

The Canadian Journal of Neurological Sciences

Le Journal Canadien des Sciences Neurologiques

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The Canadian Neurosurgical Society
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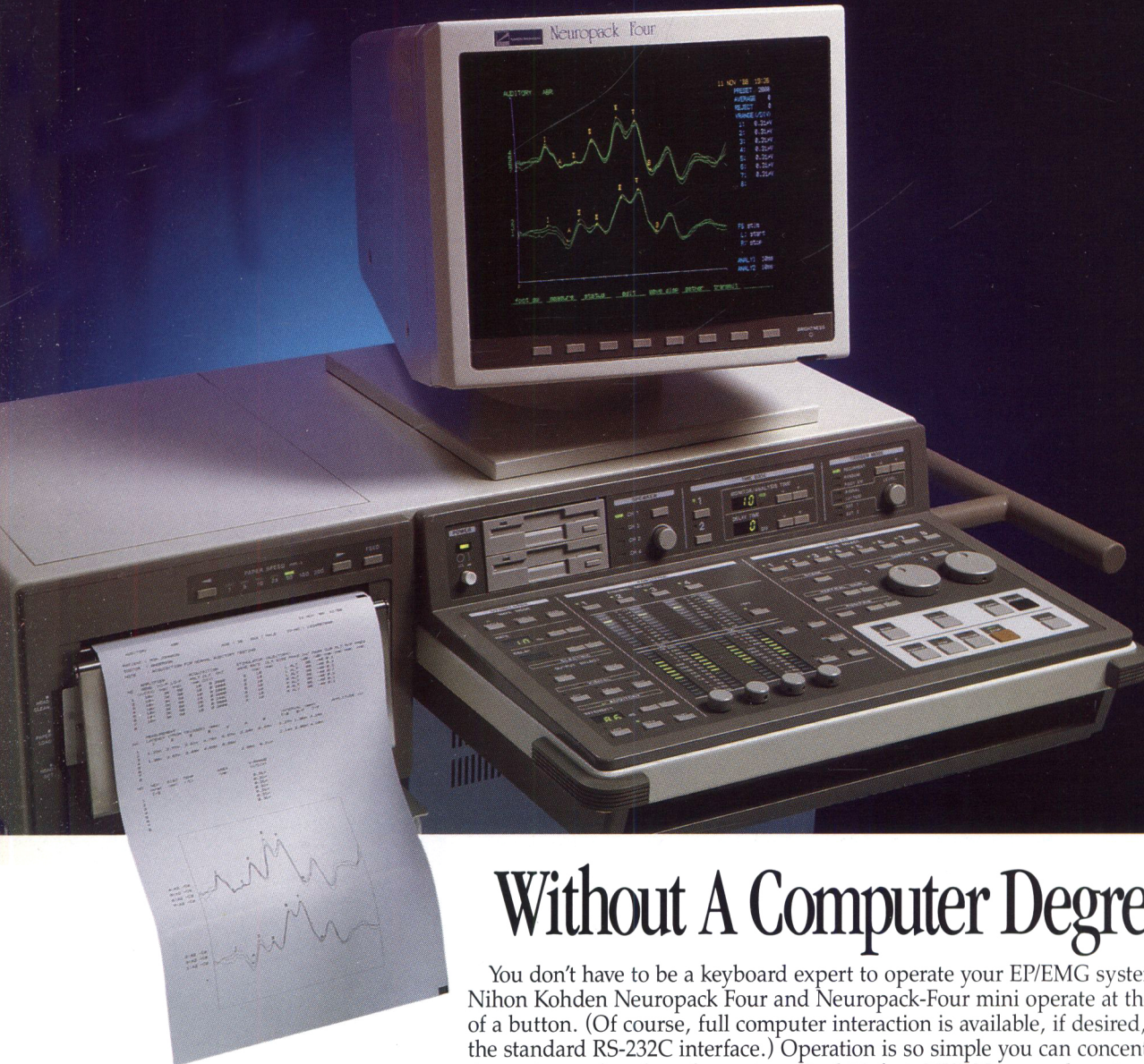
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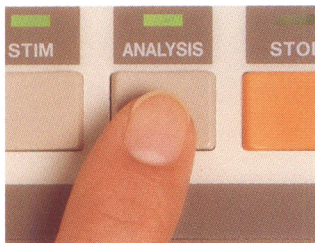
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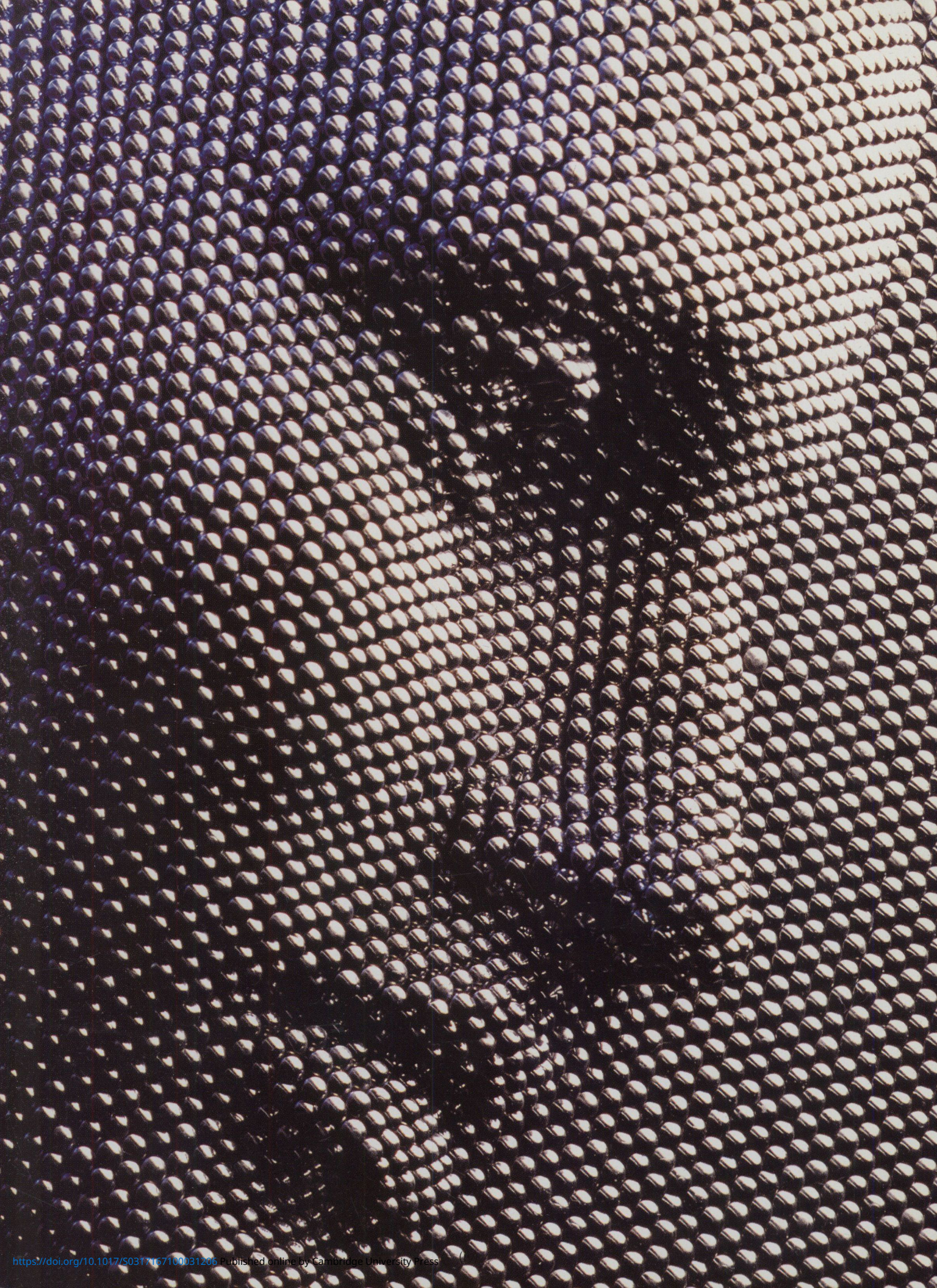
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ELDEPRYL® ADJUNCT IN THE MANAGEMENT OF PARKINSON'S DISEASE

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ACTIONS AND CLINICAL PHARMACOLOGY ELDEPRYL (selegiline hydrochloride, previously known as l-deprenyl hydrochloride), a synthetic selective inhibitor of the MAO-B enzyme when administered at the recommended doses, has been found to be of value as an adjunct to the management of some patients with Parkinson's Disease when administered as add-on therapy to levodopa. The mechanism of action of ELDEPRYL, responsible for its action as an adjunct in the symptomatic management of selected Parkinsonian patients is not well understood. Inhibitors of type MAO-B enzyme may be useful by blocking the metabolism of dopamine and by increasing the net amount of dopamine available. It may increase dopaminergic activity by blocking dopamine uptake at the synapses. Two principal metabolites of ELDEPRYL, l-amphetamine and l-metamphetamine (which with l-desmethylselegiline account for 44% of dose administered, as excreted metabolites) could also play a role. They interfere with neuronal uptake. By inhibiting MAO-B enzyme, ELDEPRYL may prevent the generation of free radicals and hydrogen peroxide resulting from oxidation of dopamine. It may also prevent the conversion of MPTP to MPP. Non-selective inhibitors of MAOs which inhibit MAO-A enzymes are not used in the management of patients with Parkinsonism because of side effects, such as hypertension, increase in involuntary movements and toxic delirium. Toxic delirium has also been reported with ELDEPRYL when used as adjunctive therapy to levodopa treatment. **Hypertensive Crisis ("Cheese Reaction")**. The MAOs are currently subclassified into two types, A and B, which differ in their substrates specificity and tissue distribution. In humans, intestinal MAO is predominantly MAO-A while most of that in the brain is MAO-B. In the CNS, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. The MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. The MAO-A found in the liver and the gastrointestinal tract is thought to provide vital protection from exogenous amines (e.g. tyramine) that have the capacity, if absorbed intact, to cause a "hypertensive crisis", the so-called "cheese reaction" (if large amounts of certain exogenous amines - e.g. from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc. - gain access to the