

# CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine



## Personality Disorders

Guest Editor—Larry J. Siever, MD

### INTRODUCTION

**Refining the Approaches to Personality Disorders**

*L.J. Siever*

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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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> basis) there was an increase in resorption, hydromorphosis, 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<sup>2</sup> 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<sup>2</sup> 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:** Safety 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,<sup>1</sup> chest pain, neck pain, chills, rigid neck, fever/chills

**Digestive:** Nausea,<sup>1</sup> diarrhea,<sup>1</sup> dry mouth,<sup>1</sup> anorexia,<sup>1</sup> abnormal liver function,<sup>2</sup> vomiting, mouth ulcer, gingivitis, thirst

**Respiratory system:** Rhinitis,<sup>1</sup> pharyngitis,<sup>1</sup> lung disorder, dyspnea, asthma, epistaxis

**Nervous system:** Nervousness,<sup>1</sup> dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,<sup>3</sup> 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<sup>4</sup>

<sup>1</sup>Incidence ≥5%, <sup>2</sup>Elevated liver enzymes, <sup>3</sup>Oro-facial dyskinesias, <sup>4</sup>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

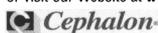
**DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence:** In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. *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](http://www.PROVIGIL.com).



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# GUIDE TO DSM-IV AND ICD-10 CODES

	<b>DSM-IV</b>	<b>ICD-10</b>
Dementia of the Alzheimer Type, With Early Onset With Depressed Mood Specify if: With Behavioral Disturbance	290.13	F00.03
Dementia of the Alzheimer's Type, With Late Onset With Depressed Mood Specify if: With Behavioral Disturbance	290.21	F00.13
Delirium Due to: Indicate General Medical Condition	293.0	F05.0
Psychotic Disorder Due to: Indicate General Medical Condition With Delusions With Hallucinations	293.81 293.82	F06.2 F06.0
Mood Disorder Due to: Indicate General Medical Condition	293.83	F06
Anxiety Disorder Due to: Indicate General Medical Condition	293.89	F06.4
Amnesic Disorder Due to: Indicate General Medical Condition	294.0	F02.8
Dementia NOS	294.8	F03
Amnesic Disorder NOS	294.8	R41.3
Schizophrenia	295	F20
Schizophrenia—Disorganized Type	295.10	F20.1
Schizophrenia—Catatonic Type	295.20	F20.2
Schizophrenia—Paranoid Type	295.30	F20.0
Schizophrenia—Residual Type	295.60	F20.5
Schizoaffective Disorder	295.70	F25
Schizophrenia—Undifferentiated Type	295.90	F20.3
Major Depressive Disorder	296	F32
Bipolar I Disorder	296	F30
Bipolar Disorder NOS	296.80	F39
Bipolar II Disorder	296.89	F31.8
Mood Disorder NOS	296.90	F39
Psychotic Disorder NOS	298.9	F29
Autistic Disorder	299.00	F84
Asperger's Disorder	299.80	F84.5
Pervasive Developmental Disorder NOS	299.80	F84.9
Anxiety Disorder NOS	300.00	F41.9
Panic Disorder Without Agoraphobia	300.01	F41
Generalized Anxiety Disorder	300.02	F41.1
Dissociative Identity Disorder	300.14	F44.81
Dissociative Disorder NOS	300.15	F44.9
Factitious Disorder NOS	300.19	F68.1
Panic Disorder With Agoraphobia	300.21	F40.01
Agoraphobia Without History of Panic Disorder	300.22	F40
Social Phobia	300.23	F40.1
Specific Phobia	300.29	F40.2
Obsessive-Compulsive Disorder	300.3	F42.8
Dysthymic Disorder	300.4	F34.1
Depersonalization Disorder	300.6	F48.1
Body Dysmorphic Disorder	300.7	F45.2
Somatization Disorder	300.81	F45
Somatoform Disorder NOS	300.81	F45.9
Cyclothymic Disorder	301.13	F34
Alcohol Dependence	303.90	F10.2
Cocaine Dependence	304.20	F14.2
Cannabis Dependence	304.30	F12.2
Amphetamine Dependence	304.40	F15.2
Alcohol Abuse	305.00	F10.1
Cannabis Abuse	305.20	F12.1
Cocaine Abuse	305.60	F14.1
Amphetamine Abuse	305.70	F15.1
Stuttering	307.0	F98.5
Anorexia Nervosa	307.1	F50
Tic Disorder NOS	307.20	F95.9
Tourette Disorder	307.23	F95.2
Primary Insomnia	307.42	F51.0
Primary Hypersomnia	307.44	F51.1
Sleepwalking Disorder	307.46	F51.3
Dyssomnia NOS	307.47	F51.9
Nightmare Disorder	307.47	F51.5
Parasomnia NOS	307.47	F51.8
Eating Disorder NOS	307.50	F50.9
Bulimia Nervosa	307.51	F50.2
Feeding Disorders of Infancy or Early Childhood	307.59	F98.2
Communication Disorder NOS	307.9	F80.9
Posttraumatic Stress Disorder	309.81	F43.1
Depressive Disorder NOS	311	F32.9
Impulse-Control Disorder NOS	312.30	F63.9
Pathological Gambling	312.31	F63.0
Pyromania	312.33	F63.1
Kleptomania	312.34	F63.2
Trichotillomania	312.39	F63.3
Disruptive Behavior Disorder NOS	312.9	F91.9
Attention-Deficit/Hyperactivity Disorder, Combined Type	314.01	F90
Attention-Deficit/Hyperactivity Disorder NOS	314.9	F90.9
Learning Disorder NOS	315.9	F81.9
Developmental Coordination Disorder	315.4	F82
Narcolepsy	347	G47.4
Sleep Disorder Due to: Indicate General Medical Condition	780	G47
Delirium NOS	780.09	F05.9





# 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.<sup>1-3</sup>

## Long-term safety

The long-term safety profile of PROVIGIL has been demonstrated for up to 136 weeks.<sup>4</sup>

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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Please see brief summary of prescribing information on adjacent page.

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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.

# Author Guidelines

## 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. *CNS Spectrums* will publish 12 issues in 2003. As the immense prevalence of comorbid diseases among patients seen by psychiatrists and neurologists increases, these physicians will jointly diagnose and treat the neuropsychiatrically ill. Our mission is to provide these physicians with an editorial package that will enhance and increase their understanding of neuropsychiatry; therefore, manuscripts that address crossover issues germane to neurology and psychiatry will be given immediate priority.

## Scope of Manuscripts

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

**Original Research:** Original Research presents methodologically sound original data.

**Reviews:** Reviews are **comprehensive** articles that summarize and synthesize the literature on various topics in a scholarly and clinically relevant fashion. Suitable topics include mood disorders, schizophrenia and related disorders, personality disorders, substance-use disorders, anxiety disorders, neuroscience, psychosocial aspects of psychiatry, child psychiatry, geriatric psychiatry, and other topics of interest to clinicians. Original flowcharts designed to aid the clinician in diagnosis and treatment will be considered for publication in reviews and are encouraged.

**Case Reports:** Single or multiple case reports will be considered for publication.

**Letters to the Editor:** Letters will be considered for publication.

## Manuscript Submission

**General information:** Two copies of the manuscript with a letter on the author's letterhead should be submitted to Jack M. Gorman, Editor (or, in Europe, to Joseph Zohar, International Editor), c/o MBL Communications, 333 Hudson Street, 7th Floor, New York, NY 10013; (F) 212.328.0600. 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 and letters will be edited for clarity and style.

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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.

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