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The International Journal of Neuropsychiatric Medicine

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Alzheimer's Disease in the 21st Century

Guest Editors

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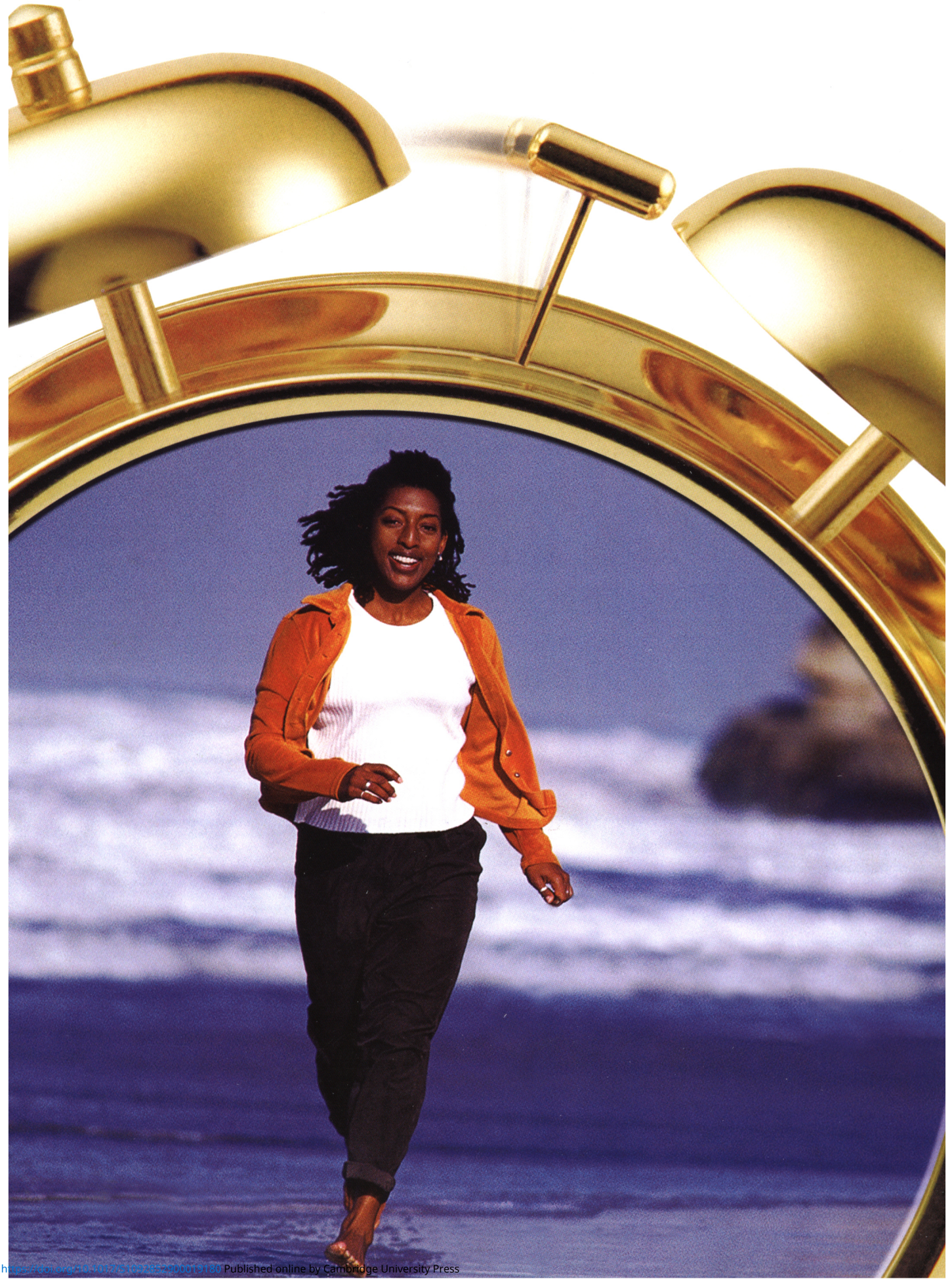

