Information for Authors

The Canadian Journal of Neurological Sciences publishes original articles in neurology, neurosurgery and basic neurosciences. Manuscripts are considered for publication with the understanding that they, or the essence of their content, have not been published elsewhere except in abstract form and are not under simultaneous consideration by another journal. Manuscripts should be submitted to:

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Manuscript Preparation

Submit five high quality copies of the manuscript. Papers will be accepted in English or French. All papers should be accompanied by an abstract of 150 words or less on a separate page, preferably in both languages, although the Journal will provide the translation if required. Submit two original sets and three copies of illustrations. All manuscripts must be double spaced throughout including references and legends for illustrations. Margins of at least 25mm should be left on all sides.

For detailed instructions regarding style and layout, authors should refer to "Uniform requirements for manuscripts submitted to biomedical journals". Copies of this document may be obtained by writing to the Journal office, but the main points are summarized here. Articles should be submitted under conventional headings of "introduction", "methods and materials", "results", "discussion", but other headings and subheadings will be considered if more suitable for a particular manuscript.

A title page should identify the title of the article, authors, name of institution(s) from which the work originated and the address, telephone and fax numbers of the corresponding author. Pages of text should be numbered consecutively. Acknowledgements, including recognition of financial support should be typed on a separate page at the end of the text.

The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

After the paper has been reviewed, the corresponding author will be requested to submit four printouts of the revised manuscript and a computer floppy disk (3½" or 5¼" size) containing the article. Identify clearly on the disk: system - i.e.: MS dos or Macintosh; format - i.e.: saved in ASCII format; software program and version; first author's name printed on the disk.

Review Articles on selected topics are also published by the Journal. They are usually invited, but unsolicited reviews will be considered. It is recommended that authors intending to submit review articles contact the Editor in advance.

Letters to the Editor: Letters concerning matters arising in recent articles are welcome. Letters should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

References

Number references in the order of their citation in the text. Those cited only in tables or in legends for illustrations are numbered according to the sequence established by the first identification in the text of a particular table or illustration. Titles of journals should be abbreviated according to the style used in Index Medicus. References should include the names of up to five authors; if there are more, cite the first three, then "et al.". Provide the full title, year of publication, volume number and inclusive pagination for journal articles. For any reference cited as "in press", five copies of the article must accompany the author's manuscript. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text and authors must provide five copies of "submitted" manuscripts. Avoid "personal communications" and, if necessary, include them in the body of the text, not among the references. Reference citations should not include unpublished presentations or other non-accessible material. Books or chapter references should also include the place of publication and the name of the publisher. Examples of correct forms of reference follow:

Journals

Yang JF, Fung M, Edamura R, et al. H-Reflex modulation during walking in spastic paretic subjects. Can J Neurol Sci 1991; 18: 443-452.

Chapter in a book

McGeer PL, McGeer EG, Amino acid neurotransmitters. *In*: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. Basic Neurochemistry. Boston: Little, Brown & Co., 1981: 233-254.

Illustrations

Submit two original sets of illustrations. Provide three additional sets for reviewers and editors; these may be prints or photocopies depending on the material to be illustrated. We will not return illustrations; therefore, authors should keep negatives for all photographs. Submit high quality glossy black and white photographs perferably 127 × 173 mm (5" x 7"). Original art work and radiographs should not be submitted. The additional cost of coloured illustration must be borne by the authors; quotations are available upon request from the Journal office. Identify each figure with a label at the back indicating top, figure number and first author. Letters and arrows applied to the figures to identify particular findings should be professional appliques suitable for publication. Photomicrographs should include a calibration bar with a scale indicated on the figure or in the legend. Legends for illustrations should be typed on a separate page from the illustrations.

Tables

Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

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Epival* divalproex sodium

THERAPEUTIC CLASSIFICATION Anticonvulsant.

INDICATIONS AND CLINICAL USE Sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal; useful in primary generalized seizures with tonic-clonic manifestations. May also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds) accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS Should not be administered to patients with hepatic disease or significant dysfunction. Contraindicated in patients with known hypersensitivity to the drug.

WARNINGS Hepatic failures resulting in fatalities have occurred in patients receiving valproic acid and its derivatives. These incidences usually have occurred during the first six months of treatment with valproic acid. A recent survey study of valproate use in the United States in nearly 400,000 patients between 1978 and 1984, has shown that children under two years of age who received the drug as part of multiple anticonvulsant therapy were at greatest risk (nearly 20-fold increase) of developing fatal hepatotoxicity. These patients typically had other medical conditions such as congenital metabolic disorders, mental retardation or organic brain disease, in addition to severe seizure disorders. The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only valproate. Risk generally declined with increasing age. No deaths have been reported in patients over 10 years of age who received valproate alone.

If Epival is to be used in children two years old or younger, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risk.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival (divalproex sodium).

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed in patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decrease in concentrations and serum ammonia for increases in concentration. If changes occur, the drug should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immmediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug. The frequency of adverse effects, particularly elevated liver enzymes, may increase with increasing dose. Therefore, the benefit gained by improved seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Use in Pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of women receiving the drug during pregnancy. The incidence of neural tube defects in the fetus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid exposed women having children with spina bifida is approximately 1.2%. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (anencephaly and spina bifida). Animal studies have demonstrated valproic acid induced teratogenicity, and studies in human females have demonstrated placental transfer of the drug.

Multiple reports in the clinical literature indicate an association between the use of anti-epileptic drugs and an increased incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women, this incidence may be increased 2-to 3-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, cleft lip or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anti-epileptics. Some reports indicate a possible similar association with the use of other anti-epileptic drugs, including trimethadione, paramethadione, and valproic acid. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anti-epileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of anti-epileptic medication is in doubt, appropriate consultation is indicated.

Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving Epival (divalproex sodium).

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses of valproic acid greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment 1 fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of divalproex sodium and valproic acid on the development of the testes and on sperm production and fertility in humans is unknown.

LONG-TERM TOXICITY STUDIES IN RATS AND MICE INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia and inhibition of platelet aggregation, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs the drug should be discontinued.

Because Epival (divalproex sodium) may interact with other anti-epileptic drugs, periodic serum level determinations of concurrently administered anti-epileptics are recommended during the early part of therapy. (See DRUG INTERACTIONS.) There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.

Epival (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproic acid; the clinical significance of these is unknown.

Driving and Hazardous Occupations: May produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: May potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproic acid serum levels. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin (See PRECAUTIONS – General). It is not known if there is a change in unbound (free) phenytoin serum levels. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may produce absence status.

ADVERSE REACTIONS The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other anti-epileptics, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal: Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anti-epileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Endocrine: There have been reports of irregular menses and secondary amenorrhea in patients receiving valproic acid.

Abnormal thyroid function tests have been reported (See PRECAUTIONS).

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (See PRECAUTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (eg. SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (See WARNINGS).

Metabolic: Hyperammonemia (See PRECAUTIONS). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Pancreatic: There have been reports of acute pancreatitis occurring in association with therapy with valproic acid.

Other: Edema of the extremities has been reported.

DOSAGE AND ADMINISTRATION The recommended initial dosage is 15/mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases.

The maximal recommended dosage is 60 mg/kg/day. When the total daily dose exceeds 125 mg, it should be given in a divided regimen (See Table).

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by improving seizure control must be weighed against the increased incidence of adverse effects.

As the dosage is raised, blood levels of phenobarbital or phenytoin may be affected (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. **The tablets should be swallowed without chewing.**

AVAILABILITY Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg supplied in bottles of 100 tablets; peach-coloured tablets of 250 mg and lavender-coloured tablets of 500 mg are supplied in bottles of 100 and 500 tablets.

Table of Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total daily dose (mg)	Dosage (mg) Equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	1,000	250	250	500
75-89.9	165-197.9	1,250	500	250	500

Product monograph available on request.

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PARLODEL® (bromocriptine mesylate) Because quality of life is the issue

ACTIONS Parlodel (bromocriptine mesylate) is a dopaminomimetic ergot derivate with D_2 type dopamine receptor agonist activity, and has also D_1 dopamine receptor antagonist properties. The dopaminomimetic activity of bromocriptine *in the striatum is considered responsible for the clinical* benefits seen in selected patients with Parkinson's disease, when low doses of the drug are gradually added to levodopa therapy in patients on long-term treatment who develop late side effects of levodopa or no longer respond to the medication. Excessive dopaminomimetic drive may, however, provoke psychotic and other adverse reactions.

The extreme variability in G.I. tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in *dose response.*

INDICATIONS† Parkinson's Disease: Parlodel (bromocriptine mesylate) has been found to be clinically useful as an adjunct to levodopa (usually with a decarboxylase inhibitor), in the symptomatic management of selected patients with Parkinson's disease who experience prominent dyskinesia or wearing off reactions on long-term levodopa therapy.

Patients on long-term treatment who are beginning to deteriorate on levodopa therapy may be controlled by reducing the dose of levodopa and adjusting the frequency and *schedule of drug administration. Patients maintained on* optimal dosages of levodopa who still experience prominent dyskinesia and/or end-of-dose failure may benefit from the concomitant use of Parlodel, by decreasing the occurrence and/or severity of these manifestations. Since rapid escalation of bromocriptine doses causes severe adverse reactions, it is recommended to combine a slow increase of Parlodel, usually with a concomitant, gradual and limited reduction of levodopa dosage. Continued efficacy of bromocriptine for more than two years has not been established and there is some evidence that its efficacy tends to wane. Evidence available indicates that there is no consistent benefit from bromocriptine in patients who have not responded previously to levodopa, and studies have shown significantly more adverse reactions in bromocriptine-treated *patients than in patients treated with levodopa. Parlodel is* not recommended in the treatment of newly diagnosed patients or as the sole medication in Parkinson's disease.

CONTRAINDICATIONS Other than sensitivity to ergot alkaloids, no absolute contraindications to treatment with Parlodel (bromocriptine mesylate) are known. For procedure during pregnancy see "Use in Pregnancy" under Precautions.

WARNINGS Long-term treatment (6-36 months) with Parlodel in doses of 20 to 100 mg/day has been associated with pul*monary infiltrates, pleural effusion and thickening of the* pleura in a few patients. Where Parlodel was discontinued, these changes slowly reverted to normal.

PRECAUTIONS Parlodel (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients dizziness (vertigo) may occur with Parlodel; patients should therefore be cautioned against activities requiring rapid and precise responses, such as driving an automobile or operating dangerous machinery, until their response has been determined.

Care should be exercised when administering Parlodel concomitantly with phenothiazines or antihypertensive agents. Due to drug interaction at the receptor site, dosage *should be adjusted accordingly.*

Alcohol should be avoided during treatment with Parlodel. In some patients, the concomitant use of Parlodel and alcohol has given rise to alcohol intolerance and an increase in the severity and incidence of Parlodel's possible adverse reactions.

Parlodel should always be taken with food. In cases where severe adverse effects, such as nausea, vomiting, vertigo or headaches are severe or persisting, the therapeutic dosage of Parlodel should be reduced to half of one tablet daily (1.25 mg) and increased gradually to that recommen*ded. The dopamine antagonist domperidone may be useful* in the control of severe gastrointestinal side effects in parkinsonian patients receiving Parlodel (see Drug Interactions).

As with all medication, Parlodel should be kept safely out of the reach of children.

