Volume 41
Number 17
September 1, 2006

Newspaper of the
American
Psychiatric
Association

PSYCHIATRIC NEWS

inside

Psychiatrists Glean Unexpected Lessons From 9/11 Disaster

Emerging from the recollections of psychiatrists is not the memory of shock, fear, and immobilization, but resilience. Trauma did not trump people's willingness and ability to do the right thing.

BY MARK MORAN

Five years ago on the morning of Tuesday, September 11, child psychiatrist Clarice Kestenbaum, M.D., was at her home on the upper west side of Manhattan when she heard the news of the attacks on the World Trade Center.

Later that day, and for many hours, Kestenbaum was at the studio of a local network affiliate counseling millions of New Yorkers—and the newscasters and staff at the broadcast station—on how to deal with the shock of an event no one could have imagined or prepared for.

"I was on the air for hours, and what was memorable was that everyone in the studio itself was very worried," she recalled. "The newscasters and staff at the station themselves wanted to know how to talk to their children about what had happened. I sat at the table and talked to them and to the people who called in, and it was like doing a live on-air consultation."

Kestenbaum is a professor of clinical psychiatry and has been the director of training in the division of child and adolescent psychiatry at Columbia University College of Physicians and Surgeons for 20 years.

Like psychiatrists throughout the city and in many other parts of the country, Kestenbaum treated and counseled people for the aftereffects of the most deadly terrorist attacks on American soil: the New York Council of the American Academy of Child and Adolescent Psychiatry (of which Kestenbaum had been president) agreed to offer free or low-cost therapy to children and parents affected by the attacks in the days after 9/11.

But what emerges from her recollections, and from those of other clinicians who spoke to *Psychiatric News*, is not the memory of shock, fear, and immobilization, but resilience. "Trauma"—heralded and in some ways perpetuated by the media in its continual replay of the colliding planes—evidently did not trump people's willingness and ability to do the next right thing: volunteers showed up everywhere, work teams formed, and every hospital in New York mobilized to meet the calamity head on.

"People are very resilient, and children are much more resilient than is typically thought," she said. "When you are in the middle of something like that, you just do what you have to do. People use their own resources and carry on."

The shock waves and aftereffects of 9/11 are still being felt by psychiatrists in the city.

"September 11 wasn't an event; it was a process that is still going on," said Spencer Eth, M.D., medical director of behavioral health services at St. Vincent Catholic Medical Center, located just blocks from ground zero.

As the closest hospital to the World Trade Center, St. Vincent's became a hub of activity following the attack. In the weeks and months afterward, the hospital developed a number of programs, some of which are still in place, to meet the needs of community members and rescue and recovery workers.

In October 2005 the Child and Adolescent Services Program of the World Trade Center Healing Services at St. Vincent's received an APA Silver Achieve-

please see ***Lessons*** *on page 19*

AP Photo/Ed Bailey

Patrick Anderson of Michigan points at a picture of the World Trade Center to indicate his location when the towers collapsed on September 11, 2001. He returned to the site in 2004 to honor three firefighters who had saved his life.

Number, Complexity of Services Blamed for Medicare Fee Cuts

CMS says Medicare expenditures for physician services have increased 10 percent over 2004.

BY MARK MORAN

Overall physician payment under the Medicare program will drop by 5.1 percent, according to a proposed rule released by the federal Centers for Medicare and Medicaid Services (CMS) last month.

At the same time, payment for certain services—specifically, evaluation and management services—will be substantially increased, a change that could benefit psychiatrists who use these "E&M" codes for coordinating care of patients.

APA's Office of Healthcare Systems and Financing is studying the changes to the formula for paying for evaluation and management to determine their impact on psychiatrists. Updates will appear in future issues of *Psychiatric News*.

In a statement announcing the new fee schedule, CMS said it will pay roughly $61.5 billion to 875,000 physicians next year. The physician fee schedule specifies payment for thousands of health care procedures and services, ranging from simple office visits to complex surgery.

CMS is required to adjust the fee schedule up or down depending on how actual expenditures of the last completed fiscal year compare with a target rate, known as the sustainable growth rate (SGR). The SGR is based on medical inflation, projected growth in the domestic economy, projected growth in the number of beneficiaries in the Medicare fee-for-service program, and changes in law or regulation.

please see ***Fee Cuts*** *on page 36*

Contents

Features

Volume 41
Number 17
September 1, 2006

Departments

Newspaper of the American Psychiatric Association
PSYCHIATRIC NEWS

An Equal Opportunity Employer
Print version: ISSN 0033-2704; printed in U.S.
Online version: ISSN 1559-1255

Published on the first and third Fridays of each month. Periodicals postage paid at Arlington, VA., and additional offices. Postmaster: send address changes to Psychiatric News, American Psychiatric Association, Suite 1825, 1000 Wilson Boulevard, Arlington, Va. 22209-3901.

Subscriptions
U.S.: individual, $82; student, $29.
International: APA members, $82; nonmembers, $148; student, $52. Single issues: U.S., $17; Canada and international, $27. Institutional subscriptions are tier priced. For site licensing and pricing information, call (800) 368-5777, or e-mail appi@psych.org.

Officers of the Association
Pedro Ruiz, M.D., *President*
Carolyn Robinowitz, M.D., *President-elect*
Nada L. Stotland, M.D., M.P.H., *Vice President*
Donna Norris, M.D., *Secretary-Treasurer*
Michael Blumenfield, M.D., *Speaker of the Assembly*
James H. Scully Jr., *Medical Director*

Staff of Psychiatric News
James P. Krajeski, M.D., *Editor in Chief*
Catherine F. Brown, *Executive Editor*
Ken Hausman, *Associate Editor*
Joan Arehart-Treichel, Jim Rosack, Aaron Levin, *Senior Staff Writers*
Eve Bender, Mark Moran, Rich Daly, *Staff Writers*
B. Alma Herndon, *Production Manager*
David Dildine, *Senior Graphic Designer*
Lynne Lamberg, David Milne, *Contributors*
Nancy Frey, *Director, Publishing Services*
Laura Abedi, *Associate Director*
Bob Pursell, *Director of Sales and Marketing*
Roger Domras, *Director of Circulation*

Editorial Advisory Board
Al Herzog, M.D. (chair), Francisco Fernandez, M.D., Geetha Jayaram, M.D., Nalini Juthani, M.D., Mary Kay Smith, M.D., William Womack, M.D., Mary Nowesnick, and Dick Walt

Editor-in-Chief Emeritus
Robert J. Campbell III, M.D., New York, N.Y.

Editorial Offices
Telephone: (703) 907-8570; fax: (703) 907-1094
E-mail: PNews@psych.org
Web site: pn.psychiatryonline.org

Advertising Sales
Pharmaceutical Advertising: Raymond J. Purkis, Director, APA, 2444 Morris Avenue, Union, N.J. 07083; (908) 964-3100
Nonpharmaceutical Advertising: Brian Skepton, APA, Suite 1825, 1000 Wilson Boulevard, Arlington, Va. 22209-3901; (888) 35-PSYCH
Classified Advertising: Joel Nepomuceno, APA, Suite 1825, 1000 Wilson Boulevard, Arlington, Va. 22209-3901; (888) 35-PSYCH

Changes of Address
Call the APA Answer Center at (888) 35-PSYCH in the U.S. and Canada; in other countries: (703) 907-7300.

New Data Add to Puzzle About Antidepressant, Youth-Suicide Link

With new research pointing to a link between antidepressants and suicidal actions in youth, clinicians struggle to find significance in the findings.

BY JIM ROSACK

A new report suggests that child and adolescent Medicaid patients who have been treated for major depression in an inpatient setting and are prescribed antidepressants may be at a significantly increased risk of a serious suicide attempt or death in the 60 days following discharge, compared with similar patients who are not prescribed antidepressant medications.

The relevance of the study is, however, open to interpretation in part due to limitations of the study design, which did not rule out the possibility that those taking antidepressant medication were more severely ill than those not receiving medication.

"These findings," said the report's lead author, Mark Olfson, M.D., M.P.H., a professor of psychiatry at Columbia University College of Physicians and Surgeons and a researcher at the New York State Psychiatric Institute, "serve to reinforce some of the concerns that have been raised [regarding an association between antidepressants and suicidality] and really emphasize the importance of paying close attention to changes in mood and actions of severely depressed young people as they start antidepressant medication."

For several years now, researchers have been striving to answer the question of whether the possible association between antidepressant medications and increased risk of suicidality in children and adolescents extends beyond less-severe expressions of suicidal thoughts or behaviors to serious suicide attempts requiring medical intervention—or ultimately to suicide deaths.

Numerous reports have postulated that the expression of suicidal thoughts and/or behaviors—such as those now addressed by the labeling mandated by the Food and Drug Administration (FDA) accompanying all antidepressant prescriptions—is a different phenomenon than serious suicide attempt and completed suicide. Yet, it is still not clear whether the reported association of the medications with FDA-defined suicidality crosses the hypothesized divide between the two phenomena.

National Case-Control Sample

The study, which appeared in the August *Archives of General Psychiatry*, analyzed data from the Centers for Medicare and Medicaid Services' (CMS) national Medicaid Analytic Extract Files (MAEF). The MAEF includes comprehensive claims data for Medicaid beneficiaries in all 50 states.

The work was funded by grants from the National Alliance for Research on Schizophrenia and Depression, the Agency for Healthcare Research and Quality, and a private foundation, the Carmel Hill Fund.

"This was a case-control study of children and adults in Medicaid in which we completed four different analyses. We looked at two outcomes each, in both adults and kids, using the same criteria for both groups," Olfson told *Psychiatric News*.

Using the Medicaid claims data, Olfson and his colleagues started with a study population of all patients aged 6 to 64 who had one or more hospitalizations for the treatment of a depressive disorder between January 1, 1999, and December 31, 2000. They then narrowed the sample by excluding patients who were pregnant, had bipolar disorder, schizophrenia, other psychoses, mental retardation, or dementia/delirium. Finally, they refined the cohort further to those beneficiaries who filled at least one prescription for any medication during the two-year study period.

Suicide Attempts Defined

Cases were defined by a diagnostic claim for a suicide attempt that occurred within 60 days following discharge from a hospital for the treatment of major depression. The suicide attempt was further defined as a self-inflicted injury or intentional overdose of medication serious enough to result in treatment in either an emergency department or inpatient setting.

A total of 784 cases with suicide attempts were then matched to 3,635 controls. Each case was matched to up to five control sub-

please see ***Youth Suicide*** *on page 36*

Do You Prefer To Vote Online?

If so, here's one way you can reduce your snail-mail load. APA voting members may now opt to receive an online ballot instead of the traditional paper ballot for voting in APA elections. Those who choose the online ballot option by November 6 will be sent an e-mail on December 22 with their ballot control number and online voting instructions for the 2007 election. Those who do not choose the online ballot option will continue to be sent a paper ballot, and those with an e-mail address will receive the December 22 e-mail. Both groups still have the option to vote online.

To select the online ballot option, go to the homepage of APA's Web site at <www.psych.org> and click on "APA Election Online Ballot Preference" in the Spotlight section.

APA RESOURCES

- **APA and the APA Answer Center:** (888) 35-PSYCH in the U.S. and Canada; in other countries: (703) 907-3700. The Answer Center is open Monday through Friday, 8:30 a.m. to 6 p.m. Eastern time. All APA departments and staff may be reached through the Answer Center.
  Fax: (703) 907-1085
  E-Mail: apa@psych.org
- **APA Web Site:** www.psych.org
- **APA Job Bank:** www.psych.org/jobbank
- **Managed Care Help Line:** (800) 343-4671
- **Member2Member List Serve (M2M):** www.psych.org/apa_members/list serves.cfm
- **American Psychiatric Publishing Inc.**
  Phone Order Line: (800) 368-5777
  Fax: (703) 907-1091
  Web Site: www.appi.org
- **APA Member Update:** To subscribe, send an e-mail to update@psych.org.
- **APA Advocacy News:** To subscribe, send an e-mail to advocacy@psych.org.
- **American Psychiatric Foundation**
  Phone: (703) 907-8512
  Web Site: www.PsychFoundation.org

Join AMA and Increase The Power of Your Voice

BY PEDRO RUIZ, M.D.

Many of our colleagues ask why should they belong to the AMA? Why is it worth joining a second organization when APA already does so much to further the interests of psychiatrists?

The answer resides in simple democracy. A single voice is more powerful when echoed. Like APA, the AMA has respect and clout on Capitol Hill. APA has the Assembly to bring forth members' issues. The AMA has a House of Delegates (HOD). Delegates from many specialty societies, including APA, and 50 states across the nation participate in the AMA's HOD.

Each specialty has a unique voice within the HOD. Once AMA policy is adopted by the HOD, the AMA becomes an advocate on that issue. For psychiatry, the AMA has been a strong advocate for nondiscriminatory health insurance and has partnered with APA and others in coalitions working to achieve insurance "parity." In addition, the AMA has organized the scope-of-practice partnership to oppose nonphysician scope-of-practice initiatives in legislatures throughout the country.

APA has gained strength and presence in the HOD through the combined forces of several groups of psychiatrists.

APA's Section Council on Psychiatry, chaired by John McIntyre, M.D., APA's senior AMA delegate, and with David Fassler, M.D., serving as vice chair, creates an impressive presence. The section council comprises psychiatrists from APA's 14-member delegation, Young Physician Section (YPS), and Resident-Fellow Section (RFS). Other members of the Section Council are representatives from the Academy of Child and Adolescent Psychiatry (AACAP) and the American Academy of Psychiatry and the Law (AAPL).

Current members of APA's delegation are Drs. Jeffrey Akaka, Don Brada, Kenneth Certa, Joseph English, Patrice Harris, Saul Levin, John McIntyre, Rodrigo Muñoz, Constance Powell, Carolyn Robinowitz, Nada Stotland, John Wernert III, and Paul Wick.

Members of APA's YPS are Drs. Karen Gennaro and Jerry Halverson. APA's RFS members are Daniel Chrzanowski and Nakia Scott. AACAP's delegation is composed of Drs. David Fassler, Louis Kraus, Jeremy Veenstra-Vander Weele (RFS), Tanya Anderson (YPS), and Shiraz Butt (YPS). AAPL delegates are Drs. Robert Phillips and Howard Zonana.

Some APA delegates have dual roles as chairs or members of various AMA councils or components that develop policy, conduct studies, and advise the AMA on actions to benefit physicians and patients. For example, APA President-elect and AMA delegate Dr. Carolyn Robinowitz is on the Council on Science and Public Health, Dr. Saul Levin is on the Council on Long-Range Planning and Development, Dr. Patrice Harris is on the Council on Legislation, and Dr. Joseph English is the AMA commissioner to the Joint Commission on Accreditation of Healthcare Organizations.

APA members who are not part of APA's delegation also serve the HOD. These members include Dr. Jeremy Lazarus, vice speaker of the HOD; Dr. Jo-Ellen Ryall, immediate past chair of the Council on Constitution and Bylaws; Dr. Priscilla Ray, immediate past chair of the Council on Ethical and Judicial Affairs; and Dr. Dudley Stewart Jr., a member of the Council on Ethical and Judicial Affairs. Altogether, there are approximately 60 psychiatrists in the HOD.

Our delegation comes from a wide variety of states and is diverse. Working as a team on the Section Council on Psychiatry, our delegates can accomplish a great deal. For example, the section council members worked with the AMA's Council on Ethical and Judicial Affairs and Section Council on Federal and Military Medicine to help shape a final report on the issue of physicians' participation in the interrogation of detainees. As APA president, I was very impressed to see this teamwork, which resulted in a mutually acceptable report that was ultimately adopted by the house.

Your delegation, in coordination with AACAP and AAPL, regularly submits resolutions and cosponsors others on a wide range of topics relevant to psychiatrists and their patients. Recent examples are Medicare Part D drug access, buprenorphine scheduling, treatment of eating disorders, and the use of SSRIs during pregnancy.

APA members' participation in AMA advocacy, especially in the HOD, clearly sends the message to hundreds of other physicians that psychiatric issues are relevant and important to everyone. APA's agendas intersect largely with the AMA's, including access to Medicare benefits, electronic health records, reimbursement, scope of practice, and health insurance coverage.

I found my experience as an alternate delegate to the HOD extremely rewarding. Other prominent APA members, too, have found AMA advocacy to be educational.

I also want to recognize the excellent staff support provided to our delegation and the section council by our medical director, Dr. Jay Scully; our advocacy director, Gene Cassel; and staff members Lisa Fields, Angela Foehl, Jessica Mikulski, and Becky Yowell. I also want to thank *Psychiatric News* for providing consistently thorough coverage of the AMA's HOD meetings.

I am confident that psychiatry's efforts with the AMA are positive and help link our specialty even closer with all other branches of medicine. APA will continue lobbying efforts with the AMA on a host of issues.

You have the opportunity to make a difference by joining the AMA and adding your voice to our important mutual advocacy endeavors. ■

APPI: Where Psychiatry's Past, Present, and Future Meet

BY JAMES H. SCULLY JR., M.D.

As you know, APA's publishing arm, American Psychiatric Publishing Inc. (APPI), is at the leading edge of our profession, publishing ground-breaking and clinically useful psychiatric research. But APPI is a treasure trove of history as well. Recently, APPI offered a wonderful gift to history lovers: the Psychiatry Legacy Collection, which makes over a century and a half of psychiatric research and clinical information easily accessible online. The project includes a collection of 162 years' worth of the *American Journal of Psychiatry*, which from 1844 to 1921 was published as the *American Journal of Insanity*.

This rich collection can be accessed at <www.journals.psychiatryonline.org/>, psychiatry's equivalent of the great Library of Alexandria. By virtue of being online, our collection is widely available around the clock and around the world. APPI CEO Ron McMillen and his team have done a terrific job at putting this resource—some 20,000 articles—at our fingertips.

In addition, the collection includes five other peer-reviewed journals from APA and APPI: *Academic Psychiatry*, *Journal of Neuropsychiatry and Clinical Neurosciences*, *Journal of Psychotherapy Practice and Research*, *Psychiatric Services*, and *Psychosomatics*.For the most part, the journals in the collection go back to their first issue.

Most APA members and subscribers have free access to the collection once they have activated the online portion of their subscription.

James H. Scully Jr., M.D., is medical director and CEO of APA.

Other Publishing News

The APA annual meeting adds life and depth to our field: research papers are presented by investigators, journal readers are there to engage and ask questions, the APPI bookstore moves beyond its usual online realm—you can pick up and peruse the latest titles and meet some of the authors. APPI always draws a big crowd to "publishers row" in the exhibit hall.

You might be interested to know that the five best-selling books sold at APA's 2006 annual meeting in Toronto were these:

- *Quick Reference to the American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric Disorders*
- *Learning Cognitive-Behavior Therapy: An Illustrated Guide*, by Jesse H. Wright, M.D., Ph.D., Monica R. Basco, Ph.D., and Michael E. Thase, M.D., with Glen O. Gabbard, M.D., as series editor
- *Bipolar Depression: A Comprehensive Guide*, edited by Rif S. El-Mallakh, M.D., and S. Nassir Ghaemi, M.D.
- *Essentials of Clinical Psychopharmacology*, edited by Alan F. Schatzberg, M.D., and Charles B. Nemeroff, M.D., Ph.D.
- *The American Psychiatric Publishing Textbook of Schizophrenia*, edited by Jeffrey A. Lieberman, M.D., and T. Scott Stroup, M.D.

These are superb books, each contributing substantially to our knowledge base and practice. You can explore these and other offerings at <www.appi.org/>.

Also on the Web is PsychiatryOnline—the portal from APPI that unifies access to journals, *DSM-IV-TR*, and other key texts. Despite its newness, it has more than 1,000 subscribers, including more than 700 APA members. Are you one of them? This is a great and growing resource that now has a new feature—"Book of the Month," which provides free electronic access (via PDF) to a new APPI book each month.

I hope you enjoy the many ways that APPI brings knowledge to us all. ■

Roeske Winners Announced

APA's Committee on Medical Student Education has announced the recipients of the 13th Annual Nancy C.A. Roeske, M.D., Certificate of Recognition for Excellence in Medical Student Education.

This certificate is awarded to APA members who have made outstanding and sustaining contributions to medical education, in both salaried and volunteer positions. Qualified nominees must have made significant contributions to the advancement of medical student education, including lectures, small-group teaching, supervision, and course design.

Voluntary

Kathleen S. Banks, M.D., University of Texas Southwestern Medical School
Harpriya A. Bhagar, M.B.B.S., Indiana University School of Medicine
Tal Burt, M.D., Columbia University
Kelly L. Cozza, M.D., Uniformed Services University of the Health Sciences
Timothy Florence, M.D., University of Michigan
Robert Grossman, M.D., Mount Sinai School of Medicine
Kimberly Ann Johnson, M.D., East Carolina University School of Medicine
Dennis Kozel, M.D., Medical College of Wisconsin
Elliott E. Levy, M.D., Medical University of South Carolina
Louis Micheels, M.D., Yale University School of Medicine
James Morrison, M.D., Oregon Health and Science University
Gerald P. Perman, M.D., George Washington University
Luther D. Robinson, M.D., Howard University College of Medicine
Lee Stevens, M.D., Louisiana State University Health Sciences Center-Shreveport
Judith Wolfberg, M.D., Tufts University School of Medicine

Salaried

Subhash C. Bhatia, M.D., Creighton University
James G. Bouknight, M.D., Ph.D., University of South Carolina School of Medicine
Eric J. Brewer, M.D., University of Rochester Medical Center
Mark Broadhead, M.D., University of Nevada
E. Cabrina Campbell, M.D., University of Pennsylvania
Daniel Carl Dahl, M.D., University of Alabama School of Medicine
Jay D. Draoua, M.D., New York Medical College
Marian Fireman, M.D., Oregon Health and Science University
Juliana Fort, M.D., Louisiana State University Health Sciences Center-Shreveport
Maria Fernanda Gomez, M.D., Albert Einstein College of Medicine
Mary Jo Hanigan, M.D., University of Nebraska Medical Center
Karen Hochman, M.D., Emory University School of Medicine
Susan M. Maixner, M.D., University of Michigan
Andrés Martin, M.D., M.P.H., Yale University School of Medicine
Gabrielle Rose Marzani-Nissen, M.D., University of Virginia School of Medicine
Scot G. McAfee, M.D., New York Medical College
Stephen A. McLeod-Bryant, M.D., Medical University of South Carolina
Erik B. Nelson, M.D., University of Cincinnati College of Medicine
Thomas Newmark, M.D., Robert Wood Johnson Medical School
Guy K. Palmes, M.D., Wake Forst University
Richard Renka, M.D., University of South Dakota
Helen Schleimer, M.D., Columbia University College of Physicians and Surgeons
Steven C. Schlozman, M.D., Harvard Medical School
Robert Schweitzer, M.D., Indiana University School of Medicine
Darin D. Signorelli, M.D., University of Southern California
Daphne Simeon, M.D., Mt. Sinai School of Medicine
Kathleen Stanley, M.D., Texas Tech University (Lubbock)
John A. Talbott, M.D., University of Maryland School of Medicine
Hendry Ton, M.D., M.S., University of California, Davis
Carol Tsao, M.D., Medical College of Wisconsin
Meenakshi Vemuri, M.D., University of Massachusetts Medical School
Jeffrey Wahl, M.D., Medical University of Ohio
Christopher Wallace, M.D., University of Texas Health Science Center, San Antonio
G. Scott Waterman, M.D., University of Vermont
Henry Weissman, M.D., Temple University
Christina Weston, M.D., Wright State University School of Medicine

More information about the Roeske award is posted at <www.psych.org/edu/nrc-cofemse.cfm>. ■

Rich Daly

Senator Honored for MH Efforts

Nicholas Meyers, director of APA's Department of Government Relations (left), and APA Medical Director **James H. Scully Jr., M.D.** (right) present **Sen. Gordon Smith** (R-Ore.) with APA's Jacob K. Javits Public Service Award in his Capitol Hill office on July 27.

The annual award from APA's Committee on Government Relations is the Association's highest recognition of a public official who has made a significant contribution to improving the lot of those who are mentally ill.

Smith was recognized for his efforts as chair of the Special Committee on Aging, where he has held hearings on the new Medicare Part D drug benefit in which he focused on ensuring that people with mental illness would have continued access to their medications.

In the last Congress, Smith led efforts to pass legislation, the Garret Lee Smith Act, to establish a new youth suicide prevention and early intervention initiative. The initiative provides over $31 million in grants that support screening, assessment, and early intervention programs in school systems, institutions of higher learning, juvenile justice systems, foster care programs, and youth support organizations. The legislation was named after Smith's son, who was diagnosed with bipolar disorder and eventually committed suicide.

APA established the Javits award in 1986 to honor the legacy of a U.S. senator from New York who achieved multiple successes on behalf of the mentally ill and on substance abuse issues. Past recipients include New York Attorney General Eliot Spitzer (D), Sen. Pete Domenici (R-N.M.), and Sen. Paul Wellstone (D-Minn.).

Unique Delivery.

*Introducing the **first** antidepressant patch*

***EMSAM**® is the first and only transdermal monoamine oxidase inhibitor (MAOI)** for treating depressive symptoms in patients with major depressive disorder (MDD).*

EMSAM® 6 mg/24 hr
(selegiline transdermal system)

Unique Delivery. Proven Results.

Please see IMPORTANT SAFETY INFORMATION, including **Boxed WARNING**, on next page.

IMPORTANT SAFETY INFORMATION

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at time of dose changes, either increases or decreases. Families and caregivers should be advised for the need for close observation and communication with the prescriber. EMSAM is not approved for use in pediatric patients (see Boxed WARNING)**

  Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking and behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials

- **To reduce the risk of hypertensive crisis, which is potentially life-threatening, foods and beverages high in tyramine must be avoided while on EMSAM 9 mg/24 hr or 12 mg/24 hr, and for 2 weeks following discontinuation of EMSAM at these doses or reducing the dose to EMSAM 6 mg/24 hr**
- Due to the potential for **serotonin syndrome**, which is potentially life-threatening, EMSAM should not be used with the following antidepressants: selective serotonin reuptake inhibitors (SSRIs), dual serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), mirtazapine, and bupropion; meperidine and analgesics such as: tramadol, methadone, propoxyphene, and pentazocine; the antitussive dextromethorphan; cyclobenzaprine; oral selegiline; and St. John's wort
- After stopping treatment with SSRIs, SNRIs, TCAs, MAOIs, mirtazapine, bupropion; meperidine and analgesics such as: tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; and buspirone, approximately 1 week (5 weeks for fluoxetine) should elapse before starting therapy with EMSAM. At least 2 weeks should elapse after stopping EMSAM before starting therapy with buspirone or a drug that is contraindicated with EMSAM
- **Carbamazepine** and **oxcarbazepine** are contraindicated in patients taking MAO inhibitors, including EMSAM
- The use of EMSAM is contraindicated for use with **sympathomimetic amines**, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (eg, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine)
- Patients taking EMSAM should not undergo **elective surgery requiring general anesthesia** or be given **local anesthesia** containing sympathomimetic vasoconstrictors
- EMSAM should not be used in the presence of **pheochromocytoma** since such tumors secrete pressor substances
- **Adults** with MDD or co-morbid depression in the setting of other psychiatric illness **being treated with antidepressants** should be observed for **clinical worsening and suicidality**, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases
- Risk of **bipolar disorder** should be ruled out prior to initiating antidepressant therapy. EMSAM is not approved for the treatment of bipolar depression
- Due to the potential for elevated blood pressure, the use of EMSAM with **buspirone** is not recommended
- As with other MAOIs, **postural hypotension** can occur with EMSAM therapy. Dose increases in the **elderly** should be made with caution and patients should be observed closely for postural changes in blood pressure throughout treatment
- EMSAM should be used with caution in patients with certain concomitant systemic illnesses that can produce **altered metabolism or hemodynamic responses**
- As with other psychoactive drugs, EMSAM may have the potential to **impair judgment, thinking, or motor skills**. Patients should not drive or operate hazardous machinery until they are certain EMSAM does not impair their ability to engage in such activities
- The use of **alcohol** is not recommended while taking EMSAM
- EMSAM should not be used in combination with **tyramine-containing nutritional supplements**
- EMSAM should be used in **pregnancy** only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised when administering EMSAM to a nursing mother
- EMSAM is contraindicated in patients with known **hypersensitivity** to selegiline or to any component of the transdermal system
- **Treatment-emergent adverse events** in short-term clinical trials that occurred at a ≥2% incidence with EMSAM and for which the incidence was greater than placebo include: application site reaction (24% vs 12%), headache (18% vs 17%), insomnia (12% vs 7%), diarrhea (9% vs 7%), dry mouth (8% vs 6%), dyspepsia (4% vs 3%), rash (4% vs 2%), pharyngitis (3% vs 2%), and sinusitis (3% vs 1%)

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including **Boxed WARNING,** on following pages.

Proven Results.

The first and only transdermal MAOI— no dietary modifications at the starting and target dose of 6 mg/24 hr

Significant relief— proven short-term efficacy with longer time to relapse

Demonstrated tolerability— reported sexual dysfunction similar to placebo; minimal weight change

INDICATION

EMSAM is indicated for the treatment of Major Depressive Disorder (MDD).

Dose-Dependent Dietary Modifications:

To reduce the risk of hypertensive crisis, which is potentially life-threatening, foods and beverages high in tyramine must be avoided while on EMSAM® 9 mg/24 hr and 12 mg/24 hr, and for 2 weeks following discontinuation of EMSAM at these doses, or reducing the dose to EMSAM 6 mg/24 hr.

- Estimates of the incidence of sexual dysfunction cited in product labeling may underestimate actual incidence

EMSAM® 6 mg/24 hr
(selegiline transdermal system)

Unique Delivery. Proven Results.

EM-K0006 05/06 Printed in USA

EMSAM® (SELEGILINE TRANSDERMAL SYSTEM) Rx only

CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

Brief Summary of Prescribing Information. For complete prescribing information please consult official package circular.

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of EMSAM or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised for the need for close observation and communication with the prescriber. EMSAM is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

INDICATIONS AND USAGE

EMSAM is indicated for the treatment of major depressive disorder.

The efficacy of **EMSAM** in the treatment of major depressive disorder was established in 6- and 8-week placebo-controlled trials of outpatients with diagnoses of DSM-IV category of major depressive disorder (see **Clinical Efficacy Trials** in Full Prescribing Information).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicide attempt or suicidal ideation.

The benefit of maintaining patients with major depressive disorder on therapy with **EMSAM** after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY** in Full Prescribing Information). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

The antidepressant action of **EMSAM** in hospitalized depressed patients has not been studied.

CONTRAINDICATIONS

EMSAM is contraindicated in patients with known hypersensitivity to selegiline or to any component of the transdermal system.

EMSAM is contraindicated with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, and paroxetine), dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline), bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; and cyclobenzaprine. **EMSAM** should not be used with oral selegiline or other MAO inhibitors (MAOIs e.g., isocarboxazid, phenelzine, and tranylcypromine) (see **WARNINGS**).

Carbamazepine and oxcarbazepine are contraindicated in patients taking selegiline (see **PRECAUTIONS, Drug Interactions**).

As with other MAOIs, **EMSAM** is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

As with other MAOIs, patients taking **EMSAM** should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. **EMSAM** should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

As with other MAOIs, **EMSAM** is contraindicated for use in patients with pheochromocytoma.

EMSAM is an irreversible MAO inhibitor. As a class, these compounds have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours.** (See **WARNINGS** and **PRECAUTIONS, Drug Interactions**, *Tyramine*.)

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for **EMSAM** (selegiline transdermal system) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with 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. It should be noted that **EMSAM** is not approved for use in treating bipolar depression.

Hypertensive Crisis

EMSAM is an irreversible MAO inhibitor. MAO is important in the catabolism of dietary amines (e.g., tyramine). In this regard, significant inhibition of intestinal MAO-A activity can impose a cardiovascular safety risk following the ingestion of tyramine-rich foods. As a class, MAOIs have been associated with hypertensive crises caused by the ingestion of foods with a high concentration of tyramine. Hypertensive crises, which in some cases may be fatal, are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Intracranial bleeding has been reported in association with the increase in blood pressure. Patients should be instructed as to the signs and symptoms of severe hypertension and advised to seek immediate medical attention if these signs or symptoms are present.

In 6 of the 7 clinical studies conducted with **EMSAM** at doses of 6 mg/24 hours–12 mg/24 hours, patients were not limited to a modified diet typically associated with this class of compounds. Although no hypertensive crises were reported as part of the safety assessment, the likelihood of developing this reaction cannot be fully determined since the amount of tyramine typically consumed during the course of treatment is not known and blood pressure was not continuously monitored.

To further define the likelihood of hypertensive crises with use of **EMSAM**, several Phase I tyramine challenge studies were conducted both with and without food (see **PRECAUTIONS, Drug Interactions**, *Tyramine*). In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours, and the results from the Phase I tyramine challenge study in fed volunteers administered **EMSAM** 12 mg/24 hours (see **PRECAUTIONS, Drug Interactions**, *Tyramine*), patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours**.

If a hypertensive crisis occurs, **EMSAM** should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Phentolamine 5 mg or labetalol 20 mg administered slowly intravenously is recommended therapy to control hypertension. Alternately, nitroprusside delivered by continuous intravenous infusion may be used. Fever should be managed by means of external cooling. Patients must be closely monitored until symptoms have stabilized.

Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours

The following foods and beverages should be avoided beginning on the first day of **EMSAM** 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for two weeks after a dose reduction to **EMSAM** 6 mg/24 hours or following the discontinuation of **EMSAM** 9 mg/24 hours or 12 mg/24 hours.

Food and beverages to avoid and those which are acceptable[1]:

Class of Food and Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods, Containing No or Little Tyramine
Meat, Poultry and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt
Beverages	All varieties of tap beer, and beers that have not been pasteurized so as to allow for ongoing fermentation	As with other antidepressants, concomitant use of alcohol with **EMSAM** is not recommended. (Bottled and canned beers and wines contain little or no tyramine.)
Miscellaneous	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu), OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain-restaurant pizzas prepared with cheeses low in tyramine

[1] Adapted from K. I. Shulman, S. E. Walker. *Psychiatric Annals.* 2001; 31:378-384.

Use With Other Drugs Affecting Monoamine Activity

Serious, sometimes fatal, central nervous system (CNS) toxicity referred to as the "serotonin syndrome" has been reported with the combination of non-selective MAOIs with certain other drugs, including tricyclic or selective serotonin reuptake inhibitor antidepressants, amphetamines, meperidine, or pentazocine. Serotonin syndrome is characterized by signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Similar less severe syndromes have been reported in a few patients receiving a combination of oral selegiline with one of these agents.

Therefore, **EMSAM** should not be used in combination with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranylcypromine), mirtazapine; bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan, or St. John's wort because of the risk of life-threatening adverse reactions. Also, **EMSAM** should not be used with sympathomimetic amines, including amphetamines as well as cold

products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine). (See **CONTRAINDICATIONS**.)

Concomitant use of **EMSAM** (selegiline transdermal system) with buspirone hydrochloride is not advised since several cases of elevated blood pressure have been reported in patients taking MAOIs who were then given buspirone HCl.

After stopping treatment with SSRIs; SNRIs; TCAs; MAOIs; meperidine and analgesics such as tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; mirtazapine; bupropion HCl; or buspirone HCl, a time period equal to 4-5 half-lives (approximately 1 week) of the drug or any active metabolite should elapse before starting therapy with **EMSAM**. Because of the long half-life of fluoxetine and its active metabolite, at least five weeks should elapse between discontinuation of fluoxetine and initiation of treatment with **EMSAM**. At least two weeks should elapse after stopping **EMSAM** before starting therapy with buspirone HCl or a drug that is contraindicated with **EMSAM**.

PRECAUTIONS

General

Hypotension

As with other MAOIs, postural hypotension, sometimes with orthostatic symptoms, can occur with **EMSAM** therapy. In short-term, placebo-controlled depression studies, the incidence of orthostatic hypotension (i.e., a decrease of 10 mmHg or greater in mean blood pressure when changing position from supine or sitting to standing) was 9.8% in **EMSAM**-treated patients and 6.7% in placebo-treated patients. It is recommended that elderly patients treated with **EMSAM** be closely observed for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with pre-existing orthostasis. Postural hypotension may be relieved by having the patient recline until the symptoms have abated. Patients should be cautioned to change positions gradually. Patients displaying orthostatic symptoms should have appropriate dosage adjustments as warranted.

Activation of Mania/Hypomania

During Phase III trials, a manic reaction occurred in 8/2036 (0.4%) patients treated with **EMSAM**. Activation of mania/hypomania can occur in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, **EMSAM** should be used cautiously in patients with a history of mania.

Use in Patients With Concomitant Illness

Clinical experience with **EMSAM** in patients with certain concomitant systemic illnesses is limited. Caution is advised when using **EMSAM** in patients with disorders or conditions that can produce altered metabolism or hemodynamic responses.

EMSAM has not been systematically evaluated in patients with a history of recent myocardial infarction or unstable heart disease. Such patients were generally excluded from clinical studies during the product's premarketing testing.

No ECG abnormalities attributable to **EMSAM** were observed in clinical trials.

Although studies of phenylpropanolamine and pseudoephedrine did not reveal pharmacokinetic drug interactions with **EMSAM**, it is prudent to avoid the concomitant use of sympathomimetic agents, such as some decongestants.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with **EMSAM** and should counsel them in its appropriate use. A patient **Medication Guide About Using Antidepressants in Children and Teenagers** is available for **EMSAM**. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking **EMSAM**.

Clinical Worsening and Suicide Risk

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment or when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly change in the medication.

General

Patients should be advised not to use oral selegiline while on **EMSAM** therapy.

Patients should be advised not to use carbamazepine or oxcarbazepine while on **EMSAM** therapy.

Patients should be advised not to use meperidine and analgesic agents such as tramadol, methadone, and propoxyphene.

Patients should be advised not to use sympathomimetic agents while on **EMSAM** therapy.

Patients should be advised not to use selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine, and St. John's wort), dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline), mirtazapine, oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranylcypromine), bupropion hydrochloride or buspirone hydrochloride while on **EMSAM** therapy.

EMSAM has not been shown to impair psychomotor performance; however, any psychoactive drug may potentially impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that **EMSAM** therapy does not impair their ability to engage in such activities.

Patients should be told that, although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol, the concomitant use of **EMSAM** and alcohol in depressed patients is not recommended.

Patients should be advised to notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbals, because of the potential for drug interactions. Patients should also be advised to avoid tyramine-containing nutritional supplements and any cough medicine containing dextromethorphan.

Patients should be advised to use **EMSAM** exactly as prescribed. The need for dietary modifications at higher doses should be explained, and a brief description of hypertensive crisis provided. Rare hypertensive reactions with oral selegiline at doses recommended for Parkinson's disease and associated with dietary influences have been reported. The clinical relevance to **EMSAM** is unknown.

