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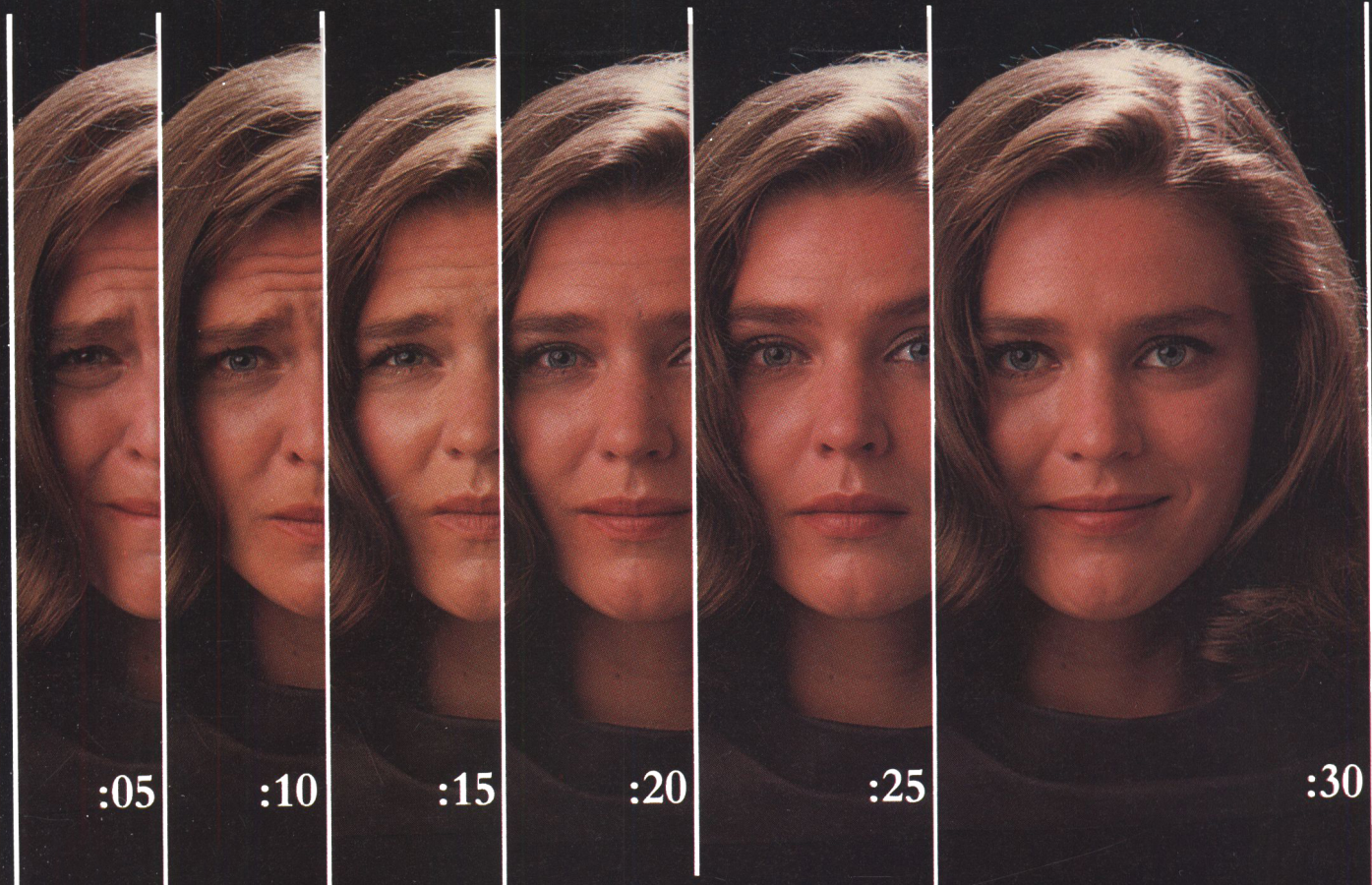
The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association for Child Neurology

Volume 10, No. 1 February 1983

Stop most headaches in just 30 minutes



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Brief prescribing information on page... (xiv)

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THE EDITORIAL BOARD wishes to publish original work in the basic and clinical neurosciences on the understanding that it has not been and will not be published elsewhere. Review articles on timely subjects will be accepted. Manuscripts must be in triplicate including illustrations. One of the copies must be the original, ribbon copy. Manuscripts should be typed double spaced, on white paper.

Papers will be accepted in French or English. All papers should be accompanied by a short résumé in both languages. The résumé translation will be done by the editorial board if requested.

Papers should be identified only by the full name of the author, or authors, and the name of the place in which the work was done.

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All illustrations should be referred to as figures, numbered consecutively, not included in the body of the text and all captions should be typed on a separate piece of paper.

Colored illustrations cannot usually be accepted unless the author is prepared to assist with the cost of reproduction.

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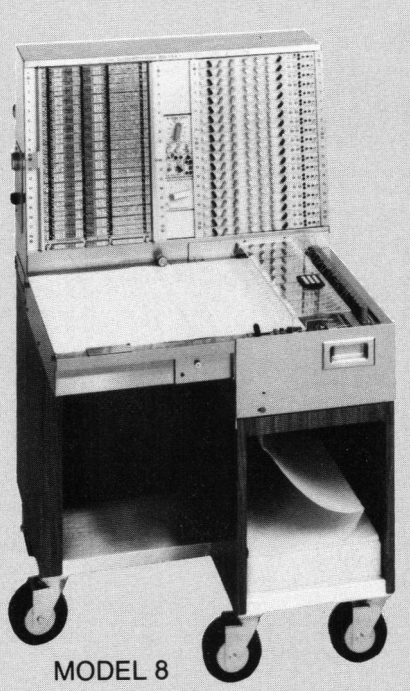

