

CNS SPECTRUMS®

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

ORIGINAL RESEARCH

Borderline Personality Disorder and Traits in Veterans: Psychiatric Comorbidity, Healthcare Utilization, and Quality of Life Along a Continuum of Severity

D.W. Black, N. Blum, E. Letuchy, C. Carney Doebbeling, V.L. Forman-Hoffman, and B.N. Doebbeling

The Efficacy and Safety of Lower Doses of Aripiprazole for the Treatment of Patients with Acute Exacerbation of Schizophrenia

A.J. Cutler, R.N. Marcus, S.A. Hardy, A. O'Donnell, W.H. Carson, and R.D. McQuade

Healthcare Resource Utilization in Bipolar Depression Compared with Unipolar Depression: Results of a United States Population-Based Study

M.A. Frye, J.R. Calabrese, M.L. Reed, and R.M.A. Hirschfeld

Adjunctive Treatment for Mood Stabilization of Patients with Bipolar I Disorder Treated with Lamotrigine

T. Spaulding, R. Westlund, C. Thomason, R. White, R. Dann, and T. Thompson

REVIEW ARTICLE

Presidential Stroke: United States Presidents and Cerebrovascular Disease

J.M. Jones and J.L. Jones

CASE REPORT

Anorexia Nervosa and Brain Tumor in a 14-Year-Old Girl

M.S. Sokol, C.K. Fujimoto, T.K. Jackson, and P.J. Silberberg

STICK IT TO ADHD.



15-mg patch (actual size)



Now Available The First and Only ADHD Patch™

Methylphenidate in a novel delivery system

Reduced core ADHD symptoms from the first time point measured (2 hours) through 12 hours when worn for the recommended 9 hours^{1,2}

May be removed earlier than 9 hours¹

- If a shorter duration of effect is desired¹
- If late-day side effects appear¹

Daytrana is indicated as an integral part of a comprehensive ADHD treatment program that may include other measures (psychological, educational, social) for patients with this syndrome. The efficacy of Daytrana was established in clinical trials in children aged 6 to 12 years¹

New
 Daytrana™ (methylphenidate transdermal system)

Important Safety Information: Daytrana should not be used in patients with allergy to methylphenidate or patch components; marked anxiety, tension and agitation; glaucoma; tics, diagnosis or a family history of Tourette's syndrome; seizures; or during or within 14 days after treatment with monoamine oxidase inhibitors (MAOIs).

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses in ADHD. Physicians should take a careful patient history, including family history, and physical exam to assess the presence of cardiac disease. Patients who report symptoms of cardiac disease such as exertional chest pain and unexplained syncope should be promptly evaluated. Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate.

New psychosis, mania, aggression, growth suppression, and visual disturbances have been associated with the use of stimulants. Use with caution in patients with a history of: psychosis; EEG abnormalities; bipolar disorder; depression. Growth and hematologic monitoring is advised during prolonged treatment. Patients should avoid applying external heat to the Daytrana patch. Skin irritation or contact sensitization may occur.

Daytrana should be given cautiously to patients with a history of drug dependence and alcoholism. Chronic abuse can lead to marked tolerance and psychological dependence. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder.

Common adverse events reported by patients who received Daytrana in clinical trials were decreased appetite, insomnia, nausea, vomiting, decreased weight, tics, affect lability, and anorexia, consistent with adverse events commonly associated with the use of methylphenidate.

Please see Brief Summary of Prescribing Information on adjacent page, including Boxed Warning.

References: 1. Daytrana [package insert]. Wayne, PA: Shire US Inc; 2006. 2. McGough JJ, Wigal SB, Abikoff H, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. *J Atten Disord.* 2006;9:476-485.

Daytrana™ is a trademark of Shire Pharmaceuticals Ireland Limited.

Shire US Inc. ...your ADHD Support Company™

1-800-828-2088

©2006 Shire US Inc., Wayne, Pennsylvania 19087

D430 09/06

Shire

BRIEF SUMMARY: Consult the full prescribing information for complete product information.

