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The White Paper Issue•1999

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This traditional year-end White Paper issue of *CNS Spectrums* highlights new and original research in the area of impulsivity and compulsivity. **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).

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

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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:

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ONCE-A-DAY
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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/m^2 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/m^2 basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m^2 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/m^2 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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...like treatment-emergent sleep disturbance, anxiety, sexual dysfunction, and weight change.

"I feel sad, anxious and agitated about everything. Hopeless. Nothing matters anymore, even things I used to love. Part of it is, I've been dragging around for weeks now. I can't remember my last good night's sleep, or what joy feels like...."

You've heard it all before. Yet so many patients are reluctant to take antidepressants, or they stop too soon. Why? Could be CONCERN ABOUT efficacy and/or treatment-emergent side effects with the potential for creating NEW PROBLEMS. What your patient may NEED is a therapy that provides COMPARABLE antidepressant RESPONSE rates to SSRIs such as fluoxetine, sertraline, and paroxetine.[1-3] One that also offers EARLY and SUSTAINED IMPROVEMENT in depression-related symptoms of ANXIETY and AGITATION.[4,5] Early IMPROVEMENT in SLEEP QUALITY[6-8] with MINIMAL treatment-emergent SLEEP DISTURBANCE[2,9,10] and minimal treatment-emergent SEXUAL DYSFUNCTION.[10] And one that is NOT associated with significant WEIGHT GAIN.[2,10] Such a therapy exists. It's called Serzone. Maybe it's time to challenge the status quo and PRESCRIBE SERZONE (nefazodone HCl) for your depressed patients.

The most common adverse events (reported at ≥ 5% and significantly different from placebo in placebo-controlled trials) were dry mouth, somnolence, nausea, dizziness, constipation, asthenia, lightheadedness, blurred vision, confusion, and abnormal vision. Coadministration of Serzone with Seldane®, Hismanal®, Propulsid®, or Orap® is contraindicated.* Coadministration with monoamine oxidase inhibitors is not recommended. Coadministration with triazolam should be avoided for most patients, including the elderly.

*Seldane® is a registered trademark of Hoechst Marion Roussel. Hismanal® and Propulsid® are registered trademarks of Janssen Pharmaceutica Inc. Orap® is a registered trademark of Gate Pharmaceuticals.

Challenge the status quo.

serzone®
nefazodone HCl
50, 100, 150, 200, 250 MG TABLETS

Please see references and brief summary of prescribing information on adjacent page.

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SERZONE®
(nefazodone hydrochloride) Tablets

Rx only

BRIEF SUMMARY

SERZONE® (nefazodone hydrochloride) Tablets

INDICATIONS AND USAGE: SERZONE (nefazodone hydrochloride) is indicated for the treatment of depression.

CONTRAINDICATIONS: Coadministration of terfenadine, astemizole, cisapride, or pimozide with SERZONE is contraindicated (see **WARNINGS** and **PRECAUTIONS** sections). SERZONE is contraindicated in patients with known hypersensitivity to nefazodone or other phenylpiperazine antidepressants. The coadministration of triazolam and nefazodone causes a significant increase in the plasma level of triazolam (see **WARNINGS** and **PRECAUTIONS** sections), and a 75% reduction in the initial triazolam dosage is recommended if the two drugs are to be given together. Because not all commercially available dosage forms of triazolam permit a sufficient dosage reduction, the coadministration of triazolam and SERZONE should be avoided for most patients, including the elderly.

