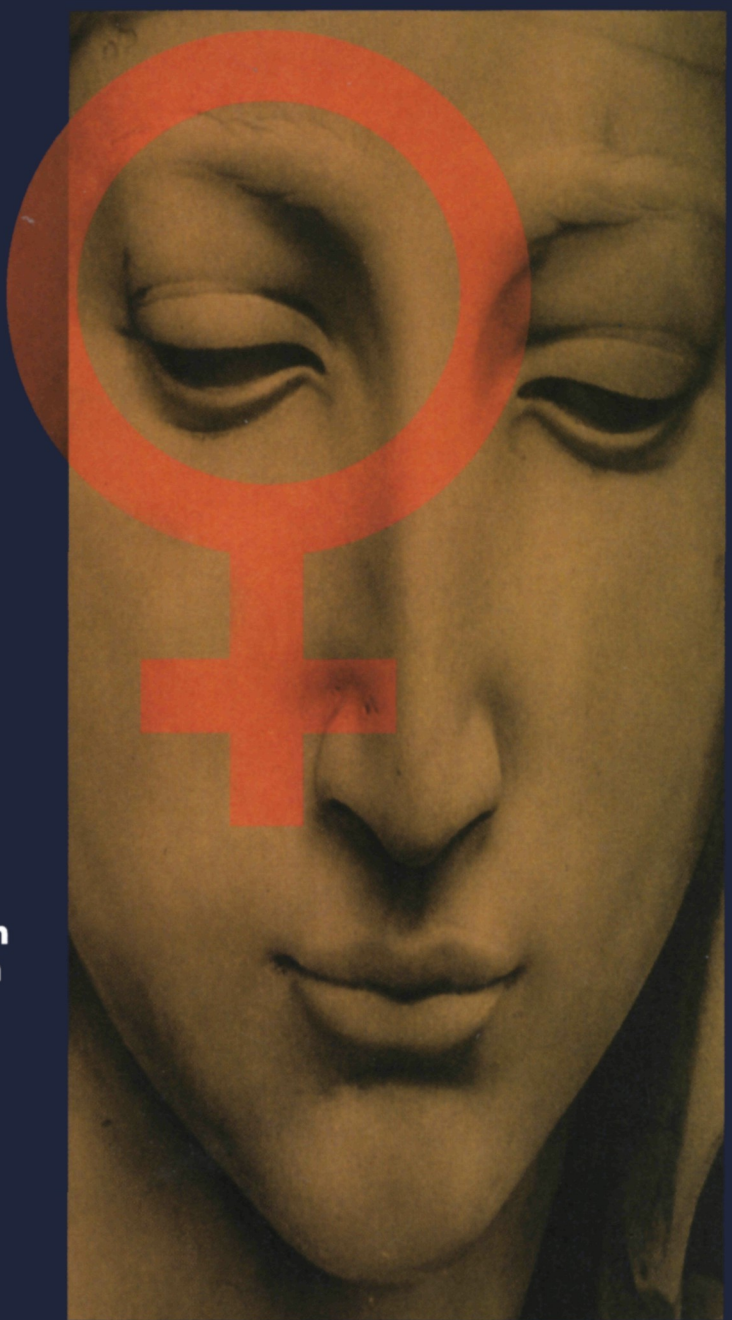

Photo Essay
This issue examines the assessment and treatment of women's psychiatric disorders using a multifactorial model with an emphasis placed on integrated services. **Articles Inside.**

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More physicians are diagnosing Alzheimer's disease.....

*The most common adverse events leading to discontinuation in clinical trials with ARICEPT® (donepezil HCl) were nausea, diarrhea, and vomiting. Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Nevertheless, cholinesterase inhibitors may be expected to increase gastric acid secretion. Therefore, patients (especially those at increased risk for developing ulcers—eg, history of ulcer disease, receiving concurrent nonsteroidal anti-inflammatory drugs) should be monitored closely for gastrointestinal bleeding. In clinical trials, syncopal episodes have been reported in association with the use of ARICEPT® (2% vs 1% for placebo).