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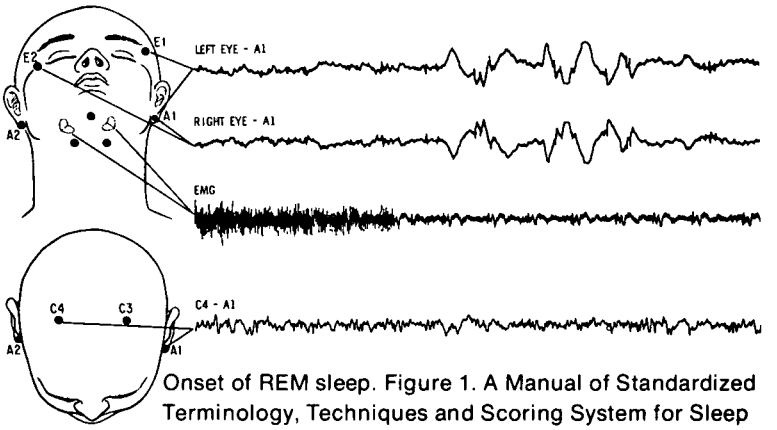
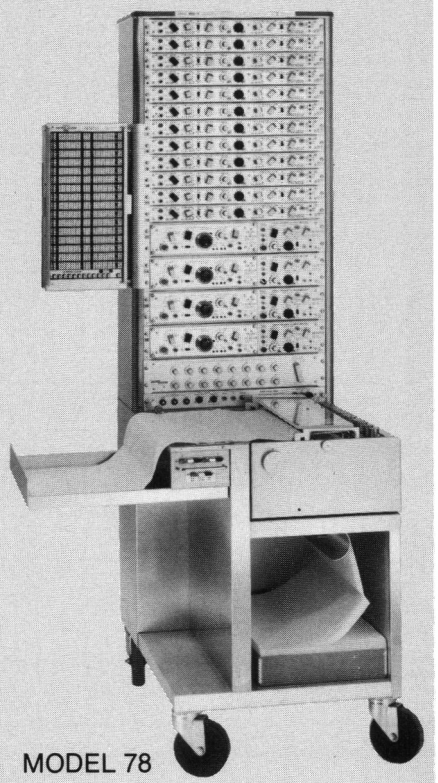


Onset of REM sleep. Figure 1. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. UCLA-BIS-DHEW.



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Depakene*

valproic acid

Brief prescribing information

INDICATIONS AND CLINICAL USE: Depakene (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. Valproic acid may also be used adjunctively in patients with multiple-seizure types which include absence.
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: Depakene (valproic acid) should not be administered to patients with hepatic disease or significant dysfunction; it is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving Depakene. These incidences usually have occurred during the first six months of treatment with Depakene. 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 nonspecific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious causes while taking sodium valproate.
Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first six 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 when administering Depakene to 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, valproic acid should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.
The drug should be discontinued immediately in the presence of significant hepatic dysfunctions, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects particularly elevated liver enzymes may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

USE IN PREGNANCY: The safety of Depakene (valproic acid) during pregnancy has not been established, however, animal studies have demonstrated teratogenicity. Therefore, the physician should weigh the potential benefits against the possible risks in treating or counselling women of childbearing age who have epilepsy.
Recent reports indicate an association between the use of anticonvulsant drugs and an elevated 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 two to three-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.
Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, including trimethadione and paramethadione. 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.
Anticonvulsant 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 antiepileptic medication is in doubt, appropriate consultation might be indicated.

NURSING MOTHERS: Depakene is secreted 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 valproic acid.

FERTILITY: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment I 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 Depakene (valproic acid) on the development of the testes and on sperm production and fertility in humans is unknown.
LONG TERM TOXICITY STUDIES IN RATS INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS: HEPATIC DYSFUNCTION: SEE CONTRAINDICATIONS AND WARNINGS

GENERAL: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients receiving Depakene (valproic acid) 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 Depakene (valproic acid) 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 valproic acid should be discontinued.
Because Depakene (valproic acid) may interact with other anticonvulsant drugs, periodic serum level determinations of such other anticonvulsants are recommended during the early part of therapy (see DRUG INTERACTIONS). There have been reports of breakthrough seizures occurring with the combination of Depakene and phenytoin.
Depakene (valproic acid) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

DRIVING AND HAZARDOUS OCCUPATIONS: Valproic acid 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: DEPAKENE (VALPROIC ACID) MAY POTENTIATE THE CNS DEPRESSANT ACTION OF ALCOHOL.
THERE IS EVIDENCE THAT VALPROIC ACID MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM IS UNKNOWN. 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. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM LEVELS. THE DOSE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.
THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.
Caution is recommended when valproic acid is administered with drugs affecting coagulation, e.g. acetylsalicylic acid and warfarin (see ADVERSE REACTIONS).

ADVERSE REACTIONS: The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since Depakene (valproic acid) has usually been used with other anticonvulsants, 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 anticonvulsant 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 who were also on 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 Depakene.

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 DRUG INTERACTIONS). 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.

HEPATIC: Minor elevations of transaminases (e.g. 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 nonketotic hyperglycinemia.

PANCREATIC: Isolated reports of pancreatitis in association with valproic acid therapy have been received.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: In a reported case of overdosage with Depakene (valproic acid) after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.
Naloxone has been reported to reverse the CNS depressant effects of Depakene overdose. Because naloxone could theoretically also reverse the anticonvulsant effects of Depakene it should be used with caution.
As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: Depakene (valproic acid) is administered orally. The recommended initial dose 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 dose is 60 mg/kg/day. When the total daily dose exceeds 250 mg, it is given in a divided regimen. A 500-mg enteric coated capsule may be substituted for two 250-mg capsules.
The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control must be weighed against the increased incidence of adverse effects.

