Stiff-Person Syndrome: Autoimmunity and the Central Nervous System

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ABSTRACT

Stiff-person syndrome (SPS) is a rare disease of severe progressive muscle stiffness in the spine and lower extremities with superimposed muscle spasms triggered by external stimuli. Patients with SPS are often referred for psychiatric evaluation and the psychiatrist may be the first to diagnosis SPS. Psychosocial stressors often precede the first manifestations of the disease; depression, anxiety, and alcohol abuse are comorbid illnesses. The identification of an association with antibodies to glutamic acid decarboxylase (GAD) was invaluable for definitively establishing a pathological basis for the disease; antibodies to amphiphysin and gephyrin are also found in cases of SPS but at much lower frequencies. Whether the antibodies inhibit GAD activity in vivo, *target GAD-expressing neurons for immune-mediated destruction, are part of a wider immune process, or are merely a marker for destruction of GAD-expressing neurons by an independent neurodegenerative process is not yet clear. Both electromyography and the detection of GAD antibodies are useful in establishing a diagnosis of SPS. Treatment of SPS includes the use of immunomodulating therapies (plasmapheresis and intravenous immunoglobulins) and symptomatic treatment with benzodiazepines and baclofen. The use of tricyclic antidepressants and rapid withdrawal from therapy should be avoided.*

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INTRODUCTION

Stiff-person syndrome (SPS) is a rare disease of severe progressive muscle stiffness in the spine and lower extremities, with superimposed muscle spasms triggered by external stimuli. Symptoms are exacerbated during periods of emotional stress and patients with SPS are frequently referred for psychiatric evaluation, particularly before antibodies to glutamic acid decarboxylase (GAD) are detected. Typically, symptoms begin between the ages of 30 and 50 years and respond to gamma-aminobutyric acid (GABA)-mediated and immunomodulating therapies. Highly specific antibodies to GAD are present in most people with the disease. Electromyography (EMG) shows a characteristic abnormality and may help identify those persons with SPS who do not produce antibodies to GAD.

PSYCHIATRIC ASPECTS OF STIFF-PERSON SYNDROME

Patients with SPS are often referred for psychiatric evaluation and the psychiatrist may be the first to consider a diagnosis of SPS. Psychosocial stressors often precede the first manifestations of the disease and the patient may be given a diagnosis of conversion disorder. EMG findings closely mimic the activity produced by volitional muscle contractions and the patient may be labeled as hysterical. In SPS, spasms and rigidity are typically triggered by sudden noise or unexpected touch and the patient may be treated for agoraphobia. The central nervous system (CNS) is closely involved in SPS and although the exact site of pathology is not known, the GABA nervous system is strongly implicated. The synapses of the GABA nervous system are the most numerous inhibitory synapses in the supraspinal nervous system, and SPS likely alters internal sensations. One patient described the onset of symptoms as follows: "I still felt the irritability and restlessness... a rather aggressive feeling... the usual, typical prelude to the rigidity and shaking spasms." Finally, the use of high doses of benzodiazepines to control muscle tone or the use of narcotic analgesia may prompt involvement of a psychiatrist.

A retrospective case review of psychiatric consultations at the Mayo Clinic[1] highlighted anxiety, depression, and alcohol abuse as possible concomitant disorders. One patient whose case was reviewed had a 15-year history of muscle spasms relieved by alcohol and benzodiazepine use, multiple admissions for detoxification, and severe muscle spasms during drug withdrawal. This patient was later found to have a positive GAD antibody titer. Alcohol has been found to alleviate stiffness in some patients. Depression was treated medically in several patients and the data suggest that tricyclic antidepressants (TCAs) worsen the symptoms of SPS but that fluoxetine is a well-tolerated antidepressant. The dose of diazepam in these patients ranged from 40–120 mg/day; one patient suffered respiratory arrest during benzodiazepine taper.

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This case review was followed by a study of interviews and psychological tests of many of these same patients.[2] The Minnesota Multiphasic Personality Inventory of this group showed a profile consistent with mild-to-moderate depression and anxiety, increased emotionality, and increased concern with bodily function. Of the 13 patients in this study, 12 were treated with benzodiazepines; the clonazepam dose ranged from 10–20 mg/day and the diazepam dose ranged from 20–100 mg/day. This group experienced increased psychiatric symptoms and increased alcohol abuse. Depression and alcoholism in these patients may arise as a consequence of a pathophysiological process involving neurons of the GABA nervous system.