That's why they're prescribing ARICEPT® (donepezil HCl)

Clinically Proven to Enhance Cognitive Function

With over 700,000 patient starts, ARICEPT® is the world's most-prescribed therapy for the treatment of mild to moderate Alzheimer's disease. Remember ARICEPT® for these important benefits:

- **Once-daily dosing**
- **No titration required**
- **Excellent safety profile**
- **Well-tolerated therapy***

ONCE-A-DAY

ARICEPT®

(donepezil HCl)

5-MG AND 10-MG TABLETS

Therapy to Remember™

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

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ONCE-A-DAY

ARICEPT® (donepezil HCl)

THERAPY TO REMEMBER™ 5-MG AND 10-MG TABLETS

ARICEPT® (Donepezil Hydrochloride Tablets)

Brief Summary—see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **CONTRAINDICATIONS** ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS** ***Anesthesia:*** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (eg, bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, eg, those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction. ***Neurological Conditions:*** Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. ***Pulmonary Conditions:*** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions** ***Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. ARICEPT® at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL), and warfarin (3 µg/mL) to human albumin. Similarly, the binding of ARICEPT® to human albumin was not affected by furosemide, digoxin and warfarin. ***Effect of ARICEPT® on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (eg, cisapride, terfenadine) or by CYP 2D6 (eg, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50 -130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT® for interaction with theophylline, cimetidine, warfarin and digoxin. No significant effects on the pharmacokinetics of these drugs were observed. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. Inducers of CYP 2D6 and CYP 3A4 (eg, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis). **Pregnancy** *Pregnancy Category C:* Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. **ADVERSE REACTIONS Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients were nausea (1% [5 mg] and 3% [10 mg] vs 1% [placebo]), diarrhea (<1% [5 mg] and 3% [10 mg] vs 0% [placebo]), and vomiting (<1% [5 mg] and 2% [10 mg] vs <1% [placebo]). **Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT®** The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue, and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 1 for a comparison of the most common adverse events following one week and six week titration regimens. **Adverse Events Reported in Controlled Trials** The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age. **Other Adverse Events Observed During Clinical Trials** ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 1 or 2, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events*—those occurring in at least 1/100 patients; *infrequent adverse events*—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. **Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydypsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus; diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block, hemolytic anemia, hyponatremia, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. Controlled clinical trials indicate that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. Because steady state is not achieved for 15 days and because the incidence of such effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

Table 1. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks

	No titration		One-week titration	Six-week titration
Adverse Event	Placebo (n=315)	5 mg/day (n=311)	10 mg/day (n=315)	10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle Cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Table 2. Adverse Events Reported in Controlled Clinical Trials In at Least 2% of Patients Receiving ARICEPT® and at a Higher Frequency Than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients With Any Adverse Event	72	74
Body as a Whole		
Headache	9	10
Pain, Various Locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		
Frequent Urination	1	2

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CNS SPECTRUMS

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Why expose your patients to the "ups and downs" of traditional carbamazepine therapy?

Peak-to-trough fluctuations in patients receiving immediate-release carbamazepine three times daily can be as great as 2.5 fold[1]

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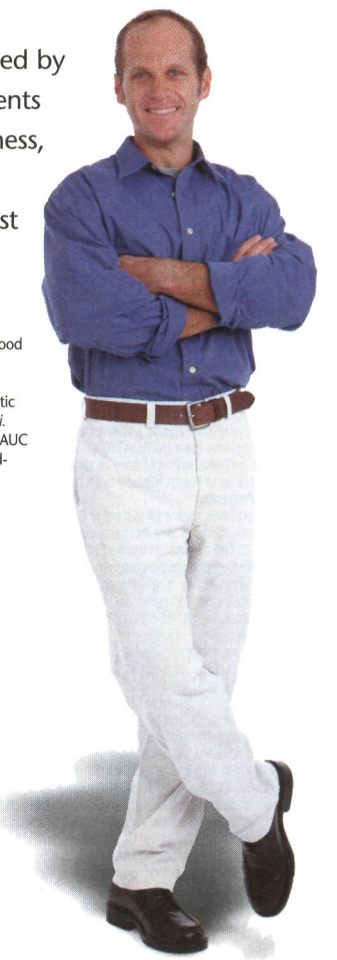
Switch to Carbatrol®—Second-generation delivery system design that targets the limitations of conventional carbamazepine[1-6]

- Bioequivalent to immediate-release carbamazepine dosed rigidly Q6h[3]
- Peak-to-trough fluctuations are not compromised[3,4]
- Smooth, consistent plasma concentrations[3,4]
- Extensive drug dispersion, dissolution, and absorption[2]
- Predictable bioavailability[5]
- BID dosing[6]
- No generic equivalent[2]

Absence seizures (petit mal) do not appear to be controlled by carbamazepine. The most frequently reported adverse events (particularly during the initial phases of therapy) are dizziness, drowsiness, unsteadiness, nausea, and vomiting. Adverse events can be minimized by initiating therapy at the lowest possible effective dose.



