May 2002 Volume 7 - Number 5

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

5

Neuropsychological Testing: Present and Future

Neuropsychology and Temporal Lobe Epilepsy
B. Hermann and M. Seidenberg

ORIGINAL RESEARCH

A Review of Adult ADHD: A Neuropsychological and Neuroimaging Perspective
R.F. Kaplan and M.C. Stevens

The Neuropsychological Assessment of Dementia
T. Benke and E. Karner

ORIGINAL RESEARCH

The Effects of Second-Language Acquisition on Verbal Fluency Among Elderly Israelis
A.M. Poreh and A. Schweiger

ORIGINAL RESEARCH

Who is Exaggerating Cognitive Impairment and Who is Not?
M.L. Rohling, L.M. Allen III, and P. Green

CNS Spectrums is indexed by EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis, and is the official journal of the International Neuropsychiatric Assoc.

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

He's the

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

NEURONTIN® (gabapentin) capsules
NEURONTIN® (gabapentin) tablets
NEURONTIN® (gabapentin) oral solution

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE

Neurontin® (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Neurontin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3–12 years.

CONTRAINDICATIONS

Neurontin® is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Neuropsychiatric Adverse Events—Pediatric Patients 3-12 Years of Age Gabapentin use in pediatric patients with epilepsy 3–12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity. In controlled trials in pediatric patients 3–12 years of age the incidence of these adverse events was: emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability. **Withdrawal Precipitated Seizure, Status Epilepticus** Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency. In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving Neurontin® was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients treated with Neurontin® across all studies (controlled and uncontrolled) 31(1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with Neurontin® is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with Neurontin®. **Tumorigenic Potential** In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.) The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans. In clinical studies comprising 2085 patient-years of exposure, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of Neurontin®. Without knowledge of the background incidence and recurrence in a similar population not treated with Neurontin®, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment. **Sudden and Unexplained Deaths** During the course of premarketing development of Neurontin®, 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure). Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving Neurontin® (ranging from 0.0005 for the general population of epileptics, to 0.003 for a clinical trial population similar to that in the Neurontin® program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the Neurontin® cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients Patients should be instructed to take Neurontin® only as prescribed. Patients should be advised that Neurontin® may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on Neurontin® to gauge whether or not it affects their mental and/or motor performance adversely. **Laboratory Tests** Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin®. The value of monitoring Neurontin® blood concentrations has not been established. Neurontin® may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs. **Drug Interactions** Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs. The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy. **Phenytoin:** In a single and multiple dose study of Neurontin® (400 mg T.I.D.) in epileptic patients (N = 8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics. **Carbamazepine:** Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg T.I.D.; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration. **Valproic Acid:** The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg T.I.D.; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid. **Phenobarbital:** Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg T.I.D.; N=12) are identical whether the drugs are administered alone or together. **Cimetidine:** In the presence of cimetidine at 300 mg Q.I.D. (N=12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated. **Oral Contraceptive:** Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg T.I.D.; N=13). The Cmax of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance. **Antacid (Maalox®):** Maalox reduced the bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration. **Effect of Probenecid:** Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid. **Drug/Laboratory Tests Interactions** Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear. Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans. Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin. No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on an mg/m² basis). **Pregnancy** Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m² basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m² basis. When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m² basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m² basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m² basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m² basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Use in Nursing Mothers** Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, Neurontin® should be used in women who are nursing only if the benefits clearly outweigh the risks. **Pediatric Use** Effectiveness in pediatric patients below the age of 3 years has not been established (see CLINICAL PHARMACOLOGY, Clinical Studies). **Geriatric Use** Clinical studies of Neurontin did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. 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 CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections).

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of Neurontin® in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of Neurontin in combination with other antiepileptic drugs in pediatric patients 3 to 12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see WARNINGS, Neuropsychiatric Adverse Events). Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3 to 12 years of age who received Neurontin® in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%). **Incidence in Controlled Clinical Trials** Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin® group. In these studies, either Neurontin® or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity. The prescriber should be aware that these figures, obtained when Neurontin® was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 Years of Age
(Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin®[a] N=543 %	Placebo[a] N=378 %	Body System/ Adverse Event	Neurontin®[a] N=543 %	Placebo[a] N=378 %
Body As A Whole			Nervous System (cont'd)		
Fatigue	11.0	5.0	Tremor	6.8	3.2
Weight Increase	2.9	1.6	Nervousness	2.4	1.9
Back Pain	1.8	0.5	Dysarthria	2.4	0.5
Peripheral Edema	1.7	0.5	Amnesia	2.2	0.0
Cardiovascular			Depression	1.8	1.1
Vasodilatation	1.1	0.3	Thinking Abnormal	1.7	1.3
Digestive System			Twitching	1.3	0.5
Dyspepsia	2.2	0.5	Coordination Abnormal	1.1	0.3
Mouth or Throat Dry	1.7	0.5	Respiratory System		
Constipation	1.5	0.8	Rhinitis	4.1	3.7
Dental Abnormalities	1.5	0.3	Pharyngitis	2.8	1.6
Increased Appetite	1.1	0.8	Coughing	1.8	1.3
Hematologic and Lymphatic Systems			Skin and Appendages		
Leukopenia	1.1	0.5	Abrasion	1.3	0.0
Musculoskeletal System			Pruritus	1.3	0.5
Myalgia	2.0	1.9	Urogenital System		
Fracture	1.1	0.8	Impotence	1.5	1.1
Nervous System			Special Senses		
Somnolence	19.3	8.7	Diplopia	5.9	1.9
Dizziness	17.1	6.9	Amblyopia[b]	4.2	1.1
Ataxia	12.5	5.6	Laboratory Deviations		
Nystagmus	8.3	4.0	WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy. [b] Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne. Among the treatment-emergent adverse events occurring at an incidence of at least 10% of Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with Neurontin®. The incidence of adverse events increased slightly with increasing age in patients treated with either Neurontin® or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race. Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of Neurontin-treated patients 3 to 12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the Neurontin group. Adverse events were usually mild to moderate in intensity.

