April 1998 Volume 3 - Number 4

CNS SPECTRUMS™

The International Journal of Neuropsychiatric Medicine

The Panic-Agoraphobic Spectrum

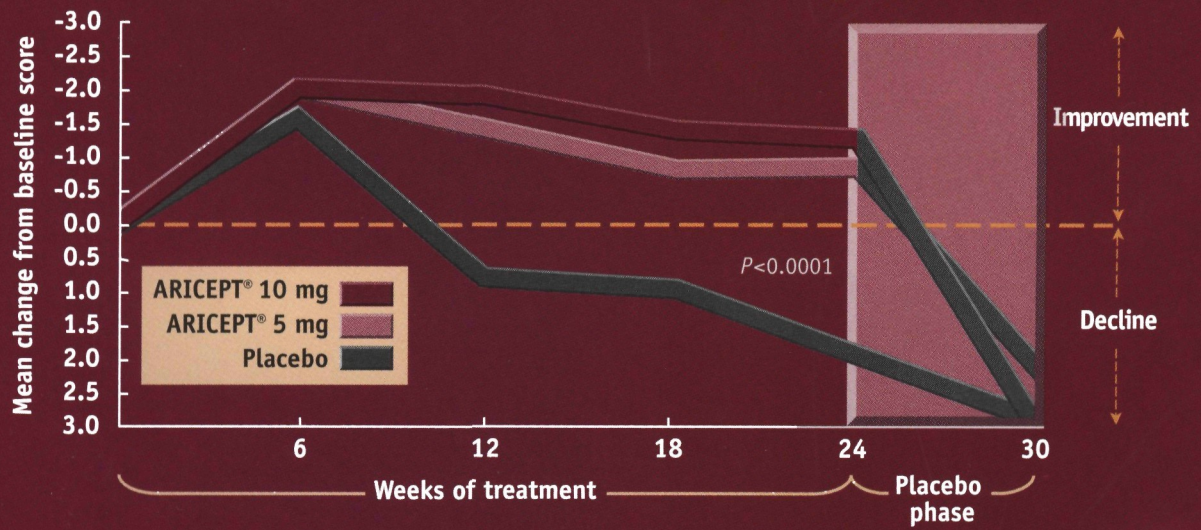
Photo Essay This issue of *CNS Spectrums* further illustrates the spectrum approach to neuropsychiatry by opening the door to the emerging panic-agoraphobia spectrum. **Articles Inside.**

CME Mount Sinai 3

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-cog[1]**



*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: 1. 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.

https://doi.org/10.1017/S1092852900005769 Published online by Cambridge University Press

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)

ONCE-A-DAY
ARICEPT®
(donepezil HCl)
5-MG AND 10-MG TABLETS

THERAPY TO REMEMBER™

ONCE-A-DAY ARICEPT® (donepezil HCl)

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

ARICEPT® (Donepezil Hydrochloride Tablets)

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

Revised December, 1997.

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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IN THE JOURNAL OF APRIL 1998

"In general, there is increasing evidence of continuity between childhood and adult psychiatric disorders, and it is widely accepted that the evaluation of the childhood antecedents of specific adult disorders is important for prevention and assessment of risk of adult disorders."

THE NEED FOR A NEW NOMENCLATURE

page 25

"The current nomenclature is too rudimentary for our current research or treatment efforts. The elegant neuroscience methodologies and sophisticated genetics techniques in the research arena appear at least partially stalled by an inadequate phenotypic nomenclature. The search for an improved understanding of etiology and pathogenesis is similarly hampered.

Marked improvements are also needed in our current ability to match patients to therapies and to achieve more complete and durable treatment effects. We must acquire an improved ability to identify those patients who would benefit from medications alone, cognitive-behavioral and/or interpersonal therapies, or some combination of these. For example, the first attempted treatment is generally successful in a maximum of 60% of mood disorder cases. This leaves 40% of patients who must proceed to try one or more additional therapies before success is achieved."

DETECTING SUBTHRESHOLD SYMPTOMATOLOGY

page 47

"The subthreshold and atypical symptomatology of panic spectrum is likely to be overlooked, resulting in no treatment, or even interpreted as personality traits, resulting in incorrect treatment. We contend that these 'trait-like' symptoms may be considered as early-onset manifestations of an illness diathesis. They occur concomitantly with and influence the course of supervening major psychiatric disorders, the outcome of which may dramatically improve when accompanying subthreshold phenomena are specifically detected and treated."