Daytrana™ (methylphenidate transdermal system)

INDICATION AND USAGE

Attention Deficit Hyperactivity Disorder (ADHD): Daytrana™ (methylphenidate transdermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and is available in 10, 15, 20, and 30 mg dosing strengths. The efficacy of Daytrana™ was established in two controlled clinical trials in children with ADHD.

Special Diagnostic Considerations: Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV-TR characteristics.

Neuroleptic Malignant Syndrome: Daytrana™ is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychiatric, educational, social) for patients with this syndrome. Treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of Daytrana™ for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Daytrana™ for extended periods should periodically re-evaluate the long-term usefulness of Daytrana™ for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation: Daytrana™ is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate: Daytrana™ is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester).

Glaucoma: Daytrana™ is contraindicated in patients with glaucoma.

Tics: Daytrana™ is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monamine Oxidase Inhibitors: Daytrana™ is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Sudden Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2–4 mmHg) and average heart rate (about 3–6 bpm) (see ADVERSE REACTIONS), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients Being Treated With Stimulant Medications

Children and adolescents who are being considered for treatment with stimulant medications should have a careful history and physical assessment for a history of sudden death or ventricular arrhythmia, and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Contact Sensitization: Use of Daytrana™ may lead to contact sensitization. Daytrana™ should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana™ and is not by itself an indication of sensitization.

However, sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. Diagnosis of allergic contact dermatitis should be corroborated by appropriate diagnostic testing.

Patients sensitized from use of Daytrana™ as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, e.g., orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch-test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting.

Patients who develop contact sensitization to Daytrana™ and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to Daytrana™ may not be able to take methylphenidate in any form.

A study designed to provoke skin sensitization resulted in a signal for Daytrana™ to be an irritant and also a contact sensitizer. This study involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, followed by a 2 week rest period, and then challenge/rechallenge. Under conditions of the study, Daytrana™ was more irritating than both the placebo patch control and the negative control (saline). Of 133 subjects who participated in the challenge phase of the sensitization study, at least 18 (13.5%) were confirmed to have been sensitized to Daytrana™ based on the results of the challenge and rechallenge phases of the study.

Using Daytrana™ as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported.

However, since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what the true incidence of sensitization is when Daytrana™ is used as directed.

Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3,482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and postmarketing experience. Some medications are indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth: Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures: There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Use in Children Under Six Years of Age: Daytrana™ should not be used in children under six years of age, since safety and efficacy in this age group have not been established.

Drug Dependence

Daytrana™ should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parental abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Patients Using External Heat: All patients should be advised to avoid exposing the Daytrana™ application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, etc., while wearing the patch. There is a potential for temperature-dependent increases in methylphenidate release of greater than 2-fold from the patch.

Hematologic Monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients: Patients should be informed to apply Daytrana™ to a clean, dry site on the hip, which is not oily, damaged, or irritated. The site of application must be alternated daily. The patch should not be applied to the waistline, or where tight clothing may rub it.

Daytrana™ should be applied 2 hours before the desired effect. Daytrana™ should be removed approximately 9 hours after it is applied, although the effects from the patch will last for several more hours.

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana™ to monitor application and removal time, and method of disposal.

If there is an unacceptable duration of appetite loss or insomnia in the evening, taking the patch off earlier may be attempted before decreasing the patch size.

Skin redness or itching is common with Daytrana™, and small bumps on the skin may also occur in some patients. If any swelling or blistering occurs the patch should not be worn and the patient should be seen by the prescriber.

Drug Interactions: Daytrana™ should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors (see CONTRAINDICATIONS-Monoamine Oxidase Inhibitors).

Because of a possible effect on blood pressure, Daytrana™ should be used cautiously with pressor agents.

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some tricyclic drugs (e.g., imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

Serious adverse events have been reported in concomitant use of methylphenidate with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity studies of transdermal methylphenidate have not been performed. In a lifetime carcinogenicity study of oral methylphenidate carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors and the significance of these results to humans is unknown.