TABLE 2. Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3 to 12 Years in a Controlled Add-On Trial
(Events in at least 2% of Neurontin patients and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Neurontin® N=119 %	Placebo[a] N=128 %	Body System/ Adverse Event	Neurontin® N=119 %	Placebo[a] N=128 %
Body As A Whole			Nervous System		
Viral Infection	10.9	3.1	Somnolence	8.4	4.7
Fever	10.1	3.1	Hostility	7.6	2.3
Weight Increase	3.4	0.8	Emotional Lability	4.2	1.6
Fatigue	3.4	1.6	Dizziness	2.5	1.6
Digestive System			Hyperkinesia	2.5	0.8
Nausea and/or Vomiting	8.4	7.0	Respiratory System		
			Bronchitis	3.4	0.8
			Respiratory Infection	2.5	0.8

[a] Plus background antiepileptic drug therapy.

Other events in more than 2% of pediatric patients 3 to 12 years of age but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Other Adverse Events Observed During All Clinical Trials Neurontin® has been administered to 2074 patients >12 years of age during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to Neurontin® who experienced an event of the type cited on at least one occasion while receiving Neurontin®. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as 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. **Body As A Whole:** *Frequent:* asthenia, malaise, face edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect. **Cardiovascular System:** *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis. **Digestive System:** *Frequent:* anorexia, flatulence, gingivitis; *Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare:* dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perleche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm. **Endocrine System:** *Rare:* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance. **Hematologic and Lymphatic System:** *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased. **Musculoskeletal System:** *Frequent:* arthralgia; Infrequent: tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare:* costochondritis, osteoporosis, bursitis, contracture. **Nervous System:** *Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture. **Respiratory System:** *Frequent:* pneumonia; *Infrequent:* epistaxis, dyspnea, apnea; *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema. **Dermatological:** *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling. **Urogenital System:** *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain. **Special Senses:** *Frequent:* abnormal vision; *Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare:* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell. Adverse events occurring during clinical trials in 449 pediatric patients 3 to 12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are: **Body As A Whole:** dehydration, infectious mononucleosis. **Digestive System:** hepatitis. **Hemic and Lymphatic System:** coagulation defect. **Nervous System:** aura disappeared, occipital neuralgia. **Psychobiologic Function:** sleepwalking. **Respiratory System:** pseudocroup, hoarseness. **Postmarketing and Other Experience** In addition to the adverse experiences reported during clinical testing of Neurontin®, the following adverse experiences have been reported in patients receiving marketed Neurontin®. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, Stevens-Johnson syndrome.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Neurontin® has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation. Acute oral *overdoses of Neurontin® up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness,* lethargy and diarrhea were observed. All patients recovered with supportive care. Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

Neurontin® is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established. Neurontin® is given orally with or without food. **Patients >12 Years of Age:** The effective dose of Neurontin® is 900 to 1800 mg/day and given in divided doses (three times a day) using 300- or 400-mg capsules or 600- or 800-mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300- or 400-mg capsules or 600- or 800-mg tablets three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours. **Pediatric Patients Age 3-12 Years:** The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of Neurontin in patients 5 years of age and older is 25–35 mg/kg/day and given in divided doses (three times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (three times a day). (See CLINICAL PHARMACOLOGY, Pediatrics.) Neurontin® may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations to optimize Neurontin® therapy. Further, because there are no significant pharmacokinetic interactions among Neurontin® and other commonly used antiepileptic drugs, the addition of Neurontin® does not alter the plasma levels of these drugs appreciably. If Neurontin® is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week. Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females $C_{Cr} = (0.85)(140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

for males $C_{Cr} = (140\text{-age})(\text{weight})/[(72)(S_{Cr})]$

where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL. Dosage adjustment in patients ≥12 years of age with compromised renal function or undergoing hemodialysis is recommended as follows:

TABLE 3. Neurontin® Dosage Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 T.I.D.
30–60	600	300 B.I.D.
15–30	300	300 Q.D.
<15	150	300 Q.O.D.[a]
Hemodialysis	—	200-300[b]

[a] Every other day. [b] Loading dose of 300 to 400 mg in patients who have never received Neurontin®, then 200 to 300 mg Neurontin® following each 4 hours of hemodialysis.