Use in Pregnancy: If the patient wishes to become pregnant, Parlodel (bromocriptine mesylate) should be stopped as soon as possible after conception is suspected. In this event immunological confirmation should be done immediately. *When pregnancy is confirmed, Parlodel, like all other drugs,* should be discontinued unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus.

In human studies with Parlodel (reviewed by Turkalj, I.), there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took Parlodel (bromocriptine mesylate) during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous *abortions (11.13%) in this group of pregnancies does not* exceed that generally reported for such occurrences in the population at large.

Use in Parkinson's Disease: Use of Parlodel (bromocriptine mesylate), particularly in high doses, may be associated with mental confusion and mental disturbances. Since patients with Parkinson's disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with Parlodel.

Parlodel administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of Parlodel may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following *discontinuation of Parlodel. Caution should be exercised* when administering Parlodel to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering Parlodel, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions: The concomitant use of erythromycin *may increase bromocriptine plasma levels.*

Domperidone, a dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonise the therapeutically relevant prolactin lowering effect of Parlodel. It is possible that the antitumorigenic effect of Parlodel in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension which can, on rare occasions, lead *to fainting and "shock-like" syndromes has been reported in* sensitive patients. This is most likely to occur during the first few days of Parlodel treatment.

When bromocriptine is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy were: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness, fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo.

Less common adverse reactions include anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizures, fatigue, headache, lethargia, mottling of skin, nasal stuffiness, nervousness, nightmares, parethesia, skin rash, urinary frequency, urinary incontinence, urinary retention and rarely signs or symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phos*phatase and uric acid, which are usually transient and not* of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSE There have been several reports of acute overdosage with Parlodel (bromocriptine mesylate) in children and adults. No life threatening reactions have occurred. Symptoms reported included nausea, vomiting, dizziness, drowsiness, hypotension, *sweating and hallucinations. Management is largely sympto*matic; the cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION Parlodel (bromocriptine mesylate) should always be taken with food.

Although Parlodel (bromocriptine mesylate) has been found clinically useful in decreasing the severity and frequency of "on-off" fluctuations of late levodopa therapy, the decision to use bromocriptine as adjunctive treatment and the selection of dosage must be individualized in each case. A low dose is recommended. The initial dose of Parlodel is one half of a 2.5 mg tablet (1.25 mg) at bedtime with food to establish initial tolerance. Thereafter, the recommended dosage is *2.5 mg daily in two divided doses, with meals, (half a 2.5 mg* tablet twice daily). The dosage may be increased very gradually, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, to be taken always in divided doses with meals. Increments should usually not exceed 2.5 mg. Clinical assessments are recommended at two week intervals or less during dosage titration, to ensure that the lowest effective dosage is not exceeded. The usual dosage range is from a few milligrams to 40 mg daily in two or three divided doses with meals. The median dose varies with the experience of individual investigators, but can be around *10 mg daily or higher. During initial titration it is recommended* that the dosage of levodopa should be maintained, if possible. Subsequently, it might be desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

AVAILABILITY
TABLETS each containing 2.5 mg bromocriptine, as mesylate, available in bottles of 100.
CAPSULES each containing 5 mg bromocriptine, as mesylate, available in bottles of 100.

†For information on other approved indications, please consult the Parlodel Product Monograph, available to physicians and pharmacists on request.

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ELDEPRYL®
selegiline hydrochloride

FIRST LINE

Rx Summary

Antiparkinson Agent

Indications and clinical use:
As an adjunct to levodopa (with or without a decarboxylase inhibitor) in the management of the signs and symptoms of Parkinson's disease.

In newly diagnosed patients before symptoms begin to affect the patient's social or professional life, at which time more efficacious treatment becomes necessary.

Contraindications:
In patients with known hypersensitivity to Eldepryl. Eldepryl should not be used in patients with active peptic ulcer, extrapyramidal disorders such as excessive tremor or tardive dyskinesia, or patients with severe psychosis or profound dementia. Eldepryl should not be used with meperidine (Demerol or other trade names). This contraindication is often extended to other opioids.

Warnings (Selective vs non-selective inhibition of MAO-B):
Eldepryl should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. It is prudent, in general, to avoid the concommitant use of Eldepryl and fluoxetine (Prozac).

Warnings to patients:
Patients should be advised of the possible need to reduce levodopa dosage after the initiation of Eldepryl therapy. The patients should be advised not to exceed the daily dose of 10 mg. The risk of using higher doses of Eldepryl should be explained, and a brief description of the "hypertensive crisis" ("cheese reaction") provided.

Precautions:
Some patients given Eldepryl may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with supersensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa by 10-30%.

NURSING MOTHERS: It is not known whether Eldepryl is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

PEDIATRIC USE: The effects of Eldepryl in children under 18 have not been evaluated.

Laboratory Tests:
No specific laboratory tests are esential for management of patients on Eldepryl. Transient or continuing abnormalities with tendency for elevated values in liver function tests have been described in long term therapy. Although serious hepatic toxicity has not been observed, caution is recommended in patients with a history of hepatic dysfunction. Periodic routine evaluation of all patients is however appropriate.

Drug Interactions:
The occurence of stupor, muscular rigidity, severe agitation and elevated temperature has been reported in a man receiving selegiline and meperidine, as well as other medications. These symptoms were resolved over days when the combination was discontinued. This case is typical of the interaction of meperidine and MAOIs. Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of ELDEPRYL and other drugs have been reported. It is also prudent to avoid the combination of ELDEPRYL and fluoxetine (Prozac).

Use during Pregnancy:
The use of Eldepryl during pregnancy has not been established. Therefore, Eldepryl should be given to a pregnant woman only if the potential benefits outweigh the potential risks.