systemic circulation, they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane bound vesicles. The subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.). In theory, therefore, patients treated with ELDEPRYL at a dose of 10 mg a day, because gut MAO-A is not inhibited, can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. To date, clinical experience appears to confirm this prediction: hypertensive crises ("cheese reactions") have not been reported in ELDEPRYL treated patients. However, until the pathophysiology of the "hypertensive crisis" is more completely understood, it seems prudent to assume that ELDEPRYL can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO-B (e.g. 10 mg/day). Hence, attention to the dose dependent nature of ELDEPRYL's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use (See WARNINGS and PRECAUTIONS). **Pharmacokinetics**. Only preliminary information about the details of the pharmacokinetics of ELDEPRYL and its metabolites is available. Data obtained in a study of 12 healthy subjects that was intended to study the effects of ELDEPRYL on the pharmacokinetics of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of ELDEPRYL to these subjects, serum levels of intact ELDEPRYL were below the limit of detection (less than 10 ng/ml). Three metabolites, N-desmethylselegiline, the major metabolite (mean half-life 2.0 hours), l-amphetamine (mean half-life 17.7 hours) and l-metamphetamine (mean half-life 20.5 hours) were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these three metabolites. In an extension of this study intended to examine the effects of steady state conditions, the same subjects were given a 10 mg dose of ELDEPRYL for seven consecutive days. Under these conditions, the mean trough levels were 3.5 ng/ml for l-amphetamine and 8.0 ng/ml for l-metamphetamine, and those for N-desmethylselegiline were below the levels of detection. The rate of MAO-B regeneration following discontinuation of treatment has not been quantified. It is this rate, dependent upon *de novo* protein synthesis, which seems likely to determine how fast normal MAO-B activity can be restored. **INDICATIONS AND CLINICAL USE** ELDEPRYL (selegiline hydrochloride) may be of value as an adjunct to levodopa (usually with a decarboxylase inhibitor) in the management of some patients with Parkinson's Disease. ELDEPRYL is not indicated as a first line treatment of Parkinson patients but may be of value as add-on therapy. Short term benefits from the drug are frequently lost in the longer run. **CONTRAINDICATIONS** ELDEPRYL (selegiline hydrochloride) is contraindicated in patients with known hypersensitivity to this drug. ELDEPRYL should not be used in patients with active peptic ulcer, in patients with other extrapyramidal disorders such as excessive tremor or tardive dyskinesia, or in patients with severe psychosis or profound dementia. **WARNINGS** **Selective