WARNINGS: ***Potential for Interaction with Monoamine Oxidase Inhibitors:*** **In patients receiving antidepressants with pharmacological properties similar to nefazodone in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizure, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. Although the effects of combined use of nefazodone and MAOI have not been evaluated in humans or animals, because nefazodone is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that nefazodone not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 1 week should be allowed after stopping nefazodone before starting an MAOI.** ***Interaction with Triazolobenzodiazepines:*** Interaction studies of nefazodone with two triazolobenzodiazepines, i.e., triazolam and alprazolam, metabolized by cytochrome P4503A4, have revealed substantial and clinically important increases in plasma concentrations of these compounds when administered concomitantly with nefazodone. **Triazolam:** When a single oral 0.25-mg dose of triazolam was coadministered with nefazodone (200 mg BID) at steady state, triazolam half-life and AUC increased 4-fold and peak concentrations increased 1.7-fold. Nefazodone plasma concentrations were unaffected by triazolam. ***Coadministration of nefazodone potentiated the effects of triazolam on psychomotor performance tests.*** If triazolam is coadministered with SERZONE, a 75% reduction in the initial triazolam dosage is recommended. Because not all commercially available dosage forms of triazolam permit sufficient dosage reduction, coadministration of triazolam with SERZONE should be avoided for most patients, including the elderly. In the exceptional case where coadministration of triazolam with SERZONE may be considered appropriate, only the lowest possible dose of triazolam should be used (see **CONTRAINDICATIONS** and **PRECAUTIONS** sections). **Alprazolam:** When alprazolam (1 mg BID) and nefazodone (200 mg BID) were coadministered, steady-state peak concentrations, AUC and half-life values for alprazolam increased by approximately 2-fold. Nefazodone plasma concentrations were unaffected by alprazolam. If alprazolam is coadministered with SERZONE, a 50% reduction in the initial alprazolam dosage is recommended. No dosage adjustment is required for SERZONE. ***Potential Terfenadine, Astemizole, Cisapride, and Pimozide Interactions:*** **Terfenadine, astemizole, cisapride, and pimozide are all metabolized by the cytochrome P450 3A4 (CYP3A4) isozyme, and it has been demonstrated that ketoconazole, erythromycin, and other inhibitors of CYP3A4 can block the metabolism of these drugs, which can result in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, cisapride, and pimozide are associated with QT prolongation and with rare cases of serious cardiovascular adverse events, including death, due principally to ventricular tachycardia of the torsade de pointes type. Nefazodone has been shown *in vitro* to be an inhibitor of CYP3A4. Consequently, it is recommended that nefazodone not be used in combination with either terfenadine, astemizole, cisapride, or pimozide** (see **CONTRAINDICATIONS** and **PRECAUTIONS** sections).

