

# CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine



## Investigating and Treating Psychosis

ORIGINAL RESEARCH

### Prescribing Conventional Antipsychotics at Two Veterans Administration Hospitals: Are There Geographical Differences?

*P.S. Masand, M. Arora, T.L. Schwartz, et al*

ORIGINAL RESEARCH

### Oculomotor Delayed Response Abnormalities in Young Offspring and Siblings at Risk for Schizophrenia

*V.A. Diwadkar, J.A. Sweeney, D. Boarts, D.M. Montrose, and M.S. Keshavan*

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### Loading Strategies in Acute Mania

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# 60-Day Planner

## December

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2 (-3) 3rd International Symposium of the Asian and Pacific Parkinson's Disease Association Hong Kong <i>contact:</i> Tel: 852-2559-9973 Fax: 852-2547-9528 icc@icc.com.uk	3 (-7) American Medical Seminars Neurology for the Non-Neurologist Sarasota, FL <i>contact:</i> Tel: 941-388-1766 Fax: 941-365-7073 mail@ams4cme.com	4	5 4th European Microvascular Workshop for Neurosurgeons Freiburg, Germany <i>contact:</i> Tel: 49-761-270-5006 Fax: 49-761-270-5102 spetzger@nz.ukl.uni-freiburg.de	6 (-8) 32nd Annual Heart & Stroke Clinical Update Toronto, Canada <i>contact:</i> Tel: 416-489-7111 x453 Fax: 416-489-7003 dmurphy@hsf.on.ca	7 Neuro-Psychiatry Update Chicago, IL <i>contact:</i> Tel: 617-572-3597 Fax: 617-859-4354 npupdates@hhcc.com	8
9 <i>Hanukkah begins</i>	10 (-14) 40th American College of Neuropsychopharmacology Waikoloa, HI <i>contact:</i> Tel: 615-322-2075 Fax: 615-343-0662 acnp@acnp.org	11	12	13	14 (-16) 2nd Neurotrauma Review Course Mumbai, India <i>contact:</i> info@refindia.net	15
16 (-17) Advanced Techniques in Image-Guided Brain & Spine Surgery An Intensive Review & Hands-On Course New York, NY <i>contact:</i> Tel: 212-241-9638 Fax: 212-831-3324 igermano@mssm.edu	17	18	19 <b>January CNS closes &amp; ships to printer</b>	20	21 <i>First Day of Winter</i>	22
23 30	24 31 <i>New Year's Eve</i>	25 <i>Christmas</i>	26	27	28	29

# 60-Day Planner

MEETINGS DEADLINES REMINDERS

January 2002

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 <i>New Year's Day</i>	2	3	4	5
		<p>American Association on Mental Retardation Orlando, FL <i>contact:</i> Tel: 800-424-3688 Fax: 202-387-2193 aamr@ access.digex.net</p>				
6	7 (-11) Wake Forest University School of Medicine Neurovascular Interpretation Winston-Salem, NC <i>contact:</i> Tel: 336-716-4505 Fax: 336-716-2447 cmu@wfubmc.edu	8	9 <i>Full Moon</i>	10	11	12
13	14	15	16 (-18) 28th Annual Meeting of the British Paediatric Neurological Association Newcastle, UK <i>contact:</i> Tel: 44-1-912-453-523 Fax: 44-1-912-453-802 BPNA2002@ benchcom.co.uk	17	18 (-20) American Headache Society Headache Now San Juan, PR <i>contact:</i> Tel: 609-423-0043 Fax: 609-423-0082 aashhq@ aash.smarthub.com	19
20	21 <i>Martin Luther King, Jr. Day</i>	22	23	24 (-25) National Advisory Mental Health Council Meeting Bethesda, MD <i>contact:</i> Tel: 301-443-5047 jsteinbe@nih.gov	25	26
27	28	29	30 February CNS closes & ships to printer	31		

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**ANTIPSYCHOTIC PRESCRIPTION PRACTICES:  
ARE THERE GEOGRAPHICAL DIFFERENCES?****page 894**

“Since novel antipsychotics are the preferred treatment for psychotic disorders, ideally all patients receiving conventional antipsychotics should be informed about why they are receiving these agents and of the availability of alternative treatments. Most patients enrolled in this study, however, were not provided with this information. Also, other recent studies found a low rate of documentation of informed consent for antipsychotic medication. Given the low rate at which patients were provided information about alternative treatments, it is of particular concern that one of the most common reasons for patients continuing on conventional antipsychotics was personal choice.