PANIC IN PSYCHOSIS

page 55

"The occurrence of panic attacks in psychosis may be overshadowed by prominent psychotic disturbances or trivialized by clinicians who are treating severe delusions, hallucinations, or other psychological abnormalities. However, an increasing number of studies and clinical reports show that the assessment of panic features provides a useful clinical construct to capture additional components of the heterogeneous phenomenology of psychoses. Revealing panic in psychotic patients may have substantial therapeutic implications."

EXAMINING PANIC AND CARDIOVASCULAR DISEASE

page 58

"Although cardiovascular diseases (such as myocardial infarction or hypertension) and anxiety disorders have been found to be closely related, their reciprocal relationships are not completely clear. Similarly, anxiety symptoms often present with cardiac manifestations. In the past, these conditions often have been described as 'irritable heart,' 'effort syndrome,' or 'neurocircular asthenia.'

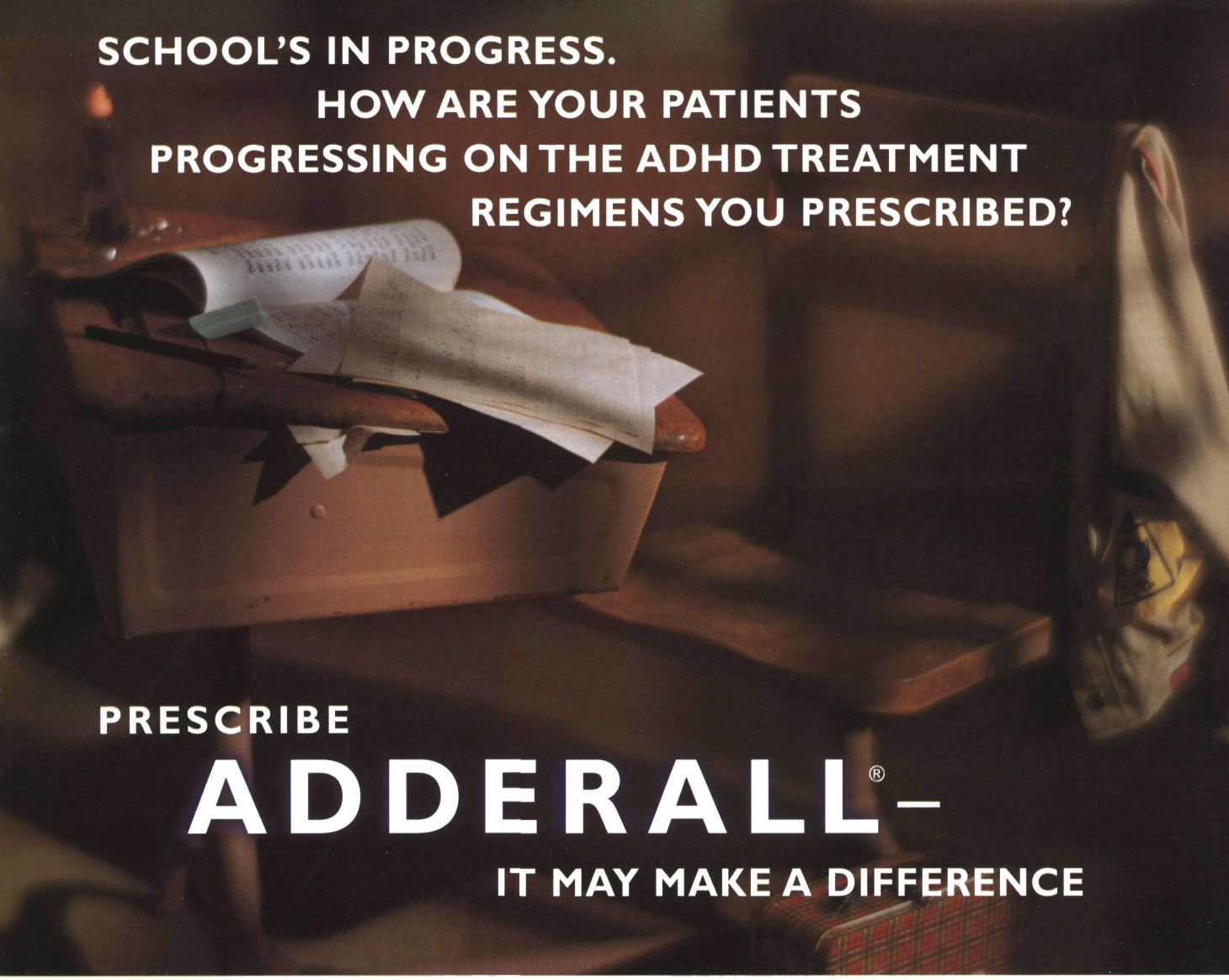
Systematic identification of the full range of anxiety symptoms in patients with cardiovascular diseases in clinical practice is important for two reasons. First, anxiety syndromes frequently complicate the course of cardiovascular disease. Second, the treatment strategy may be quite different when the two disorders occur concomitantly in the same individual.