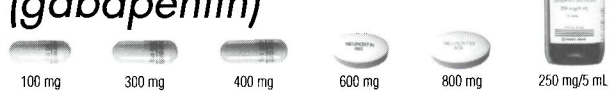
The use of Neurontin® in patients <12 years of age with compromised renal function has not been studied.

℞ only

Distributed by:
PARKE-DAVIS
Div of Warner-Lambert Co
A Pfizer Company

Rev. 0, July 2001

NEURONTIN®
(gabapentin)



100 mg 300 mg 400 mg 600 mg 800 mg 250 mg/5 mL

Products pictured are not actual size.

STRONG SILENT TYPE.
LIKE HIS NEURONTIN.

ADD-ON PARTIAL-SEIZURE CONTROL WITH EXCELLENT TOLERABILITY

Efficacy in a range of patients

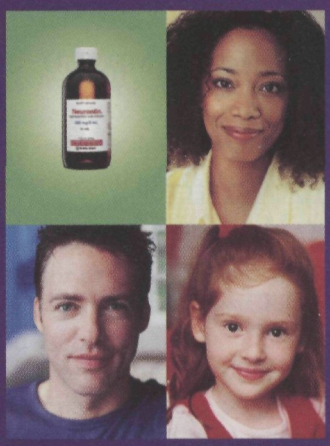
Well tolerated

Effective starting dose

Rapid titration to maximum efficacy

Simple, safe pharmacokinetics

Available in 100-mg, 300-mg, and 400-mg capsules, 600-mg and 800-mg tablets, and an oral solution



NEURONTIN is indicated as adjunctive treatment for partial seizures in pediatric patients (3-12 years old) and for partial seizures with and without secondary generalization in adults (>12 years old). NEURONTIN is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. NEURONTIN use in pediatric patients aged 3 to 12 years has been associated with mild to moderate neuropsychiatric adverse events, including emotional lability, hostility, thought disorder, and hyperkinesia.

In controlled clinical trials, the most common adverse events reported with NEURONTIN vs placebo in adults (>12 years old) were somnolence (19.3% vs 8.7%), dizziness (17.1% vs 6.9%), ataxia (12.5% vs 5.6%), fatigue (11.0% vs 5.0%), and nystagmus (8.3% vs 4.0%); the most common adverse events in pediatric patients (3-12 years old) were viral infection (10.9% vs 3.1%), fever (10.1% vs 3.1%), nausea and/or vomiting (8.4% vs 7.0%), somnolence (8.4% vs 4.7%), and hostility (7.6% vs 2.3%).

Please see brief summary of full prescribing information on adjacent pages.

add control. add confidence. add NEURONTIN® (gabapentin)

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

CNS SPECTRUMS

The International Journal of Neuropsychiatric Medicine

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

TEMPORAL LOBE EPILEPSY THROUGH THE LENS OF NEUROPSYCHOLOGY

page 343

"Neuropsychological studies have consistently demonstrated that an earlier age of onset of recurrent seizures is associated with poorer cognitive functioning. This relationship, reported early in the last century, has been noted in studies of adult patients with diverse seizure types and observed in neuropsychological studies of younger patients with complex partial and other types of seizures. As noted earlier, generalized neuropsychological difficulties are evident among adults with the syndrome of MTLE, a syndrome defined by a focal neuropathological substrate and early onset of recurrent seizures or initial precipitating injury."

NOVEL TECHNIQUES FOR ADULT ADHD

page 355

"The efficacy of psychostimulant medications in attenuating ADHD symptoms has also led to studies of DA and other catecholamine pathways in the basal forebrain. Ernst and colleagues showed diminished left and medial prefrontal cortex dopaminergic neurotransmission. Other studies have found that psychostimulants appear to normalize electrophysiological abnormalities. In those studies, medicated ADHD subjects showed comparable ERP signal amplitudes to normal controls, and altered activity in basal ganglia. This and other frontal brain areas are widely known to involve DA in extracellular signaling. Psychostimulant medications like meythlphenidate have been shown to increase extracellular DA. Differences in DA receptor density in individuals with ADHD, particularly in young boys, may help to explain the gender prevalence of the disorder.These studies and others have led to the suggestions that catecholamine dysregulation may be important to ADHD pathophysiology."