A prospective interview study pointed to the frequency of psychiatric encounters in patients with SPS. "An initial misdiagnosis of psychogenic or hysteric movement disorder was made in all patients except one.... In most patients, this false diagnosis was made by neurologists."[3] Several patients in this study reported acute task-specific phobias similar to agoraphobia several months before they had any conscious awareness of a fixed gait disorder; several reported a transient experience of motor symptoms in emotionally distressing situations. The frequent occurrence of traumatic events in childhood among the patients in this study suggests that an increased susceptibility of the immune system may exist during certain periods of development.

History

SPS was initially called "stiff-man" syndrome when characterized by Moersch and Woltman in 1956.[4] Their report of 14 patients seen over 27 years is a landmark description of the clinical syndrome. A literature review a decade later sharply delineated the characteristics of the disease, proposed seven diagnostic criteria, and postulated that the symptoms might be due to a failure of inhibitory function.[5] A follow-up report of the Mayo Clinic study by Lorish and colleagues (1989)[6] describing 13 patients seen over 30 years detailed revised standard criteria for diagnosing the disease. The criteria of Lorish and colleagues, most widely referenced, are: a prodrome of axial muscle stiffness and rigidity; a slow progression to stiffness of the proximal limb muscles, making ambulation and volitional movements difficult; a fixed deformity of the spine (typically increased lumbar lordosis); superimposed spasms triggered by unexpected touch, noise, or emotional distress; normal motor and sensory examinations; normal intellect; and continuous motor unit activity on an EMG, abolished by intravenous or oral diazepam (Table 1). A review by Blum and Jankovic[7] summarized the world literature through 1990. A clinical study by Dalakas and colleagues[8] of 20 patients with SPS is the largest of its kind. Effective treatment with a benzodiazepine was described by Howard in 1963.[9] Baclofen has been an important component of symptomatic therapy since 1980.[10] Other therapies have developed slowly; immunomodulating therapy was introduced in 1989 and is still not widely used.[11] Identifying an association with GAD antibodies definitively established a pathological basis for the disease.[12] Subsequently, other autoimmune antibodies have been associated with SPS: amphiphysin, reported in 1993 and gephyrin, in 2000.[13,14]

Clinical Features

Most often, SPS begins insidiously and progresses over years, although in some cases symptoms have developed over weeks. Initial episodes may be transient and occur only in the context of emotional distress. The first symptom is usually a persistent progressive stiffening of muscles in the back or in a limb, which may be worse in pressure situations, such as crossing a busy street. A sensation of aching or stiffness progresses with time and is described as stiffness, rigidity, hypertonia, or increased tone. In addition to the stiffness, patients experience spasms of the involved muscles. The spasms are characterized as severe, tremendous, intense, and painful. The examiner may suspect that a volitional

TABLE 1.
SUMMARY OF DIAGNOSTIC CRITERIA[6]

- Prodrome of axial stiffness and rigidity
- Slow progression to involvement of proximal muscles
- Spine deformity, typically increased lumbar lordosis
- Triggered spasms
- Normal motor and sensory exam
- Normal intellect
- CMUA on EMG[1] or oral benzodiazepine response

CMUA on EMG=continuous motor unit activity on electromyography.

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component exists. When stiffness and spasms are present together, patients have difficulty walking and are prone to unprotected falls likened to the toppling of a statue. While in spasm, the muscles are palpably hardened and may produce sustained abnormal joint position, especially extension of the legs and flexor contraction of the arms. Spasms may be triggered by sudden noise, touch, electrical shock, and passive or volitional movement, and are typically relieved by sleep.[5] The onset of stiffness commonly begins in the spine and legs, and less commonly in the face and arms. Isolated involvement of the upper extremities and rostral spine may be more common in amphiphysin-associated SPS.[13] An increase in the curvature of the lumbar spine or hyperlordosis is characteristic, but other spinal deformities, including cervico-thoracic hyperkyphosis, are seen.[6] GAD-associated SPS is strongly associated with other autoimmune diseases, such as diabetes, hyperthyroidism, hypothyroidism, pernicious anemia, and vitiligo.[15] High titers of GAD antibodies are rarely found in children.[16]