Patients should be advised that certain tyramine-rich foods and beverages should be avoided while on **EMSAM** 9 mg/24 hours or **EMSAM** 12 mg/24 hours, and for two weeks following discontinuation of **EMSAM** at these doses (see **CONTRAINDICATIONS** and **WARNINGS**).

Patients should be instructed to immediately report the occurrence of the following acute symptoms: severe headache, neck stiffness, heart racing or palpitations, or other sudden or unusual symptoms.

Patients should be advised to avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight since heat may result in an increase in the amount of selegiline absorbed from the **EMSAM** patch and produce elevated serum levels of selegiline.

Patients should be advised to change position gradually if lightheaded, faint, or dizzy while on **EMSAM** therapy.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during **EMSAM** therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

While patients may notice improvement with **EMSAM** (selegiline transdermal system) therapy in one to several weeks, they should be advised of the importance of continuing drug treatment as directed.

Patients should be advised not to cut the **EMSAM** system into smaller portions.

For instructions on how to use **EMSAM**, see **DOSAGE AND ADMINISTRATION, How to Use EMSAM**.

Drug Interactions

The potential for drug interactions between **EMSAM** and a variety of drugs was examined in several human studies. Drug interaction studies described below were conducted with **EMSAM** 6 mg/24 hours. Although no differences are expected, drug interaction studies have not been conducted at higher doses (see In vitro *Metabolism* in Full Prescribing Information). In all of the studies described below, no drug-related adverse events were noted that required discontinuation of any subjects. Further, the incidence and nature of the adverse events were consistent with those known for selegiline or the test agent.

Alcohol

The pharmacokinetics and pharmacodynamics of alcohol (0.75 mg/kg) alone or in combination with **EMSAM** 6 mg/24 hours for 7 days of treatment was examined in 16 healthy volunteers. No clinically significant differences were observed in the pharmacokinetics or pharmacodynamics of alcohol or the pharmacokinetics of selegiline during co-administration. Although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol (0.75 mg/kg) and failed to alter the pharmacokinetic properties of alcohol, patients should be advised that the use of alcohol is not recommended while taking **EMSAM**.

Alprazolam

In subjects who had received **EMSAM** 6 mg/24 hours for 7 days, co-administration with alprazolam (15 mg/day), a CYP3A4/5 substrate, did not affect the pharmacokinetics of either selegiline or alprazolam.

Carbamazepine

Carbamazepine is an enzyme inducer and typically causes decreases in drug exposure, however, slightly increased levels of selegiline and its metabolites were seen after single application of **EMSAM** 6 mg/24 hours in subjects who had received carbamazepine (400 mg/day) for 14 days. Changes in plasma selegiline concentrations were nearly two-fold, and variable across the subject population. The clinical relevance of these observations is unknown. Carbamazepine is contraindicated with MAOIs, including selegiline (see **CONTRAINDICATIONS**).

Ibuprofen

In subjects who had received **EMSAM** 6 mg/24 hours for 11 days, combined administration with the CYP2C9 substrate ibuprofen (800 mg single dose) did not affect the pharmacokinetics of either selegiline or ibuprofen.

Ketoconazole

Seven-day treatment with ketoconazole (200 mg/day), a potent inhibitor of CYP3A4, did not affect the steady-state pharmacokinetics of selegiline in subjects who received **EMSAM** 6 mg/24 hours for seven days and no differences in the pharmacokinetics of ketoconazole were observed.

Levothyroxine

In healthy subjects who had received **EMSAM** 6 mg/24 hours for 10 days, single dose administration with levothyroxine (150 µg) did not alter the pharmacokinetics of either selegiline or levothyroxine (as judged by T_3 and T_4 plasma levels).

Olanzapine

In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with olanzapine, a substrate for CYP1A2, CYP2D6, and possibly CYP2A6, did not affect the pharmacokinetics of either selegiline or olanzapine.

Phenylpropanolamine (PPA)

In subjects who had received **EMSAM** 6 mg/24 hours for 9 days, co-administration with PPA (25 mg every 4 hours for 24 hours) did not affect the pharmacokinetics of PPA. There was a higher incidence of significant blood pressure elevations with the co-administration of **EMSAM** and PPA than with PPA alone, suggesting a possible pharmacodynamic interaction. It is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Pseudoephedrine

EMSAM 6 mg/24 hours for 10 days, co-administered with pseudoephedrine (60 mg three times a day) did not affect the pharmacokinetics of pseudoephedrine. The effect of pseudoephedrine on **EMSAM** was not examined. There were no clinically significant changes in blood pressure during pseudoephedrine administration alone, or in combination with **EMSAM**. Nonetheless, it is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Risperidone

In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with risperidone (2 mg per day for 7 days), a substrate for CYP2D6, did not affect the pharmacokinetics of either selegiline or risperidone.

Tyramine

Selegiline (the drug substance of **EMSAM**) is an irreversible inhibitor of monoamine oxidase (MAO), a ubiquitous intracellular enzyme. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline shows greater affinity for MAO-B; however, as selegiline concentration increases, this selectivity is lost with resulting dose-related inhibition of MAO-A. Intestinal MAO is predominantly type A, while in the brain both isoenzymes exist.

MAO plays a vital physiological role in terminating the biological activity of both endogenous and exogenous amines. In addition to their role in the catabolism of monoamines in the CNS, MAOs are also important in the catabolism of exogenous amines found in a variety of foods and drugs. MAO in the gastrointestinal tract (primarily type A) provides protection from exogenous amines with vasopressor actions, such as tyramine, which if absorbed intact can cause a hypertensive crisis, the so-called "cheese reaction." If a large amount of tyramine is absorbed systemically, it is taken up by adrenergic neurons and causes norepinephrine release from neuronal storage sites with resultant elevation of blood pressure. While most foods contain negligible amounts or no tyramine, a few food products (see **WARNINGS**) may contain large amounts of tyramine that represent a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAOIs. Tyramine-containing nutritional supplements should be avoided by patients taking **EMSAM**.

Animal studies have indicated the transdermal administration of selegiline via **EMSAM** 6 mg/24 hours allows for critical levels of MAO inhibition to be achieved in the brain while avoiding levels of gastrointestinal inhibition. To further define the risk of hypertensive crises with use of **EMSAM**, several Phase I tyramine challenge studies were conducted both with and without food.

Fourteen tyramine challenge studies including 214 healthy subjects (age range 18-65; 31 subjects >50 years of age) were conducted to determine the pressor effects of oral tyramine with concurrent **EMSAM** treatment (6 mg/24 hours–12 mg/24 hours), measured as the dose of tyramine required to raise systolic blood pressure by 30 mmHg (TYR30). Studies were conducted with and without concomitant administration of food. Studies conducted with food are most relevant to clinical practice since tyramine typically will be consumed in food. A high-tyramine meal is considered to contain up to 40 mg of tyramine.

One study using a crossover design in 13 subjects investigated tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours and oral selegiline (5 mg twice daily) for 9 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 338 mg and 385 mg in subjects treated with **EMSAM** and oral selegiline, respectively.

Another study using a crossover design in 10 subjects investigated tyramine pressor doses after administration of **EMSAM** 6 mg/24 hours or tranylcypromine 30 mg/day for 10 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 270 mg in subjects treated with **EMSAM** 6 mg/24 hours and 10 mg in subjects treated with tranylcypromine.

In a third crossover study, tyramine without food was administered to 12 subjects. The mean tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours for 9 and 33 days were 292 mg and

204 mg, respectively. The lowest pressor dose was 50 mg in one subject in the 33-day group.

Tyramine pressor doses were also studied in 11 subjects after extended treatment with **EMSAM** (selegiline transdermal system) 12 mg/24 hours. At 30, 60, and 90 days, the mean pressor doses (TYR30) of tyramine administered without food were 95 mg, 72 mg, and 88 mg, respectively. The lowest pressor dose without food was 25 mg in 3 subjects at day 30 while on **EMSAM** 12 mg/24 hours. Eight subjects from this study, with a mean tyramine pressor dose of 64 mg at 90 days, were subsequently administered tyramine with food, resulting in a mean pressor dose of 172 mg (2.7 times the mean pressor dose observed without food, $p < 0.003$).

With the exception of one study (N=153), the phase III clinical development program was conducted without requiring a modified diet (N=2553, 1606 at 6 mg/24 hours, and 947 at 9 mg/24 hours or 12 mg/24 hours). No hypertensive crises were reported in any patient receiving **EMSAM**.

In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours**. (See **WARNINGS**.)

Warfarin

Warfarin is a substrate for CYP2C9 and CYP3A4 metabolism pathways. In healthy volunteers titrated with Coumadin® (warfarin sodium) to clinical levels of anticoagulation (INR of 1.5 to 2), co-administration with **EMSAM** 6 mg/24 hours for 7 days did not affect the pharmacokinetics of the individual warfarin enantiomers. **EMSAM** did not alter the clinical pharmacodynamic effects of warfarin as measured by INR, Factor VII or Factor X levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In an oral carcinogenicity study in rats, selegiline given in the diet for 104 weeks was not carcinogenic up to the highest evaluable dose tested (3.5 mg/kg/day, which is 3 times the oral maximum recommended human dose on a mg/m² basis).

Carcinogenicity studies have not been conducted with transdermal administration of selegiline.

Mutagenesis

Selegiline induced mutations and chromosomal damage when tested in the *in vitro* mouse lymphoma assay with and without metabolic activation. Selegiline was negative in the Ames assay, the *in vitro* mammalian chromosome aberration assay in human lymphocytes, and the *in vivo* oral mouse micronucleus assay.

Impairment of Fertility

A mating and fertility study was conducted in male and female rats at transdermal doses of 10, 30, and 75 mg/kg/day of selegiline (8, 24 and 60 times the maximum recommended human dose of **EMSAM** [12 mg/ 24 hours] on a mg/m² basis). Slight decreases in sperm concentration and total sperm count were observed at the high dose; however, no significant adverse effects on fertility or reproductive performance were observed.

Teratogenic Effects - Pregnancy Category C

In an embryofetal development study in rats, dams were treated with transdermal selegiline during the period of organogenesis at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the maximum recommended human dose [MRHD] of **EMSAM** [12 mg/24 hours] on a mg/m² basis). At the highest dose there was a decrease in fetal weight and slight increases in malformations, delayed ossification (also seen at the mid dose), and embryofetal post-implantation lethality. Concentrations of selegiline and its metabolites in fetal plasma were generally similar to those in maternal plasma. In an *oral* embryofetal development study in rats, a decrease in fetal weight occurred at the highest dose tested (36 mg/kg; no-effect dose 12 mg/kg); no increase in malformations was seen.

In an embryofetal development study in rabbits, dams were treated with transdermal selegiline during the period of organogenesis at doses of 2.5, 10, and 40 mg/kg/day (4, 16, and 64 times the MRHD on a mg/m² basis). A slight increase in visceral malformations was seen at the high dose. In an *oral* embryofetal development study in rabbits, increases in total resorptions and post-implantation loss, and a decrease in the number of live fetuses per dam, occurred at the highest dose tested (50 mg/kg; no-effect dose 25 mg/kg).

In a prenatal and postnatal development study in rats, dams were treated with transdermal selegiline at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the MRHD on a mg/m² basis) on days 6-21 of gestation and days 1-21 of the lactation period. An increase in post-implantation loss was seen at the mid and high doses, and an increase in stillborn pups was seen at the high dose. Decreases in pup weight (throughout lactation and post-weaning periods) and survival (throughout lactation period), retarded pup physical development, and pup epididymal and testicular hypoplasia, were seen at the mid and high doses. Retarded neurobehavioral and sexual development was seen at all doses. Adverse effects on pup reproductive performance, as evidenced by decreases in implantations and litter size, were seen at the high dose. These findings suggest persistent effects on the offspring of treated dams. A no-effect dose was not established for developmental toxicity. In this study concentrations of selegiline and its metabolites in milk were ~ 15 and 5 times, respectively, the concentrations in plasma, indicating that the pups were directly dosed during the lactation period.

There are no adequate and well-controlled studies in pregnant women. **EMSAM** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of **EMSAM** on labor and delivery in humans is unknown.

Nursing Mothers

In a prenatal and postnatal study of transdermal selegiline in rats, selegiline and metabolites were excreted into the milk of lactating rats. The levels of selegiline and metabolites in milk were approximately 15 and 5 times, respectively, steady-state levels of selegiline and metabolites in maternal plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised administering **EMSAM** to a nursing mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS, Clinical Worsening and Suicide Risk**).

Anyone considering the use of **EMSAM** in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

One hundred ninety-eight (198) elderly (≥65 years of age) patients participated in clinical studies with **EMSAM** 6 mg/24 hours to 12 mg/24 hours. There were no overall differences in effectiveness between elderly and younger patients. In short-term, placebo-controlled depression trials, patients age 50 and older appeared to be at higher risk for rash (4.4% **EMSAM** versus 0% placebo) than younger patients (3.4% **EMSAM** versus 2.4% placebo).

ADVERSE REACTIONS

The premarketing development program for **EMSAM** included selegiline exposures in patients and/or normal subjects from two different groups of studies: 702 healthy subjects in clinical pharmacology/pharmacokinetics studies and 2036 exposures from patients in controlled and uncontrolled major depressive disorder clinical trials. The conditions and duration of treatment with **EMSAM** varied and included double-blind, open-label, fixed-dose, and dose titration studies of short-term and longer-term exposures. Safety was assessed by monitoring adverse events, physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials

Adverse Events Associated with Discontinuation of Treatment

Among 817 depressed patients who received **EMSAM** (selegiline transdermal system) at doses of either 3 mg/24 hours (151 patients), 6 mg/24 hours (550 patients) or 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours (116 patients) in placebo-controlled trials of up to 8 weeks in duration, 7.1% discontinued treatment due to an adverse event as compared with 3.6% of 668 patients receiving placebo. The only adverse event associated with discontinuation, in at least 1% of **EMSAM**-treated patients at a rate at least twice that of placebo, was application site reaction (2% **EMSAM** vs. 0% placebo).

*Adverse Events Occurring at an Incidence of 2% or More Among **EMSAM**-Treated Patients*

Table 1 enumerates adverse events that occurred at an incidence of 2% or more (rounded to the nearest percent) among 817 depressed patients who received **EMSAM** in doses ranging from 3 to 12 mg/24 hours in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 2% or more of patients treated with **EMSAM** and for which the incidence in patients treated with **EMSAM** was greater than the incidence in placebo-treated patients.

Only one adverse event was associated with a reporting of at least 5% in the **EMSAM** group, and a rate at least twice that in the placebo group, in the pool of short-term, placebo-controlled studies: application site reactions (see *Application Site Reactions*, below). In one such study which utilized higher mean doses of **EMSAM** than that in the entire study pool, the following events met these criteria: application site reactions, insomnia, diarrhea, and pharyngitis.

These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physicians with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder with EMSAM[1]

Body System/Preferred Term	EMSAM (N=817)	Placebo (N=668)
	(% of Patients Reporting Event)	
Body as a Whole		
Headache	18	17
Digestive		
Diarrhea	9	7
Dyspepsia	4	3
Nervous		
Insomnia	12	7
Dry Mouth	8	6
Respiratory		
Pharyngitis	3	2
Sinusitis	3	1
Skin		
Application Site Reaction	24	12
Rash	4	2

[1] Events reported by at least 2% of patients treated with **EMSAM** are included, except the following events which had an incidence on placebo treatment ≥ to **EMSAM**: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis, and palpitations.

Application Site Reactions

In the pool of short-term, placebo-controlled major depressive disorder studies, application site reactions (ASRs) were reported in 24% of **EMSAM**-treated patients and 12% of placebo-treated patients. Most ASRs were mild or moderate in severity. None were considered serious. ASRs led to dropout in 2% of **EMSAM**-treated patients and no placebo-treated patients.

In one such study which utilized higher mean doses of **EMSAM**, ASRs were reported in 40% of **EMSAM**-treated patients and 20% of placebo-treated patients. Most of the ASRs in this study were described as erythema and most resolved spontaneously, requiring no treatment. When treatment was administered, it most commonly consisted of dermatological preparations of corticosteroids.

Male and Female Sexual Dysfunction with MAO-Inhibitors

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 2 shows that the incidence rates of sexual side effects in patients with major depressive disorder are comparable to the placebo rates in placebo-controlled trials.

Table 2. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials with EMSAM

Adverse Event	EMSAM	Placebo
	IN MALES ONLY	
	(N=304)	(N=256)
Abnormal Ejaculation	1.0%	0.0%
Decreased Libido	0.7%	0.0%
Impotence	0.7%	0.4%
Anorgasmia	0.2%	0.0%
	IN FEMALES ONLY	
	(N=513)	(N=412)
Decreased Libido	0.0%	0.2%

There are no adequately designed studies examining sexual dysfunction with **EMSAM** treatment.

Vital Sign Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. In the pool of short-term, placebo-controlled major depressive disorder studies, 3.0% of **EMSAM**-treated patients and 1.5% of placebo-treated patients experienced a low systolic blood pressure, defined as a reading less than or equal to 90 mmHg with a change from baseline of at least 20 mmHg. In one study which utilized higher mean doses of **EMSAM**, 6.2% of **EMSAM**-treated patients and no placebo-treated patients experienced a low standing systolic blood pressure by these criteria.

In the pool of short-term major depressive disorder trials, 9.8% of **EMSAM**-treated patients and 6.7% of placebo-treated patients experienced a notable orthostatic change in blood pressure, defined as a decrease of at least 10 mmHg in mean blood pressure with postural change.

Prison MH Care Ruling Could Push Salaries Higher

Low salaries have made public health psychiatrists—especially child psychiatrists—a rare breed. A court order may change that situation in one large state.

BY RICH DALY

A court-ordered expansion of California's mental health system for prisoners could help close a long-running deficit of psychiatrists in the system and affect funds earmarked to pay psychiatrists in public health systems throughout the state.

The state has scrambled to improve mental health care for inmates since U.S. District Judge Lawrence Karlton in Sacramento ruled in 1995 that prison officials showed deliberate indifference to the needs of mentally ill prisoners. Soon after the ruling, the judge appointed Michael Keating as special master of mental health for the state prison system. In April, still unhappy with mental health care in California prisons, Karlton ordered the state to spend more than $600 million to improve mental health services, including building new hospitals with space for 695 inmates.

Karlton's latest order, which came in July, required Gov. Arnold Schwarzenegger (R) to ask state lawmakers for the money to hire 552 additional mental health staff, ranging from psychiatrists to therapists and nurses. Although the governor had not proposed a breakdown of how many employees would be hired in any mental health staff category as of press time, state officials estimated the new hires could cost more than $30 million annually.

The increased focus on filling new and existing mental health staff positions would be a drastic change from the state's standard hiring practices and incentives, which resulted in a 23 percent vacancy rate among prison psychiatrists. The system has about 300 full-time psychiatrists and about 90 vacancies, according to the Union of American Physicians and Dentists (UAPD), which represents public psychiatrists in the state.

Gary Robinson, executive director of UAPD, said the state was unlikely to fill the open positions or new psychiatrist positions had salaries not been increased in July. At that time, the prison psychiatrists got a 13.5 percent court-mandated salary increase—the first since 2003—which raised the starting salary from $160,000 to about $175,000 a year. Psychiatrists are slated to get another 5 percent boost January 1, 2007.

"Salary has been a big barrier; that's why [judges and state officials] had to go for this 13.5 percent raise," Robinson said. "There is not a lot of psychiatrists who want to work in a prison. It's a tough job."

Robinson said it is "entirely possible" for an increase in prison psychiatry salaries to lead to an increase in psychiatrist salaries across the public health care system so that other care settings remain competitive. The Department of Mental Health (DMH) has since requested a 10 percent increase for DMH psychiatrists.

"For many years there haven't been psychiatrist salary increases, and they fell behind," he said. "This is catch up now," Robinson said about the prison system to *Psychiatric News*.

During the August special legislative session—called to address a variety of prison health care issues raised by lawsuits—UAPD opposed the construction of new prisons, preferring that the money be invested in more rehabilitation programs and halfway houses and an expansion of the parole system. If new facilities are funded, UAPD urged the construction of new prison hospitals so that the number of prisoners who can be treated for mental illness and other chronic health conditions can be increased. The union also pushed for full funding of previously approved mental health staff positions.

Schwarzenegger proposed building or contracting for community correctional and "re-entry" facilities that would provide mental health care and other services. An estimated 4,500 female inmates would be moved to similar facilities, which would free a women's prison for use by male inmates at a cost of $2 billion.

Phil Angelides, Democratic candidate for governor, promised to boost education, training, and treatment programs for inmates if he wins in November.

Schwarzenegger previously announced plans to build two prisons and new units in existing prisons to relieve extreme inmate overcrowding, estimated to cost $6 billion, according to Acting Corrections Secretary James Tilton.

In a July report, Keating, the court-appointed master, criticized the state prison system's mental health effort, saying that the state's Department of Finance had not sought the necessary resources to bring prison mental health staffing in compliance with the judge's requirements.

The special master's report did not delineate what positions would be needed or how much they would cost. It did state that the number of suicides in the prison system is "soaring." Prisoner advocates said 40 inmates committed suicide last year, and the number increased to 25 inmates in the first six months of 2006. The number of suicides in 2005 exceeded the previous record of 36 in 2003.

Many of the suicides occurred in the prisons' "administrative segregation units" or solitary-confinement cells, where those

please see ***Prison*** *on page 8*

legal news

Most States Say Mental Illness Reason to Bar Gun Ownership

Over the past five years, a growing number of states have enacted legislation to restrict people with mental illness from gaining access to guns.

BY EVE BENDER

State laws that restrict people with mental illness, including substance use problems, from gaining access to firearms differ widely across the nation, according to a review of these laws in the August *American Journal of Psychiatry*.

The laws differ in their definition of mental illness, type and duration of gun restriction, and reporting practices on the part of physicians caring for these patients, according to the report.

This diversity is why psychiatrists must familiarize themselves with the laws governing the state in which they practice regarding the licensure, purchase, possession, and carrying of firearms, lead author Donna Norris, M.D., told *Psychiatric News*.

"We as psychiatrists should be prepared to deal with these issues, whether we practice in rural or inner-city areas," said Norris, APA's secretary-treasurer and an assistant professor of psychiatry at Harvard Medical School.

When Norris and her colleagues began to review the state laws in 2000, only 19 states had legislation restricting gun ownership for people with mental illness, she noted. But by the end of the review in 2005, 43 states, Washington, D.C., and Puerto Rico had laws prohibiting people with mental illness from obtaining firearm licensure, 36 states and Puerto Rico had similar prohibitions for those with substance use problems, and 31 states, Washington D.C., and Puerto Rico had similar prohibitions for those with alcohol problems.

Twenty states and Washington, D.C., have databases containing information submitted by courts or mental health treatment facilities on people with mental illness. In California, for instance, people who have been admitted to a psychiatric hospital and ruled a danger to themselves or others must be reported to the local law enforcement agency by an attending health care professional, according to the report.

"In most jurisdictions, law enforcement authorities have access to these mental health data and can use them to determine legal access to firearms," the report stated.

The flurry of legislation may be related to isolated incidents of violence perpetrated by people with mental illness using guns and the firestorm of publicity often generated as a result, noted Norris.

She found that many of the variations between state laws prohibiting people with mental illness from legally obtaining or carrying firearms depended on each state's definition of restricted individuals.

According to the report, individuals who are restricted from gun ownership include those who currently receive outpatient psychiatric treatment, those who have been civilly committed to treatment, and those who have been declared not guilty by reason of insanity. Some are prohibited because they have a history of alcohol or substance abuse.

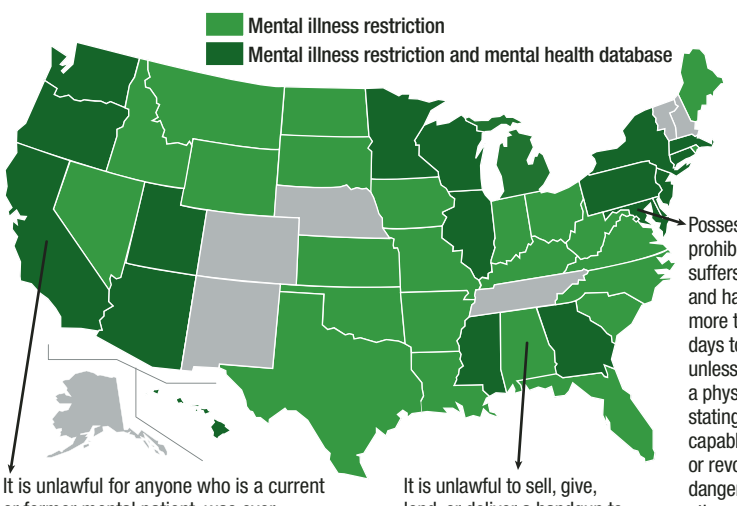
The laws vary in their range of restrictiveness. In Pennsylvania, for example, prohibitions extend to those who have been "adjucated as an incompetent," been committed to receive psychiatric care on an inpatient unit, or been convicted of driving under the influence of alcohol or a controlled substance on three or more occasions within a five-year period.

Texas law prohibits the ownership and carrying of guns by those with certain psychiatric diagnoses, including schizophrenia, delusional disorder, bipolar disorder, chronic dementia, dissociative identity disorder, intermittent explosive disorder, and antisocial personality disorder. In addition, gun restrictions are in place for five years following an involuntary psychiatric hospitalization, inpatient or residential treatment for substance abuse, diagnosis of alcohol or drug dependence, or diagnosis of mental illness by a licensed physician.

please see ***Gun Ownership*** *on page 36*

Gun Laws All Over the Map on Mental Illness

While their statutes differ, all but seven states have gun law restrictions for people with mental illness. Many states also keep databases containing information submitted by courts or mental health treatment facilities on people with mental illness.



Source: Donna Norris, M.D., et al., *American Journal of Psychiatry*, August 2006

For your patients with treatment-resistant depression

VNS Therapy...

Sustained efficacy to help her reconnect

Adding VNS Therapy has been shown to provide sustained efficacy and clinical benefits that improve over time[1]

- A unique mechanism of action[2]
- Efficacy that improves over time and is sustained long term[1,3]
  - 70% of patients who responded maintained their response at 24 months[3]
- Safety and tolerability, with side effects that typically decrease over time[1,3]
- High continuation and adherence rates[3]

Adding VNS Therapy has been shown to succeed where other treatments have failed[1,3,4]

For more information, visit **www.VNSTherapy.com**.

PLEASE REFER TO THE BRIEF SUMMARY ON THE FOLLOWING PAGE FOR INDICATION, PRESCRIBING, AND SAFETY INFORMATION.

VNS THERAPY™
VAGUS NERVE STIMULATION

Court Treads New Ground In Child-Custody Fight

Vermont rules in favor of visitation rights after a lesbian couple's civil union is dissolved.

BY AARON LEVIN

One year ago, *Psychiatric News* reported on a most contemporary child custody case, pitting two halves of a fractured lesbian civil union—and two states—against each other. Now the Vermont Supreme Court has ruled that Vermont and not Virginia holds exclusive jurisdiction in the case.

The custodial and biological mother, Lisa Miller-Jenkins, now lives in Virginia, while her former partner, Janet Miller-Jenkins, lives in Vermont, where civil unions are legal. They joined there in a civil union in 2000, and Lisa filed in Vermont to dissolve the union in November 2003. Vermont recognizes the parental rights of Janet Miller-Jenkins to the child, Isabella, now 4 years old, and its Supreme Court has ruled in favor of her right to see the girl. It also reaffirmed a Vermont Family Court contempt order against Lisa Miller-Jenkins for failing to comply with its visitation order. The Vermont Psychiatric Association filed an amicus brief in the case, supporting Janet Miller-Jenkins's right to parental visitation.

Action in the case is expected to move to a three-judge panel of the Virginia Court of Appeals, which stayed an earlier ruling in the case pending the Vermont court's ruling. If Lisa Miller-Jenkins files an appeal, which is highly likely, the Virginia court will have to uphold or reject a lower court's decision that Virginia's Marriage Affirmation Act supersedes Vermont law. Lisa Miller-Jenkins's attorneys also cited the federal Defense of Marriage Act on their client's behalf.

Were this a case of battling heterosexual parents, there would be little to argue about, said Cheryl Lynn Hepfer, J.D., of Rockville, Md., president of the American Academy of Matrimonial Lawyers. Federal laws in place for two decades say that the state where parties first file holds jurisdiction, she said.

"Anything else would be truly contrary to general law in custody cases," she said. "Today lawyers advise parents not to take the child to another state in the hopes of finding a more favorable court. The consequence is substantial and not in the best interests of the child."

A reversal of such general law would have the effect of overturning standards for all custody proceedings, not just those involving same-sex couples, said Hepfer.

Janet Miller-Jenkins's legal argument would appear to also have the backing of other legal precedents, said attorney Joseph Price, J.D., her pro bono Virginia lawyer. "The rule is to apply the most specific and most recent legislation, and since the Parental Kidnapping Protection Act was amended more recently than the federal Defense of Marriage Act, I would expect a favorable outcome."

However, with an appeal in Virginia by Lisa Miller-Jenkins likely, said Price, a final ruling may not come soon. Delays may have more than legal ramifications if Janet Miller-Jenkins cannot see her child for several years, he added. He cited another case in which so much time went by during appeals that the second parent was barred from seeing the child on the grounds that she was now a stranger.

Letting that happen, he said, "would amount to allowing Lisa to get away with kidnapping."

The Vermont Supreme Court decision in* Miller-Jenkins v. Miller-Jenkins *[2006 VT 78, Nos. 2004-443 & 2005-030] is posted at <http://dol.state.vt.us/gopher_root3/supct/current/2004-443.op>. ■

Prison

continued from page 5

with mental illness are often kept.

Randall Hagar, the California Psychiatric Association's director of government affairs, told *Psychiatric News* that "obviously the state's efforts to recruit and retain psychiatrists have failed."

Hagar said the psychiatrist salary increases and additional positions will likely "create a squeeze elsewhere" in the state public health system, such as in hospitals and community health centers.

"We expect a domino effect on salaries throughout the health care system," Hagar said. "We already find vacancy rates throughout the public health sector that are fairly high and limit access to mental health care."

Some prisoner-rights advocates have called for creation of a new department for prisoners with mental illness, or as an alternative that the state move them to DMH facilities. The only prisoners now treated by DMH are those who have completed their sentences but are deemed a continuing threat and are civilly committed. Almost all of the roughly 5,000 patients in state mental hospitals are forensic patients, said Hagar.

"We feel that mentally ill prisoners ought to be afforded special facilities to accommodate them," Hagar said. "It's bad enough they are incarcerated, but at least they need to be cared for adequately."

Information on Schwarzenegger's proposed prison system health care funding increases is posted at <www.ebudget.ca.gov/Revised/BudgetSummary/CLE/8875412.html>. ■

Start with LUNESTA
for a full 7-8 hours of sleep[1]

- LUNESTA provides rapid sleep onset[1]
- LUNESTA provides a full night of sleep (7 to 8 hours)[1]
- No next-day residual effects in most patients[1,2]

The failure of insomnia to remit after 7 to 10 days of treatment should be medically evaluated.

Any night or every night

Leave the rest to...

Lunesta™
(eszopiclone)C
1, 2 AND 3 MG TABLETS

Important Safety Information

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients should not take LUNESTA unless they are prepared to get a full night's sleep. As with other hypnotics, patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (eg, operating machinery or driving a motor vehicle) after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of LUNESTA. In clinical trials, the most common adverse events associated with LUNESTA were unpleasant taste, headache, somnolence, dizziness, dry mouth, infection, and pain.

LUNESTA has been classified as a Schedule IV controlled substance. Sedative hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnotic. Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

References: 1. Zammit GK, McNabb LJ, Caron J, et al. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. *Curr Med Res Opin.* 2004;20:1979-1991. **2.** LUNESTA prescribing information.

Please see brief summary of complete prescribing information.

SEPRACOR

4/06

6SRZO355

Lunesta™
(eszopiclone)
1, 2 AND 3 MG TABLETS

BRIEF SUMMARY

INDICATIONS AND USAGE
LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, LUNESTA administered at bedtime decreased sleep latency and improved sleep maintenance.

CONTRAINDICATIONS
None known.

WARNINGS
Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including LUNESTA. Because some of the important adverse effects of LUNESTA appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see **DRUG ABUSE AND DEPENDENCE**).

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of LUNESTA. LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. LUNESTA should not be taken with alcohol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents, because of the potentially additive effects.

PRECAUTIONS
General
Timing Of Drug Administration: LUNESTA should be taken immediately before bedtime. Taking a sedative/hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Use In The Elderly And/Or Debilitated Patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. The recommended starting dose of LUNESTA for these patients is 1 mg (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

Use In Patients With Concomitant Illness: Clinical experience with eszopiclone in patients with concomitant illness is limited. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

A study in healthy volunteers did not reveal respiratory-depressant effects at doses 2.5-fold higher (7 mg) than the recommended dose of eszopiclone. Caution is advised, however, if LUNESTA is prescribed to patients with compromised respiratory function.

The dose of LUNESTA should be reduced to 1 mg in patients with severe hepatic impairment, because systemic exposure is doubled in such subjects. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment. No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of eszopiclone is excreted unchanged in the urine.

The dose of LUNESTA should be reduced in patients who are administered potent inhibitors of CYP3A4, such as ketoconazole, while taking LUNESTA. Downward dose adjustment is also recommended when LUNESTA is administered with agents having known CNS-depressant effects.

Use In Patients With Depression: Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information For Patients: Patient information is printed in the complete prescribing information.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions
CNS-Active Drugs

Ethanol: An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

Paroxetine: Coadministration of single doses of eszopiclone 3 mg and paroxetine 20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.

Lorazepam: Coadministration of single doses of eszopiclone 3 mg and lorazepam 2 mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.

Olanzapine: Coadministration of eszopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

Drugs That Inhibit CYP3A4 (Ketoconazole): CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days. C_{max} and $t_{1/2}$ were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

Drugs That Induce CYP3A4 (Rifampicin): Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

Drugs Highly Bound To Plasma Protein: Eszopiclone is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

Drugs With A Narrow Therapeutic Index

Digoxin: A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady state following dosing of 0.5 mg twice daily for one day and 0.25 mg daily for the next 6 days.

Warfarin: Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (R)- or (S)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). However, in a carcinogenicity study in Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-1 mice were given eszopiclone at doses up to 100 mg/kg/day by oral gavage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD—i.e., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Mutagenesis: Eszopiclone was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary cell chromosomal aberration assay. It was not mutagenic or clastogenic in the bacterial Ames gene mutation assay, in an unscheduled DNA synthesis assay, or in an *in vivo* mouse bone marrow micronucleus assay.

(S)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro* ^{32}P-postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

Impairment Of Fertility: Eszopiclone was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks premating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks premating through day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopiclone decreased fertility, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 times the MRHD on a mg/m^2 basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), abnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

Pregnancy
Pregnancy Category C: Eszopiclone administered by oral gavage to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity up to the highest doses tested (250 and 16 mg/kg/day in rats and rabbits, respectively; these doses are 800 and 100 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). In the rat, slight reductions in fetal weight and evidence of developmental delay were seen at maternally toxic doses of 125 and 150 mg/kg/day, but not at 62.5 mg/kg/day (200 times the MRHD on a mg/m^2 basis). Eszopiclone was also administered by oral gavage to pregnant rats throughout the pregnancy and lactation periods at doses of up to 180 mg/kg/day. Increased postimplantation loss, decreased postnatal pup weights and survival, and increased pup startle response were seen at all doses; the lowest dose tested, 60 mg/kg/day, is 200 times the MRHD on a mg/m^2 basis. These doses did not produce significant maternal toxicity. Eszopiclone had no effects on other behavioral measures or reproductive function in the offspring.

There are no adequate and well-controlled studies of eszopiclone in pregnant women. Eszopiclone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor And Delivery: LUNESTA has no established use in labor and delivery.

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

Pediatric Use: Safety and effectiveness of eszopiclone in children below the age of 18 have not been established.

Geriatric Use: A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopiclone were 65 to 86 years of age. The overall pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with nighttime dosing of 2 mg eszopiclone was not different from that seen in younger adults. LUNESTA 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the elderly population.

ADVERSE REACTIONS
The premarketing development program for LUNESTA included eszopiclone exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient-exposure years. The conditions and duration of treatment with LUNESTA varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

Adverse Findings Observed in Placebo-Controlled Trials
Adverse Events Resulting in Discontinuation of Treatment: In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received placebo, 2.3% of 215 patients who received 2 mg LUNESTA, and 1.4% of 72 patients who received 1 mg LUNESTA discontinued treatment due to an adverse event. In the 6-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse event. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received placebo and 12.8% of 593 patients who received 3 mg LUNESTA discontinued due to an adverse event. No event that resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Events Observed at an Incidence of ≥2% in Controlled Trials. The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2 or 3 mg in non-elderly adults. Treatment duration in this trial was 44 days. Data are limited to adverse events that occurred in 2% or more of patients treated with LUNESTA 2 mg (n=104) or 3 mg (n=105) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients (n=99).[1]

Body as a whole: headache (13%, 21%, 17%), viral infection (1%, 3%, 3%). Digestive system: dry mouth (3%, 5%, 7%), dyspepsia (4%, 4%, 5%), nausea (4%, 5%, 4%), vomiting (1%, 3%, 0%). Nervous system: anxiety (0%, 3%, 1%), confusion (0%, 0%, 3%), depression (0%, 4%, 1%), dizziness (4%, 5%, 7%), hallucinations (0%, 1%, 3%), libido decreased (0%, 0%, 3%), nervousness (3%, 5%, 0%), somnolence (3%, 10%, 8%). Respiratory system: infection (3%, 5%, 10%). Skin and appendages: rash (1%, 3%, 4%). Special senses: unpleasant taste (3%, 17%, 34%). Urogenital system: dysmenorrhea* (0%, 3%, 0%), gynecomastia** (0%, 3%, 0%).

*Gender-specific adverse event in females

**Gender-specific adverse event in males

[1]Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abnormal dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis.

Adverse events that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste.

The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of LUNESTA at doses of 1 or 2 mg in elderly adults (ages 65-86). Treatment duration in these trials was 14 days. Data are limited to events that occurred in 2% or more of patients treated with LUNESTA 1 mg (n=72) or 2 mg (n=215) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients.[1]

Body as a whole: accidental injury (1%, 0%, 3%), headache (14%, 15%, 13%), pain (2%, 4%, 5%). Digestive system: diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%), dyspepsia (2%, 6%, 2%). Nervous system: abnormal dreams (0%, 3%, 1%), dizziness (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuralgia (0%, 3%, 0%). Skin and appendages: pruritus: (1%, 4%, 1%). Special senses: unpleasant taste (0%, 8%, 12%). Urogenital system: urinary tract infection (0%, 3%, 0%).

[1]Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

Adverse events that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste. These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice because patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and non-drug factors to the adverse event incidence rate in the population studied.

