# CNS SPECTRUMS

The International Journal of Neuropsychiatric Medicine

Life Charting of Affective Disorders

G. Leverich

Through the Looking Glass: A Psychologist's Experience of Depression

M. Manning

to the Course and Treatment of Bipolar Disorder

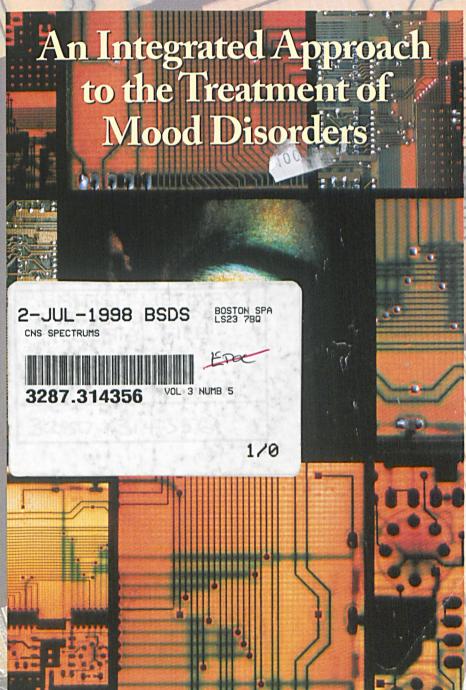
D. Miklowitz

Treatment of Refractory
Bipolar Illness:
The Role of Complex
Combination Therapy

R. Post

Grand Rounds
Teaching Monograph:
Current Treatments in
Bipolar Disorder

N. Sussman, C. Bowden, G. Asnis



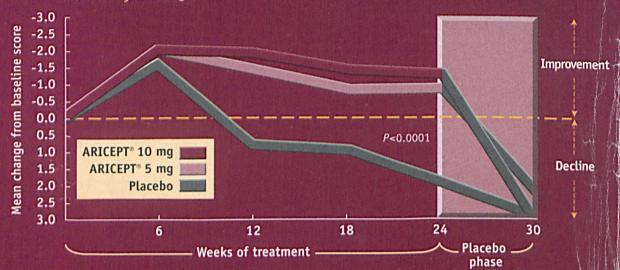
CME Mount 3
Category 1

Photo Essay This issue charts the course of mood disorders and suggests integrated treatmer and complex polypharmacy approaches to affective illness. Articles Inside.

## Once-a-day ARICEPT® (donepezil HCl)-First-line therapy for mild to moderate Alzheimer's disease

PROVEN EFFECTIVE IN ENHANCING COGNITIVE FUNCTION

Effect on cognitive function over 24 weeks of active treatment and 6 weeks of placebo as measured by ADAS-cog1\*



\*Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) is a 70-point, clinically validated psychometric scale for measuring cognitive function in patients with Alzheimer's disease. In one controlled clinical trial of 30 weeks' duration in 473 patients, 154 patients were randomly assigned to receive daily doses of 5 mg. One hundred fifty-seven patients were randomly assigned to receive daily doses of 10 mg. One hundred sixty-two patients were randomized to placebo. The 30-week trial was divided into a 24-week double-blind active treatment phase followed by a 6-week single-blind placebo washout period.

- Significant benefits observed in 24-week study in both 5 mg/day and 10 mg/day ARICEPT® groups
- Placebo washout demonstrates that beneficial effects of ARICEPT® abate following discontinuation

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

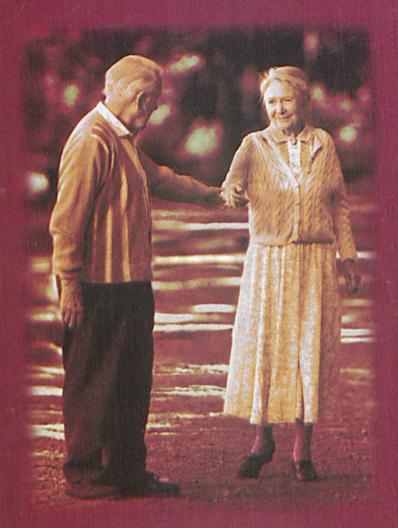
Reference: I. Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*. 1998;50:136-145. ARICEPT® is a registered trademark of Eisai Co., Ltd.