PRECAUTIONS: ***General:*** **Postural Hypotension:** A pooled analysis of the vital signs monitored during placebo-controlled premarketing studies revealed that 5.1% of nefazodone patients compared to 2.5% of placebo patients ($p \leq 0.01$) met criteria for a potentially important decrease in blood pressure at some time during treatment (systolic blood pressure ≤90 mmHg *and* a change from baseline of ≥ 20 mmHg). While there was no difference in the proportion of nefazodone and placebo patients having adverse events characterized as 'syncope' (nefazodone, 0.2%; placebo, 0.3%), the rates for adverse events characterized as 'postural hypotension' were as follows: nefazodone (2.8%), tricyclic antidepressants (10.9%), SSRI (1.1%), and placebo (0.8%). Thus, the prescriber should be aware that there is some risk of postural hypotension in association with nefazodone use. SERZONE should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication). **Activation of Mania/Hypomania:** During premarketing testing, hypomania or mania occurred in 0.3% of nefazodone-treated unipolar patients and 1.6% of bipolar patients. Activation of mania/hypomania is a known risk in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, SERZONE should be used cautiously in patients with a history of mania. **Suicide:** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for SERZONE should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Seizures:** During premarketing testing, a recurrence of a petit mal seizure was observed in a patient receiving nefazodone who had a history of such seizures. In addition, one nonstudy participant reportedly experienced a convulsion (type not documented) following a multiple-drug overdose (see **OVERDOSAGE** section). Rare occurrences of convulsions (including grand mal seizures) following nefazodone administration have been reported since market introduction. A causal relationship to nefazodone has not been established (see **ADVERSE REACTIONS** section). **Priapism:** While priapism did not occur during premarketing experience with nefazodone, rare reports of priapism have been received since market introduction. A causal relationship to nefazodone has not been established (see **ADVERSE REACTIONS** section). If patients present with prolonged or inappropriate erections, they should discontinue therapy immediately and consult their physicians. If the condition persists for more than 24 hours, a urologist should be consulted to determine appropriate management. **Use in Patients with Concomitant Illness:** SERZONE has 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 clinical studies during the product's premarketing testing. Evaluation of electrocardiograms of 1153 patients who received nefazodone in 6- to 8-week, double-blind, placebo-controlled trials did not indicate that nefazodone is associated with the development of clinically important ECG abnormalities. However, sinus bradycardia, defined as heart rate ≤50 bpm and a decrease of at least 15 bpm from baseline, was observed in 1.5% of nefazodone-treated patients compared to 0.4% of placebo-treated patients ($p \leq 0.05$). Because patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical trials, such patients should be treated with caution. In patients with cirrhosis of the liver, the AUC values of nefazodone and HO-NEF were increased by approximately 25%. ***Laboratory Tests:*** There are no specific laboratory tests recommended. ***Drug Interactions:*** **Drugs Highly Bound to Plasma Protein:** Because nefazodone is highly bound to plasma protein (see **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, of the full prescribing information), administration of SERZONE to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of nefazodone by other highly bound drugs. **CNS-Active Drugs:** *Monoamine Oxidase Inhibitors* — See **WARNINGS** section. *Haloperidol* — When a single oral 5-mg dose of haloperidol was coadministered with nefazodone (200 mg BID) at steady state, haloperidol apparent clearance decreased by 35% with no significant increase in peak haloperidol plasma concentrations or time of peak. This change is of unknown clinical significance. Pharmacodynamic effects of haloperidol were generally not altered significantly. There were no changes in the pharmacokinetic parameters for nefazodone. Dosage adjustment of haloperidol may be necessary when coadministered with nefazodone. *Lorazepam* — When lorazepam (2 mg BID) and nefazodone (200 mg BID) were coadministered to steady state, there was no change in any pharmacokinetic parameter for either drug compared to each drug administered alone. Therefore, dosage adjustment is not necessary for either drug when coadministered. *Triazolam/Alprazolam* — See **CONTRAINDICATIONS** and **WARNINGS** sections. *Alcohol* — Although nefazodone did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of