Both hospitals had a low rate of informed consent, suggesting that this may be a problem across the country. However, the significant difference in the rate of informed consent between the two institutions suggests that the magnitude of the problem may vary. Clearly, further studies are needed to verify the scope of this problem.”

**OCULOMOTOR DELAYED RESPONSE  
ABNORMALITIES: BIOBEHAVIORAL MARKERS  
FOR SCHIZOPHRENIA?****page 899**

“Identifying biobehavioral markers that signal vulnerability to schizophrenia has been a major challenge for biologic psychiatry. The results of our study indicate that young individuals at familial risk for schizophrenia have abnormalities in spatial working memory, as assessed by the ODR paradigm. Compared with healthy individuals, high-risk subjects showed nonsignificantly greater errors of memory-guided saccades at longer delay intervals. Furthermore, these abnormalities appeared to be developmentally mediated. Although ODR performance improved significantly with normal maturation, we found evidence of a decrement in performance with age in the high-risk group. This finding suggests that the abnormality may be developmentally progressive and may reflect alterations in developmental neurobiologic processes during this period, such as synaptic pruning and myelination. However, caution should be exercised in making inferences about longitudinal developmental processes based on cross-sectional relationships between age and putative developmental parameters. Longitudinal follow-up studies of high-risk and healthy control subjects are needed to definitively address the progressive versus nonprogressive nature of developmental abnormalities in individuals at risk for schizophrenia.”

**THE USEFULNESS OF AUGMENTATION  
STRATEGIES IN SCHIZOPHRENIA TREATMENT****page 904**

“Although the therapeutic advantages of combination treatment with two or more antipsychotics remain to be demonstrated, potential adverse effects are clear. Of greatest concern are additive pharmacodynamic effects, such as QT interval prolongation, which might result from addition of thioridazine to ziprasidone, or anticholinergic toxicity, which might result from addition of a low-potency phenothiazine to clozapine. The potential pharmacokinetic interactions are less clear. Two case series found no significant interaction between clozapine and risperidone, although case reports have described significant elevations of clozapine serum concentrations after addition of risperidone. Other potential drug-drug interactions have not been adequately studied and represent a potential complication of this approach. Finally, combinations of atypical antipsychotics can substantially increase the cost of treatment, an expense that is difficult to justify in the absence of efficacy data.”

**NOVEL ANTIPSYCHOTICS: WHAT ARE THE  
CARDIOVASCULAR SIDE EFFECTS?****page 912**

“For the past 50 years, despite the introduction of numerous antipsychotics, we have been at a limited-benefit level of symptom control regarding cognition in the treatment of schizophrenia patients. We are unable to put most patients with schizophrenia back to work in a competitive environment. Hence, every new agent for the treatment of schizophrenia is a welcome addition to our armamentarium. In the area of neuropsychopharmacology, we are preoccupied with medication-related side effects. In other fields of medicine, patients are treated with efficacious medications and monitored for associated side effects.”

**TREATING ACUTE MANIA: LOADING DOSES****page 919**

“We used the method proposed by Keck and colleagues and found it to be generally well tolerated. In this method, there was no increase in the side effects of divalproex. Once the patient was determined to be a candidate, we immediately began oral divalproex loading. The conversion factor is 20 mg/kg of body weight per day. Alternatively, this involves adding a zero to the weight in pounds. This amount is given in single or divided doses the first day and is continued for 4–7 days. Blood levels were drawn on the fourth day. Clinical improvement may be seen in the first week. Some have reported that divalproex could be loaded in those patients on lithium or antipsychotics without significant adverse effects. Oral divalproex loading appears to be a useful treatment strategy for the treatment of acute mania and mixed states. Furthermore, Keck and colleagues found that this strategy reduced inpatient psychiatric length of stay.”

**References:** 1. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR™*. 4th ed. Washington, DC: American Psychiatric Association; 2000. 2. Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on generalised anxiety disorder. In press. 3. Paxil® (paroxetine HCl) Prescribing Information.