Adverse reactions:
A) IN COMBINATION WITH LEVODOPA
THE SIDE EFFECTS OF ELDEPRYL ARE USUALLY THOSE ASSOCIATED WITH DOPAMINERGIC EXCESS. ELDEPRYL MAY POTENTIATE THE SIDE EFFECTS OF LEVODOPA, THEREFORE ADJUSTMENT OF THE DOSAGE OF LEVODOPA MAY BE REQUIRED. ONE OF THE MOST SERIOUS ADVERSE REACTIONS REPORTED WITH ELDEPRYL USED AS AN ADJUNCT TO LEVODOPA THERAPY ARE HALLUCINATIONS/CONFUSION, PARTICULARLY VISUAL HALLUCINATIONS.

Other reactions include nausea, dizziness, faintness, abdominal pain, dry mouth, vivid dreams, dyskinesias and headache.

B) IN MONOTHERAPY
The incidence of adverse reactions occurring in trials using Eldepryl as monotherapy has not been fully reported to date. Serious adverse reactions include depression, chest pain, myopathy and diarrhea. Other reported adverse reactions include insomnia, headache, nausea, dizziness and vertigo.

In prospective clinical trials, the following adverse effects (listed in decreasing order of frequency), led to the discontinuation of Eldepryl: Nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetyic involuntary movements, agitation, arrhythmia, bradykinesia chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only rarely as a cause of discontinuation of treatment include anxiety, drowsiness/lethargy, nervousness, dystonia, increased episodes of freezing, increased tremor, weakness, excessive perseperation, constipation, weight loss, burning lips/mouth, ankle edema, gastroitestinal bleeding and hair loss.

Dosage:
The recommended dosage of Eldepryl as monotherapy in newly diagnosed patients, or as adjunct to levodopa (usually with a decarboxylase inhibitor) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. When ELDEPRYL adjunctive therapy is added to the existing levodopa therapeutic regime, a reduction, usually of 10 to 30% in the dose of levodopa (in some instances a reduction in the dose of Eldepryl to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects. Doses higher than 10 mg per day should not be used. There is no evidence that additional benefit will be obtained from the administation of higher doses. Furthermore, higher doses will result in a loss of selectivity of Eldepryl towards MAO-B with an increase in the inhibition of type MAO-A.

There is an increased risk of adverse reactions with higher doses as well as an increased risk of hypertensive episode ("cheese reaction")

Supplied:
Eldepryl 5 mg tablets, available in bottles of 60 tablets.

References:
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Product Monograph available upon request. PAAB

DEPRENYL RESEARCH LIMITED — PURDUE FREDERICK INC.
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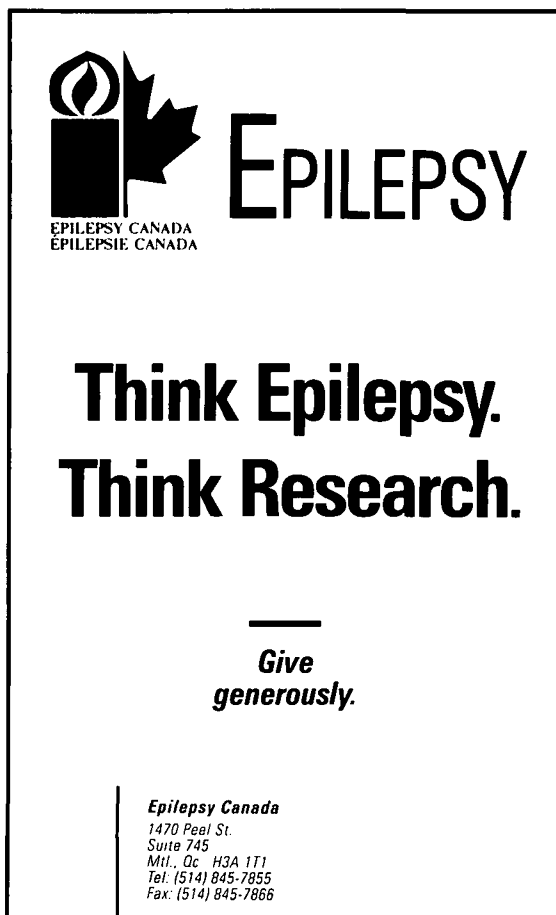

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Award for Excellence in Neurological Science

CIBA—GEIGY is offering an Award for Excellence for the best article published in the Journal within the period of one year.

A cash prize of $2500 will be announced at the annual meeting of the Canadian Congress of Neurological Sciences in June. Articles published in Volume 19 will be adjudicated by the editorial board for the 1992 award.

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Intermediate Prescribing Information

℞ TEGRETOL® *(carbamazepine tablets)*
TEGRETOL® 200 mg

℞ TEGRETOL Chewtabs®
(carbamazepine chewable tablets)
TEGRETOL® Chewtabs™ 100 mg
TEGRETOL® Chewtabs™ 200 mg

℞ TEGRETOL® CR
(carbamazepine controlled release tablets)
TEGRETOL® CR 200 mg TEGRETOL® CR 400 mg
Anticonvulsant
For symptomatic relief of trigeminal neuralgia
Antimanic