Variants of SPS can be characterized by either the particulars of the clinical presentation or the specific antibodies involved. Clinically, variants of SPS are described as: focal, involving only a single limb; progressive and affecting cognition, as in progressive encephalitis rigidity and myoclonus; and chronically progressive with myoclonus, a variant with brainstem involvement.[17-19] The variants appear to be less common than SPS itself and asymmetrical stiffness is more common than previously thought.[8]

SPS is very rare and may be associated with antibodies to GAD, amphiphysin, gephyrin, or no defined antigen.[20] The most common form is GAD-associated SPS. The prevalence is not known; however, high titers of antibodies to GAD are extremely rare in normal serum. Amphiphysin-associated SPS represents less than 10% of SPS cases and gephyrin-associated SPS has been identified in only one patient. No clear racial or ethnic predisposition has been found. Women have more cases of GAD-associated SPS than men and the variant of SPS associated with anti-amphiphysin antibodies occurs almost exclusively in women. The association with neoplasia of the breast, lung, and mediastinum is apparently particular to amphiphysin- and gephyrin-associated forms of SPS.[21]

PATHOPHYSIOLOGY

The aggregate of symptoms in SPS suggests a disruption of muscle tone, normally controlled by spinal cord reflexes. Stiffness, spasm, pain, startle, and falls could all result from failed modulation of spinal cord reflexes, but the relief of symptoms by sleep and the sensitivity to noise suggest involvement of supraspinal pathways.[22] Sudden visual stimuli are not known to trigger spasms. Electrophysiological studies have demonstrated some characteristic abnormalities, including abnormal simultaneous contraction of antagonistic muscles.[23] Spinal cord-mediated abnormalities are evidenced by spasmodic reflex myoclonus, diminished vibration-induced inhibition of the H-reflex, and a hypersynchronous response to transcranial magnetic stimulation.[24-26] Cortical abnormalities have been shown by transcranial magnetic stimulation.[27] All of the abnormalities could be explained by a failure of GABA neuron-induced inhibition, both centrally and at the spinal interneuron level. Spinal reflexes are controlled by glycine as well as by GABA receptors. Glycine receptors are defective in hyperexplexia, a hereditary con-

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TABLE 2. AUTOANTIBODIES AND CLINICAL SYNDROMES

GAD		Amphiphysin		Gephyrin
High titer	Low titer	Breast cancer	SCLC	Carcinoma*
SPS	Diabetes	SPS	Encephalomyelitis/ sensory neuropathy	SPS (single case)
Cerebellar ataxia	Adult-onset epilepsy		Cerebellar degeneration	
	Endocrinopathy		Opsoclonus	

SCLC=small-cell lung cancer; SPS=stiff-person syndrome; GAD=glutamic acid decarboxylase.
*Undifferentiated carcinoma in the mediastinum.

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dition also known as startle disease. The onset of spasms in SPS occurs less precipitously than in hyperexplexia, consistent with GABA-mediating slow inhibitory postsynaptic potentials and glycine mediating fast inhibitory postsynaptic potentials.[22]

SPS has not been described in members of the same family and no genetic predisposition is known other than an association with human leukocyte antigen, consistent with an immunological etiology.[28]

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High titers of GAD autoantibodies are almost exclusively associated with SPS, although associations with cerebellar ataxia and autoimmune polyendocrine syndrome have been reported.[29,30] Cerebellar syndromes associated with GAD antibodies may be more common that previously recognized; GABA is an important transmitter in cerebellar Purkinje cells. Low titers of GAD antibodies have been found in cases of refractory localization-related epilepsy.[31] The search for GAD antibodies in cases of adult-onset epilepsy was undertaken because epilepsy can arise from a disruption of GABA neuron function. In fact, the first patient with SPS in which GAD antibodies were found also had adult-onset epilepsy and diabetes.[12] GAD is also found in pancreatic β cells and is an important autoantigen in diabetes (Table 2).[32,33]

The association between the failure of GABA neuron transmission and antibodies to GAD, the enzyme responsible for GABA synthesis, is not yet clear. Whether the antibodies inhibit GAD activity *in vivo*, target GAD-expressing neurons for immune-mediated destruction, are part of a wider immune process, or are merely a marker for destruction of GAD-expressing neurons by an independent neurodegenerative process is not yet clear. As in diabetes, the antibodies may be part of an immune response that also includes cytotoxic T-cells that cause the loss of GAD-containing cells. Pathological investigations show mixed results, but one study describing cell loss had highly atypical clinical