Time for wakefulness

PROVIGIL® (modafinil) TABLETS
BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information
INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.
CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL
PRECAUTIONS: ***General:*** Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.
Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.
Central Nervous System: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.
Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.
Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased.
Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.
Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL:
Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. ***Nursing:*** Patients should notify their physician if they are breast feeding. ***Concomitant Medication:*** Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. ***Alcohol:*** It is prudent to avoid alcohol while taking PROVIGIL. ***Allergic Reactions:*** Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.
Drug Interactions: ***CNS Active Drugs:*** In a single-dose study, coadministration of PROVIGIL 200 mg with *methylphenidate* 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of *clomipramine* 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of *clomipramine* and its active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and *triazolam* 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with *monoamine oxidase (MAO) inhibitors,* caution should be exercised.
Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in ~20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of CYP3A4 (eg, carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) could alter the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant *in vivo* effects of PROVIGIL based on *in vitro* data are:
A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed.
A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg, cyclosporine, steroidal contraceptives, theophylline).
An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 substrates (eg, warfarin, phenytoin).
A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg, diazepam, propranolol, phenytoin, S-mephenytoin).
In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger. Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg, clomipramine, desipramine).
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m^2 basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. ***Mutagenesis:*** There was no evidence of mutagenic or clastogenic potential of PROVIGIL. ***Impairment of Fertility:*** When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m^2 basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects on fertility.
Pregnancy: Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m^2 basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m^2 basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m^2 basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk.
Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy.
Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to a nursing woman.
PEDIATRIC USE: Safely and effectiveness in individuals below 16 years of age have not been established.
GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.
ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (≥5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] hypertonia, confusion, amnesia, emotional lability, ataxia, tremor
Cardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope
Hemic/Lymphatic: Eosinophilia
Special senses: Amblyopia, abnormal vision
Metabolic/Nutritional: Hyperglycemia, albuminuria
Musculo-skeletal: Joint disorder
Skin/Appendages: Herpes simplex, dry skin
Urogenital: Abnormal urine, urinary retention, abnormal ejaculation[4]
[1]Incidence ≥5%,[2] Elevated liver enzymes,[3] Oro-facial dyskinesias,[4] Incidence adjusted for gender.
Dose Dependency: In US trials, the only adverse experience more frequent (≥5% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.
Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials.
Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.
Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant.
ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.
Postmarketing Reports
In addition to the adverse events observed during clinical trials, the following adverse events have been identified during post-approval use of PROVIGIL in clinical practice. Because these adverse events are reported voluntarily from a population of uncertain size, reliable estimates of their frequency cannot be made.
Hematologic: Agranulocytosis
Central Nervous System: Symptoms of psychosis, symptoms of mania
DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. *In vitro,* PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg, incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse.
Withdrawal: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.
OVERDOSAGE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. **Overdose Management:** No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.
Manufactured for: **Cephalon, Inc.,** West Chester, PA 19380
For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at **www.PROVIGIL.com.**

PROVIGIL® (MODAFINIL) C Tablets

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Supported by an educational grant from Janssen Pharmaceutica

Time for wakefulness

A unique wake-promoting agent

PROVIGIL promotes daytime wakefulness, improving patients' ability to participate in daily activities—with no effect on nighttime sleep.[1-3]

Long-term safety

The long-term safety profile of PROVIGIL has been demonstrated for up to 136 weeks.[4]

PROVIGIL was generally well tolerated. Most frequently reported adverse events in clinical trials were headache, nausea, nervousness, anxiety, infection, and insomnia. Most adverse events were mild to moderate. PROVIGIL may interact with drugs that inhibit, induce, or are metabolized by cytochrome P450 isoenzymes.

Dosing

Recommended dose for PROVIGIL is 200 mg taken orally once daily in the morning. Both PROVIGIL doses, 200 mg and 400 mg QD, were effective.