**PAXIL® (brand of paroxetine hydrochloride)**

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature. The following is a brief summary.

**INDICATIONS AND USAGE:** Paxil is indicated for the treatment of depression, obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in DSM-IV, panic disorder, with or without agoraphobia, as defined in DSM-IV, social anxiety disorder, as defined in DSM-IV, and generalized anxiety disorder, as defined in DSM-IV.

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

**WARNINGS:** Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use Paxil in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping Paxil before starting a MAOI.

**Potential Interaction with Thioridazine**

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit P<sub>450</sub>2D<sub>6</sub>, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine.

**PRECAUTIONS:** As with all antidepressants, use Paxil cautiously in patients with a history of mania.

Use Paxil cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Write Paxil prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Reversible hyponatremia has been reported, mainly in elderly patients; patients taking diuretics or those who were otherwise volume depleted. Abnormal bleeding (mostly ecchymosis and purpura), including a case of impaired platelet aggregation, has been reported; the relationship to paroxetine is unclear.

Clinical experience with Paxil in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment, a lower starting dose (10 mg) should be used.

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that Paxil therapy does not affect their ability to engage in such activities. Tell patients 1) to continue therapy as directed; 2) to inform physicians about other medications they are taking or plan to take; 3) to avoid alcohol while taking Paxil; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy, or if they're nursing.

Weakness, hyperreflexia, and incoordination following use of an SSRI and sumatriptan have been rarely reported.

Concomitant use of Paxil with tryptophan is not recommended. Use cautiously with warfarin. When administering Paxil with cimetidine, dosage adjustment of Paxil after the 20 mg starting dose should be guided by clinical effect. When co-administering Paxil with phenobarbital or phenytoin, no initial Paxil dosage adjustment is needed; base subsequent changes on clinical effect. Concomitant use of Paxil with drugs metabolized by cytochrome P<sub>450</sub>2D<sub>6</sub> (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines; Type 1C antiarrhythmics such as propafenone, flecainide 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. However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be co-administered. An *in vivo* interaction study revealed that paroxetine had no effect on terfenadine pharmacokinetics. Additional *in vitro* studies showed that the inhibitory effects of paroxetine on other IIIA<sub>1</sub> substrates (astemizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent than ketocazole, a potent IIIA<sub>1</sub> inhibitor. Assuming that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other IIIA<sub>1</sub> substrates, paroxetine's inhibition of IIIA<sub>1</sub> activity should have little clinical significance. Use caution when co-administering Paxil with tricyclic antidepressants (TCAs). TCA plasma concentrations may need monitoring and the TCA dose may need to be reduced. Administration of Paxil with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug. Concomitant use of Paxil and alcohol in depressed patients is not advised. Undertake concomitant use of Paxil and lithium or digoxin cautiously. If adverse effects are seen when co-administering Paxil with prochlorperazine, reduce the prochlorperazine dose. Elevated theophylline levels have been reported with Paxil co-administration; monitoring theophylline levels is recommended.

In 2-year studies, a significantly greater number of male rats in the 20 mg/kg/day group developed reticulum cell sarcomas vs. animals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with Paxil.

Rats receiving paroxetine at 15 mg/kg/day (2.4 times the MRHD on a mg/m<sup>2</sup> basis) showed a reduced pregnancy rate.

**Pregnancy Category C.** Reproduction studies performed in rats and rabbits at doses up to 6 mg/kg/day, 8.1 (rat) and 1.9 (rabbit) times the MRHD on a mg/m<sup>2</sup> basis, have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Paxil should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The effect of Paxil on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when administering Paxil to a nursing woman. Safety and effectiveness in the pediatric population have not been established.

In worldwide premarketing Paxil clinical trials, 17% of Paxil-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly and a lower starting dose is recommended. However, there were no overall differences in the adverse event profile between older and younger patients.