Other Events Observed During The Premarketing Evaluation Of LUNESTA. Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section and reported by approximately 1550 subjects treated with LUNESTA at doses in the range of 1 to 3.5 mg/day during Phase 2 and 3 clinical trials throughout the United States and Canada. All reported events are included except those already listed here or listed elsewhere in labeling, minor events common in the general population, and events unlikely to be drug-related. Although the events reported occurred during treatment with LUNESTA, they were not necessarily caused by it.

Events are listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those that occurred on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those that occurred in fewer than 1/100 patients but in at least 1/1,000 patients; **rare** adverse events are those that occurred in fewer than 1/1,000 patients. Gender-specific events are categorized based on their incidence for the appropriate gender.

Frequent: chest pain, migraine, peripheral edema.

Infrequent: acne, agitation, allergic reaction, alopecia, amenorrhea, anemia, anorexia, apathy, arthritis, asthma, ataxia, breast engorgement, breast enlargement, breast neoplasm, breast pain, bronchitis, bursitis, cellulitis, cholelithiasis, conjunctivitis, contact dermatitis, cystitis, dry eyes, dry skin, dyspnea, dysuria, eczema, ear pain, emotional lability, epistaxis, face edema, female lactation, fever, halitosis, heat stroke, hematuria, hernia, hiccup, hostility, hypercholesteremia, hypertension, hypertonia, hypesthesia, incoordination, increased appetite, insomnia, joint disorder (mainly swelling, stiffness, and pain), kidney calculus, kidney pain, laryngitis, leg cramps, lymphadenopathy, malaise, mastitis, melena, memory impairment, menorrhagia, metrorrhagia, mouth ulceration, myasthenia, neck rigidity, neurosis, nystagmus, otitis externa, otitis media, paresthesia, photosensitivity, reflexes decreased, skin discoloration, sweating, thinking abnormal (mainly difficulty concentrating), thirst, tinnitus, twitching, ulcerative stomatitis, urinary frequency, urinary incontinence, urticaria, uterine hemorrhage, vaginal hemorrhage, vaginitis, vertigo, vestibular disorder, weight gain, weight loss.

Rare: abnormal gait, arthrosis, colitis, dehydration, dysphagia, erythema multiforme, euphoria, furunculosis, gastritis, gout, hepatitis, hepatomegaly, herpes zoster, hirsutism, hyperacusis, hyperesthesia, hyperlipemia, hypokalemia, hypokinesia, iritis, liver damage, maculopapular rash, mydriasis, myopathy, neuritis, neuropathy, oliguria, photophobia, ptosis, pyelonephritis, rectal hemorrhage, stomach ulcer, stomatitis, stupor, thrombophlebitis, tongue edema, tremor, urethritis, vesiculobullous rash.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: LUNESTA is a Schedule IV controlled substance under the Controlled Substances Act. Other substances under the same classification are benzodiazepines and the nonbenzodiazepine hypnotics zalepion and zolpidem. While eszopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, it shares some of the pharmacologic properties of the benzodiazepines.

Abuse, Dependence, and Tolerance
Abuse and Dependence: In a study of abuse liability conducted in individuals with known histories of benzodiazepine abuse, eszopiclone at doses of 6 and 12 mg produced euphoric effects similar to those of diazepam 20 mg. In this study, at doses 2-fold or greater than the maximum recommended doses, a dose-related increase in reports of amnesia and hallucinations was observed for both LUNESTA and diazepam.

The clinical trial experience with LUNESTA revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for uncomplicated sedative/hypnotic withdrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last LUNESTA treatment: anxiety, abnormal dreams, nausea, and upset stomach. These reported adverse events occurred at an incidence of 2% or less. Use of benzodiazepines and similar agents may lead to physical and psychological dependence. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnotic.

Tolerance: Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks.

No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for LUNESTA in a placebo-controlled 44-day study, and by subjective assessments of time to sleep onset and WASO in a placebo-controlled study for 6 months.

OVERDOSAGE
There is limited premarketing clinical experience with the effects of an overdosage of LUNESTA. In clinical trials with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Individuals have fully recovered from racemic zopiclone overdoses up to 340 mg (56 times the maximum recommended dose of eszopiclone).

Signs And Symptoms: Signs and symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Impairment of consciousness ranging from somnolence to coma has been described. Rare individual instances of fatal outcomes following overdose with racemic zopiclone have been reported in European postmarketing reports, most often associated with overdose with other CNS-depressant agents.

Recommended Treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. The value of dialysis in the treatment of overdosage has not been determined.

Poison Control Center: As with the management of all overdosage, 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 hypnotic drug product overdosage.

Rx only.

SEPRACOR 3/05

Health Technology Bill Raises Privacy Concerns

Psychiatrists may benefit from provisions in the bill that would encourage the use of "telehealth" or other technology to treat those in remote locations.

BY RICH DALY

Concerned about proposals that could weaken patient-privacy protections, APA and other advocacy groups helped win an amendment to a health technology bill to prevent it from overriding strong state privacy rules with a weaker federal version.

The bill (HR 4157), passed by the House of Representatives in July, would codify the duties and responsibilities of the Office of the National Coordinator for Health Information Technology (HIT) and promote an interoperable, secure, national health information system. It would authorize $20 million a year in Fiscal 2007 and 2008 for grants—including funding demonstration projects in small practices—to facilitate implementation of a national HIT system.

Earlier versions of the bill included a preemption of state privacy laws that provide a higher degree of protection than HIPAA or other federal laws in favor of a weaker federal standard. As the measure advanced through the chamber's committees, APA and other mental health advocacy groups suggested alternative language to remove the weaker federal privacy standard.

"This was a huge improvement on a bill that may still face significant changes," said Nicholas Meyers, director of APA's Department of Government Relations.

The bill would require the secretary of the Department of Health and Human Services (HHS) to conduct a comprehensive medical records privacy study to determine whether greater commonality in privacy laws is needed "to better protect, strengthen, or otherwise improve the secure, confidential, and timely exchange of information."

The HHS secretary would also recommend, in the form of legislation, methods to implement such changes. APA strongly approves of a measure that would require congressional review, amendment, and approval of the secretary's privacy recommendations.

Privacy advocates and others—including many Democrats—have attacked the legislation for not strengthening the patient privacy protections covered under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and for failing to enforce sanctions against offenders. These provisions were designed to protect the use and disclosure of individually identifiable health information.

"It does not provide privacy protections which will ensure that patients can control access to their own sensitive electronic health information," Rep. Carolyn Maloney (D-N.Y.) said during floor debate in the House. "In fact, the Congressional Budget Office has stated that 'enacting this would not significantly affect either the rate at which the use of health technology will grow or how well that technology will be designed and implemented.' "

Privacy advocates also were critical of a provision granting an exemption to an antikickback law, written by Rep. Pete Stark (D-Calif.), that prohibits physicians from referring Medicare patients for certain designated services to entities, such as hospitals, with which the physician has a financial relationship. Such practices could be seen as illegally inducing referrals of patients or recruitment of enrollees, but supporters of the legislation said it is needed to let physicians help hospitals adopt the new, expensive technology.

The legislation stemmed from research indicating that increased use of electronic medical records can improve patient safety and reduce costs. The RAND Corporation recently estimated that by implementing health information technology, the federal government could save up to $162 billion annually. Critics point out, however, that wide adoption of electronic records could also endanger patient privacy by making them more accessible, so strong protections are needed.

The legislation also would update the federal government's use for coding purposes of the *International Classification of Diseases (ICD)* from the ninth edition to the 10th edition by October 1, 2010. *DSM-IV-TR* can be used in tandem with *ICD-10*.

The House bill would promote the use of telehealth services, which could help psychiatrists reach patients in remote or rural areas. Among other efforts, the bill would "facilitate the adoption of State reciprocity agreements for practitioner licensure in order to expedite the provision across State lines of telehealth services."

Senate Version Varies Widely

Among the many differences between the House bill and a version (S 1418) passed by the Senate last November, those concerning funding may be the greatest. As an incentive to adopt HIT, the Senate bill provides grants to providers to invest in HIT systems: $116 million in Fiscal 2006 and $141 million in Fiscal 2007, and such sums as may be necessary in Fiscal 2008 through 2010 for grants to facilitate the widespread adoption of interoperable health information technology.

please see ***Technology*** *on page 38*

Govt. Makes It Easier for M.D.s To Adopt E-Prescribing Systems

E-prescribing requirements should not force psychiatrists to either pay the entire cost of an e-prescribing system or accept assistance from external entities but risk being subject to federal sanctions.

BY MARK MORAN

The federal government has issued regulations designed to make electronic health care records and electronic prescribing more attractive to physicians.

The regulations are spelled out in two rules issued separately in August by the Centers for Medicare and Medicaid Services (CMS) and the Office of the Inspector General (OIG). They were required by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.

The new rules, which will become effective on October 7, create new exceptions and "safe harbors" to existing federal fraud and abuse laws governing the provision of electronic health information technology and services by health plans and other entities to physicians and hospitals for handling electronic health records and electronic prescribing (e-prescribing).

In some respects the CMS and IOG rules mirror each other, but they are dealing with separate sections of the Social Security Act. The CMS rule deals with prohibitions on physician self-referral, while the OIG rule addresses prohibitions on kickbacks.

Specifically, the CMS rule creates two exceptions to the federal prohibition on physician self-referral that will protect doctors from violating that law when they accept compensation in the form of computer products and services. One exception allows physicians to accept items and services used solely to facilitate electronic prescribing; the other exception allows them to accept information technology, software, and training services used predominantly to handle electronic health records.

The scope of donors and recipients included in the final rule is considerably broader than originally proposed by CMS last year.

The OIG rule is similar, establishing two "safe harbors" from the federal antikickback statute to protect arrangements in which certain health care organizations provide specified recipients with remuneration in the form of technology and services used for electronic prescribing and electronic health records systems.

A buzzword in the field of health information technology is "interoperability," the ability of information systems to "talk" to each other to allow seamless transfer of information across the health care landscape—a concept that presupposes widespread adoption of computerization. Yet one of the barriers to widespread adoption is the reluctance of physician groups to invest in technology that may not be compatible, and hence will have to be replaced at some point.

Consequently, some health plans and other entities may offer physicians hardware and software for e-prescribing as well as reimbursement for first-year subscription fees; such transactions could be interpreted as violating federal laws, hence the importance of the new rules providing exceptions and safe harbors.

"These important regulations will help promote the adoption of essential health information technology while protecting

please see ***E-Prescribing*** *on page 38*

Confidentiality of NPI Information Worries Physicians

As physicians obtain their new HIPAA identification code, many question whether the information they must provide on the application will remain private.

BY RICH DALY

Beginning October 1, psychiatrists and other physicians participating in Medicare will have the option to identify themselves on claims by using only their National Provider Identifier (NPI).

Until that date, however, the Centers for Medicare and Medicaid Services (CMS) asks physicians to use their current Uniform Provider Identification Number (UPIN) and their new NPI on the claims they file.

The NPI system was federally mandated by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The NPI, which replaces the UPIN, functions much like a Social Security number—each is assigned for life and never expires.

All HIPAA "covered entities" are required to obtain an identifier. "Covered entities" are defined as providers, health plans, hospitals, insurers, and health care clearinghouses that conduct certain financial and administrative functions electronically, such as claims, coordination of benefits transactions, and enrollment in health-plan networks.

The NPI is the only identifier that most health plans, both public and private, can use after May 23, 2007, to identify physicians. Smaller health entities have until May 23, 2008, to comply.

NPIs are issued through the National Plan and Provider Enumeration System (NPPES), which accepts applications filed online or through the mail.

As of mid-August, NPIs had been issued to about 850,000 of the nearly 2.5 million physicians and other providers that CMS believes needs them, according to a CMS spokesperson.

As the transition to the NPI system progresses, however, concerns remain over the security of the personal information that physicians must submit as part of their NPI application. In a May 26 letter to CMS, the AMA said it wanted to limit access to the CMS database of physician information and prohibit the use of NPIs for any commercial purposes. CMS is now developing a "data-dissemination policy" that will provide guidelines to control access to the NPI database.

"Until CMS publishes the data-dissemination policy, however, little is known about who will have access to the" to the NPI database, wrote Michael Maves, M.D., executive vice president of AMA.

In a CMS-sponsored panel discussion on NPIs in July, a CMS representative said that the data-dissemination policy had undergone many drafts, but no date has been set for its release.

More information on the NPI and applications forms can be accessed at <https://nppes.cms.hhs.gov/NPPES/StaticForward.do?forward=static.npistart>. ■

government news

Patient Limit Keeping Many From Buprenorphine Treatment

APA and other physician groups are pushing for removal of the federally mandated 30-patient limit on buprenorphine treatment and encourage broader physician use of the opioid treatment.

BY RICH DALY

The cost of buprenorphine treatment and the 30-patient limit on physicians who offer the in-office opioid addiction treatment were identified as the leading barriers to broader physician use of this intervention, a recent study found.

The study was required by the Drug Addiction Treatment Act of 2000, the legislation that legalized the office-based treatment for addiction to heroin and opioid painkillers.

The findings also undercut concerns that led to the inclusion of the law's requirement that physicians can provide buprenorphine treatment to no more than 30 patients at a time. Despite concerns by federal drug officials, little evidence has emerged that the only available office-based treatment for opioid addiction has spurred further illegal drug use.

In 2005 the law was amended to eliminate the 30-patient limit on group practices and entire clinics.

The study reported on the results of surveys conducted by the Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Substance Abuse Treatment. About 1,800 physicians who have received waivers to prescribe the drug were interviewed, as were nearly 400 drug abusers under treatment with buprenorphine. The data represented responses received through May.

The surveys found consistently high treatment continuation or treatment completion rates among all treatment groups, and 74 percent of prescribing physicians reported the drug was effective by one month into treatment.

The study found evidence that the 30-patient limit has, however, had a major impact. More than 25 percent of physicians reported that the limit led to reduced prescribing of buprenorphine.

> **"This study confirms our hopes about the effectiveness of buprenorphine and also helps to illuminate the things that need to be done to help more patients reach this powerful medicine."**

A separate postmarketing survey required by the Food and Drug Administration and conducted by researchers at Wayne State University similarly found that in the first quarter of 2006, among surveyed physicians who prescribe buprenorphine, 29 percent had turned away at least one patient because of the limit. On average, physicians turned away 9.3 patients, with a total of 2,009 patients turned away by the survey respondents.

"I was surprised how high this number was, and it speaks to the need to raise the limit and increase the number of physicians who provide this service," said Charles Schuster, Ph.D., the postmarketing study author and director of the Clinical Research Division on Substance Abuse at Wayne State University. Schuster made his remarks during a Senate symposium on buprenorphine in August.

The postmarketing study, which included surveys of physicians and drug abusers and Internet searches to gauge the level of abuse of the drug, found little illegal diversion. The three-year study found buprenorphine treatment is clinically effective and well accepted by patients and has increased the availability of medication-assisted treatment well beyond the estimated 240,000 methadone treatment slots available.

Although federal drug-enforcement officials expressed fears that buprenorphine would work its way onto the illicit drug market, the postmarketing study was unable to identify a single case of a drug-addicted patient who began his or her drug "career" with buprenorphine.

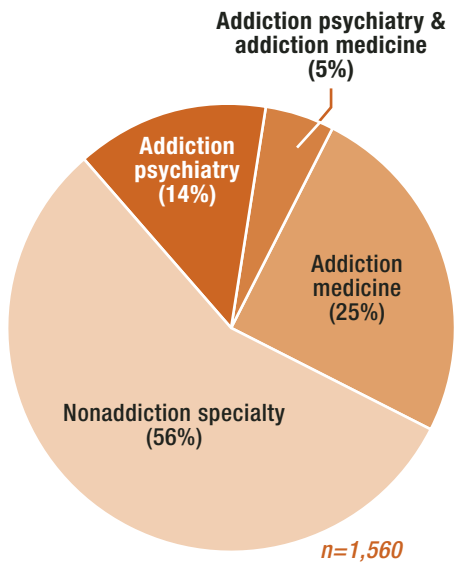
Herbert Kleber, M.D., director of the Division on Substance Abuse at the New York State Psychiatric Institute and a former deputy director in the Office of National Drug Control Policy, said at the Senate forum that office-based buprenorphine treatment has brought into treatment many patients who were reluctant to seek care when the only option was frequent attendance at a methadone clinic. The treatment of an estimated 200,000 patients by more than 7,800 physicians authorized to prescribe buprenorphine has not had the negative outcomes feared by some drug enforcement officials.

Kleber and others at the symposium said that blame for the lack of access to treatment for the estimated 1 million heroin addicts and 4.4 million nonmedical users of prescription opioid analgesics also lies with insurance programs that do not

please see ***Buprenorphine*** *on page 38*

Who Gives Treatment?

Most physicians who prescribe buprenorphine for opioid addiction are not addiction specialists.



Source: SAMHSA/CSAT evaluation of the buprenorphine waivers

KNOW THE FACTS

41% of all patients had the metabolic syndrome at baseline in the landmark CATIE schizophrenia study.[1]

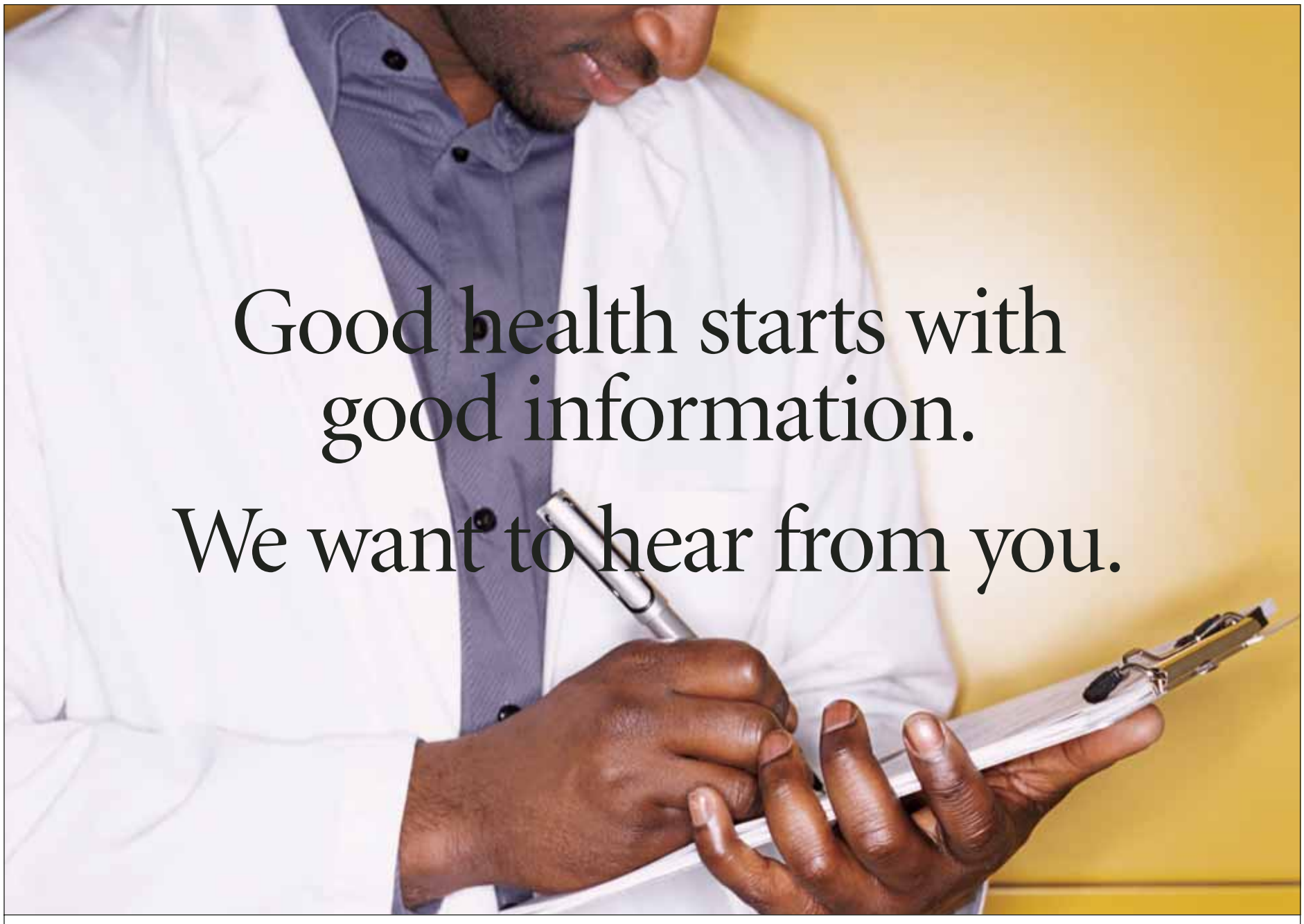
Be aware.
Screen and monitor your patients.
Make a difference.

Pfizer

Reference: 1. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005;80:19-32.

GZ274682T

Printed in USA/May 2006



We understand that accurate information about disease and treatment options makes patients and physicians better partners. And getting that information to patients and physicians is the goal of direct-to-consumer (DTC) advertising of prescription medicines. Studies show DTC advertising brings patients into their physician's office and starts important patient-physician conversations about health that otherwise might not have happened.

Still, some physicians have raised concerns about DTC advertising. To address many of these concerns, the Pharmaceutical Research and Manufacturers of America (PhRMA) developed a set of principles to guide DTC advertising of prescription medicines. The Guiding Principles call on PhRMA to set up an Office of Accountability to accept comments from the public on DTC advertising under the new Principles. These comments, which the Office of Accountability will forward to the appropriate member company, will help to inform signatories of the Principles of opinions about their advertisements.

Other commitments from signatories of the Guiding Principles include:

- **Submitting all new DTC television advertisements to the FDA before broadcasting.**
- **Educating health professionals about new medicines before the first DTC advertising campaign.**
- **Presenting information on the benefits and risks associated with the medicine in clear, understandable language.**
- **Including information on other treatment options, such as diet and exercise.**
- **Providing information on programs that can assist the uninsured or underinsured.**

Comments or concerns about DTC? We want to hear from you.

Commenting on DTC advertising under the Guiding Principles is easy:

- Please submit your comment in writing and mail it to the PhRMA Office of Accountability, 950 F Street, NW, Suite 300, Washington, DC 20004.
- You can also fax your comment to 202-775-0258.
- Please give us as much information as you can about the specific ad about which you are concerned so we can forward your comment to the relevant company.
- Please be sure to include a return address so the Office of Accountability can acknowledge receipt of your comment.

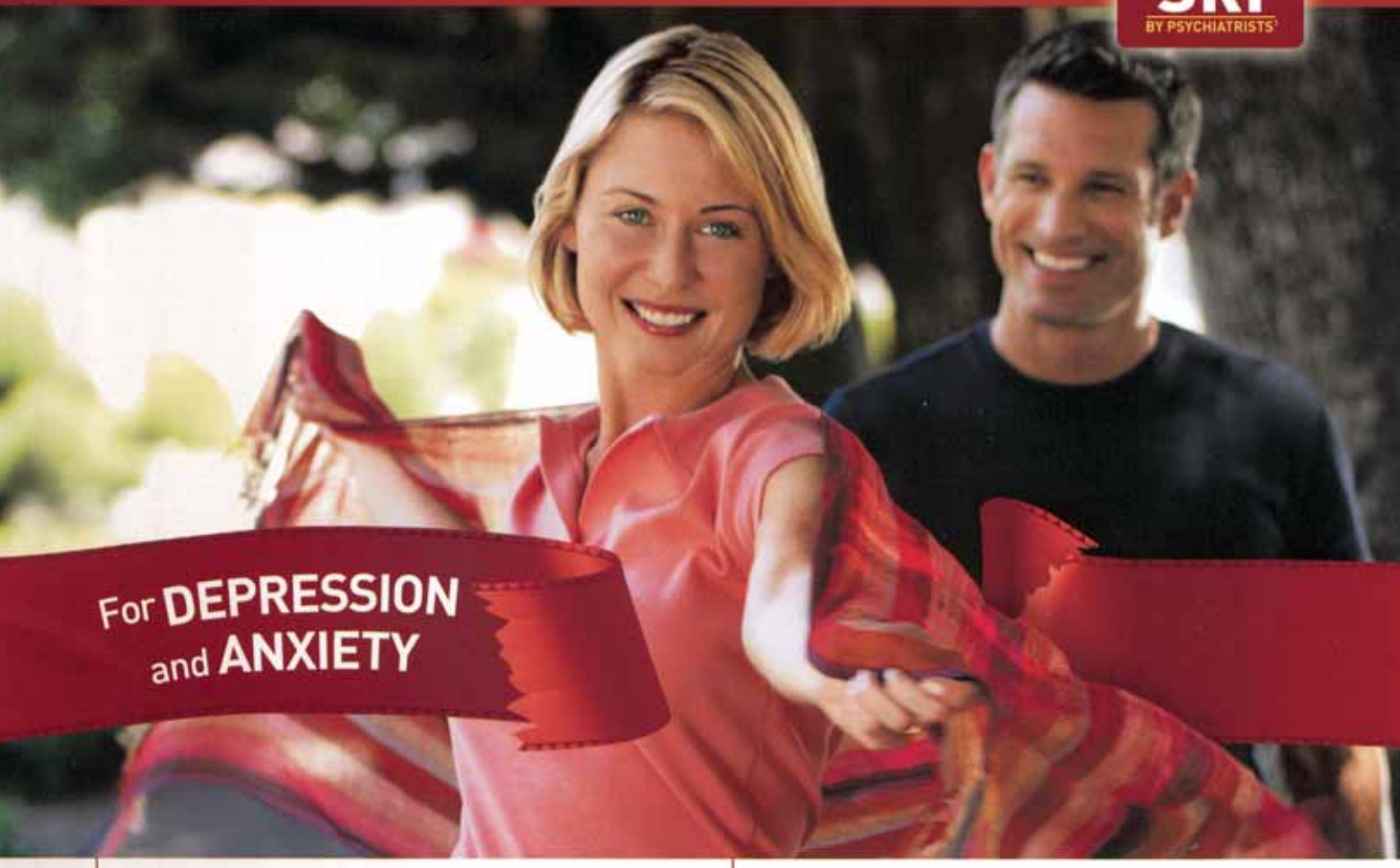
The Office of Accountability will forward your comment to the relevant company for consideration and make a summary of comments available to the public, an Independent Review Panel and the Food and Drug Administration.

PhRMA

To learn more about DTC advertising and see the complete Guiding Principles, please visit www.phrma.org/dtc.

A POWERFUL SSRI that's well tolerated

#1 PRESCRIBED SRI BY PSYCHIATRISTS[1]



UP TO 90% of depressed patients present with symptoms of anxiety[2]

PROVEN EFFICACY for Major Depressive Disorder and Generalized Anxiety Disorder[3]

Lexapro escitalopram oxalate

POWER TO ENJOY LIFE™

IMPORTANT SAFETY INFORMATION – Depression is a serious condition that can lead to suicidal thoughts and behavior. Antidepressants increased the risk of suicidal thinking and behavior (2% to 4%) in short-term studies of 9 antidepressant drugs in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially at the beginning of therapy or at the time of dose changes. This risk may persist until significant remission occurs. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients.

Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), pimozide (see DRUG INTERACTIONS – Pimozide and Celexa), or in patients with hypersensitivity to escitalopram oxalate. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Lexapro. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. The most common adverse events with Lexapro versus placebo (approximately 5% or greater and approximately 2x placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia.

References: 1. IMS National Prescription Audit. May 2005. **2.** Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry.* 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins;2003:552. **3.** LEXAPRO [package insert]. St Louis, Mo: Forest Pharmaceuticals, Inc.; 2005.

Please see brief summary of prescribing information for LEXAPRO on following page.

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

Brief Summary: For complete details, please see full prescribing information for Lexapro.

Suicidality in Children and Adolescents Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use) Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**). Concomitant use in patients taking pimozide is contraindicated (see **Drug Interactions** – Pimozide and Celexa). Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro. **WARNINGS-Clinical Worsening and Suicide Risk Clinical Worsening and Suicide Risk** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. A causal role for antidepressants in inducing suicidality has been established in pediatric patients. Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with 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. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.** **PRECAUTIONS General** Discontinuation of Treatment with Lexapro During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Abnormal Bleeding Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **Drug Interactions**). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. Hyponatremia Cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Lexapro treatment. All patients with these events have recovered with discontinuation of escitalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder. Activation of Mania/Hypomania In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. Interference with Cognitive and Motor Performance In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. Use in Patients with Concomitant Illness Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION** in full prescribing information). **Drug Interactions** CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol - Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS**. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with Lexapro. Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium - Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. Pimozide and Celexa - In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. Theophylline - Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Warfarin - Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine - Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. Triazolam - Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole - Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. Ritonavir - Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. CYP3A4 and -2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. Drugs Metabolized by Cytochrome P4502D6 - *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. Metoprolol- Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of ECT and escitalopram. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown. Mutagenesis Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays. Impairment of Fertility When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day. **Pregnancy-Nonteratogenic Effects** Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**). When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION** in full prescribing information). **Labor and Delivery** The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers** Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or Lexapro therapy should take into account the risks of citalopram exposure for the infant and the benefits of Lexapro treatment for the mother. **Pediatric Use** Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS-Clinical Worsening and Suicide Risk). **Geriatric Use** Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see **CLINICAL PHARMACOLOGY**). 10 mg/day is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse event information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder** Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder** Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder** Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 1**). **TABLE 1: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* [Lexapro (N=715) and Placebo (N=592)]: Autonomic Nervous System Disorders:** Dry Mouth (6% and 5%); Sweating Increased (5% and 2%). **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%). **Gastrointestinal Disorders:** Nausea (15% and 7%); Diarrhea (8% and 5%); Constipation (3% and 1%); Indigestion (3% and 1%); Abdominal Pain (2% and 1%). **General:** Influenza-like Symptoms (5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1 %); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder[1,2] (9% and <1%); Impotence[2] (3% and <1%); Anorgasmia[3] (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=225 Lexapro; N=188 placebo). [3]Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder** Table 2 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see **TABLE 2**). **TABLE 2: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* [Lexapro (N=429) and Placebo (N=427)]: Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1 %); Lethargy (3% and 1%); Yawning (2% and 1 %). **Urogenital:** Ejaculation Disorder[1,2] (14% and 2%); Anorgasmia[3] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=182 Lexapro; N=195 placebo). [3]Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 3 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 3: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125)]: Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%).*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 4 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 4: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials [In Males Only: Lexapro (N=407) and Placebo (N=383)]: Ejaculation Disorder** (primarily ejaculatory delay) (12% and 1%); **Libido Decreased** (6% and 2%); **Impotence** (2% and <1%). **[In Females Only: Lexapro (N=737) and Placebo (N=636)]: Libido Decreased** (3% and 1%); **Anorgasmia** (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 1 & 2, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only: N= 905 Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during postmarketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, angioedema, atrial fibrillation, diplopia, dystonia, extrapyramidal disorders, gastrointestinal hemorrhage, grand mal seizures (or convulsions), hepatitis, hypotension, myocardial infarction, neuroleptic malignant syndrome, orthostatic hypotension, pancreatitis, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, thrombocytopenia, torsades de pointes, toxic epidermal necrolysis, ventricular tachycardia and visual hallucinations. **Events Reported Subsequent to the Marketing of Racemic Citalopram** Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of citalopram: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, delirium, dyskinesia, ecchymosis, erythema multiforme, gastrointestinal hemorrhage, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolongation, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, torsades de pointes, toxic epidermal necrolysis and ventricular arrhythmia.

Rx Only Licensed from H. Lundbeck A/S Rev. 02/05

PSYCHIATRIC PRACTICE & MANAGED CARE
APA OFFICE OF HEALTHCARE SYSTEMS AND FINANCING

Psychiatry Leads Specialties in Opting Out of Managed Care

A report from the Center for Studying Health System Change (HSC) released in May notes that the percentage of physicians who do not have contracts with any managed care plans has taken its first jump after remaining stable for a number of years—from 9.2 percent in 2000-2001 to 11.5 percent in 2004-05. Although the increase doesn't seem large, HSC believes it signals a significant trend.

HSC is a nonprofit research organization that studies the U.S. health care system and is funded primarily by the Robert Wood Johnson Foundation. A survey group of 12,000 practicing physicians provides HSC with information about how health care delivery is changing.

Despite complaints, most physicians continue to contract with managed care organizations (MCOs). However, according to the HSC survey, 34.6 percent of psychiatrists have chosen to opt out of managed care. This contrasts with 9.4 percent of primary care physicians and 10.5 percent of all medical specialists.

The HSC report notes that physicians in solo or two-physician practices are less likely to contract with MCOs, possibly because of the administrative burden. It also notes that physicians who have been in practice for more than 20 years are less likely to have managed care contracts than those who have been in practice for 10 years or less, suggesting that more experienced practitioners may have a patient base and reputation enabling them to bypass managed care plans.

According to the HSC, psychiatry is the medical specialty that has always had the largest number of physicians without managed care contracts. The reasons include low reimbursements and the utilization management imposed on psychiatry by MCOs and managed behavioral health companies. HSC also suggests that the high percentage of nonparticipating psychiatrists may reflect the shortage of psychiatrists in many areas. ■

Psychiatric Practice & Managed Care (PP&MC) provides news and updates on practice management issues to APA members. PP&MC is printed bimonthly in *Psychiatric News* and is posted in PDF format under "Psychiatric Practice" on APA's Web site.

Don't Take 'No' For Answer

If you are a solo practitioner or work in a group practice with fewer than 10 full-time employees, you are defined as a "small provider" and are not required to file Medicare claims electronically.

This reminder was prompted by a recent call to APA's Managed Care Help Line from a psychiatrist in New Jersey. The psychiatrist had received a notice from his Medicare carrier, Empire, that as of July 31 he would no longer be permitted to submit paper claims—and that the decision could not be appealed. The notice stated that the doctor had failed to respond to a letter he had been sent earlier in the year requesting justification that he qualified for the exemption allowing him to submit paper claims to Medicare. As far as the psychiatrist knew, he had never received such a letter.

Ellen Jaffe, the Medicare specialist in APA's Office of Healthcare Systems and Financing, contacted the office of Empire's medical director, Dr. Kathleen Moynihan, to find out what the psychiatrist could do. He was a solo practitioner with no employees. Dr. Moynihan's assistant implied that the letter referred to in the notice may never have gone out and that he should write a letter to the contact identified in the notice stating that he was a physician with fewer than 10 full-time-equivalent employees and therefore could continue to file paper claims.

The Administrative Simplification Compliance Act mandated that as of October 16, 2003, all claims for Medicare reimbursement were to be submitted electronically, with limited exceptions. Apparently an audit is under way to ensure that those currently filing paper claims are, in fact, entitled to do so. If you receive a letter from your Medicare carrier asking you to justify your right to continue filing paper claims or stating that you can no longer file paper claims, respond by explaining that you are a small provider with fewer than 10 full-time employees.

If you have any questions about this issue, please contact the Managed Care Help Line at (800) 343-4671. ■

Is Part D Working Better? Share Your Experience

According to Irvin L. "Sam" Muszynski, J.D., director of APA's Office of Healthcare Systems and Financing (OHSF), the jury is still out on whether most of the problems encountered with the launch of Medicare's new Part D prescription drug benefit have been resolved. Are beneficiaries now getting access to the medications they need? Or have physicians and patients simply given up the quest to obtain them?

"All we know at this point," said Muszynski, "is that we've had some success in making the Centers for Medicare and Medicaid Services [CMS] aware of the problems facing psychiatrists who are trying to maintain their Medicare and dual-eligible Medicaid patients on the drugs they were taking before they entered Part D. We've been able to get a number of concessions from CMS when we've explained the kind of problems that are arising.

"However, **we need to keep hearing from APA members about the problems they're encountering if we are to continue making progress with CMS.** What we've found is that CMS is willing to solve problems on a case-by-case basis and to intervene with plans when complaints can be documented."

One important change that has resulted from OHSF advocacy is that CMS issued a clarification explaining that coverage of medications cannot be denied because the prescribed dose exceeds the dose approved by the FDA *(Psychiatric News*, July 21). Part D prescription drug plans (PDPs) had been routinely denying access to brand-name medications that were prescribed at doses higher than those approved by the FDA. Although the reason given for these denials was often "patient safety," the same kind of edits were rarely being used for generic drugs.

An issue that OHSF is now exploring with CMS is how physicians can be compensated for the extra time they are putting in so that their patients can have access to needed medications under Part D. Although CMS reports quick responses to physician requests, OHSF is hearing from APA members that they are still experiencing long waits on the telephone for prior authorizations. Such extensive expenditure of physician time had not been anticipated in the CPT coding system that forms the basis for determining Medicare payments.

As the first year of Part D nears its close (open season for Medicare beneficiaries to switch drug plans for 2007 is November 15 to December 31, 2006), Muszynski reminds APA members that any exceptions for drug coverage obtained in 2006 will probably have to be requested again for coverage in 2007. Although PDPs have the option of continuing exceptions beyond the plan year, it seems unlikely that many of them will do so.

Please inform OHSF about any problems you're having with Part D so staff can continue having a dialog with CMS based on actual problems and work toward their resolution.

Send e-mails to partd@psych.org or call (866) 882-6227. For the latest Part D information for psychiatrists, go to <www.mentalhealthpartd.org>. ■

Nine-Day Hold on Medicare Claims

The Deficit Reduction Act of 2006 mandates a one-time hold on Medicare payments during the last nine days of the 2006 fiscal year, September 22 to September 30. Claims that would have been paid during this period will be held until the first business day of October (October 2). No interest or penalty will be paid because of the delay.

While the hold on Medicare payments is not expected to have a major impact on individual practices, it's helpful to be aware of the policy so that you'll know why payment of your claims is taking more time than usual in late September. ■

Remember To Renew Opt-Out Status

Since 1998, physicians have been able to opt out of Medicare and instead care for Medicare patients under private contracts. Opting out requires physicians to file an opt-out affidavit with their local Medicare Part B carrier and to sign a private contract with each Medicare patient. Templates of both types of documents can be accessed on APA's Web site with a full explanation of the process at <www.psych.org/members/practpsych/optingoutofmedicare112701.cfm>.

The opt-out period is two years. During this time, neither the physician nor the beneficiary is permitted to file claims with Medicare for the physician's services. Some patients, however, may be asked to submit claims to Medicare by their secondary payers before they will pay their share. The Centers for Medicare and Medicaid Services (CMS) suggests that when a secondary payer has this requirement, patients should provide that payer with copies of the doctor's opt-out affidavit and the private contract they signed. If the insurer still demands that a claim be submitted to Medicare, CMS says that patients may submit the claim but note on it that their physician has opted out and that they understand that Medicare will not pay the claim. Even though the contract expressly states such claims should not be filed, says CMS, patients can do so without worry because CMS has no sanctions in place against patients who file a claim for care from a physician who has opted out.

The Managed Care Help Line has recently received a number of calls from APA members that make it clear that some secondary payers and Medicare carriers are tracking physicians' opt-out status. These APA members had opted out of Medicare but failed to renew their opt-out status when the two-year period expired.

Failure to renew opt-out status can create an administrative snarl. In one case, an APA member was told by the Medicare carrier's customer service representative that since he was not in the Medicare provider database, he did not have to take any action to continue his opt-out status, except for submitting an enrollment application for reinstatement.