## EXPERIENCE & CONVENIENCE

- Over 250,000 prescriptions written to date
- Once-daily administration, with or without food
- Some patients might derive additional benefit from escalation to 10-mg daily after 4 to 6 weeks of 5-mg once-daily therapy

## SAFETY & TOLERABILITY

- No liver function testing required
- No significant drug-drug interactions observed in clinical trials with the following commonly prescribed medications: cimetidine, digoxin, theophylline, and warfarin
- The most common adverse events leading to discontinuation in clinical trials with ARICEPT® 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)



ARICEPT®

(done pezil HC)

5-MG AND 10-MG TABLETS

THERAPY TO REMEMBER

# ARICEPT® (donepezil HCI)

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) those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIUS). 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\*, effontive unique of the production of the continued 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* Binding 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; about 50 –130 µM), that, given the therapeutic plasma concentrations of donepezi (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 the property of the control of ARICEPT\* has any potential for enzyme induction is not known. Formal pharmacowniant studies evaluated the potential of ARICEPT\* for interaction with theophylline, cimetidine, warfaria 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 the control of the c 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 Anticholinergias: Because 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 cholinesteras 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 does on a mg/m² basis). **Pregnancy** *Pregnancy Category* C: Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT's 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%

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

Adverse Event	No ti	tration	One-week titration	Six-week titration
	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%

[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\* he 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, taligue, and anorexia. These adverse events were often indict intensity and transient, resolving during continued ARICEPT\* retainment 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 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 cocurred more frequently in female patients and with advancing age. Other Adverse Events

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

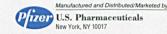
Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients With Any Adverse Event	72	74
Body as a Whole		Control Section Control
Headache	9	10
Pain, Various Locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		AND THE RESERVE
Syncope	and the distance of the force of the con-	2
Digestive System	a system of the state of the st	gradition (Committee)
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System	I Mentingang patulangang a	GOOD WARREN WATER
Ecchymosis	3	4
Metabolic and Nutritional Systems	Action on the grant story story of	National Community
Weight Decrease	and a control of the state of t	3
Musculoskeletal System	description for the second	Anna Property Control
Muscle Cramps	2	6
Arthritis	Andreas Inches	2
Nervous System		distribution de la constitución
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		A STATE OF THE STA
Frequent Urination	Approximation of the contraction of	2

Observed During Clinical Trials ARIOLET has been administered to over 1700 individuals during clinical mais 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 expand for summings, 775 patients treated for over 1 year. The range of patient properties from 110 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 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; \*infequent\* adverse events—those occurring in 1/100.01 adverse events—those occurring in a least trivial patients, implementation accesses events—those occurring in 17 rou of 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, events were seen in studies conducted outside the United States. Body as a Whole: Frequent: Influenza, chest pain, toothache; Infrequent: tever, 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, drobling, dry mouth, fever sore, gastriis, iritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrholds, ileus, increased thirst, jaundice, melena, polydypsia, duodenal ulcer, stomach ulcer. Endocrine System: Infrequent: diabetes mellitus, goiter, Hemic and Lymphatic System: Infrequent: diabetes mellitus, goiter, Hemic and Lymphatic and Nutritional Disorders: Frequent: dehydration; Infrequent: gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. Musculoskeletal System: Frequent: delisions, tremor, Infrequent: misscle weakness, muscle fasciculation. Nervous System: Frequent: delisions, termor, hyperglycemia, weignt increase, increases usuate veryorigeriase, musculoskeletal system: Frequent: bone fracture; Interquent: moste descributation. Nervous System: Frequent: deliusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; Intrequent: cerebrovascular accident, intracranial hemorrhage, translend 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 considerations and procedure of the withdrawal, nystagmus, pacing. Respiratory System: Frequent: dyspnea, sore throat, bronchitis; Infrequent: withdrawal, nystagmus, pacing, **Hespiratory System**. Frequent, systems, site timost, proncinits; *intrequent*, epistaxis, postasaal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages**: *Frequent*: pruritus; diaphoresis, urticaris; *Intrequent*: dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, here soster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses**: *Frequent*: cataract, eye irritation, vision blurred; *Intrequent*: dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis burleu, mieguem, dry yeys, guacona, caracte, mimos, dispirantis, decreaser interity, fetinal nemorrhage, ontite sexterna, otitis media, bad taste, conjunctival hemorrhage, ear buzziling, motion sickness, spots before eyes Urogenital System: Frequent: urinary incontinence, nocturia; infrequent: dysuria, hematuria, urinary urgency metrorrhagia, cystilis, enuresis, prostate hypotrophy, pyelonephritis, inability to empty badder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal tailure, vaginitis. Postiatroduction Reports Voluntary reports of adverse htdrocystic preast, missuus, pyuna, rena famor, argumes. Postnitude that nepurs voluntary reports or adverse events temporally associated with ARICET® that have been received since market introduction that are not listed above, and that may have no causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, pancreatitis, and rash. OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control for the management of overlose 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, bradysardia, 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 inidea set of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate to 2.0 mig twith susception to see asset upon timical response. Adjutant responses in blood pressure and near that 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, pertitioneal 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, freatment 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 0 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.