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

Weight		Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup		
kg	lb		Dose 1	Dose 2	Dose 3
10 – 24.9	22 – 54.9	250	0	0	1
25 – 39.9	55 – 87.9	500	1	0	1
40 – 59.9	88 – 131.9	750	1	1	1
60 – 74.9	132 – 164.9	1,000	1	1	2
75 – 89.9	165 – 197.9	1,250	2	1	2

As the dosage of valproic acid is raised, blood levels of phenobarbital and/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. Such patients may benefit from administration of the enteric-coated capsule. The capsules should be swallowed without chewing to avoid local irritation of the mouth and throat.

AVAILABILITY: Depakene (valproic acid) is available as orange-coloured, soft-gelatin capsules of 250 mg in bottles of 100 capsules (Number 5681; DIN 443840); pale yellow, oval soft gelatin enteric-coated capsules of 500 mg in bottles of 100 capsules (Number D795; DIN 507989) and as a red syrup containing the equivalent of 250 mg valproic acid, as the sodium salt, per 5 mL in bottles of 450 mL (Number 5682; DIN 443832).

Depakene is now available in a 500-mg enteric-coated capsule.

REFERENCES:
1. BMJ editorial, March 3, 1979.
2. Data on file, Abbott Laboratories.
3. Jeavons PM et al: Treatment of generalized epilepsies of childhood and adolescence with sodium valproate. Dev Med Child Neurol 1977; 19: 9-25.
4. Wilder BJ: Valproic acid in clinical use: An overview. Proceedings of the Valproic Acid Round Table Conference, June 1978, Vancouver. Excerpta Medica 1979.
5. Coulter DL et al: Valproic acid in childhood epilepsy. JAMA 1980; 244 (8): 785-88.

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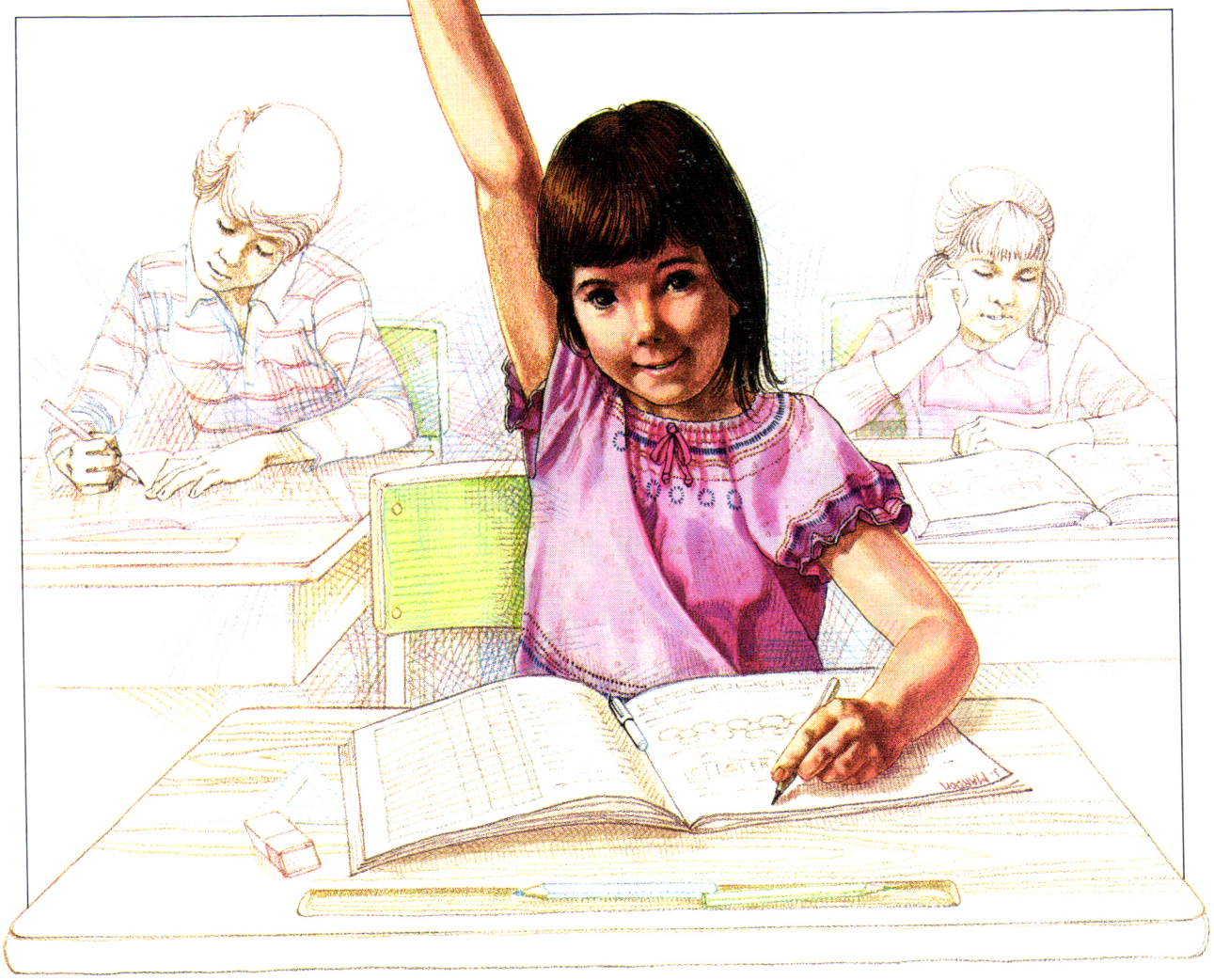
you wouldn't guess Jane's an epileptic



Epileptic therapy doesn't have to interfere with her life. Depakene can effectively control seizures, with little risk of disturbed behaviour or poor performance.