SERZONE and alcohol in depressed patients is not advised. *Buspirone* — In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg BID) with nefazodone (250 mg BID) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C_{max} and up to 50-fold in AUC) and statistically isignificant decreases (about 50%) in plasma concentrations of the buspirone metabolite 1-pyrimidinylpiperazine. With 5-mg BID doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metaboiltes hydroxynefazodone (17%) and mCPP (9%). The side effect profile for subjects receiving buspirone 2.5 mg BID and nefazodone 250 mg BID was similar to that for subjects receiving either drug alone. Subjects receiving buspirone 5 mg BID and nefazodone 250 mg BID experienced side effects such as lightheadedness, asthenia, dizziness, and somnolence. If the two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg BID) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment. *Pimozide* — See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS:** *Pharmacokinetics of Nefazodone in 'Poor Metabolizers' and Potential Interaction with Drugs that Inhibit and/or Are Metabolized by Cytochrome P450 Isozymes. General Anesthetics* — Little is known about the potential for interaction between nefazodone and general anesthetics; therefore, prior to elective surgery, SERZONE should be discontinued for as long as clinically feasible. *Other CNS-Active Drugs* — The use of nefazodone in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if concomitant administration of SERZONE and such drugs is required. **Cimetidine:** When nefazodone (200 mg BID) and cimetidine (300 mg QID) were coadministered for one week, no change in the steady-state pharmacokinetics of either nefazodone or cimetidine was observed compared to each dosed alone. Therefore, dosage adjustment is not necessary for either drug when coadministered. **Cardiovascular-Active Drugs:** *Digoxin* — When nefazodone (200 mg BID) and digoxin (0.2 mg QD) were coadministered for 9 days to healthy male volunteers (n = 18) who were phenotyped as CYP2D6 extensive metabolizers, C_{max}, C_{min} and AUC of digoxin were increased by 29%, 27%, and 15%, respectively. Digoxin had no effects on the pharmacokinetics of nefazodone and its active metabolites. Because of the narrow therapeutic index of digoxin, caution should be exercised when nefazodone and digoxin are coadministered; plasma level monitoring for digoxin is recommended. *Propranolol* — The coadministration of nefazodone (200 mg BID) and propranolol (40 mg BID) for 5.5 days to healthy male volunteers (n = 18), including 3 poor and 15 extensive CYP2D6 metabolizers, resulted in 30% and 14% reductions in C_{max} and AUC of propranolol, respectively, and a 14% reduction in C_{max} for the metabolite, 4-hydroxypropranolol. The kinetics of nefazodone, hydroxynefazodone, and triazole-dione were not affected by coadministration of propranolol. However, C_{max}, C_{min}, and AUC of m-chlorophenylpiperazine were increased by 23%, 54%, and 28%, respectively. No change in initial dose of either drug is necessary, and dose adjustments should be made on the basis of clinical response. *HMG-CoA Reductase Inhibitors* — When single 40-mg doses of simvastatin or atorvastatin, both substrates of CYP3A4, were given to healthy adult volunteers who had received SERZONE 200 mg BID for 6 days, approximately 20-fold increases in plasma concentrations of simvastatin and simvastatin acid and 3-4-fold increases in plasma concentrations of atorvastatin and atorvastatin lactone were seen. These effects appear to be due to the inhibition of CYP3A4 by SERZONE because, in the same study, SERZONE had no significant effect on the plasma concentrations of pravastatin, which is not metabolized by CYP3A4 to a clinically significant extent. There have been rare reports of rhabdomyolysis involving patients receiving the combination of SERZONE and either simvastatin or lovastatin, also a substrate of CYP3A4 (see **ADVERSE REACTIONS: Postintroduction Clinical Experience** section). Rhabdomyolysis has been observed in patients receiving HMG-CoA reductase inhibitors administered alone (at recommended dosages) and in particular, for certain drugs in this class, when given in combination with inhibitors of the CYP3A4 isozyme. Caution should be used if SERZONE is administered in combination with HMG-CoA reductase inhibitors that are metabolized by CYP3A4, such as simvastatin, atorvastatin, and lovastatin, and dosage adjustments of these HMG-CoA reductase inhibitors are recommended. Since metabolic interactions are unlikely between SERZONE and HMG-CoA reductase inhibitors that undergo little or no metabolism by the CYP3A4 isozyme, such as pravastatin or fluvastatin, dosage adjustments should not be necessary. **Cyclosporine:** There have been rare reports of increased serum cyclosporine levels (up to seven times higher) in patients