versus non-selective inhibition of MAO-B**. ELDEPRYL (selegiline hydrochloride) should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO (See CLINICAL PHARMACOLOGY). The selectivity of ELDEPRYL for MAO-B may not be absolute even at the recommended daily dose of 10 mg/day and selectivity is further diminished with increasing daily doses. The precise dose at which ELDEPRYL becomes a non-selective inhibitor of all MAO is unknown. Doses in the range of 30 to 40 mg a day are known to be non-selective. Because of reports of fatal interactions, MAO inhibitors are ordinarily contraindicated for use with meperidine. This warning is often extended to other opioids. Because the mechanism of interaction between MAO inhibitors and meperidine is unknown, it seems prudent, in general, to avoid this combination. **PRECAUTIONS** **General**. Some patients given ELDEPRYL (selegiline hydrochloride) 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 approximately 10 to 30%. The decision to prescribe ELDEPRYL should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with ELDEPRYL. Consequently the full spectrum of possible responses to ELDEPRYL may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe the patients closely for atypical responses. **Warning to Patients**. Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL therapy. The patients (or their families) if the patient is incompetent) should be advised not to exceed the recommended daily dose of 10 mg. The risk of using higher daily doses of ELDEPRYL should be explained, and a brief description of the "hypertensive crisis" ("cheese reaction") provided. While hypertensive reactions with ELDEPRYL have not been reported, documented experience is limited. Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAO inhibitors induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced. **Laboratory Tests**. No specific laboratory tests are deemed essential for the 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**. 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. Because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. **Carcinogenesis** Studies to evaluate the carcinogenic potential of ELDEPRYL have not been completed. **Use during Pregnancy**. Insufficient animal reproduction studies with ELDEPRYL have been done to conclude that ELDEPRYL poses no teratogenic potential. However, one rat study carried out at doses as high as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether ELDEPRYL can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. ELDEPRYL should be given to a pregnant woman only if clearly needed, and the benefit versus risk must be evaluated carefully. **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 have not been evaluated. **ADVERSE REACTIONS** **Introduction**. THE SIDE EFFECTS OF ELDEPRYL (selegiline HCl) ARE USUALLY THOSE ASSOCIATED WITH DOPAMINERGIC EXCESS. THE DRUG