

THE CANADIAN JOURNAL OF

Neurological Sciences

LE JOURNAL CANADIEN DES

Sciences Neurologiques

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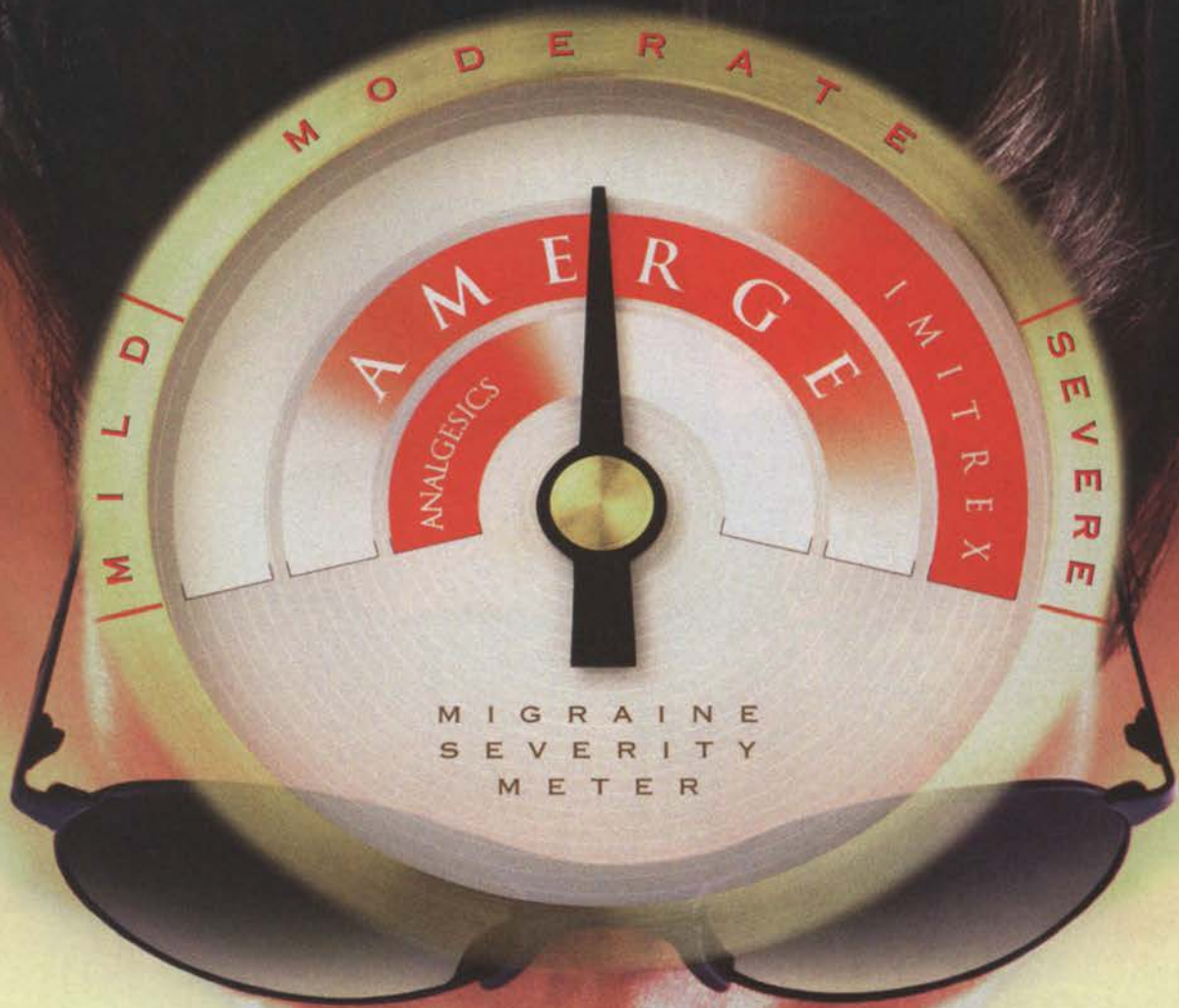
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For brief prescribing information see pages A-40, A-41

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**A successful conversion to lamotrigine monotherapy was achieved in 50 of the 69 patients.

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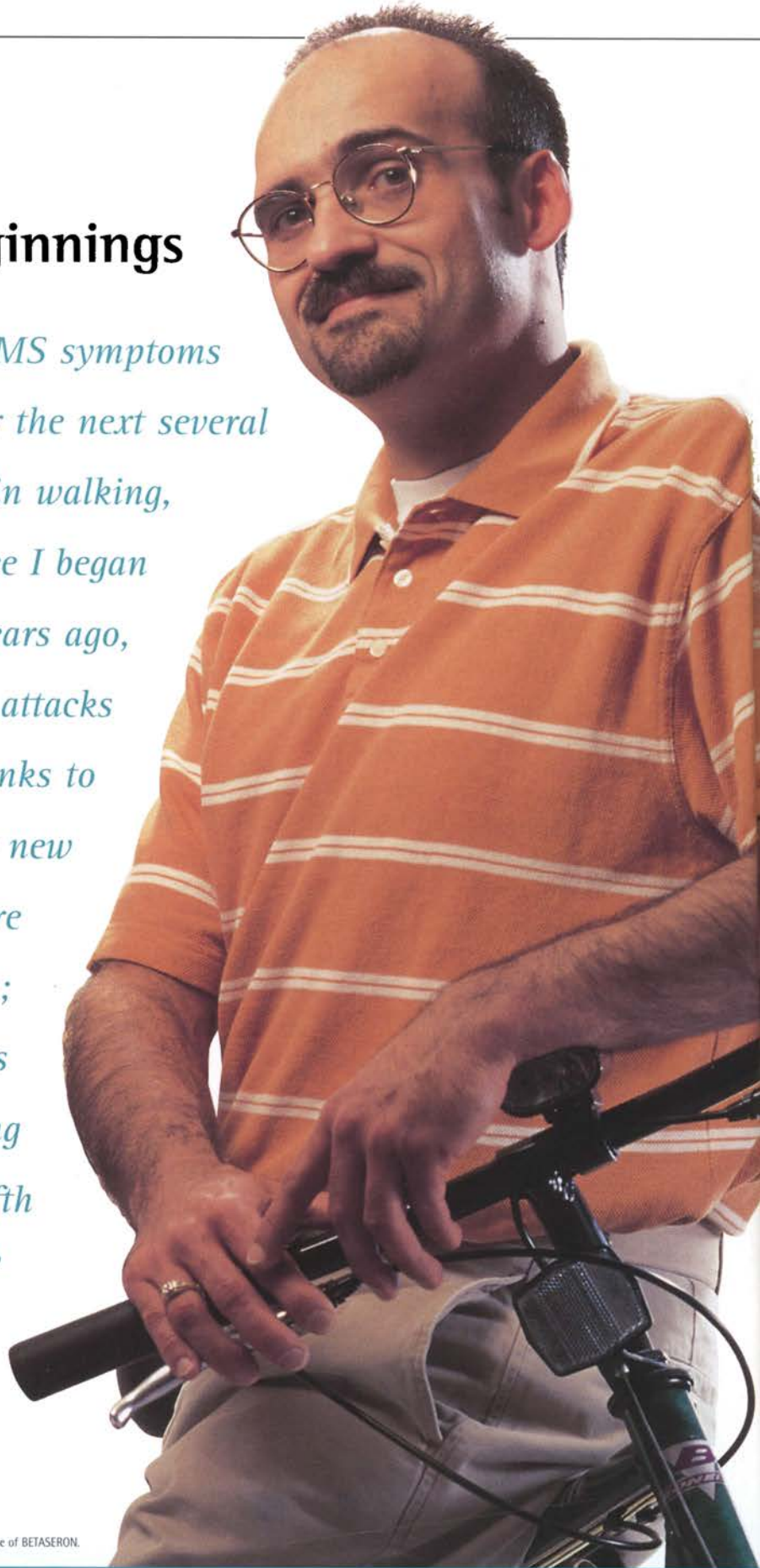


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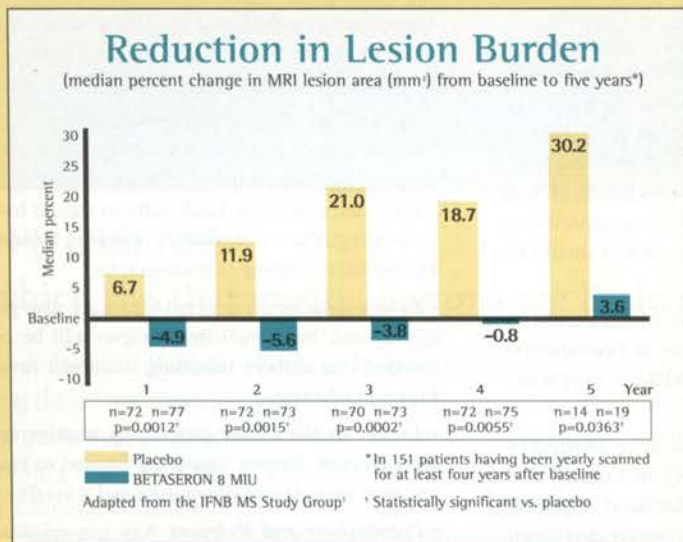
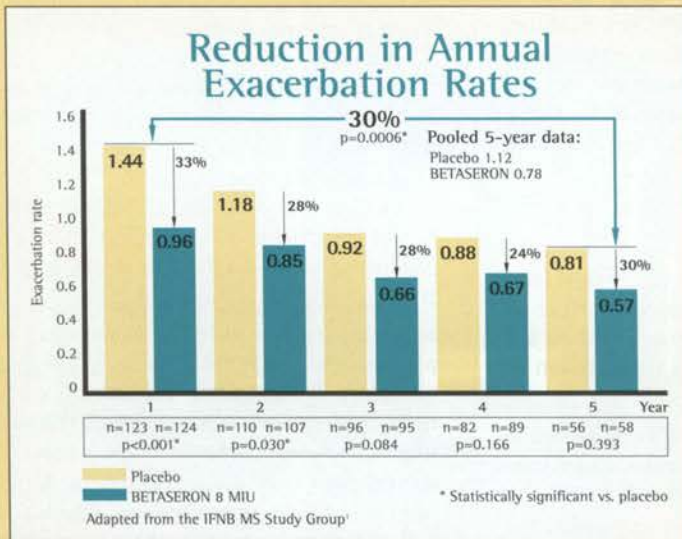


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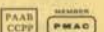
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A Renewed Opportunity

PARKINSON'S DISEASE

A world in which the therapeutic options are limited¹

For those who have it, treat it, live with it; managing their Parkinson's disease can be quite frustrating. Yet there are moments that can be most rewarding. Motor function improves, the number of "off" hours decreases, rigidity subsides, gait improves. Their levodopa seems to be working... at least for today! Then there are times when nothing seems to help. Even their medication seems to be causing problems. It seems hopeless...