Depakene provides broad-spectrum seizure control Depakene is considered a drug of first choice for simple and complex absence seizures[1,2] and has been successfully used in tonic-clonic or myoclonic seizures with absence components.[3,4]

No impairment of learning Depakene has made patients more alert, more lively and better able to perform daily tasks.[5]

Positive effect on behaviour Depakene, unlike phenobarbital, rarely affects behaviour, and may actually improve it.[5]

Low incidence of disturbing side effects Depakene does not cause hirsutism, gum hyperplasia or acne, nor has it been associated with aplastic anemia or agranulocytopenia.

Minimizes problems of polypharmacy Depakene is often effective as single therapy. When other anticonvulsants are necessary, their dosage may be reduced.

New dosage convenience A 500-mg enteric-coated capsule is now available.

valproic acid

Depakene*

brings many epileptic patients closer to normal

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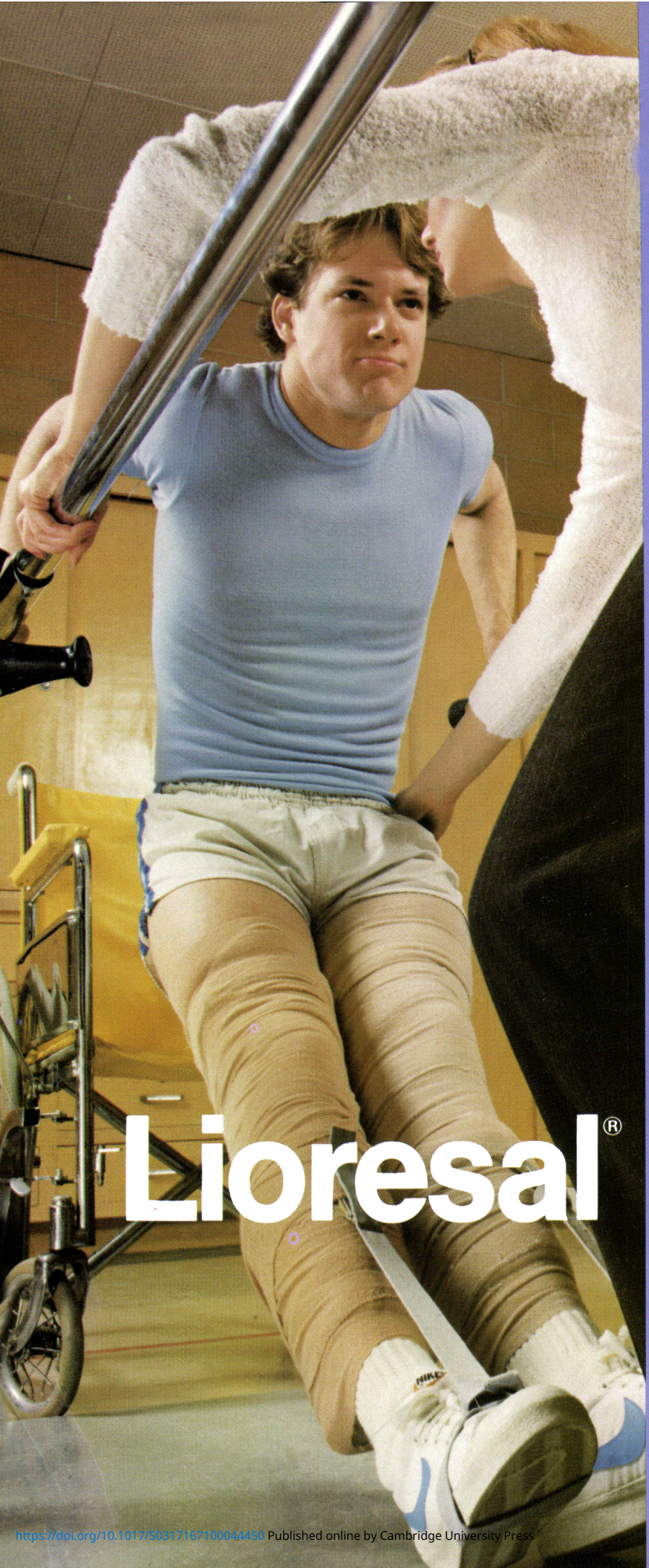