This preliminary study explored in detail the phenomenology of anxiety symptoms in a cohort of cardiovascular patients in an internal medicine setting who were willing to take the Structured Clinical Interview for Panic-Agoraphobic Spectrum (SCI-PAS)."

CONTINUITY BETWEEN CHILDHOOD AND ADULT PSYCHIATRIC DISORDERS

page 65

"In general, there is increasing evidence of continuity between childhood and adult psychiatric disorders, and it is widely accepted that the evaluation of the childhood antecedents of specific adult disorders is important for prevention and assessment of risk of adult disorders. Thus, a number of investigators have undertaken the examination of a possible link between childhood separation anxiety disorder and adult psychiatric disorders. In particular, a prominent theory of panic disorder hypothesized that panic attacks can be conceptualized as a manifestation of separation anxiety, and predicted a specific relationship between childhood separation anxiety disorder and adult panic disorder."



As children settle into the routine of a structured classroom environment and teachers become more familiar with individual capabilities and behavior patterns, potential problem behavior and academic underachievement may become more apparent. A change in medication may be warranted to optimize individual ADHD treatment plans.

The ADDERALL® (mixed salts of a single-entity amphetamine product) Formulation and Starting Dosage Frequency of One to Two Times Per Day[1] May Make a Difference

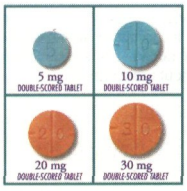
ADDERALL is the only ADHD product available to contain both dextro (*d*) and levo (*l*) amphetamine

ADDERALL usage data (n=611) indicate that **OVER 90% OF PATIENTS** can be maintained on a dosage frequency of one to two times per day[2]*

ADDERALL usage data (n=611) indicate that most patients, across a range of doses, do not experience adverse events with a frequency of more than 1%[2]*

ADDERALL is available in 5 mg, 10 mg, 20 mg, and **NEW 30 mg** double-scored tablets which allows you to achieve precise dosage correlation with individual therapeutic needs in a single prescription

As with most psychostimulants indicated for ADHD, the possibility of growth suppression and the potential for precipitating motor tics and Tourette's syndrome exists with ADDERALL treatment, and in rare cases exacerbations of psychosis have been reported. Since amphetamines have a high potential for abuse, ADDERALL should only be prescribed as part of an overall multimodal treatment program for ADHD with close physician supervision.



ADDERALL® C II

5 mg, 10 mg, 20 mg & 30 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

Please see reverse side for references and brief summary of prescribing information.

*Thirty-four patients receiving greater than 40 mg per day were excluded from this analysis.

https://doi.org/10.1017/S1092852900005769 Published online by Cambridge University Press

REFERENCES: 1. ADDERALL Package Insert, Richwood Pharmaceutical Company Inc. **2.** Data on file, Richwood Pharmaceutical Company Inc. Analysis of open-label data collected from March 1995 through February 1996.

ADDERALL® C II

5 mg, 10 mg, 20 mg & 30 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate — Amphetamine Sulfate
Dextroamphetamine Saccharate — Amphetamine Aspartate