Today, however, there is another way to renew their hope. Even after its discovery more than fifteen years ago, Permax (pergolide mesylate) is still considered the most potent dopamine agonist available for the treatment of Parkinson's disease.¹⁻³ With its unique mode of action, i.e. stimulating both D₁ and D₂ dopamine receptors, Permax has demonstrated (n=376) statistically significant improvement in virtually all those numerous parameters of parkinsonian function, including bradykinesia, rigidity, gait, dexterity, etc. Equally important, these benefits were achieved with significantly less levodopa... 24.7% (p <.001), and by starting Permax at low doses "Adverse reactions were, for the most part, mild, reversible, and not of major clinical significance."^{3*}

Successful treatment with Permax can last for up to 3-5 years^{4,5} and renewed improvement has been demonstrated when Permax was given to patients (n=10) in whom the beneficial effect of bromocriptine had waned,⁴ whereas the reverse was not true in a separate, non-comparable study (n=11) when bromocriptine was given to Parkinson's patients in whom Permax had waned.⁶

So, when given an opportunity to manage Parkinson's disease, there may be a way of renewing hope.



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pergolide mesylate

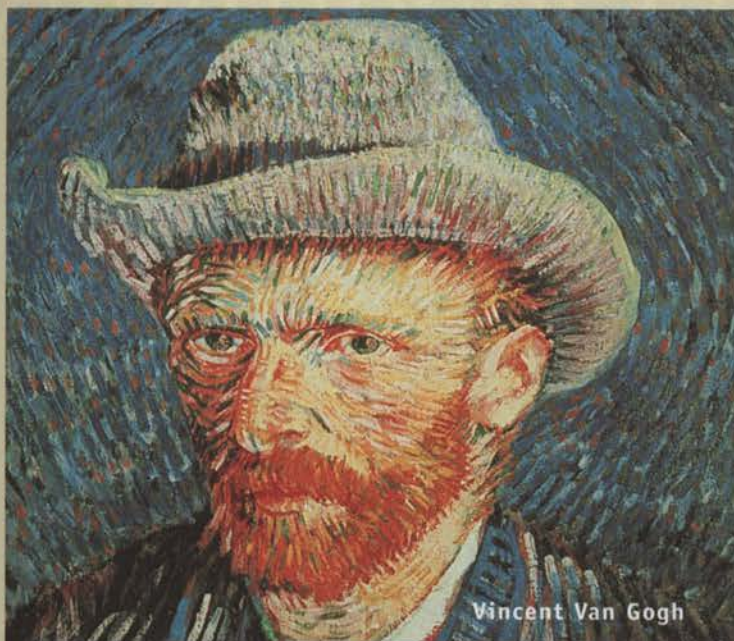


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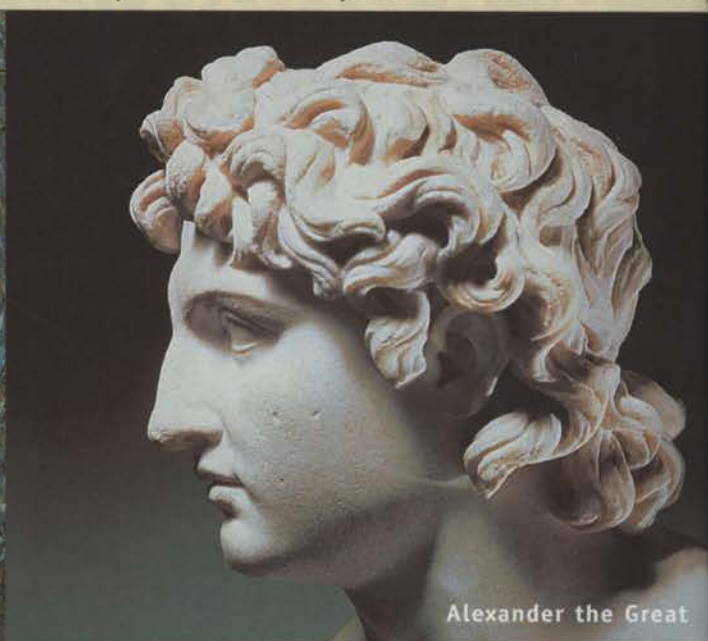
PAAB

* Rapid escalation of pergolide dosage may cause severe adverse reactions. Therefore a slow increase combined with a concomitant gradual and limited reduction of levodopa is recommended. See ADVERSE REACTIONS section in Prescribing Information

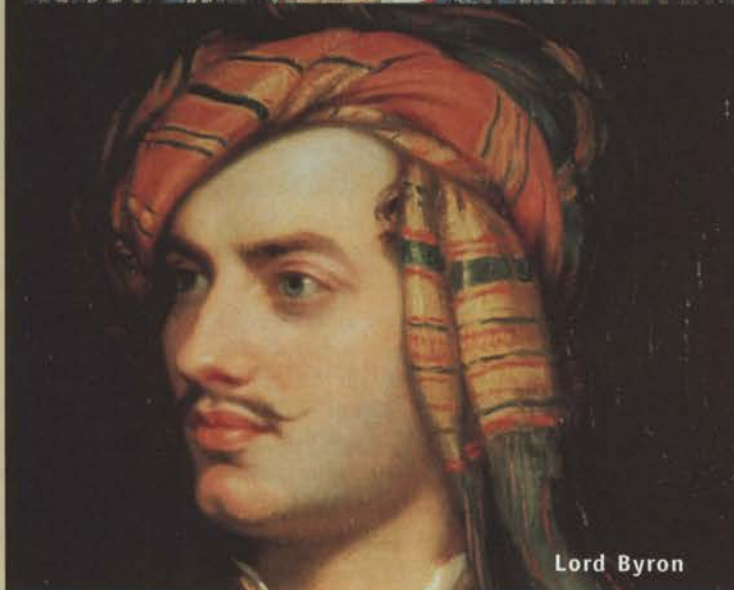
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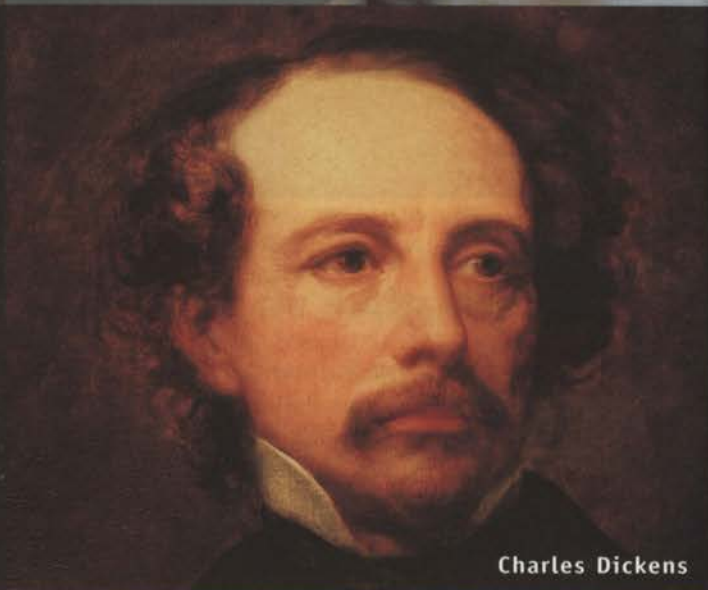
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Alexander the Great

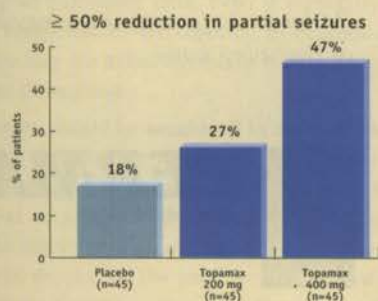


Lord Byron



Charles Dickens

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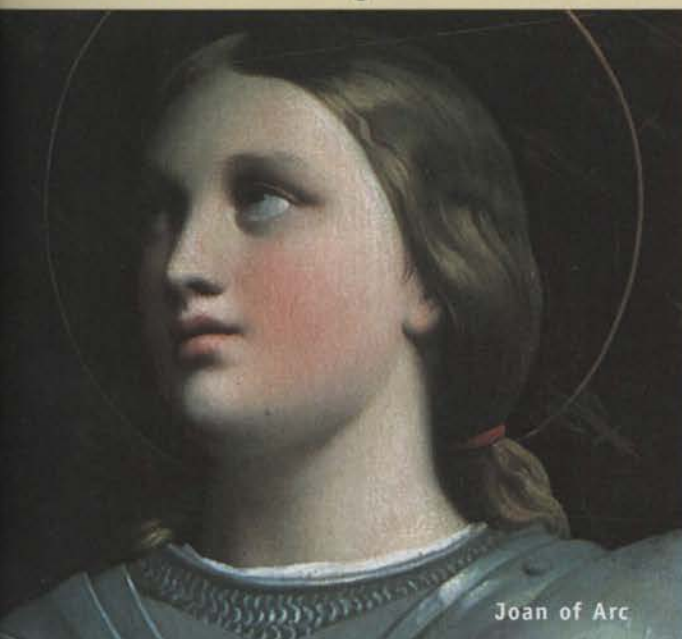


Adapted from reference 1. Double-blind trial of placebo vs. TOPAMAX b.i.d. as adjunctive therapy in 181 patients with refractory partial onset epilepsy receiving one or two other AEDs. *p=0.013.