Orally administered methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats, the highest dose used was approximately 45 mg/kg/day.

In a 24-week oral carcinogenicity study in the transgenic mouse strain p53⁺, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. In this study, male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse bone marrow micronucleus assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response. In an *in vitro* assay in cultured Chinese hamster ovary cells.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day.

Pregnancy

Pregnancy Category C: Animal reproduction studies with transdermal methylphenidate have not been performed. In a study in which oral methylphenidate was given to pregnant rabbits during the period of organogenesis at doses up to 200 mg/kg/day no teratogenic effects were seen, although an increase in the incidence of a variation, dilation of the lateral ventricles, was seen at 200 mg/kg/day; this dose also produced maternal toxicity. A previously conducted study in rabbits showed teratogenic effects of methylphenidate at an oral dose of 200 mg/kg/day. In a study in which oral methylphenidate was given to pregnant rats during the period of organogenesis at doses up to 100 mg/kg/day, no teratogenic effects were seen although a slight delay in fetal skeletal ossification was seen at doses of 60 mg/kg/day and above; these doses caused some maternal toxicity.

In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity. Adequate and well-controlled studies in pregnant women have not been conducted. Daytrana™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Daytrana™ is administered to a nursing woman.

Pediatric Use: The safety and efficacy of Daytrana™ in children under 6 years old have not been established. Long-term effects of methylphenidate in children under 6 years old have not been well established (see WARNINGS).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) or continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS

The pre-marketing clinical development program for Daytrana™ included exposures in a total of 1,158 participants in clinical trials (758 pediatric patients and 400 healthy adult subjects). These participants received Daytrana™ in patch sizes ranging from 6.25 cm² to 50 cm². The 758 pediatric patients (age 6 to 16 years) were evaluated in 9 controlled clinical studies, 2 open-label clinical studies, and 4 clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events data. Refer to the Full Prescribing Information for details of adverse event data collection.

Adverse Findings in Clinical Trials With Daytrana™

Adverse Events Associated With Discontinuation of Treatment: In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana™ discontinued due to adverse events compared with 1.2% (1/85) receiving placebo. The reasons for discontinuation among the patients treated with Daytrana™ were application site erythema, application site reaction, confusional state, crying, tics, headaches, irritability, infectious mononucleosis, and viral infection.

Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated With Daytrana™: Table 1 enumerates the incidence of treatment-emergent adverse events reported in a 7 week double-blind, parallel group, placebo-controlled study in children with ADHD conducted in the outpatient setting.

TABLE 1: Most Commonly Reported Treatment-Emergent Adverse Events ($\geq 5\%$ and $\geq 2x$ Placebo) in a 7-week Placebo-controlled Study

Adverse Event	Number (%) of Subjects Reporting Adverse Events
Daytrana™ (N = 98)	Placebo (N = 85)
Number of Subjects With ≥ 1 Adverse Event	74 (76)
Nausea	12 (12)
Vomiting	10 (10)
Nasopharyngitis	5 (5)
Weight decreased	9 (9)
Anorexia	5 (5)
Decreased appetite	25 (26)
Affect labile*	6 (6)
Insomnia	13 (13)
Tic	7 (7)
Nasal congestion	6 (6)

* Six subjects had affect labile, all judged as mild and described as increased emotional sensitivity, emotionally, emotional instability, emotional lability, and intermittent emotional lability.

and headache (53 subjects, 28%). A total of 45 (42%) subjects were withdrawn from the study because of treatment-emergent adverse events. The most common events leading to withdrawal were application site reaction (12 subjects, 4%), and insomnia (7 subjects, 4%).