**ADVERSE REACTIONS: Incidence in Controlled Trials—Commonly Observed Adverse Events in Controlled Clinical Trials:** The most commonly observed adverse events associated with the use of Paxil in the treatment of depression (incidence of 5% or greater and incidence for Paxil at least twice that for placebo) were: 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 placebo) were: nausea (23% vs. 10%), dry mouth (18% vs. 9%), decreased appetite (9% vs. 3%), constipation (16% vs. 6%), dizziness (12% vs. 6%), somnolence (24% vs. 7%), tremor (11% vs. 1%), sweating (9% vs. 3%), impotence (8% vs. 1%) and abnormal ejaculation (23% vs. 1%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of panic disorder (incidence of 5% or greater and incidence for Paxil at least twice that for placebo) were: asthenia (14% vs. 5%), sweating (14% vs. 6%), decreased appetite (7% vs. 3%), libido decreased (9% vs. 1%), tremor (9% vs. 1%), abnormal ejaculation (21% vs. 1%), female genital disorders (9% vs. 1%) and impotence (5% vs. 0%).

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

The most commonly observed adverse events associated with the use of paroxetine in the treatment of generalized anxiety disorder (incidence of 5% or greater and incidence for Paxil at least twice that for placebo) were: asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Twenty percent (1,199/6,145) of Paxil patients in worldwide clinical trials in depression and 16.1% (84/522), 11.8%

(64/542), 9.4% (44/469) and 10.7% (79/735) of Paxil patients in worldwide trials in social anxiety disorder, OCD, panic disorder and generalized anxiety disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related include the following: depression—somnolence, agitation, tremor, nausea, diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating; OCD—insomnia, dizziness, constipation, nausea, asthenia, abnormal ejaculation, impotence; panic disorder—somnolence, insomnia, nausea; social anxiety disorder—somnolence, insomnia, tremor, anxiety, dizziness, nausea, vomiting, flatulence, asthenia, abnormal ejaculation, sweating, libido decreased; generalized anxiety disorder—somnolence, dizziness, nausea, asthenia, abnormal ejaculation, sweating.

The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequency of 1% or more, in patients dosed (20 to 50 mg/day) for the treatment of depression: headache, asthenia, palpitation; vasodilation; sweating; rash; nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, oropharynx disorder, dyspepsia; myopathy, myalgia, myasthenia; somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesia, libido decreased, drugged feeling, confusion; yawn; blurred vision, taste perversion; ejaculatory disturbance, other male genital disorders, urinary frequency, urination disorder, female genital disorders.

The following adverse events occurred at a frequency of 2% or more among OCD patients on Paxil who participated in placebo-controlled trials of 12 weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on Paxil who participated in placebo-controlled trials of 10 to 12 weeks duration in which patients were dosed in a range of 10 to 60 mg/day or among patients with social anxiety disorder on Paxil who participated in placebo-controlled trials of 12 weeks duration in which patients were dosed in a range of 20 to 50 mg/day: asthenia, abdominal pain, chest pain, back pain, chills, trauma; vasodilation, palpitation; sweating; rash; nausea, dry mouth, constipation, diarrhea, decreased appetite, dyspepsia, flatulence, increased appetite, vomiting; myalgia; insomnia, somnolence, dizziness, tremor, nervousness, libido decreased, agitation, anxiety, abnormal dreams, concentration impaired, depersonalization, myoclonus, amnesia, rhinitis, pharyngitis, yawn; abnormal vision, taste perversion; abnormal ejaculation, dysmenorrhea, female genital disorder, impotence, urinary frequency, urination impaired, urinary tract infection.

The following adverse events occurred at a frequency of 2% or more among GAD patients on Paxil who participated in placebo-controlled trials of 8 weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day: asthenia, headache, infection, vasodilation, sweating, nausea, dry mouth, constipation, diarrhea, decreased appetite, vomiting, insomnia, somnolence, dizziness, tremor, nervousness, libido decreased, respiratory disorder, sinusitis, yawn, abnormal vision, abnormal ejaculation, female genital disorder, impotence.

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

In placebo-controlled clinical trials involving more than 2,500 patients with depression, OCD, panic disorder, social anxiety disorder or generalized anxiety disorder, the following incidences of untoward sexual experiences for patients receiving Paxil were reported, varying with the disease state: In males: decreased libido (6% to 15%), ejaculatory disturbance, mostly delayed ejaculation (13% to 28%), impotence (2% to 8%). In females: decreased libido (0% to 9%), orgasmic disturbance (2% to 9%). The reported incidence of each of these adverse events was <5% among male and female patients receiving placebo.