ADDERALL® TABLETS C II BRIEF SUMMARY

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

INDICATIONS: Attention Deficit Disorder with Hyperactivity: ADDERALL is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted. **In Narcolepsy: CONTRAINDICATIONS:** Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result). **WARNINGS:** Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment. **Usage in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing. **PRECAUTIONS: General:** Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. **Information for Patients:** Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly. **Drug Interactions:** *Acidifying agents* - Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines. *Urinary acidifying agents* - (ammonium chloride, sodium acid phosphate, etc.) Increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines. *Adrenergic blockers* - Adrenergic blockers are inhibited by amphetamines. *Alkalinizing agents* - Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines. *Antidepressants, tricyclic* - Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. *MAO inhibitors* - MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results. *Antihistamines* - Amphetamines may counteract the sedative effect of antihistamines. *Antihypertensives* - Amphetamines may antagonize the hypotensive effects of antihypertensives. *Chlorpromazine* - Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning. *Ethosuximide* - Amphetamines may delay intestinal absorption of ethosuximide. *Haloperidol* - Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines. *Lithium carbonate* - The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate. *Meperidine* - Amphetamines potentiate the analgesic effect of meperidine. *Methenamine therapy* - Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy. *Norepinephrine* - Amphetamines enhance the adrenergic effect of norepinephrine. *Phenobarbital* - Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action. *Phenytoin* - Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action. *Propoxyphene* - In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. *Veratrum alkaloids* - Amphetamines inhibit the hypotensive effect of veratrum alkaloids. **Drug/Laboratory Test Interactions:** • Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. • Amphetamines may interfere with urinary steroid determinations. **Carcinogenesis/Mutagenesis:** Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed. **Pregnancy - Teratogenic Effects:** Pregnancy Category C. Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude. **Pediatric Use:** Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE. Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications. Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated. **ADVERSE REACTIONS: Cardiovascular:** Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. **Central Nervous System:** Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome. **Gastrointestinal:** Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. **Allergic:** Urticaria. **Endocrine:** Impotence, changes in libido. **DRUG ABUSE AND DEPENDENCE:** Dextroamphetamine sulfate is a Schedule II controlled substance. Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines. **OVERDOSAGE:** Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal. In rats, the oral LD50 of dextroamphetamine sulfate is 96.8 mg/kg. **Symptoms:** Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomolysis. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma. **Treatment:** Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine (Regitine®, CIBA) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication. **DOSAGE AND ADMINISTRATION:** Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia. **Attention Deficit Disorder with Hyperactivity:** Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. **Narcolepsy:** Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response. Narcolepsy seldom occurs in children under 12 years of age; however, when it does dextroamphetamine sulfate, may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. **CAUTION:** Federal law prohibits dispensing without prescription.

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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.

SCOPE OF MANUSCRIPTS

CNS Spectrums will consider the following types of articles for publication:

Original reports: Original reports present methodologically sound original data.

Reviews: Reviews are overview articles that summarize and synthesize the literature on various topics in a scholarly and clinically relevant fashion. Suitable topics include mood disorders, schizophrenia and related disorders, personality disorders, substance-use disorders, anxiety disorders, neuroscience, psychosocial aspects of psychiatry, child psychiatry, geriatric psychiatry, and other topics of interest to clinicians. nb: Original flowcharts designed to aid the clinician in diagnosis and treatment will be considered for publication in reviews and are encouraged.

Case reports: Single or multiple case reports will be considered for publication.

Letters to the editor: Letters will be considered for publication.

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General information: Two copies of the manuscript should be submitted to Eric Hollander, editor (or in Europe to Joseph Zohar, international editor), c/o MBL Communications, Inc., 665 Broadway, New York, NY 10012; (T) 212-328-0800, (F) 212-328-0600. Authors are required to submit their manuscripts on computer disks. If possible, please provide them in MSWord, WordPerfect, or Word for Windows in either a Macintosh or IBM format (saving the file in a lower version, eg, MSWord 3.0, is also encouraged). Disks should be labeled with the word-processing program, title of paper, and first author's name.

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Length: Reviews should not exceed 40 manuscript pages (10,000 words). Original reports should not exceed 15–25 manuscript pages (6,250 words, maximum). Letters should not exceed 2–6 manuscript pages (1,500 words, maximum). Single case reports should not exceed 10–15 manuscript pages (3,750 words, maximum) and may be submitted with a photograph, if applicable. Diagnostic/treatment algorithms (see Reviews) should contain an extensive introduction, a flowchart or series of graphs that fill eight to 12 journal pages, and a concise summary.

Spacing: One space should be left after commas and periods. manuscripts should also be double-spaced.