This information was incorrect. **If you wish to retain your opt-out status after two years, you must renew it by filing another affidavit with the appropriate Medicare carrier and by updating your private contracts with your Medicare patients.** Otherwise, you are obligated to file claims for your patients with Medicare and to charge only the Medicare-allowed amount for the treatment you provide. ■

NIDA Head Wants Closer Collaboration With APA

The psychiatrist who heads the federal government's substance abuse research efforts says it is time that substance abuse stops playing second fiddle to other mental illnesses.

BY JIM ROSACK

National Institute on Drug Abuse (NIDA) Director Nora Volkow, M.D., told APA's Board of Trustees that she would like the Association's help in attaining three high-priority goals: "changing the culture of psychiatric practice, changing residency education, and changing reimbursement policies."

Volkow addressed the Board at its July meeting. She was the first of three directors of the National Institutes of Health's mental illness agencies invited to address the Board by APA President Pedro Ruiz, M.D.

In addition to Volkow, Ruiz has invited National Institute of Mental Health (NIMH) Director Thomas Insel, M.D., and National Institute on Alcohol Abuse and Alcoholism (NIAAA) Director Ting-Kai Li, M.D. The NIMH and NIAAA directors are expected to address the Board later this year.

"One of my objectives during my presidential year is to try to build very close relationships—on the institutional level—between APA and the three institutes," Ruiz told the Board.

He asked Volkow to provide the Trustees with an update on NIDA's current research priorities and future research goals. He then asked Volkow to tell the Board "whether there are any areas in which APA and [NIDA] can work a bit closer in order to help each other achieve their goals."

Volkow began by describing her concern over a long-running problem, one she first became aware of "during the very first days of my training as a psychiatrist, and that was being told that I could not admit an addicted patient to a psychiatric unit. The problem then was that many psychiatrists were not—and many still are not—recognizing that substance abuse is a mental disease."

The problem persists today, according to APA's immediate past president, Steven Sharfstein, M.D., who noted that for about the last 10 years the care of patients admitted to a hospital with a diagnosis of substance abuse alone is not covered; patients are eligible for coverage only if they have a co-occurring psychiatric diagnosis.

Substance abuse has long played "second fiddle" to other mental illnesses, Volkow noted, always being separated, sounding like an afterthought when people discuss "mental illness and substance abuse." The separation, she said, "helps no one."

"Most patients—the overwhelming majority—have problems with substance abuse and another mental illness," Volkow said. "We must work both actively and proactively to end this separation of the two."

Volkow recounted significant advances in research showing that substance-abuse disorders appear to have significant genetic influences that seem to be most important during adolescent development and are subject to environmental influences as well.

NIDA, Volkow said, currently has three primary research priorities. "First, how do we generate science that will help us prevent drug abuse and addiction? Second, how do we develop better treatments? And the third relates to HIV/AIDS. Drug abuse and addiction is a significant contributor to HIV/AIDS in this country and worldwide. We must address this."

Following her presentation of recent research advances and future research goals, Volkow was asked by APA President-elect Carolyn Robinowitz, M.D., "How do you see [APA] partnering with, or assisting with, the institute in such areas as public policy, appropriations, and public information?"

"I think APA plays an extraordinary role," Volkow replied, "and that's why I'm interested in solidifying our partnership. First of all, recognition that substance abuse is a primary mental disorder is a must."

National Institute on Drug Abuse

Nora Volkow, M.D.: "Most patients—the overwhelming majority—have problems with substance abuse and another mental illness. We must work both actively and proactively to end this separation of the two."

Noting that she was being candid, Volkow added that "two recent APA presidential presentations that I attended were very good, very eloquent. Yet there was not a single word about drug abuse or addiction." That "silence" on drug abuse, she said, "is a form of stigmatization."

For those already in practice, "the notion of education, of changing the culture of psychiatry, is extraordinarily important," she emphasized, and APA can play a vital role in that change.

For those in medical school and residency, more information must be included on substance abuse. Too little attention is currently being paid to this important topic, she noted.

Finally, Volkow said, on the policy front, "I cannot lobby, but I can tell you what the roadblocks are. It does not help us at all that we do not have parity for substance abuse."

After Volkow concluded her presentation, Ruiz said that he "will be following up on those challenges" and will offer to hold a meeting between NIDA officials and members of APA staff and components to explore the issues she raised.

More information on NIDA's research priorities is posted at <www.nida.nih.gov>. ■

Eliminating Minority MH Disparities Requires Multilevel Strategy

Interventions include national public policy reforms, changes at the community level focusing on differential pathways to specialty care, and interventions to improve clinician-patient communication.

BY MARK MORAN

Disparities in access to mental health services should be addressed at the public-policy, community, and provider-to-patient levels.

So said Margarita Alegria, Ph.D., a professor of psychology in the Department of Psychiatry at Harvard Medical School, in a presentation on mental health disparities to the APA Board of Trustees in July at a retreat preceding its regular summer meeting *(Psychiatric News*, August 18). She was invited by APA President Pedro Ruiz, M.D.

Alegria presented data from the pooled National Co-Morbidity Survey Replication (NCS-R) and the National Latino and Asian American Study (NLAAS). The latter is a national psychiatric epidemiologic survey conducted to measure prevalence of psychiatric disorders and mental health service usage in a nationally representative sample of Latinos and Asian Americans.

She also discussed interventions to remedy disparities, including national public-policy reforms, changes at the community level focusing on the differential pathways to specialty care affecting minorities, and interventions to improve clinician-patient communication.

Resolving the problem will require working at all three levels. "One level is the failure of health care markets and how they affect both the low-quality options and the choices of providers that people might have," she said. "The second level is the differential pathway to care that might happen, leaving people with limited access, particularly to specialty treatments. The third level is patient-provider interaction and how that affects differential treatment outcomes that lead to lower functioning, greater burden of illness, and lower quality of life."

A fundamental problem, Alegria said, is entry into the health care system and the widespread lack of insurance.

"If we really want to change things in terms of access to care and delivery of services to our populations, it's very important to think about health policy and market interventions that could really bring the whole population into a better state of care," Alegria said.

Disparities in access to services are largely related to lack of insurance, Alegria said. In 2004, 45.8 million people were without health insurance coverage, up from 45 million people in 2003, with no change in the percentage of people without health insurance coverage (15.7 percent) between 2003 and 2004. This lack of insurance especially affects Latino and Asian-American communities. Forty percent of Latinos have no health insurance, and for Latinos who have been in the United States less than five years—and for that reason are eligible for Medicaid—the rate is 58.6 percent.

One solution to this problem is to revise the Personal Responsibility and Work Opportunity Reconciliation Act of 1996, also known as the welfare reform law. That law, Alegria pointed out, restricts states from using federal funds to provide Medicaid and SCHIP coverage for certain groups, shifts health care costs from the federal to state level, and differentially affects ethnic groups depending on citizenship or refugee status.

At the community level, Alegria said addressing differential pathways into care is another target to explore. Such interventions might facilitate access to specialty services through social marketing campaigns and incentives for successful referral and engagement.

Alegria told the Board that the NLAAS found that only one-quarter of the respondents reported ever having been asked by a clinician about alcohol or drug use. Moreover, less than 20 percent reported ever having been asked about emotions, nerves, or mental health problems, she said.

Of those unable to communicate with a primary care provider in their language of choice, fewer than 4 in 10 had interpreter services available, she said.

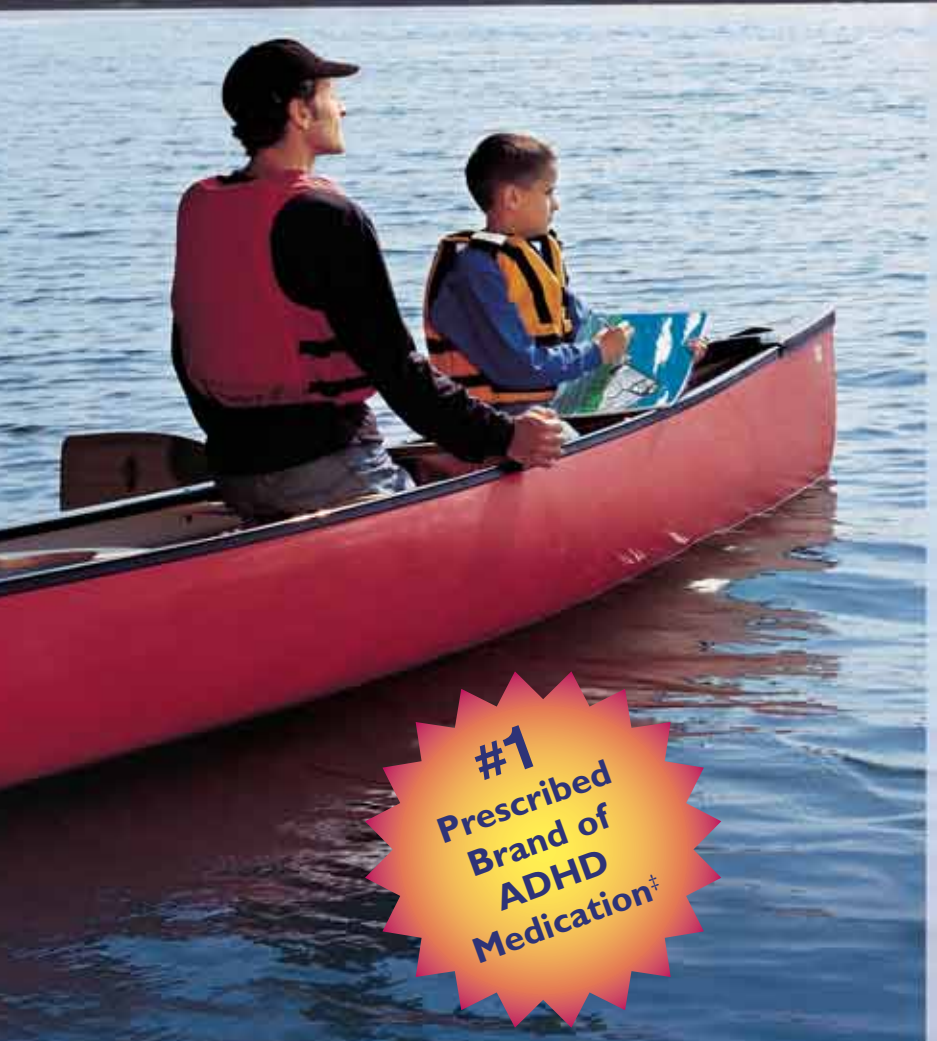
Finally, a third avenue of intervention might be efforts to improve clinician-patient communication, such as "patient activation" and provider communication trainings. Patient activation refers to the enhancement of involvement of patients in their own health care through teaching health management techniques and problem-solving skills.

Alegria said that about 20 percent of the NLAAS respondents indicated having had a negative experience with service providers. Only 50 percent rated psychiatric treatment as being helpful, and just 57 percent said they completed treatment.

"The question is how we can help patients ask for what they want and get what they need out of mental health care and how we can train providers to be more facilitating and attentive to what patients want," Alegria said. ■

When You Treat ADHD…

AIM HIGHER



#1 Prescribed Brand of ADHD Medication‡

ONE DOSE DAILY

ADDERALL XR® CII

5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg CAPSULES

(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Dextroamphetamine Saccharate
Amphetamine Aspartate Monohydrate Amphetamine Sulfate

ADDERALL XR® Provides Efficacy That May Help Pediatric Patients Realize Their Potential

- Demonstrated improvement in attention and behavior to a level comparable to that of non-ADHD peers*[1-3]
- Works quickly (1.5 hours) with up to 12-hour efficacy† for day-long improvement in both academic and social settings†[4-6]
- 6 dosage strengths for maximum flexibility
- Generally well tolerated—low discontinuation rates due to adverse events in placebo-controlled trials[4,5]

Important Safety Information

Patients with pre-existing structural cardiac abnormalities or other serious heart problems should generally not be treated with CNS stimulants, including Adderall XR. 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.

The most common adverse events in clinical studies of Adderall XR included: *pediatric*–loss of appetite, insomnia, abdominal pain, and emotional lability; *adolescent*–loss of appetite, insomnia, abdominal pain, and weight loss; *adult*–dry mouth, loss of appetite, insomnia, headache, and weight loss.

The effectiveness of Adderall XR for long-term use has not been systematically evaluated in controlled trials. Abuse of amphetamines may lead to dependence. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events. These events have also been reported rarely with amphetamine use. Adderall XR is contraindicated in patients with marked agitation, glaucoma, hyperthyroidism, tics, diagnosis or a family history of Tourette's syndrome, history of drug abuse, or current/recent use of monoamine oxidase inhibitors (MAOIs). New psychosis, mania, aggression, growth suppression, and visual disturbances have been associated with the use of stimulants and discontinuation of treatment may be appropriate. Use with caution in patients with a history of psychosis, seizures/EEG abnormalities, bipolar disorder or depression. Growth monitoring is advised during prolonged treatment. Adderall XR should be prescribed with close physician supervision.

References: 1. Ambrosini PJ, Sallee FR, Lopez FA, et al, on behalf of the LADD.CAT Study Group. A community assessment, open-label study of the safety, tolerability, and effectiveness of mixed amphetamine salts extended release in school-age children with ADHD. *Curr Med Res Opin.* 2006;22:427-440. **2.** Ambrosini PJ, Lopez FA, Chandler MC, et al. An open-label community assessment trial of ADDERALL XR® in pediatric ADHD. Poster presented at: 155th Annual Meeting of the American Psychiatric Association; May 22, 2002; Philadelphia, Pa. **3.** Conners CK. *Conners' Rating Scales-Revised: Technical Manual.* North Tonawanda, NY: Multi-Health Systems, Inc; 2001:97-103. **4.** Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2002;110:258-266. **5.** McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (ADDERALL XR), in children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2003;42:673-683. **6.** Lopez FA, Ambrosini PJ, Chandler MC, et al. ADDERALL XR in pediatric ADHD: quality of life measures from an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla.

Shire
Shire US Inc.
…your ADHD Support Company™
1-800-828-2088

Please see Brief Summary of Prescribing Information on adjacent page.

 AJ176 09/06

*Population norm and not from participants in studies.
†Average mean for all doses tested. ‡IMS Dataview, June 2006.

www.ADDERALLXR.com
www.ADHDSupport.com

Medicaid Innovations May Make MH Care Less Accessible

The cost-containment impetus that has driven changes to state Medicaid programs has raised concerns about what future measures might take aim at psychiatric care.

BY RICH DALY

Federal officials announced the availability of grants in late July to help states make "innovative" reforms to their Medicaid programs, prompting concerns about the impact of some of those reforms on people with mental illness.

The grants, and the changes they aim to spur, are part of ongoing efforts to rein in Medicaid spending growth while enabling states to adopt innovative methods to improve service effectiveness and efficiency and do "more to help people get the kind of care they prefer," according to a statement by the Centers for Medicare and Medicaid Services (CMS). The funds were authorized by the Deficit Reduction Act of 2005 (DRA) under the Medicaid Transformation Grant program.

Two states—West Virginia and Kentucky—have already implemented reforms approved by CMS that exemplify the goals of the new grant program, although those states did not receive additional funds to implement the changes.

West Virginia's Medicaid redesign included a choice of two benefit packages: a basic plan based on the current Medicaid service package and an enhanced plan for those who sign and adhere to a compliance agreement, which includes benefits not traditionally offered under Medicaid. In a major change from the previous Medicaid program, the new plan limits access for most adults to chemical dependency and mental health services to those who choose the enhanced package. Access to those services is based on compliance factors such as taking medication as directed and keeping all medical appointments.

Selby Jacobs, M.D., chair of the APA Committee on Funding for Psychiatric Services, said the program raises concerns because the illnesses of many people with mental disorders may cause them to refuse to agree to such a plan, or they are too disorganized to comply with it.

The Kentucky-redesigned Medicaid program, called Ky-Health Choices, offered various benefit packages aimed at meeting the needs of the general Medicaid population, as well as populations such as children, the elderly, and people with disabilities who need institutional care.

Sheila Schuster, Ph.D., executive director of the Kentucky Mental Health Coalition, said Medicaid participants with mental illness will be most impacted by the program's institution of medication copayments. She noted, however, that the copayments of up to $3 are significantly less than the $15 copayments that state officials initially proposed and allowed by the DRA.

Federal officials said that the grants will give states the flexibility to try out changes to their plans that may have higher short-term implementation costs than their current Medicaid programs. But they emphasized that the changes are meant to "streamline and modernize their systems, stabilize the growth of the program, and protect it into the future," according to Mark McClellan, M.D., Ph.D., CMS administrator.

The changes are meant to use funds in states' Medicaid programs more efficiently. Medicaid budgets have grown precipitously in recent years and threatened to consume state budgets. Kentucky's Medicaid deficit reached $675 million by July 1, 2005, and the new plan should save the state about $120 million in the first year and $1 billion over seven years, according to Kentucky health officials.

CMS officials reported that changes in recent years had already lowered Medicaid's spending projections nationwide for 2006 through 2015 by $224 billion, or 8 percent, from earlier estimates.

As part of the grant program, federal health officials have encouraged states to consider particular areas "for improved efficiency," including increased use of health care information technology, stepped up fraud-fighting efforts, and reduced Medicaid expenditures for covered outpatient medications.

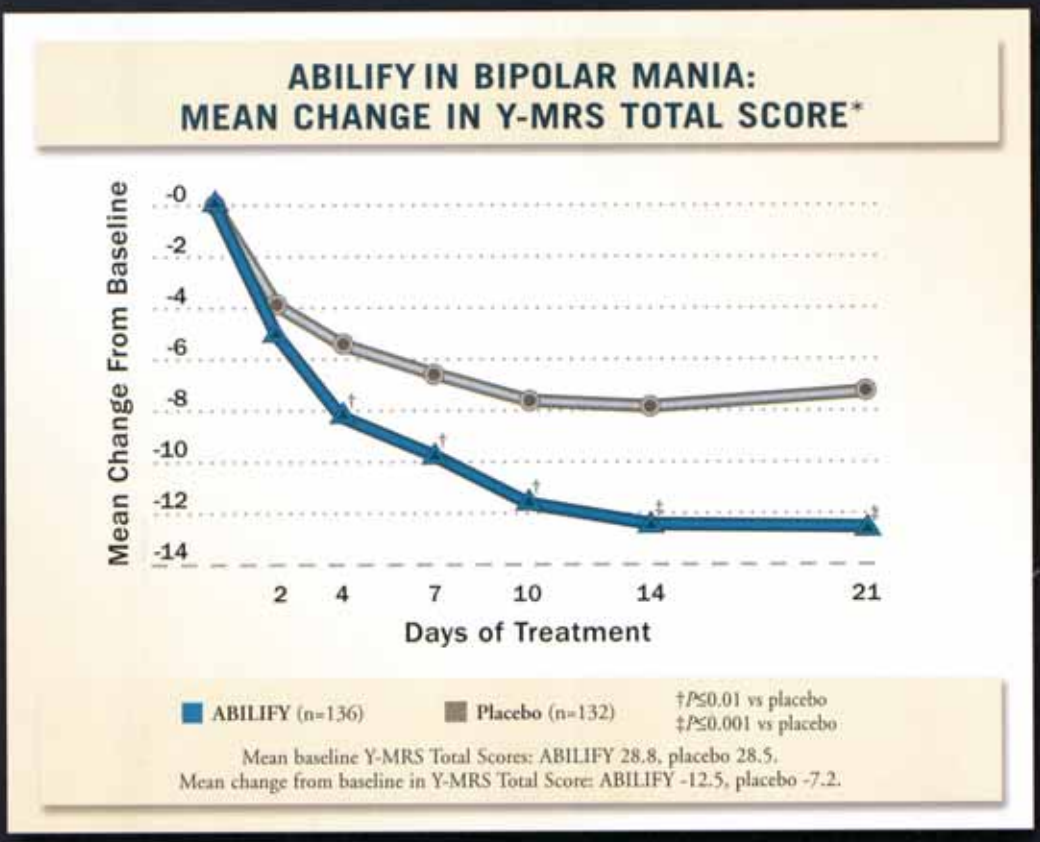
The last category raised concerns for Jacobs because Medicaid patients with severe and persistent mental illness are among the biggest users of outpatient medications. No states have yet announced plans to limit patient access or choices for psychiatric medications, but Jacobs is concerned that future Medicaid overhaul proposals may include such a measure.

Ten more states have applied for CMS approval of Medicaid program changes that would also mandate cost sharing or allow benefit cutting, according to the National Health Law Program (NHLP), a nonprofit patient advocacy group.

No state matching funds are required for the grants. The deadline for applications is September 15.

More information on the grants is posted at <www.cms.hhs.gov/MedicaidTransGrants>. ■

ABILIFY® (aripiprazole) efficacy looks good on paper...



Adapted from Sachs et al. *J Psychopharmacol.* 2006.

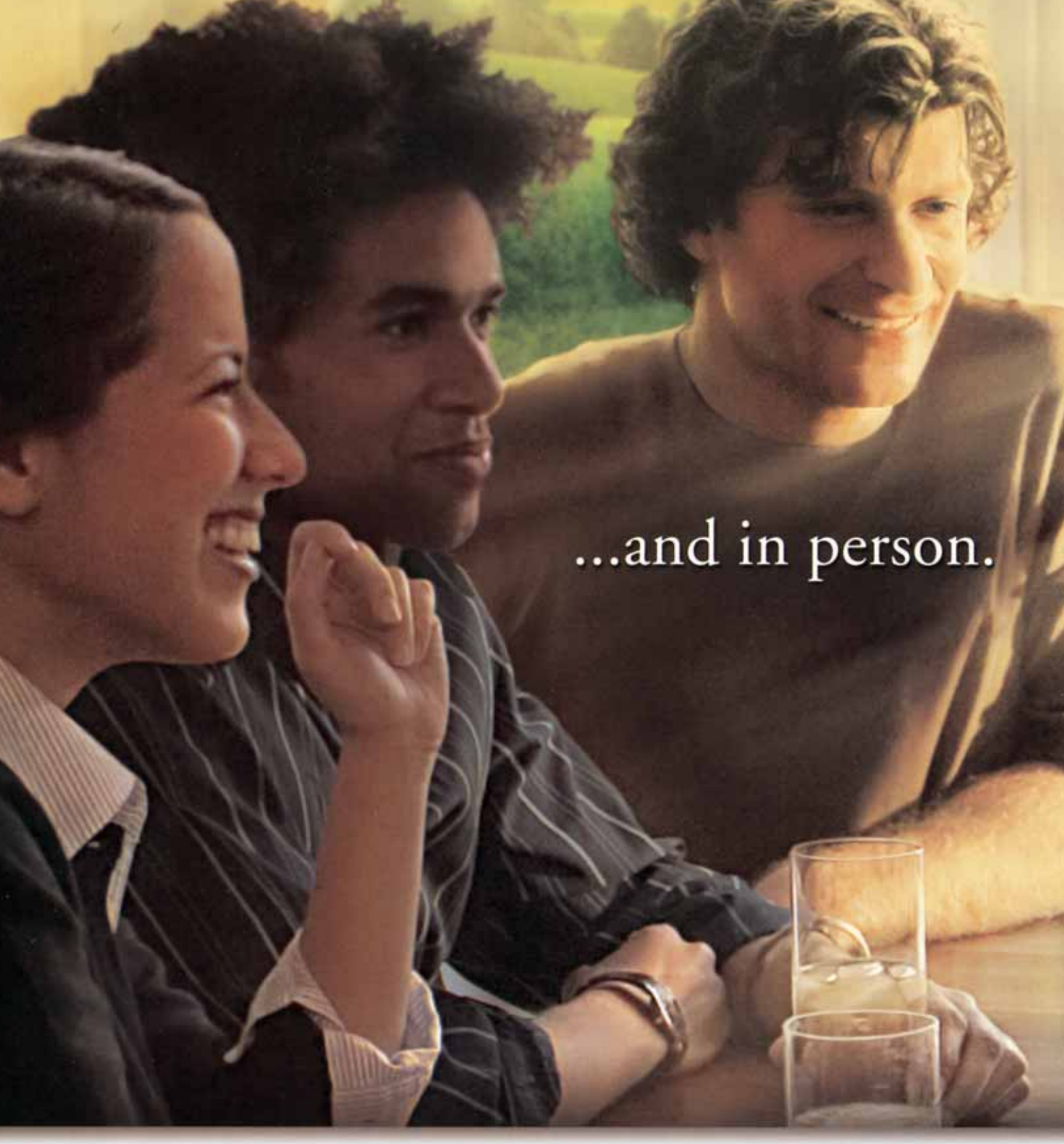
Data from a 3-week, double-blind, randomized, placebo-controlled trial in patients with **Bipolar I Disorder** experiencing acute manic or mixed episodes. Patients were randomized to receive either placebo or aripiprazole with a starting dose of 30 mg/day that could be reduced to 15 mg/day for tolerability and subsequently increased to 30 mg/day for clinical response.

* Last observation carried forward (LOCF).

Y-MRS: Young Mania Rating Scale (range 0 to 60).

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder.

Please see IMPORTANT SAFETY INFORMATION, including **Bolded WARNING**, and INDICATIONS on page 4.



Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular or infectious in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Please see IMPORTANT SAFETY INFORMATION and INDICATIONS on page 4.

ABILIFY®
(aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

HELP ILLUMINATE THE PERSON WITHIN

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole)

IMPORTANT SAFETY INFORMATION:

- Increased Mortality in Elderly Patients With Dementia-Related Psychosis
  Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular or infectious in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).
- ABILIFY is contraindicated in patients with a known **hypersensitivity** to the product.
- As with all antipsychotic medications, including ABILIFY, a rare condition referred to as **neuroleptic malignant syndrome** (NMS) has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of **tardive dyskinesia** (TD).
- **Cerebrovascular adverse events** (eg, stroke, transient ischemic attack), including fatalities, have been reported at an increased incidence in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY, including a significant dose-response relationship in a fixed-dose trial. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **Hyperglycemia**, including some serious cases ranging from ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients on ABILIFY should be appropriately tested before and monitored during treatment.

ABILIFY may be associated with **orthostatic hypotension** and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of **seizures** or with conditions that lower the seizure threshold.

Like other antipsychotics, ABILIFY may have the potential to **impair judgment, thinking, or motor skills.** Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

Disruption of the body's ability to reduce **core body temperature** has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

As antipsychotics have been associated with **esophageal dysmotility and aspiration**, ABILIFY should be used cautiously in patients at risk for aspiration pneumonia.

As the possibility of a **suicide** attempt is inherent in psychotic illness and bipolar disorder, close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY (aripiprazole) should be written for the smallest quantity consistent with good patient management to reduce the risk of overdose.

Physicians should determine if a patient is **pregnant** or intends to become pregnant while taking ABILIFY. Patients should be advised not to breast-feed while taking ABILIFY.

Patients should be advised to avoid alcohol while taking ABILIFY.

Both CYP3A4 and CYP2D6 are responsible for ABILIFY metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in ABILIFY clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit ABILIFY elimination and cause increased blood levels.

Commonly observed adverse events reported with ABILIFY in 3-week bipolar mania trials at a ≥5% incidence for ABILIFY and at a rate at least twice the rate of placebo include, respectively, akathisia (15% vs 4%), constipation (13% vs 6%), and accidental injury (6% vs 3%).

Treatment-emergent adverse events reported with ABILIFY in short-term trials at an incidence ≥10% and greater than placebo, respectively, include headache (31% vs 26%), agitation (25% vs 24%), anxiety (20% vs 17%), insomnia (20% vs 15%), nausea (16% vs 12%), dyspepsia (15% vs 13%), somnolence (12% vs 8%), akathisia (12% vs 5%), lightheadedness (11% vs 8%), vomiting (11% vs 6%), and constipation (11% vs 7%).

The adverse events reported in a 26-week, double-blind schizophrenia trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled schizophrenia trials, except for a higher incidence of tremor: 9% for ABILIFY vs 1% for placebo.

INDICATIONS: ABILIFY is indicated for the treatment of:

- Schizophrenia, including maintaining stability in patients who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer and observed for relapse during a period of up to 26 weeks*
- Acute manic and mixed episodes associated with Bipolar I Disorder
- Maintaining efficacy in patients with Bipolar I Disorder with a recent manic or mixed episode who had been stabilized and then maintained for at least 6 weeks*

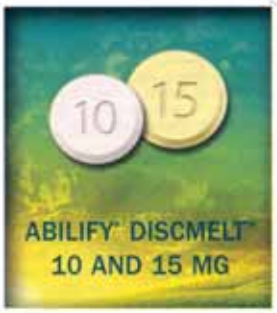
*Physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

ABILIFY is taken once daily with or without food.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the following pages.

New ABILIFY® DISCMELT™ (aripiprazole)

Orally Disintegrating Tablets



Similar efficacy and safety to ABILIFY tablets

No liquid needed

Rapidly disintegrates

Convenient delivery of an effective dose

ABILIFY® DISCMELT™ (aripiprazole)
ORALLY DISINTEGRATING TABLETS 15 mg

HELP ILLUMINATE THE PERSON WITHIN

Bristol-Myers Squibb Otsuka America Pharmaceutical, Inc.

ABILIFY®(aripiprazole) Tablets
ABILIFY® DISCMELT™ (aripiprazole)
Orally Disintegrating Tablets
ABILIFY®(aripiprazole) Oral Solution

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information please consult official package circular.

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS

ABILIFY (aripiprazole) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILIFY is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING**, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**, and **PRECAUTIONS:** *Use in Patients with Concomitant Illness: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease.*)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY (aripiprazole) included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%).

The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (in schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients).

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) of placebo-treated patients experienced seizures. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS**: *Use in Patients with Concomitant Illness*).

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations:** *Renal Impairment* and *Hepatic Impairment* in Full Prescribing Information) is limited.

ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were asthenia (placebo 3%, aripiprazole 8%), somnolence (placebo 3%, aripiprazole 9%), urinary incontinence (placebo 1%, aripiprazole 5%), excessive salivation (placebo 0%, aripiprazole 4%), and lightheadedness (placebo 1%, aripiprazole 4%).

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration. (See also **Boxed WARNING**, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**, and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis.**)

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY:

Interference with Cognitive and Motor Performance: Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY.

Nursing: Patients should be advised not to breast-feed an infant if they are taking ABILIFY.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking ABILIFY.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Sugar Content: Patients should be advised that each mL of ABILIFY oral solution contains 400 mg of sucrose and 200 mg of fructose.

Phenylketonurics: Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT orally disintegrating tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and 15 mg - 1.68 mg phenylalanine.

Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Quinidine: Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Carbamazepine: Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information).

Potential for ABILIFY (aripiprazole) to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information).

Alcohol: There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice; however, the response was shown to be due to a mechanism not considered relevant to humans.

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Pregnancy

Pregnancy Category C

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Labor and Delivery

The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Mothers

Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

Geriatric Use

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **Boxed WARNING**; **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**; **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis**; and **PRECAUTIONS:** *Use in Patients with Concomitant Illness*). The safety and efficacy of ABILIFY (aripiprazole) in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; ie, all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2 to 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole- and placebo-treated patients.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

The following findings are based on a pool of 3-week, placebo-controlled, bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Commonly observed adverse events associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 1. There were no adverse events in the short-term trials of schizophrenia that met these criteria.

Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

	Percentage of Patients Reporting Event	
Adverse Event	**Aripiprazole (n=597)**	**Placebo (n=436)**
Accidental Injury	6	3
Constipation	13	6
Akathisia	15	4

Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials

Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials

	Percentage of Patients Reporting Event[a]	
Body System Adverse Event	**Aripiprazole (n=1523)**	**Placebo (n=849)**
Body as a Whole		
Headache	31	26
Asthenia	8	7
Accidental Injury	5	4
Peripheral Edema	2	1
Cardiovascular System		
Hypertension	2	1
Digestive System		
Nausea	16	12
Dyspepsia	15	13
Vomiting	11	6
Constipation	11	7
Musculoskeletal System		
Myalgia	4	3
Nervous System		
Agitation	25	24
Anxiety	20	17
Insomnia	20	15
Somnolence	12	8
Akathisia	12	5
Lightheadedness	11	8
Extrapyramidal Syndrome	6	4
Tremor	4	3
Increased Salivation	3	1
Respiratory System		
Pharyngitis	4	3
Rhinitis	4	3
Coughing	3	2
Special Senses		
Blurred Vision	3	1

[a] Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis[f], dysmenorrhea[f].

[f] Percentage based on gender total.

An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

Dose-Related Adverse Events

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

Laboratory Test Abnormalities

A between group comparison for 3- to 6-week, placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

Weight Gain

In 4- to 6-week trials in schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%).

Table 3 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 3: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23-27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 4 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 4: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for a pooled analysis of placebo-controlled trials in patients with schizophrenia or bipolar mania, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 5 beats per minute compared to a 1 beat per minute increase among placebo patients.

Additional Findings Observed in Clinical Trials

Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY (aripiprazole) and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for ABILIFY was 4% (34/859). A similar adverse event profile was observed in a long-term study in bipolar disorder.

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in Table 2, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent – flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* – face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* – moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke.

Cardiovascular System: Frequent – tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* – bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

Digestive System: Frequent – nausea and vomiting; *Infrequent* – increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* – esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis.

Endocrine System: Infrequent – hypothyroidism; *Rare* – goiter, hyperthyroidism.

Hemic/Lymphatic System: Frequent – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* – thrombocythemia, thrombocytopenia, petechiae.

Metabolic and Nutritional Disorders: Frequent – weight loss, creatine phosphokinase increased, dehydration; *Infrequent* – edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; *Rare* – lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction.

Musculoskeletal System: Frequent – muscle cramp; *Infrequent* – arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; *Rare* – rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis.

Nervous System: Frequent – depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* – emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking; *Rare* – blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage.

Respiratory System: Frequent – sinusitis, dyspnea, pneumonia, asthma; *Infrequent* – epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* – pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis.

Skin and Appendages: Frequent – skin ulcer, sweating, dry skin; *Infrequent* – pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria.

Special Senses: Frequent – conjunctivitis; *Infrequent* – ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* – diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia.

Urogenital System: Frequent – urinary incontinence; *Infrequent* – urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* – nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (e.g., anaphylactic reaction, angioedema, laryngospasm, pruritus, or urticaria).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

Human Experience

A total of 76 cases of deliberate or accidental overdosage with aripiprazole have been reported worldwide. These include overdoses with aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a known outcome involved 1080 mg of aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdosage in children (age 12 and younger) involving aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse events (reported in at least 5% of all overdose cases) reported with aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or
Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Orally disintegrating tablets manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Oral Solution manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
US Patent Nos: 5,006,528 and 6,977,257

Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.

Otsuka America Pharmaceutical, Inc.
Rockville, MD 20850 U.S.A.

D6-B0001A-06-06
1156731B9 1158571B9 1155/06-06 June 2006

Women Psychiatrists Mentor APA's Future Leaders

Women psychiatrists who have excelled in leadership positions at the district branch and national levels of APA and other medical associations share valuable tips on how they moved ahead.

BY EVE BENDER

Even in the 21st century, women psychiatrists encounter glass ceilings and brick walls in their quest to assume leadership positions in organized psychiatry.

Certain skills and attitudes can go a long way in helping them to get ahead, according to seasoned psychiatrists who have distinguished themselves with many career firsts.

To help women members-in-training (MITs) and early career psychiatrists (ECPs) break through those walls and ceilings, Roslyn Seligman, M.D., the Assembly's Women's Caucus representative, convened a professional development seminar focusing on women in leadership in Kansas City in July.

Seligman told *Psychiatric News* that "women aren't given the opportunity to assume leadership positions" on the scale that men are, and that by convening the meeting, she hoped to provide Area 4 MITs and ECPs with the ability to network with one another and discuss strategies to assume leadership roles in their district branches and professional medical associations.

Attending meetings and asking questions, volunteering to take on new tasks, learning how to negotiate, and getting a basic understanding of finances were among the suggestions shared by faculty at the seminar.

Being a Mother and a Leader

One topic that provoked discussion at the meeting was balancing leadership and family responsibilities.

By the time APA President-elect Carolyn Robinowitz, M.D., graduated from medical school at Washington University in St. Louis, she was one of six women in her class. "We were seen as a bit of an oddity" by the male students, she noted.

When during medical school it was discovered that she was getting married, she was the object of any number of salacious jokes from male students, she recalled.

While a psychiatry resident at Albert Einstein College of Medicine/Bronx Municipal Hospital Center, she had two children. Robinowitz volunteered to be chief resident to ensure that she could coordinate her schedule with that of her husband's so that one of them was always home with their children. "I tried to be fair, and none of the residents complained," she remarked. "I learned to be a nurturing leader."

Robinowitz joined APA as a deputy medical director and director of the Department of Education in 1976 and was one of two women psychiatrists on staff (Jeanne Spurlock, M.D., joined APA as deputy medical director and head of APA's Office of Minority/National Affairs in 1974). In addition, Robinowitz was the first woman elected to the American Board of Psychiatry and Neurology. She also went on to be one of the few women to serve as a dean at a medical school: from 1995-2000, she was associate dean and then academic dean at Georgetown University.

In the early days especially, being a woman leader was often lonely, she said, because there were few other women leaders with whom she could talk. "What I learned is that you really need a support system—like-minded people with whom you can communicate."

Robinowitz advised women psychiatrists poised to assume leadership positions to look to the business literature for helpful information regarding leadership and gender roles. A good dose of humor, she observed, can be an effective tool for bringing people together and diffusing uncomfortable or difficult situations. She also suggested that women ally themselves not only with other women, but with male colleagues and leaders as well.

Seligman seconded this last advice, noting that "it is important to formally recognize those men who support women" in their careers. Putting that belief into action, she presented Ronald Burd, M.D., with the Good Guy Award for suggesting the leadership seminar. Burd was recently elected recorder of the APA Assembly

Eve Bender

From left: Ann Genovese, M.D., Jo-Ellyn Ryall, M.D., Carolyn Robinowitz, M.D., Jeanne Lackamp, M.D., Cheryl Jennifer Buda, M.D., Judith Kashtan, M.D., Roslyn Seligman, M.D., Juliette Petersen, M.D., DeLaney Smith, M.D., Laura Hirshbein, M.D., and Kelly Rogalski, M.D., pose after a professional-development seminar in which women leaders in psychiatry helped younger colleagues prepare to become the next generation of leaders.

Never Sell Yourself Short

Judith Kashtan, M.D., the Minnesota Psychiatric Society representative to the Assembly and a member of APA's Finance and Budget Committee, began to be aware of women's issues by participating in what were known as "consciousness-raising" groups as an undergraduate at Brown University in the 1960s.

"This was my first experience of bonding with women and understanding them as strong, capable people," she noted.

She joined a women medical student's group at Wayne State University as one of about 30 women in a class of 256. During medical school, Kashtan joined the medical school's admissions committee and learned a great deal from that experience, she said.

One of the valuable lessons she learned during residency training was that women physicians should not shy away from demanding the same salaries as their male colleagues. Women physicians and other women professionals, she found, tend to ask for less pay at the start of their careers, which keeps them on a lower salary track despite periodic raises.