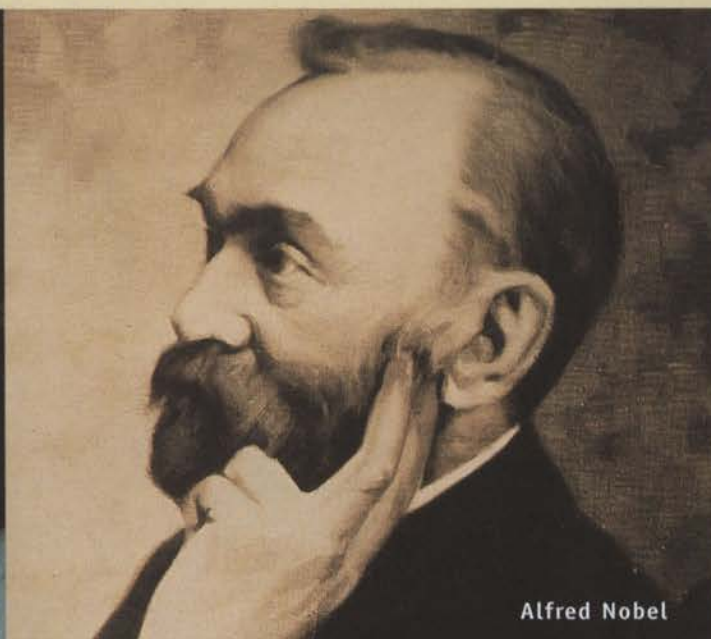
Improved control over a wide range of seizure types

- TOPAMAX is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled with conventional therapy. There is limited information on the use of TOPAMAX in monotherapy at this time.
- High responder rate: 27% (200mg/day, n=45) and 47% (400mg/day, n=45) of patients experienced $\geq 50\%$ reduction in partial seizures (16 week study)¹
- Effective control for patients with secondarily generalized tonic-clonic seizures: 36% of patients experienced a 100% reduction (200-600 mg, n=42, 16 week study)¹
- Unique three-way mechanism of action (Na⁺ channel blockade, GABA potentiation, glutamate antagonism)²

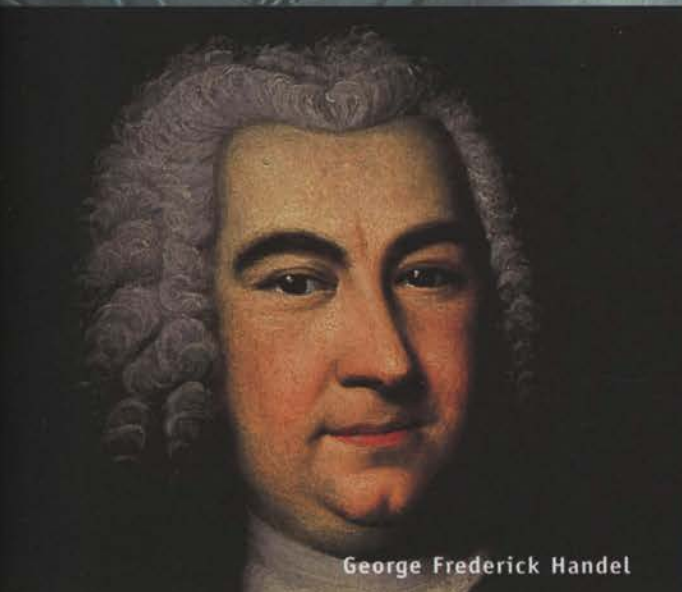
NOVA SCOTIA & QUEBEC FORMULARIES.



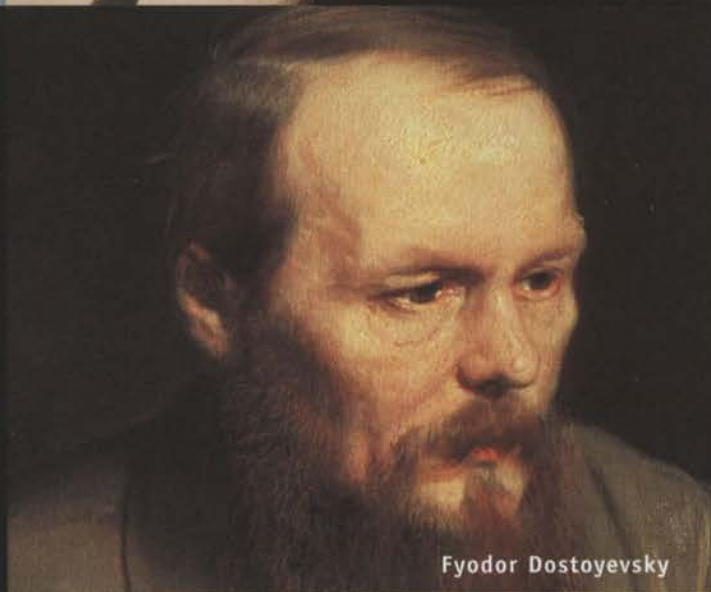
Joan of Arc



Alfred Nobel



George Frederick Handel



Fyodor Dostoyevsky

TALENT FOR PEOPLE WITH EPILEPSY TO SUCCEED. ENJOY LESS TAXING ALTERNATIVES.

- Generally well tolerated: Discontinuations due to adverse events were 10.6% at 200-400 mg/day compared to 5.8% in the placebo group (this appeared to increase at dosages above 400 mg/day)²
- No evidence of serious rash or aplastic anemia²
- Dosage adjustments to primary therapy are generally not required; patients on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored¹²
- Convenient BID dosing

†As with other AEDs, please see prescribing information for complete information on drug interactions. A 1.5% (n=1715) incidence of kidney stones has been reported.² In one study (n=1200), 83% (15 of 18) of patients elected to continue therapy.¹ Ensure adequate hydration and avoid concomitant use with other carbonic anhydrase inhibitors.² *Trademark © Janssen-Ortho Inc. 1997

JANSSEN-ORTHO Inc.
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Favourable side effect profile (the most common are CNS related)

	TOPAMAX 200-400 mg (n=113)	PLACEBO (n=216)
Somnolence	30.1	9.7
Dizziness	28.3	15.3
Ataxia	21.2	6.9
Psychomotor slowing	16.8	2.3
Speech disorders	16.8	2.3
Nervousness	15.9	7.4
Nystagmus	15.0	9.3
Paresthesia	15.0	4.6



TOPAMAX
topiramate

Helping patients make more of their lives



Always

TOGETHER
180 MI

GlaxoWellcome



there,

WE'VE TREATED
MILLION MIGRAINES.[†]



^P **IMITREX**[®]
SUMATRIPTAN SUCCINATE
SUMATRIPTAN NASAL SPRAY

A faster way back.^{TM*}

Available in tablets, nasal spray and subcutaneous formats.

[†]Worldwide estimates January 1999. Data on file, Glaxo Wellcome Inc.

^{*}Onset of action: 10-15 min. subcutaneous, 15 min. nasal spray, 30 min. tablet.

IMITREX (sumatriptan succinate/sumatriptan) is a selective 5-HT₁ receptor agonist indicated for the acute treatment of migraine attacks with or without aura. IMITREX is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic, basilar, ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache. IMITREX is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX. IMITREX is also contraindicated in patients with uncontrolled or severe hypertension.

^{*}IMITREX[®] is a registered trademark of Glaxo Group Limited, Glaxo Wellcome Inc. licensed use. Product Monograph available to health care professionals upon request.

25 Years Ago in the Canadian Journal of Neurological Sciences

³H LEUCINE INCORPORATION INTO MYOFIBRILS OF NORMAL AND DYSTROPHIC MOUSE SKELETAL MUSCLE

G Monckton and H Marusyk

SUMMARY: The study of ³H leucine incorporation into skeletal muscle of mouse muscular dystrophy (129 ReJ/dy Bar Harbour strain) shows the uptake of isotope into myofibrils. The techniques employed were light and EM auto-radiography before and after glycerination (Szent-Gyorgyi 1947). The results indicate a marked drop in uptake of the ³H-Leucine into myofibrils in the dystrophic animals, supporting the contention of Nihei et al (1971) that reduced myosin synthesis occurs in mouse muscular dystrophy.

Can. J. Neurol. Sci. 1975;2:1

PATTERNS OF MOTONEURON DYSFUNCTION AND RECOVERY

Alan McComas, Adrian Upton and Per Jorgensen

Summary: Electrophysiological studies have been carried out on five patients with neuropathies of different etiologies. In each patient serial estimates were made of the numbers of functioning motor units in various muscles. It was found that the intensity of the neuropathic process and the rate of recovery differed in a consistent way among the motoneuron pools investigated. The lesion was more severe in extensor digitorum brevis neurons than in thenar neurons, while the hypothenar ones were least affected. A stage of partial synaptic failure has been recognized in which a motoneuron appears to be no longer able to excite a muscle fiber, but still capable of maintaining certain trophic activities. By comparing the number of functioning motor units with the size of the maximum evoked muscle response it has been possible to detect the adoption of denervated muscle fibers by axonal sprouts from 'healthy' surviving neurons (collateral reinnervation). Lastly, in some muscles it appears that the adopted muscle fibers may subsequently be recaptured by the original motoneurons following recovery of the latter from the neurotoxic insult.