Adverse Events With Oral Methylphenidate Products: Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include: **Cardiac:** angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia; **Gastrointestinal:** abdominal pain, nausea; **Immune:** hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura; **Metabolism/Nutrition:** anorexia, weight loss during prolonged therapy; **Nervous System:** dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis; **Vascular:** blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate: **Blood/Lymphatic:** leukopenia and/or anemia; **Hepatobiliary:** abnormal liver function, ranging from transaminase elevation to hepatic coma; **Psychiatric:** transient depressed mood; **Skin/Subcutaneous:** scalp hair loss; **Neuroleptic Malignant Syndrome:** Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Daytrana™ (methylphenidate transdermal system), like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance: See WARNINGS-Drug Dependence for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Symptoms and Signs: Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment: Remove all patches immediately and cleanse the area(s) to remove any remaining adhesive. The continuing absorption of methylphenidate from the skin, even after removal of the patch, should be considered when treating patients with overdose. Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Intensive care must be provided to maintain adequate circulation and respiratory exchange, external cooling procedures may be required for hyperpyrexia.

Poison Control Center: As with the management of all overdoses, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdoses with methylphenidate.

No store patches unpouched. Store at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F) [see USP Controlled Room Temperature]. Once the tray is opened, use contents within 2 months. Apply the patch immediately upon removal from the protective pouch. Do not store patches unpouched. **For transdermal use only.**

REFERENCE

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association 1994.

Manufactured for Shire US Inc., Wayne, PA 19087 by Noven Pharmaceuticals, Inc., Miami, FL 33186.

For more information call 1-800-828-2088 or visit www.shire.com.

Dot Matrix™ is a trademark of Noven Pharmaceuticals, Inc.

Daytrana™ is a trademark of Shire Pharmaceuticals Ireland Limited.

© 2006 Shire Pharmaceuticals Ireland Limited.

Because of a possible effect on blood pressure, Daytrana™ should be used cautiously with pressor agents.

Rx Only
102086-1 552 1027 002 Rev. 06/06 DBS4



EDITORS

EDITOR EMERITUS

Jack M. Gorman, MD
Mount Sinai School of Medicine
New York, NY

EDITOR

Eric Hollander, MD
Mount Sinai School of Medicine
New York, NY

INTERNATIONAL EDITOR

Joseph Zohar, MD
Chaim Sheba Medical Center
Tel-Hashomer, Israel

ASSOCIATE INTERNATIONAL EDITORS

EUROPE

Donatella Marazziti, MD
University of Pisa
Pisa, Italy

MID-ATLANTIC

Dan J. Stein, MD, PhD
University of Cape Town
Cape Town, South Africa

FAR EAST

Shigeto Yamawaki, MD, PhD
Hiroshima University School
of Medicine
Hiroshima, Japan

CONTRIBUTING WRITERS

Donald W. Black, MD
Andrew J. Cutler, MD
Mark A. Frye, MD
Jeffery M. Jones, MD, FAAN
Mae S. Sokol, MD
Theodore Spaulding, PhD

COLUMNIST

Dan J. Stein, MD, PhD

MEDICAL REVIEWER

David L. Ginsberg, MD

CME COURSE DIRECTOR

Eric Hollander, MD

SUPPLEMENT EDITOR

Joseph Zohar, MD

PUBLICATION STAFF

CEO & PUBLISHER

Darren L. Brodeur

ASSOCIATE PUBLISHER

Elizabeth Katz

VP, MANAGING EDITOR

Christopher Naccari

VP, SENIOR EDITOR

Deborah Hughes

SENIOR GLOBAL ACCOUNT DIRECTOR

Richard Ehrlich

SENIOR EDITOR—CNS SPECTRUMS

José Ralat

SENIOR ACQUISITIONS EDITOR

Lisa Arrington

EDITORIAL ADVISORY BOARD

NEUROLOGISTS

Mitchell F. Brin, MD
University of California, Irvine
Irvine, CA

Jeffrey L. Cummings, MD
University of California, Los Angeles
Los Angeles, CA

Jerome Engel, Jr., MD, PhD
University of California, Los Angeles
Los Angeles, CA

Mark S. George, MD
Medical University of South Carolina
Charleston, SC

Richard B. Lipton, MD
Albert Einstein College of Medicine
Bronx, NY

C. Warren Olanow, MD, FRCPC
Mount Sinai School of Medicine
New York, NY

Steven George Pavlakis, MD
Maimonides Medical Center
Brooklyn, NY

Stephen D. Silberstein, MD, FACP
Thomas Jefferson University
Philadelphia, PA

Michael Trimble, MD, FRCP, FRPsych
National Hospital for Neurology
and Neurosurgery
London, United Kingdom