Revised December, 1997.



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The International Journal of Neuropsychiatric Medicine

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## **CNS Spectrums**

The International Journal of Neuropsychiatric Medicine

### INTRODUCTION

CNS Spectrums is a peer-reviewed journal that publishes original scientific literature and reviews on a wide variety of neuroscientific topics of interest to the clinician. CNS Spectrums will publish 10 issues in 1998. As the immense prevalence of comorbid diseases among patients seen by psychiatrists and neurologists increases, these physicians will jointly diagnose and treat the neuropsychiatrically ill. Our mission is to provide these physicians with an editorial package that will enhance and increase their understanding of neuropsychiatry. To this end, manuscripts that address crossover issues germane to neurology and psychiatry will be given immediate priority.

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**References:** American Medical Association style. See the following examples:

- 1. Jones J. Necrotizing Candida esophagitis. JAMA. 1980;244:2190-2191.
- Stryer L. Biochemistry. 2nd ed. San Francisco, Calif: WH Freeman Co; 1980:559-596.

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Pain Management	□ 5	□ 4	□ 3	□ 2	□ 1	
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Thank you.

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Address:	

Each responder will receive a complimentary copy of a pocket reference guide: 1998 Black Book of Psychotropic Dosing and Monitoring and the premiere issue of our new mental health magazine, **Mental Fitness by** filling out this faxback form.



PAXIL® (brand of paroxetine hydrochloride)
See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or PDR. The following is a brief summary.
INDICATIONS AND USAGE: Paxil is indicated for the treatment of depression, obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in DSM-IV, and panic disorder, with or without agoraphobia, as defined in DSM-IV.
CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. (See WARNINGS and PRECAUTIONS.)
WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use Paxil in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping Paxil before starting a MAOI.
PRECAUTIONS: As with all antidepressants, use Paxil cautiously in patients with a history of mania.
Use Paxil cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

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.

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 Paul in patients with concomitant systemic illness is limited. Use cautiously in natients with diseases as conditions that could affect metabolism or hamodynamic responses. Observe 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

the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <a href="#">-30 mL/min.</a>) 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.

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 PasolIDs (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines such as thoridazine; 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 IIIA4, substrates (astemizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent than ketoconazole, a potent IIIA4 inhibitor. Assuming that the relationship between paroxetines in vitro ki and its lack of effect on terfenadine's in vivo clearance predicts its effect on other IIIA4 substrates, paroxetine's inhibition of IIIA4 activity should have little clinical significance. Use caution when co-administraring 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 lithium or digoxin cautiously. If adverse effects are seen when co-administering Paxil with procyclidine, reduce the procyclidine dose. Elevated theophylline levels have been re

evidence of mutagenicity with *Paxil*.