INDICATIONS A. Management of psychomotor (temporal lobe) epilepsy. As an adjunct in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when combined with other antiepileptic agents.
As an alternative in patients with generalized tonic-clonic seizures and marked side effects or who fail to respond to other anticonvulsant drugs.
Ineffective for controlling petit mal, minor motor, myoclonic *and predominantly unilateral seizures, and does not prevent* generalization of epileptic discharge. Exacerbation of seizures may occur in patients with atypical absences.
B. Symptomatic relief of pain of true or primary trigeminal neuralgia (tic douloureux). Not for prophylactic use. Glossopharyngeal neuralgia has been relieved in some patients. Other measures must be considered for patients failing to respond or who are sensitive to TEGRETOL.
C. Treatment of Acute Mania and Prophylaxis in Bipolar (Manic-Depressive) Disorders: may be used as monotherapy or adjunct to lithium in patients who are resistant to or are intolerant of conventional antimanics. Possibly an alternative to neuroleptics in such patients. Patients with severe mania, dysphoric mania or rapid cycling who are non-responsive to lithium may respond positively to carbamazepine. Recommendations are based on extensive clinical experience and some comparative trials.
CONTRAINDICATIONS History of hepatic disease, acute intermittent porphyria or serious blood disorder, in patients with AV heart block (see Precautions), hypersensitivity to carbamazepine or to tricyclic compounds, or their analogues or metabolites.
Do not give with, immediately before or immediately after treatment with monoamine oxidase inhibitors. There should be as long a drug free interval as the clinical condition allows, in no case less than 14 days. Then TEGRETOL dosage should be low initially, increased very gradually.
WARNINGS ***Although reported infrequently, serious adverse effects have been observed during use of TEGRETOL (carbamazepine). Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, thrombocytopenia, hepatocellular and cholestatic jaundice, and hepatitis also reported. It is important that TEGRETOL be used carefully and close clinical and frequent laboratory supervision be maintained throughout treatment to detect signs and symptoms of possible blood dyscrasia, as early as possible. Discontinue TEGRETOL if any evidence of significant bone marrow depression appears. (See "PRECAUTIONS"). Should signs and symptoms suggest a severe skin reaction such as Steven-Johnson syndrome or Lyell's syndrome, withdraw TEGRETOL at once. Long-term toxicity studies in rats indicated a potential carcinogenic risk. Weigh possible risk of TEGRETOL against potential benefits before prescribing.***
Pregnancy and nursing: Women with epilepsy who are, or intend to become pregnant, should be treated with special care.
In women of childbearing potential, TEGRETOL (carbamazepine) should, whenever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in offspring of women treated with more than one antiepileptic drug is greater than in those receiving single antiepileptic.
Minimum effective doses should be given and plasma levels monitored.
If woman receiving TEGRETOL becomes pregnant, or if the problem of initiating TEGRETOL arises during pregnancy, weigh the drug's potential benefits against its hazards, particularly during the first 3 months of pregnancy. Do not discontinue TEGRETOL or withhold from patients if required to prevent major seizures because of the risks posed, to both mother and fetus, by status epilepticus with attendant hypoxia.
Possibility that carbamazepine, like all major antiepileptic drugs, increases the risk of malformations has been reported. Rare reports on developmental disorders and malformations, including spina bifida, in association with carbamazepine. Conclusive evidence from controlled studies with carbamazepine monotherapy is lacking.
Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate folic acid deficiency, which may contribute to increased incidence of birth defects in offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy.
Vitamin K_1 administration to mother during last weeks of pregnancy, and to newborn, has been recommended to prevent neonatal bleeding disorders.
Carbamazepine passes into breast milk in concentrations of about 25-60% of the plasma level. No reports available on long-term effect of breast feeding. Weigh benefits of breast feeding against possible risks to infant. Observe infant for possible adverse reactions, e.g., somnolence, should mother taking carbamazepine nurse.
A severe hypersensitivity skin reaction in a breast-fed baby has been reported.
Reliability of oral contraceptives may be adversely affected by carbamazepine (see **PRECAUTIONS, Drug Interactions**).
PRECAUTIONS Clinical Monitoring of Adverse Reactions: Prescribe TEGRETOL only after a critical risk-benefit appraisal in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with TEGRETOL. **Maintain careful clinical and laboratory supervision throughout treatment.** Should any signs or symptoms or abnormal laboratory findings be suggestive of blood dyscrasia or liver disorder, discontinue TEGRETOL immediately until case is carefully reassessed.
(a) **Bone marrow function:** Carry out complete blood counts, including platelets and possibly reticulocytes and serum iron, before treatment is instituted. Suggested guidelines for monitoring are weekly for the first month, monthly for the next 5 months, thereafter 2-4 times/year.
If definitely low or decreased white blood cell or platelet *counts are observed during treatment, patient and complete* blood count should be monitored closely. Non-progressive fluctuating asymptomatic leucopenia encountered, does not generally call for TEGRETOL withdrawal. However, treatment should be discontinued if the patient develops leucopenia which is progressive or accompanied by clinical manifestations, e.g. fever or sore throat, which could indicate onset of significant bone marrow depression.
Because onset of potentially serious blood dyscrasias may be rapid, patients should be made aware of early toxic signs and symptoms of potential hematological problem, and symptoms of dermatological or hepatic reactions. If reactions, e.g. fever, sore throat, rash, ulcers in mouth, easy bruising, petechial or purpuric hemorrhage appear, advise patient to consult his/her physician immediately.
(b) **Hepatic function:** Baseline and periodic evaluations of hepatic function must be performed, particularly in elderly patients and those with history of liver disease. Withdraw TEGRETOL immediately in cases of aggravated liver dysfunction or active liver disease.
(c) **Kidney function:** Perform pretreatment and periodic complete urinalysis and BUN determinations.
(d) **Ophthalmic examinations:** Carbamazepine has been associated with pathological eye changes. Periodic eye examinations, including slit-lamp funduscopy and tonometry recommended.
(e) **Plasma levels:** Although correlations between dosage and plasma levels, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; pregnancy; when treating children or adolescents; suspected absorption disorders; suspected toxicity, especially where more than one drug is used (see "Interactions").