PROVIGIL is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.

References: 1. PROVIGIL full prescribing information. **2.** US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol*. 1998;43:88-97. **3.** US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology*. 2000;54:1166-1175. **4.** Data on file, Cephalon, Inc.

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For more information, call 1-800-896-5855 or visit our Website at www.PROVIGIL.com.

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CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

EDITORIAL MISSION

CNS Spectrums' *editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.*

Introduction

CNS Spectrums is an Index Medicus journal that publishes original scientific literature and reviews on a wide variety of neuroscientific topics of interest to the clinician on a monthly basis. Our mission is to provide physicians with an editorial package that will enhance and increase their understanding of neuropsychiatry; therefore, manuscripts that address crossover issues between neurology and psychiatry will be given immediate priority.

Scope of Manuscripts

CNS Spectrums will consider and encourages the following types of articles for publication:

Original Research presents methodologically sound original data.

Reviews are comprehensive articles summarizing and synthesizing the literature on various neuropsychiatric topics and presented in a scholarly and clinically relevant fashion. Diagnostic and treatment algorithms should be designed to aid the clinician in diagnosis and treatment.

Case Reports Single or multiple are encouraged for publication.

Letters to the Editor will be considered and are encouraged for publication. All letters will be edited for style, clarity, and length.

Manuscript Submission

General Information Two copies of the manuscript with a letter on the author's letterhead should be submitted to Jack M. Gorman, MD, Editor (or, in Europe, to Joseph Zohar, MD, International Editor), c/o MBL Communications, 333 Hudson Street, 7th Floor, New York, NY 10013. Authors are also required to submit their manuscripts on computer disk in Microsoft Word format. Disks should be labeled with the word processing program, title of paper, and lead author's name. Accepted manuscripts will be edited for clarity and style.

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Peer Review Authors must provide three to five names of qualified potential reviewers with no conflict of interest in reviewing the work. Contact information with affiliations and e-mail address should be included. Peer review is anonymous.

Manuscript Preparation

Length Reviews and Original Research should not exceed 5,000 words *(excluding References)*. Diagnostic and treatment algorithms should contain an introduction, flowcharts or a series of graphs, and a concise summary. Letters should not exceed 1,500 words. Single Case Reports should not exceed 3,750 words and may be submitted with a photograph, if applicable.

Please note: If your article is Original Research, it should be formatted as: Abstract (100–200 words); Introduction, Methods; Findings; Discussion; Conclusion; References (numbered and comprehensive list).

Spacing and Pagination One space should be left after commas and periods. Manuscripts should be double-spaced and numbered.

Abstract Authors must provide a brief abstract of 100–200 words.

Focus Points Please provide three to six points that dictate the main focus of the manuscript and clearly illustrates what you are trying to convey in the article.

Figures/Tables Please provide figures and/or tables if content is amenable to it.

References Please use American Medical Association style. References should be superscripted in text, then numbered, and comprehensive in list. See the following examples:

1. Jones J. Necrotizing Candida esophagitis. JAMA. 1980;244:2190-2191.
2. Stryer L. *Biochemistry*. 2nd ed. San Francisco, Calif: WH Freeman Co; 1980:559-596.

Continuing Medical Education Authors must submit six multiple-choice questions (three Type A and three Type K), with answers.

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Disclosure of Commercial and Non-Commercial Interests

Authors must include a statement about all forms of support, including grant and pharmaceutical support, affiliations, and, honoraria, received for past and present material. Such information may, at the editor's discretion, be shared with reviewers. If the article is accepted for publication, the editors will consult with the authors as to whether this information should be included in the published paper.

Submission Checklist

- ☐ Original manuscript plus one copy, with cover letter on author's letterhead
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- ☐ Six CME multiple-choice questions with answers
- ☐ Three to six focus points
- ☐ Disk labeled with the word processing program, title of paper, and lead author's name
- ☐ Names and affiliations of three to five potential peer reviewers

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Feature Articles

CME-Accredited Articles

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It is also indexed by DIALOG, EMBASE/Excerpta Medica, Lexis-Nexis, OVID, and SilverPlatter.