"Never be afraid to discuss money" with potential employers, Kashtan said. "Don't treat money as a dirty topic—learn about what others in the community earn and make sure that you get paid a comparable amount."

In the experience of Area 4 Assembly Representative Jo-Ellyn Ryall, M.D., "if you volunteer to take the lead and do a good job, you'll be asked [to take the lead role] again." Ryall, who also serves as chair of the Assembly Procedures Committee, has held many leadership positions within APA and other medical organizations both locally and nationally.

Ryall served as the first speaker of the American Medical Women's Association from 1993 to 1995. She has also been a Missouri delegate to the AMA since 1995 and an alternate delegate since 1989.

"We need to show others that it is possible for women to take the lead and to excel even as they continue to balance responsibilities in other areas that remain important to them—such as family and community," said Ryall. "Women need to make choices and prioritize at all times since it is impossible to do everything and be everything. Being able to choose what is important is a sign of leadership." ■

World Mental Health Day Shines Global Spotlight on Suicide Concerns

This year's World Mental Health Day, to be held October 10, focuses on a widespread public health problem that ends 1 million lives per year, yet is preventable.

BY EVE BENDER

The World Federation for Mental Health (WFMH) will turn the global spotlight on suicide next month to increase public awareness of the problem and reduce the incidence of suicide around the world.

World Mental Health Day falls on October 10 and the theme is "Building Awareness—Reducing Risk: Mental Illness and Suicide."

"The devastation that suicide can cause should be a major concern both in the United States and across the globe. We know the facts—that left untreated, mental illnesses can be as lethal as untreated cancer," said James H. Scully Jr., M.D., medical director of APA. "Bringing attention to mental illnesses and suicide during World Mental Health Day 2006 is both timely and essential. The more information psychiatrists and other mental health professionals can provide to the public through public-awareness events, educational tools, and one-to-one outreach, the more lives we can save."

Scully is a member of the World Mental Health Day 2006 Scientific Advisory Panel.

According to the WFMH, there are 1 million suicide deaths each year around the world, representing 1.4 percent of the total global burden of disease.

At least 90 percent of those who die by suicide have at least one undiagnosed mental illness, which includes drug or alcohol use disorders.

"These facts should motivate governmental bodies and officials to pay greater attention to the negative social and economic consequences that result from failure to implement progressive national policies and strategies to address the unmet needs of people with mental illness and at risk for suicide," according to the WFMH.

This year, the WFMH has collaborated with the International Association for Suicide Prevention to promote World Suicide Prevention Day, which falls on September 10.

Each year since 1992, local, regional, and national mental health agencies across the world have commemorated World Mental Health Day by planning activities to educate the public about the prevalence, prevention, and treatment of certain mental illnesses.

This summer the WFMH distributed thousands of informational packets to mental health agencies and clinics, governmental organizations, and medical associations thousands of packets. Information covered suicide prevention and the responsible reporting of incidents of suicide by the media.

Also included were tips on how to commemorate the day, such as connecting with local suicide-prevention programs and support groups, planning walks or marches to raise awareness of suicide, and scheduling media conferences. Other materials expose prevalent myths about suicide—that people who talk about suicide won't really act on it; that if a person is determined to commit suicide, nothing can stop him or her; and that talking about suicide may give others the idea to commit suicide.

More information about World Mental Health Day 2006 is posted at <www.wfmh.org/wmhday2006.htm>. ■

Huge Demand Didn't Thwart Groundbreaking MH Project

As the nation pauses to note the fifth anniversary of the September 11, 2001, terrorist attacks, one project stands as a shining example of how to deliver mental health services after a disaster and measure their effectiveness.

BY JIM ROSACK

The attack on the World Trade Center the morning of September 11, 2001, was the deadliest terrorist act ever committed on U.S. soil. Arriving at a final tally of the dead—about 2,800—stretched out agonizingly for months, and confirming victims' identities seemed like a never-ending puzzle. But if it is possible that something good can come out of something almost too horrible to imagine, it is this: officials of the New York State Office of Mental Health (OMH) knew that many people would be severely traumatized by the attack and realized the importance of providing mental health assistance quickly. They also realized they had an unprecedented opportunity to learn lessons that could inform future disaster-response plans.

"Disasters present terrible opportunities to learn about how to get people needed mental health services," said Susan Essock, Ph.D., a professor of psychiatry and director of the Division of Health Services Research at Mount Sinai School of Medicine in New York City.

Essock collaborated with OMH staff on the development and implementation of Project Liberty, New York state's crisis counseling program.

Project Liberty, funded by grants totaling $155 million from the Federal Emergency Management Agency (FEMA), quickly became the largest federal government-funded disaster mental health program in history. New York's OMH took the lead in implementing the program in collaboration with approximately 200 local agencies.

The Project Liberty program was implemented to "provide free and anonymous community-based mental health services to help individuals recover from their psychological distress and regain their predisaster level of functioning," according to project literature. The services offered were based on the assumption that most people's stress reactions, although significantly disturbing to them personally, constituted normal responses to a traumatic event, and that the reactions would dissipate over the short term.

As such, the range of interventions offered under Project Liberty was aimed at helping people identify their trauma responses, understand that those responses were normal, and reconnect with previously existing social support networks.

"One of the fundamental things we learned," said Chip Felton, M.S.W., an OMH senior deputy commissioner and chief information officer for OMH's Center for Information Technology and Evaluation Research, "was that it proved possible to set up and run a very large crisis counseling and emergency mental health program and that, in fact, it seemed to be something that really resonated with a large number of people."

The September issue of the APA journal *Psychiatric Services* presents a special section containing a series of 15 reports detailing data on numerous aspects of the project, from demographic characteristics of those who used Project Liberty services to data on outcomes of interventions and quality assurance/quality improvement metrics.

According to those reports, between the time of Project Liberty's launch in the weeks following September 11 and the point when its services ceased on December 31, 2003, Project Liberty provided face-to-face counseling and educational and outreach sesrvices to an estimated 1.2 million individuals in the New York City metropolitan area. About 465,000 individuals received nearly 690,000 individual crisis counseling sessions. Almost 550,000 individuals were provided public education on trauma.

Just under 700 counseling and educational sessions were provided in September 2001, and the number of sessions each month almost doubled through April 2002. The project reached its peak during May 2002, during which 41,000 sessions were provided to individuals by Project Liberty counselors. Service utilization remained near that level through August 2003, when the project began its phase-down in preparation for its cessation at the end of 2003 (see chart).

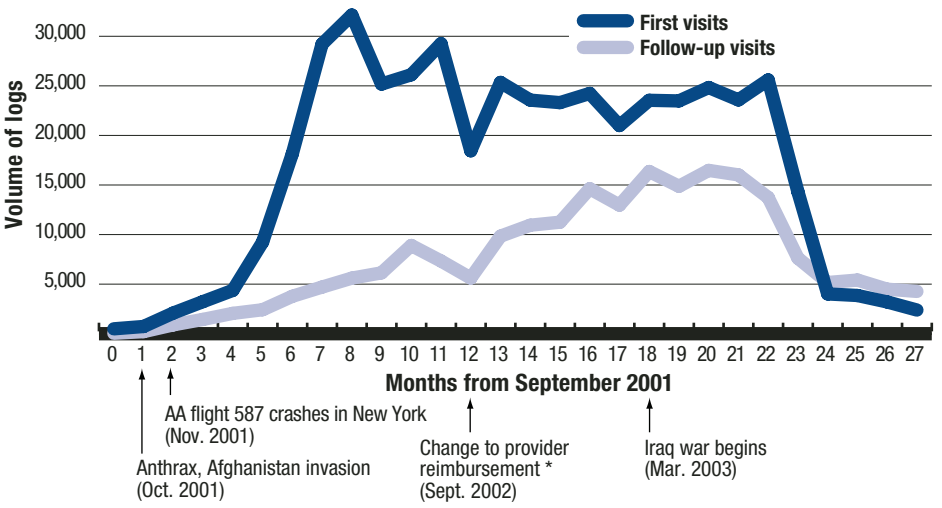
For those with mild to moderate symptoms, "crisis counseling" under Project Liberty ranged from informal sessions with counselors that included simply discussing and validating a patient's feelings to more structured sessions focusing on recovery skills, coping mechanisms, and reliance on social-support networks.

By early summer 2002, it became apparent to Project Liberty staff that there was

please see ***Project*** *on facing page*

Project Liberty's Reach Unprecedented

The graph tracks the number of first and follow-up crisis-counseling sessions with individuals seeking Project Liberty services from the project's start after 9/11 till its end in December 2003.



* From fee-for-service to cost-based system based on anticipated service volume

Post-9/11 MH Intervention Evaluates Its Performance

A quick and simple metric provided valuable feedback that revealed which Project Liberty counselors faithfully adhered to the fundamentals of the program's enhanced therapy services.

BY JIM ROSACK

In the early days and weeks following any disaster, according to researcher Susan Essock, Ph.D., "there has always been a notion that conducting research involving disaster response and following victims' responses to trauma along with long-term outcomes are just unconscionable."

In the early days and weeks following September 11, 2001, this dictum was little challenged, with one notable exception—Project Liberty, which became the largest federal disaster mental health program in history. It was funded through grants totaling $155 million from the Federal Emergency Management Agency (FEMA) and led by the New York State Office of Mental Health (OMH) in collaboration with nearly 200 local agencies. To Susan Essock's way of thinking, a good chunk of scarce public funds were being fed into the effort, so "it seemed to me to be unconscionable to *not* learn something from the effort."

Essock is a professor of psychiatry and director of the Division of Health Services Research at Mount Sinai School of Medicine in New York City.

OMH officials in New York were successful in requesting that FEMA designate part of the total Project Liberty funding for quality assurance/quality improvement activities. As a result, in addition to numerous other metrics tied to recipients of the program's services, such as demographic variables, symptom clusters, variables predictive of further need versus recovery, and long-term outcome measures, Project Liberty included monitoring mechanisms to gauge how well the services rendered adhered to treatment manuals and guidelines.

In a report in the September *Psychiatric Services*, Essock and her Project Liberty colleagues highlighted one of the monitoring mechanisms by describing outcomes associated with how faithfully clinicians adhered to the key elements of the cognitive-behavioral treatment intervention developed for Project Liberty's enhanced services counseling program (see story above). All recipients of enhanced services were invited to participate in a telephone interview involving only six questions. Five questions rated how often their clinician (counseling was largely provided by nondoctoral licensed counselors and social workers) provided each of five components of the intervention, using Likert scales ranging from 0 (not at all) to 3 (a lot). A sixth question asked how often the clinician gave homework, also a required component of the intervention.

In an effort to tie performance directly to training on the Project Liberty model of CBT for posttraumatic stress reactions, the researchers looked at responses for those clinicians at sites where all clinicians received training, compared with those clinicians at sites where only some clinicians received training. Essock and her colleagues were not surprised to find that interviewees who received services at the partial-training sites were less likely to report that their clinician adhered to all five techniques considered central to the intervention. Similarly, homework was given less frequently by counselors at sites where only some clinicians were trained.

"In five short questions, we were able—with good confidence—to identify the people who got their intervention at a site where all clinicians were trained versus a site where only some clinicians were trained," Essock told *Psychiatric News*. "So, through an easy, inexpensive means, we were able to be quite confident that our training program was effective. OMH contracted with these providers to do a specific intervention. This measure asked, 'Did they do it?' Purchasers of health care services all over the country are interested in answering that question." ■

Lessons

continued from page 1

ment Award. The program has expanded throughout lower Manhattan to encompass 16 elementary, middle, and high schools, where therapists have provided evaluations and treatment to students with anxiety, depression, and stress-related conditions (*Psychiatric Services*, October 2005).

Today, the WTC Healing Services maintains an office overlooking ground zero and has served nearly 50,000 people.

"St. Vincent's has a long history of helping in disasters," said Joseph T. English, M.D., chair of the Department of Psychiatry at the hospital and past president of APA, but it had never faced a disaster of this magnitude before. Because of the close proximity of the hospital to ground zero, however, staff knew the hospital's emergency room was a logical destination for the injured, and they quickly geared up to handle what they expected to be an inundation of survivors. But that didn't happen. Few people showed up there—an artifact of the devastating nature of the attack: many people were killed, while others escaped unharmed or with minor injuries.

Clarice Kestenbaum, M.D.: "People are very resilient, and children are much more resilient than is typically thought."

What St. Vincent's did become a magnet for was the countless people seeking loved ones. "By 2 o'clock that afternoon, people had started putting flyers up everywhere with a face and a name," recalls Camille Archer, M.D., a psychiatry resident at the time. "People were everywhere crying in the streets; the whole place seemed very different."

English recalled that former Nebraska Sen. Bob Kerry, now president of New York's New School, called to ask how he could help, and the hospital set up a family relief center in the school's atrium across the street from St. Vincent's.

For two weeks after 9/11, the center served those families. "It is not an exaggeration to say it was the finest hour for our attending staff and house staff, who in addition to their regular duties worked around the clock," English said. "It was the finest demonstration I have ever seen of selfless, professional commitment."

Spencer Eth, M.D.: "The natural process [in reaction to trauma] appears to be symptom formation followed by healing."

Normative Response Is Symptom Formation

Prior to coming to St. Vincent's, Eth had worked in Los Angeles in a VA hospital treating Vietnam veterans and been involved in treating people following the riots in Los Angeles. "I went into this experience primed to help organize the St. Vincent's response to 9/11," he said.

Joseph T. English, M.D.: The 9/11 performance of St. Vincent's staff "is the finest demonstration I have ever seen of selfless, professional commitment."

"One of the lessons I have learned is that the vast majority of people who were in lower Manhattan on that day and had direct exposure to this catastrophe became symptomatic," Eth told *Psychiatric News*. "There have been a number of telephone surveys confirming the fact that the normative response was symptom formation. However, most of the people who became symptomatic had their symptoms subside. They recovered. The natural process appears to be symptom formation followed by healing.

"There were a minority of people who went on to have persistent symptoms, and a small minority has gone on to be chronically and severely ill," Eth said. "For these people, PTSD can be as disabling as schizophrenia and bipolar illness. Something we knew from working with Vietnam vets and relearned after 9/11 was that our best treatments are not effective for everyone. I continue to see people who are severely affected."

Eth cited the case of a firefighter who was rescuing people from the towers and got out just before they collapsed. "He never leaves his apartment now," he said. "Even treatment is not effective."

Speaking to *Psychiatric News* just a week prior to the news that British authorities had arrested individuals believed to be plotting an attack that might have rivaled or surpassed 9/11 in bloodshed, Eth said New Yorkers—and Americans everywhere—will have to live with a constant threat of terror.

"We are entering an era in which more and more people will have to be aware of threats and danger," he said. "This is going to become a factor in our lives. Growing up during the cold war, [I was always aware of the] threat of world war and the use of atomic weapons. But it didn't seem as real as suicide bombers. In New York City there are people who are quite anxious and vigilant going over a bridge or through the Lincoln Tunnel, knowing that at any moment something dreadful could happen.

"The statement is often made that 9/11 changed everything," he continued. "One of the things it changed is that the general feeling of safety and security we had all taken for granted in America has been lost. For large numbers of people in New York, it's not an issue for which they seek treatment, but it has become a baseline source of anxiety." ■

Project

continued from facing page

a group of individuals who were repeatedly showing up, looking for help. Felton and his colleagues decided to seek permission from federal regulators to expand the scope of Project Liberty to offer more intensive crisis counseling. Regulators approved offering enhanced services, which included a cognitive-behavioral intervention that was specifically developed to treat posttraumatic stress (see article on facing page).

In total, 753,015 counseling and educational sessions were provided between September 2001 and December 2003.

Disaster Response Matures, Evolves

"We found that as part of putting together this large, overall infrastructure supporting a very-large-scale public health initiative, it was in fact feasible to collect anonymous but key pivotal data from thousands of people who served as crisis counselors," Felton told *Psychiatric News*. "Those data were important to us in many different ways as we tried to manage the ongoing program, and hopefully in the longer term, [we will all be] more prepared for disaster response in the future."

In a "Taking Issue" column in the September *Psychiatric Services*, Betty Pfefferbaum, M.D., J.D., a professor of psychiatry at the University of Oklahoma Health Sciences Center, and Bradley Stein, M.D., Ph.D., a visiting associate professor of psychiatry at the University of Pittsburgh School of Medicine and Western Psychiatric Institute and Clinic, wrote, "The reports from Project Liberty in this issue of *Psychiatric Services* attest to the wealth of experience and the explosion of knowledge and understanding gained in work associated with the September 11, 2001, terrorist attacks.

"Disaster mental health care has evolved, and its growth is reflected in the ability to respond to succeeding disasters of increased dimensions in the context of more complex and devastated environments. Research is also advancing."

"The reports from Project Liberty show us how far we've come," Stein told *Psychiatric News*. The field of disaster response has significantly improved compared with where the field of disaster response was 10 years ago, he said.

"In particular, the federal response has matured," Stein explained. "When you get federal regulators, researchers, state officials, and counseling providers together, it is indeed possible to build quality indicators into a disaster response program."

Tracking Quality in Disaster Response

Project Liberty was the first FEMA-funded disaster response program to include quality assurance/quality improvement measures.

Felton, Essock, and their colleagues requested that the federal Substance Abuse and Mental Health Services Administration (SAMHSA) specifically allocate funds for program evaluation.

"The data analysis was as close to real time as we could get with a paper-based reporting system," Felton explained. Every two weeks, Project Liberty leaders got a new feed of data from the service encounters.

"We were able to use that information, not just centrally as the state mental health authority administering the program," added Sheila Donahue, M.A., who served as the director of Project Liberty, "but also to provide the data to the counties and at the individual provider level on an ongoing basis."

The federal investment in the evaluation structure needed to collect this information and use it in proactive ways was absolutely vital and led to a significant pay off, said Donahue, who is currently the director of data analysis and performance measures at the New York OMH.

"Of course, we were pleased with how the quality assurance measures in Project Liberty worked," Felton noted. "But one of the things that is not mentioned in any of the *Psychiatric Services* articles is that today, if you look at SAMHSA's Center for Mental Health Services toolkit for crisis counseling programs, you will see that some of the Project Liberty assessment tools are now included as recommended tools."

The* Psychiatric Services *special section on Project Liberty is posted at <www.ps.psychiatryonline.org>. ■

AP Photo/Mary Altaffer)

Chihuahua El Duque was one of the tools used in therapy sessions at the St. Vincent's World Trade Center Healing Services for the loved ones of 9/11 victims.

...wait until you see Janssen's renewed commitment to fighting it.

Schizophrenia. It's a challenge for all of us. And there's so much more that can be done. That's why at Janssen there's no stronger force than our commitment to discovering and delivering new, innovative treatment options to help you manage this debilitating disease now and in the future. It's why we're dedicated to working more closely with you to better understand your ongoing needs. And why we will always persevere in the face of any storm.

Janssen, L.P.

EXCLUSIVELY DEDICATED TO MENTAL HEALTH

 July 2006 01JN100T

Depression can recur many times...

Or not.

Extending the body of evidence

2-YEAR RECURRENCE PREVENTION

data for EFFEXOR XR[1]

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**
- Adult and pediatric patients with MDD can experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressants. **Patients treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the**

Reference: 1. Data on file, Wyeth Pharmaceuticals Inc.

Length and results of positive, randomized, double-blind, placebo-controlled antidepressant clinical studies[1]

CLINICAL DATA

	6 months	1 year	2 years
EFFEXOR XR® (venlafaxine HCl)	✔	✔	✔
Cymbalta® (duloxetine HCl)	✔		
Lexapro® (escitalopram oxalate)	✔	✔	
Wellbutrin XL® (bupropion HCl)	✔		
Zoloft® (sertraline HCl)	✔	✔	*
Paxil® (paroxetine HCl)	✔	✔	†

✔ = demonstrated relapse/recurrence prevention at end point.

***Zoloft has been studied in 2-year recurrence prevention as monotherapy but failed to show a significant difference vs. placebo at end point. Wilson KCM, et al. *Br J Psychiatry*. 2003;182:492-497.**

†Paxil has been studied in 2-year recurrence prevention in combination with psychotherapy/clinical management sessions with or without augmentation, but not as monotherapy. In patients with recurrent depression, no significant difference was seen between Paxil and placebo. Reynolds CF, et al. *N Engl J Med*. 2006;354:1130-1138.

In the EFFEXOR XR PREVENT study, patients had at least 3 prior episodes of depression in their lifetime.

beginning of drug therapy, or at the time of increases or decreases in dose. Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.

- The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.
- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

Please see brief summary of Prescribing Information on adjacent page.

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® *EXTENDED RELEASE CAPSULES*

The change they deserve.

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk—** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Families and caregivers of pediatric patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be 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. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Serotonin Syndrome—**The development of potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with (i) concomitant use of serotonergic drugs and (ii) with drugs that impair metabolism of serotonin (see **CONTRAINDICATIONS—MAOIs**). If concomitant treatment of Effexor XR with an SSRI, SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension—**Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. ***Mydriasis***: Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **PRECAUTIONS: General—*Discontinuation of Treatment with Effexor XR.*** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness***: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. ***Changes in Weight***: ***Adult Patients***: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients***: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; $P<0.001$) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Height***: ***Pediatric Patients***: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled SAD study, both the Effexor XR (n=109) and the placebo (n=112) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Appetite***: ***Adult Patients***: Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide About Using Antidepressants in Children and Teenagers* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; and 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**—***Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans (see WARNINGS: Serotonin Syndrome):** Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility—*Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy—*Teratogenic Effects—Pregnancy Category C***. Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***. Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS—General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS: *Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalciuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease (including pulmonary eosinophilia), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C024, revised June 2006.

Wyeth®

When Stress Gets Severe, Police Turn to POPPA

A peer-counseling program succeeds in helping New York City police deal with stress and mental health problems by providing easy access to confidential and supportive assistance.

BY EVE BENDER

Each day, about 40,000 men and women working for the New York Police Department (NYPD) help save countless lives.

Sometimes, however, they are the ones who need to be saved.

While in the line of duty, they may be called to the scene of a fatal car accident or a grisly crime or find themselves dodging an assailant's bullets.

When New York City's finest are overwhelmed by the stress associated with their work or are experiencing personal problems, they can turn to POPPA.

The Police Organization Providing Peer Assistance (POPPA) is an independent agency that works in conjunction with the NYPD to help police cope with their distress and find mental health treatment when necessary.

The program uses a cadre of volunteer officers who are trained to counsel their peers and guide them to a panel of mental health professionals who are also trained to work with police.

POPPA founder and director Bill Genet created the program in 1996 in response to 26 NYPD suicides that occurred in 1995 and 1996. It is a 501(c)3 organization and relies largely on funding from donations and corporate support.

POPPA's headquarters is located at 26 Broadway in lower Manhattan in space donated by Koeppel Companies L.L.C., a real estate investment and management firm. There, POPPA staff administer its programs, train volunteers, and coordinate client services.

Genet worked for 33 years as a police officer with the NYPD, but it was his longstanding position as trustee of the Patrolmen's Benevolent Association that opened his eyes to the emotional difficulties experienced by his fellow officers and the need for an independent organization through which officers could find support without worrying about whether they were jeopardizing their careers by doing so.

He also recognized that many police are reluctant to seek professional help and so contracted with a counseling and psychotherapy group to train 25 police to become peer support officers (PSOs).

The nerve center of the POPPA program is the 24-hour helpline, which can be reached by dialing (888) COPS-COP.

The thrust of the program is preventative, Genet told *Psychiatric News*. "The idea from the beginning was to aid these officers before they reached crisis and destroyed their jobs, families, and other aspects of their lives."

Call volume has increased since the program began, and in recent years, about 800 officers have called the help line annually.

Police Linked to Professional Help

When an officer in distress calls, he or she is asked to leave a name and number on a digital answering service. Two PSOs, one primary and one secondary, receive a page with this information, and the primary PSO returns the call. In case the primary PSO is unable to return the call, the secondary PSO assumes this duty.

The PSO speaks to the caller and tries to determine the nature of his or her problem. Within a day, the PSO meets with the officer in a public place—usually a car, coffee shop, or diner—to listen supportively and screen the officer for major safety risks, including suicidal or homicidal ideation, alcohol abuse, or risk of violence.

The 150 or so PSOs working with POPPA have received training on spotting signs and symptoms of mental health problems, such as depression, anxiety, and posttraumatic stress disorder, and knowing when to refer their peers to a trained mental health professional.

The PSOs refer about 40 percent of the callers to a panel of mental health professionals who have been trained by POPPA staff. Many callers do not need professional help, while others may be identified as needing professional help but are not given a referral because they've made it clear they will not follow up.

The training of clinicians "is more of an indoctrination into police culture," Genet said.

Less than 5 percent of the calls are what Genet refers to as "critical cases"—officers who pose a risk to themselves or others. These officers are usually hospitalized until they are more stable.

Interactive Style Best

Psychiatrist and POPPA medical adviser Frank Dowling, M.D., grew up in a family of police officers, firefighters, and bricklayers in what he described to *Psychiatric News* as "a typical Brooklyn Irish and Italian family."

As medical adviser, Dowling helps to train PSOs about mental health issues and POPPA clinicians about how to work effectively with the police officers. Sometimes he sees the officers in distress if a POPPA clinician can't see them soon enough "to bridge the gap," he said.

Educating POPPA clinicians involves giving them the dos and don'ts of working with police.

"Police will be more receptive to clinicians who are expressive or interactive" he noted, which indicates to officers that they are being heard and understood. He advises them to speak to their police clients "intelligently but in plain English" and to avoid using mental health jargon.

When Dowling informs clinicians that "police are the most psychologically minded individuals you will ever meet," he is sometimes met by blank stares, he said.

"What do police do all day long?" Dowling asks them. "They are listening and watching," whether observing the community or reading the body language of a crime suspect.

Police clients need only to turn that acute level of observation inward—though not always an easy task, he acknowledged—and they make great strides in the therapeutic setting.

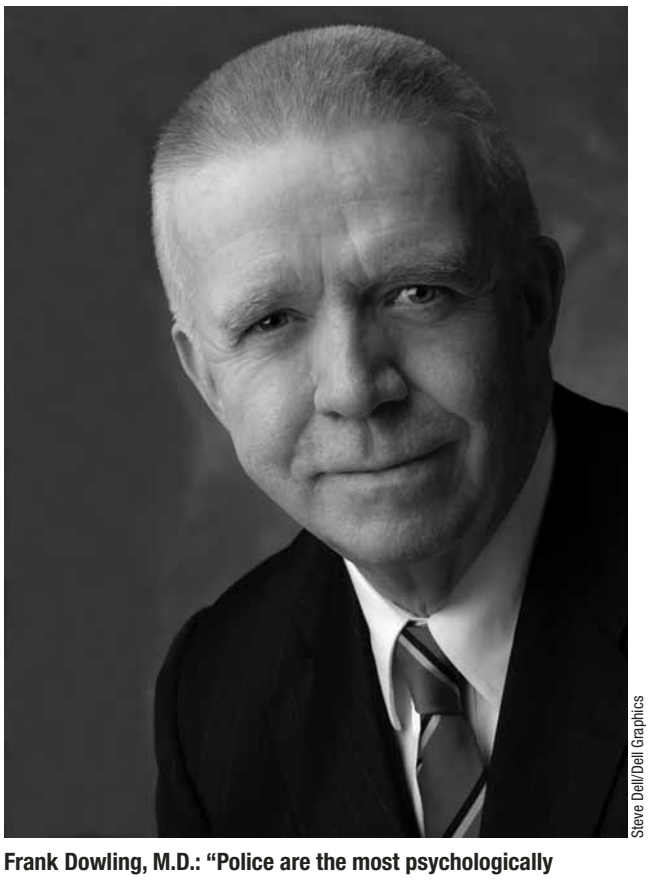
'Psychological Battering Ram'

The average police officer is exposed to some type of traumatic event multiple times over the course of his or her career, Dowling noted, including "injuries and deaths from drive-by shootings, pulling bodies out of cars mangled in collisions, and dealing with victims of rape, child abuse, and assault."

"This job is like a psychological battering ram," he declared.

Each traumatic event can have a cumulative effect on officers' mental health, he

please see ***POPPA*** *on page 35*



Steve Dell/Dell Graphics

Frank Dowling, M.D.: "Police are the most psychologically minded individuals you will ever meet."

Peer Program a Life Saver

Sgt. Lisa Pomerance has been with the New York Police Department (NYPD) for 17 years and is one of the original group of peer-support officers who began training and working with the Police Organization Providing Peer Assistance (POPPA) when the program started in 1995.

Peer-support officers are assigned to the POPPA help line for 24-hour shifts about three or four times a year, Pomerance told *Psychiatric News.*

Over the years, Pomerance has counseled peers dealing with marital or relationship problems, depression, anxiety, and alcohol problems and successfully urged many to seek professional help. One of the most frustrating aspects of her volunteer work is an officer's refusal to get help after he or she has been identified as needing it, Pomerance noted. But the rewards far outweigh the challenges for her. Pomerance is part of an outreach effort to educate NYPD employees about the program and its services and to dispel stigma surrounding mental health problems.

Before speaking about the program at roll call in one precinct recently, she received a moving introduction by a fellow officer: "A long time ago, I reached out to POPPA because I was having major difficulties in my life. The person who saved my life is standing right here," he said, pointing to Pomerance.

"That felt absolutely wonderful," she noted. "POPPA works, and it saves lives."

When Disaster Struck on 9/11, POPPA Was Prepared

As television viewers watched the second terrorist attack on the World Trade Center complex and the subsequent collapse of its two towers on September 11, 2001, members of the New York Police Department risked their lives to pull survivors from the rubble and witnessed scenes of carnage too horrible to describe.

Between 1,500 and 2,000 officers arrived at ground zero before the second plane struck. Twenty-three officers were killed as a result of the attacks.

By mid-2002, an estimated 20,000 to 25,000 police officers had worked at ground zero, the city morgues, or the retrieval operation at the Staten Island landfill.

During this time, the Police Organization Providing Peer Assistance (POPPA) was in full swing, according to director Bill Genet.

Nearly 200 peer support volunteers working with POPPA had been trained in critical-incident response before the attacks occurred.

The program sent outreach teams to ground zero to talk with rescue workers about posttraumatic stress disorder and the services available at POPPA's crisis centers at the Federal Reserve Bank and at the Staten Island retrieval operation. They reached an estimated 8,000 rescue workers and distributed 100,000 information brochures to emergency personnel and police commands across the city.

In addition, POPPA volunteers urged their fellow officers to join small groups of officers in "debriefing" or "diffusing" sessions to discuss their feelings associated with their activities at ground zero.

By September 11, 2002, POPPA volunteers, together with a number of mental health outreach teams from around the country, had counseled more than 5,000 officers.

Genet believes that for the largest proportion of officers who developed posttraumatic stress disorder after 9/11, the terrorist attacks were only partly to blame for their symptoms. For these individuals, "the attacks merely triggered the accumulated trauma from years past associated with shootings and other incidents," he said. ■

Another Residency Program Joins APA's 100% Club

The psychiatry residency training program at Bergen Regional Medical Center in Paramus, N.J., is the latest residency program to have all of its psychiatry residents become members of APA.

It joins the ranks of an exclusive organization within APA: the 100% Club. This club was established to encourage residents throughout the United States and Canada to join APA and to do so with other trainees in their programs, according to Deborah Hales, M.D., director of APA's Division of Education and Career Development.

A photo of each program that joins the 100% Club is turned into a poster and mailed to every medical school in the United States and Canada to encourage medical students to join APA. In addition, programs in the 100% Club receive a major textbook from American Psychiatric Publishing Inc. and a free online subscription to *Focus: The Journal of Lifelong Learning* for each year that all of their residents are APA members.

Top row, from left: Drs. Mohammad Mallick, Seokkon Cho, Oxana Matsenko, Felix Sterling, Sreenivas Katragadda, Mohammad Niazi, Imran Shafi, Syed Ali, Praveen Madadi, Alfred Sorrentino. Middle row, from left: Drs. Helene Miller, Cecilia Wang, Karine Airepetian, Olga Tchikindas, Marina Cozort, Pubdini Muthukuda, Judie Kwolek, Parool Patel, Maria Saiz, Masood Jilani. Bottom row, from left: Drs. Saima Shafiq, Sajjad Khan, Nahla Mahgoub, Daniela Ganescu, M. Javed Iqbal (program director), Aijaz Nanjiani, Amel Badr, Lynda Mandell, Syed Rasheed.

M. Javed Iqbal, M.D., the program's training director, said, "Our psychiatry residency training program is designed to give residents clinical experience in all areas of adult and child psychiatry, to provide sound theoretical and clinical training, and to establish a foundation for future specialization. The residents, under the guidance and supervision of an experienced faculty, gain a broad clinical expertise in care and treatment of a diversified patient population."

More information about the 100% Club is available from Nancy Delanoche of APA's Division of Education and Career Development at (703) 907-8635. Programs that are interested in signing up all their residents should also contact Delanoche. ■

Control acute agitation with

GEODON®

*for **Injection** (ziprasidone mesylate)*

In schizophrenia…

Rapid improvement with low EPS[1,2]

- Significant control achieved between 15 and 30 minutes* after injection[1,3]
- Proven advantages over haloperidol IM
  - twice the improvement as measured on the BPRS[4†]
  - significantly lower incidence of movement disorders[2‡]
- Smooth transition, with continued improvement, from IM to oral therapy[2,4]
- May be used concomitantly with benzodiazepines

*In 2 pivotal studies vs control, significance was achieved at 15 minutes (with 10 mg dose) and 30 minutes (with 20 mg dose), respectively.

†In a 7-day, open-label IM-to-oral transition study.

‡In a 6-week, open-label IM-to-oral transition study.

GEODON®
***Oral Capsules** (ziprasidone HCl)*
*and **Injection** (ziprasidone mesylate)*

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_C interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

In fixed-dose, pivotal studies, the most commonly observed adverse events associated with the use of GEODON for Injection (incidence ≥5%) and observed at a rate in the higher GEODON dose groups (10 mg, 20 mg) of at least twice that of the lowest GEODON dose group (2 mg control) were somnolence (20%), headache (13%), and nausea (12%).

Please see brief summary of prescribing information on adjacent page.

Brain Changes May Explain Long-Term Antisocial Behavior

Abnormalities in the amygdala-orbitofrontal system may be the neurological basis of persistent, impulsive antisocial and violent behavior.

BY MARK MORAN

Men with schizophrenia and a history of violence may have neurobiological signs that distinguish them from schizophrenia patients with no such history.

A review of studies comparing neurobiological correlates among persons with schizophrenia who do and do not have a history of violence found inconsistent and contradictory evidence—largely due to varying definitions of violence, differences in sample characteristics, and use of different measures to tap neurobiological correlates of violent behavior.

The findings suggest, however, that men with schizophrenia who have displayed a stable pattern of antisocial and aggressive behavior since childhood have some distinct signs compared with patients with no such history.

Those signs include reductions in amygdala volume, more structural abnormalities of the orbitofrontal system, more abnormalities of white matter in the amygdala-orbitofrontal system, and smaller reductions of volume in the hippocampus. Those men also appeared to perform better on neuropsychological tests tapping specific executive functions and more poorly on assessment of orbitofrontal functions.

The authors suggested that abnormalities in the amygdala-orbitofrontal system may be the neurological basis of persistent, impulsive antisocial and violent behavior.

"Persons with schizophrenia and a history of violence may present abnormalities in the amygdalae from early life that are associated with reduced abilities to experience emotions and to recognize emotions in others," wrote Kris Naudts, M.D., and Sheilagh Hodgins, M.D., of the Department of Forensic Mental Health Science at the Institute of Psychiatry, King's College London, in the July *Schizophrenia Bulletin*. "As the individual matures, the connections with the orbitofrontal cortex do not develop. . . . In addition, abnormalities of the orbitofrontal cortext may be associated with difficulty in inhibiting impulsive decision making and behavior."

They used Medline, PsycINFO, and Embase to identify studies of neuropsychological test performance, neurological soft signs, and structural and functional brain imaging of persons with schizophrenia and a history of violence.

Seventeen studies were identified. Because of differences in the definition of violence, sample characteristics, and measures used to identify neurobiological correlates, some of the findings are inconsistent and contradictory. But some findings do emerge from the review.

Six of nine studies looking at performance on neuropsychological tests indicate that patients with a history of violence perform better on these tests than patients without a similar history, suggesting fewer abnormalities of the prefrontal cortex. "This is reflected in better executive function and verbal skills, particularly in samples of outpatients with a history of violence," the authors observed.

But impulsivity may stem from abnormalities in the orbitofrontal cortex, which Naudts and Hodgins said is necessary for inhibiting impulsive decision making and behavior and for anticipation of punishment or negative consequences.

"Persons with schizophrenia and a history of violence may present abnormalities in the amygdalae from early life that are associated with reduced abilities to experience emotions and to recognize emotions in others."

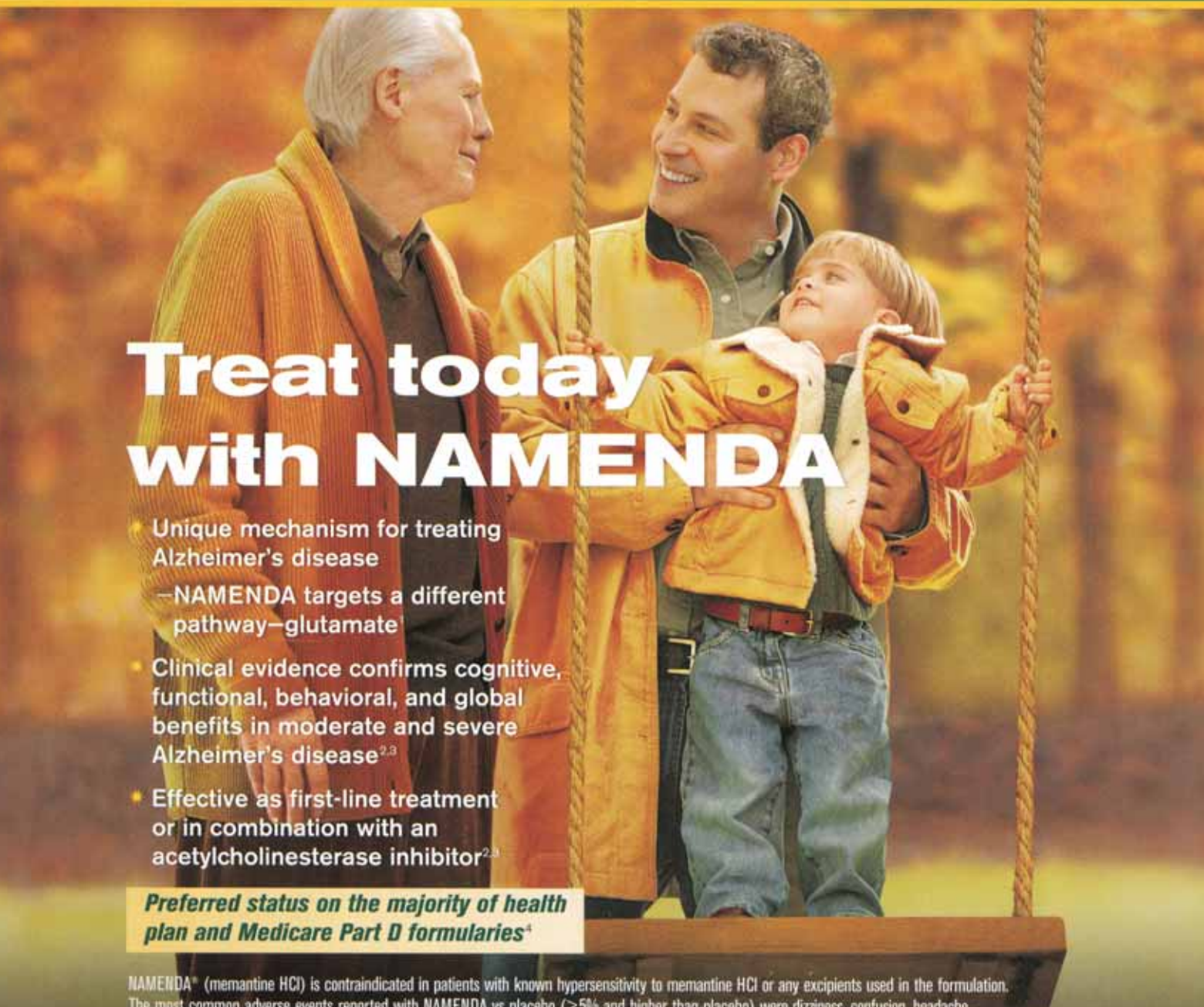
In four studies that examined structural brain scans among men with schizophrenia who did and did not have a history of violence, the violent patients were distinguished by volume reductions in the amygdala and abnormalities in the orbitofrontal cortex-amygdala.

