March 2002 Volume 7 - Number 3

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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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/S1092852900017508 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/m^2 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/m^2 basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m^2 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/m^2 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/m^2 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/m^2 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/m^2 basis.

https://doi.org/10.1017/S1092852900017508 Published online by Cambridge University Press

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®[a] N=119 %	Placebo[a] N=128 %	Body System/ Adverse Event	Neurontin®[a] 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

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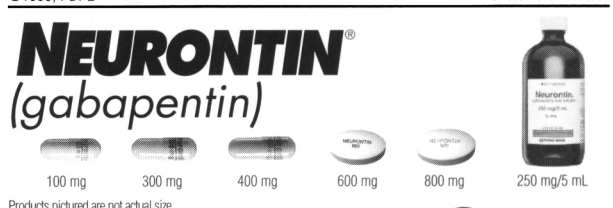
Revised November 2000



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Pfizer U.S. Pharmaceuticals

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STRONG SILENT TYPE.
LIKE HER NEURONTIN.

ADD-ON PARTIAL-SEIZURE CONTROL WITH EXCELLENT TOLERABILITY

Efficacy in a range of patients

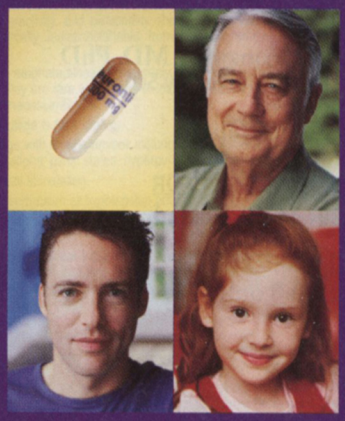
Well tolerated

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)

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CNS SPECTRUMS

The International Journal of Neuropsychiatric Medicine

ADDERALL® XR

5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg & 30 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

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

DESCRIPTION: A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate.

EACH TABLET CONTAINS:	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	20 mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Aspartate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg	4.7 mg	6.3 mg	7.8 mg	9.4 mg	12.6 mg	18.8 mg

Inactive Ingredients: sucrose, lactose, corn starch, acacia and magnesium stearate.

Colors: ADDERALL 5 mg, 7.5 mg and 10 mg contain FD & C Blue #1.

ADDERALL 12.5 mg, 15 mg, 20 mg and 30 mg contain FD & C Yellow #6 as a color additive.

CLINICAL PHARMACOLOGY: Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence which clearly establishes the mechanism whereby amphetamine produces mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

INDICATIONS: Attention Deficit Disorder with Hyperactivity: Adderall is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

In Narcolepsy

CONTRAINDICATIONS:
Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.
Agitated states.
Patients with a history of drug abuse.
During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS: Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Usage in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

PRECAUTIONS: General: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents* - Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines.
Urinary acidifying agents -
(ammonium chloride, sodium acid phosphate, etc.) Increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.
Adrenergic blockers -
Adrenergic blockers are inhibited by amphetamines.
Alkalinizing agents -
Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.
Antidepressants, tricyclic -
Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
MAO inhibitors -
MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Antihistamines -
Amphetamines may counteract the sedative effect of antihistamines.
Antihypertensives -
Amphetamines may antagonize the hypotensive effects of antihypertensives.
Chlorpromazine -
Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.
Ethosuximide -
Amphetamines may delay intestinal absorption of ethosuximide.
Haloperidol -
Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.
Lithium carbonate -
The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.
Meperidine -
Amphetamines potentiate the analgesic effect of meperidine.
Methenamine therapy -
Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.
Norepinephrine -
Amphetamines enhance the adrenergic effect of norepinephrine.
Phenobarbital -
Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.
Phenytoin -
Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.
Propoxyphene -
In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.
Veratrum alkaloids -
Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions:
- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed.

Pregnancy - Teratogenic Effects: Pregnancy Category C. Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Pediatric Use: Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical *evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.*

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

ADVERSE REACTIONS:
Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE: Dextroamphetamine sulfate is a Schedule II controlled substance.
Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral *amphetamines.*

OVERDOSAGE: Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.

In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse.

Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

DOSAGE AND ADMINISTRATION: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

Attention Deficit Disorder with Hyperactivity: Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

Narcolepsy: Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

HOW SUPPLIED:
ADDERALL® 5 mg: Blue double-scored tablet, debossed "AD" on one side and "5" on the other side (NDC 58521-031-01)
ADDERALL® 7.5 mg: Blue double-scored tablet, debossed "AD" on one side and "7.5" on the other side (NDC 58521-075-01)
ADDERALL® 10 mg: Blue double-scored tablet, debossed "AD" on one side and "10" on the other side (NDC 58521-032-01)
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In bottles of 100 tablets.

Dispense in a tight, light-resistant container as defined in the USP.
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Rx only.

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https://doi.org/10.1017/S1092852900017508 Published online by Cambridge University Press

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Feature Articles

CNS SPECTRUMS®
The International Journal of Neuropsychiatric Medicine
Volume 7 • Number 3
March 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.

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

https://doi.org/10.1017/S1092852900017508 Published online by Cambridge University Press

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Departments/Monthly Columns

NEW
FDA-approved
for PTSD

Still fighting monsters

Paxil
The courage to dream

PROVEN on the CAPS-2* including all symptom clusters[1]

- Reexperiencing
- Hyperarousal
- Avoidance/numbing

PROVEN across trauma types[1]

- Physical/sexual assault
- Accidental injury
- Witnessing traumatic death/injury
- Combat
- Natural disaster

ONCE-DAILY
PAXIL®
PAROXETINE HCl

The anxiolytic antidepressant

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, GAD or PTSD studies include asthenia, infection, sweating, nausea, dry mouth, constipation, diarrhea, decreased appetite, somnolence, dizziness, insomnia, libido decreased, tremor, nervousness, yawn, abnormal ejaculation, female genital disorders and impotence. Patients should not be abruptly discontinued from antidepressant medication, including *Paxil*. Concomitant use of *Paxil* in patients taking monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated.

Please see brief summary of prescribing information on adjacent page.

https://doi.org/10.1017/S1092852900017508 Published online by Cambridge University Press

PAXIL® (brand of paroxetine hydrochloride)
See complete prescribing information in GlaxoSmithKline literature. The following is a brief summary.

INDICATIONS AND USAGE: *Paxil* is indicated for the treatment of major depressive disorder, 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, generalized anxiety disorder, as defined in DSM-IV and posttraumatic stress disorder, as defined by 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 an MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping *Paxil* before starting an 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 $P_{450}IID_6$, 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 drugs effective in the treatment of major depressive disorder, 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 major depressive disorder 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. Use the same precautions when treating patients with major depressive disorder as when treating patients with other psychiatric disorders.

In GAD and PTSD clinical trials, the following adverse events were reported at an incidence of 2% or greater for *Paxil* and were at least twice that reported for placebo: abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention. During *Paxil* marketing, there have been spontaneous reports of similar adverse events, which may have no causal relationship to the drug, upon the discontinuation of *Paxil* (particularly when abrupt), including the following: dizziness, sensory disturbances (e.g., parethesias such as electric shock sensations), agitation, anxiety, nausea, and sweating. These events are generally self-limiting. Similar events have been reported for other selective serotonin reuptake inhibitors.

Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which *Paxil* is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION in complete prescribing information).

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. As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with *Paxil*. A few cases of acute angle closure glaucoma have been reported. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when prescribing *Paxil* for these patients. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment, a lower starting dose (10 mg) should be used.

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

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

Concomitant use of *Paxil* with tryptophan is not recommended. Use cautiously with warfarin. When administering *Paxil* with cimetidine, dosage adjustment of *Paxil* after the 20 mg starting dose should be guided by clinical effect. When co-administering *Paxil* with phenobarbital or phenytoin, no initial *Paxil* dosage adjustment is needed; base subsequent changes on clinical effect. Concomitant use of *Paxil* with drugs metabolized by cytochrome $P_{450}IID_6$ (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines; Type 1C antiarrhythmics such as propafenone, fecainide and encainide) or with drugs that inhibit this enzyme (e.g., quinidine) may require lower doses than usually prescribed for either *Paxil* or the other drug; approach concomitant use cautiously. 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 $IIIA_4$ substrates (astemizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent than ketoconazole, a potent $IIIA_4$ inhibitor. Assuming that the relationship between paroxetine's *in vitro* Ki and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's inhibition of $IIIA_4$ activity should have little clinical significance. Use caution when co-administering *Paxil* with tricyclic antidepressants (TCAs). TCA plasma concentrations may need monitoring and the TCA dose may need to be reduced. Administration of *Paxil* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug. Concomitant use of *Paxil* and alcohol in depressed patients is not advised. Undertake concomitant use of *Paxil* and lithium or digoxin cautiously. If adverse effects are seen when co-administering *Paxil* with procyclidine, reduce the procyclidine dose. Elevated theophylline levels have been reported with *Paxil* co-administration; monitoring theophylline levels is recommended.