**Other Events Observed During the Premarketing Evaluation of Paxil:** During premarketing assessment in depression multiple doses of Paxil were administered to 6,145 patients in phase 2 and 3 studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder and generalized anxiety disorder, 542, 469, 522 and 735 patients, respectively, received multiple doses of Paxil. The following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = less than 1/1000 patients. Events are classified within body system categories and enumerated in order of decreasing frequency using the above definitions. It is important to emphasize that although the events occurred during Paxil treatment, they were not necessarily caused by it.

**Body as a Whole:** frequent: chills, malaise; infrequent: allergic reaction, face edema, moniliasis, neck pain; rare: adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer. **Cardiovascular System:** frequent: hypertension, tachycardia; infrequent: bradycardia, hematoma, hypotension, migraine, syncope; rare: angina pectoris, arrhythmic nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. **Digestive System:** infrequent: bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; rare: aphthous stomatitis, bloody diarrhea, bulimia, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. **Endocrine System:** rare: diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** infrequent: anemia, eosinophilia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare: abnormal erythrocytes, basophilia, bleeding time increased, hypochromic anemia, iron deficiency anemia, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocytopenia, thrombocytopenia. **Metabolic and Nutritional:** frequent: weight gain, weight loss; infrequent: alkaline phosphatase increased, edema, peripheral edema, SGOT increased, SGPT increased, thirst; rare: bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. **Musculoskeletal System:** frequent: arthralgia, infrequent: arthritis, arthrosis; rare: bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. **Nervous System:** frequent: emotional lability, vertigo; infrequent: abnormal thinking, alcohol abuse, ataxia, delirium, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis; paranoid reaction, psychosis; rare: abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome. **Respiratory System:** infrequent: asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; rare: emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, voice alteration. **Skin and Appendages:** frequent: pruritus; infrequent: acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, maculopapular rash, photosensitivity, urticaria; rare: angiodema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, herpes zoster, hirsutism, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. **Special Senses:** frequent: tinnitus; infrequent: abnormality of accommodation, corneal opacity, eye pain, eye pain; mydriasis, otitis media, photophobia; rare: amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacuity, keratoconjunctivitis, night blindness, otitis externa, parosmia, ptosis, retinal hemorrhage, taste loss, visual field defect. **Urogenital System:** infrequent: abortion, amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal moniliasis, vaginitis; rare: breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, pyuria, urethritis, uterine spasm, uterine vaginal hemorrhage.

**Postmarketing Reports**

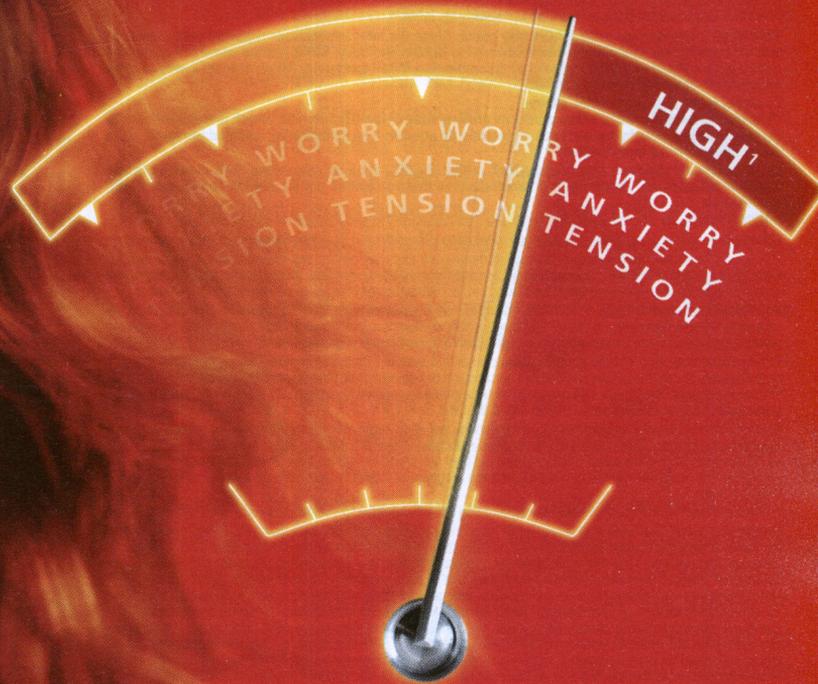
Voluntary reports of adverse events that have been received since market introduction and not listed above that may have no causal relationship with Paxil include: acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis (which has been associated with concomitant use of pimozide), tremor and trismus; 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, tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eczematous, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, and events related to impaired hemopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia and agranulocytosis). There have been spontaneous reports that discontinuation (particularly when abrupt) 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, increments of dose, drug-seeking behavior).