Two functional brain imaging studies also suggest differences among patients with a history of violence. Positron emission tomography brain scans of 17 patients who had a history of repetitive violent offending and 14 patients who had committed only one offense showed reduced activity in the anterior inferior temporal cortex of the left hemisphere in the repetitive-violent group.

A study using single photon emission tomography to assess the relationship between prefrontal function and aggression in 12 nonviolent patients and three violent patients found significantly reduced prefrontal cerebral blood flow during completion of the Wisconsin Card Sorting Test in the violent patients.

"Neurobiological Correlates of Violent Behavior Among Persons With Schizophrenia" is posted at <http://schizophreniabulletin.oxfordjournals.org/cgi/content/abstract/32/3/562>. ■

At the first sign of moderate Alzheimer's disease



Treat today with NAMENDA

- Unique mechanism for treating Alzheimer's disease
  - –NAMENDA targets a different pathway–glutamate[1]
- Clinical evidence confirms cognitive, functional, behavioral, and global benefits in moderate and severe Alzheimer's disease[2,3]
- Effective as first-line treatment or in combination with an acetylcholinesterase inhibitor[2,3]

Preferred status on the majority of health plan and Medicare Part D formularies[4]

NAMENDA® (memantine HCl) is contraindicated in patients with known hypersensitivity to memantine HCl or any excipients used in the formulation. The most common adverse events reported with NAMENDA vs placebo (≥5% and higher than placebo) were dizziness, confusion, headache, and constipation. In patients with severe renal impairment, the dosage should be reduced.

References: 1. NAMENDA® (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, Mo. **2.** Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ, for the Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med.* 2003;348:1333-1341. **3.** Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, for the Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA.* 2004;291:317-324. **4.** Data on file. Forest Laboratories, Inc.

For more details, visit **www.namenda.com**

Forest Pharmaceuticals, Inc.

Namenda memantine HCl

Extending memory and function

Please see brief summary of Prescribing Information on the adjacent page.

62-1008558 04/06

Namenda
memantine HCl

Rx Only

Brief Summary of Prescribing Information.

For complete details, please see full Prescribing Information for Namenda.

INDICATIONS AND USAGE
Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS
Namenda (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS
Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions
Seizures: Namenda has not been systematically evaluated in patients with a seizure disorder. In clinical trials of Namenda, seizures occurred in 0.2% of patients treated with Namenda and 0.5% of patients treated with placebo.

Genitourinary Conditions
Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations
Hepatic Impairment
Namenda undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

Renal Impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment.

Drug-Drug Interactions
N-methyl-D-aspartate (NMDA) antagonists: The combined use of Namenda with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of Namenda *on substrates of microsomal enzymes: In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on Namenda: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Coadministration of Namenda with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of Namenda and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Carcinogenesis, Mutagenesis and Impairment of Fertility
There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy
Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

Pediatric Use
There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

ADVERSE REACTIONS
The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia.

Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of Namenda up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the Namenda group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of Namenda-treated patients and at a rate greater than placebo.

Adverse Events Reported in Controlled Trials: The reported adverse events in Namenda (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Namenda than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo-treated Patients.

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in Namenda-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abnormal gait, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with Namenda. A comparison of supine and standing vital sign measures for Namenda and placebo in elderly normal subjects indicated that Namenda treatment is not associated with orthostatic changes.

Laboratory Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

ECG Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with Namenda treatment.

Other Adverse Events Observed During Clinical Trials
Namenda has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: *Frequent:* syncope. *Infrequent:* hypothermia, allergic reaction.

Cardiovascular System: *Frequent:* cardiac failure. *Infrequent:* angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent:* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

Gastrointestinal System: *Infrequent:* gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: *Frequent:* anemia. *Infrequent:* leukopenia.

Metabolic and Nutritional Disorders: *Frequent:* increased alkaline phosphatase, decreased weight. *Infrequent:* dehydration, hyponatremia, aggravated diabetes mellitus.

Psychiatric Disorders: *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, neurosis, suicide attempt.

Respiratory System: *Frequent:* pneumonia. *Infrequent:* apnea, asthma, hemoptysis.

Skin and Appendages: *Frequent:* rash. *Infrequent:* skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

Special Senses: *Frequent:* cataract, conjunctivitis. *Infrequent:* macula lutes degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.

Urinary System: *Frequent:* frequent micturition. *Infrequent:* dysuria, hematuria, urinary retention.

Events Reported Subsequent to the Marketing of Namenda, both US and Ex-US
Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, claudication, colitis, dyskinesia, dysphagia, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatic failure, hyperlipidemia, hypoglycemia, ileus, impotence, malaise, neuroleptic malignant syndrome, acute pancreatitis, aspiration pneumonia, acute renal failure, prolonged QT interval, restlessness, Stevens-Johnson syndrome, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, and thrombocytopenia.

ANIMAL TOXICOLOGY
Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m² basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE
Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an overdosage with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

Forest Pharmaceuticals, Inc.
Pharmaceuticals • Therapeutics • Healthcare • Efficacy • Managed Care • Specialty Sales

Licensed from Merz Pharmaceuticals GmbH

Rev. 07/05

Are Violent Patients More Often Subject to 'Leveraged Treatment'?

Leveraged treatment encompasses a range of strategies to induce patients to comply with treatment, such as making access to subsidized housing or disability income dependent on treatment adherence.

BY MARK MORAN

Approximately three-quarters of subjects with psychiatric illness who report committing serious violent crimes also report experiencing some form of "leveraged treatment."

A number of demographic and clinical factors are associated with the experience of leveraged treatment. These include younger age, male gender, poorer clinical functioning, more years in treatment, more frequent hospitalizations, higher frequency of outpatient visits, and negative attitudes toward medication adherence.

Those findings suggest that a combination of concerns about safety and treatment nonadherence may influence decisions by clinicians and judges to apply legal leverage, wrote Jeffrey Swanson, Ph.D., and colleagues in the August *American Journal of Psychiatry*.

Leveraged treatment refers to any of a wide range of strategies to induce patients to comply with treatment. These may include mandated community treatment whereby incarceration or placement in subsidized housing can be made contingent on compliance, appointment of a money manager to make a patient's access to funds contingent on treatment adherence, and lenient sentencing by judges on the condition that a person participate in treatment.

"The findings suggests that a history of violence per se is not considered a sufficient rationale for applying legal leverage to psychiatric outpatients, assuming the patient is willing to accept treatment voluntarily," Swanson told *Psychiatric News*. "They also suggest that a patient's unwillingness to take medication is not, in and of itself, sufficient to warrant legally mandating treatment in the community, as long as the patient poses no risk of violence. However, if a potentially violent patient is unwilling to take medication, psychiatrists are more likely to resort to legal leverage, partly out of concern for their own professional liability in an adverse event. Similarly in the criminal-justice system, a judge may order a defendant with mental illness to participate in treatment as a condition of living in the community, especially if the person isn't likely to accept treatment voluntarily and may become violent without it."

Swanson is an associate professor of psychiatry at Duke University School of Medicine.

In the study, approximately 200 outpatients were recruited at publicly funded mental health treatment programs in each of five cities: Chicago, Durham, N.C., San Francisco, Tampa, Fla., and Worcester, Mass. A single structured interview lasting about 90 minutes was administered in person by a trained lay interviewer. Participants were paid $25 for the interview.

The researchers assessed whether respondents had experienced no leverage, social leverage only (such as leverage involving money or housing), legal leverage only (outpatient commitment or leverage applied through the criminal justice system), or both types of leverage.

They used the MacArthur Community Violence Interview to assess study participants for violent and aggressive behavior during the previous six months.

Across study sites, 18 percent to 21 percent of participants reported having committed violent acts in the prior six months. Those who reported having used or made threats with a lethal weapon, committed sexual assault, or caused injury ranged from 3 percent to 9 percent.

About three-quarters of subjects who reported such serious violence also reported having experienced some form of leveraged treatment, compared with about one-half of subjects who did not report serious violence.

Across the five sites, the proportion of respondents reporting social welfare leverage alone ranged from 15.7 percent to 26.3 percent of respondents. Legal leverage alone was reported by 11.2 percent to 17.0 percent.

The proportion of respondents who experienced both types ranged from 12.8 percent to 18.5 percent.

People who reported any physically assaultive behavior and also did not take medication voluntarily were more than twice as likely to have experienced legal leverage (see chart).

"Treating clinicians should understand that the use of leveraged community treatment is now a common part of the landscape of mental health services for adults in the United States," Swanson told *Psychiatric News*. "Violence risk is sometimes cited as the reason for this, but clearly leverage is not all about preventing violence. In fact, the use of leverage is far more common than violence itself is among public psychiatric outpatients."

Is leverage being applied appropriately? "We don't know enough about that," Swanson said. "It's likely that the use of leverage to ensure adherence does prevent violence to some extent. That's probably why about three-quarters of patients with serious violent behavior have received some type of legally leveraged mental health treatment. But the main goal in the application of leverage should be to improve the effectiveness of treatment in the community—that is, to help meet the complex needs of people with severe mental illness and not to focus only on reducing serious violence, which is actually quite a rare phenomenon among these patients. Otherwise it's going to be a misapplied policy in most cases."

Paul Appelbaum, M.D., chair of APA's Council on Psychiatry and Law, said the study brings to light for the first time the frequency with which various forms of leverage are used.

Appelbaum was in charge of the study site at Worcester, Mass., and was involved in planning the study and analyzing the data.

"Until the study from which these data were drawn, we had no idea of the frequency of these forms of leverage," he said. "So a major effect of the underlying study, as well as this analysis, has been to surface these behaviors and enable discussion about their legitimacy to begin.

"It can be concluded that people who are subject to leverage are at higher risk for reporting violence, but it's not clear that violence was the reason that they were subjected to leverage," Appelbaum told *Psychiatric News*. "As an alternative hypothesis, it could be that violent patients are also more symptomatic, and it was their higher levels of symptomatology that led to leverage use."

In an editorial accompanying the article, Appelbaum noted that "it remains an open question" whether leveraged treatment is effective in reducing violence.

"Among the variables likely to determine effectiveness in a given population are the extent to which violence is linked to psychiatric symptoms, the efficacy of treatment in reducing those symptoms, the availability of treatment, the degree of compliance with treatment (which may relate to how aggressively the mandates are enforced), and the degree to which positive effects carry over after the termination of the mandate," he wrote.

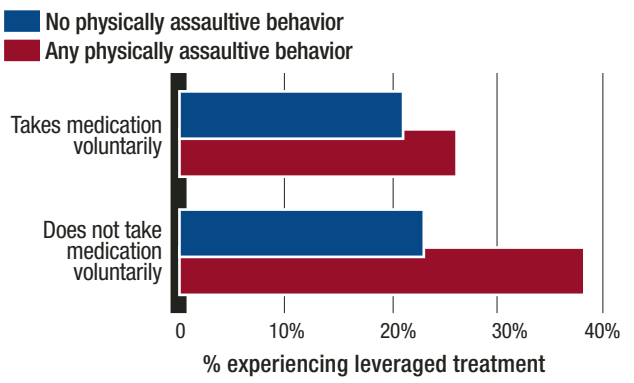
In his comments to *Psychiatric News*, Appelbaum drew a distinction between mandated outpatient treatment and the forms of leverage experienced by most of the patients in the study.

"Only a minority of subjects in this study were exposed to outpatient commitment," he said. "The other forms of leverage that were used tend to be much less visible, though they may—ironically—be more coercive. Most outpatient commitment statutes lack real enforcement provisions. But treatment requirements imposed by the criminal justice system are ignored only at the risk of being incarcerated, and leverage using housing or control of money has real consequences as well."

"Violence and Leveraged Community Treatment for Persons with Mental Disorders" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/8/1404>. Appelbaum's editorial is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/8/1319>. ■

Dangerous Combination

These data are from a survey of 1,011 persons with psychiatric disorders being treated in public mental health service systems in five U.S. cities. Data collection ran from October 2002 through December 2003.



Source: Jeffrey Swanson Ph.D., et al., *American Journal of Psychiatry*, August 2006

Small Percentage of Violent Crime Attributable to Mental Illness

Women who commit a violent crime may be more likely to have severe mental illness than men who commit a violent crime.

BY MARK MORAN

Patients with severe mental illness commit approximately 1 in 20 violent crimes, according to a study of mental illness and violence in Sweden.

Researchers using Swedish national registry data determined that the overall contribution of patients with severe mental illness to violent crime in Sweden between 1988 and 2000 was about 5 percent.

"Although Sweden is average for Western Europe in terms of violent crime per head of population, it has lower rates of homicides than countries with more liberal gun-ownership laws," wrote study authors Seena Fazel, M.B.Ch.B., and Martin Grann, C.Psych. Ph.D., in the August *American Journal of Psychiatry*. "This will alter the attributable risk for homicide, which is likely to be lower in countries such as the United States, but it is unlikely to substantially modify the overall attributable risk for violent crime, which is mostly accounted for by much more common crimes, such as assault."

They linked 98,082 individuals discharged with an *ICD* diagnosis of schizophrenia to a national crime registry to determine the population-attributable risk of patients with severe mental illness to violent crime. Population-attributable risk is an epidemiologic term referring to the proportion of any disease or phenomenon (in this case, violence) that is attributable to a risk factor (in this case, severe mental illness).

Though the measure does not estimate the dangerousness of any one individual with mental illness, it does provide a population perspective on the extent to which mental illness contributes to violent crime.

The researchers found that over a 13-year period, there were 45 violent crimes committed per 1,000 inhabitants. Of these, 2.4 were attributable to patients with severe mental illness, corresponding to a population-attributable risk of 5.2 percent.

The attributable risk was higher in women than men across all ages: in women aged 25 to 39 it was 14 percent, and in women over age 40 it was 19 percent. It was lowest in the 15 to 24 age group—2.3 percent for men and 2.9 percent for women.

"This population study demonstrated that the overall contribution of patients with severe mental illness to such crime was about 5 percent in Sweden between 1988 and 2000," wrote Fazel and Grann. "Although this contribution varied by gender, age, and type of violent crime, this finding should generate a more informed debate on the contribution of persons with severe mental illness to societal violence."

"The Population Impact of Severe Mental Illness on Violent Crime" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/8/1397>. ■

Melatonin Effective In Totally Blind People

Melatonin corrects circadian-rhythm disturbances that often lead to severe and persistent insomnia in individuals who are totally blind.

BY LYNNE LAMBERG

Totally blind people—those who cannot perceive light—often report difficulty falling asleep and staying asleep, as well as fatigue, poor concentration, and irritability while awake.

More than half of these individuals, an estimated 50,000 to 100,000 people in the United States alone, may have a potentially correctable circadian-rhythm sleep disorder, sleep specialists say.

Exogenous melatonin is the treatment of choice for blind people with non-24-hour sleep-wake disorder," said Robert Sack, M.D., a professor of psychiatry at Oregon Health and Science University (OHSU) in Portland.

Sack chaired a symposium on using melatonin in the blind at the annual meeting of the Associated Professional Sleep Societies (APSS) in Salt Lake City, Utah, in June. He and other speakers recently discussed their research with *Psychiatric News*.

The high prevalence of sleep problems in the blind underscores the importance of light in regulating circadian rhythms in the sighted, Sack said. In sighted people, sunlight signals travel from the eyes to the body's master biological clock in the hypothalamus over a pathway distinct from that for vision. Shifting levels of light across the day entrain, or synchronize, the sleep-wake cycle, endogenous melatonin release, and other biological rhythms with the earth's day/night cycle.

Most people, sighted and blind, have innate daily cycles of 24-25 hours, noted Alfred Lewy, M.D., professor and senior vice chair of psychiatry at OHSU.

In sighted people, daily exposure to sunlight automatically resets cycle length to the world's 24-hour day. More than half of totally blind people have a 24.5-hour circadian cycle, Lewy said. They commonly drift later and later around the real time clock, a phenomenon known as "free-running."

Even if they try to sleep at regular times, they typically sleep well only a few days a month, when their internal clocks fall in sync with preferred schedules. At other times, they sleep poorly and feel drowsy while awake. Some experience depressive symptoms.

Daily oral doses of melatonin can entrain these blind free-runners, researchers at the University of Surrey in the United Kingdom reported in January 2000 in the *Journal of Endocrinology*.

Lewy's group suggests doses of about 0.02-0.3 mg/day, approximating physiological secretion, usually taken in the late afternoon or early evening, may be most effective. They published a dose-response curve for use of exogenous melatonin in the physiological range in totally blind people in *Chronobiology International* in December 2005.

Jonathan Emens, M.D., an assistant professor of psychiatry at OHSU, working with Lewy and others, reported at the APSS meeting that his group had shown for the first time that exogenous melatonin also can entrain blind free-runners with periods less than 24 hours. The researchers helped a blind 41-year-old woman and a blind 9-year-old girl stop drifting earlier around the clock. (The long-term safety of giving melatonin to prepubertal children has not been established.)

Melatonin also may help blind people with 24-hour rhythms that persistently run early or late, disrupting work and social life, Emens said. Melatonin shifts biological rhythms earlier or later depending on when it is taken.

Findings from research in the blind, he suggested, may be applicable to shift work, jet travel, and other circadian sleep disorders.

Determining the optimal dose and timing of melatonin administration for the individual user is a key focus of ongoing research, said Debra Skene, Ph.D., a professor of neuroendocrinology at the School of Biomedical and Molecular Sciences, University of Surrey in Guildford, Surrey, United Kingdom. An individual's response to melatonin depends on both clock time and circadian time, she said,

*please see **Melatonin** on page 28*

© iStockphoto.com/hidesy

KNOWTHEFACTS

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.

Pfizer

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.

GZ274981T

Printed in USA/May 2006

Physicians Urged to Warn Of SSRIs' Bleeding Risk

Combining SSRIs with NSAIDs may create an increased—but manageable—risk for patients taking both drugs.

BY AARON LEVIN

Physicians prescribing selective serotonin-reuptake inhibitors (SSRIs) should make patients aware of the possibility of gastrointestinal bleeding, especially if they have pre-existing risk factors or are taking other drugs that increase risk, said a University of Pennsylvania psychiatrist.

"The research shows that this is not a frequent event, but it is an event," said Robert Weinrieb, M.D., an associate professor of psychiatry at the University of Pennsylvania School of Medicine and Philadelphia Veterans Affairs Medical Center and director of medical and consultative psychiatry at the Hospital of the University of Pennsylvania in Philadelphia. The risk to patients is about the same as that for ibuprofen, he said in an interview.

Weinrieb is a substance abuse specialist and backed into his interest in the relation between SSRIs and bleeding.

"People had been using SSRIs to prevent psychiatric side effects when interferon was used to treat patients with hepatitis C," he said. These side effects included depression, irritability, and insomnia.

He wondered if these drugs would also work with patients on methadone, many of whom were infected with hepatitis C. However, conventional wisdom among doctors said that using interferon in methadone-using patients would cause them to relapse or send them into depression or psychosis, although there were no prospective placebo-controlled trials on the subject. He set up a pilot experiment at the Philadelphia Veterans Affairs hospital to see if the SSRI paroxetine would prevent psychiatric side effects from developing in patients taking interferon.

After data gathering was completed in that study, a patient died of gastrointestinal bleeding. The patient had several risk factors for bleeding, but Weinrieb nevertheless did a full MEDLINE search dating back to 1966, looking for any association of SSRIs and gastrointestinal bleeding.

In a paper published last year, Weinrieb and three colleagues found seven retrospective analytic studies supporting an association between SSRI use and upper gastrointestinal and perioperative bleeding. Other literature reviews have come to the same conclusion.

U.S. Food and Drug Administration labeling requirements for some SSRIs say that "concurrent use of an NSAID or aspirin potentiated the risk of bleeding."

Combining aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) with SSRIs appeared to increase the risk, as did concurrent use of warfarin or low-molecular-weight heparin. The researchers estimated that SSRI use increases risk of bleeding by 3.6 times, compared with the risk in the general population for those who don't use SSRIs, but that there is a 12-fold risk increase when NSAIDs and SSRIs are combined. He noted that these

Melatonin

continued from page 26

and on how long the person takes it.

Individual circadian cycle length also may affect treatment outcome, Skene said. People with an innate period longer than 24.5 hours seem to have more trouble entraining than those with shorter cycles. Different formulations of melatonin, including fast release, sustained release, and controlled release, may have different effects.

Before treatment starts, every patient needs a correct diagnosis, said Steven Lockley, Ph.D., an assistant professor of medicine at Harvard Medical School.

"I know of blind people with non-24-hour sleep-wake disorder who have been given hypnotics to use at night and stimulants to use in the day because their physicians did not recognize the cyclic nature of their disorder," he said.

An estimated 1 in 4 totally blind people can entrain to 24-hour rhythms using nonphotic time cues in their environment, Lockley noted. These cues include regular times for sleep, meals, exercise, work, social relationships, caffeine, and medications. Some blind people with no conscious light perception still may have light-sensitive cells in the retina that enable entrainment.

Blind people able to perceive any light are unlikely to have a circadian rhythm sleep disorder, he said. However, visually impaired people overall have higher rates of sleep disorders than people with normal vision.

Asking a patient to keep a sleep diary or wear a wrist activity monitor for at least two months probably will reveal a cyclic sleep-wake disorder if one exists, he said. Collection of urine samples every four to eight hours for 48 hours every two weeks for two months to assess melatonin or cortisol rhythms can help make a definitive diagnosis and aid a decision about appropriate treatment timing. These noninvasive, relatively inexpensive measures, he said, are practical in primary care practice.

Melatonin may improve sleep regardless of circadian entrainment, he added, but correcting an underlying circadian disorder, if one is present, can improve daytime performance, alertness, and overall quality of life. ■

estimates were drawn from retrospective studies and thus reflect some uncertainty.

"We don't know if SSRIs cause mucosal injury but they can cause bleeding from existing lesions in the stomach," said study co-author James Lewis, M.D., an assistant professor of medicine in the Department of Gastroenterology at the University of Pennsylvania. SSRIs have a broad antiplatelet effect, he said, but SSRI-related bleeding occurs mainly in the gastrointestinal system. There's no indication that SSRIs increase risk of bleeding strokes in the brain, for instance.

Cardiologists have hypothesized that the antiplatelet effects of SSRIs might actually benefit patients with occlusive heart disease, even if its use were offset by bleeding risks. At least one manufacturer also noted the effect. The makers of one SSRI once applied to market its drug to treat coronary artery disease because of its platelet-inhibition ability, said Weinrieb, although the application was turned down.

Physicians prescribing SSRIs should be aware of their potential to cause bleeding, but should not exaggerate the risk, Lewis told *Psychiatric News*.

"The relative risk is similar to that of NSAIDs, but remember that NSAIDs are sold over the counter," said Lewis. "It's important to balance potential benefits and harms. Usually, if there is a legitimate indication for treatment with an SSRI, the benefits outweigh the harms."

Physicians prescribing SSRIs should be aware of any added risk factors for gastrointestinal bleeding, such as stomach ulcers or a history of bleeding. They should counsel patients about the risk and tell them to call their doctor if they have any of the signs or symptoms of bleeding, said Weinrieb. The effects of SSRIs on bleeding are not predicted by standard blood tests but are revealed by a platelet-aggregation test, he noted.

It is not necessary to stop the SSRIs when elevated bleeding risk is present, said Lewis. Alternative steps are available. Patients taking aspirin or NSAIDs for noncardiac reasons could be directed to acetaminophen to relieve pain. Aspirin users with a history of ulcer bleeding have done well in randomized clinical trials with a combination of aspirin and a proton pump inhibitor to suppress stomach-acid production, said Lewis.

Weinrieb suggested that physicians caution patients who have two or more risk factors and consider switching them to dopaminergic antidepressants (such as bupropion) or drugs with less serotonin reuptake inhibition (such as mirtazapine), if needed.

"Selective Serotonin Re-Uptake Inhibitors and the Risk of Bleeding" is posted at <www.expertopin.com/doi/abs/10.1517/14740338.4.2.337>. ■

Free Subscription

U.S. and Canadian APA members can receive a free subscription to *Psychiatric Services* as a benefit of their membership. To subscribe, go to APA's Web site at <www.psych.org/ps>, download the one-page form, sign it, and fax it as instructed on the form. The first issue of your subscription will be mailed in four to six weeks.

As a subscriber, you can activate a free online subscription by going to <www.psychiatryonline.org>, clicking on "Subscriptions," and entering your customer number (it appears on the mailing label above your name and address).

Placebo-Based Brain Changes Affect Depression Outcome

Because of treatment expectations, the therapeutic alliance, or other factors, patients' brain activity can change even before they get psychotropic medications. These changes in turn can influence how they respond to the drugs.

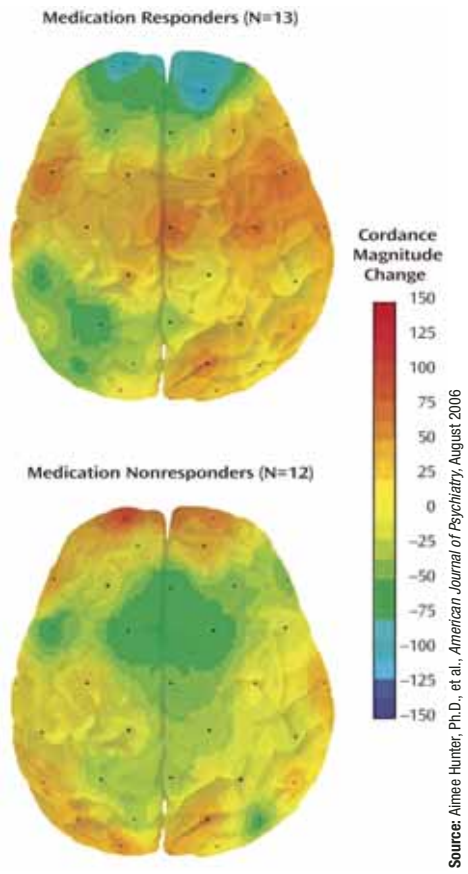
BY JOAN AREHART-TREICHEL

The power of a placebo is nothing new to psychiatrists, but documenting a placebo's punch inside the brain is more novel.

More specifically, changes in a depressed person's brain before treatment can predict, to a sizable extent, whether the individual will respond to treatment, a new study has found.

The placebo lead-in phase is common to many efficacy studies of antidepressant medications. Typically, subjects receive a placebo from three to 14 days before being randomly assigned to a placebo or medication. This initial drug-free interval allows the effects of the study drug to be evaluated without being compromised by pre-existing medications. Aimee Hunter, Ph.D., a research psychologist at the UCLA Semel Institute for Neuroscience and Human Behavior, and her coworkers decided to capitalize on the placebo lead-in phase of an antidepressant trial to learn more about a placebo's impact on the brain and the possible influence of this impact on treatment outcome.

Fifty-one subjects diagnosed with major depression and participating in a double-blind, placebo-controlled antidepressant trial with a placebo lead-in phase were included in this experiment. Brain electrical activity was measured both before and after the one-week placebo lead-in phase with a technique developed at UCLA called quantitative EEG cordance. The technique involves placing electrodes on a subject's scalp to pick up electrical signals, which are then fed into a computer. The computer then measures the electrical signals coming from the subject's brain and processes them into colorful patterns.



Source: Aimee Hunter, Ph.D., et al., *American Journal of Psychiatry*, August 2006

Researchers measured brain changes during the placebo lead-in period in 25 subjects who later got an antidepressant. They found significant differences between the brain changes in the 13 who responded to an antidepressant and the 12 who did not. The brain changes predicted, at least to some degree, subjects' clinical outcomes.

The subjects' level of depression was then assessed using the Hamilton Rating Scale for Depression (HAM-D). Subjects were randomized to receive either an antidepressant or a placebo for eight weeks; at the end of that time, depression levels were measured once more with the HAM-D. Finally, the scientists looked to see whether there were changes in subjects' brain electrical activity during the placebo lead-in period, and if so, whether the changes could be linked with their clinical outcome.

The answer was yes on both counts, and not just for those subjects getting an antidepressant, but also for those getting a placebo, the researchers reported in the August *American Journal of Psychiatry*.

In the subjects given an antidepressant, decreases in prefrontal cortex electrical activity during the placebo lead-in period were significantly associated with lower depression scores at the end of the eight-week treatment period. Nineteen percent of the variance in depression scores, in fact, could be explained by brain electrical activity that occurred during the lead-in period.

In the case of the subjects given a placebo, increases in right temporal lobe electrical activity during the placebo lead-in period were significantly linked with lower depression scores at the end of the eight-week treatment period. Twenty percent of the variance in depression scores could be explained by brain electrical activity that occurred during the lead-in period.

"We were surprised that 19 percent of the variance in final HAM-D scores was predicted by brain changes occurring before start of drug," Hunter told *Psychiatric News*. "That's a fairly large proportion, especially considering that the placebo lead-in period was only one week

please see ***Placebo*** *on page 36*

the edge

Lilly

Important Safety Information for ZYPREXA® (olanzapine)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ZYPREXA is not approved for the treatment of elderly patients with dementia-related psychosis.

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia—Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in trials of ZYPREXA in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with ZYPREXA compared to patients treated with placebo. ZYPREXA is not approved for the treatment of elderly patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ZYPREXA. All patients taking atypicals should be monitored for symptoms of hyperglycemia. Persons with diabetes who are started on atypicals should be monitored regularly for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Neuroleptic malignant syndrome (NMS)—As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended.

Tardive dyskinesia (TD)—As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

Orthostatic hypotension—In premarketing schizophrenia trials, some patients taking ZYPREXA may have experienced orthostatic hypotension associated with dizziness, tachycardia, and, in some cases, syncope (15/2500, 0.6%).

Seizures—Occurred infrequently in premarketing clinical trials (22/2500, 0.9%). ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Effect on prolactin—Modest elevations of prolactin were seen with ZYPREXA in acute-phase schizophrenia trials (incidence 34% vs 13% with placebo), although mean changes from baseline to endpoint were not statistically significantly different between olanzapine and placebo. Some patients may have persisting modest prolactin elevations.

Transient, asymptomatic elevations of hepatic transaminase—In placebo-controlled schizophrenia trials, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA compared to none (0/115) of the placebo patients. None of these patients developed jaundice. Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

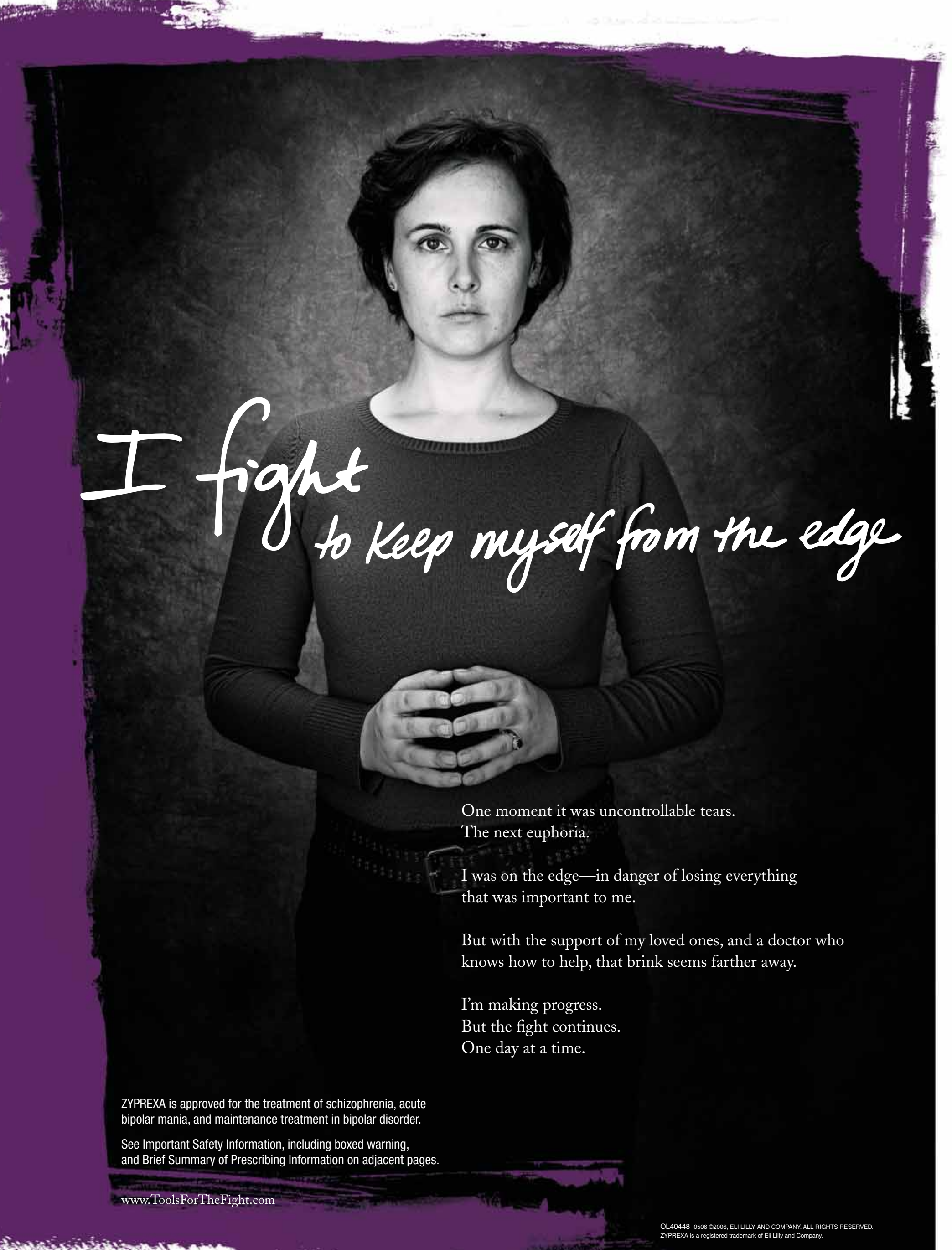
Special populations, elderly—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Olanzapine should be used with caution in patients at risk for aspiration pneumonia. In 5 studies in elderly patients with dementia-related psychosis, adverse events reported more commonly with olanzapine than with placebo were falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, and visual hallucinations. Olanzapine should be used with caution in elderly patients with dementia. Olanzapine is not approved for treatment of patients with dementia-related psychosis.

Drug interactions—Coadministration of diazepam or ethanol with ZYPREXA may potentiate orthostatic hypotension. Lower doses of ZYPREXA should be considered in patients receiving concomitant therapy with fluvoxamine.

Medication dispensing and prescribing errors have occurred between ZYPREXA® (olanzapine) and Zyrtec® (cetirizine HCl). These errors could result in unnecessary adverse events or potential relapse in patients suffering from schizophrenia or bipolar disorder. To reduce the potential for dispensing errors, please write ZYPREXA clearly.

The most common treatment-emergent adverse events associated with ZYPREXA (vs placebo) in 6-week acute-phase schizophrenia trials were somnolence (26% vs 15%), dizziness (11% vs 4%), weight gain (6% vs 1%), personality disorder (COSTART term for nonaggressive objectionable behavior; 8% vs 4%), constipation (9% vs 3%), akathisia (5% vs 1%), and postural hypotension (5% vs 2%).

The most common treatment-emergent adverse events associated with ZYPREXA (vs placebo) in 3- and 4-week bipolar mania trials were somnolence (35% vs 13%), dry mouth (22% vs 7%), dizziness (18% vs 6%), asthenia (15% vs 6%), constipation (11% vs 5%), dyspepsia (11% vs 5%), increased appetite (6% vs 3%), and tremor (6% vs 3%).



One moment it was uncontrollable tears.
The next euphoria.

I was on the edge—in danger of losing everything
that was important to me.

But with the support of my loved ones, and a doctor who
knows how to help, that brink seems farther away.

I'm making progress.
But the fight continues.
One day at a time.

ZYPREXA is approved for the treatment of schizophrenia, acute bipolar mania, and maintenance treatment in bipolar disorder.

See Important Safety Information, including boxed warning, and Brief Summary of Prescribing Information on adjacent pages.

www.ToolsForTheFight.com

ZYPREXA® Olanzapine

ZYPREXA® Olanzapine Tablets
ZYPREXA® ZYDIS® Olanzapine Orally Disintegrating Tablets
ZYPREXA® IntraMuscular Olanzapine for Injection
Brief Summary: Please consult package insert for complete prescribing information.

WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS AND USAGE: ZYPREXA and ZYPREXA Zydis are indicated for short- and long-term treatment of schizophrenia, for acute manic and mixed episodes of bipolar I disorder, and for maintenance treatment in bipolar disorder. The use of ZYPREXA for extended periods should be periodically re-evaluated as to the long-term usefulness of the drug for the individual patient. ZYPREXA IntraMuscular is indicated for treatment of agitation associated with schizophrenia and bipolar I mania.

CONTRAINDICATIONS: Known hypersensitivity to olanzapine.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis (*see* BOX WARNING).

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients (3.5%) was significantly greater than placebo-treated patients (1.5%).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia—Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Patients diagnosed with diabetes who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes who are starting treatment with atypicals should have fasting blood glucose (FBG) testing at baseline and periodically during treatment. Any patient treated with atypicals should be monitored for symptoms of hyperglycemia. Patients who develop symptoms of hyperglycemia during treatment with atypicals should undergo FBG testing.