TESTING THE SCALES: DEMENTIA AND ASSESSMENT BATTERIES

page 371

"A large number of assessment procedures have been developed, among them screening measures, test batteries, and tests for specific functions. Screening measures are short tests which can be administered rapidly and inexpensively, and were developed to differentiate dementia from pseudodementia. Frequently used tests for dementia screening are the Mini-Mental State Exam, Dementia Rating Scale, Clinical Dementia Rating protocol, or the Information-Memory-Concentration test. These measures may have high rates of false negatives in early-stage dementia, are affected by education and sociocultural variables. Furthermore, they are poor at differentiating among various types of dementia. Assessment scales such as the Consortium to Establish a Registry for AD, Global Deterioration Scale, AD Assessment Scale, or Halstead-Reitan Neuropsychological Test Battery take specialized measures of language, perception, attention, memory, and problem-solving skills. They may also include information from the patient's relatives or caregiver (Cambridge Examination for Mental Disorders of the Elderly). Full batteries are lengthy and need an experienced neuropsychologist for application and data evaluation, but are valuable for early dementia detection, provide differential diagnosis, staging, and longitudinal delineation of dementia. More detailed assessment procedures are available for many cognitive domains. Although there is no ideal 'dementia test battery,' comprehensive assessment should, as a minimum requirement, include tests tapping orientation and memory (working-, short- and long-term memory); language (confrontation naming, comprehension, writing); executive functions (set shifting, problem solving, fluency, control of interference, attention); and visuoperceptual and construction segments (copying, drawing). Additional tests of motor functions (articulation, gait, rigidity, apraxia, oculomotor functions) will increase the stringency of the diagnosis to a great extent. Ideally, these examinations should also contain instruments to assess the patient's daily activity and functioning level, such as self-maintenance behaviors (mobility, dressing, bathing, etc.) and instrumental activities (managing finances, traveling, etc.)."

BILINGUALISM AND COGNITION IN OLD AGE

page 377

"On a practical level, our study extends previous research regarding the importance of immigration in the assessment of verbal fluency in older adults. Specifically, our data suggest that clinicians should take special care in assessing the role of the age of second-language acquisition on verbal skills across the lifespan. Furthermore, if indeed bilinguals have a distinct anterior cortical representation of speech for each language acquired, then bilingual and polyglot Alzheimer's patients should have a more distinct pattern of language deficits than their monolingual counterparts. This notion is similar to the one proposed by Ribot. Namely, that as the disease progresses, polyglots revert to their mother tongue. This hypothesis has yet to be empirically studied."

IS IT POSSIBLE TO FEIGN MENTAL ILLNESS?

page 387

"Following assessment, each NPT score was assigned to one of seven cognitive/ability domains in which prior research has found the highest factor loadings. Specifically, the NPT domains were: (a) Verbal Comprehension; (b) Perceptual Organization; (c) Executive Functioning; (d) Auditory Memory and Learning; (e) Visual Memory and Learning; (f) Attention/Working Memory; and (g) Psychomotor/Processing Speed. For example, the California Verbal Learning Test (Total Score) was assigned to the Auditory Memory and Learning domain. However, scores on the Rey-Complex Figure Test (Immediate and Delayed Recall) were assigned to the Visual Memory and Learning domain. The entire NPT battery is listed in the Appendix."

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

Administration of *Paxil CR* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug.

Concomitant use of *Paxil CR* and alcohol in depressed patients is not advised. Undertake concurrent use of *Paxil CR* and lithium or digoxin cautiously. If adverse effects are seen when co-administering *Paxil CR* with procyclidine, reduce the procyclidine dose. Elevated theophylline levels have been reported with immediate-release paroxetine treatment co-administration; monitoring theophylline levels is recommended.

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. Female rats were not affected. 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 CR*.

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

Pregnancy Category C: Reproduction studies performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits, approximately 8 (rat) and 2 (rabbit) times the MRHD on a mg/m^2 basis, have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. *Paxil CR* should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The effect of paroxetine on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when *Paxil CR* is administered to a nursing woman. Safety and effectiveness in the pediatric population have not been established.

In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. 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 elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in complete prescribing information). In a controlled study focusing specifically on elderly patients with major depressive disorder, *Paxil CR* was demonstrated to be safe and effective in the treatment of elderly patients (>60 years of age) with major depressive disorder. (See CLINICAL TRIALS and ADVERSE REACTIONS—Table 2 in complete prescribing information.)

ADVERSE REACTIONS: Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with *Paxil CR*:

Adverse Events Associated with Discontinuation of Treatment

Ten percent (21/212) of *Paxil CR* patients discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for *Paxil CR* compared to placebo) included: nausea (3.7% vs. 0.5%); asthenia (1.9% vs. 0.5%), dizziness (1.4% vs. 0.0%); somnolence (1.4% vs. 0.0%), respectively. In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of *Paxil CR* patients discontinued due to these adverse events: nausea (2.9% vs. 0.0%), headache (1.9% vs. 0.9%), depression (1.9% vs. 0.0%), LFT's abnormal (1.9% vs. 0.0%), for *Paxil CR* and placebo, respectively. Eleven percent (50/444) of *Paxil CR* patients in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included: nausea (2.9% vs. 0.4%); insomnia (1.8% vs. 0.0%); headache (1.4% vs. 0.2%), asthenia (1.1% vs. 0.0%) for *Paxil CR* and placebo, respectively.