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

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

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

Safety and effectiveness in the pediatric population have not been established.

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

ADVERSE REACTIONS: Incidence in Controlled Trials—*Commonly Observed Adverse Events in Controlled Clinical Trials:* The most commonly observed adverse events associated with the use of *Paxil* in the treatment of major depressive disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo): asthenia (15% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs. 2%), somnolence (23% vs. 9%), dizziness (13% vs. 6%), insomnia (13% vs. 6%), tremor (8% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (13% vs. 0%) and other male genital disorders (10% vs. 0%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of obsessive compulsive disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that of placebo) were: nausea (23% vs. 10%), dry mouth (18% vs. 9%), decreased appetite (9% vs. 3%), constipation (16% vs. 6%), dizziness (12% vs. 6%), somnolence (24% vs. 7%), tremor (11% vs. 1%), sweating (9% vs. 3%), impotence (8% vs. 1%) and abnormal ejaculation (23% vs. 1%).

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

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

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.

The most commonly observed adverse events associated with the use of paroxetine in the treatment of posttraumatic stress disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders and impotence.

Twenty percent (1,199/6,145) of *Paxil* patients in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735) and 11.7% (79/676) of *Paxil* patients in worldwide trials in social anxiety disorder, OCD, panic disorder, generalized anxiety disorder and posttraumatic stress 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: **major depressive disorder**–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; **posttraumatic stress disorder**–somnolence, tremor, nausea, asthenia.

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 major depressive disorder: 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.

The following adverse events occurred at a frequency of 2% or more among PTSD patients 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, infection, abdominal pain, trauma, vasodilation, sweating, nausea, dry mouth, constipation, diarrhea, decreased appetite, vomiting, dyspepsia, insomnia, somnolence, dizziness, tremor, libido decreased, abnormal dreams, 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.

https://doi.org/10.1017/S1092852900017508 Published online by Cambridge University Press

In placebo-controlled clinical trials involving more than 3,200 patients with major depressive disorder, OCD, panic disorder, social anxiety disorder, generalized anxiety disorder or post-traumatic stress 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 major depressive disorder 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: *infrequent:* allergic reaction, chills, face edema, malaise, neck pain; *rare: adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.* **Cardiovascular System:** *frequent:* hypertension, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine, syncope; *rare:* angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, *phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis,* varicose vein, vascular headache, ventricular extrasystoles. **Digestive System:** *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. **Endocrine System:** *rare:* diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia. **Metabolic and Nutritional:** *frequent:* weight gain; *infrequent:* edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, 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, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, 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, psychosis, 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, stridor, voice alteration. **Skin and Appendages:** *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. **Special Senses:** *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect. **Urogenital System:** *infrequent:* amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports

Voluntary reports of adverse events that have been received since market introduction and not *listed above that may have no causal relationship with Paxil include–acute pancreatitis,* elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, 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 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, and events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia and agranulocytosis). There has been a report of an elevated phenytoin level after 4 weeks of *Paxil* and phenytoin co-administration, and a report of severe hypotension when *Paxil* was added to chronic metoprolol treatment.

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

BRS–PX:L22

https://doi.org/10.1017/S1092852900017508 Published online by Cambridge University Press

For an Alzheimer's disease patient...

Just achieving the ordinary can be extraordinary

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

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

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Printed in U.S.A. 9/01 C-EXL-1024

https://doi.org/10.1017/S1092852900017508 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...*[1]

  Activities of daily living **Behavior** **Cognition**

- 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*

- 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).

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.)

https://doi.org/10.1017/S1092852900017508 Published online by Cambridge University Press

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.

T2000-74
89007403

REV: JANUARY 2001 Printed in U.S.A.

Manufactured by
Novartis Pharma AG
Basle, Switzerland

Manufactured for
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936