receiving SERZONE and cyclosporine concomitantly. Since cyclosporine is a substrate of CYP3A4 and nefazodone is known to inhibit this enzyme, monitoring of serum cyclosporine levels is recommended when the two agents are coadministered. **Pharmacokinetics of Nefazodone in 'Poor Metabolizers' and Potential Interaction with Drugs that Inhibit and/or Are Metabolized by Cytochrome P450 Isozymes:** *CYP3A4 Isozyme* — Nefazodone has been shown *in vitro* to be an inhibitor of CYP3A4. This is consistent with the interactions observed between nefazodone and triazolam, alprazolam, buspirone, atorvastatin, and simvastatin, drugs metabolized by this isozyme. Consequently, caution is indicated in the combined use of nefazodone with any drugs known to be metabolized by the CYP3A4. In particular, the combined use of nefazodone with triazolam should be avoided for most patients, including the elderly. The combined use of nefazodone with terfenadine, astemizole, cisapride, or pimozide is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS** sections). *CYP2D6 Isozyme* — A subset (3% to 10%) of the population has reduced activity of the drug-metabolizing enzyme CYP2D6. Such individuals are referred to commonly as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. The pharmacokinetics of nefazodone and its major metabolites are not altered in these "poor metabolizers." Plasma concentrations of one minor metabolite (mCPP) are increased in this population; the adjustment of SERZONE (nefazodone hydrochloride) dosage is not required when administered to "poor metabolizers." Nefazodone and its metabolites have been shown *in vitro* to be extremely weak inhibitors of CYP2D6. Thus, it is not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme. *CYP1A2 Isozyme* — Nefazodone and its metabolites have been shown *in vitro* not to inhibit CYP1A2. Thus, metabolic interactions between nefazodone and drugs metabolized by this isozyme are unlikely. **Electroconvulsive Therapy (ECT):** There are no clinical studies of the combined use of ECT and nefazodone. ***Carcinogenesis, Mutagenesis, Impairment of Fertility.*** **Carcinogenesis.** There is no evidence of carcinogenicity with nefazodone. The dietary administration of nefazodone to rats and mice for 2 years at daily doses of up to 200 mg/kg and 800 mg/kg, respectively, which are approximately 3 and 6 times, respectively, the maximum human daily dose on a mg/m² basis, produced no increase in tumors. **Mutagenesis:** Nefazodone has been shown to have no genotoxic effects based on the following assays: bacterial mutation assays, a DNA repair assay in cultured rat hepatocytes, a mammalian mutation assay in Chinese hamster ovary celis, an *in vivo* cytogenetics assay in rat bone marrow cells, and a rat dominant lethal study. **Impairment of Fertility:** A fertility study in rats showed a slight decrease in fertility at 200 mg/kg/day (approximately three times the maximum human daily dose on a mg/m² basis) but not at 100 mg/kg/day (approximately 1.5 times the maximum human daily dose on a mg/m² basis). ***Pregnancy:*** **Teratogenic Effects — Pregnancy Category C:** Reproduction studies have been performed in pregnant rabbits and rats at daily doses up to 200 and 300 mg/kg, respectively (approximately 6 and 5 times, respectively, the maximum human daily dose on a mg/m² basis). No malformations were observed in the offspring as a result of nefazodone treatment. However, increased early pup mortality was seen in rats at a dose approximately 5 times the maximum human dose, and decreased pup weights were seen at this and lower doses when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 1.3 times the human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Nefazodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of SERZONE on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether SERZONE (nefazodone hydrochloride) or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SERZONE is administered to a nursing woman. ***Pediatric Use:*** Safety and effectiveness in individuals below 18 years of age have not been established. ***Geriatric Use:*** Over 500 elderly (≥65 years) individuals participated in clinical studies with nefazodone. No unusual adverse age-related phenomena were identified in this cohort of elderly patients treated with nefazodone. Due to the increased systemic exposure to nefazodone seen in single dose studies in elderly patients (see **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, of the full prescribing information), treatment should be initiated at half the usual dose, but titration upward should take place over the same range as in younger patients (see **DOSAGE AND ADMINISTRATION** section of the full prescribing information). The usual precautions should be observed in elderly patients who have concomitant medical illnesses or who are receiving concomitant drugs.