PSYCHIATRISTS

Margaret Altemus, MD
Cornell University Medical College
New York, NY

Dennis S. Charney, MD
Mount Sinai School of Medicine
New York, NY

Dwight L. Evans, MD
University of Pennsylvania
Philadelphia, PA

Siegfried Kasper, MD
University of Vienna
Vienna, Austria

Martin B. Keller, MD
Brown Medical School
Providence, RI

Lorrin M. Koran, MD
Stanford University School of Medicine
Stanford, CA

Yves Leclubier, MD
Hôpital de la Salpêtrière
Paris, France

Herbert Y. Meltzer, MD
Vanderbilt University Medical Center
Nashville, TN

Stuart A. Montgomery, MD
St. Mary's Hospital Medical School
London, United Kingdom

Charles B. Nemerooff, MD, PhD
Emory University School of Medicine
Atlanta, GA

Humberto Nicolini, MD, PhD
National Mexican Institute of Psychiatry
Mexico City, Mexico

Stefano Pallanti, MD, PhD
University of Florence
Florence, Italy

Katharine Phillips, MD
Brown Medical School
Providence, RI

Harold A. Pincus, MD
Western Psychiatric Institute & Clinic
RAND-University of Pittsburgh Health Institute,
Pittsburgh, PA

Scott L. Rauch, MD
Massachusetts General Hospital
Charlestown, MA

Alan F. Schatzberg, MD
Stanford University School of Medicine
Stanford, CA

Thomas E. Schlaepfer, MD
University of Bonn
Bonn, Germany

Stephen M. Stahl, MD, PhD
University of California, San Diego
La Jolla, CA

Norman Sussman, MD
New York University Medical School
New York, NY

Karen Dineen Wagner, MD, PhD
The University of Texas Medical Branch
Galveston, Texas

Herman G.M. Westenberg, MD
University Hospital Utrecht
Utrecht, The Netherlands

Stuart C. Yudofsky, MD
Baylor College of Medicine
Houston, TX

ACQUISITIONS EDITOR

Virginia Jackson

ASSOCIATE EDITOR—ENDURING MATERIALS

Shelley Wong

ASSOCIATE EDITORS

Peter Cook
Dena Croog

PUBLISHING SALES ASSOCIATE

Kimberly Schneider

MEDIA SALES REPRESENTATIVE

Jodi Malcom

ASSISTANT EDITOR

Rebecca Sussman

INTERNS

Rebecca Nison
Carlos Perkins, Jr.
Stephanie Spano

ART DIRECTOR

Derek Oscarson

GRAPHIC DESIGNER

Michael J. Vodilko

CHIEF FINANCIAL OFFICER

John Spano

OFFICE MANAGER

Manuel Pavón

INFORMATION TECHNOLOGY

Clint Bagwell Consulting

CORPORATION COUNSEL

Lawrence Ross, Esq.
Bressler, Amery, and Ross



Publishers of

PRIMARY PSYCHIATRY
The Leading Voice of Clinical Psychiatric Medicine

CNS SPECTRUMS
The International Journal of Neuropsychiatric Medicine

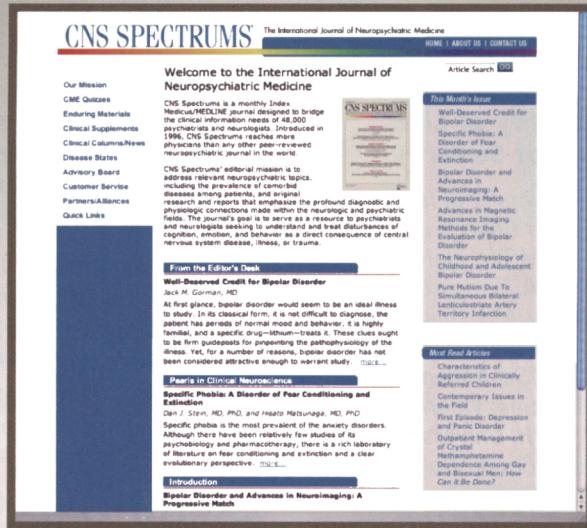
Psychiatry Weekly
The Leading News Service from Primary Psychiatry® and Physician's Weekly®

CNS Spectrums' 2005 ISI Impact Factor Ranking: 2.037

FACELIFT COMPLETE!