Can. J. Neurol. Sci. 1975;2:5

SEMIOLOGY OF TREMORS

P. Molina-Negro and J. Hardy

SUMMARY: Since the description by Galen in the 2nd Century A.D., clinical neurology has acknowledged the existence of two types of tremor: that which occurs at rest and that occurring during execution of movement. With the help of refined methods of analysis, E.M.G. and cinephotography, the authors have carried out a detailed clinical assessment in more than 400 patients. The basic criterion used to define a tremor was the classical definition of Dejerine: "An involuntary, rhythmical and symmetrical movement about an axis of equilibrium." As a result of this study, the conclusion has been reached that there are two types of tremor: postural tremor and tremor of attitude. Both are present while the limb remains immobile whether by willful design or when at rest in a position of posture and subject only to the action of gravity. During voluntary movement, tremor is not present, Irregular, asymmetrical and non-rhythmic oscillations may appear however - as in so-called intention tremor, of cerebellar origin - but this abnormal movement can hardly be called a real tremor. It is merely a manifestation of ataxia. As a consequence of this study, it is suggested that further understanding of the basic mechanism of tremor can be reached by the investigation of the central neural structures which are involved in the physiology of posture and attitude.

Can. J. Neurol. Sci. 1975;2:23

RELATIVE EFFICACY OF ALCOHOL AND PROPRANOLOL IN ACTION TREMOR

A.H. Rajput, H Jamieson, S. Hirsh and A. Quraishi

SUMMARY: Thirty-nine patients with a variety of diseases, including essential tremor, Parkinson's Disease, olivopontocerebellar degeneration, ataxia telangiectasia, and cervical cord injury with action tremor, were evaluated for the effect of one ounce of absolute alcohol ingestion. Tremor significantly subsided in 61.9% of E.T.; 46.6% of P.D.; one patient with A.T.; and one patient with C6 lesion. The tremor became worse in one patient with O.P.C.D. Twenty of these patients were treated with propranolol, an average dose of 92 mgm. per day, and re-evaluated three to six months later. All those who improved on alcohol improved on propranolol and the one whose tremor accentuated with alcohol had a similar response to propranolol. It is concluded that the tremorolytic effect of alcohol is neither specific for, nor limited to, essential tremor and is of no value in differentiating various neurological disorders which manifest as action tremor. It is recommended that one ounce of absolute alcohol by mouth be used as an office procedure to predict the response of patients' tremor to propranolol.

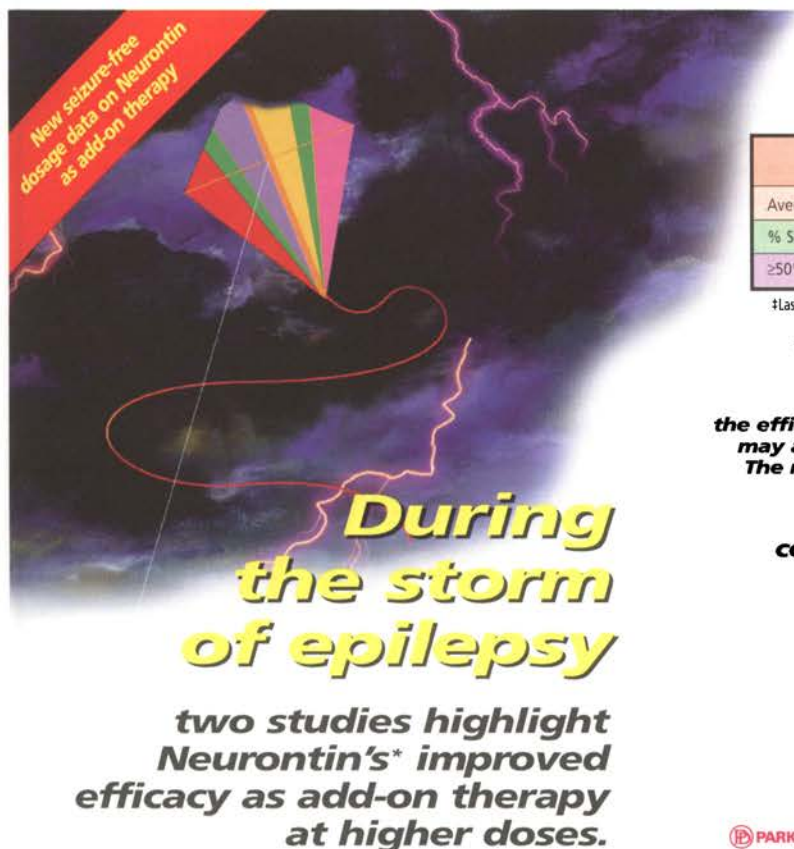
Can. J. Neurol. Sci. 1975;2:31

POLYGLYCOLIC ACID SUTURE IN PERIPHERAL NERVE: AN ELECTRON MICROSCOPE STUDY

Alan R. Hudson, Juan M. Bilbao and Daniel Hunter

SUMMARY: The aim of this experiment was to investigate the reaction of peripheral nerve tissue to a synthetic absorbable suture material. Polyglycolic acid suture material was placed within the sciatic nerve of rats and the absorption of the material was investigated by means of electron photomicrographs. It was concluded that placement of polyglycolic acid into the peculiar environment of endoneurial tissues results in minimal scarring and in minimal disturbance of the surrounding nerve fibers. The material was progressively absorbed with minimal disturbance of intrafascicular structures.

Can. J. Neurol. Sci. 1975;2:17



New seizure-free dosage data on Neurontin as add-on therapy

During the storm of epilepsy

two studies highlight Neurontin's* improved efficacy as add-on therapy at higher doses.

Neurontin* was effective when titrated to individual effectiveness^{1,2}:

	NEON Study ¹ (n=141)	STEPS Study ² (n=1055)
Average % Decrease in Seizures	N/A	60%
% Seizure-Free	46%	46%
≥50% Improvement	71%	76%

¹Last 8 weeks of study. Study included patients with complex partial seizures and was a prospective, open-label, 20-week, multicentre study.

²Last 4 weeks of study. Study examined patients with partial seizures with or without secondary generalizations. STEPS was a prospective, open-label, 16-week, multicentre study.

Doses higher than 1200 mg/day may increase the efficacy in some patients¹; however, higher doses may also increase the incidence of adverse events.¹ The maximum recommended dose is 2400 mg/day.²

To help them through the storm – consider moving patients to a higher dosage of Neurontin*

NEURONTIN
gabapentin
USER FRIENDLY EFFICACY

PARKE-DAVIS

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¹In previous fixed dosage studies somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54) experienced approximately a two-fold increase as compared to patients on lower doses of 600 to 1200 mg/day in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Neurontin is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.¹

25 Years Ago in the Canadian Journal of Neurological Sciences

THE DORSOMEDIAL HYPOTHALAMIC NUCLEUS IN AUTONOMIC AND NEUROENDOCRINE HOMEOSTASIS

Lee L. Bernardis

SUMMARY: Median eminence and ventromedial hypothalamus have in the past been the principal foci of research in neuroendocrine and neurovisceral control mechanisms. The present report provides an overview of work involving the dorsomedial hypothalamic nucleus (DMN). This structure is located dorsal to the ventromedial hypothalamic nucleus (VMN) and extends anteroposteriorly from the plane of the largest cross section of the VMN to the plane of the dorsal premammillary nucleus. Fibers from the DMN pass with the periventricular system and the dorsal longitudinal fasciculus of Schütz and have been traced to the midbrain tegmentum and reticular formation. Intrahypothalamic connections involve intensive networks between DMN, lateral hypothalamic nucleus (LHN) and VMN. Regarding neurotransmitters, recent studies indicate that the DMN receives noradrenergic innervation along two pathways, a dorsal and a ventral one. Monoamine-containing systems approach the DMN from the lateral hypothalamus and the bulk of these fibers are carried in the medium forebrain bundle from their cells of origin in the brain stem. Studies of the vascular supply indicate that both VMN and DMN receive their blood supply from the internal carotid artery. It has been recently demonstrated that the DMN is involved in the control of food intake and possibly water intake as well. Discrete lesions in the DMN have caused hypophagia and hypodipsia, and implantation of epinephrine and norepinephrine in this area has initiated eating. Many years ago, electrical stimulation of this area was reported to cause eating. Although DMN lesions cause hypodipsia, they do not result in the reduced water/food intake rations that are so characteristic of the VMN syndrome. DMN lesions are also followed by reduced spontaneous activity (running wheel), but this reduced activity is not accompanied by increased weight gain and accretion of adipose tissue, the latter being consistently observed in the VMN rat. Rather, carcass fat remains normal in the DMN rat and carcass protein is either normal or slightly increased. Many of the aforementioned changes in weanling rats with DMN lesions, however, are not matched by similar alterations in the intermediary metabolism of carbohydrate and lipid. Possibly this is due to a "resetting" of a central autonomic control system that makes it possible for the DMN rat to adapt more efficiently to a reduced influx of substrate, i.e. the consistent hypophagia. From a review of the literature it appears that the DMN and their circuitry are involved in only a few neuroendocrine, i.e. hypothalamo-hypophyseal control mechanisms. Both lesion and cervical stimulation experiments suggest an involvement of DMN in the control of LTH. Circumstantial evidence points to the DMN as a possible formation and/or storage site of growth hormone inhibiting factor (GIF). Although DMN rats show reduced ponderal and linear growth, they have been found to have normal or elevated plasma growth hormone (GH) levels. Both lesion and stimulation studies have yielded the impression that the DMN is not involved in thyroid, i.e. thyrotropin stimulating hormone releasing factor (TSHRF) control. Electrical stimulation of the DMN has been reported to result in a positive correlation between adrenal blood flow and adrenal corticoid release in hypophysectomized dogs. This has been interpreted as a coordinated response at the level of a "dorsomedial sympathetic vasodilator relay" rather than a "true" neuroendocrine effect via corticotrophin releasing factor (CRF). Experiments that failed to demonstrate a relationship between the DMN and the tonic and cyclic control of luteinizing hormone releasing factor (LHRF) are discussed. The data reviewed indicate the existence in the dorsomedial hypothalamus of an area that exerts a profound influence on many aspects of neurovisceral and some neuroendocrine control systems.