ADVERSE REACTIONS: ***Associated with Discontinuation of Treatment:*** Approximately 16% of the 3496 patients who received SERZONE in worldwide premarketing clinical trials discontinued treatment due to an adverse experience. The more common (≥1%) events in clinical trials associated with discontinuation and considered to be drug related included: nausea, dizziness, insomnia, asthenia, and agitation. ***Incidence in Controlled Trials:*** **Commonly Observed Adverse Events in Controlled Clinical Trials:** The most commonly observed adverse events associated with the use of SERZONE (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients were: somnolence (25% vs 14%), dry mouth (25% vs 13%), nausea (22% vs 12%), dizziness (17% vs 5%), constipation (14% vs 8%), asthenia (11% vs 5%), lightheadedness (10% vs 3%), blurred vision (9% vs 3%), confusion (7% vs 2%), and abnormal vision (7% vs 1%). The following adverse events occurred at an incidence of 1% or more in patients treated with SERZONE dosed at ranges of 300 mg to 600 mg/day and were more frequent than in the placebo groups in 6- to 8-week placebo-controlled trials. **Body as a Whole:** headache, asthenia, infection, flu syndrome, chills, fever, neck rigidity. **Cardiovascular:** postural hypotension, hypotension. **Dermatological:** pruritus, rash. **Gastrointestinal:** dry mouth, nausea, constipation, dyspepsia, diarrhea, increased appetite, nausea and vomiting. **Metabolic:** peripheral edema, thirst. **Musculoskeletal:** arthralgia. **Nervous:** somnolence, dizziness, insomnia, lightheadedness, confusion, memory impairment, paresthesia, vasodilatation, abnormal dreams, concentration decreased, ataxia, incoordination, psychomotor retardation, tremor, hypertonia, libido decreased. **Respiratory:** pharyngitis, cough increased. **Special Senses:** blurred vision, abnormal vision, tinnitus, taste perversion, visual field defect. **Urogenital:** urinary frequency, urinary tract infection, urinary retention, vaginitis, breast pain. Events for which the SERZONE incidence was equal to or less than placebo included the following: abdominal pain, pain, back pain, accidental injury, chest pain, neck pain, palpitation, migraine, sweating, flatulence, vomiting, anorexia, tooth disorder, weight gain, edema, myalgia, cramp, agitation, anxiety, depression, hypesthesia, CNS stimulation, dysphoria, emotional labiilty, sinusitis, rhinitis, dysmenorrhea, dysuria. Studies show a clear dose dependency for some of the more common adverse events associated with SERZONE use. **Vital Sign Changes:** (See PRECAUTIONS section, Postural Hypotension Subsection.) **Weight Changes:** In a pooled analysis of placebo-controlled premarketing studies, there were no differences between nefazodone and placebo groups in the proportions of patients meeting criteria for potentially important increases or decreases in body weight (a change of ≥ 7%). **Laboratory Changes:** Pooled analysis revealed a statistical trend between nefazodone and placebo for potentially important decrease in hematocrit, ie, 2.8% of nefazodone patients compared to 1.5% of placebo patients ($0.05 < p \leq 0.10$). **ECG Changes:** Pooled analysis revealed a statistically significant difference between nefazodone and placebo for sinus bradycardia, ie, 1.5% of nefazodone patients compared to 0.4% of placebo patients ($p < 0.05$). ***Other Events Observed During the Premarketing Evaluation of SERZONE:*** During its premarketing assessment, multiple doses of SERZONE were administered to 3496 patients. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Body as a Whole** — *Infrequent:* allergic reaction, malaise, photosensitivity reaction, face edema, hangover effect, abdomen enlarged, hernia, pelvic pain, and halitosis. *Rare:* cellulitis. **Cardiovascular System** — *Infrequent:* tachycardia, hypertension, syncope, ventricular extrasystoles, and angina pectoris. *Rare:* AV block, congestive heart failure, hemorrhage, pallor, and varicose vein. **Dermatological System** —*Infrequent:* dry skin, acne, alopecia, urticaria, maculopapular rash, vesiculobullous rash, and eczema. **Gastrointestinal System** — *Frequent:* gastroenteritis. *Infrequent:* eructation, periodontal abscess, abnormal liver function tests, gingivitis, colitis, gastritis, mouth ulceration, stomatitis, esophagitis, peptic ulcer, and rectal hemorrhage. *Rare:* glossitis, hepatitis, dysphagia, gastrointestinal hemorrhage, oral moniliasis, and ulcerative colitis. **Hemic and Lymphatic System** — *Infrequent:* ecchymosis, anemia, leukopenia, and lymphadenopathy. **Metabolic and Nutritional System** — *Infrequent:* weight loss, gout, dehydration, lactic dehydrogenase increased, SGOT increased, and SGPT increased. *Rare:* hypercholesteremia and hypoglycemia. **Musculoskeletal System** — *Infrequent:* arthritis, tenosynovitis, muscle stiffness, and bursitis. *Rare:* tendinous contracture. **Nervous System** — *Infrequent:* vertigo, twitching, depersonalization, hallucinations, suicide attempt, apathy, euphoria, hostility, suicidal thoughts, abnormal gait, thinking abnormal, attention decreased, derealization, neuralgia, paranoid reaction, dysarthria, increased libido, suicide, and myoclonus. *Rare:* hyperkinesia, increased salivation, cerebrovascular accident, hyperesthesia, hypotonia, ptosis, and neuroleptic malignant syndrome. **Respiratory System**—*Frequent:* dyspnea and bronchitis. *Infrequent:* asthma, pneumonia, laryngitis, voice alteration, epistaxis, hiccup. *Rare:* hyperventilation and yawn. **Special Senses**—*Frequent:* eye pain. *Infrequent:* dry eye, ear pain, abnormality of accommodation, diplopia, conjunctivitis, mydriasis, keratoconjunctivitis, hyperacusis, and photophobia. *Rare:* deafness, glaucoma, night blindness, and taste loss. **Urogenital System**—*Frequent:* impotence.[a] *Infrequent:* cystitis, urinary urgency, metrorrhagia,[a] amenorrhea,[a] polyuria, vaginal hemorrhage,[a] breast enlargement,[a] menorrhagia,[a] urinary incontinence, abnormal ejaculation,[a] hematuria, nocturia, and kidney calculus. *Rare:* uterine fibroids enlarged,[a] uterine hemorrhage,[a] anorgasmia, and oliguria.