Increased Seizure Frequency: Use TEGRETOL with caution in patients with mixed seizure disorder that includes atypical absence seizures, since use has been associated with increased frequency of generalized convulsions. In case of exacerbation of seizures, discontinue TEGRETOL.
Dermatologic: Mild skin reactions, e.g., isolated macular or maculopapular exanthema, usually disappear within a few days or weeks, either during continued course of treatment or following dosage decrease. However, patient should be kept under close surveillance because of rare possibility of Steven-Johnson syndrome or Lyell's syndrome occurring (see WARNINGS).
Urinary Retention and Increased Intraocular Pressure: Because of its anticholinergic action, carbamazepine should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Follow such patients closely while on the drug.
Occurrence of Behavioural Disorders: Because it is closely related to other tricyclic drugs, there is a possibility that carbamazepine might activate latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Exercise caution in alcoholics.
Use in Patients with Cardiovascular Disorders: Use TEGRETOL cautiously in patients with history of coronary artery disease, organic heart disease, or congestive failure. If defective conductive system suspected, perform an ECG before administering TEGRETOL, to exclude patients with atrioventricular block.
Driving and Operating Hazardous Machinery: Because dizziness and drowsiness are possible side effects of TEGRETOL, warn patients about possible hazards of operating machinery or driving automobiles.
Drug Interactions: Induction of hepatic enzymes in response to carbamazepine may diminish or abolish activity of certain drugs also metabolized in the liver. Dosage of the following drugs may have to be adjusted: clobazam, clonazepam, ethosuximide, primidone, valproic acid, alprazolam, corticosteroids (e.g. prednisolone, dexamethasone), cyclosporin, digoxin, doxycycline, felodipine, haloperidol, thioridazine, imipramine, methadone, oral contraceptives, theophylline, and oral anticoagulants (warfarin, phenprocoumon, dicumarol).
Phenytoin plasma levels reported to be both raised and lowered by carbamazepine, and mephenytoin plasma levels reported to increase in rare instances.
The following drugs have been shown to raise plasma carbamazepine levels: erythromycin, troleandomycin, possibly josamycin, isoniazid, verapamil, diltiazem, propoxyphene, viloxazine, fluoxetine, cimetidine, acetazolamide, danazol, and possibly desipramine. Nicotinamide raises carbamazepine plasma levels in children, but only at high dosage in adults. Since an increase in carbamazepine plasma levels may result in unwanted effects (e.g. dizziness, drowsiness, *ataxia, diplopia and nystagmus), adjust* TEGRETOL *dosage* accordingly and monitor the blood levels.
Plasma levels of carbamazepine may be reduced by phenobarbitone, phenytoin, primidone, progabide, or theophylline, and possibly by clonazepam. Alternatively, valproic acid, valpromide, and primidone have been reported to raise plasma levels of pharmacologically active metabolite, carbamazepine-10, 11 epoxide. TEGRETOL dose may consequently require adjustment.
Combined use with lithium, metoclopramide, or haloperidol, may increase risk of neurotoxic side effects (even in presence of "therapeutic plasma levels").
Concomitant use with isoniazid reported to increase isoniazid-induced hepatotoxicity.
TEGRETOL, like other anticonvulsants, may adversely affect the reliability of oral contraceptives; breakthrough bleeding may occur. Patients should accordingly be advised to use *some alternative, non-hormonal method of contraception.*
Concomitant medication with TEGRETOL and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.
TEGRETOL may antagonize effects of non-depolarising muscle relaxants (e.g. pancuronium); their dosage may need to be raised and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.
Isotretinoin reported to alter the bioavailability and/or clearance of carbamazepine and its active 10, 11-epoxide; carbamazepine plasma levels should be monitored.
Carbamazepine, may reduce tolerance to alcohol; advisable to abstain from alcohol consumption during treatment.
TEGRETOL should not be administered in conjunction with MAO inhibitor. (See CONTRAINDICATIONS).
ADVERSE REACTIONS Reactions most frequently reported are CNS (e.g. drowsiness, headache, unsteadiness on feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), and allergic skin reactions. These reactions usually occur only during the initial phase of therapy, if initial dose is too high, or when treating elderly patients. They have rarely necessitated discontinuing TEGRETOL therapy, and can be minimized by initiating treatment at low dosage.
Occurrence of CNS adverse reactions may be manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor plasma levels and possibly lower daily dose and/or divide it into 3-4 fractional doses.
More serious adverse reactions observed are hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy. If treatment is to be withdrawn abruptly, effect the change-over to another antiepileptic under cover of diazepam.
Adverse reactions reported:
Hematologic: Occasional or frequent – leucopenia; occasional – eosinophilia, thrombocytopenia; rare – leucocytosis, lymphadenopathy; isolated cases – agranulocytosis, aplastic anemia, pure red cell aplasia, macrocytic anemia, acute intermittent porphyria, reticulocytosis, folic acid deficiency, thrombocytopenic purpura, and possibly hemolytic anemia. In few instances, deaths occurred.
Hepatic: Frequent – elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant; occasional – elevated alkaline phosphatase; rarely – transaminases; rare – jaundice, hepatitis of cholestatic, parenchymal, hepatocellular, or mixed type; isolated cases – granulomatous hepatitis.
Dermatologic: Occasional to frequent – skin sensitivity reactions and rashes, erythematous rashes, urticaria; rare – exfoliative dermatitis and erythroderma, Steven-Johnson syndrome, systemic lupus erythematosus-like syndrome; isolated cases – toxic epidermal necrolysis (Lyell's syndrome), photosensitivity, erythremia multiform and nodosum, skin pigmentation changes, pruritus, purpura, acne, diaphoresis, alopecia and neurodermatitis.
Neurologic: Frequent – vertigo, somnolence, ataxia and fatigue. Occasionally – an increase in motor seizures (see INDICATIONS), headache, diplopia, nystagmus, accommodation disorders (e.g. blurred vision); rare – abnormal involuntary disorders (e.g. tremor, asterixis, orofacial dyskinesia, choreoathetosis disorders, dystonia, tics); isolated cases – oculomotor disturbances, speech disorders (e.g. dysarthria or slurred speech), peripheral neuritis, paraesthesiae. There have been some reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to the administration of TEGRETOL could be established.
Cardiovascular: Disturbances of cardiac conduction, bradycardia, arrhythmias, Stokes-Adams in patients with AV-block, congestive heart failure, hypertension or hypotension, aggravation of coronary artery disease, thrombophlebitis, thromboembolism. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds.
Psychiatric: Isolated cases – hallucinations (visual or acoustic), depression, sometimes with talkativeness, agitation, loss of appetite, restlessness, aggressive behaviour, confusion, activation of psychosis.