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

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

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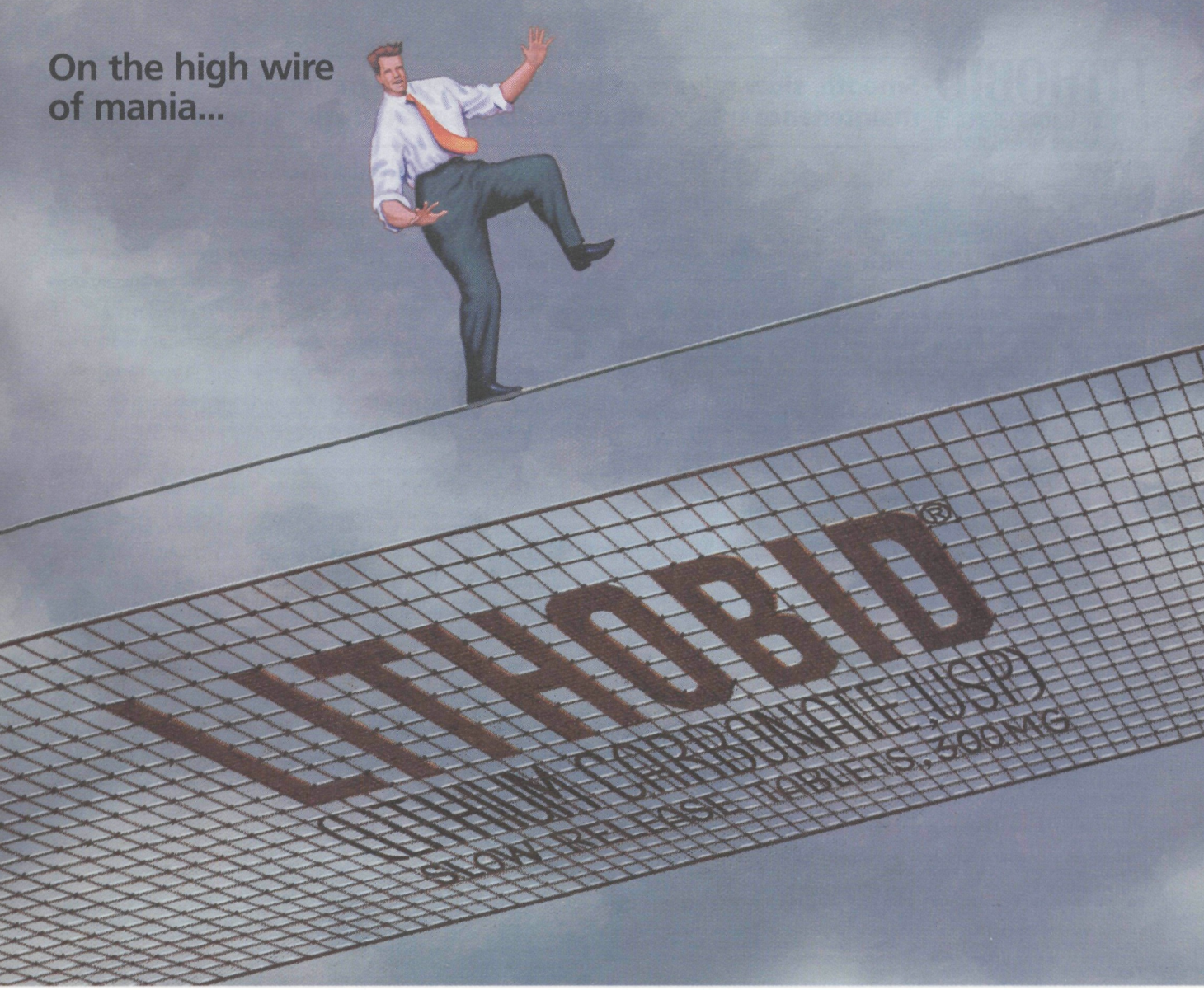

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WARNING: Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.

Please see brief summary of prescribing information on adjacent page.

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LITHOBID® (Lithium Carbonate, USP) Slow-Release Tablets, 300 mg

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BRIEF SUMMARY:

The following is a brief summary only. Before prescribing, see complete prescribing information in LITHOBID® Slow-Release Tablets product labeling.

WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy (see DOSAGE AND ADMINISTRATION).

INDICATIONS:

Lithium is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

Typical symptoms: of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1 to 3 weeks.

WARNINGS:

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation, dehydration, sodium depletion, and to patients receiving diuretics, or angiotensin converting enzyme (ACE) inhibitors, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.

Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal function and morphologic changes and their association with lithium therapy have not been established.

Kidney function should be assessed prior to and during lithium therapy. Routine urinalysis and other tests may be used to evaluate tubular function (e.g., urine specific gravity or osmolality following a period of water deprivation, or 24-hour urine volume) and glomerular function (e.g., serum creatinine or creatinine clearance). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for reevaluation of treatment.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic, most notably haloperidol. In some instances, the syndrome was followed by irreversible brain damage. Because of possible causal relationship between these events and the concomitant administration of lithium and neuroleptic drugs, patients receiving such combined therapy or patients with organic brain syndrome or other CNS impairment should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as Neuroleptic Malignant Syndrome (NMS).

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to the therapeutic concentrations (see DOSAGE AND ADMINISTRATION).

Outpatients and their families should be warned that the patient must discontinue lithium therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

Usage in Pregnancy: Adverse effects on nidation in rats, embryo viability in mice, and metabolism in vitro of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palate in mice.

In humans, lithium may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised by their physician of the potential hazard to the fetus.

Usage in Nursing Mothers: Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazard to the child. Signs and symptoms of lithium toxicity such as hypertonia, hypothermia, cyanosis and ECG changes have been reported in some infants.

Usage in Children: Since the safety and effectiveness of lithium in children under 12 years of age has not been established, its use in such patients is not recommended at this time.