Can. J. Neurol. Sci. 1975;2:45

VENTRICULAR OBSTRUCTION DUE TO ECTASIA OF THE INTERNAL CAROTID ARTERY

A.R. Hudson and C.G. Gonsalves

SUMMARY: This is a report of the first recorded instance of ventricular obstruction at the foramen of Monroe by an ectatic carotid artery. The clinical course, investigations and treatment are described.

Can. J. Neurol. Sci. 1975;2:75

SIMULTANEOUS RECORDINGS OF VISUAL CORTEX AND SUPERIOR COLLICULUS FIELD POTENTIALS IN THE RABBIT

Stephane Molotchnikoff, Michel Dubuc and Jean Real Brunette

SUMMARY: The field potentials recorded simultaneously at various depths of the rabbit's visual cortex and superior colliculus were analyzed following light ON and light OFF. The collicular ON and OFF potentials exhibited three slow components superimposed by fast rhythmic oscillations. Only the first slow component reversed its polarity with penetration from surface negative to positive in depth. The cortical ON and OFF responses similarly contained three slow waves which all reversed their polarity with electrode penetration: from surface positive to negative in deeper layers. The most striking difference between ON and OFF cortical responses is the absence of fast rhythmic oscillations in the cortical ON response.

Can. J. Neurol. Sci. 1975;2:61

SKIN PUNCH BIOPSIES AND LYMPHOCYTES IN THE DIAGNOSIS OF LIPIDOSES

C.L. Dolman, P.M. MacLeod and E. Chang

SUMMARY: Skin punch biopsies and buffy coats of white blood cells were examined electron microscopically in patients suffering from a variety of storage diseases. No specific abnormalities could be detected in Gaucher's disease and adreno-leucodystrophy. While characteristic deposits were found in cutaneous nerves in globoid and metachromatic leucodystrophy, this method was deemed inferior to sural nerve biopsy. In gangliosidoses, on the other hand, pathognomonic membranous cytoplasmic bodies were common in axons of cutaneous nerves, and in generalized gangliosidoses marked vacuolation of many other cells was prominent. Specific deposits were found in various cells in skin punch biopsies and in lymphocytes of children suffering from ceroid lipofuscinoses, and in lymphocytes of their parents. This constitutes the easiest diagnostic laboratory procedure in such cases.

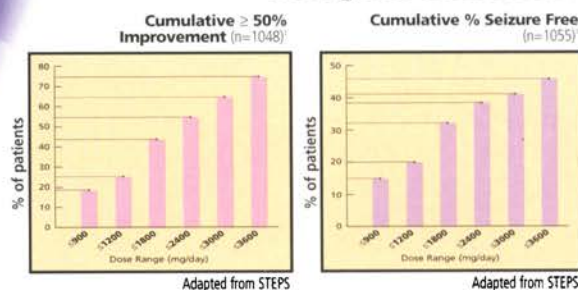
Can. J. Neurol. Sci. 1975;2:67

NEW RESEARCH: STEPS STUDY
(Study of Titration to Effect Profile of Safety)

Clearing the storm of epilepsy

STEPS study highlights Neurontin's* improved efficacy as add-on therapy at higher doses.

To help them through the storm – consider moving patients to a higher dosage of Neurontin*



Study examined patients with partial seizures with or without secondary generalizations. STEPS was a prospective, open-label, 16-week, multicentre study.

Doses higher than 1200 mg/day may increase the efficacy in some patients¹; however, higher doses may also increase the incidence of adverse events.² The maximum recommended dose is 2400 mg/day.³

NEURONTIN
USER FRIENDLY EFFICACY

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¹In previous fixed dosage studies somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54) experienced approximately a two-fold increase as compared to patients on lower doses of 600 to 1200 mg/day in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Neurontin is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.³

Le premier et le seul parmi les nouveaux antiépileptiques* indiqué en monothérapie après une polythérapie



* C'est-à-dire la lamotrigine, la gabapentine, la vigabatrine et le topiramate, qui se distinguent des antiépileptiques traditionnels.
** Un passage réussi à la lamotrigine en monothérapie a été obtenu chez 50 patients sur 69.
*** L'essai comprenait trois phases : traitement d'appoint, retrait des autres antiépileptiques et monothérapie. Ne doit pas être considéré comme une mesure absolue de l'efficacité parce que les patients n'ont pas terminé toutes les phases de l'essai lorsque leur réponse n'était pas satisfaisante.
† Les effets indésirables le plus fréquemment associés à un arrêt de la monothérapie à LAMICTAL ont été les éruptions cutanées (6,1 %), l'asthénie (1,1 %), la céphalée (1,1 %), la nausée (0,7 %) et les vomissements (0,7 %)³. Pour de plus amples renseignements, consulter la monographie de LAMICTAL.
†† Veuillez consulter la monographie pour ce qui est de l'ajustement posologique de LAMICTAL lors du retrait des antiépileptiques administrés en concomitance.

Pour la maîtrise d'un vaste éventail de crises, associée à un profil discret d'effets indésirables liés au SNC

D'une manière générale, une monothérapie efficace a été reconnue comme le traitement de choix pour obtenir la maîtrise des crises avec le minimum d'effets indésirables chez les patients souffrant d'épilepsie¹. Maintenant, renforçant son succès éprouvé comme traitement d'appoint², LAMICTAL est indiqué comme monothérapie chez l'adulte après le retrait d'antiépileptiques administrés en concomitance³.

MONOTHÉRAPIE HAUTEMENT EFFICACE

Dans le cadre d'un essai ouvert sur le passage d'un traitement d'appoint à la monothérapie incluant le retrait des antiépileptiques administrés en concomitance, la monothérapie à LAMICTAL a permis à 30 % (n = 50) des patients traités avec succès de rester exempts de crises^{**4}. Dans un autre essai du même type, ≥ 40 % des patients ont obtenu une réduction de la fréquence de leurs crises d'au moins 50 % pendant toutes les étapes successives de l'essai^{***5}.

GÉNÉRALEMENT MIEUX TOLÉRÉ[†]

Selon les données regroupées de trois essais sur la monothérapie, la fréquence des retraits

dus aux effets indésirables sur le SNC était de 2,5 % (n = 443) avec la monothérapie à LAMICTAL, par rapport à 7,4 % pour la phénytoïne (n = 95) ou à 7,7 % pour la carbamazépine (n = 246)⁶. La fréquence de somnolence, d'asthénie et d'ataxie a été moins élevée pour LAMICTAL que pour la carbamazépine et la phénytoïne. On n'a noté aucune différence quant à la fréquence des retraits dus aux éruptions cutanées entre LAMICTAL (6,1 %) et la phénytoïne (5,3 %) ou la carbamazépine (8,9 %)⁶. Une fréquence plus élevée d'éruptions cutanées a été associée à une augmentation posologique plus rapide de la dose initiale de LAMICTAL ou à l'utilisation concomitante d'acide valproïque³.

MAÎTRISE SUR UN VASTE ÉVENTAIL DE CRISES

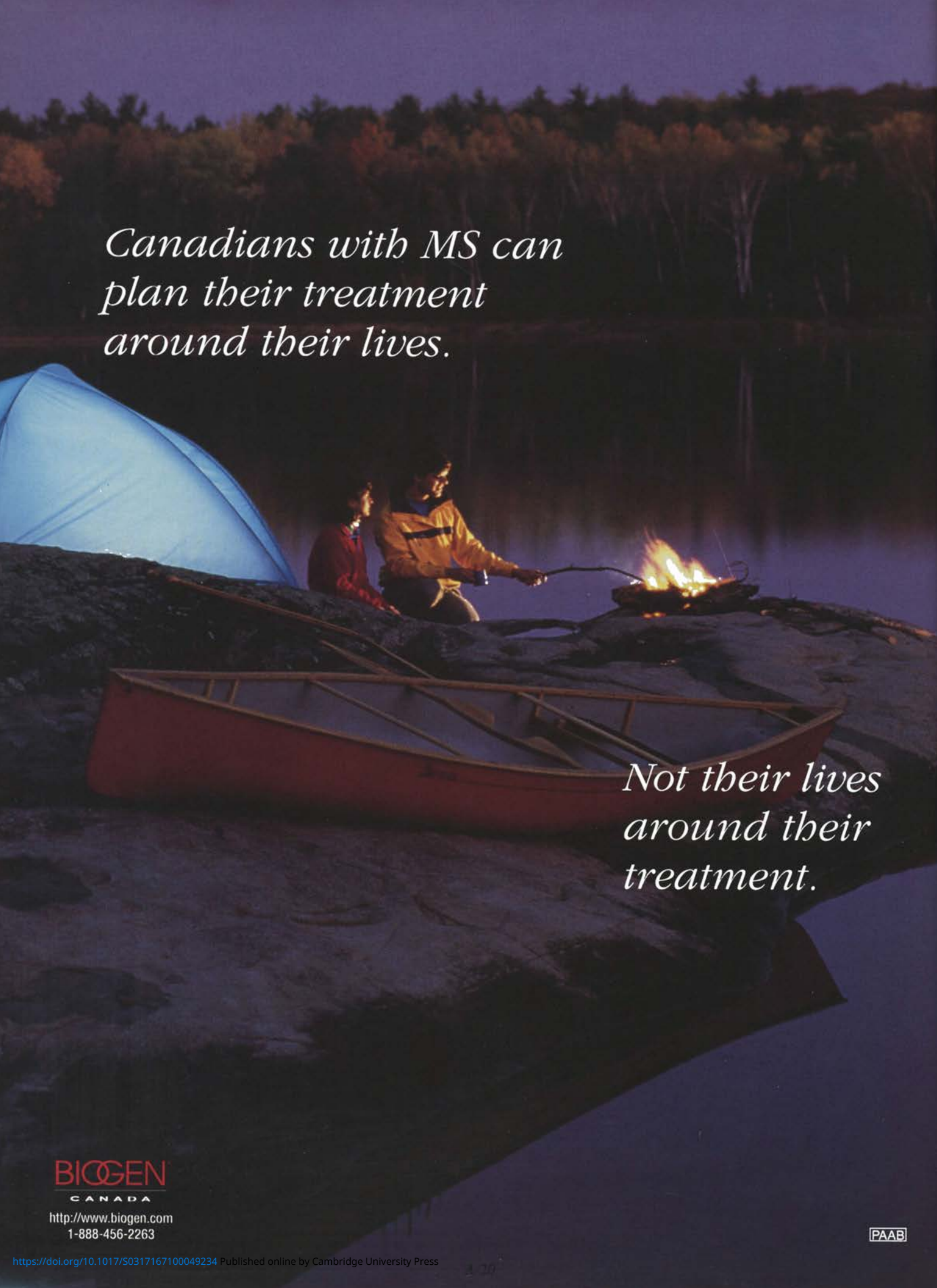
LAMICTAL a été utilisé avec succès pour un vaste éventail de crises comme traitement d'appoint dans une polythérapie². Vous pouvez passer avec confiance de LAMICTAL comme traitement d'appoint en polythérapie à LAMICTAL en monothérapie^{††}, en particulier lorsque les effets indésirables liés au SNC sont une considération importante.