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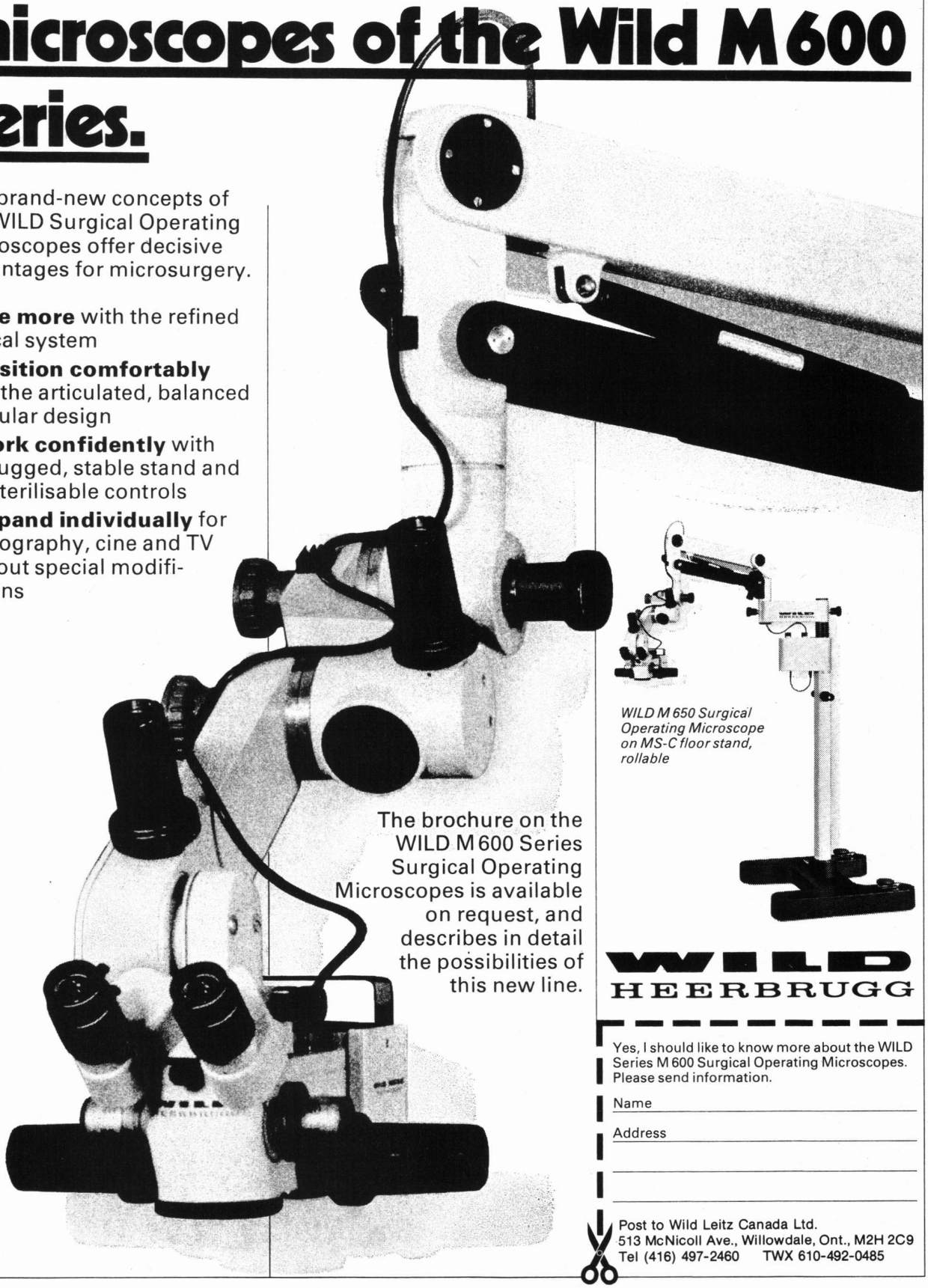

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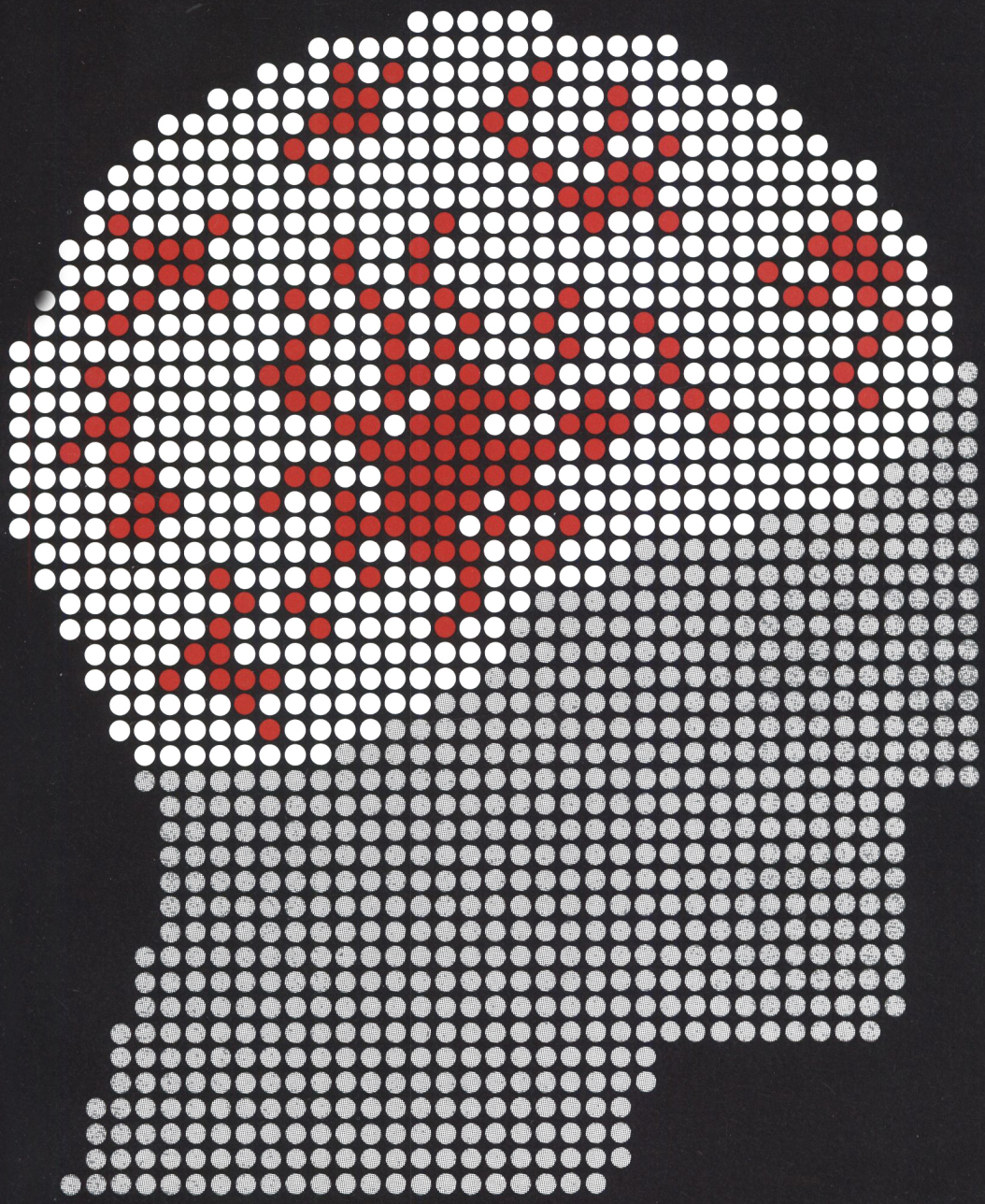
without excessive sedation



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Geigy

Brief Prescribing Information

Tegretol® No substitution.