[a]Adjusted for gender.

Postintroduction Clinical Experience: Postmarketing experience with SERZONE has shown an adverse experience profile similar to that seen during the premarketing evaluation of nefazodone. Voluntary reports of adverse events temporally associated with SERZONE have been received since market introduction that are not listed above and for which a causal relationship has not been established. These include: Rare occurrences of convulsions (including grand mal seizures) and priapism (see **PRECAUTIONS** section); Rare reports of rhabdomyolysis involving patients receiving the combination of SERZONE and lovastatin or simvastatin (see **PRECAUTIONS** section); Rare reports of liver necrosis and liver failure, in some cases leading to liver transplantation and/or death.

DRUG ABUSE AND DEPENDENCE: ***Controlled Substance Class:*** SERZONE (nefazodone hydrochloride) is not a controlled substance. However, evaluate patients carefully for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SERZONE (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE: In premarketing clinical studies, seven patients ingested from 1000 mg to 11,200 mg of nefazodone; commonly reported symptoms included nausea, vomiting, and somnolence. None of the patients died. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Due to the wide distribution of nefazodone in body tissues, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for nefazodone are known. In managing overdosage, consider the possibility of multiple drug involvement.

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ADVENTURE: DOWN TO A SCIENCE

page 21

"Platelet monoamine oxidase (MAO) activity has been described as a peripheral marker of cerebral MAO activity. Platelet MAO activity has been found to be lower in individuals with a high level of impulsiveness and a tendency toward sensation-seeking behaviors. Increased platelet MAO levels have also been found in some psychiatric disorders related to the control of impulse, such as bulimia nervosa and pathological gambling."

IMPULSIVITY AND PLAYING THE ODDS

page 25

"Pathologic gambling is an impulse-control disorder associated with psychosocial decay, drug and alcohol abuse, depression, and anxiety. From a neurobiologic point of view, some evidence of altered function in the serotonin and norepinephrine systems has been observed. Compared with healthy volunteers, male and female gamblers have a blunted prolactin response to intravenously administered clomipramine (a serotonin reuptake inhibitor). In contrast, an elevated prolactin response to an oral dose of the partial serotonin agonist meta-chlorophenylpiperazine has been reported. Pathologic gamblers also have a significantly higher centrally produced fraction of the norepinephrine metabolite 4-hydroxy-3-methoxyphenyl glycol (HMPG), as well as a significantly higher urinary output of norepinephrine than controls."

THE POWER OF KUNDALINI YOGA

page 34

"The present investigation and our uncontrolled study yielded similar results, demonstrating reproducibility and suggesting that the KY protocol has therapeutic value without apparent side effects. Since the group using RR and MM showed no significant improvement, it can be assumed that the improvements in the KY group are not the consequence of a placebo effect or of attention, but rather a therapy-specific factor. While the KY protocol included a technique claimed by yogis to be specific for OCD, this protocol was complex; therefore, it is not clear which components led to efficacy. Studies evaluating subjects on the basis of electroencephalography, magnetoencephalography (MEG), cognitive performance, and mood all demonstrate that left-nostril breathing techniques selectively stimulate the right hemisphere of the brain. The results of other reviews identify right-hemispheric abnormalities with OCD, suggesting that the efficacy of this yogic technique may be due to a related effect. Our preliminary unpublished MEG results on the effects of the purportedly OCD-specific left-nostril breathing technique in a trained normal subject suggest that, while stimulation of the right hemisphere is diffuse and dramatic, a strong effect on the frontal and prefrontal right hemisphere may help to compensate for the OCD-related defect."

TRAZODONE TREATMENT: HALTING OBSESSION

page 48

"The results of these preliminary observations in five outpatients suffering from moderate to severe OCD suggest that trazodone augmentation may be beneficial in this disorder. Trazodone appears to be particularly effective in reducing the side effects produced by SSRIs, such as nausea, gastrointestinal distress, anxiety, sleep disturbances, weight gain, and sexual dysfunction. Resolution of these symptoms occurred quite rapidly in all SSRI-treated patients in whom trazodone augmentation was added. We believe that the peculiar pharmacologic properties of trazodone render it very tolerable and a useful addition to long-term therapy with an SSRI, such as is commonly necessary for OCD patients."