lamotrigine
Lamictal[®]
DE LA POLYTHÉRAPIE À LA
MONOTHÉRAPIE



GlaxoWellcome
Glaxo Wellcome Inc.
Bureau d'affaires du Québec





*Canadians with MS can
plan their treatment
around their lives.*

*Not their lives
around their
treatment.*

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PAAB

New Once-A-Week AVONEX™ (Interferon beta-1a)

*Helping people with relapsing forms
of MS get on with their lives.*

*The therapy prescribed in 18 countries
is now available in Canada*

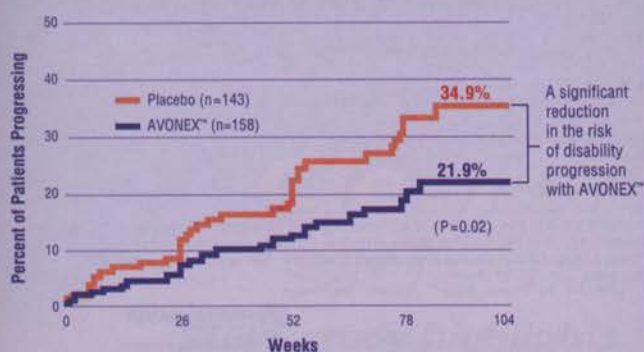
Treatment with once-a-week AVONEX™ results in minimal disruption of patients' lives and mild side effects that decrease over time for most patients.^{1,2}

Our easy to plan, once-a-week IM injections may promote patient compliance.

*AVONEX™ is proven to slow the progression
of disability in relapsing forms of MS**

Prophylactic use of AVONEX™ can help patients maintain function longer. In a clinical trial, patients treated with AVONEX™ showed a significant reduction in risk of disability progression and a 32% reduction in annual exacerbation rate over two years.^{3†}

*Onset of sustained disability progression by
time on study (Kaplan-Meier Methodology)[†]*



AVONEX™ also demonstrated a significant MRI effect, showing an 89% reduction in gadolinium-enhanced lesions in patients with enhancement at baseline.^{2‡}

The Avonex Support Line™: 1-888-456-2263

Biogen Canada is committed to providing healthcare professionals and their patients with the information and support they require. Our toll-free Avonex Support Line™ provides patients with information on injection training, delivery options and reimbursement counseling. Healthcare professionals are also available to answer your questions about AVONEX™.

*Once-a-week AVONEX™
is generally well tolerated[†]*

The unique once-weekly dosing regimen with AVONEX™, means fewer opportunities for injection-related side effects to disrupt patient's lifestyle.[†]

- The most common side effects associated with AVONEX™ treatment are flu-like side effects and usually resolve within 24 hours after injection.^{1,2}
- Incidence of side effects decrease over time with continued treatment for most people.²
- Compared to subcutaneous injections, intramuscular injections result in far fewer site reactions.²
- No cases of injection site necrosis have been reported for patients on AVONEX™ therapy.⁴
- Please see product monograph for important patient selection and monitoring information.

ONCE-A-WEEK
AVONEX™
(Interferon beta-1a)
IM Injection

[†]Versus a more frequent dosing regimen.

[‡]P=0.002; Placebo annual exacerbation rate 0.90, N=87; Avonex annual exacerbation rate 0.61, N=85.

[‡]P=0.041; Placebo median ratio 0.50, N=44; Avonex median ratio 0.11, N=44. The exact relationship between MRI findings and clinical status is unknown.



(Gabapentin) 100 mg, 300 mg, 400 mg Capsules
(Antiepileptic Agent)

INDICATIONS AND CLINICAL USE

Neurontin (gabapentin) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

Neurontin (gabapentin) is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

PRECAUTIONS

General

Neurontin (gabapentin) is not considered effective in the treatment of absence seizures and should therefore be used with caution in patients who have mixed seizure disorders that include absence seizures.

Tumorigenic Potential

Gabapentin produced an increased incidence of acinar cell adenomas and carcinomas in the pancreas of male rats, but not female rats or in mice, in oncogenic studies with doses of 2000 mg/kg which resulted in plasma concentrations 14 times higher than those occurring in humans at the maximum recommended dose of 2400 mg/day. The relevance of these pancreatic acinar cell tumours in male rats to humans is unknown, particularly since tumours of ductal rather than acinar cell origin are the predominant form of human pancreatic cancer.

Drug Discontinuation

As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. When in the judgement of the clinician there is a need for dose reduction, discontinuation or substitution with alternative medication, this should be done gradually over a minimum of one week.

Occupational Hazards

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were somnolence, ataxia, fatigue and nystagmus. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that Neurontin does not affect them adversely.

Drug Interactions

Antiepileptic Agents:

There is no interaction between Neurontin and phenytoin, valproic acid, carbamazepine, or phenobarbital. Consequently, Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the plasma concentrations of gabapentin or the other antiepileptic drugs.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

Oral Contraceptives:

Coadministration of Neurontin with the oral contraceptive Norelgestin does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Antacids:

Coadministration of Neurontin with an aluminum and magnesium-based antacid reduces gabapentin bioavailability by up to 24%. Although the clinical significance of this decrease is not known, coadministration of similar antacids and gabapentin is not recommended.

Probenecid:

Renal excretion of gabapentin is unaltered by probenecid.

Cimetidine:

A slight decrease in renal excretion of gabapentin observed when it is coadministered with cimetidine is not expected to be of clinical importance.

Use in Pregnancy

No evidence of impaired fertility or harm to the fetus due to gabapentin administration was revealed in reproduction studies in mice at doses up to 62 times, and in rats and rabbits at doses up to 31 times the human dose of 2400 mg/day. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.

Use in Lactation

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, and because of the potential for serious adverse reactions in nursing infants from gabapentin, breast-feeding is only recommended if the potential benefit outweighs the potential risks.

Use in Children

Systematic studies to establish safety and efficacy in children have not been performed. Data in 39 patients between the ages of 12 and 18 years included in the double-blind, placebo-controlled trials showed that gabapentin was superior to placebo in reducing seizure frequency. Safety data showed that the incidence of adverse events in this group of patients were similar to those observed in older individuals.

Use in the Elderly

Systematic studies in geriatric patients have not been conducted. Adverse clinical events reported among 59 patients over the age of 65 years treated with Neurontin did not differ from those reported for younger individuals. The small number of individuals evaluated and the limited duration of exposure limits the strength of any conclusions reached about the influence of age, if any, on the kind and incidence of adverse events associated with the use of Neurontin. As Neurontin is eliminated primarily by renal excretion, dosage adjustment may be required in elderly patients because of declining renal function (See Dosage and Administration).

Use in Renal Impairment

Gabapentin clearance is markedly reduced in this patient population and dosage reduction is necessary (See Table 3 in Dosage and Administration).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin. Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or other antiepileptic drugs. For urinary protein determination the sulfosalicylic acid precipitation procedure is recommended, as false positive readings were reported with the Ames N-Multistix SG[®] dipstick test, when gabapentin or placebo was added to other anticonvulsant drugs.

ADVERSE REACTIONS

Adverse Events in Controlled Trials

The most commonly observed adverse events associated with the use of Neurontin in combination with other antiepileptic drugs, not seen at an equivalent frequency in placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, nystagmus and tremor. Among the treatment-emergent adverse events occurring in Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54, from one controlled study) experienced approximately a two-fold increase, as compared to patients on lower doses of 600 to 1200 mg/day (n=489, from several controlled studies), in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Adverse events were usually mild to moderate in intensity, with a median time to resolution of 2 weeks. Since Neurontin was administered most often in combination with other antiepileptic agents, it was not possible to determine which agent(s) was associated with adverse events. Data from long-term, open, uncontrolled studies shows that Neurontin treatment does not result in any new or unusual adverse events.

Withdrawal From Treatment Due to Adverse Events

Approximately 6.4% of the 543 patients who received Neurontin in the placebo-controlled studies withdrew due to adverse events. In comparison, approximately 4.5% of the 378 placebo-controlled participants withdrew due to adverse events during these studies. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue, nausea and/or vomiting and dizziness (all at 0.6%).

Other Adverse Events Observed in All Clinical Trials

Adverse events that occurred in at least 1% of the 2074 individuals who participated in all clinical trials are described below, except those already listed in the previous section:

Body As a Whole	: asthenia, malaise, facial edema
Cardiovascular System	: hypertension
Digestive System	: anorexia, flatulence, gingivitis
Hematologic/Lymphatic System	: purpura, most often described as bruises resulting from physical trauma
Musculoskeletal System	: arthralgia
Nervous System	: vertigo, hyperkinesia, parasthesia, anxiety, hostility, decreased or absent reflexes
Respiratory System	: pneumonia
Special Senses	: abnormal vision

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute, life-threatening toxicity has not been observed with Neurontin (gabapentin) overdoses of up to 49 grams ingested at one time. 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. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, reduce toxicity from overdoses.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

DO dosage AND ADMINISTRATION

Adults

The usual effective maintenance dose is 900 to 1200 mg/day. Treatment should be initiated with 300 to 400 mg/day. Titration to an effective dose, in increments of 300 mg or 400 mg/day, can progress rapidly and can be accomplished over three days (see Table 1). Neurontin is given orally with or without food.