200 mg carbamazepine

Indications and clinical use

a) *Trigeminal Neuralgia:*
Tegretol is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used preventively during periods of remission. In some patients, Tegretol has relieved glossopharyngeal neuralgia. For patients who fail to respond to Tegretol, or who are sensitive to the drug, recourse to other accepted measures must be considered. Tegretol is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

b) *Tegretol has been found useful:*
1. in the management of psychomotor (temporal lobe) epilepsy and,
2. as an adjunct, in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when administered in combination with other antiepileptic medication.
3. as an alternative medication in patients with generalized tonic-clonic seizures who are experiencing marked side effects or fail to respond to other anticonvulsant drugs.

Tegretol is essentially ineffective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge.

Contraindications

Tegretol should not be administered to patients with a history of hepatic disease or serious blood disorder.

Tegretol should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer Tegretol to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clincal condition allows, but in no case should this be less than 14 days. Then the dosage of Tegretol should be low initially, and increased very gradually.

Tegretol should not be administered to patients presenting atrioventricular heart block.

Safe use in pregnancy has not been established. Therefore, Tegretol should not be administered during the first three months of pregnancy.

Tegretol should not be given to women of childbearing potential unless, in the opinion of the physician, the expected benefits to the patient outweigh the possible risk to the foetus (See Reproductive Studies). Because of demonstrated toxicity in nursing animals, Tegretol should not be administered to nursing mothers.

Because of the similarity of chemical structure, Tegretol should not be administered to patients with known hypersenitivity to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites.

Warnings

Although reported infrequently, serious adverse effects have been observed during the use of Tegretol. Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, thrombocytopenia and hepatocellular and cholestatic jaundice have also been reported. It is, therefore, important that Tegretol should be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia.

Long-term toxicity studies in rats indicated a potential carcinogenic risk. Therefore, the possible risk of drug use must be weighed against the potential benefits before prescribing carbamazepine to individual patients.

Precautions

Monitoring of Haematological and Other Adverse Reactions: Complete blood studies, including platelet counts, and evaluation of hepatic and renal function and urinalysis should be carried out before treatment is instituted. Careful clinical and laboratory supervision should be maintained throughout treatment, including frequent performance of complete blood counts, in order to detect any early signs or symptoms or blood dyscrasia. Should any signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur, Tegretol should be immediately discontinued until the case is carefully reassessed.

Urinary Retention and Increased Intraocular Pressure: Because of its anticholinergic action, Tegretol should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug.

Occurrence of Behavioural Disorders: Because it is closely related to the other tricyclic drugs, there is some possibility that Tegretol might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Caution should also be exercised in alcoholics.

Use in Patients with Cardiovascular Disorders: Tegretol should be used cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, an E.K.G. should be performed before administering Tegretol, in order to exclude patients with atrioventricular block.

Use in Patients taking Oral Contraceptives: In women under treatment with Tegretol, the reliability of oral contraceptives may be adversely affected; such patients should accordingly be advised to use some alternative, non-hormonal method of contraception.

Driving and Operating Hazardous Machinery: Because dizziness and drowsiness are possible side effects of Tegretol, patients should be warned about the possible hazards of operating machinery or driving automobiles.

Adverse Reactions

The reactions which have been most frequently reported with Tegretol are drowsiness, unsteadiness on the feet, vertigo, dizziness, gastrointestinal disturbances, and nausea. These reactions usually occur only during the initial phase of therapy. They have rarely necessitated discontinuing Tegretol therapy, and can be minimized by initiating treatment at a low dosage.

The more serious adverse reactions observed are the haematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy.

The following adverse reactions have been reported:

Haematological reactions: Transitory leucopenia, eosinophilia, leucocytosis, thrombocytopenic purpura, agranulocytosis, macrocytic anemia and aplastic anemia. In a few instances, deaths have occurred.

Hepatic disturbances: During the long-term administration of Tegretol abnormalities in liver function tests and cholestatic or hepatocellular jaundice have been observed.

Dermatological reactions: The following reactions occurred during treatment with Tegretol: skin sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis and in rare cases Stevens-Johnson syndrome, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosm, and aggravation of disseminated lupus erythematosus.

Neurological reactions: The reactions reported as occurring during treatment with Tegretol include vertigo, somnolence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements and increase in motor seizures. In addition, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, and tinnitus have been reported but only very rarely. 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 systems: Recurrence of thrombophlebitis in patients with a prior history of thrombophlebitis, congestive heart failure, aggravation of hypertension, Stokes-Adams in patients with AV block, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds.

Genitourinary reactions: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, and impotence, Elevation of BUN, albuminuria and glycosuria also have been observed.

Digestive tract: Disturbances associated withn Tegretol therapy have included nausea, vomiting, gastric or abdominal discomfort, diarrhoea, anorexia and dryness of the mouth and throat, glossitis and stomatitis.

Eyes: There is no conclusive evidence that Tegretol produces pathological changes in the cornea, lens or retina. However, it should be recognized that many phenothiazines and related drugs have been shown to cause eye changes. By analogy, periodic eye examinations, including slitlamp fundoscopy and tonometry, are recommended.

Other reactions reported during treatment with Tegretol include fever and chills, lymphadenopathy, aching joints and muscles, leg cramps and conjunctivitis.