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Genitourinary: Isolated cases – interstitial nephritis and renal failure, as well as signs of renal dysfunction (e.g. albuminuria, glycosuria, hematuria, oliguria sometimes associated with elevated blood pressure, and elevated BUN/azotemia), urinary frequency, urinary retention, and renal failure.
Isolated reports – sexual disturbances/impotence.
Gastrointestinal: Occasional or frequent – nausea, vomiting. Occasional: dryness of the mouth and throat; rare – diarrhoea or constipation; isolated cases – abdominal pain, glossitis, stomatitis, anorexia.
Sense Organs: Isolated cases – lens opacities, conjunctivitis, retinal changes, tinnitus, hyperacusis, and taste disturbances.
Endocrine System and Metabolism: Occasionally edema, fluid retention, weight increase, hyponatremia and reduced plasma osmolality due to antidiuretic hormone (ADH)-like effect, leading in isolated cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities. Isolated cases of gynecomastia or galactorrhea have been reported, as well as abnormal thyroid function tests (decreased L-thyroxine, i.e., FT_4, T_4, T_3, and increased TSH, usually without clinical manifestations), disturbances of bone metabolism (decrease in plasma calcium and 25-OH-calciferol), leading in isolated cases to osteomalacia, as well as reports of elevated levels of cholesterol, including HDL cholesterol and triglycerides.
Musculoskeletal System: Isolated cases – arthralgia, muscle pain or cramp.
Respiratory: Isolated cases – pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.
Hypersensitivity reactions: Rare delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests, occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium).
Isolated cases: aseptic meningitis, with myoclonus and eosinophilia; anaphylactic reaction. Treatment should be discontinued should such hypersensitivity reactions occur.
SYMPTOMS AND TREATMENT OF OVERDOSAGE Lowest Known Lethal Dose: estimated 3.2g (24 year old woman). Highest known doses survived: 80g (34 year old man); 34g (13 year old girl); 1.4g (23 month old girl).
Symptoms of Overdosage: The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, and respiratory systems.
Central Nervous System: CNS depression, disorientation, tremor, restlessness, somnolence, agitation, hallucination, coma, blurred vision, nystagmus, mydriasis, slurred speech, dysarthria, ataxia, dyskinesia, abnormal reflexes (slow/hyperactive), convulsions, psychomotor disturbances, myoclonus, opisthotonia, hypothermia/hyperthermia, flushed skin/cyanosis, EEG changes.
Respiratory System: Respiratory depression, pulmonary edema.
Cardiovascular System: Tachycardia, hypotension/hypertension, conduction disturbance with widening of QRS complex, syncope in association with cardiac arrest.
Gastrointestinal System: Nausea, vomiting, delayed gastric emptying, reduced bowel motility.
Renal Function: Urinary retention, oliguria or anuria; fluid retention, and water intoxication.
Laboratory Findings: Hyponatremia, hypokalemia, leukocytosis, reduced white cell count, metabolic acidosis, hyperglycemia, glycosuria, acetonuria, increased muscle creatinine phosphokinase.
Treatment of Overdosage: There is no known specific antidote to TEGRETOL (carbamazepine).
Evacuate the stomach, with an emetic or by gastric lavage, then administer activated charcoal.
Observe vital signs and administer symptomatic treatment as required. Hyperirritability or convulsions may be controlled by the administration of parenteral diazepam or barbiturates but they may induce respiratory depression, particularly in children. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory depression.
When barbiturates are employed, it is advisable to have equipment available for artificial ventilation and resuscitation. Barbiturates should not be used if drugs that inhibit monoamine oxidase have been taken by the patient, either in overdosage or in recent therapy (within two weeks).
Hyponatremia should be treated by restricting fluids and a slow and careful NaCl 0.9% infusion i.v. These measures may be useful in preventing brain damage.
Shock (circulatory collapse) should be treated with supportive measures, including intravenous fluids, oxygen, and corticosteroids. For hypotension unresponsive to measures taken to increase plasma volume, dopamine or dobutamine i.v. may be administered.
It is recommended that ECG be monitored, particularly in children, to detect cardiac arrhythmias or conduction defects.
Charcoal hemoperfusion has been recommended. Forced diuresis, hemodialysis, and peritoneal dialysis reported to be ineffective.
Relapse and aggravation of the symptomatology on the 2nd or 3rd day after overdose, due to delayed absorption, should be anticipated.
DOSAGE AND ADMINISTRATION Use in Epilepsy (See INDICATIONS): Low initial daily dosage of TEGRETOL (carbamazepine) with a gradual increase in dosage is advised. Adjust dosage to the needs of the individual patient.
TEGRETOL tablets and CHEWTABS should be taken in 2 to 4 divided doses daily, with meals when possible.
Controlled release characteristics of TEGRETOL CR reduce the daily fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole or, if so prescribed, half a tablet) should be swallowed unchewed with a little liquid during or after a meal. Controlled release tablets should be prescribed as a b.i.d. dosage. If necessary, 3 divided doses may be prescribed.
Adults and Children Over 12 Years: Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. Initial dosage is progressively increased, in divided doses, until best response is obtained. Usual optimal dosage is 800 to 1200 mg daily. In rare instances some adult patients have received 1600 mg. As soon as disappearance of seizures has been obtained and maintained, reduce dosage very gradually until reaching minimum effective dose.
Children 6-12 Years: Initially, 100 mg in divided doses on first day. Increase gradually by adding 100 mg/day until best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, reduce dosage very gradually until reaching minimum effective dose.
Use in Trigeminal Neuralgia: Initial daily dosage 200 mg taken in 2 doses of 100 mg is recommended. Total daily dosage can be increased by 200 mg/day until relief of pain is obtained, usually achieved at dosage 200-800 mg daily; occasionally up to 1200 mg/day necessary. As soon as relief of pain has been obtained and maintained, attempt progressive reduction in dosage until reaching minimal effective dosage. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of TEGRETOL at intervals of not more than 3 months, depending on individual clinical course.
Prophylactic use in trigeminal neuralgia is not recommended.
Use in Mania and Bipolar (Manic Depressive) Disorders: Low initial dosage of 200-400 mg/day, in divided doses, higher starting doses of 400-600 mg/day may be used in acute mania. May be gradually increased until symptomatology is controlled or a total daily dose of 1600 mg. Adjust dosage increments for optimal tolerability. Usual dose is 400-1200 mg/day in divided doses. For maintenance, continue with doses used to achieve optimal acute responses and tolerability. In combination with lithium, neuroleptics: initially a low dosage of 100-200 mg/day; gradually increase. Daily dose > 800 mg is rarely required when given in combination with neuroleptics, lithium or other psychotropics, e.g., benzodiazepines. Plasma levels are probably not helpful for guidance in bipolar disorders.
AVAILABILITY TEGRETOL Tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. Protect from heat (store below 30°C) and humidity. Bottles of 100/500. **TEGRETOL CHEWTABS 100 mg:** Pale pink, round, flat, bevelled-edge tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each contains 100 mg carbamazepine. Protect from heat (store below 30°C), light and humidity. Bottles of 100. **TEGRETOL CHEWTABS 200 mg:** Pale pink, oval, biconvex tablets with distinct red spots. GEIGY engraved on one side and PU engraved on the other. Fully bisected between the P and U. Each contains 200 mg carbamazepine. Protect from heat (store below 30°C), light and humidity. Bottles of 100. **TEGRETOL CR 200 mg:** Beige-orange, oval, slightly biconvex tablet, engraved CG on one side and HC on the other. Fully bisected on both sides. Each contains 200 mg carbamazepine. Protect from heat (store below 25°C) and humidity. Bottles of 100. **TEGRETOL CR 400 mg:** Brownish-orange, oval, slightly biconvex tablet, engraved CG/CG on one side and ENE/ENE on the other. Fully bisected on both sides. Each contains 400 mg carbamazepine. Protect from heat (store below 25°C) and humidity. Bottles of 100. TEGRETOL is available to patients only by prescription.
Product Monograph available on request. January 4, 1993