MAY POTENTIATE THE SIDE EFFECTS OF LEVODOPA. THEREFORE ADJUSTMENT OF DRUG DOSAGES MAY BE REQUIRED. ONE OF THE MOST SERIOUS ADVERSE REACTIONS REPORTED WITH SOME FREQUENCY WITH ELDEPRYL USED AS AN ADJUNCT TO LEVODOPA THERAPY ARE HALLUCINATIONS/CONFUSION, PARTICULARLY VISUAL HALLUCINATIONS. Although a cause and effect relationship has not been established, a tendency to a progressive rise in several liver enzymes has been reported after long term therapy. The number of patients investigated in controlled clinical trials is limited, and therefore the kind of information required to provide an estimate of incidence of adverse reactions is not available. In prospective clinical trials, the following adverse effects, in decreasing order of frequency, led to discontinuation of treatment with ELDEPRYL: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased

abnormal involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increase of episodes of freezing, gastrointestinal bleeding, hair loss, increasing tremor, nervousness, weakness and weight loss. In controlled clinical trials involving a very limited number of patients (N = 49 receiving ELDEPRYL; N = 50 receiving placebo) the following adverse reactions were reported (incidences are devoid of practical statistical significance):

ADVERSE EVENT	INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS IN CLINICAL TRIAL	
	ELDEPRYL	PLACEBO
Nausea	10	3
Dizziness/Lightheaded/ Faintness	7	1
Abdominal pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Visual dreams	2	0
Dyskinesias	2	5
Headache	2	1
Ache, generalized	1	0
Anxiety/tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary retention	1	0
Weight loss	1	0

The following is a list of all adverse reactions reported classified by body system: **Central Nervous System. Motor/Coordination/Extrapyramidal:** increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch, myoclonic jerks, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps. **Mental Status/Behavioural/Psychiatric:** hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, light-headedness, impaired memory, increased energy, transient high, hollow feeling, lethargy/ malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability. **Pain/Altered Sensation:** headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, loss of sensation. **Autonomic Nervous System.** Dry mouth, blurred vision, sexual dysfunction. **Cardiovascular.** Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope. **Gastrointestinal.** Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism. **Genitourinary/Gynecologic/ Endocrine.** Transient anorgasmia, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation, urinary frequency. **Skin and Appendages.** Increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity. **Miscellaneous.** Asthma, diplopia, shortness of breath, speech affected. **SYMPTOMS AND TREATMENT OF OVERDOSE** No specific information is available about clinically significant overdoses with ELDEPRYL (selegiline HCl).