TABLE 3. TREATMENT OF STIFF-PERSON SYNDROME WITH IMMUNOTHERAPY

Author/Year	#	GAD status	Therapeutic modality		
			Intravenous immunoglobulin	Plasmapheresis	High-dose steroid
Khanlou 1999	1	+	Improved		
Sevrin 1998	1		Improved		
Barker 1997	1	+	Improved		
Nakamogoe 1995	1	-		Marked improvement	
Amato 1994	3	+ + +	Striking improvement Striking improvement Transiently improved		Not reported Not reported No effect
Karlson 1994	3	+ + -	Improved Improved Improved	Transiently improved Transiently improved Not tried	Given with pheresis Given with pheresis
Vieregge 1994	4	+ + + -	No effect Not reported Not reported Not reported		Not reported Relief Improved Not reported
Blum 1991	2	+ +			Improved Improved
Brashear 1991	1	+	Marked improvement		
Harding 1989	2	+		No effect No effect	
Vicari 1989	1	+		Improved	

GAD=glutamic acid decarboxylase.

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features.[34,35] The evidence for the pathogenic role of GAD antibodies is growing. Antibodies derived from a patient with cerebellar ataxia acted presynaptically to suppress GABA transmission in a cerebellar slice preparation, and immunoglobulin G derived from a patient with high titers of GAD antibodies inhibited the *in vitro* activity of GAD from rat cerebellums.[36,37] These studies indicated that antibodies to GAD can alter GAD activity, but to do so ***in vivo***, the antibodies must penetrate the blood-brain barrier and bind to the cytosolic enzyme. Antibodies that are directly pathogenic should be able to transfer disease to experimental animals and this has not been demonstrated with antibodies from SPS patients. Nevertheless, the positive response of some patients to plasma exchange, which reduces circulating antibodies, and the recovery of some patients to near normal function after treatment indicates that SPS is likely an antibody-mediated condition. Whether GAD antibodies have a causative role in SPS or are the consequence of a process that leads to impairment of neurotransmission is not known, but most of the evidence suggests that the antibodies play a pathogenic role.

In contrast to GAD, amphiphysin and gephyrin are not specific to GABA synapses. Antibodies in the synapses are unlikely to be pathogenic, but detection of these antibodies indicates the presence of a tumor. Amphyphysin is localized to all presynaptic nerve terminals and is involved in endocytosis. Gephyrin was first identified in glycinergic synapses and is important to the clustering of glycine and GABA-A receptors in the postsynaptic membrane (Figure). Amphiphysin antibodies are not exclusive to SPS, but can be found with other paraneoplastic CNS conditions, including encephalomyelitis, sensory neuropathy, cerebellar degeneration, and opsoclonus.[38,39] In these cases, antibodies to the paraneoplastic antigen Hu can also be detected if small-cell lung cancer is present.[40] SPS associated with antibodies to amphiphysin has been reported only in cases of breast cancer. Gephyrin antibodies were very recently identified in a patient with SPS who had an undifferentiated carcinoma of the *mediastinum*.[14]

DIAGNOSIS

The presence of GAD antibodies strongly supports a diagnosis of SPS (99% specific by immunocytochemistry); however, the absence of antibodies in the serum does not rule out SPS. Antibodies to GAD may be measured by immunocytochemistry and Western blotting methods. Immunocytochemistry allows the detection of multiple antigens in a tissue section whereas Western blotting visualizes protein antigens which have been separated by size. Enzyme-linked immunosorbent assay and radioimmunoassay methods attach labeled substrates to the antibodies in serum by antigen-specific binding.[41] These recently developed assays quantitatively assess a patient's level of GAD antibody. They can only detect a specifically targeted antigen but they may be easily standardized for routine laboratory use.