BRS-PXL20

NEW: 1ST AND ONLY  
SSRI FDA-APPROVED  
FOR GAD

Overpowered by  
**ANXIETY**



Empowered  
by *Paxil*

Generalized anxiety disorder (GAD) patients may suffer for up to **10 years** before diagnosis and treatment,<sup>2</sup> often believing their anxiousness is a part of their personality. With *Paxil*, the **first and only** SSRI FDA-approved for generalized anxiety,<sup>3</sup> they can now find help...and hope.



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

VISIT [www.paxil.com](http://www.paxil.com)

Please see brief summary of prescribing information on adjacent page.

ONCE-DAILY  
**PAXIL**  
PAROXETINE HCl



The **anxiolytic** antidepressant

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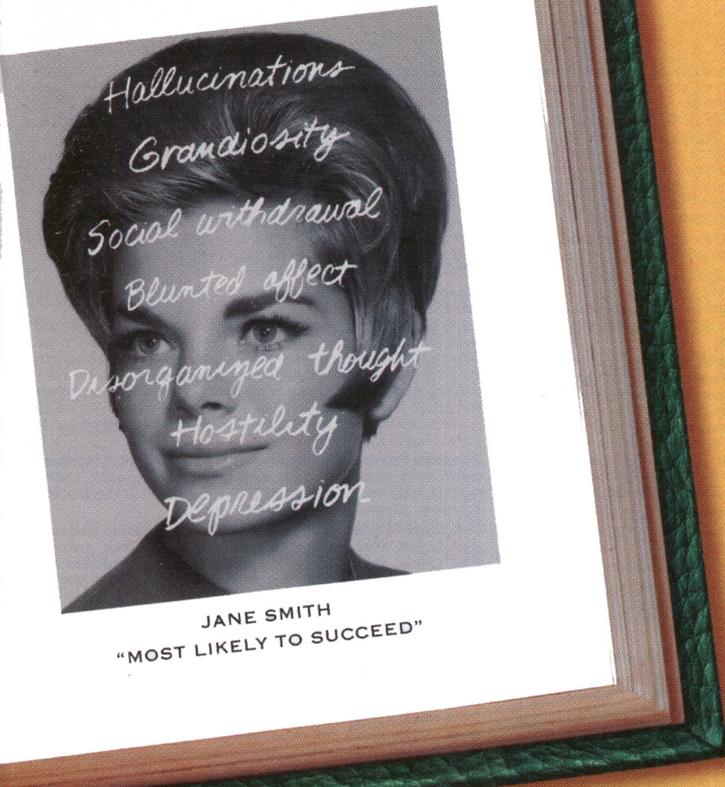
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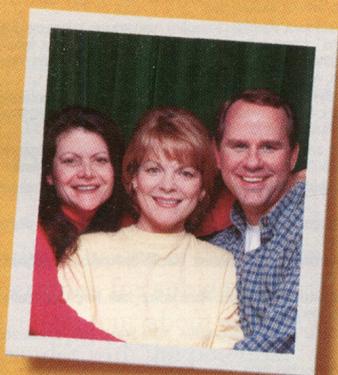
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**"Nothing could have prepared me for the devastation of psychosis."**

**"RISPERDAL gave me a new start."**



- Incidence of diabetes <1%
- Well established cardiac safety profile
- Low weight gain
  - Only 5.0 lb average in a long-term trial\*

**Risperdal**<sup>®</sup>   
tablets and oral solution 1 mg/mL RISPERIDONE

**The #1 prescribed antipsychotic<sup>1</sup>**

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Reference: 1. IMS Health, NPA Plus, New and Total Prescriptions, 12 months ending November 2000.

\*Data on file, 2000. Submitted for publication.