Dosage and Administration

Use in Epilepsy (see Indications): A low initial daily dosage with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.

Adults and Children over 12 years of age: Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, until the best response is obtained, up to 600 mg daily. The usual optimal dosage is 600 mg daily, but occasionally dosage up to 800 to 1000 mg have been used for short periods. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Use in-trigeminal neuralgia: The initial daily dosage should be small; 200 mg, taken in two doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg per day until relief of pain is obtained. This is usually achieved at a dosage between 200 and 800 mg daily, but occasionally up to 1200 mg per day may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimum effective dosage is reached. 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 upon the individual clinical course.

Prophylactic use of the drug in trigeminal neuralgia is not recommended.

Tegretol should be taken in two or three divided doses daily, with meals whenever possible.

Dosage Forms

Tegretol is available as a 200 mg white, round, flat bevelled edge single-scored tablet, engraved with Geigy signet.

Availability

Bottles of 50 and 500 tables. Protect from heat and humidity.

Full information available on request.

Geigy

Mississauga, Ontario
L5N 2W5

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CCPP

G-2005

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Brief Prescribing Information

℞ **Lioresal®** baclofen

Action

The precise mechanisms of action of **Lioresal** (baclofen) are not fully known. It inhibits both *monosynaptic and polysynaptic reflexes at the* spinal level, probably by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although **Lioresal** is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. Peak plasma concentrations of **Lioresal** are achieved within 2 hours and the plasma half-life is 2-4 hours.

Indications and Clinical Uses

Lioresal (baclofen) is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis.

Lioresal may also be of some value in patients with spinal cord injuries and other spinal cord diseases.

Contraindications

Hypersensitivity to **Lioresal** (baclofen).

Warnings

Abrupt Drug Withdrawal: Following abrupt withdrawal of **Lioresal** (baclofen), visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, insomnia, and worsening of spasticity have occurred. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued. *Impaired Renal Function:* Because **Lioresal** is primarily excreted unchanged through the kidneys, it should be given with caution, and it may be necessary to reduce the dosage. *Stroke:* **Lioresal** has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug. *Pregnancy:* Safe use of **Lioresal** during pregnancy or lactation has not been established. High doses are associated with an increased incidence of abdominal hernias in the fetuses of rats and of ossification defects in those of rats and rabbits. Therefore, the drug should be administered to pregnant patients, or women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Precautions

Safe use of **Lioresal** (baclofen) in children under age 12 has not been established and it is, therefore, not recommended for use in children. Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system effects of **Lioresal** may be additive to those of alcohol and other CNS depressants. **Lioresal** should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function. Extreme caution should be exercised in patients with epilepsy or a history of convulsive disorders. In such patients, the clinical state and electroencephalogram should be monitored at regular intervals during therapy, as deterioration in seizure control and EEG has been reported occasionally in patients taking **Lioresal.** Caution should be used in treating patients with peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and in patients receiving antihypertensive therapy. It is not known whether **Lioresal** is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Adverse Reactions

The most common adverse reactions associated with **Lioresal** (baclofen) are transient drowsiness, dizziness, weakness and fatigue. Others reported: *Neuropsychiatric:* Headache (<10%), insomnia (<10%), and, rarely, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, *mydriasis, diplopia, dysarthria, epileptic* seizures. *Cardiovascular:* Hypotension (<10%), rare instances of dyspnea, palpitation, chest pain, syncope. *Gastrointestinal:* Nausea, (approx. 10%), constipation (<10%), and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool. *Genitourinary:* Urinary frequency (<10%), and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria. *Other:* Instances of rash, pruritus, *ankle edema, excessive perspiration, weight* gain, nasal congestion. Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

The following laboratory tests have been found to be abnormal in a few patients receiving **Lioresal:** SGOT, alkaline phosphatase and blood sugar (all elevated).

Symptoms and Treatment of Overdosage

Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, coma, respiratory depression, and seizures. The signs and symptoms may be further aggravated by coadministration of a variety of other agents including alcohol, diazepam, and tricyclic antidepressants. *Treatment:* The treatment is symptomatic. In the alert patient, empty the stomach promptly by induced emesis followed by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Maintain adequate respiratory exchange; do not use respiratory stimulants. Muscular hypotonia may involve the respiratory muscles and require assisted respiration. A high urinary output should be maintained since **Lioresal** (baclofen) is excreted mainly by the kidneys. Dialysis is indicated in severe poisoning associated with renal failure.

Dosage and Administration

The determination of optimal dosage of **Lioresal** (baclofen) requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily).

The following dosage titration schedule is suggested:

5 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see Warnings).

Availability: Lioresal (baclofen) 10 mg tablets. *Description:* White to off-white flat-faced, oval tablets with Geigy monogram on one side and the identification code 23 below the monogram. Fully bisected on the reverse side. Available in bottles of 100 tablets.

References:

1. R.F. Jones, J.W. Lance, Medical Journal of Australia, 1976, May:654-657.
2. R.G. Feldman: Symposia Reporter, Vol. 3, No. 2 June 1979.
3. Lioresal Product Monograph.

Product monoraph supplied on request.