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Get your patients with depression

Into life again

Vivactil starts working fast to improve symptoms of depression[1]

- ✔ Faster than either amitriptyline (reference product, Elavil®*) or imipramine (reference product, Tofranil®-PM†) in some clinical trials
- ✔ Noticeable improvement of symptoms has occurred in less than 1 week
- ✔ Patients can experience increased energy and activity early in the course of treatment

Vivactil is nonsedating and nontranquilizing[1]

- ✔ An especially appropriate choice for withdrawn and anergic patients

Adverse events associated with TCAs should be considered when prescribing Vivactil. Vivactil may aggravate agitation and anxiety and produce cardiovascular reactions, such as tachycardia and hypotension

Please see brief summary of prescribing information on adjacent page

Exploring the Advantages of Tricyclic Antidepressants — **an important roundtable discussion featuring leading experts in the treatment of depression — is now available. Ask your Sales Representative for a copy or call Odyssey at 1-877-427-9068.**

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Vivactil® (Protriptyline HCl, USP) 5-mg and 10-mg Tablets

Brief Summary: See package insert for full prescribing information

INDICATIONS AND USAGE: Protriptyline hydrochloride tablets are indicated for the treatment of symptoms of mental depression in patients who are under close medical supervision. Its activating properties make it particularly suitable for withdrawn and anergic patients.

CONTRAINDICATIONS: Protriptyline hydrochloride tablets are contraindicated in patients who have shown prior hypersensitivity to it.

It should not be given concomitantly with a monoamine oxidase inhibiting compound. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simultaneously. When it is desired to substitute protriptyline for a monoamine oxidase inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. Protriptyline should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Protriptyline is contraindicated in patients taking cisapride because of the possibility of adverse cardiac interactions including prolongation of the QT interval, cardiac arrhythmias and conduction system disturbances.

This drug should not be used during the acute recovery phase following myocardial infarction.

WARNINGS: Protriptyline may block the antihypertensive effect of guanethidine or similarly acting compounds.

Protriptyline should be used with caution in patients with a history of seizures, and, because of its autonomic activity, in patients with a tendency to urinary retention, or increased intraocular tension.

Tachycardia and postural hypotension may occur more frequently with protriptyline than with other antidepressant drugs. Protriptyline should be used with caution in elderly patients and patients with cardiovascular disorders; such patients should be observed closely because of the tendency of the drug to produce tachycardia, hypotension, arrhythmias, and prolongation of the conduction time. Myocardial infarction and stroke have occurred with drugs of this class.

On rare occasions, hyperthyroid patients or those receiving thyroid medication may develop arrhythmias when this drug is given.

In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

Pediatric Use: The safety and effectiveness of protriptyline in pediatric patients have not been established.

Usage in Pregnancy: Safe use in pregnancy and lactation has not been established; therefore, use in pregnant women, nursing mothers or women who may become pregnant requires that possible benefits be weighed against possible hazards to mother and child.

In mice, rats, and rabbits, doses about ten times greater than the recommended human doses had no apparent adverse effects on reproduction.

PRECAUTIONS: General - When protriptyline HCl is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated. Likewise, in manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant drug. Paranoid delusions, with or without associated hostility, may be exaggerated. In any of these circumstances, it may be advisable to reduce the dose of protriptyline or to use a major tranquilizing drug concurrently.

Symptoms, such as anxiety or agitation, may be aggravated in overactive or agitated patients.

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs. This type of patient should not have access to large quantities of the drug.

Concurrent administration of protriptyline and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to patients for whom it is essential.

Discontinue the drug several days before elective surgery, if possible.

Both elevation and lowering of blood sugar levels have been reported.