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

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to RISPERDAL therapy include diabetes mellitus aggravated, including diabetic ketoacidosis.

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. Risperidone has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease.

Percentage of patients experiencing weight gain ( $\geq 7\%$  of baseline body weight) in controlled clinical trials was 9% placebo versus 18% risperidone. This difference is statistically significant. Weight gain was dose dependent in short-term clinical trials. Other weight-related adverse events occurring in premarketing studies and listed as infrequent include increased appetite, weight increase, and weight decrease.

# Risperdal

tablets and oral solution 1 mg/mL

## RISPERIDONE

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

### INDICATIONS AND USAGE

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

### CONTRAINDICATIONS

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

### WARNINGS

#### Neuroleptic Malignant Syndrome (NMS)

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

#### Tardive Dyskinesia

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

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

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

### PRECAUTIONS

#### General

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

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

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

**Hyperprolactinemia:** As with other drugs that antagonize dopamine D<sub>2</sub> 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 overdose with certain drugs or of conditions such as intestinal obstruction, Ray's syndrome, and brain tumor.

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

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

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

Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS). Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment and in patients with severe hepatic impairment. A lower starting dose should be used in such patients.

#### Information for Patients

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

#### Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

**Drugs that Inhibit Cytochrome P<sub>2</sub>IID, and Other P<sub>2</sub> Isozymes:** Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P<sub>2</sub>IID, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P<sub>2</sub> isozymes, including 1A1, 1A2, 1C9, MP, and 1IA4, are only weak inhibitors of risperidone metabolism.

**Drugs Metabolized by Cytochrome P<sub>2</sub>IID:** In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome P<sub>2</sub>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 expectation are not available.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis:** Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m<sup>2</sup> basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas.

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

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

**Impairment of Fertility:** Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose on a mg/m<sup>2</sup> basis.

#### Pregnancy

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

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

#### Labor and Delivery

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

#### Nursing Mothers

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

#### Pediatric Use

Safety and effectiveness in children have not been established.

#### Geriatric Use

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

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

### ADVERSE REACTIONS

#### Associated with Discontinuation of Treatment

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

#### Incidence in Controlled Trials

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

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgasmic 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\*, headache, dizziness. **Gastrointestinal System:** constipation, nausea, dyspepsia, vomiting, abdominal pain, saliva increased, toothache. **Respiratory System:** rhinitis, coughing, sinusitis, pharyngitis, dyspnea. **Body as a Whole:** back pain, chest pain, fever. **Dermatological:** rash, dry skin, seborrhea. **Infections:** upper respiratory. **Visual:** abnormal vision. **Musculo-Skeletal:** arthralgia. **Cardiovascular:** tachycardia.

\* 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, orgasmic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

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

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

**Laboratory Changes:** A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important

changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Reproductive Disorders, Female:** Frequent: menorrhagia\*, orgasmic 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: gynaecomastia, male breast pain, anti-diuretic hormone disorder.

**Special Senses:** Rare: bitter taste.

\* Incidence based on elicited reports.

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

#### DRUG ABUSE AND DEPENDENCE

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

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

More detailed professional information is available upon request.

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**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 the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart attack in patients both with or without known underlying cardiac conduction abnormalities. Syncope 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, e.g., 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 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K<sub>i</sub> 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. **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 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. **Use with Anticholinergics:** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. **Use with Cholinomimetics and Other Cholinesterase Inhibitors:** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m<sup>2</sup> basis). **Pregnancy Pregnancy Category C:** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m<sup>2</sup> basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m<sup>2</sup> basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m<sup>2</sup> 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, are shown in Table 1.



**Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® (donepezil HCl) and at a Higher Frequency than Placebo-treated Patients**

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

**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 2 or 3. 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: **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, polydipsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocytopenia, 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, paresis, 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, hypertension, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. Evidence from the controlled trials indicates 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. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward 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. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

**Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group**

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
<b>Patients Randomized</b>	355	350	315
<b>Event%/Discontinuing</b>			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

**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 2 for a comparison of the most common adverse events following one and six week titration regimens.

**Table 2. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks**

Adverse Event	Placebo (n=315)	No titration 5 mg/day (n=311)	One-week titration 10 mg/day (n=315)	Six-week titration 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%

**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 3 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.



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