Rats receiving paroxetine at 15 mg/kg/day (2.4 times the MRHD on a mg/m² basis) showed a reduced preg-

Pregnancy Category C. Reproduction studies performed in rats and rabbits at doses up to 6 mg/kg/day, 8.1 (rat) and 1.9 (rabbit) times the MRHD on a mg/m² basis, have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Paxil should be used in pregnanty only if the potential benefit justifies the potential risk to the fetus. The effect of Paxil on labor and delivery in humans is unknown. Paroxetine is secreted in human milk, exercise caution when administering Paxil to a nursing woman. Safety and effectiveness in the pediatric population have not been established. In worldwide premarketing Paxil clinical trials, 17% of Paxil-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly, however, there were no overall differences in the adverse event profile between older and younger patients.

ADVERSE REACTIONS: Incidence in Controlled Trials—Commonly Observed Adverse Events in Controlled Clinical Trials: The most commonly observed adverse events associated with the use of Paxil in the treatment of depression (incidence of 5% or greater and incidence for Paxil asst twice that for placebol: 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 for placebol: asthenia (15% vs. 5%), events and incidence for Paxil at least twice

orders (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%).
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. 5%), seveating (14% vs. 5%), escential (14% vs. 5%), sweating (14% vs. 5%), escential (14% vs. 5%), sweating (14% vs. 5%), decreased appetite (7% vs. 3%), libido decreased (9% vs. 1%), tremor (9% vs. 1%), abnormal ejaculation (21% vs. 1%), female genital disorders (9% vs. 1%) and impotence (5% vs. 0%).
Twenty percent (1,199/6,145) of *Paxil* patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with dis-

y, 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; https://doi.org/10.1017/51092852900031060 Published online by Cambridge University Press OCD-insomnia, dizziness, constipation, nausea, asthenia, abnormal ejaculation, impotence; panic dis-

order—somnolence, insomnia, nausea.

The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequen-

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 10 to 12 weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on Paxil who participated in placebo-controlled trials of 10 to 12 weeks duration in which patients were dosed in a range of 10 to 60 mg/day; asthenia, abdominal pain\*, chest pain\*, back pain\*, chills; vasodilation\*, palpitation\*, palpitation\*, palpitation\*, palpitation\*, sweating, rash\*\*; nausea, dry mouth, constipation, diarrhea, decreased appetite, increased appetite; insomnia, somnolence, dizziness, tremor, nervousness\*\*, libido decreased, agitation\*, anxiety\*, abnormal dreams\*\*, concentration impaired\*\*, depersonalization\*, myoclonus, amnesia\*\*, finitis\*, abnormal vision\*\*, taste perversion\*\*; abnormal ejaculation, female genital disorder, impotence, urinary frequency, urination impaired\*\*, urinary tract infection. \*denotes panic disorder patients only. \*\*denotes OCD patients only. \*\*denotes OCD patients only. \*\*denotes OCD patients only. \*\*denotes OCD patients only. patients only.

Studies show a clear dose dependency for some of the more common adverse events associated with Paxil use. There was evidence of adaptation to some adverse events with continued Paxil therapy (e.g., nausea and dizziness). Significant weight loss may be an undesirable result of Paxil treatment for some patients but, on average, patients in controlled trials had minimal (about 1 lb) loss. In placebo-controlled clinical trials, Paxil-treated patients exhibited abnormal values on liver function tests no more frequent-

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 exhibited abnormal values on liver function tests no more frequently than placebo-treated patients.

Other Events Observed During the Premarketing Evaluation of Paxil: During premarketing assessment in depression multiple doses of Paxil were administered to 6,145 patients in phase 2 and 3 studies. During premarketing clinical trials in OCD and panic disorder, 542 and 469 patients, respectively, received multiple doses of Paxil. The following adverse events were reported. Note: "frequent" e-yents occurring in at least 1/100 patients; "infrequent" adverse events were reported. Note: "frequent" e-less than 1/1000 patients. Events are classified within body system categories and enumerated in order of decreasing frequency using the above definitions. It is important to emphasize that although the events occurred during Paxil treatment, they were not necessarily caused by it.