Table 1. Titration Schedule

DOSE	Day 1	Day 2	Day 3
900 mg/day	300 mg QD	300 mg BID	300 mg TID
1200 mg/day	400 mg QD	400 mg BID	400 mg TID

Data from clinical trials suggest that doses higher than 1200 mg/day may have increased efficacy in some patients; however, higher doses may also increase the incidence of adverse events (See Adverse Reactions).

Daily maintenance doses should be given in three equally divided doses (See Table 2), and the maximum time between doses in a three times daily schedule should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations in order to optimize Neurontin therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, Neurontin may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

Table 2. Maintenance Dosage Schedule

Total Daily Dose (mg/day)	Schedule
900	300 mg TID
1200	400 mg TID
1800	2 x 300 mg TID
2400	2 x 400 mg TID

Dosage adjustment in elderly patients due to declining renal function and in patients with renal impairment or undergoing hemodialysis is recommended as follows:

Table 3. Maintenance Dosage of Neurontin in Adults With Reduced Renal Function

Renal Function	Total Daily Dose (mg/day)	Dose Regimen (mg)
Creatinine Clearance (mL/min)		
>60	1200	400 Three Times a Day
30-60	600	300 Twice a Day
15-30	300	300 Once a Day
<15	150	300 Once Daily Every Other Day
Hemodialysis*	--	200-300*

* Loading dose of 300 to 400 mg

* Maintenance dose of 200 to 300 mg Neurontin following each 4 hours of hemodialysis

Children Over 12 Years of Age

The dosage used in a limited number of patients in this age group was 900-1200 mg/day. Doses above 1200 mg/day have not been investigated.

AVAILABILITY OF DOSAGE FORMS

Neurontin (gabapentin) capsules are supplied as follows:

100-mg capsules:

Hard gelatin capsules with white opaque body and cap printed with "PD" on one side and "Neurontin/100 mg" on the other. -bottles of 100 capsules

300-mg capsules:

Hard gelatin capsules with yellow opaque body and cap printed with "PD" on one side and "Neurontin/300 mg" on the other. -bottles of 100 capsules

400-mg capsules:

Hard gelatin capsules with orange opaque body and cap printed with "PD" on one side and "Neurontin/400 mg" on the other. -bottles of 100 capsules

Full Prescribing Information Available On Request

Parke-Davis Division
Warner-Lambert Canada Inc.
Scarborough, Ontario M1L 2N3

References

1. The Neurontin STEPS Study Team. Study of Neurontin: Titration to Effect, Profile of Safety. In: Program and Abstracts of the I.L.A.E., Dublin, Ireland July 1997. 2. Data on file. Bruni, J.: "Outcome Evaluation of Gabapentin as Add-on Therapy for Partial Seizures". Canadian Journal of Neurological Science. 1998; vol 25: 134-140. 3. Neurontin Product Monograph



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Don't forget to Register!

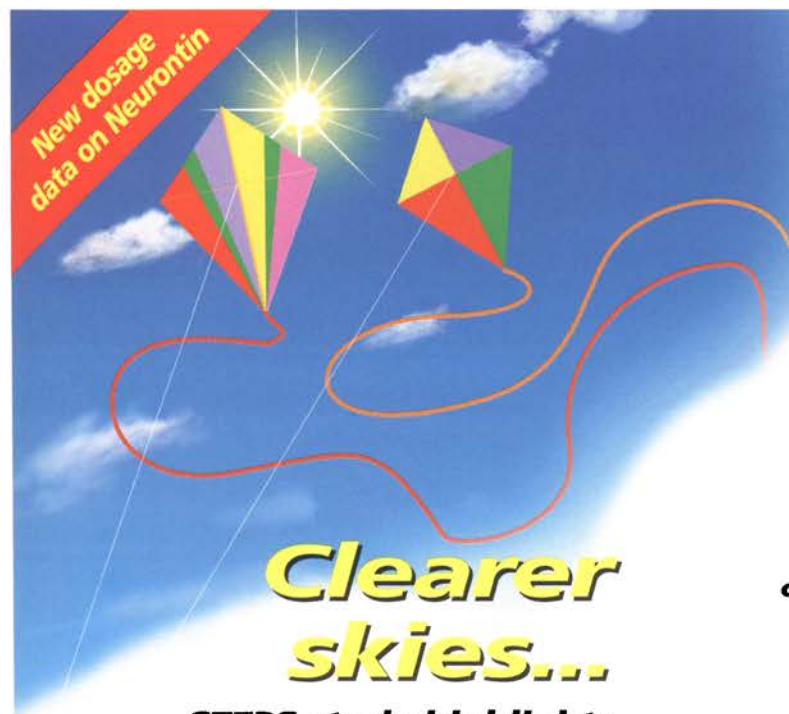
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Registration packages will be sent in March 1999

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- ✓ Spinal Instrumentation
- ✓ Controversies in Neurocritical Care
- ✓ Roles of Intraoperative Brain Imaging
- ✓ The Triptans in Migraine Therapy
- ✓ Management Issues in Epilepsy
- ✓ Pediatric Epilepsy
- ✓ Behavioural Neurology
- ✓ Symptom Management and Current Therapies in Multiple Sclerosis
- ✓ Dementia, Treatment and ethics
- ✓ Stroke



The dose of Neurontin* should be determined on an individual basis to optimize response^{††}

Tolerability Analysis Results (n=281)

Adverse Event	≤1800 mg/day	>1800 mg/day	P Values
Asthenia	9 (3.3%)	1 (0.4%)	0.01
Dizziness	17 (6.2%)	0 (0.0%)	<0.001
Headache	6 (2.2%)	0 (0.0%)	0.014
Somnolence	15 (5.4%)	10 (3.6%)	0.317

Adapted from STEPS

Study examined patients with partial seizures with or without secondary generalizations.

STEPS was a prospective, open-label, 16-week, multicentre study.

Doses higher than 1200 mg/day may increase the efficacy in some patients[†]; however, higher dose may also increase the incidence of adverse events[†].

Gabapentin was generally well tolerated at dosages >1800 mg/day (up to 3600 mg/day). Patients who tolerated gabapentin at dosages ≤1800 mg/day were able to tolerate increased dosages.[†] The maximum recommended dosage is 2400 mg/day.[†]

To help them through the storm – consider moving patients to a higher dosage of Neurontin*

Clearer skies...

STEPS study highlights Neurontin's* improved efficacy as add-on therapy at higher doses.

NEURONTIN
gabapentin capsules
USER FRIENDLY EFFICACY



PARKE-DAVIS

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^{††}In previous fixed dosage studies somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54) experienced approximately a two-fold increase as compared to patients on lower doses of 600 to 1200 mg/day in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Neurontin is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.[†]



Turn the agony
of migraine into
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Introducing Zomig[®]

Consistent migraine
relief that patients can
depend on time after time.

ZOMIG[®] is a new oral 5-HT₁ agonist
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ZOMIG[®] offers consistent efficacy
with significant headache
response* rates at 2 hours
following a single 2.5 mg dose.^{2,3}
In addition, efficacy is maintained
across multiple migraine attacks and
within different migraine subtypes.^{1,4,5}

ZOMIG[®] has a proven
safety and tolerability profile
with studies in over
3,000 patients treating
more than 34,000 attacks.^{6†}

For consistent migraine relief,
prescribe ZOMIG[®] 2.5 mg.

*Improvement from severe or moderate headache to mild or no pain.

†The most common side effects reported with ZOMIG[®]
compared to placebo were nausea (9% vs. 3.7%),
head/face sensations (8.6% vs. 1.7%), dizziness (8.4% vs. 4%)
and neck/throat/jaw sensations (7% vs. 3%).¹

ZOMIG[®] is not intended for use prophylactically or
in hemiplegic, basilar, or ophthalmoplegic migraine.
Safety and efficacy have not been established for cluster headache,
which is present in an older, predominantly male population.

ZOMIG[®] is contraindicated in patients with history,
symptoms, or signs of ischemic, cardiac, cerebrovascular
or peripheral vascular syndromes, valvular heart disease
or cardiac arrhythmias (especially tachycardias).