ANALYZING THE SCHIZO-OBSESSIVE SUBTYPE

page 50

"Obsessive-compulsive (OC) symptoms can occur in patients with other psychiatric disorders, including mental retardation, mood disorders, and schizophrenia. Using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV), and the symptom checklist of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), three subgroups of patients with an interrelation between OC symptoms and their principal psychotic disorder have been described: (1) those whose OC symptoms are independent, (2) those whose OC symptoms are partially related to their psychosis, and (3) those whose OC symptoms represent a continuum of their psychosis. Other phenomenologic discussions have suggested an interrelated pathology within the schizophrenia and obsessive-compulsive disorder (OCD) symptom spectrum. These two conditions have many overlapping as well as some distinct symptoms. For patients with chronic psychotic disorders and prominent OC symptoms, the diagnostic classification of schizo-obsessive subtype has been proposed. Its prevalence, apparently poorer outcome, and possibly distinct pharmacotherapeutic approach, emphasize its importance. In patients with chronic psychotic disorders, a recent cohort study found OCD and panic disorder to be the most prevalent comorbid psychiatric conditions. Although most prevalence studies of schizophrenia and OCD have reported rates ranging from 10% to 25%, some studies have found the prevalence of obsessions and/or compulsions in patients with psychotic disorders to be as high as 50%."

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/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 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%), abnormal 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

SB SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

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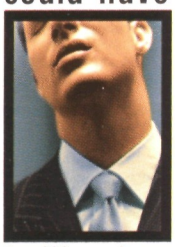
should have

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.

NEUROSCIENCE DIVISION

For more information call 1-800-454-6163 or visit us at www.paxil.com

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. PX2987

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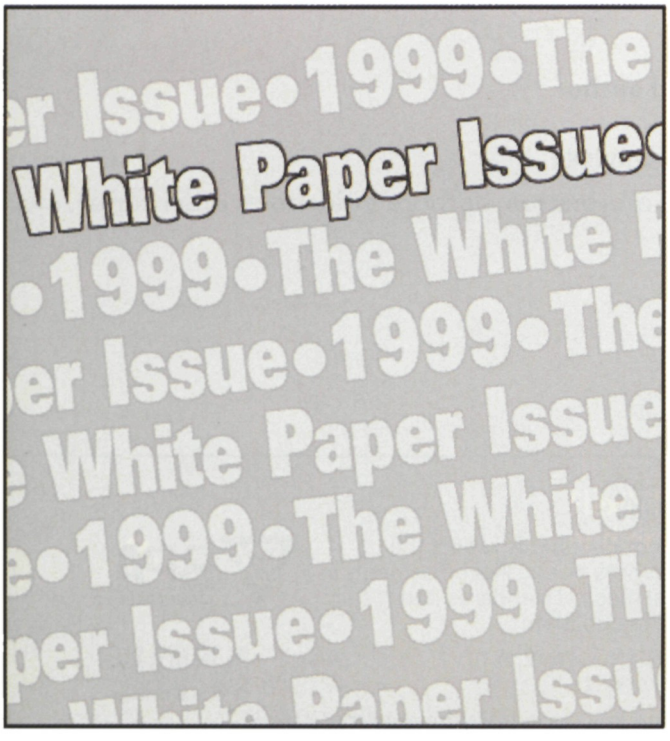

Photo Essay
This traditional year-end White Paper issue of *CNS Spectrums* highlights new and original research in the area of impulsivity and compulsivity. Novel topics covered in this issue include platelet monoamine oxidase activity in sensation-seeking Spanish bullfighters, neurotransmitter metabolite levels in the cerebrospinal fluid of pathological gamblers, yogic meditation treatment of obsessive-compulsive disorder (OCD), trazodone treatment of refractory OCD, the schizo-obsessive subtype of schizophrenia, and savant syndrome.

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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/m^2 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/m^2 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, gastroesophageal 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:* polyuna/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.

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