However, experience gained during the development of ELDEPRYL reveals that some individuals exposed to doses of 600 mg/day of ELDEPRYL suffered severe hypotension and psychomotor agitation. Since the selective inhibition of MAO-B by ELDEPRYL is achieved only at doses recommended for the treatment of Parkinson's Disease (i.e. 10 mg per day), overdoses are likely to cause significant inhibition of both MAO-A and MAO-B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g. tranylcypromine, isocarboxazide, and phenelzine]. Characteristically, signs and symptoms of overdose with non-selective MAO inhibitors may not appear immediately. Delays of up to 12 hours between ingestion of the drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdose with non-selective MAO inhibitors. Therefore, immediate hospitalization, with continuous patient observation and monitoring is strongly recommended. The clinical picture of MAO inhibitor overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous system and cardiovascular systems are prominently involved. Signs and symptoms of overdose may include, alone or in combination, any of the following: dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse; hypertension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin. Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response. Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanically supported ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential. **DOSE AND ADMINISTRATION** The recommended dosage of ELDEPRYL (selegiline HCl) as an adjunct in the management of patients with Parkinson's Disease is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. Doses higher than 10 mg/day should not be used. There is no evidence that additional benefit will be obtained from the administration of higher doses. The dose of 10 mg/day results in an almost complete selective inhibition of MAO-B enzyme. The inhibitory action of ELDEPRYL is irreversible, the duration of drug effect depends on enzyme regeneration. Higher doses will result in a loss of selectivity of ELDEPRYL towards MAO-B with an increase in the inhibition of type MAO-A. Moreover, there is an increased risk of adverse reactions with higher doses as well as an increased risk of the "cheese reaction" with its hypertensive response. 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 of 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. **AVAILABILITY** ELDEPRYL (selegiline HCl) 5 mg tablets, available in bottles of 60 tablets. Each almost white, flat tablet, with one face engraved with "JU", contains 5 mg of the l-isomer of selegiline HCl (formerly l-deprenyl HCl). The inactive ingredients are Lactose, Starch, Povidone, Magnesium Stearate, and Talc. Product Monograph available to physicians and pharmacists upon request.