Welcome to CNS Spectrums' New Web Portal...

www.cnsspectrums.com



After a six-month top-to-bottom redesign, *CNS Spectrums'* new Web portal is now better than ever — a one-stop source providing the following integrated services based on input from you... *our readers:*

- **Must Read Articles** automatically tabulated
- **Quick Links** to Clinical Review Articles, Columns, News, & Educational Reviews
- **Key Word or Disease State-based Article Search**
- **Integrated Customer Service Tools**
- **eLearning** via Enduring Materials & Monthly CME Section
- And a host of additional services and features... including simple hyper-link access to MBL's other CNS sources: **www.primarypsychiatry.com** and **www.psychiatryweekly.com**

To learn more, please visit: www.cnsspectrums.com or www.mblcommunications.com

PRIMARY PSYCHIATRY
The Leading Voice of Clinical Psychiatric Medicine

CNS SPECTRUMS
The International Journal of Neuropsychiatric Medicine

Psychiatry Weekly
The Leading News Service From Primary Psychiatry® and Physician's Weekly®

A Global Commitment to Advancing CNS Science, Clinical Practice, and Evidence-Based Medicine

EDITOR'S LETTER**654 A New Academic Year at CNS Spectrums**

Eric Hollander, MD, Mount Sinai School of Medicine

ORIGINAL RESEARCH**680 Borderline Personality Disorder and Traits in Veterans: Psychiatric Comorbidity, Healthcare Utilization, and Quality of Life Along a Continuum of Severity**

Donald W. Black, MD, University of Iowa Roy J. and Lucille A. Carver College of Medicine; Nancee Blum, MSW, University of Iowa Roy J. and Lucille A. Carver College of Medicine; Elena Letuchy, MS, University of Iowa College of Public Health; Caroline Carney Doebeeling, MD, MSc, Indiana University School of Medicine; Valerie L. Forman-Hoffman, PhD, MPH, University of Iowa Roy J. and Lucille A. Carver College of Medicine; and Bradley N. Doebeeling, MD, MSc, Indiana University School of Medicine

691 The Efficacy and Safety of Lower Doses of Aripiprazole for the Treatment of Patients with Acute Exacerbation of Schizophrenia

Andrew J. Cutler, MD, CORE Research, Inc.; Ronald N. Marcus, MD, Bristol-Myers Squibb Company; Sterling A. Hardy, MS, Bristol-Myers Squibb Company; Amy O'Donnell, MD, Bristol-Myers Squibb Company; William H. Carson, MD, Otsuka America Pharmaceutical, Inc.; and Robert D. McQuade, PhD, Otsuka America Pharmaceutical, Inc.

704 Healthcare Resource Utilization in Bipolar Depression Compared with Unipolar Depression: Results of a United States Population-Based Study

Mark A. Frye, MD, David Geffen School of Medicine at the University of California, Los Angeles; Joseph R. Calabrese, MD, Case Western Reserve University; Michael L. Reed, PhD, Vedanta Research; and Robert M.A. Hirschfeld, MD, University of Texas Medical Branch

711 Adjunctive Treatment for Mood Stabilization of Patients with Bipolar I Disorder Treated with Lamotrigine

Theodore Spaulding, PhD, GlaxoSmithKline; Ronald Westlund, MS, GlaxoSmithKline; Christine Thomason, PhD, i3 Research; Robin White, MS, GlaxoSmithKline; Rebekkah Dann, GlaxoSmithKline; and Thomas Thompson, MD, GlaxoSmithKline