There has been a report of transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.

PRECAUTIONS:

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see DOSAGE AND ADMINISTRATION).

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The elimination half-life of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2500-3500 mL) at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.

In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing thyroid disorders do not necessarily constitute a contraindication to lithium treatment. Where hypothyroidism preexists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters and/or adjustment of lithium doses, if any. If hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

In general, the concomitant use of diuretics or angiotensin converting enzyme (ACE) inhibitors with lithium carbonate should be avoided. In those cases where concomitant use is necessary extreme caution is advised since sodium loss from these drugs may reduce the renal clearance of lithium resulting in increased serum lithium concentrations with the risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium serum concentrations is recommended. See WARNINGS for additional caution information.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations and alkalinizing agents such as sodium bicarbonate.

Concomitant extended use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism. Indomethacin and piroxicam have been reported to significantly increase steady state serum lithium concentrations. In some cases lithium toxicity has resulted from such interactions. There is also some evidence that other nonsteroidal, anti-inflammatory agents may have a similar effect. When such combinations are used, increased serum lithium concentrations monitoring is recommended.

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Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea and/or tinnitus. Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

Concurrent use of fluoxetine with lithium has resulted in both increased and decreased serum lithium concentrations. Patients receiving such combined therapy should be monitored closely.

Lithium may impair mental and/or physical abilities. Patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

Usage in Pregnancy: Pregnancy Category D (see WARNINGS).

Usage in Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from lithium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS).

Usage in Children: Safety and effectiveness in children below the age of 12 have not been established (see WARNINGS).

Usage in the Elderly: Elderly patients often require lower lithium dosages to achieve therapeutic serum concentrations. They may also exhibit adverse reactions at serum concentrations ordinarily tolerated by younger patients. Additionally, patients with renal impairment may also require lower lithium doses (see WARNINGS).

ADVERSE REACTIONS:

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations and to individual patient sensitivity to lithium. They generally occur more frequently and with greater severity at higher concentrations.

Adverse reactions may be encountered at serum lithium concentrations below 1.5 mEq/L. Mild to moderate adverse reactions may occur at concentrations from 1.5-2.5 mEq/L, and moderate to severe reactions may be seen at concentrations from 2.0 mEq/L and above.

Fine hand tremor, polyuria and mild thirst may occur during initial therapy for the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration.

These side effects usually subside with continued treatment or with a temporary reduction or cessation of dosage. If persistent, a cessation of lithium therapy may be required. Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium concentrations below 2.0 mEq/L. At higher concentrations giddiness, ataxia, blurred vision, tinnitus and a large output of dilute urine may be seen. Serum lithium concentrations above 3.0 mEq/L may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium concentrations should not be permitted to exceed 2.0 mEq/L during the acute treatment phase.

The following reactions have been reported and appear to be related to serum lithium concentrations, including concentrations within the therapeutic range:

Central Nervous System: tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreoathetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes. Cases of Pseudotumor Cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs. **Cardiovascular:** cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope); **Gastrointestinal:** anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion; **Genitourinary:** glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst and polydipsia; **Dermatologic:** drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angioedema; **Autonomic Nervous System:** blurred vision, dry mouth, impotence/sexual dysfunction; **Thyroid Abnormalities:** euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T_3 and T_4. ^{131}Iodine uptake may be elevated (see PRECAUTIONS). Paradoxically, rare cases of hyperthyroidism have been reported. **EEG Changes:** diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm. **EKG Changes:** reversible flattening, isoelectricity or inversion of T-waves. **Miscellaneous:** Fatigue, lethargy, transient scotomata, exophthalmos, dehydration, weight loss, leucocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, albuminuria, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, and dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypothyroidism which persist after lithium discontinuation have been received.

A few reports have been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of starting lithium treatment. The mechanism through which these symptoms (resembling Raynaud's Syndrome) developed is not known. Recovery followed discontinuance.

OVERDOSAGE:

The toxic concentrations for lithium (≥1.5 mEq/L) are close to the therapeutic concentrations (0.6-1.2 mEq/L). It is therefore important that patients and their families be cautioned to watch for early toxic symptoms and to discontinue the drug and inform the physician should they occur. (Toxic symptoms are listed in detail under ADVERSE REACTIONS).

Treatment: No specific antidote for lithium poisoning is known. Treatment is supportive. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient.

Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance and 3) regulation of kidney functioning. Urea, mannitol, and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. However, patient recovery may be slow.

Infection prophylaxis, regular chest X-rays, and preservation of adequate respiration are essential.