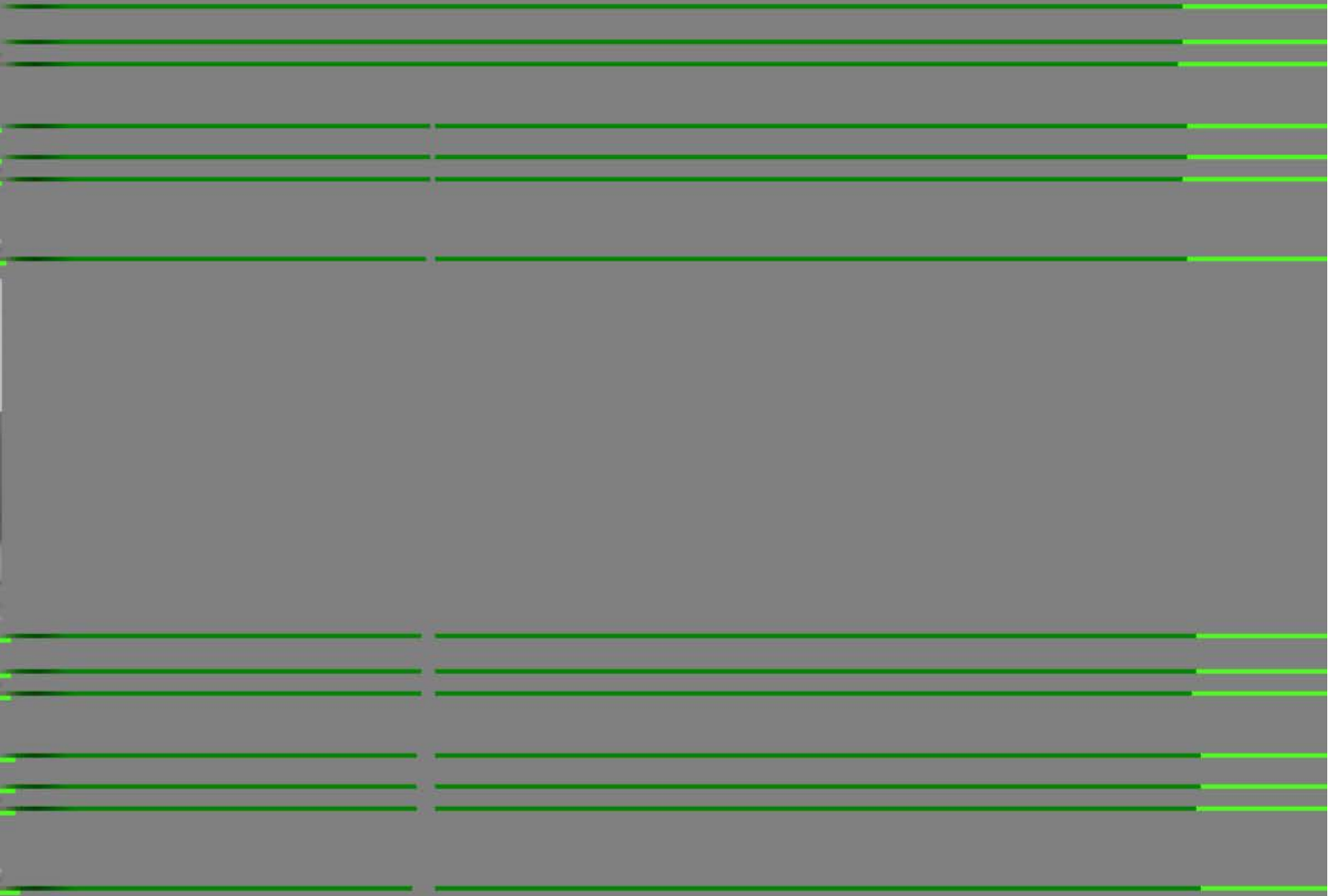
In addition, patients with other significant underlying
cardiovascular disease should not receive ZOMIG[®].
Please see Product Monograph.

For more information about ZOMIG[®], please contact
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fax (905) 821-8882 or e-mail at canada.medinfo@cams.zeneca.com

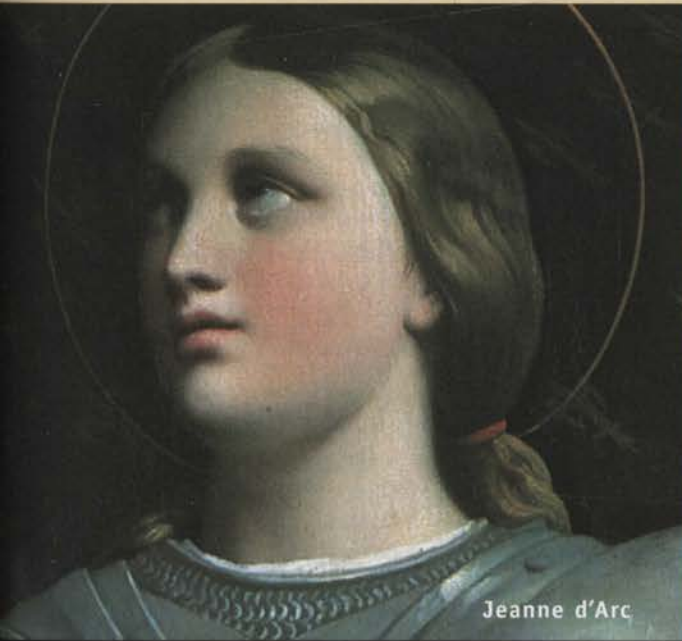
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zolmitriptan tablets 2.5 mg

Consistent migraine relief.

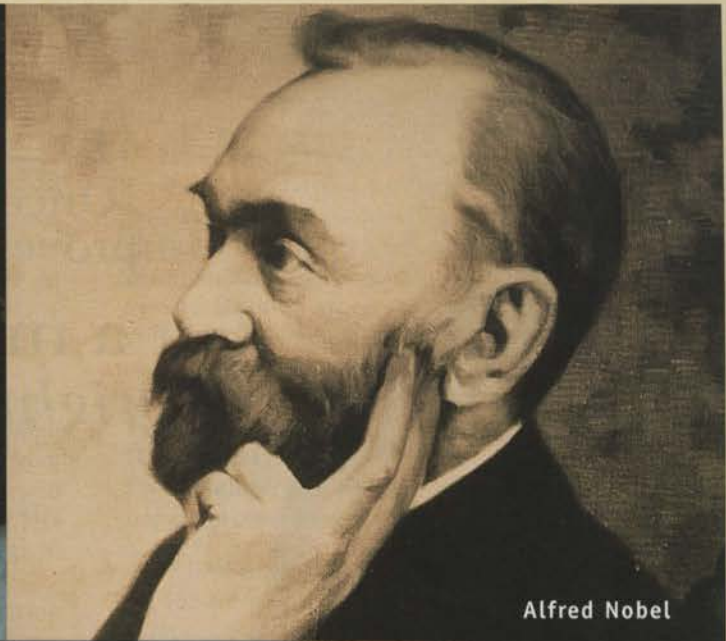
DU NOUVEAU EN ÉPILEPSIE. MAINTENANT REMBOURSÉ PAR LES FORMULAIRES



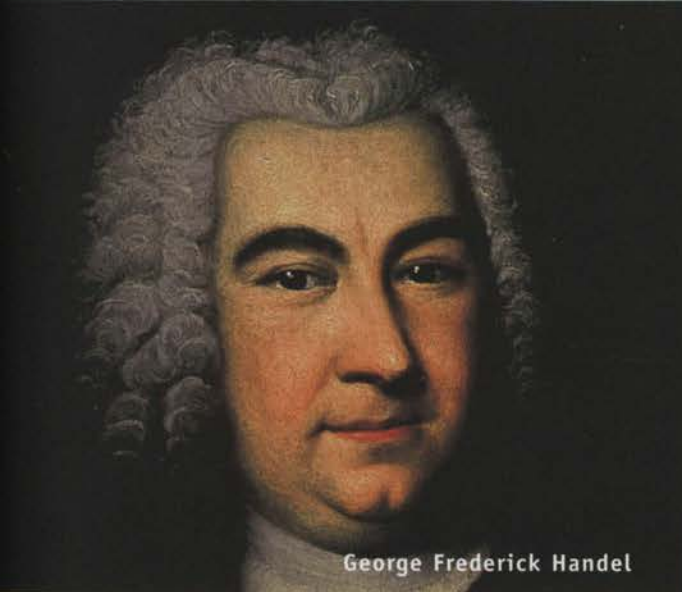
DE LA C.-B., L'ALBERTA, LA SASKATCHEWAN, LA NOUVELLE-ÉCOSSE ET DU QUÉBEC.



Jeanne d'Arc



Alfred Nobel



George Frederick Handel



Fyodor Dostoyevsky

DES EFFORTS EXCEPTIONNELS OU UN TALENT EXTRAORDINAIRE. MAINTENANT DES SOLUTIONS PLUS ACCESSIBLES.

- Généralement bien toléré: les interruptions entraînées par des réactions adverses étaient de 10,6 % pour les doses journalières de 200 à 400 mg, comparé à 5,8 % pour le groupe placebo (cela semblerait augmenter pour les doses journalières supérieures à 400 mg)²
- Aucune preuve d'éruption cutanée sérieuse ni d'anémie aplasique²
- Il n'est généralement pas nécessaire de changer le dosage des médicaments principales; les patients prenant de la phénytoïne et manifestant des signes ou symptômes de toxicité devraient faire contrôler leurs niveaux de phénytoïne¹²
- Dosage commode BID

Profil favorable des effets secondaires (les plus courants affectent le SNC)

	TOPAMAX 200-400 mg (n = 113)	PLACEBO (n = 216)
Somnolence	30,1	9,7
Étourdissements	28,3	15,3
Ataxie	21,2	6,9
Ralentissement psychomoteur	16,8	2,3
Troubles de la parole	16,8	2,3
Nervosité	15,9	7,4
Nystagmus	15,0	9,3
Paresthésie	15,0	4,6

¹Comme pour les autres traitements antiépileptiques, veuillez vous reporter aux renseignements thérapeutiques pour plus de détails concernant les interactions médicamenteuses. On a rapporté l'occurrence de 1,5 % (n = 1715) de calculs rénaux¹. Dans une étude (n = 1200), 83 % des patients (15 sur 18) ont choisi de continuer le traitement¹. Assurer un taux d'hydratation adéquat et éviter l'utilisation parallèle d'autres inhibiteurs de l'anhydrase carbonique¹.



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For a more *active* day,
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Once-a-day Aricept[®]. To help your Alzheimer's patients enjoy more active days, and look forward to a brighter tomorrow.



Once-a-day
Aricept[®]
donepezil HCl 5 & 10 mg tablets

Hope for a brighter tomorrow

Aricept[®] is indicated for the symptomatic treatment of patients with mild to moderate Alzheimer's disease. Aricept[®] has not been studied in controlled clinical trials for longer than 6 months.

† Cognition measured by ADAS-cog and MMSE; Function measured by CIBIC plus.

‡ The most common side effects observed with Aricept[®] include diarrhea, muscle cramps, nausea and insomnia; these effects are usually mild and transient, resolving with continued use.

§ For patients not responding after 4-6 weeks of therapy at 5 mg/d, a 10 mg/d dose may be considered. Please see enclosed Prescribing Information before prescribing.

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