Neuroleptic Malignant Syndrome (NMS)—Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. See complete prescribing information for information on management of NMS. Patients requiring antipsychotic drug treatment after recovery from NMS should be carefully monitored since recurrences have been reported.

Tardive Dyskinesia (TD)—Potentially irreversible TD may develop in patients treated with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are more likely to develop the syndrome. If signs and symptoms of TD appear, consider drug discontinuation.

PRECAUTIONS: Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness; tachycardia; and in some patients, syncope. Hypotension, bradycardia with/without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. Incidence of syncope was 0.6%, 15/2500 with oral olanzapine in phase 2-3 trials and 0.3%, 2/722 with intramuscular olanzapine for injection in clinical trials. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of events may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. Patients should remain recumbent if drowsy or dizzy after injection with intramuscular olanzapine for injection until examination has indicated they are not experiencing postural hypotension, bradycardia, and/or hypoventilation. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put them at increased medical risk. Caution is necessary in patients receiving treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or CNS depression (*see* Drug Interactions). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is not recommended. If such combination treatment is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures—During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients, regardless of causality. Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

Hyperprolactinemia—Like other drugs that antagonize dopamine D2 receptors, olanzapine elevates prolactin levels; a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro. However, neither clinical nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is inconclusive.

Transaminase Elevations—In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of normal) were observed in 2% (6/243) of patients exposed to olanzapine compared to no (0/115) placebo patients. None of these patients experienced jaundice. Among about 2400 patients with baseline SGPT ≤90 IU/L, 2% (50/2381) had asymptomatic SGPT elevations to >200 IU/L. Most were transient changes that tended to normalize while olanzapine treatment was continued. Among 2500 patients in oral olanzapine trials, about 1% (23/2500) discontinued treatment due to transaminase increases. Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period. Exercise caution in patients who have signs and symptoms of hepatic impairment; preexisting conditions associated with limited hepatic functional reserve; or concomitant treatment with potentially hepatotoxic drugs (*see* Laboratory Tests, below).

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported, dose-related adverse event in premarketing trials (olanzapine 26% vs placebo 15%). Somnolence led to discontinuation in 0.4% (9/2500) of patients in the oral premarketing database.

Body Temperature Regulation—Use appropriate care when prescribing olanzapine for patients who will be experiencing conditions that may contribute to an elevation in core body temperature.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide—The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management.

Use in Patients with Concomitant Illnesses—Olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In 5 placebo-controlled studies in elderly patients with dementia-related psychosis (n=1184), these treatment-emergent adverse events were reported with olanzapine at an incidence of ≥2% and significantly greater than with placebo: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, visual hallucinations. Discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat this patient population, vigilance should be exercised (*see* BOX WARNING *and* WARNINGS).

Because of the risk of orthostatic hypotension with olanzapine, use caution in cardiac patients (*see* Hemodynamic Effects).

Information for Patients—See full prescribing information for information to discuss with patients taking olanzapine.

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Drug Interactions—Use caution when olanzapine is taken in combination with other centrally acting drugs and alcohol. Olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists. Agents that induce CYP1A2 or glucuronyl transferase enzymes (e.g., omeprazole, rifampin) may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. A dosage adjustment may need to be considered with specific drugs.

Activated charcoal (1 g) reduced the C_{max} and AUC of oral olanzapine by about 60%. Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine. Carbamazepine (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance. Neither ethanol (45 mg/70 kg single dose) nor warfarin (20 mg single dose) had an effect on olanzapine pharmacokinetics. Fluoxetine at 60 mg (single or multiple doses) causes a small increase in the C_{max} of olanzapine and a small decrease in olanzapine clearance; however, the impact of this factor is small in comparison to the overall variability between individuals, and dose modification is not routinely recommended. Fluvoxamine decreases the clearance of olanzapine; lower doses of olanzapine should be considered in patients receiving fluvoxamine concomitantly. In vitro data suggest that a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Olanzapine is unlikely to cause clinically important drug interactions mediated by the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Single doses of olanzapine did not affect the pharmacokinetics of imipramine/desipramine or warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam/N-desmethyldiazepam, lithium, ethanol, or biperiden. However, coadministration of either diazepam or ethanol potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites. Co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone (*see* Hemodynamic Effects).

Carcinogenesis, Mutagenesis, Impairment of Fertility—The incidence of liver hemangiomas and hemangiosarcomas in female mice was significantly increased in one carcinogenicity study at 2 times the maximum human daily oral dose (MHDOD) but not in another study at 2-5 times the MHDOD (mg/m^2 basis). In this study there was a high incidence of early mortalities in males in the 30/20 mg/kg/d group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice and rats given olanzapine at 0.5 and 2 times the MHDOD respectively (mg/m^2 basis). In other studies, serum prolactin measurements of olanzapine showed elevations up to 4-fold in rats at the same doses used in the carcinogenicity studies. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown. No evidence of mutagenic potential for olanzapine has been found.

In rats, fertility (females) and mating performance (males and females) were affected at doses 1.5-11 times the MHDOD (mg/m^2 basis). Diestrous was prolonged and estrous delayed at 0.6 times the MHDOD (mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Pregnancy Category C—There are no adequate and well-controlled studies in pregnant women. Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery, Nursing Mothers—Parturition in rats was not affected by olanzapine; its effect on labor and delivery in humans is unknown. In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal dose. It is recommended that women receiving olanzapine should not breast-feed.

Use in Pediatric and Geriatric Patients—Safety and effectiveness in pediatric patients have not been established. In premarketing clinical trials in patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested there may be a different tolerability profile in these patients. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat these patients, vigilance should be exercised. Consider a lower starting dose for any geriatric patient in the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine (*see* BOX WARNING, WARNINGS, *and* PRECAUTIONS).

ADVERSE REACTIONS: The following findings are based on a clinical trial database consisting of 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection, including patients with schizophrenia, bipolar mania, or Alzheimer's disease (oral olanzapine trials) and patients with agitation associated with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia (intramuscular olanzapine for injection trials). See the full prescribing information for details on these trials. Certain portions of the discussion below relating to dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or agitation; however, this information is also generally applicable to bipolar mania and agitation.

Associated with Discontinuation—Overall there was no difference in discontinuations due to adverse events in placebo-controlled oral olanzapine trials (olanzapine vs placebo: schizophrenia, 5% vs 6%; bipolar mania monotherapy, 2% vs 2%; bipolar mania cotherapy, 11% [olanzapine plus lithium or valproate] vs 2% [lithium or valproate alone]); or in placebo-controlled intramuscular olanzapine for injection trials (olanzapine for injection, 0.4%; placebo 0%). Discontinuations in oral schizophrenia trials due to increases in SGPT were considered to be drug related (olanzapine 2% vs placebo 0%; *see* PRECAUTIONS).

Commonly Observed Adverse Events—In 6-week, placebo-controlled, premarketing schizophrenia trials, the most common treatment-emergent adverse events associated with oral olanzapine (incidence ≥5% and olanzapine incidence at least twice that for placebo) were: postural hypotension, constipation, weight gain, dizziness, personality disorder (COSTART term for nonaggressive objectionable behavior), and akathisia. In 3- and 4-week placebo-controlled bipolar mania monotherapy trials, the most common treatment-emergent adverse events associated with oral olanzapine were: asthenia, dry mouth, constipation, dyspepsia, increased appetite, somnolence, dizziness, and tremor. In short-term bipolar mania combination therapy trials, the most common treatment-emergent adverse events observed with olanzapine plus lithium or valproate were dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, and paresthesia. In 24-hour placebo-controlled trials of intramuscular olanzapine for injection for agitation associated with schizophrenia or bipolar mania, somnolence was the one adverse event observed at an incidence of ≥5% and at least twice that for placebo (olanzapine for injection 6%, placebo 3%).

Adverse Events with an Incidence ≥2% in Oral Monotherapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥2.5 mg/d), and at a greater incidence with olanzapine than with placebo in short-term placebo-controlled trials (olanzapine N=532, placebo N=294): ***Body as a Whole***—accidental injury, asthenia, fever, back pain, chest pain; ***Cardiovascular***—postural hypotension, tachycardia, hypertension; ***Digestive***—dry mouth, constipation, dyspepsia, vomiting, increased appetite; ***Hemic and Lymphatic***—ecchymosis; ***Metabolic and Nutritional***—weight gain, peripheral edema; ***Musculoskeletal***—extremity pain (other than joint), joint pain; ***Nervous System***—somnolence, insomnia, dizziness, abnormal gait, tremor, akathisia, hypertonia, articulation impairment; ***Respiratory***—rhinitis, cough increased, pharyngitis; ***Special Senses***—amblyopia; ***Urogenital***—urinary incontinence, urinary tract infection.

Adverse Events with an Incidence ≥2% in Oral Combination Therapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥5 mg/d) plus lithium or valproate (N=229), and at a greater incidence than with placebo plus lithium or valproate (N=115) in short-term placebo-controlled trials: ***Body as a Whole***—asthenia, back pain, accidental injury, chest pain; ***Cardiovascular***—hypertension; ***Digestive***—dry mouth, increased appetite, thirst, constipation, increased salivation; ***Metabolic and Nutritional***—weight gain, peripheral edema, edema; ***Nervous System***—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; ***Respiratory***—pharyngitis, dyspnea; ***Skin and Appendages***—sweating, acne, dry skin; ***Special Senses***—amblyopia, abnormal vision; ***Urogenital***—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5 -10 mg/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: ***Body as a Whole***—asthenia; ***Cardiovascular***—hypotension, postural hypotension; ***Nervous System***—somnolence, dizziness, tremor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—*Extrapyramidal Symptoms*—In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5+2.5, 10+2.5, or 15+2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of oral olanzapine (15+2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events—Dose-relatedness of adverse events was assessed using data from a clinical trial involving 3 fixed oral dosage ranges compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 56% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation,* amenorrhea,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation,* glycosuria, gynecomastia, hematuria, impotence,* increased menstruation,* menorrhagia,* metrorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged,* vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been rarely reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

Literature revised March 20, 2006

PV 5195 AMP

Eli Lilly and Company
Indianapolis, IN 46285, USA

www.ZYPREXA.com

ZYPREXA® Olanzapine Tablets
ZYPREXA® ZYDIS® Olanzapine Orally Disintegrating Tablets
ZYPREXA® IntraMuscular Olanzapine for Injection
PV 5195 AMP

Tradition, Innovation Starring on Broadway

In most people's minds, Broadway is synonymous with musical theater, and the APA Institute on Psychiatric Services provides a perfect opportunity to indulge. Here is just a taste.

BY KEN HAUSMAN

At the core of the Big Apple is its astounding array of theater offerings from comedies to drama, from classical to cutting edge, and from intimate to spectacular.

But what many visitors can't wait to sample is New York's unmatched contribution to theater around the world—the Broadway musical. Visitors to New York during the Institute on Psychiatric Services, which meets from October 5 to 8 at the Marriott Marquis, will be able to select from an eclectic mix of long-running blockbusters and newer shows that will probably not play in their hometowns for years.

Among the shows that have generated considerable buzz—and multiple Tony awards—in the last few years is "Avenue Q," a funny and often touching musical about accepting and embracing people's differences. The show is sung by a collection of puppet-like "monsters" and real-life actors, all of whom are in their 20s and live in a downscale Brooklyn apartment building where each is trying to find his or her purpose in life. The definitely for-adults-only show received Tony awards in 2004 for best musical, best score, and best book of a musical.

The clever and inventive comedy "The Drowsy Chaperone" opened earlier this year. It's actually a musical, a fantasized one, inside a musical. The male lead plays a recording of his favorite musical, the eponymous, old-fashioned one that opened in 1928 about an up-and-coming Broadway starlet who prefers marriage to stardom and the Machiavellian producer who plots to keep her nuptials from occurring. In best Broadway tradition, the old musical that the modern-day fan is listening to miraculously begins to unfold in his living room, which is of course our stage.

Great and not-so-great Hollywood films have also presented considerable fodder for hit musicals in recent years, probably because the audience is already familiar with them. Among the enduring ones that will likely still be playing in October are "Spamalot," based on "Monty Python and the Holy Grail"; "Dirty Rotten Scoundrels"; "Hairspray"; and "The Lion King." Joining the roster this year was "The Color Purple," based on Steven Spielberg's 1985 film, which was in turn based on a story by Alice Walker.

Paul Kolnik

"A Chorus Line" will make its way to the Great White Way this fall.

Many Broadway aficionados are eagerly anticipating the revival of one of Broadway's groundbreaking musicals, "A Chorus Line," scheduled to open on October 5. The show, in which more than a dozen dancers at an audition use song, and of course, dance, to reveal the pain and joy they have endured in their lives, held the record for the longest-running Broadway show until the era of blockbuster spectacles in the 1980s.

Also to be revived by fall is that musical war horse "Les Misérables."

"The Times They Are a-Changin'," a dance musical based on songs by Bob Dylan and choreographed by Twyla Tharp, begins previews on September 25, though its formal opening is October 26. Tharp had a major success a few years ago when she choreographed "Movin' Out," a show based on songs by Billy Joel.

And by the way, that famous chandelier is still plummeting to the stage in "Phantom of the Opera," the producers of "Springtime for Hitler" are still hoping for a tax-dodging flop, it's still hard to be green in "Wicked," and mama mia, that collection of good-timey ABBA songs just won't go away.

Tickets to all of the shows noted above can be ordered online at <www.ticketmaster.com/broadway/showlistings?tm_link=tm_bdwy_moreshowslink1>. ■

How to Register

It's not too late to register and reserve a hotel room for APA's 2006 Institute on Psychiatric Services, being held in New York from October 5 to 8. With the meeting only weeks away, hotel rooms at the meeting's headquarters, the Marriott Marquis, are already booked, but arrangements for preferred rates for registrants have been made at the nearby Sheraton New York Hotel. To reserve a room there, go to <www.psych.org/edu/ann_mtgs/ips/06/preliminary program/index.cfm> and click on "Overflow Hotel Manhattan Sheraton."

To register online for the institute, go to <www.psych.org/edu/ann_mtgs/ips/06/index.cfm>.

More information is available by calling (888) 357-7924.

POPPA

continued from page 21

noted, and one incident may be "the proverbial straw that broke the camel's back."

Dowling also observed that police are typically extremely resilient people but tend to cope with traumatic issues in solitude.

"In police culture, the thinking is, 'We're strong and our job is to protect others. We take care of everyone else.' " They tend to view their mental health problems as weaknesses or even "a betrayal of other police officers," Dowling said.

Genet noted, "It's their job to make the public feel safe. So if they break, they feel as if they are not doing their jobs."

In addition, officers may be reluctant to seek help for mental health problems because of their experiences on the job.

Dowling said, "Many have brought psychotic and agitated people to the psychiatric emergency room and think, 'This is not my world.' "

One of POPPA's long-term goals is to persuade officers that seeking help for mental health problems is not a deficiency and that recognizing such problems and reaching out to others are signs of strength.

One of the reasons POPPA works, Genet said, is because the PSOs assure the officers who contact POPPA that disclosures about mental health problems will not get back to their supervisors or jeopardize their careers. The assurance of confidentiality is of utmost importance to the officers, Genet observed.

The vast majority of officers who are referred to a mental health professional stay on the job, Genet said.

About 10 percent of the officers require time off to deal with their mental health problems. This is known as "blue-line sick" time, and no one at the NYPD is told the reason for the absence other than they are out sick with POPPA.

Almost all of the officers who take blue-line sick leave return to their full-time duties, noted Dowling. Returning officers to work is a goal of the program.

According to POPPA Clinical Director Gene Moynihan, L.C.S.W., nearly 70 officers have told him they would have committed suicide if it were not for POPPA—they remembered seeing one of the POPPA posters or hearing PSOs and mental health professionals talk about the program at their precincts.

The program has gained recognition through POPPA's outreach efforts, Moynihan said. For about five years, outreach teams composed of two PSOs and a mental health clinician have been traveling to different precincts to talk to the officers about POPPA after roll call.

"They talk about the confidentiality of the program and how it works," he said. Actors Michael Douglas and Danny Aiello have also appeared in PSAs for the program.

Moynihan served as a police officer for 20 years. He was involved in a number of shooting incidents that left him with symptoms of PTSD, but he didn't seek help until he had retired from the force and entered a social work program.

"Even though being a cop was my job and I functioned well, I didn't understand what was going on inside me," he said. This is not uncommon, he added. "There are walking wounded all over the NYPD right now."

POPPA won APA's Silver Achievement Award in 2005 in recognition of its success in encouraging NYPD officers to seek help for mental health problems. More information about POPPA is posted at <www.poppainc.com>. ■

letters to the editor

Death Penalty

This letter is in response to the article "Participation in Death Penalty: Where Should Line Be Drawn?" in the May 5 issue. A majority of the American population believes that abortion is morally right. It is legal. Doctors are allowed and even encouraged to take part in it. A majority of the American population believes that the death penalty is morally right. It is legal. So doctors are being told not to take part in it?

People who want doctors not to take part in the death penalty on "medical ethics" grounds are simply using a ploy to force their moral beliefs on the majority.

JOHN BEZIRGANIAN, M.D.
Ithaca, N.Y.

APA Leader Has It Right

As I read the words of APA President Steven Sharfstein, M.D., in the June 16 issue— ". . .we *must* be there as advocates for our patients"—the hairs on the back of my neck stood up. His message was in the speech he delivered at APA's 2006 annual meeting in which he urged APA members to advocate for a single-payer, universal health care system.

This is exactly the attitude and the moral space that this issue must have from all health care professionals if we are to overcome the profit power of the private insurance/pharmaceutical industrial complex.

GEORGE SAVAGE
Los Angeles, Calif.

Savage is the Los Angeles chapter director of the OneCareNow.org campaign for universal health insurance in California.

Readers are invited to submit letters not more than 500 words long for possible publication. *Psychiatric News* reserves the right to edit letters and to publish them in all editions, print, electronic, or other media. Receipt of letters is not acknowledged. Letters should be sent by mail to *Psychiatric News*, APA, Suite 1825, 1000 Wilson Boulevard, Arlington, Va. 22209 or by e-mail to pnews@psych.org. Clinical opinions are not peer reviewed and thus should be independently verified.

Youth Suicide

continued from page 2

jects based on date of discharge from an inpatient stay for the treatment of major depression. Matching was also based on age, sex, race/ethnicity, and state providing their Medicaid services.

For suicide deaths, cases were defined as a death within 60 days of discharge from a hospitalization for major depression. Date and cause of death were cross-referenced between the Medicaid database and death certificate data from the National Center for Health Statistics National Death Index. A total of 94 cases with completed suicide were matched, using the same matching criteria as used for suicide attempts, with 435 controls.

Finally, the study population of 4,948 cases and controls was divided into two groups: those aged 18 and younger, and those aged 19 to 64.

Similar but Unexpected Findings

Within the defined cases and controls, Olfson and his colleagues—including noted suicide expert David Shaffer, M.D., chief of the Division of Child Psychiatry at Columbia University Medical Center, New York State Psychiatric Institute, and New York Presbyterian Hospital—first looked for any association between suicide attempt and whether the patient had been prescribed and dispensed an antidepressant medication. Then they repeated the analysis for those who died by suicide.

In the adult group, Olfson's team found no significant association between the medications and suicide attempts or suicide deaths. However, in the child and adolescent group, antidepressants were significantly associated with both suicide attempts and completed suicide.

Olfson and his colleagues found that patients in their study population who filled prescriptions for antidepressant medications following an inpatient stay for major depression were 1.52 times more likely to make a serious attempt at suicide (263 cases matched with 1,241 controls) than similar patients who were not prescribed antidepressants.

Patients who filled antidepressant prescriptions following an inpatient stay were 15.62 times more likely to die by suicide (8 cases matched with 39 controls) than similar patients not prescribed antidepressant medications.

While the study's findings are similar to those found by other researchers, Olfson said, he expected to find no real association between the medications and suicide attempts or deaths in either children or adults.

Finding Meaning Is Difficult

Olfson is quick to note that case-control, observational studies have significant limitations, often making it difficult to determine what the findings really mean.

"There's always the nagging doubt with studies like this," he said, "that even within this defined population of patients following hospitalization for depressive disorder, those receiving antidepressant medications may well have simply been more severely ill."

Olfson and his team did not have any data indicating the severity of individual patients' symptoms, he noted. Severity was inferred by the necessity for inpatient treatment for major depression. By limiting the analysis to events within the first 60 days following discharge, Olfson added, "in theory, all of the patients were in the same period of their recovery from that index hospitalization."

David Fassler, M.D., an APA trustee and child and adolescent psychiatrist, said the study "should be interpreted with caution. The methodology doesn't allow us to draw definitive conclusions in either direction from the results."

There are many intervening variables, Fassler told *Psychiatric News*, that could explain the results, including the possibility that patients with more severe symptoms were more likely to receive antidepressant medications.

While numerous studies have found associations between antidepressants and suicidality, Olfson noted there is no clear indication of what factors might help clinicians predict which patients prescribed the medications might be at increased risk versus which patients aren't at risk.

"There is a feeling among clinicians that a personal history or family history of suicide attempt, or bipolar disorder, can increase risk of future suicidal thoughts, behaviors, and actions," Olfson said. Also helpful, and possibly predictive, is the patient's or family members' response to antidepressant medications, especially in the first few weeks and months of treatment.

"But, bottom line, I don't think at this point the research has done much to give us clear a priori risk factors," Olfson concluded. "Clearly, more research needs to be done to establish these or other indicators as true risk factors."

"Antidepressant Drug Therapy and Suicide in Severely Depressed Children and Adults" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/63/8/865>. ■

Fee Cuts

continued from page 1

If actual spending exceeds the SGR, then CMS must reduce the update and most reimbursement levels.

In its statement, CMS said the negative update is projected for 2007 because spending on physicians' services has been growing at a much faster rate than target spending. "Expenditures for physicians' services in 2005 increased 10 percent over 2004, even faster than had been previously projected, mainly due to an increase in the number and complexity of services furnished to Medicare beneficiaries, including more frequent and intensive office visits and rapid growth in the use of imaging techniques, laboratory services, and physician-administered drugs," the agency stated.

The update formula would have imposed payment cuts every year beginning in 2002, except that Congress intervened and temporarily suspended the requirements in favor of updates it set legislatively through 2006.

But in passing these measures, Congress did not adjust the target, further increasing the gap between actual spending and the targets, according to CMS.

"We need to get out of the vicious circle of rapid growth in utilization and spending and falling real payment rates," said CMS Administrator Mark McClellan, M.D., M.P.H. "Physician groups have been working hard to identify better ways to pay—ways that help them provide higher-quality care without increasing overall health care costs. We will continue to work with Congress and with physician groups to provide more efficient and higher quality care for beneficiaries without increasing Medicare spending."

APA, the AMA, and other specialty medical groups have insisted that the SGR be scrapped and a new formula for paying physicians be devised *(Psychiatric News*, August 18).

Cecil Wilson, M.D., chair of the AMA's Board of Trustees, said in a statement that the new payment rule again highlights the need to fix the "fatally flawed" physician payment system.

"Medicare has expanded the treatments it covers more than 90 times since 1999, yet under the current Medicare payment system physicians are penalized with lower payments per service the more care they provide," he said. "In fact, Medicare currently reimburses physicians about the same in 2006 as it did in 2001. Without congressional intervention, Medicare physician payments will be slashed 37 percent over the next nine years, as practice costs increase 22 percent."

At press time the fee schedule was expected to be published in the *Federal Register* on August 22. Comments are being accepted until October 10, and a final rule will be published later in the fall. The new payment rates and policies included in the final rule will be effective January 1, 2007. ■

legal news

Gun Ownership

continued from page 6

Patients in certain states who wish to apply for permission to purchase, possess, or transfer a handgun must present with their application a written affidavit from their psychiatrist or physician. In Massachusetts, for instance, this affidavit must state that the physician is aware of the patient's mental illness and the patient is not disabled by the illness "in a manner that should prevent the applicant from possessing a firearm, rifle, or shotgun. . . ." The statute goes on to specify that if the applicant has been treated for drug or alcohol addiction, he or she must have been "cured" of the addiction by a licensed physician to own a firearm.

"There is some risk attached to this responsibility," Norris noted. "Can you really testify that the patient is 'cured,' and what does this really mean?" she asked.

In Rhode Island, a restricted person must be pronounced "cured" by a physician for at least five years to be considered a "mentally stable person and a proper person to possess firearms." For handgun licensure in Oklahoma, individuals who have been treated for mental illness must have their physician testify that they have been mentally stable for at least 10 years.

Psychiatrists may also have other duties. In California and Colorado, psychiatrists treating inpatients must report gun possession to local law enforcement or judicial authorities.

In states with no specified restrictions, federal law takes effect. The Federal Gun Control Act "prohibits the transfer of any firearm to any person who. . . is an unlawful user of or addicted to any controlled substance [or] has been adjucated as a mental defective or committed to a mental institution."

In an editorial appearing in that same issue of *American Journal of Psychiatry*, Paul Appelbaum, M.D., chair of APA's Council on Psychiatry and Law, noted that the variability in statutes across the United States poses "a dilemma for advocates for persons with mental disorders, including psychiatrists and their national organizations. . . . But given that only a tiny fraction of violence, including gun violence, is perpetrated by persons with mental disorders, efforts that center disproportionately on restricting their access reflect a deeply irrational public policy."

Appelbaum also expressed concern about the creation of databases that accumulate information about people with mental illness and can be assessed by states before the sale of a firearm. Such access may threaten the confidentiality of psychiatric treatment.

"Whether singling out persons with mental disorders, including substance abuse problems, for restrictions with regard to gun purchases is an effective means of protecting the public cries out for careful assessment," he said.

"Firearm Laws, Patients, and the Roles of Psychiatrists" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/8/1392>. ■

clinical & research news

Placebo

continued from page 30

long compared to eight weeks of treatment with medication. We also were surprised to find different brain changes [that is, increases in right temporal electrical activity] during placebo lead-in that were associated with eventual response in the placebo group."

However, when asked why decreased prefrontal activity predicted less depression in subjects getting an antidepressant, and why increased right temporal activity predicted less depression in subjects getting a placebo, Hunter said that she and her team do not know. Nor do they have an answer for why brain electrical activity changes at all during a placebo lead-in period. But as Ian Cook, M.D., an associate professor of psychiatry at UCLA and senior author of the study, told *Psychiatric News*, "We are now conducting a study, with NIH support, to examine some candidate factors—for example, prior experience with treatment, beliefs about treatment, and empathic alliance with care providers."

Meanwhile, he said, a practical implication of their study results for clinical psychiatrists "is that the 'treatment' to which our patients respond extends beyond the molecules in our pills and capsules, and that many other features of the overall treatment system count."

The study was funded by the National Alliance for Research in Schizophrenia and Depression, the National Center for Complementary and Alternative Medicine, the National Institute of Mental Health, Lilly Research Laboratories, and Wyeth Pharmaceuticals.

"Changes in Brain Function (Quantitative EEG Cordance) During Placebo Lead-In and Treatment Outcomes in Clinical Trials for Major Depression" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/8/1426>. ■

Still working to solve the problem of unresolved depression?

residual symptoms

sadness
low energy
anxiety

relapse

recurrence

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving anti-depressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**

- Adult and pediatric patients with MDD can experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressants. **Patients treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy,**

Break the cycle with EFFEXOR XR

EFFEXOR XR is proven to help prevent new episodes of depression up to 1 year.[1]

or at the time of increases or decreases in dose. Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.

- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.
- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

Please see brief summary of Prescribing Information on adjacent page.

Reference: 1. Effexor XR® (venlafaxine HCl) Extended-Release and Effexor Immediate-Release Prescribing Information, Wyeth Pharmaceuticals Inc.

Wyeth®

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® *EXTENDED RELEASE CAPSULES*

The change they deserve.

ONCE-DAILY
VENLAFAXINE HCl
EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

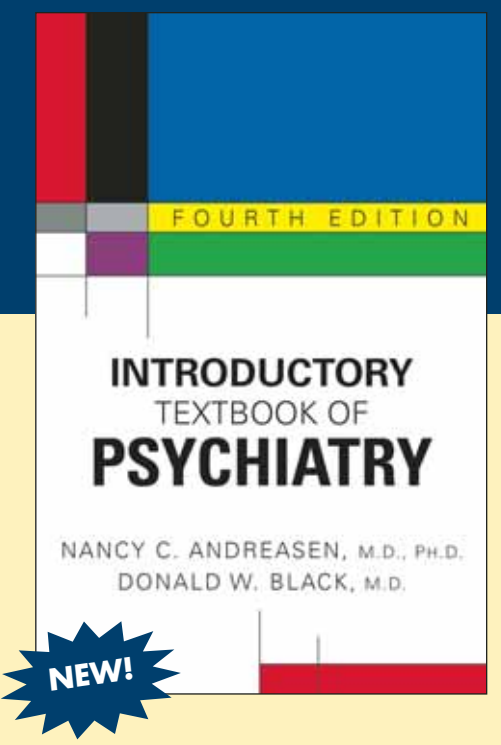
Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk—** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Families and caregivers of pediatric patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be 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. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **PRECAUTIONS: General—*Discontinuation of Treatment with Effexor XR.*** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness***: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. ***Changes in Weight: Adult Patients***: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients***: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% vs. 3.6%; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents >12 years old. ***Changes in Height: Pediatric Patients***: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). In a 6-month study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents >12 years old. ***Changes in Appetite: Adult Patients***: Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Mydriasis***: Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide About Using Antidepressants in Children and Teenagers* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to avoid alcohol while taking Effexor XR and to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations, they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions— *Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. Based on its mechanism of action and the potential for serotonin syndrome, use caution when coadministering venlafaxine with other drugs affecting the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors, or lithium. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility—*Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy—*Teratogenic Effects—Pregnancy Category C.*** Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***. Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS: *Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalciuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, breast pain, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C019, revised November 2005.

Wyeth®

Introductory Textbook of Psychiatry, Fourth Edition

Nancy C. Andreasen, M.D., Ph.D., and Donald W. Black, M.D.



An established resource, the *Introductory Textbook of Psychiatry* has been thoroughly revised to make it an even more effective text. This edition is more practical and easier to use. The authors continue to interweave recent advances in psychiatry with the core knowledge that students new to the field need—from grasping the neurobiology and genetics of mental illness to understanding the DSM system to assessing patients.

Hailed as a "classic text," this user-friendly volume is written in an accessible, conversational style for introductory psychiatry courses or psychiatry clerkships—or as an authoritative introduction to abnormal psychology for students of psychology, social work, or nursing.

- It introduces students to a wide range of psychiatric diagnoses—covering epidemiology, clinical features, and treatment
- Provides additional coverage of special topics such as violence and suicide, legal issues that affect psychiatry, childhood disorders, sleep disorders, and both psychosocial and somatic therapies

As a teaching resource, it boasts several benefits:

- Tools that enhance learning, such as compelling case vignettes and "clinical pearls"—even more numerous in this edition—plus self-assessment questions
- A detailed introduction to the interview process, including specific questions that the clinician might ask patients
- A critical review of DSM-IV-TR covering all disorders, arranged by diagnostic class
- Eleven chapters devoted to specific conditions, from cognitive disorders to personality disorders to impulse-control disorders, with handy tables of DSM-IV-TR diagnostic criteria, practical assessment tips, and other key points
- A single-chapter introduction to the basics of child psychiatry, covering mental retardation, autism, ADHD, and more
- Up-to-date information on drugs—including newer antidepressants—and guidelines for electroconvulsive therapy
- A glossary of key psychiatric terms, new to this edition

2006 • 688 pages • ISBN 1-58562-223-0 • Hardcover • $78.00 | 2006 • 688 pages • ISBN 1-58562-272-9 • Paperback • $58.00

E-Prescribing

continued from page 9

the federal health care programs and beneficiaries from fraud and abuse," said Health and Human Services Inspector General Daniel Levinson in a statement.

In comments submitted to CMS last year, APA Medical Director James H. Scully Jr., M.D., said APA generally supports the movement toward e-prescribing and electronic health records. But he expressed a range of concerns including the potential for federal sanction of physicians who receive in-kind donations of computer technology and services related to e-prescribing.

Until adequate exceptions and safe harbors are provided under existing federal laws, "any physician dealing with Medicare patients who accepts value in-kind such as software, hardware, Web access, training, educational materials, discounts, rebates, or other assistance related to e-prescribing infrastructures may be subject to federal sanctions," he wrote.

"Managed care entities, software, computer hardware, and Web services companies will make various offers to physicians to make their products competitive and otherwise induce them to adopt e-prescribing practices," Scully wrote. "E-prescribing requirements should not force psychiatrists to either pay the entire cost of an e-prescribing system or accept assistance from external entities but risk potential federal action."

The OIG's final rule on e-prescribing is posted at <www.oig.hhs.gov/authorities/docs/06/OIG%20E-Prescribing%20Final%20Rule%20080806.pdf>. The CMS's final rule is posted at <www.cms.hhs.gov/PhysicianSelfReferral/Downloads/CMS-1303-F.pdf >. ■

Technology

continued from page 9

The Senate bill would clarify that Health Information Technology Resource Center privacy rules apply to any health information stored or transmitted electronically. The measure also specifies that it would not affect privacy-related provisions in the Social Security Act or HIPAA.

The legislation is likely to undergo extensive changes during conference committee negotiations over a variety of issues, including privacy.

"Our work is not done," Meyers said. "Rest assured that APA will continue to promote and seek the strongest possible patient privacy rights within a HIT infrastructure and beyond."

Health and Human Services Secretary Michael Leavitt also is expected to push for the addition of HIT interoperability requirements, which he said are vital to the success of health information technology. Mandating such requirements now is more cost-effective and efficient than doing so later so that incompatible systems aren't created.

Information on the House bill is posted at <http://thomas.loc.gov/cgi-bin/query/D?c109:3:./temp/~c1095Ui416> and the Senate bill at <http://thomas.loc.gov/cgi-bin/query/D?c109:4:./temp/~c109EiZDbI::>. ■

Buprenorphine

continued from page 10

adequately cover buprenorphine's cost or the costs to the prescribing physician who provides this intervention. Many unemployed people and low-income working people, for example, lack access to medical care, and many addicts are unaware that the medication is an option available to them.

The SAMHSA surveys found that nearly half of the prescribing physicians surveyed reported that the cost of the drug was among the top challenges to prescribing buprenorphine.

Another limit repeatedly cited by physicians at the symposium was the reluctance of many physicians to deal with "both the stigma attached to addicts and the extensive oversight exercised by federal and state law enforcement agencies," Kleber said.

Congressional supporters of buprenorphine treatment promised they would push for removal of the 30-patient limit on physicians authorized to prescribe the drug.

"We need to remove this limit and frankly, I don't know how anyone could oppose that at this point," said Sen. Orrin Hatch (R-Utah), in an interview with *Psychiatric News*. He said he plans to push for removal of the limit before the end of the current session of Congress as a crime-control measure. The measure is included in legislation to reauthorize the Office of National Drug Control Policy (S 2560), which the full Senate is slated to consider in September. There is no House bill aimed at removing the 30-patient limit.

Sen. Carl Levin (D-Mich.), who described the buprenorphine treatment option as a "landmark" in addiction treatment, said more effort is needed to expand the treatment's use beyond the less than 2 percent of primary care physicians authorized to use it. He noted that only 2,910 general practitioners out of 242,924 have been certified to prescribe the drug. The evidence of the treatment's benefits and lack of adverse impact, Levin said, show the need to remove legislative limits that have resulted in long waiting lists and lack of access for many addicts.

"This [SAMHSA] study confirms our hopes about the effectiveness of buprenorphine and also helps to illuminate the things that need to be done to help more patients reach this powerful medicine," Levin said.

Supporters of buprenorphine treatment hope to increase physician participation by expanding the required eight-hour training sessions to include an online alternative. Elinore McCance-Katz, M.D., Ph.D., president-elect of the American Academy of Addiction Psychiatry, said her organization—like APA—developed a Web-based course that leads to waiver eligibility. The alternative will make it easier and less costly for physicians to receive training in office-based opioid addiction care.

"Going forward, we plan to continue to try to train as many physicians as possible to provide these services to patients," she said.

Further information on buprenorphine treatment is posted at <http://buprenorphine.samhsa.gov>. APA's online buprenorphine course is posted at <www.psych.org/edu/bup_training.cfm>. ■

Treating Patients with Hearing Impairments or Limited English Proficiency: *What Are the Emerging Duties for Psychiatrists?*

The Americans with Disabilities Act of 1990, commonly referred to as the "ADA," became effective in 1992 and requires the provision of appropriate auxiliary aids and services to ensure adequate communication between a physician and a patient with hearing or vision impairments. The ADA does not require the use of an interpreter for a deaf or hearing-impaired person in every medical setting but "effective communication" is the required standard. Lip reading, note-taking or interpretation by a family member might not be considered effective communication when a psychiatrist is engaging in psychotherapy with a patient.

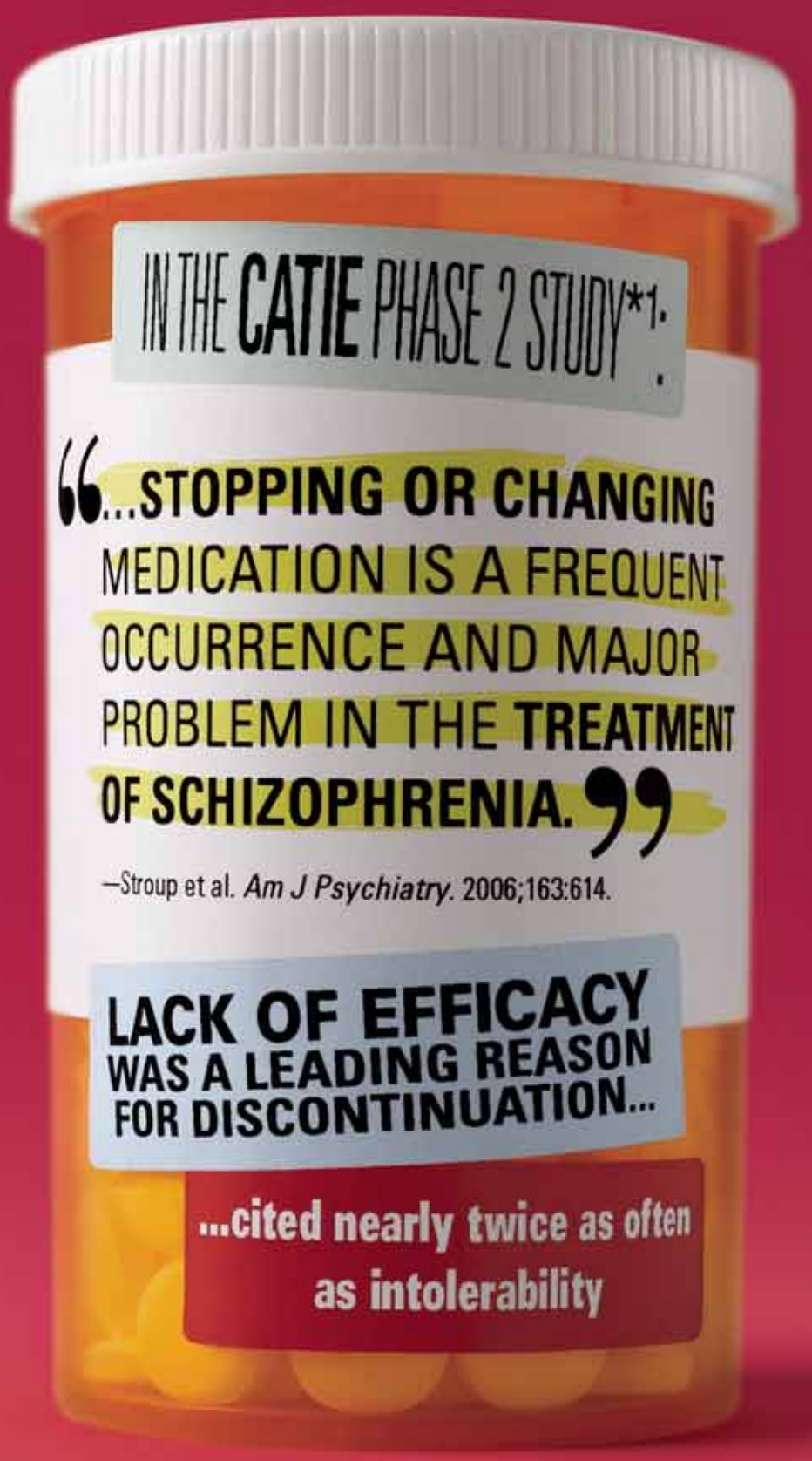
A psychiatrist is not required to provide an interpreter for a deaf or hearing-impaired patient where it would present an "undue burden" on the professional. However, the single factor of interpreter cost exceeding the cost of the medical consultation has not been found by the courts to be an undue burden. Factors that may create an "undue burden" include the practice's overall income, eligibility for tax credits and the frequency of patient visits requiring an interpreter. Further information on such issues may be obtained from the United States Department of Justice, Civil Rights Division, Public Access Section.[i] Federal tax credits may be available for part of the cost of providing an interpreter, so any psychiatrist affected by the law should consult his/her accountant.