References: **1.** Jensen PK, Moller A, Gram L, Jenson NO, Dam M. Pharmacokinetic comparison of two carbamazepine slow-release formulations. *Acta Neurol Scand.* 1990;82:135-137. **2.** Data on file, Shire Richwood Inc. **3.** Garnett WR, Levy B, McLean AM, et al. Pharmacokinetic evaluation of twice-daily extended-release carbamazepine (CBZ) and four-times-daily immediate-release CBZ in patients with epilepsy. *Epilepsia.* 1998;39(3):274-279. **4.** Stevens RE, Limsakun T, Evans G, Mason DH. Controlled, multidose, pharmacokinetic evaluation of two extended-release carbamazepine formulations (Carbatrol® and Tegretol-XR®). *J Pharm Sci.* 1998;87(12):1531-1534. **5.** Mahmood I, Chamberlin N. A limited sampling method for the estimation of AUC and C_{max} of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product. *Br J Clin Pharmacol.* 1998;45:241-246. **6.** Carbatrol package insert, Shire Richwood Inc.

Please see brief summary of prescribing information on adjacent pages.

Carbatrol®

carbamazepine extended-release capsules

200 mg capsule ~ 300 mg capsule

COMFORTABLY PREDICTABLE

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CARBATROL®

(carbamazepine extended-release capsules)
200 mg and 300 mg

Brief Summary Prescribing Information

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW. APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Carbatrol, the physician should be thoroughly familiar with the details of the full prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

INDICATIONS AND USAGE

Epilepsy

Carbatrol* is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvements than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

Trigeminal Neuralgia

Carbatrol is indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline and nortriptyline. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. 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. Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m² basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg. Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. Tests to detect defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

General

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported. Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy. Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

If necessary, the Carbatrol capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. Carbatrol capsules or their contents should not be crushed or chewed.

Laboratory Tests

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone. Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs. Interference with some pregnancy tests has been reported.

Drug Interactions

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following:

Agents that may affect carbamazepine plasma levels:

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include:

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketoconazole, itraconazole, verapamil, valproate.*

CYP 3A4 inducers can increase the rate of carbamazepine metabolism and can thus decrease plasma carbamazepine levels. Drugs that have been shown, or would be expected, to decrease plasma carbamazepine levels include:

cisplatin, doxorubicin HCL, felbamate, rifampin*, phenobarbital, phenytoin, primidone, theophylline.

Effect of carbamazepine on plasma levels of concomitant agents:

Carbatrol increases levels of clomipramine HCL, phenytoin and primidone.

Carbatrol induces hepatic CYP activity. Carbatrol causes, or would be expected to cause decreased levels of the following:

acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, valproate, warfarin.

The doses of these drugs may therefore have to be increased when carbamazepine is added to the therapeutic regimen. Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications. Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of carbamazepine to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day (low dose approximately 0.2 times the maximum human daily dose of 1200 mg on a mg/m² basis), resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Usage in Pregnancy

Pregnancy Category D (See WARNINGS)

Labor and Delivery

The effect of carbamazepine on human labor and delivery is unknown.

Nursing Mothers

Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its epoxide metabolite are approximately 50% of the maternal plasma concentration. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of carbamazepine effectiveness for use in the management of children with epilepsy (see INDICATIONS for specific seizure types) is derived from clinical investigations performed in adults and from studies in several *in vitro* systems which support the conclusion that (1) the pathogenic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children. Taken as a whole, this information supports a conclusion that the generally acceptable therapeutic range of total carbamazepine in plasma (i.e., 4-12 µg/mL) is the same in children and adults. The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

Adverse Reactions

General: If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive patient with epilepsy may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic system (see BOX WARNING), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

The following additional adverse reactions were previously reported with carbamazepine:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy. Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported. Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, *it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels* of 50 mg/kg/day and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills, inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants. A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

*increased levels of the active 10, 11-epoxide

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DEPRESSION AND GENDER—ARE SYMPTOMS SEX-SPECIFIC?