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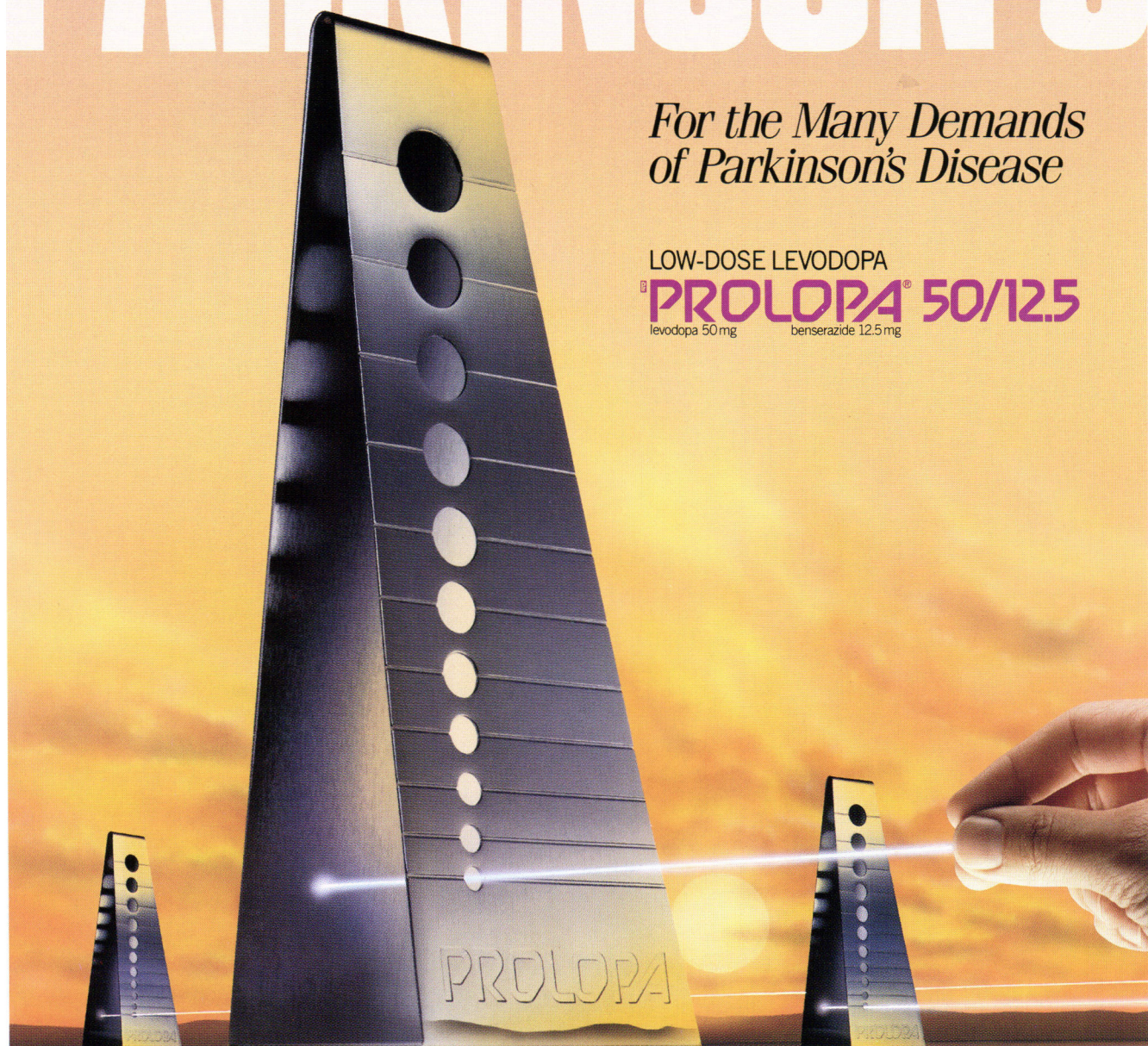
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