The most commonly observed adverse events associated with *Paxil CR* in a pool of two trials for major depressive disorder (incidence of 5.0% or greater and incidence for *Paxil CR* at least twice that for placebo) were: abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning. Using the same criteria, the adverse events associated with the use of *Paxil CR* in a study of elderly patients with major depressive disorder were: abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

In the pool of panic disorder studies, the adverse events meeting these criteria were: abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Incidence in Controlled Clinical Trials

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥1% of patients with major depressive disorder were: **Body as a Whole:** Headache (27% vs. 20%), asthenia (14% vs. 9%), infection (8% vs. 5%), abdominal pain (7% vs. 4%), back pain (5% vs. 3%), trauma (5% vs. 1%), pain (3% vs. 1%), allergic reaction (2% vs. 1%); **Cardiovascular System:** tachycardia (1% vs. 0%), vasodilatation (2% vs. 0%); **Digestive System:** Nausea (22% vs. 10%), diarrhea (18% vs. 7%), dry mouth (15% vs. 8%), constipation (10% vs. 4%), flatulence (6% vs. 4%), decreased appetite (4% vs. 2%), vomiting (2% vs. 1%); **Nervous System:** somnolence (22% vs. 8%), insomnia (17% vs. 9%); dizziness (14% vs. 4%); libido decreased (7% vs. 3%), tremor (7% vs. 1%), hypertonia (3% vs. 1%), paresthesia (3% vs. 1%), agitation (2% vs. 1%), confusion (1% vs. 0%); **Respiratory System:** yawn (5% vs. 0%), rhinitis (4% vs. 1%), cough increased (2% vs. 1%), bronchitis (1% vs. 0%); **Skin and Appendages:** sweating (6% vs. 2%), photosensitivity (2% vs. 0%); **Special Senses:** abnormal vision (5% vs. 1%), taste perversion (2% vs. 0%); **Urogenital System:** abnormal ejaculation (26% vs. 1%), female genital disorder (10% vs. <1%), impotence (5% vs. 3%), urinary tract infection (3% vs. 1%), menstrual disorder (2% vs. <1%), vaginitis (2% vs. 0%).

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥5% of elderly patients with major depressive disorder were: **Body as a Whole:** headache (17% vs. 13%), asthenia (15% vs. 14%), trauma (8% vs. 5%), infection (6% vs. 2%); **Digestive System:** dry mouth (18% vs. 7%), diarrhea (15% vs. 9%), constipation (13% vs. 5%), dyspepsia (13% vs. 10%), decreased appetite (12% vs. 5%), flatulence (8% vs. 7%); **Nervous System:** somnolence (21% vs. 12%), insomnia (10% vs. 8%), dizziness (9% vs. 5%), libido decreased (8% vs. <1%), tremor (7% vs. 0%); **Skin and Appendages:** sweating (10% vs. <1%); **Urogenital System:** abnormal ejaculation (17% vs. 3%), impotence (9% vs. 3%).

The most commonly observed treatment-emergent adverse events associated with *Paxil CR*, occurring in ≥1% of patients with panic disorder were: **Body as a Whole:** asthenia (15% vs. 10%), abdominal pain (6% vs. 4%); trauma (5% vs. 4%), **Cardiovascular System:** vasodilation (3% vs. 2%); **Digestive System:** nausea (23% vs. 17%), dry mouth (13% vs. 9%), diarrhea (12% vs. 9%), constipation (9% vs. 6%), decreased appetite (8% vs. 6%); **Metabolic/ Nutritional Disorders:** weight loss (1% vs. 0%); **Musculoskeletal System:** Myalgia (5% vs. 3%); **Nervous System:** insomnia (20% vs. 11%), somnolence (20% vs. 9%), libido decreased (9% vs. 4%), nervousness (8% vs. 7%); tremor (8% vs. 2%), anxiety (5% vs. 4%), agitation (3% vs. 2%), hypertonia (2% vs. <1%), myoclonus (2% vs. <1%); **Respiratory System:** sinusitis (8% vs. 5%), yawn (3% vs. 0%); **Skin and Appendages:** sweating (7% vs. 2%); **Special Senses:** abnormal vision (3% vs. <1%); **Urogenital System:** abnormal ejaculation (27% vs. 3%), impotence (10% vs. 1%), female genital disorders (7% vs. 1%), urinary frequency (2% vs. <1%), urination impaired (2% vs. <1%), vaginitis (1% vs. <1%).

Studies in major depressive disorder show a clear dose-dependent relationship for some of the more common adverse events associated with the use of immediate-release paroxetine. The percentage of patients in clinical trials reporting symptoms of sexual dysfunction in non-elderly patients with major depressive disorder and in patients with panic disorder are in males: decreased libido (10% and 9%), ejaculatory disturbance (26% and 27%), impotence (5% and 10%); in females: decreased libido (4% and 8%), orgasmic disturbance (10% and 7%).

Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with *Paxil CR*, or the immediate-release formulation, had minimal weight loss (about 1 pound).