page 25

"Studies that focus on gender differences in the processing of emotional stimuli are particularly relevant. For example, George and colleagues asked subjects undergoing positron emission tomography scanning to imagine their saddest experience, and found more significant increases in blood flow in women than men in a number of limbic regions. Similarly, a study using functional magnetic resonance imaging scanning while subjects viewed neutral, pleasant, and unpleasant pictures showed that activation in the right posterior region was higher in the women when they viewed unpleasant pictures, as compared with neutral or pleasant pictures, while the men had the opposite pattern of activation. In addition, psychophysiological work by the same investigators has indicated that women's faces are more expressive of their feelings. When men and women were presented with a standardized set of pictures designed to elicit a variety of emotional responses, women showed a more robust correlation between self-reported emotional valence (positive or negative) and facial muscle activity than did men. Men, on the other hand, showed a more consistent relationship between self-reported arousal and skin conductance measures, although the authors noted that they were unable to rule out the possible artifact of sex-specific differences in sweat regulation."

LOOKING AT THE WHOLE PICTURE: TREATING DEPRESSION DURING PREGNANCY

page 34

"The literature is replete with references on the adverse impact of maternal depression on infant well-being. The majority have found impairment in mother-infant attachment and child development. While much of these data are considered novel, the potential deleterious effects of maternal stress and separation have been demonstrated for more than four decades and have been seen in a variety of animal models dating back to 1966. One line of investigation in preclinical studies has demonstrated an adverse effect of both maternal stress and increased maternal glucocorticoid concentrations on fetal brain development. Clearly, maternal separation and stress in laboratory animals cannot be easily extrapolated to clinical practice, although the potential for such should be considered as further investigations are forthcoming. Overall, the clinical and laboratory data indicate that untreated maternal mental illness and/or stress during the critical periods of infant development may pose an ominous, though not readily visible, threat to infant well-being and should be considered in clinical treatment planning."

BLASTING MYTHS ABOUT BREAST CANCER AND ANXIETY

page 40

"It is important to note that, taken collectively, available data refute a second myth, that breast cancer patients experience more psychological symptoms than other cancer patients. For many years, the thrust of psychosocial research in breast cancer was largely focused on the epidemiology of women's adaptation to illness. More recently, researchers have begun to shift their attention to the late effects of cancer, focusing on the quality of life of women posttreatment. While considerable information is available on the challenges women face during treatment, relatively less is known about how women fare years after therapy ends. With most women expected to be cured of, or live long periods without evidence of, disease, it is increasingly important to understand the situations to which we may be returning women when active treatment ends. In the next section, two studies addressing this question will be briefly reviewed."

THE COMPLEXITY OF MODERN MOTHERHOOD

page 55

"Society had rewarded me quite nicely for being to put words together, but when it came to raising a child—nada. The government did recognize my new status by giving me a yearly child care allowance—but it was pretty measly (and I notice recent efforts to increase it died in Congress this past session). In the eyes of the IRS, once my paycheck stopped I was now a 'dependent'—the term the government uses for 'people who do not contribute to the gross national product.' Yet, I was supposed to stay home. That was the message I kept getting from a bunch of new studies about the importance of mother-child bonding in the crucial early years. The message is: it's important to stay home with your child, but don't expect us to respect you for it."

A PSYCHODYNAMIC PERSPECTIVE ON WOMEN'S ISSUES

page 61

"This patient had a very strong wish to be loved exclusively by her father, which was in direct conflict with her harsh and critical conscience. Any gratification of this wish had to be 'paid' for in some way, like tithing. In many respects she was the Oedipal victor in her home, being the child who was closest to her father. This was reinforced by her mother's death. She retreated and inhibited herself whenever she began to function on an Oedipal level. She often would say that she had to 'cut off' her feelings, perhaps expressing the need to castrate herself before it was done to her. The repressed sexual feelings were often converted into physical phenomena such as her feeling tense or having headaches. The night terrors may have been a discharge of these same feelings. The patient was repeating a pattern that began in childhood at age 5 years when she first exhibited neurotic symptoms of withdrawal and inhibition. Later in childhood she adopted a 'little mother' role in her family vis-à-vis her siblings, perhaps as an expression of her wish to have her father to herself. She devalued her mother and found it difficult to identify with her despite her mother's self-confidence and autonomy."

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, panic disorder, with or without agoraphobia, as defined in DSM-IV and social anxiety disorder, as defined in DSM-IV.