Information for Patients: While on therapy with protriptyline, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Drug Interactions: When protriptyline is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side-effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

Tricyclic antidepressants may enhance the seizure risk in patients taking ULTRAM (tramadol hydrochloride).

Protriptyline may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Drugs Metabolized by Cytochrome P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C anti-arrhythmics, propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic anti-depressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Pediatric Use: The safety and effectiveness of protriptyline in pediatric patients have not been established.

Geriatric Use: Clinical studies of protriptyline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (see WARNINGS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing are a few adverse reactions which have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when protriptyline is administered. Protriptyline is more likely to aggravate agitation and anxiety and produce cardiovascular reactions such as tachycardia and hypotension.

Cardiovascular: Myocardial infarction; stroke; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; hypertension; tachycardia; palpitation.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; hypomania; exacerbation of psychosis; insomnia, panic, and nightmares.

Neurological: Seizures; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of extremities; extrapyramidal symptoms; drowsiness; dizziness; weakness and fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention, delayed micturition, dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased intraocular pressure, mydriasis; dry mouth and rarely associated sublingual adenitis.

Allergic: Drug fever; petechiae, skin rash, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general, or of face and tongue).

Hematologic: Agranulocytosis; bone marrow depression; leukopenia; thrombocytopenia; purpura; eosinophilia.

Gastrointestinal: Nausea and vomiting; anorexia; epigastric distress; diarrhea; peculiar taste; stomatitis; abdominal cramps; black tongue.

Endocrine: Impotence, increased or decreased libido; gynecomastia in the male; breast enlargement and galactorrhea in the female; testicular swelling; elevation or depression of blood sugar levels.

Other: Jaundice (simulating obstructive); altered liver function; parotid swelling; alopecia; flushing; weight gain or loss; urinary frequency, nocturia; perspiration.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE:

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

MANIFESTATIONS:

Critical manifestations of overdosage include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under **ADVERSE REACTIONS**.

MANAGEMENT:

General:

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose. These patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination:

All patients suspected of a tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular:

A maximal limb-lead QRS duration of ≥0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a pCO2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS:

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

PSYCHIATRIC FOLLOW-UP:

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

PEDIATRIC MANAGEMENT:

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION:

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Usual Adult Dosage – Fifteen to 40 mg a day divided into 3 or 4 doses. If necessary, dosage may be increased to 60 mg a day. Dosages above this amount are not recommended. Increases should be made in the morning dose.

Adolescent and Elderly Patients – In general, lower dosages are recommended for these patients. Five mg 3 times a day may be given initially, and increased gradually if necessary. In elderly patients, the cardiovascular system must be monitored closely if the daily dose exceeds 20 mg.

When satisfactory improvement has been reached, dosage should be reduced to the smallest amount that will maintain relief of symptoms.

Minor adverse reactions require reduction in dosage. Major adverse reactions or evidence of hypersensitivity require prompt discontinuation of the drug.

The safety and effectiveness of protriptyline in pediatric patients have not been established.

METABOLISM:

Metabolic studies indicate that protriptyline is well absorbed from the gastrointestinal tract and is rapidly sequestered in tissues. Relatively low plasma levels are found after administration, and only a small amount of unchanged drug is excreted in the urine of dogs and rabbits. Preliminary studies indicate that demethylation of the secondary amine moiety occurs to a significant extent, and that metabolic transformation probably takes place in the liver. It penetrates the brain rapidly in mice and rats, and moreover that which is present in the brain is almost all unchanged drug.

Studies on the disposition of radioactive protriptyline in human test subjects showed significant plasma levels within 2 hours, peaking at 8 to 12 hours, then declining gradually.

Urinary excretion studies in the same subjects showed significant amounts of radioactivity in 2 hours. The rate of excretion was slow. Cumulative urinary excretion during 16 days accounted for approximately 50% of the drug. The fecal route of excretion did not seem to be important.

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References

1. Vivactil [package insert]. East Hanover, NJ:Odyssey Pharmaceuticals, Inc. 2000.

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