In a study of elderly patients with major depressive disorder, three of 104 *Paxil CR* patients and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern. Two of the *Paxil CR* patients dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, four of 444 *Paxil CR* patients and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of *Paxil CR*. The clinical significance of these findings is unknown. In placebo-controlled clinical trials with the immediate release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Other Events Observed During the Clinical Development of Paroxetine: During premarketing assessment in major depressive disorder and panic disorder, multiple doses of *Paxil CR* were administered to 760 patients in phase 3 double-blind, controlled, outpatient studies. The following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included. The extent to which these events may be associated with *Paxil CR* is unknown.

Body as a Whole: Infrequent were anaphylactoid reaction, chills, flu syndrome, malaise; also observed were adrenergic syndrome, face edema, neck rigidity, sepsis. **Cardiovascular System:** Frequent were hypertension, hypotension; Infrequent were angina pectoris, bradycardia, bundle branch block, palpitation, postural hypotension, syncope; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, hematoma, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles. **Digestive System:** Infrequent were bruxism, dysphagia, eructation, gastroenteritis, gastroesophageal reflux, gingivitis, glossitis, gum hyperplasia, hemorrhoids, hepatosplenomegaly, increased salivation, intestinal obstruction, melena, pancreatitis, peptic ulcer, rectal hemorrhage, stomach ulcer, toothache, ulcerative stomatitis; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, colitis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gastritis, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, throat tightness, tongue discoloration, tongue edema. **Endocrine System:** Infrequent were hyperthyroidism, ovarian cyst, testes pain; also observed were diabetes mellitus, goiter, hypothyroidism, thyroiditis. **Hemic and Lymphatic System:** Infrequent were anemia, eosinophilia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, hypochromic anemia, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia. **Metabolic and Nutritional Disorders:** Infrequent were bilirubinemia, dehydration, generalized edema, hyperglycemia, hyperkalemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. **Musculoskeletal System:** Infrequent were arthritis, bursitis, myasthenia, myopathy, myositis, tendonitis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany. **Nervous System:** Infrequent were amnesia, ataxia, convulsion, diplopia, dystonia, emotional lability, hallucinations, hypesthesia, hypokinesia, incoordination, neuralgia, neuropathy, nystagmus, paralysis, paranoid reaction, vertigo, withdrawal syndrome; also observed were abnormal gait, akathisis, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, dyskinesia, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hostility, hyperalgesia, irritability, libido increased, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis, trismus. **Respiratory System:** Infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia, stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased. **Skin and Appendages:** Infrequent were acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, pruritus, seborrhea, urticaria; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. **Special Senses:** Infrequent were abnormality of accommodation, conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus, visual field defect; also observed were amblyopia, anisocoria, blepharitis, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss. **Urogenital System:** Infrequent were albuminuria, amenorrhea*, breast enlargement*, breast pain*, cystitis, dysuria, hematuria, kidney calculus, menorrhagia*, nocturia, prostatitis*, urinary incontinence, urinary retention; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, female lactation, fibrocystic breast, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, polyuria, pyuria, salpingitis, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Postmarketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug 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 paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor); status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin co-administration. There has been a report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

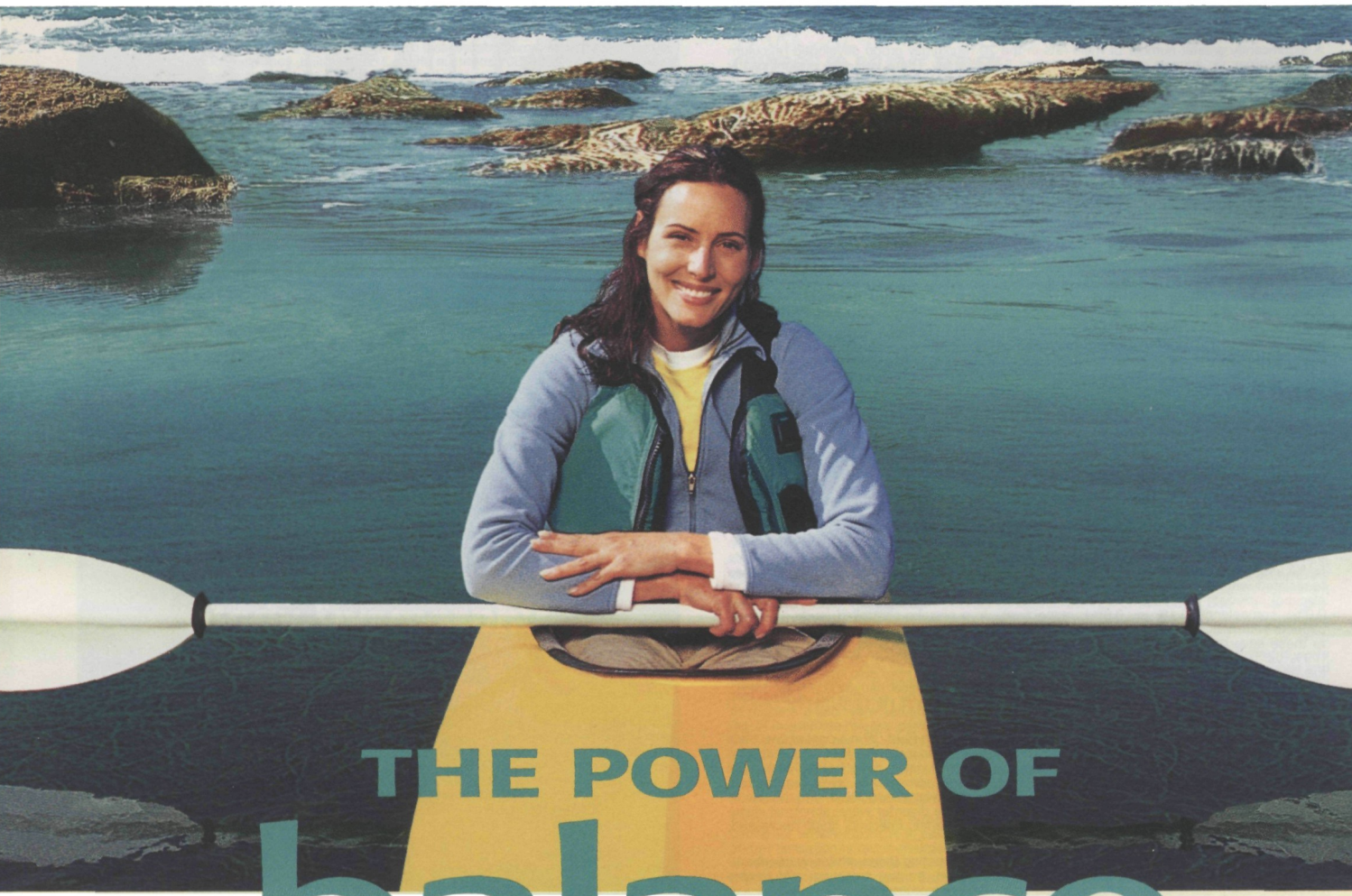
DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: *Paxil CR* is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil CR* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