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. (See WARNINGS and PRECAUTIONS.) Contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in *Paxil*.

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/m² basis) showed a reduced pregnancy rate.

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

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

In worldwide premarketing *Paxil* clinical trials, 17% of *Paxil*-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly and a lower starting dose is recommended. 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%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of social anxiety disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: sweating (9% vs. 2%), nausea (25% vs. 7%), dry mouth (9% vs. 3%), constipation (5% vs. 2%), decreased appetite (8% vs. 2%), *somnolence (22% vs. 5%), tremor (9% vs. 1%), libido decreased (12% vs. 1%), yawn (5% vs. 1%), abnor*mal ejaculation (28% vs. 1%), female genital disorders (9% vs. 1%) and impotence (5% vs. 1%).

Twenty percent (1,199/6,145) of *Paxil* patients in worldwide clinical trials in depression and 16.1% (84/522), 11.8% (64/542) and 9.4% (44/469) of *Paxil* patients in worldwide trials in social anxiety disorder, 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; **social anxiety disorder**–somnolence, insomnia, tremor, anxiety, dizziness, nausea, vomiting, flatulence, asthenia, abnormal ejaculation, sweating, libido decreased.

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 or among patients with social anxiety disorder on *Paxil* who participated in placebo-controlled trials of 12 weeks duration in which patients were dosed in a range of 20 to 50 mg/day: asthenia, abdominal pain, chest pain, back pain, chills, trauma; vasodilation, palpitation; sweating, rash; nausea, dry mouth, constipation, diarrhea, decreased appetite, dyspepsia, flatulence, increased appetite, vomiting; myalgia; increased appetite; insomnia, somnolence, dizziness, tremor, nervousness, libido decreased, agitation, anxiety, abnormal dreams, concentration impaired, depersonalization, myoclonus, amnesia, rhinitis, pharyngitis, yawn; abnormal vision, taste perversion; abnormal ejaculation, dysmenorrhea, female genital disorder, impotence, urinary frequency, urination impaired, urinary tract infection.

Studies in depression 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.

In placebo-controlled clinical trials involving more than 1,800 patients with depression, OCD, panic disorder or social anxiety disorder, the following incidences of untoward sexual experiences for patients receiving *Paxil* were reported, varying with the disease state: In males: decreased libido (6% to 14%), ejaculatory disturbance, mostly delayed ejaculation (13% to 28%), impotence (2% to 8%). In females: decreased libido (1% to 9%), orgasmic disturbance (2% to 9%). The reported incidence of each of these adverse events was <5% among male and female patients receiving placebo.

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, panic disorder, and social anxiety disorder, 542, 469, and 522 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, face edema, neck pain; *rare:* adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, ulcer. **Cardiovascular System:** *frequent:* hypertension, syncope, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine, *rare:* angina pectoris, arrhythmia nodal, 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, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. **Endocrine System:** *rare:* diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** *infrequent:* anemia, eosinophilia, leukocytosis, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, hypochromic anemia, iron deficiency anemia, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia. **Metabolic and Nutritional:** *frequent:* weight gain, weight loss; *infrequent:* alkaline phosphatase increased, edema, peripheral edema, SGOT increased, SGPT increased, thirst; *rare:* bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, 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, alcohol abuse, ataxia, delirium, depersonalization, dystonia, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction, psychosis; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesia, convulsion, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus, withdrawal syndrome. **Respiratory System:** *frequent:* cough increased, rhinitis, sinusitis; *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, voice alteration. **Skin and Appendages:** *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, maculopapular rash, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, fungal dermatitis, furunculosis, herpes zoster, hirsutism, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, vesiculobullous rash. **Special Senses:** *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, photophobia, tinnitus; *rare:* amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, keratoconjunctivitis, night blindness, otitis externa, parosmia, ptosis, retinal hemorrhage, taste loss, visual field defect. **Urogenital System:** *infrequent:* abortion, amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal moniliasis, vaginitis; *rare:* breast atrophy, breast enlargement, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, pyuria, urethritis, uterine spasm, urolith, vaginal hemorrhage.

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:L16

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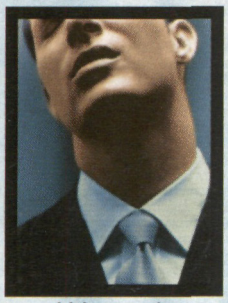
should have

I should have joined in more often, but...

could have



I could have taken the promotion, except...

would have

I would have found someone special, only...

can't. I just can't.