SPS remains a clinical diagnosis. A detailed history and neurological exam are necessary, and isolated laboratory results do not stand alone. The symptoms of stiffness, rigidity or increased tone, and spasm or pain are essential. Typically involved are the legs and lumbar spine, but the face, neck, abdomen, or arms may also be involved. Fixed spinal deformity is almost universally present in cases of SPS; if it is absent, Lorish suggests that the diagnosis is probably not SPS.[6] The

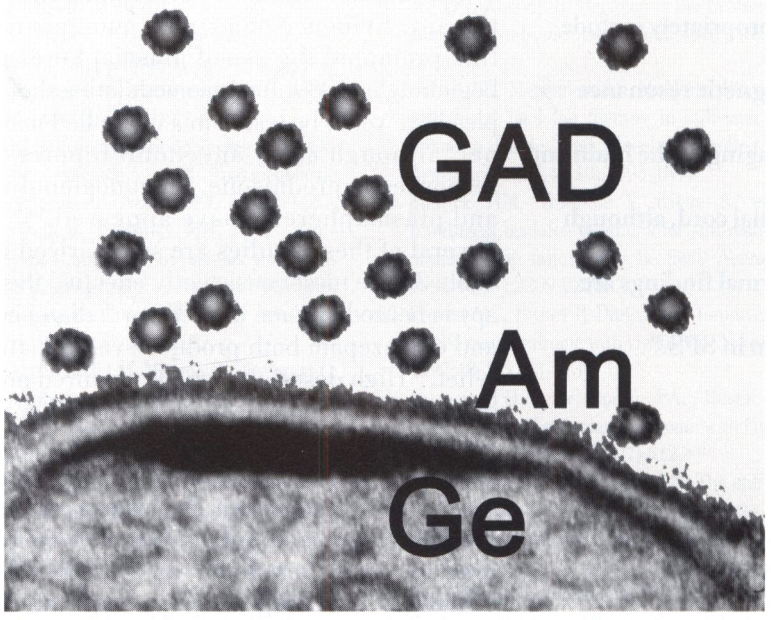

FIGURE. Idealized representation of GABA synapse showing the proposed location of autoantigens associated with SPS: glutamic acid decarboxylase (GAD), amphiphysin (Am), and gephyrin (Ge). The presynaptic terminal is shown on the top and the postsynaptic element is shown on the bottom. GAD is associated with the membranes of presynaptic vesicles containing gamma-aminobuytric acid (GABA); Am may bind to vesicles near the terminal membrane during endocytosis and exocytosis. Am is not specific to GABA synapses; Ge is localized postsynaptically in GABA and glycinergic synapses.

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response to medications may discriminate between SPS and other causes of stiffness, such as Parkinson's disease, spasticity, multiple sclerosis, and transverse myelitis. If autoimmune antibodies are not found, evaluation could appropriately include magnetic resonance imaging of the brain and spinal cord, although normal findings are seen in SPS.

EMG is an important diagnostic tool in evaluating patients for SPS. The typical pattern of continuous low-frequency firing of normal motor units is found simultaneously in agonist and antagonist muscles of the affected region.[23] This abnormal firing pattern is abolished by centrally- and peripherally-acting agents such as general anesthesia, intravenous diazepam, and neuromuscular blockades.[5] High-dose benzodiazepines are known to abolish the motor unit activity of SPS, and if administered immediately before the exam will interfere with the diagnostic usefulness of the EMG. The EMG findings of SPS may be subtle or absent in patients who are fully treated for the symptoms of SPS.

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TREATMENT

The treatment of this disease consists of drugs which act on the GABA pathway for symptomatic relief and immune-mediated therapy. Evidence of a strong autoimmune link prompted the use of plasmapheresis, beginning in 1989. Immunomodulating therapies have yet to be tested in a controlled manner, although many anecdotal reports of responses to prednisone, immunoglobulin, and plasmapheresis have appeared.[10,42-52] Several of these studies are summarized in Table 3. The most consistently effective therapy is benzodiazepine medication[7,9]; diazepam and clonazepam both produce symptomatic relief.[53] High doses are usually required and discontinuation often leads to reemergence of symptoms. Sudden discontinuation, especially of diazepam, may endanger the patient and should not be undertaken. Baclofen is another drug which modulates the function of GABA neurons and has been employed with efficacy,[11,54,55] although serious complications occurred after baclofen pump failure in one reported case.[56] Vigabatrin reportedly treats the symptoms of SPS successfully, but numerous adverse drug reactions have subsequently been described.[57,58] TCAs should not be used to treat depression in patients with SPS.[59] Physical therapy may exacerbate spasms in some patients and should be used carefully in those for whom passive motion may be a trigger of spasm. The course of the disease is variable; some patients with SPS reportedly respond well to medical therapy and are able to resume vigorous exercise. However, abrupt withdrawal of pharmacotherapy in patients with SPS may be life-threatening.[60,61] Overwhelming spasms, autonomic instability, respiratory arrest, and death have reportedly occurred during withdrawal from benzodiazepines.[62]