GlaxoSmithKline
Research Triangle Park, NC 27709

BRS–PC:L2

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

INTRODUCING **NEW *PAXIL CR***



THE POWER OF balance

The efficacy to get them there...the tolerability to keep them going.

NEW *PAXIL CR*™
PAROXETINE HCl
CONTROLLED-RELEASE TABLETS

EFFICACY THAT BEGINS WITH TOLERABILITY

Most common adverse events (incidence of 5% or greater and incidence for *Paxil CR* at least twice that for placebo) in major depressive disorder and panic disorder studies include trauma, nausea, diarrhea, constipation, somnolence, dizziness, decreased libido, tremor, yawning, sweating, abnormal vision, abnormal ejaculation, female genital disorders and impotence. Patients should not be abruptly discontinued from antidepressant medication, including *Paxil CR*. Concomitant use of *Paxil CR* in patients taking monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated.

gsk GlaxoSmithKline

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

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

Table of Contents

Feature Articles

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 7 • Number 5
May 2002

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

CNS Spectrums
(ISSN 1092-8529)
is published monthly by MedWorks Media,
333 Hudson Street, 7th Floor
New York, NY 10013.

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

One year subscription rates:
domestic $120;
foreign $185;
in-training $75.
For subscriptions:
Fax: 212-328-0600
E-mail:
jrr@medworksmedia.com

Postmaster:
Send address changes to
CNS Spectrums
c/o PPS Medical Marketing Group
264 Passaic Ave.
Fairview, NJ 07004-2595

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 7 • Number 5
May 2002

Table of Contents

Departments/Monthly Columns

https://doi.org/10.1017/S1092852900017752 Published online by Cambridge University Press

EXELON...The first choice that stays the course

- Proven efficacy in global functioning, based on evaluation of 3 key domains of Alzheimer's disease...*
  Activities of daily living **B**ehavior **C**ognition
- Dosing flexibility allows customized treatment[1]
  - *Simple 1-step dosing to therapeutic dosage range*
  - *Clear dose response that can maximize efficacy*[1]
    - *Higher doses can be associated with increased incidence of adverse events, especially during dose titration*
- Also available in oral solution
- Established safety profile
  - *Minimal metabolism by the CYP450 isoenzyme system*[1]
  - *No clinically significant drug interactions in clinical trials*[1]
  - *No dosage adjustment needed for patients with renal or hepatic impairment*[1]

For mild to moderate Alzheimer's disease

EXELON®
(rivastigmine tartrate)

1.5, 3.0, 4.5, 6.0 mg Capsules
2 mg/ml Oral Solution

More than memories

*Measured by the Clinician's Interview-Based Impression of Change With Caregiver Input (CIBIC-Plus).

Reference: 1. EXELON® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2000.

Please see brief summary of complete prescribing information on the next page.