Body as a Whole: frequent: chills, malaise; infrequent: allergic reaction, carcinoma, face edema, moniliasis, neck pain; rare: abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, shock, ulcer. Cardiovascular System: frequent: hypertension, syncope, tachycardia; infrequent: bradycardia, conduction abnormalities, electrocardiogram abnormal, hematoma, hypotension, migraine, peripheral vascular disorder; rare: angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles. Digestive System: infrequent: bruxism, colitis, dysphagia, eructation, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rect esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatiis, ileus, intestinal obstruction, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries, tooth malformation. Endocrine Systems: nifrequent: anemia, leukopenia, lymphadenopathy, purpura; rare: ahonmal erythrocytes, basophilia, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphadema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia. Metabolic and Nutritional: frequent: edema, weight gain, weight loss; infrequent: hyperglycemia, peripheral edema, SGOT increased, SGPT increased, dehydration, gamma globulins increased, gout, hypercalcemia, hyporatremia, ketosis, lactic dehydrogenase increased. Musculoskeletal System: frequent arthralgia; infrequent: arthralgia; infrequent; are: anonal electronecephalogram, anonama jait, artisocial reaction, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus, withdrawal syndrome. R

leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, prostatic carcinoma, pyuria, urethritis, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports

Voluntary reports of adverse events that have been received since market introduction and not listed above that may have no causal relationship with Paxil include—acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, thrombocytopenia, syndrome of inappropriate ADH secretion, symptoms augestive of pro-lactinemia 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—PXL14

BRS-PX:L14

ST SmithKline Beecham Pharmaceuticals Philadelphia, PA 19101



COLURALS

PANIC DISORDER

The symptoms may overlap...

but the solution is the same

DEPRESSION

Mass common adverse events (incidence of 5% or greater and incidence for *Paxil* at least spice that for placebo) in depression or OCD or pane disorder studies include nausea sommolence, abnormal ejaculation, dry mount constipation, asthenia, sweating userness, insomnia, tremor, female general disorders, libido decreased decreased usorders, libido decreased, libido de

Please see brief summary of prescribing information at the end of this advertisement.

ONCE-DAILY

PAROXETINE HCI

Lifts depression. Lowers associated anxiety symptoms.

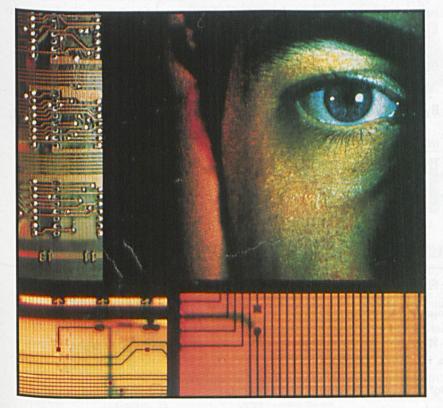
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## CNS SPECTRUMS

The International
Journal of Neuropsychiatric Medicine
Volume 3 • Number 5
May 1998

#### PHOTO ESSAY

This issue charts the course of mood disorders and suggests integrated treatment and complex polypharmacy approaches to affective illness. According to guest editor, David Goldstein, MD, it should be remembered that "The current explosion of biological data about the brain has dazzled many of us...Our technological advances should not blind us to the truth and values of the humanistic psychosocial world...This issue [is] part of an effort to integrate existing knowledge rather than to extend one area at the expense of another."

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## CNS Spectrums (ISSN 1092-8529)

is published monthly except combined Jul/Aug & Nov/Dec by MBL Communications, 665 Broadway, New York, NY 10012-2302.

Periodicals postage paid at New York, NY, and at additional mailing offices.

One year subscription rates: domestic \$90; foreign \$145; in-training \$50. For subscriptions: Fax 212-328-0600.