CONCLUSION

SPS is a rare neurological disorder which requires sophisticated neurological and psychiatric care. The diagnosis of SPS relies on both clinical acumen and laboratory results. Treatment combines immunomodulating therapies and GABA-acting drugs. Treatment with tricyclic antidepressants may worsen symptoms. Rapid withdrawal of therapy should be avoided. The pathogenesis of this disorder remains a focus of ongoing research. CNS

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NEURONTIN®
(Gabapentin)

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 adults with epilepsy.

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

WARNINGS
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, 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 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. Studies to attempt to define a mechanism by which this relatively rare tumor type is occurring are in progress. The relevance of this finding to carcinogenic risk in humans is unclear.
Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and two *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.
No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on an mg/m² basis).

Pregnancy
Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m² basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m² basis.
When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m² basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m² basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m² basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m² basis.
In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers
It is not known if gabapentin is excreted in human milk and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, Neurontin® should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use
No systematic studies in geriatric patients have been conducted. Adverse clinical events reported among 59 Neurontin®-exposed patients over age 65 did not differ in kind from those reported for younger individuals. The small number of older individuals evaluated, however, limits the strength of any conclusions reached about the influence, if any, of age on the kind and incidence of adverse events or laboratory abnormality associated with the use of Neurontin®.
Because Neurontin® is eliminated primarily by renal excretion, the dose of Neurontin® should be adjusted as noted in DOSAGE AND ADMINISTRATION (Table 2) for elderly patients with compromised renal function. Creatinine clearance is difficult to measure in outpatients and serum creatinine may be reduced in the elderly because of decreased muscle mass. Creatinine clearance (C_{Cr}) can be reasonably well estimated using the equation of Cockcroft and Gault:

for females $C_{Cr} = (0.85)(140\text{-age})(wt)/(72)(S_{Cr})$
for males $C_{Cr} = (140\text{-age})(wt)/(72)(S_{Cr})$

where age is in years, wt is in kilograms and S_{Cr} is serum creatinine in mg/dL.

ADVERSE REACTIONS
The most commonly observed adverse events associated with the use of Neurontin® in combination with other antiepileptic drugs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.
Approximately 7% of the 2074 individuals who received Neurontin® in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%).

Incidence in Controlled Clinical Trials
Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of Neurontin®-treated patients 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 (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 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.

Other Adverse Events Observed During All Clinical Trials
Neurontin® has been administered to 2074 individuals 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 individuals 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, periodic, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.
Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, hypoesthesia, 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, hypertonia, 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, aphasia, 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, micturition 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.

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, 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 over 12 years of age. Evidence bearing on its safety and effectiveness in pediatric patients below the age of 12 is not available.
Neurontin® is given orally with or without food.
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.
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.
Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended as follows:

TABLE 2. 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

℞ only

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NEURONTIN®
ADD-ON THERAPY THAT'S A PLUS FOR YOUR PATIENTS

When you add on Neurontin you add:

- Proven efficacy in partial-seizure patients
- Well-tolerated therapy
- Simple, predictable pharmacokinetics
- The #1 branded antiepileptic drug*

For dosing flexibility, Neurontin is available in:

- 100 mg, 300 mg, and 400 mg capsules
- 600 mg and 800 mg tablets

NEURONTIN is indicated as adjunctive therapy in the treatment of 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.

In controlled clinical trials, the most common adverse events reported with NEURONTIN vs placebo were somnolence (19.3% vs 8.7%), dizziness (17.1% vs 6.9%), ataxia (12.5% vs 5.6%), fatigue (11% vs 5%), and nystagmus (8.3% vs 4%).

Proven efficacy
Well tolerated
Easily titrated

NEURONTIN®
(gabapentin)

*Based on new and total prescriptions, IMS Health prescription audit through 11/00 (data on file).

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