In controlled clinical trials, the most common adverse events were nausea, vomiting, anorexia, dyspepsia, and asthenia. **EXELON use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. If therapy is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose in order to avoid the possibility of severe vomiting and its potentially serious sequelae.** In the controlled trials, 47% of patients experienced nausea and 31% of patients experienced vomiting. Weight loss associated with EXELON occurred more commonly among women receiving high doses in clinical trials. Due to increased cholinergic activity, cholinesterase inhibitors may be expected to increase gastric acid secretion and/or have vagotonic effects on heart rate. Therefore, EXELON should be used with caution in patients with peptic ulcers, gastrointestinal bleeding, and "sick sinus syndrome" or other supraventricular cardiac conduction conditions. (Please see important WARNINGS in brief summary of full prescribing information.)

Exelon®

(rivastigmine tartrate)

Capsules

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE: Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS: Exelon® (rivastigmine tartrate) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation *(see DESCRIPTION in the full prescribing information).*

WARNINGS: Gastrointestinal Adverse Reactions: Exelon® (rivastigmine tartrate) use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg BID and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose *(see DOSAGE AND ADMINISTRATION in the full prescribing information)* to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5-mg dose after 8 weeks of treatment interruption).

***Nausea and Vomiting:* In the controlled clinical trials, 47% of the patients treated with an Exelon dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Exelon-treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% vs. 3% for placebo) than in the maintenance phase (14% vs. 3% for placebo). The rates were higher in women than men. Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of Exelon-treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs. 9% for placebo) than in the maintenance phase (17% vs. 4% for placebo).**

***Weight Loss:* In the controlled trials, approximately 26% of women on high doses of Exelon (greater than 9 mg/day) had weight loss of equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.**

Anorexia: In the controlled clinical trials, of the patients treated with an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course or the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological 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 Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia: Exelon as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions: Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6-12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary: Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions: Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions: Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS: Information for Patients and Caregivers: Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Drug-Drug Interactions: ***Effect of Exelon® (rivastigmine tartrate) on the Metabolism of Other Drugs:*** Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), ß-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

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: In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m² basis.

Rivastigmine was clastogenic in two *in vitro* assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three *in vitro* assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the *in vivo* mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m² basis.

Pregnancy: ***Pregnancy Category B:*** Reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 2.3 mg-base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m² basis) revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m² basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Exelon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether rivastigmine is excreted in human breast milk. Exelon has no indication for use in nursing mothers.

Pediatric Use: There are no adequate and well-controlled trials documenting the safety and efficacy of Exelon in any illness occurring in children.

ADVERSE REACTIONS: Adverse Events Leading to Discontinuation: The rate of discontinuation due to adverse events in controlled clinical trials of Exelon® (rivastigmine tartrate) was 15% for patients receiving 6-12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on Exelon compared to 4% for those on placebo.

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 1. Most Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)	Placebo (n=788)	Exelon ≥6-12 mg/day (n=987)	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)
Event / % Discontinuing						
Nausea	<1	8	<1	1	1	8
Vomiting	<1	4	<1	1	<1	5
Anorexia	0	2	<1	1	<1	3
Dizziness	<1	2	<1	1	<1	2

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon: The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions: Exelon use is associated with significant nausea, vomiting, and weight loss *(see WARNINGS).*

Adverse Events Reported in Controlled Trials: Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 6-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined on the incidence of adverse events in the controlled studies. Nausea, vomiting and weight loss were more frequent in women than men.

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Exelon® (6-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Exelon (6-12 mg/day) (n=1189)
Percent of Patients with any Adverse Event	79	92
Autonomic Nervous System		
Sweating increased	1	4
Syncope	2	3
Body as a Whole		
Accidental Trauma	9	10
Fatigue	5	9
Asthenia	2	6
Malaise	2	5
Influenza-like Symptoms	2	3
Weight Decrease	<1	3
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	21
Headache	12	17
Somnolence	3	5
Tremor	1	4
Gastrointestinal System		
Nausea	12	47
Vomiting	6	31
Diarrhea	11	19
Anorexia	3	17
Abdominal Pain	6	13
Dyspepsia	4	9
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	9
Confusion	7	8
Depression	4	6
Anxiety	3	5
Hallucination	3	4
Aggressive Reaction	2	3
Resistance Mechanism Disorders		
Urinary Tract Infection	6	7
Respiratory System		
Rhinitis	3	4

Other adverse events observed at a rate of 2% or more on Exelon 6-12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infections, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Other Adverse Events Observed During Clinical Trials: Exelon has been administered to over 5297 individuals during clinical trials worldwide. Of these, 4326 patients have been treated for at least 3 months, 3407 patients have been treated for at least 6 months, 2150 patients have been treated for 1 year, 1250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 2809 patients were exposed to doses of 10-12 mg, 2615 patients treated for 3 months, 2328 patients treated for 6 months, 1378 patients treated for 1 year, 917 patients treated for 2 years, and 129 treated for over 3 years.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa, and Japan 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 WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely 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 Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paraesthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goitre, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, dermatitis contact.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Post-Introduction Reports: Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

Store below 77°F (25°C) in a tight container.

REV: JANUARY 2001 Printed in U.S.A. T2000-74 89007403

Manufactured by
Novartis Pharma AG
Basle, Switzerland

Manufactured for
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936