REVIEW ARTICLE**674 Presidential Stroke: United States Presidents and Cerebrovascular Disease**

Jeffrey M. Jones, MD, FAAN, Neurology of Battle Creek; and Joni L. Jones, PhD, RN, Western Michigan University

CASE REPORT**669 Anorexia Nervosa and Brain Tumor in a 14-Year-Old Girl**

Mae S. Sokol, MD, Creighton University School of Medicine; Chrystie K. Fujimoto, BS, Creighton University School of Medicine; Tammy K. Jackson, MA, Children's Hospital; and Phillip J. Silberberg, MD, Creighton University School of Medicine

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.

KNOW THE FACTS



13% of patients had diabetes in the landmark CATIE schizophrenia study at baseline—4 times more common than in the general population.¹

Be aware.
Screen and monitor your patients.
Make a difference.



Reference: 1. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res.* 2005;80:45-53.

CLINICAL UPDATES IN NEUROPSYCHIATRY**658 News From the Field of Neuroscience**

- **FDA Approves Aripiprazole Orally Disintegrating Tablets for the Treatment of Schizophrenia and Bipolar I Disorder**
- **Rivastigmine Patch Shows Potential as Alzheimer's Disease Treatment**
- **The Safety of Donepezil in Treating Vascular Dementia**
- **Leuprorelin Acetate Benefits Women with Mild to Moderate Alzheimer's Disease**
- **Emotional Signals Affect Decision-Making in Patients with History of Attempted Suicide**
- **Long-Term Use of Zolpidem ER May Benefit Patients with Chronic Insomnia**
- **R-Flurbiprofen Demonstrates Impressive Results in Alzheimer's Disease**
- **Failure of Early Treatment Response and Symptom Worsening May Predict Treatment Discontinuation**
- **Impaired Lung Function Boosts Dementia Risk**

Founded in 1996, CNS Spectrums is indexed in the Index Medicus database and is available on MEDLINE under the citation CNS Spectr. CNS Spectrums is also distributed to all CINP members and is accredited for international CME by EACIC.

CNS Spectrums (ISSN 1092-8529) is published monthly by MBL Communications, Inc. 333 Hudson Street, 7th Floor, New York, NY 10013.

One-year subscription rates: domestic \$120; foreign \$195; in-training \$85. For subscriptions: Tel: 212-328-0800; Fax: 212-328-0600; Web: www.cnsspectrums.com. Single issues: \$15 – E-mail ks@mblcommunications.com

For editorial inquiries, please fax us at 212-328-0600 or E-mail José R. Ralat at jrr@mblcommunications.com. For bulk reprint purchases, please contact Christopher Naccari at cdn@mblcommunications.com.

Subscribers: send address changes to CNS Spectrums c/o MMS, Inc., 185 Hansen Court, Suite 110, Wood Dale, IL 60191-1150.

This month's issue of CNS Spectrums, as well as a host of educational resources, enduring materials, and archived issues, is available at www.cnsspectrums.com.

CME-ACCREDITED MONOGRAPH SUPPLEMENT**Are We Treating Schizophrenia Effectively? Understanding the Primary Outcomes of the CATIE Study**

William M. Glazer, MD, Robert R. Conley, MD, and Leslie Citrome, MD, MPH

CME QUIZ**719 The quiz is CME-accredited by Mount Sinai School of Medicine for 3.0 credit hours.**

Opinions and views expressed by authors are their own and do not necessarily reflect the views of the publisher, MBL Communications, Inc., CNS Spectrums, LLC, or the editorial advisory board.

Advertisements in CNS Spectrums are accepted on the basis of adherence to ethical medical standards, but acceptance does not imply endorsement by CNS Spectrums or the publisher.

CNS Spectrums is a registered trademark of CNS Spectrums, LLC, New York, NY. Permission to reproduce articles in whole or part must be obtained in writing from the publisher.



BPA member since July 2005.

Copyright © 2006 by MBL Communications, Inc. All rights reserved.
Printed in the United States.