Postmaster: Send address changes to CNS Spectrums 665 Broadway New York, NY 10012-2302

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Medical Broadcast Limited

## Hostile outside.

# Fragile inside.



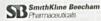
- Improving a broad range of psychotic symptoms\*
  - Hostility, delusions, excitement, suspiciousness, hallucinations
  - Blunted affect, emotional withdrawal, poor rapport, apathy
- Low incidence of<sup>†</sup>
  - -Movement disorders
  - —Excessive sedation
  - —Anticholinergic effects
- The #1 prescribed antipsychotic in long-term care¹
- Available in tablets and oral solution; convenient B.I.D. and Q.D. dosing

For additional medical information on the use of RISPERDAL, please call **1-800-JANSSEN** (1-800-526-7736).

- \* The Positive and Negative Syndrome scale (PANSS) in its entirety also includes 16 general psychopathology score items; therefore, conclusions as to efficacy outcomes of individual items should not be drawn.
- <sup>†</sup>Percentage of adult patients reporting adverse events and using 2 mg/day dose in a clinical trial: movement disorders (13%), excessive sedation (2%), anticholinergic effects (up to 5%).











## Gentler days ahead.

Clinical trials were conducted in adult patients with chronic schizophrenia; limited data are available in geriatric patients with psychoses.

The most common adverse events reported in premarketing clinical trials in adults (n>2600) were insomnia, agitation, movement disorders, headache, anxiety, and rhinitis; less common were somnolence, dizziness, constipation, nausea, and tachycardia.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia; if its signs and symptoms appear, discontinuation of RISPERDAL should be considered.

Reference: 1. IMS Long-Term Care Audit, January 1998.

Please see brief summary of Prescribing Information on adjacent page.



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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychoic 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

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

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 lifethreatening 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 In U.2% (0/20/7) of HISPENDAL\* treated patients in phase 2.5 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). 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

Hyperprolactinemia: As with other drugs that antagonize dopamine D, 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® **Laboratory Tests** 

No specific laboratory tests are recommended.

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.

Drugs that Inhibit Cytochrome P\_IID, and Other P\_Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P\_IIID, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARIMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydrox ase 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  $P_{\rm ss}$  isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome P\_IID.: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P\_IID. 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 expectations are not available. 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 nince and viristar rats. rispendore 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 (file mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas.

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

Mutagenesis: No evidence of mutagenic potential for risperidone was found. Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis.

Pregnancy

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

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

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

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

Pediatric Use

Safety and effectiveness in children have not been established

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. 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 a greater tendency to postural hypotension.

ADVERSE REACTIONS

ociated 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, treatmentemergent 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 se 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<sup>1</sup>, 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, sebornea. Infections: upper respiratory. Visual: abnormal vision. Musculo-Skeletal: arthralgia. Cardiovascular: tachycardia.

<sup>1</sup> 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 process of line received in the proportions or patients expeniencing 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 (nspendone) 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 6 in 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 is re not necessarily caused by it.)

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: dysarthna, vertigo, stupor, paraesthesia, confusion. Rare: aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, le leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoa-

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, broncho-spasm, pneumonia, stridor. Rare: asthma, increased sputum, aspiration.

spasin, preutionia, stroot. Fate: astimna, increased sputum, aspiration. Skin and Appendage Disorders: Frequent: increased pigmentation\*, photo-sensitivity\*. Infrequent: increased sweating, acne, decreased sweating, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

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

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

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

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

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

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

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

Platelet, Bleeding and Clotting Disorders: Infrequent: epistaxis, purpura.
Rare: hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia. Hearing and Vestibular Disorders: Rare: tinnitus, hyperacusis, decreased hearing

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

Reproductive Disorders, Male: Frequent: erectile dysfunction\* Infrequent: ejaculation failure White Cell and Resistance Disorders: Rare: leukocytosis,

lymphadenopathy, leucopenia, Pelger-Huet anomaly. Endocrine Disorders: Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: bitter taste

Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market intro-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. drugs.

DRUG ABUSE AND DEPENDENCE

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

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

More detailed professional information is available upon request.

Q Janssen Pharmaceutica, Inc. 1998 US Patent 4,804,663 June 1997, November 1997

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