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

Please see brief summary of prescribing information adjacent to this advertisement. PX9652

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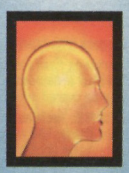
Show them they

can



ONCE-DAILY

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Relieve the anxiety.
Reveal the person.

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Table of Contents

Feature Articles

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 4 • Number 10
October 1999

CNS Spectrums is a peer review journal and is indexed in EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis. *CNS Spectrums* is endorsed by, and is the official journal of, the International Neuropsychiatric Association, with members in 30 countries.

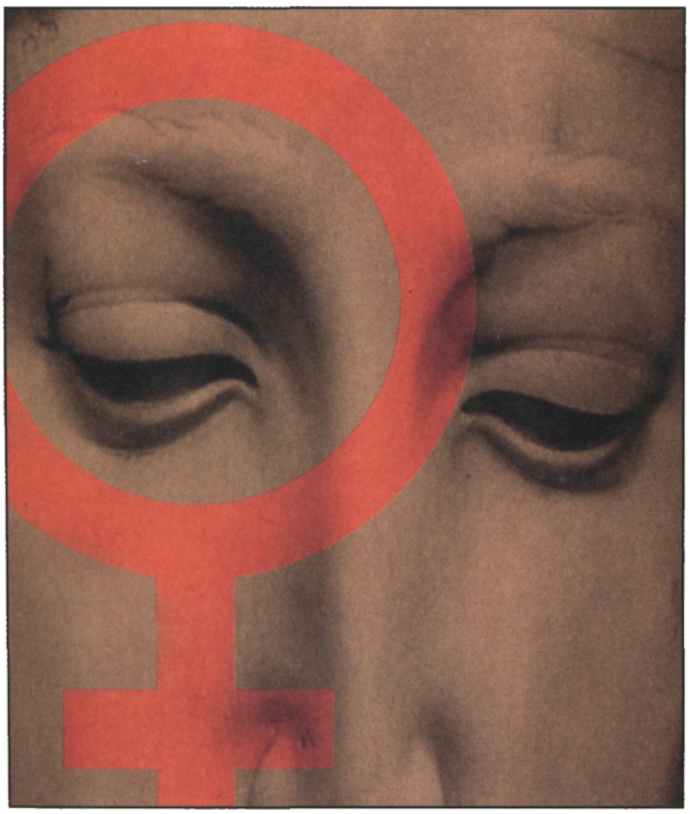

Photo Essay
In the United States and throughout the world, prevalence rates in women for psychiatric disorders like major depression are two to three times the rates seen in men. This issue examines the assessment and treatment of women's psychiatric disorders using a multifactorial model with an emphasis placed on integrated services.

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 4 • Number 10
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Risperdal®

tablets and oral solution 1 mg/mL

RISPERIDONE

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders.

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment and in patients with severe hepatic impairment. A lower starting dose should be used in such patients.

Information for Patients

Physicians are advised to consult full prescribing information to review issues to be discussed with patients for whom they prescribe RISPERDAL®.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas.

These findings are considered to be prolactin medicated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis.

Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. Women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% percent (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included: extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following *additional common and drug-related adverse events were present at least 5%* and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

The following adverse events occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL® treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials: ***Psychiatric Disorders:*** insomnia, agitation, anxiety, somnolence, aggressive reaction. ***Nervous System:*** extrapyramidal symptoms[1], headache, dizziness. ***Gastrointestinal System:*** constipation, nausea, dyspepsia, vomiting, abdominal pain, saliva increased, toothache. ***Respiratory System:*** rhinitis, coughing, sinusitis, pharyngitis, dyspnea. ***Body as a Whole:*** back pain, chest pain, fever. ***Dermatological:*** rash, dry skin, seborrhea. ***Infections:*** upper respiratory. ***Visual:*** abnormal vision. ***Musculo-Skeletal:*** arthralgia. ***Cardiovascular:*** tachycardia.

[1] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders.

Dose Dependency of Adverse Events:

Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: A statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies and the following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.)

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastro-esophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

For information on symptoms and treatment of overdosage, see full prescribing information.

More detailed professional information is available upon request.

US Patent 4,804,663

7503217

July 1998, May 1999

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