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An exciting and challenging opportunity exists for a neuroscientist to play a pivotal role in the development of the PET scan research program at the Clarke Institute of Psychiatry. This is a joint position with the Rotman Research Institute of Baycrest Centre. Both institutions are fully affiliated with the University of Toronto.

The Clarke Institute of Psychiatry promotes research on psychiatric disorders throughout the lifespan. Current psychobiological research strengths are in schizophrenia, mood disorders, anxiety disorders, forensic psychiatry, neuroendocrinology, and neuropsychiatric genetics. To support its multidisciplinary clinical research and training, the Clarke Institute offers a broad range of hospital, day treatment, and out-patient assessment and treatment programs.

The Rotman Research Institute of Baycrest Centre focuses on research into memory and frontal lobe disorders in normal elderly patients, and on patients with various neurological and psychiatric disorders. Baycrest Centre includes a geriatric hospital, home for the aged, senior apartment residence, Alzheimer's day care program, community centre for older adults, and many ambulatory and community outreach programs.

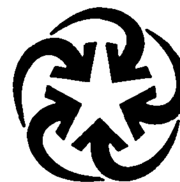
This position provides the researcher with unique access to the strengths in cognitive neuroscience developed at the Rotman Research Institute, and the considerable psychiatric research expertise, patient population, and the PET scan technology at the Clarke Institute of Psychiatry.

The individual sought will be at the associate or full professor level, although outstanding candidates at the assistant professor level will be considered. Salary offered will be commensurate with that offered by the University of Toronto.

The University of Toronto encourages applications from qualified women and men, members of visible minorities, aboriginal peoples and persons with disabilities. In accordance with Canadian immigration requirements, this advertisement is directed firstly to Canadian citizens and permanent residents.

Applicants should submit a curriculum vitae together with the names of three references by April 20, 1993, to:

Dr. Donald T. Stuss
Vice President – Research
Rotman Research Institute of Baycrest Centre
3560 Bathurst Street
Toronto, Ontario M6A 2E1



The Canadian Movement Disorder Group

has recently sponsored the

SECOND ANNUAL
NATIONAL RESIDENTS' SEMINAR
ON MOVEMENT DISORDERS.

We would like to thank the final year residents for their participation and the faculty for their valued contribution. We are planning to continue this educational event in 1994.

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PEDIATRIC NEUROLOGY

The Department of Pediatrics, Division of Pediatric Neurology, Faculty of Health Sciences at McMaster University is seeking a Pediatric Neurologist at the assistant professor rank. Certification in neurology or pediatrics by the Royal College of Physicians and Surgeons is required. Salary is commensurate with experience. In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Interested individuals should forward curriculum vitae and enquiries to:

Dr. G.M. Ronen
Department of Pediatrics
McMaster University
1200 Main Street West
Hamilton, Ontario
L8N 3Z5

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