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Geigy Dorval, Qué. H9S 1B1 G-0018

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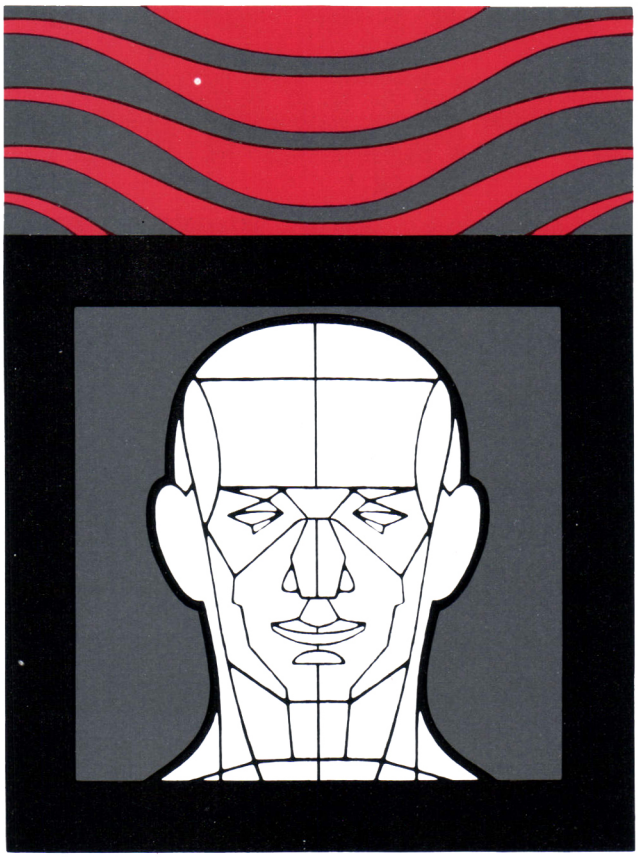
1 mg tablet double strength

Help prevent recurrent throbbing headaches with **Sandomigran DS** (double strength)



Sandomigran maintenance therapy helps prevent recurrent headaches

Taken daily, Sandomigran can reduce the frequency, severity and duration of vascular or mixed headaches.[1-3] In fact, Sandomigran has suppressed throbbing headaches altogether in many patients.[3-5]

Double-strength DS tablet improves compliance

Patients have fewer tablets to take and find it easier to comply with maintenance therapy. The DS tablet also simplifies dosage: with a half-life of 23 hours,[6] treatment can be initiated h.s.; the dosage may be increased to a maximum of 6 DS tablets a day in divided doses (see prescribing information).

Sandomigran DS for at least 4 weeks

Sandomigran DS must be taken daily for at least four weeks — not to relieve headaches but to prevent them.

Sandomigran® DS 1 mg
pizotyline

Doesn't give recurrent throbbing headaches a second chance.

SANDOZ®

MEMBER PMAC PAAB

Dosage information page (xiv)

SANDOZ (Canada) LTD. Dorval, Quebec H9R 4P5

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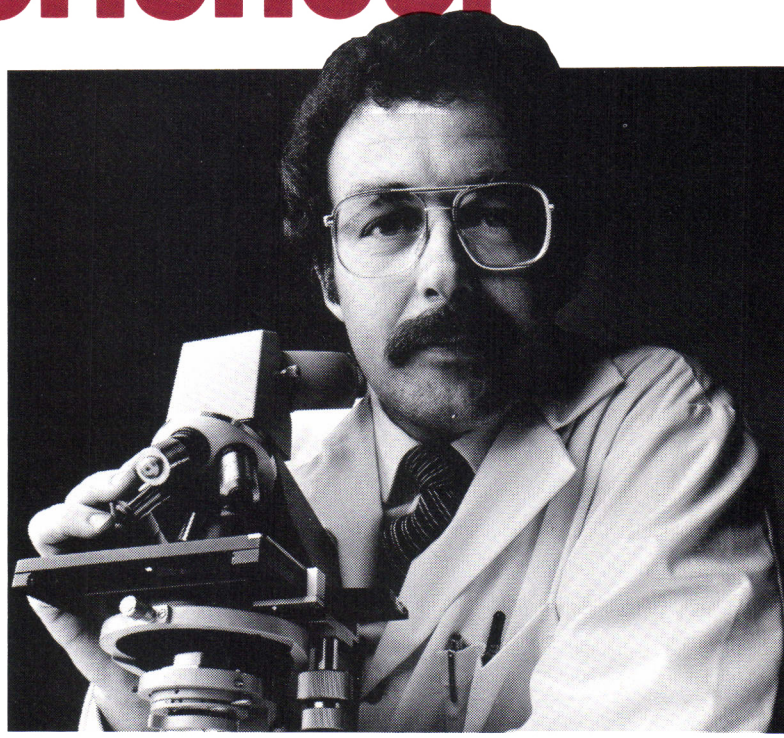
In the effective treatment of epilepsy, there is no substitute for experience.



The original carbamazepine, TEGRETOL®, was first introduced by Geigy in 1969 and subsequently became the drug of choice for trigeminal neuralgia.

But this development marked only the beginning.

Geigy research soon provided the basis for approval in the treatment of psychomotor/ temporal lobe epilepsy in 1973.

And in 1979, this indication was again expanded to include usage in refractory generalized tonic/clonic seizures.

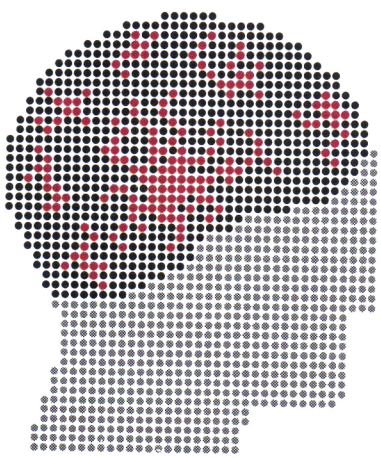
This committment to the ongoing potential of TEGRETOL does not end here: continuing research indicates that further applications are possible in the future.

While the provision of a quality pharmaceutical is a primary objective of Geigy, other services to both doctor and patient have not gone unaddressed.

Medical information, support to continuing medical education and attention to the needs of epileptic patients, their families and Associations have been important elements in the overall attention given to this disorder.

In fact, a prescription for TEGRETOL does far more in the fight against epilepsy than just control patient symptoms.

Tegretol®



No Substitution.

Because there is no substitute for experience. Yours, or ours.

Geigy
Mississauga, Ontario
L5N 2W5

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