SOLVAY PHARMACEUTICALS
Marietta, GA 30062

22E0803 Rev 2/95

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Feature Articles

CNS SPECTRUMS
The International Journal of Neuropsychiatric Medicine
Volume 3 • Number 4
April 1998

PHOTO ESSAY

This issue of *CNS Spectrums* further illustrates the spectrum approach to neuropsychiatry by opening the door to the emerging panic-agoraphobia spectrum. In this issue, guest editor Giovanni B. Cassano fleshes out the subthreshold and atypical features of panic disorders into eight spectrum domains. Page 35

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BRIEF SUMMARY. *Consult the package insert for complete prescribing information.*

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. **WARNINGS: Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT in combination with an MAOI. Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Therefore, it is recommended that ZOLOFT not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI. PRECAUTIONS: General—Activation of Mania/Hypomania –** During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT treated patients. Activation of mania/hypomania has also been reported in a *small proportion of patients with Major Affective Disorder treated with other marketed antidepressant and antiobsessional drugs.* **Weight Loss –** *Significant* weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss. **Seizure –** ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with ZOLOFT in the development program for depression. However, 4 patients out of approximately 1800 exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, ZOLOFT should be introduced with care in patients with a seizure disorder. **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 ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Because of the well-established comorbidity between both OCD and depression and panic disorder and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD or panic disorder. **Weak Uricosuric Effect –** ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with ZOLOFT. **Use in Patients with Concomitant Illness –** Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities. ZOLOFT is extensively metabolized by the liver. In subjects with mild, stable cirrhosis of the liver, the clearance of sertraline was decreased, thus increasing the elimination half-life. A lower or less frequent dose should be used in patients with cirrhosis. Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until the pharmacokinetics of ZOLOFT have been studied in patients with renal impairment and until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with ZOLOFT, it should be used with caution in such patients. **Interference with Cognitive and Motor Performance –** In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. **Hyponatremia –** Several cases of hyponatremia have been reported and appeared to be reversible when ZOLOFT was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted. **Platelet Function –** There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking ZOLOFT. While there have been reports of abnormal bleeding or purpura in several patients taking ZOLOFT, it is unclear whether ZOLOFT had a causative role. ***Information for Patients:*** Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT: Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol is not advised. Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding an infant. ***Laboratory Tests:*** None. ***Drug Interactions:*** **Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins –** Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs. In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, *prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.* **Cimetidine –** In a study assessing disposition of ZOLOFT (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in ZOLOFT mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown. **CNS Active Drugs –** In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown. In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is *advised if the concomitant administration of ZOLOFT and such drugs is required. There is limited controlled experience regarding the optimal timing of* switching from other antidepressants to ZOLOFT. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established. **Drugs Metabolized by P450 3A4 –** In two separate *in vivo* interaction studies, sertraline was coadministered with the cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline coadministration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. **Drugs Metabolized by P450 2D6 –** Many antidepressants, e.g., the SSRIs, including sertraline, and most tricyclic antidepressants inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of coadministered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressants and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the coadministered drug. There is variability among the antidepressants in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT may require lower doses than usually prescribed for the other drug. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the coadministered drug may be required (see Tricyclic Antidepressants under PRECAUTIONS). **Tricyclic Antidepressants (TCAs) –** The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with ZOLOFT, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT (see Drugs Metabolized by P450 2D6 under PRECAUTIONS). **Hypoglycemic Drugs –** In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown. **Atenolol –** ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol. **Digoxin –** In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance. **Microsomal Enzyme Induction –** Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy –** There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT. **Alcohol –** Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol is not recommended. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (*MRHD*) on a mg/m² basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25 - 1.0 times the MRHD on a mg/m² basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m² basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5 - 2.0 times the MRHD on a mg/m² basis) compared to placebo controls, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum human dose on a mg/m² basis). ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. *ZOLOFT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.* **Labor and Delivery –** The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers –** It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman. **Pediatric Use –** Safety and effectiveness in children have not been established. **Geriatric Use –** Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients. **ADVERSE REACTIONS –** Table below enumerates the most common treatment-emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT and at least twice that for placebo within at least one of the indications) for the treatment of depression/other,* OCD, and panic disorder in placebo-controlled clinical trials.

MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	PERCENTAGE OF PATIENTS REPORTING EVENT					
	Depression/Other*		OCD		Panic Disorder	
BODY SYSTEM/ ADVERSE EVENT	***ZOLOFT*** (N=861)	***Placebo*** (N=853)	***ZOLOFT*** (N=533)	***Placebo*** (N=373)	***ZOLOFT*** (N=430)	***Placebo*** (N=275)
Autonomic Nervous System Disorders						
Ejaculation Failure (1)	7	<1	17	2	19	1
Sweating Increased	8	3	6	1	5	1
Central & Peripheral Nervous System Disorders						
Somnolence	13	6	15	8	15	9
Tremor	11	3	8	1	5	1
Gastrointestinal Disorders						
Anorexia	3	2	11	2	7	2
Constipation	8	6	6	4	7	3
Diarrhea/Loose Stools	18	9	24	10	20	9
Dyspepsia	6	3	10	4	10	8
Nausea	26	12	30	11	29	18
Psychiatric Disorders						
Agitation	6	4	6	3	6	2
Insomnia	16	9	28	12	25	18
Libido Decreased	1	<1	11	2	7	1

(1) Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT depression/other*; N=271 placebo depression/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder).

*Depression and other premarketing controlled trials.

Associated With Discontinuation of Treatment: The adverse events associated with discontinuation of ZOLOFT treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT) in depression and other premarketing controlled trials are agitation, diarrhea, dry mouth, ejaculation failure (primarily ejaculatory delay), headache, insomnia, nausea, somnolence, and tremor; in OCD are diarrhea, dizziness, ejaculation failure (primarily ejaculatory delay), insomnia, nausea, and somnolence; in panic disorder are agitation, anorexia, anxiety, impaired concentration, depersonalization, diarrhea, dizziness, dry mouth, dyspepsia, ejaculation failure (primarily ejaculatory delay), fatigue, headache, insomnia, nausea, nervousness, paresthesia, somnolence, and vomiting. ***Other Events Observed During the Premarketing Evaluation of ZOLOFT:*** During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 3800 subjects. Events are further 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. Events of major clinical importance are also described in the PRECAUTIONS section. **Autonomic Nervous System Disorders –** *Frequent:* impotence; *Infrequent:* flushing, increased saliva, cold clammy skin, mydriasis; *Rare:* pallor, glaucoma, priapism, vasodilation. **Body as a Whole – General Disorders –** *Rare:* allergic reaction, allergy. Cardiovascular – *Frequent:* palpitations, chest pain; *Infrequent:* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder. **Central and Peripheral Nervous System Disorders –** *Frequent:* hypertonia, hypoesthesia; *Infrequent:* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare:* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia. **Disorders of Skin and Appendages –** *Infrequent:* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare:* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash. **Endocrine Disorders –** *Rare:* exophthalmos, *gynecomastia.* **Gastrointestinal Disorders –** *Frequent: appetite increased; Infrequent: dysphagia, tooth caries aggravated, eructation,* esophagitis, gastroenteritis; *Rare:* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration. **General –** *Frequent:* back pain, asthenia, malaise, weight increase; *Infrequent:* fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis. **Hearing and Vestibular Disorders –** *Rare:* hyperacusis, labyrinthine disorder. **Hematopoietic and Lymphatic –** *Rare:* anemia, anterior chamber eye hemorrhage. **Liver and Biliary System Disorders –** *Rare:* abnormal hepatic function. **Metabolic and Nutritional Disorders –** *Infrequent:* thirst; *Rare:* hypoglycemia, hypoglycemia reaction. **Musculoskeletal System Disorders –** *Frequent:* myalgia; *Infrequent:* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness. **Psychiatric Disorders –** *Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent:* depression, amnesia, paronia, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare:* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion. **Reproductive –** *Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare:* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis. **Respiratory System Disorders –** *Frequent:* rhinitis; *Infrequent:* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare:* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis. **Special Senses –** *Frequent:* tinnitus; *Infrequent:* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare:* xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect. **Urinary System Disorders –** *Infrequent:* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare:* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury. **Laboratory Tests:** In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT administration. These hepatic enzyme elevations usually occured within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. The safety profile observed with ZOLOFT treatment in patients with depression, OCD and panic disorder is similar. **Other Events Observed During the Postmarketing Evaluation of ZOLOFT –** Reports of adverse events temporally associated with ZOLOFT 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: galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, psychosis, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson Syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events – clinical features (which in the majority of cases appeared to be reversible with discontinuation of ZOLOFT) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death. **OVERDOSAGE:** Symptoms of overdose with ZOLOFT alone included somnolence, nausea, vomiting, tachycardia, ECG changes, anxiety and dilated pupils. Treatment was primarily supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration. Although there were no reports of death when ZOLOFT was taken alone, there were 4 deaths involving overdoses of ZOLOFT in combination with other drugs and/or alcohol, as of November 1992. Therefore, any overdosage should be treated aggressively.

Pfizer U.S. Pharmaceuticals