Another law which gives rise to the potential duty of the psychiatrist to provide interpreters – not for the hearing-impaired but for limited English proficiency patients – is Title VI of the Civil Rights Act of 1964.[ii] This law prohibits discrimination on the basis of race, color or national origin. The "national origin" language has been broadly construed by regulation to require providers who receive certain federal funds[iii] to take steps to provide effective communication. Although a large facility (e.g., a hospital emergency room) may be subject to greater scrutiny than a small psychiatric practice, psychiatrists should consider adopting plans to effectively communicate with patients who cannot fully communicate in English. Furthermore, state human rights laws may impose requirements on health care providers to assure effective communication. Psychiatrists could also be vulnerable in malpractice suits for violation of the standard of care where treatment was compromised due to ineffective communication.

This update was provided by Anne Marie "Nancy" Wheeler, J.D., Coordinator of the APA Legal Information and Consultation Plan. For further information about the Plan, which has been revised for 2006, please call 301-384-6775 or e-mail ***apaplan@comcast.net****.*

[i] The information line at the Department of Justice for ADA compliance (including the need for interpreters) is 1-800-514-0301.
[ii] *See* 42 U.S.C. §§ 2000d *et seq., as amended*. Guidance is available at **http://www.usdoj.gov/crt/cor/lep/DOJFinLEPFRJun182002.htm**.
[iii] These funds do not include Medicare Part B payments.

In a schizophrenia trial measuring time to all-cause discontinuation...



EFFICACY MATTERS

For many patients in the treatment of schizophrenia

RISPERDAL

Count on the long-standing history

RISPERDAL is indicated for the treatment of schizophrenia.

Increased Mortality in Elderly Patients with Dementia–Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

Commonly observed events: In short-term trials, the most commonly observed adverse events associated with RISPERDAL at an incidence of ≥5% and at least 2x placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Hyperglycemia and diabetes: Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS), including RISPERDAL. Patients starting treatment with APS who have or are at risk for diabetes, should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Tardive dyskinesia (TD): As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD; if its signs and symptoms appear, discontinuation of RISPERDAL should be considered. Elderly patients appeared to be at increased risk for TD.

Neuroleptic malignant syndrome (NMS): NMS has been reported rarely with this class of medications, including RISPERDAL and appropriate management should be employed.

DELIVERS

of RISPERDAL—

- Proven symptom control in schizophrenia[†2]
  - —More than 12 years of experience[3]

Risperdal®
tablets and
oral solution 1 mg/mL RISPERIDONE

Cerebrovascular adverse events (CAEs): CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking risperidone in clinical trials. The incidence of CAEs with risperidone was significantly higher than with placebo. RISPERDAL is not approved for treating these patients.

Please see brief summary of full Prescribing Information, including Boxed Warning, on adjacent page.

Visit our Web site at risperdal.com

*Subjects with schizophrenia (N=444) who had discontinued the atypical antipsychotic randomly assigned during phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigation were randomly reassigned to double-blind treatment with a different antipsychotic (olanzapine, 7.5–30 mg/day [N=66]; quetiapine, 200–800 mg/day [N=63]; risperidone, 1.5–6.0 mg/day [N= 69]; or ziprasidone, 40–160 mg/day [N= 135]). Identical capsules (risperidone, 1.5 mg qd or bid; olanzapine, 7.5 mg qd or bid; quetiapine, 200 mg bid; ziprasidone, 40 mg bid) were flexibly dosed (within 1 to 4 capsules daily) on the basis of the study doctor's judgment. Patients were assigned to a treatment they had not received in phase 1. This phase 2 study was recommended to patients who poorly tolerated treatment in phase 1, but also included individuals who 1) discontinued previous treatment in phase 1 because of inefficacy and who did not want to consider treatment with clozapine, and 2) discontinued their previous treatment independently of their doctor's recommendation. The primary aim was to determine if there were differences among the four treatments in effectiveness, as measured by time until discontinuation for any reason.

† Demonstrated in two 8-week, randomized, double-blind, placebo-controlled trials comparing the efficacy and safety of risperidone and haloperidol in patients with schizophrenia (N=513). Patients were randomly assigned to 1 of 6 fixed-dose, parallel-treatment groups: 2, 6, 10, or 16 mg/day of risperidone, 20 mg/day of haloperidol, or placebo. The study was not powered to show a difference between RISPERDAL and haloperidol.

References: 1. Stroup TS, Lieberman JA, McEvoy JP, et al, for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry.* 2006;163:611–622. **2.** Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry.* 1997;58:538–546. **3.** FDA approval 1993.

 August 2006 01RS1845T

Together Rx Access is a trademark of Together Rx Access, LLC.

Janssen, L.P.

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

Increased Mortality in Elderly Patients with Dementia–Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS AND USAGE: RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia. **Monotherapy:** RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder. **Combination Therapy:** The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

CONTRAINDICATIONS: RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning). Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome. **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis:** Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

PRECAUTIONS: General: Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION in full PI). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication. **Seizures:** RISPERDAL® should be used cautiously in patients with a history of seizures. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely. **Priapism:** Rare cases of priapism have been reported. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown. **Antiemetic Effect:** Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. **Use in Patients With Concomitant Illness:** Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Increased plasma concentrations of risperidone and 9–hydroxyrisperidone occur in patients with severe renal impairment, and in patients with severe hepatic impairment. A lower starting dose should be used in such patients. **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®: **Phenylketonurics:** Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine. **Drug Interactions:** The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Carbamazepine and Other Enzyme Inducers:** In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9–hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. **Fluoxetine and Paroxetine:** Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9–hydroxyrisperidone have not been studied. **Lithium:** Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone. **Digoxin:** RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Drugs That Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9–hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY in full PI). Drug interactions that reduce the metabolism of risperidone to 9–hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9–hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. *In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY in full PI). **Drugs Metabolized by CYP 2D6:** *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. These findings are considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia). **Mutagenesis:** No evidence of mutagenic potential for risperidone was found. **Impairment of Fertility:** Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed. **Pediatric Use:** Safety and effectiveness in children have not been established. **Geriatric Use:** Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in full PI). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION in full PI). **Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis:** In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)

ADVERSE REACTIONS: Associated With Discontinuation of Treatment: Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%). In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo). **Incidence in Controlled Trials: Commonly Observed Adverse Events in Controlled Clinical Trials: *Bipolar Mania:*** In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence. *Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania*: Adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial-Monotherapy in Bipolar Mania.* **Body System/Preferred Term: Central & peripheral nervous system:** Dystonia, Akathisia, Dizziness, Parkinsonism, Hypoaesthesia **Psychiatric:** Somnolence, Agitation, Manic reaction, Anxiety, Concentration impaired **Gastrointestinal system:** Dyspepsia, Nausea, Saliva increased, Mouth dry **Body as a whole - general:** Pain, Fatigue, Injury **Respiratory system:** Sinusitis, Rhinitis, Coughing **Skin and appendages:** Acne, Pruritus **Musculo-Skeletal:** Myalgia, Skeletal pain **Metabolic and nutritional:** Weight increase **Vision disorders:** Vision abnormal **Cardiovascular, general:** Hypertension, Hypotension **Heart rate and rhythm:** Tachycardia. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial – Adjunctive Therapy in Bipolar Mania.* **Body System/Preferred Term: Gastrointestinal system:** Saliva increased, Diarrhea, Abdominal pain, Constipation, Mouth dry, Tooth ache, Tooth disorder **Central & peripheral nervous system:** Dizziness, Parkinsonism, Akathisia, Dystonia **Psychiatric:** Somnolence, Anxiety, Confusion **Respiratory system:** Rhinitis, Pharyngitis, Coughing **Body as a whole - general:** Asthenia **Urinary system:** Urinary incontinence **Heart rate and rhythm:** Tachycardia **Metabolic and nutritional:** Weight increase **Skin and appendages:** Rash. **Dose Dependency of Adverse Events:** Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation. ***Vital Sign Changes:*** RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). ***Weight Changes:*** A statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%). ***Laboratory Changes:*** A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS). ***ECG Changes:*** Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). **Other Events Observed During the Premarketing Evaluation of RISPERDAL®:** During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies and the following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it). **Psychiatric Disorders:** *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning. **Central and Peripheral Nervous System Disorders:** *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis. **Gastrointestinal Disorders:** *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis. **Body as a Whole/General Disorders:** *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing. **Respiratory System Disorders:** *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration. **Skin and Appendage Disorders:** *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria. **Cardiovascular Disorders:** *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis. **Vision Disorders:** *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation. **Metabolic and Nutritional Disorders:** *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia. **Urinary System Disorders:** *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency. **Musculo-Skeletal System Disorders:** *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain. Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage. **Liver and Biliary System Disorders:** *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage. Platelet, Bleeding, and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia. **Hearing and Vestibular Disorders:** *Rare:* tinnitus, hyperacusis, decreased hearing. **Red Blood Cell Disorders:** *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia. **Reproductive Disorders, Male:** *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure. **White Cell and Resistance Disorders:** *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly. **Endocrine Disorders:** *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder. **Special Senses:** *Rare:* bitter taste.*Incidence based on elicited reports. **Postintroduction Reports:** Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

For more information on symptoms and treatment of overdosage, see full Prescribing Information.

7503231B Revised March 2006

Janssen L.P.

01RS1795BB

EDWARD
HOSPITAL & HEALTH SERVICES

Child & Adolescent Psychiatry Practice Opportunity

Excellent opportunity for a Board Certified or Board Eligible Child & Adolescent Psychiatrist to join Linden Oaks at Edward Hospital located in Naperville Illinois, just 35 miles west of downtown Chicago. Linden Oaks is a JCAHO accredited Behavioral Health facility affiliated with Edward, a community based hospital with a Medical Staff of over 800 members. Linden Oaks currently offers a specialized treatment in Child & Adolescence, eating disorders, chemical dependency services and self injury programs. Our Child Psychiatry Institute offers physicians the ability to practice in an on-site outpatient program and an acute care setting.

Naperville is one of the fastest growing communities in the country and includes a primary service area of over 250,000 lives. The fastest growing segment of the service area is children and adolescents.

This is one of the most desirable Child & Adolescent Psychiatry opportunities in the Chicago metropolitan area. We offer a competitive benefits package in addition to affiliation with a progressive state of the art facility.

Interested individuals should contact or directly forward their Curriculum Vitae to:
Jason Shenefield • Physician Recruiter • Edward Hospital
801 S. Washington Street • Naperville, IL 60540
PH 630-527-5306 • FX 630-527-3069
E-mail: Jshenefield@edward.org

PSYCHIATRIST

Tomah & La Crosse, Wisconsin
Full-time, Federal Benefits

Provide inpatient and outpatient psychiatric care and psychiatric consultation services to veterans at the Tomah VA and/or the satellite La Crosse Community Based Outpatient Clinic.

Non-citizen applicants will be considered if no US citizens are available. Requires a BC/BE or equivalent experience and possession of a valid and unrestricted license.

VAMC Tomah is a general medical, extended care, primary care and mental health services facility with a large outpatient population. Tomah is an attractive, family-oriented, small town in mid-western Wisconsin with tremendous recreational opportunities, high quality public and parochial education facilities and two nearby colleges.

Full Federal Benefits including:
- Competitive salary
- Paid vacation
- Malpractice exempt
- Sick/military leave
- Manageable workload/ Light call
- Retirement/Tax deferred plan
- And more!

Offering recruitment incentives, reimbursement for relocation expenses and the opportunity to apply for the debt reduction program.

For additional information please contact Rita Puttkammer, Administrative Assistant at: (608) 372-1631
E-mail: Rita.Puttkammer@va.gov

Interested candidates should mail or fax CV to:

TOMAH VA MEDICAL CENTER
Mental Health Service Line
500 E. Veterans St.
Tomah, WI 54660
Fax: (608) 372-1224

EOE/Random Drug Screen

smile more.

When you join Kaiser Permanente Southern California, you'll have a lot more reasons to smile. That's because we'll be taking care of your administrative concerns **(smile)…**and offering you a balanced call and work schedule **(big smile)…**which means you can enjoy all that sunny Southern California has to offer **(even bigger smile).** Most importantly, we'll give you the support, resources and autonomy you need to give your patients the exceptional care they deserve **(the biggest smile of all).**

Psychiatrists

Throughout Southern California

Cross-specialty collaboration and a comprehensive network of support are just a few of the advantages that make working with us so enjoyable. We also offer a highly competitive compensation and benefits package plus a location that's known the world over for its amazing climate and natural attractions.

For consideration, please forward your CV to: Kaiser Permanente, Professional Recruitment, 393 East Walnut Street, Pasadena, CA 91188-8013. Phone: (800) 541-7946. Email: Joan.X.Little@kp.org. We are an AAP/EEO employer. **http://physiciancareers.kp.org.**

KAISER PERMANENTE® thrive
Southern California Permanente Medical Group

Psychiatrist

Miramichi Regional Health Authority has an immediate opening for a **Full Time Bilingual (French and English) Psychiatrist** for our inpatient and community service. Successful candidates would join our team of 3 Psychiatrists for the 12-bed inpatient unit and provide service to a community of 50,000 people, which includes 25% of those who are French speaking.

The Miramichi offers an excellent recreational and family living experience. To find more details about the Miramichi area, please visit the Miramichi City website at www.miramichi.org

The Miramichi Regional Health Authority offers competitive pay scale and relocation allotment. Earning potential would be in excess of $200,000 for a Canadian or US Certified Psychiatrist.

If interested in joining our team, please forward a resume to:
Dr. Sanjay Siddhartha, Chief of Psychiatry
Miramichi Regional Health Authority
500 Water Street Miramichi, NB E1V 3G5
Telephone 506 - 623-3195
E-mail sanjay@rha7.ca
or
Luc Dube, Acting Regional Director of Mental Health Service
Telephone: 506-623-3198
E-mail: luc.dube2@gnb.ca

Miramichi Regional Health Authority
Régie régionale de la santé de Miramichi

Miramichi Regional Health Authority promotes a scent-reduced and smoke free environment.

Locum Tenens Psychiatry

MEDICAL DOCTOR ASSOCIATES
100% Employee-Owned

Reliable

There For You When You Need Us

Meet one of the owners

Bernie's doctors rely on her to be there for them before, during, and after they are working an assignment. She is well known for not letting her physicians down.

Bernie is RELIABLE.
Bernie is an MDA owner

Nationwide Opportunities Available . . . **Call Today!**

800.780.3500 x.2136 www.mdainc.com

THE REWARDING CAREER YOU HAVE BEEN WAITING FOR MAY BE RIGHT AROUND THE CORNER...

STAFF PSYCHIATRIST POSITIONS AVAILABLE
Part Time and Full Time

Remuda Ranch provides residential and inpatient programs for women and girls suffering from eating disorders and related issues. In our unique, non-institutional settings, our treatment teams offer Biblically-based intensive care to patients of all faiths.

Competitive compensation
Relocation assistance available
Peaceful healing environment
Low patient-to-staff ratios
Excellent benefits programs

Contact our Staff Recruiter today at
1-800-445-1900 ext. 4297
EOE

REMUDA
Nourishment for Life Ranch
Programs for Eating Disorders

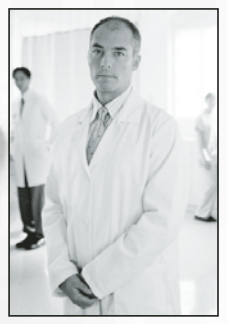
Psychiatrist

The Veterans Affairs Northern California Health Care System (VANCHCS) Mental Health Service is recruiting for an Addiction Psychiatrist to lead the Substance Abuse Program at the Sacramento Mental Health Clinic. VANCHCS is academically affiliated with the University of California, Davis School of Medicine(UC Davis), and is a training site for medical students and psychiatry residents. The ideal candidate will have ABPN Certificate in Psychiatry with added qualifications in Addiction Psychiatry, and be eligible for a faculty appointment at the UC Davis. The successful candidate will be provided time to develop his/her teaching skills and to participate in educational programs at UC Davis. Salary is competitive and based on credentials and experience.

Please send inquiry and CV to:
Lesa Roderick
HRMS-05, VA NCHCS
10535 Hospital Way Bldg. 707
Sacramento, California 95655.
Telephone: 916-843-7376
FAX: 916-364-0239. EOE.

The doctor is in.

Whether you are a practicing physician or talented applicant, the American Psychiatric Association (APA) Job Bank is your psychiatric job placement resource.



IN FOCUS
Candidates:
Post your résumé online for free.
Search psychiatric jobs by specialty or location.
Gain access to employment tools.

Employers:
Post psychiatric career opportunities quickly and easily.
Tap into an online résumé database.
Find the right candidate for your psychiatric position.

IN THE KNOW
Access sample cover letters and curriculum vitae, career development articles, salary surveys, interview worksheets and other tools on the APA Job Bank.

APA JOB BANK
The best source for psychiatric job placement

Visit www.psych.org/jobbank today.

Advertise your psychiatric opportunity in APA's *Psychiatric News* or *Psychiatric Services* classifieds and with the APA Job Bank online to receive a 10 percent discount on both. For more information, call (888) 35-PSYCH ext. 7330 or direct at (703) 907-7330, or email classads@psych.org.

CLASSIFIED ADVERTISING INFORMATION

2006 RATES:
- $22 per line for orders of 1 to 2 insertions
- $20 per line for orders of 3 or more consecutive insertions, only if your written order specifies a 3 or more consecutive issue run.
- $19 per line for orders of 6 or more insertions, only if your written order specifies a 6 or more issue run.
- 1 line = approximately 43 characters
- 6 line minimum
- $30 extra for confidential blind box number
- $50 extra for email and web page links
- Classified rates are non-commissionable to agencies

FREE ONLINE ADVERTISING:
Psychiatric News classified ads are posted on **pn.psychiatryonline.org** as each issue is published on the first and third Friday of each month.

EMAIL AND WEB PAGE LINKS: For an additional $50 your prospects can e-mail a response to your ad in seconds. A web link transports prospects directly to your web site in just one click.

LOGOS: Insert a 4-color logo above your ad for $265 per issue or a black-and-white logo for $190 per issue. Submit logo as 300 dpi TIFF or EPS.

BLIND BOX REPLIES: A blind box address is available to provide confidentiality to advertisers. Please address all blind box advertising replies to:

ATTN.: Box P-XXX
Psychiatric News Classifieds
American Psychiatric Publishing Inc.
1000 Wilson Blvd, Suite 1825
Arlington, Virginia 22209-3901

SUBMISSIONS: Email, Fax or Mail ad copy, including issue dates desired, contact name, phone number, and billing address, to:

Joel Nepomuceno
Psychiatric News Classifieds
American Psychiatric Publishing Inc.
1000 Wilson Blvd, Suite 1825
Arlington, Virginia 22209-3901
(703) 907-7330 • Fax (703) 907-1093
classads@psych.org

All advertising copy, changes and cancellations received after the deadline will be placed in the next available issue. We do not provide proofs of ads before publication.

DEADLINES: All new advertising copy, changes, and cancellations must be received *in writing* by Friday, 2 p.m. (E.T) two weeks prior to publication date. Publication dates are the first and third Fridays of every month. Specific deadline dates for upcoming issues are as follows:

Issue	Deadline (Friday, 2 p.m. E.T.)
October 6	September 22
October 20	October 6

The publisher reserves the right to accept or reject advertisements for Psychiatric News. All advertisers in this section must employ without regard for race, sex, age, nationality, or religion in accordance with the law. APA policy also prohibits discrimination based on sexual orientation or country of origin. Readers are urged to report any violations immediately to the executive editor.

Nationwide

LocumTenens.com

www.LocumTenens.com/pn
1-888-223-7950

www.PsychiatryJobsOnline.com

User-friendly site with over 200 job listings in great states like FL, NC, GA, PA, MD, MT, OH, IL, MA, NY, TX, TN, MI. All states represented. Email updates and customized Searches available. For Personal Assistance (800) 880-2028 (Psych455)

FCS

THE 1ST CHOICE IN PSYCHIATRIC RECRUITMENT

Visit our website www.fcspsy.com
Over 300 psychiatric searches nationwide.
800-783-9152

CompHealth Locum Tenens. CompHealth offers more psychiatric locum tenens opportunities nationwide. Paid travel, lodging, malpractice insurance, and more. Work full- or part-time schedules that best fit your lifestyle. Earn an income comparable to or better than many permanent positions. Finding the right opportunities for physicians, like you, is something we've perfected over the last 25 years. **Call today. 800.328.3041 www.ifoundmore.com/psyn.**

CompHealth
COMPREHENSIVE HEALTHCARE STAFFING

Psychiatrists Only
locum tenens and permanent placement

PHYSICIAN OWNED AND MANAGED
www.psyonly.com
Over 400 Locum Tenens and Permanent Placement Opportunities
Don Ceniza
800-583-2256

ALABAMA

Short drive to Nashville - Work **100% Outpatient** at financially stable, well run CMHC. Work in a team setting seeing 18-20 patients per day. 4.5 day workweek. Salary starts at $160K. **Underserved area for Visas or Loan Repayment**. Contact **Karen Brennan at 800-575-2880 x307**. E-mail to **KBrennan@MedSourceConsultants.com.**

PSYCHIATRIST

Birmingham - The University of Alabama at Birmingham Department of Psychiatry is accepting applications from BC/BE psychiatrists for a faculty position in its Division of Medical/Surgical Psychiatry, assistant professor rank, non-tenure earning. Primary responsibilities include provision of consultation/liaison services to the medical center and delivery of clinical care to the division's outpatients. Participation in the teaching and supervision of medical students and psychiatry residents expected. Involvement in research encouraged. Competitive salary/benefits package. Applications to James H. Meador-Woodruff, M.D., Heman E. Drummond Professor and Chair, UAB Department of Psychiatry, 1720 7th Avenue South, Birmingham, AL 35294-0017. UAB is an affirmative action/equal opportunity employer.

UNIVERSITY OF ALABAMA AT BIRMINGHAM DEPARTMENT OF PSYCHIATRY

The Department of Psychiatry at UAB invites applications for positions at the rank of Assistant, Associate, or Full Professor, some on research track. Tenure status and rank commensurate with qualifications and experience. The Department is under new leadership and undergoing significant expansion. We are recruiting outstanding scientists and clinical investigators with either MD or PhD degrees in the research areas of schizophrenia and psychotic illnesses, affective and anxiety disorders, substance abuse, developmental disorders including autism, and geropsychiatry, with an emphasis on scientific excellence regardless of research area or faculty rank.

The Department of Psychiatry offers a supportive research environment in new labs housed primarily in the Sparks Center, with abundant opportunities for collaboration with neuroscience faculty in other departments including Neurology, Neurobiology, Psychology, Physiology and Biophysics, Cell Biology, and Neuropathology. UAB is one of the leading academic medical centers in the country and is currently ranked 18th in NIH funding among all US medical schools. Senior applicants should submit a CV. Junior applicants should provide a CV, description of proposed research and names of 3-5 references to: James H. Meador-Woodruff, M.D., Heman E. Drummond Professor and Chair, UAB Department of Psychiatry, 1720 7th Avenue South, Birmingham, AL 35294-0017. UAB is an affirmative action/equal opportunity employer.

ALASKA

ANCHORAGE: Child or General Psychiatrist. Inpatient, residential treatment and/or outpatient. Compensation includes salary, incentive plan & full benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

Strengthen your recruitment effort through the APA Job Bank! Post your career opportunity online, receive candidate responses instantly, and access APA's resume database of psychiatrists.

Call 703.907.7330 for more info

Enjoy Alaska's Pacific Maritime Climate on the Inland Passage!

Bartlett Regional Hospital in Juneau, Alaska's Capital City, is seeking a BE/BC child-adolescent psychiatrist or an adult psychiatrist for an outpatient and inpatient setting. Eligible for National Health Service Corps loan repayment program. University of Washington clinical faculty affiliation. The benefit package is State of Alaska Public Employees Retirement System and City and Borough of Juneau. Salary is most competitive, with excellent fringe benefits, which include five CME days in addition to 28 leave days during the first year with subsequent increases.

Please direct questions or CV to:

Verner Stillner, MD, MPH
Medical Director for Behavioral Health
Bartlett Regional Hospital
3260 Hospital Drive
Juneau, AK 99801
PH: (907) 796-8498
FX: (907) 796-8497
Email: vstillner@bartletthospital.org

ARIZONA

PSYCHIATRIST

West Yavapai Guidance Clinic, a non-profit organization with a 40-year history of providing quality service to the Prescott Arizona area, has openings for adult and child and adolescent psychiatrists to augment its current staff of five psychiatrists. The clinic is experiencing rapid growth and presently has 220 employees who provide inpatient and outpatient behavioral health services. We offer a competitive salary, excellent employer-paid benefits, a 401k plan, generous paid time off, 10 paid holidays, paid CME days and allowance, and a relocation and/or hire-on bonus. Positions eligible for National Health Services Corp loan and scholarship programs. Prescott, 96 miles north of Phoenix, is Arizona's quaint mile-high city bordered by the Prescott National Forest offering four seasons of mild weather with year round outdoor activities. Please contact: Human Resources, 642 Dameron Drive, Prescott, AZ 86301. Phone: 928-445-5211, Fax: 928-445-6542, e-mail: wygc.org. EOE.

Assistant Professor, Clinical Psychiatry University of Arizona (UPH Hospital-Kino)

The University of Arizona's Department of Psychiatry is recruiting adult psychiatrists to join a progressive and growing academic department located in the beautiful Southwest with academic appointments as Assistant Professor of Clinical Psychiatry. Individual must be Board certified or eligible in Psychiatry and have current credentials to practice medicine in the United States. Incumbent will provide clinical care in an inpatient facility with adult and geriatric populations. Other duties may include supervising and teaching adult psychiatry residents and medical students. Competitive salary and excellent benefits package offered. For more complete information about the positions, and to apply, go to: http://www.uacareertrack.com and reference job #35321. If you have questions, please contact Betsy Pepping, Administrative Associate, Dept of Psychiatry, 1501 N. Campbell Avenue, P.O. Box 245002, Tucson, AZ, 85724-5002, peppingb@email.arizona.edu or (520) 626-3819. Review of applications begins July 15, 2006 and is ongoing until positions are filled.

The University of Arizona is an EEO/AA Employer-M/W/D/V.

Mohave Mental Health Clinic, Inc., a non-profit organization located in northwest Arizona has an opening for a Psychiatrist for its Bullhead City clinic. We offer a competitive salary, 5 weeks PDO the first year, 401k, and excellent employer paid benefits. The area offers lots of outdoor activities and is just a few hours drive from Phoenix, Las Vegas and Flagstaff. Contact: Human Resources, 1743 Sycamore Ave, Kingman, AZ 86409. Phone: 888-757-8111 Fax: 928-757-3256 or email Barbt.mohave@narbha.org.

PHOENIX - GENERAL ADULT AND FORENSIC PSYCHIATRISTS

Come to the beautiful and sunny southwest! Arizona State Hospital in Phoenix is recruiting for full-time board certified/qualified psychiatrists at our 338 bed JCAHO accredited hospital, including 160 beds-adult civil, 162 beds-forensic, and 16 beds-adolescent.

Phoenix offers a rich variety of cultural, sporting and recreational opportunities. The state of Arizona offers a diversity of climates and recreational opportunities all within a few hours of the sixth largest city in the U.S.

Starting salary of $160K or higher DOE with an excellent fringe benefit package and additional compensation for Officer-of-the-Day duty. Bilingual Spanish applicants are encouraged to apply. Arizona state license required for process of application. Open until filled. Apply via e-mail to John C. Cooper, CEO @ cooperj@azdhs.gov.

Arizona State Hospital
2500 East Van Buren Street
Phoenix, Arizona 85008
www.azdhs.gov/azsh
602.220.6000

The Arizona Department of Health Services is an Equal Opportunity Employer.

ARKANSAS

Fort Smith: Looking for Child Psychiatrist
Great salary plus an additional production bonus that could combine for over $200+ / year. J1 Visa's & foreign grads welcome. A private hospital located in an under served area that provides Inpatient, Residential, Day Treatment, & O/P. Full benefits including paid holidays, medical, dental, 401K. Fort Smith's MSA serves 312,000 people with a low cost of living. Please submit resume to kylen@vistahealthservices.com or fax to: (479) 521-4926 www.vistahealthservices.com

CALIFORNIA

Dominican Hospital is offering a full-time contract position for a board eligible or board certified psychiatrist. The hospital currently contracts with five psychiatrists who provide inpatient, partial hospitalization and consultation-liaison services to a wide variety of patients. Expertise in medication management and psychotherapy skills are required. Ability to work in a multi-disciplinary team setting is essential. Dominican Hospital is a large multi-specialty hospital. Santa Cruz is a beautiful seaside community near San Francisco. Please send CV and cover letter to: Freddie Weinstein, MD, Medical Director, Dominican Hospital Behavioral Health Services 1555 Soquel Drive Santa Cruz, CA 95065, 831-462-7646 or fax 831-462-7570.

GREATER BAY AREA - Modesto, California

General & Child Psychiatrists needed, for unique, stable County Mental Health system in a welcoming community. Serve both public & private sector patients, in both inpatient/outpatient settings that have been benchmarked for their quality. Possibilities for Resident teaching & consultation with a full range of providers. When patients require hospitalization, inpatient & outpatient staff work **TOGETHER** to optimize care. Stanislaus County is located only 1 1/2 hours from both San Francisco and Yosemite, enjoying the best of both worlds.

Excellent salary scale, with steps from $159K to $194K; **PLUS** full benefits; **PLUS** 5% additional for each of following: Inpatient, General Boards, Child Boards; **PLUS** extra for limited On-Call; **PLUS** Union-negotiated increases already set for next few years. Negotiable hourly contract also an option. Fax CV to Marshall Lewis, MD, 209-558-8641 or call 209-558-4639.

COALINGA STATE HOSPITAL

Get in on the ground floor!

Coalinga State Hospital, in conjunction with UC Irvine, is inviting applications for psychiatrists.

Coalinga State Hospital is the first new State psychiatric hospital built in California in over 50 years. With its 1,500 beds, almost exclusively devoted to the treatment of sexually violent predators, it is a state-of-the-art facility. It is closely affiliated with the University of California, Irvine School of Medicine, and will train medical students and residents. A forensic fellowship program is being developed.

This is an excellent opportunity for a Board Certified or Board Eligible clinician interested in general adult psychiatry as well as forensic psychiatry. Coalinga State Hospital's salary package is competitive and we offer job security, flexible work schedules, and a generous California State benefit package, including paid leave, medical insurance, and CalPERS Retirement.

Staff Psychiatrist (Safety) $162,792 - $172,572*
(Board Certified) *(Includes Recruitment & Retention incentives.)

Coalinga State Hospital is a young organization with an idealistic staff. We invite you to come and visit our new facility and to meet our staff; travel expenses may be covered. Coalinga is located in the San Joaquin Valley, equidistant from Los Angeles, San Francisco, and Sacramento, and only two hours from the coast and National Parks.

If you are interested in discussing any of our psychiatric positions, please contact: Erica Weinstein, M.D., at (559) 935-4343, or E-mail EWeinstein@csh.dmh.ca.gov. For more information, visit our website at www.dmh.ca.gov/Statehospitals/Coalinga. CSH is an equal opportunity employer.

SANTA BARBARA - THE AMERICAN RIVIERA

Santa Barbara County is an unrivaled natural paradise. Beautiful valleys, rugged mountains, and 50 miles of spectacular coastline make Santa Barbara County one of the most desirable locales in the world.

Live and work in Paradise! Culture, urban resources, and rural beauty - for quality of life Santa Barbara County is the place to be.

Santa Barbara County has **immediate openings** in adult outpatient psychiatry.

$136,207 - $166,723/yr including benefit allowance.

We offer a stable work schedule, competitive salary, and a **generous benefits package**, including paid holiday, vacation, and sick leave; medical, dental, and vision care coverage; and a retirement package that includes both a defined-benefit pension and an optional deferred compensation plan through your choice of several competitive investment options.

For more information, or to apply online, visit our Website at
www.sbcountyjobs.com
Or call 805-568-2800

Central California Opportunity of a Lifetime!

Live in a lovely city in Central California with a growing population of over 100,000 and enjoy an abundance of cultural and recreational activities along with affordable housing. There are two inpatient openings in a hospitalist model at a 68-bed behavioral health facility. Work with a team of therapists, social workers, and nurses in providing consultation, pharmacotherapy, and psychotherapy to inpatients with diverse cases. The call coverage is one weekday night per week and one weekend in every four. Call 1-888-229-9495 for more information. **Send your CV to Tina Wilkins wilkinstina@earthlink.net or fax it to 916-482-1154**.

Scenic California Central Coast

Atascadero State Hospital

BE/BC Psychiatrist

Atascadero State Hospital now pays board certified psychiatrists $159,000, plus a generous year-end retention bonus. Atascadero is the nation's premier center for the treatment of forensically committed mentally ill patients. Our hospital is a teaching site affiliated with the University of California, accredited by JCAHO, and recipient of the prestigious Codman Award. All of our psychiatrists are board eligible and most are board certified. Many of our psychiatrists have forensic subspecialty boards.

We are located midway between San Francisco and Los Angeles on the scenic central California Coast, south of Big Sur. We offer a spectacularly beautiful environment in San Luis Obispo County with temperate climate, beaches, world class wineries, cultural activities, golfing, sailing, riding, clean air, and excellent schools through the University level.

Our benefit package is valued at an additional 30%, which includes retirement plans (including safety retirement), health plans, professional liability coverage, paid holidays, educational leave, and generous annual leave. On-call duty is compensated hour for hour over and above the base salary. Applicants must hold a current California license, or have pending application with the Medical Board of California.

For a prompt and confidential review, send CV to Jeanne Garcia, M.D., P. O. Box 7001, Atascadero, CA 93423-7001; (805) 468-2005 or fax (805) 468-2138; or e-mail us at jgarcia@dmhash.state.ca.us. We are an equal opportunity employer.

Great Psychiatrist Opportunities

Join our team of competent, committed, and caring medical staff. Live and work in our ideal climate within minutes of Southern California beaches and the greater L.A. metropolitan areas' vast array of cultural, educational, sporting and recreation opportunities, and with some of the most affordable housing in California.

The County of Riverside in beautiful Southern California is seeking general adult and sub-specialty trained psychiatrists to serve the growing needs of clients in our rapidly expanding County-operated public mental heath system. Be a part of our new and innovative behavioral health service programs.

We offer excellent compensation for psychiatrists through regular employment with a great benefit package, including retirement (3%@60), or per diem hourly rates ($100.16/h non-Bd.C., $105.65/h Bd.C., $113.25/h Child) Psychiatrists are needed for acute inpatient, psychiatric ER, and outpatient clinic and correctional work throughout our large geographic area, including Riverside, the Palm Springs/Indio area, and other smaller rapidly growing communities in the County. California license required. No Visa issues accepted. Bilingual Spanish applicants encouraged to apply.

For more information please contact Jerry L. Dennis, MD, Medical Director (Ph: 951-358-4621). Please send CV to Ryan Schulte by E-mail to rschulte@co.riverside.ca.us or Mail to:

County of Riverside
Department of Mental Health
4095 County Circle Dr.
Riverside, Ca. 92503

The Perfect Positions in Northern California!

Outstanding Adult Psychiatrist and C & A Psychiatrist positions are available in one of California's fastest growing communities. It is located 45 minutes south of Sacramento with a population of over 260,000. **The positions are highly sought after employed outpatient opportunities with no call!** You can have a flexible schedule while you care for the full range of psychiatric cases. Work in an environment of collegiality with other highly trained Adult and C & A Psychiatrists along with their superb team of therapists, social workers, nurses, and case managers. These are perfect positions to balance your personal and professional life! **Send your CV to Tina Wilkins at wilkinstina@earthlink.net; fax to 916-482-1154; call 1-888-229-9495**.

COLORADO

Sol Vista - Colorado's brand new cutting edge adolescent forensic treatment center needs a well-qualified psychiatrist. Responsibilities include heading a clinic treatment team for 20 beds. Position includes full benefits from employer, University of Colorado Medical School. Adolescent fellowship preferred, but experienced psychiatrists will be considered. Complimentary interviews will be provided to qualified applicants. We are not an underserved area. If interested, contact A. O. Singleton, III, M.D. @ (719) 546-4637 or Michelle Manchester, MA, CACIII @ (719) 546-4498

CONNECTICUT

University of Connecticut Health Center

CORRECTIONAL MANAGED HEALTH CARE

Seeking board certified and board eligible psychiatrists to provide care to patients in the Connecticut Department of Correction. Opportunities include patient care, research, teaching, and leadership in both an academic and public health care setting. Opportunities exist throughout the state. Exciting employment, excellent state benefits, regular working hours, and competitive salaries. Please contact Noreen Logan, Human Resources, for information and an application at (860) 679-7691 or e-mail at logan@uchc.edu.

AA/EEO M/F/PWD/V

LEDYARD: Southeast CT - General or Child Psychiatrist - clinical care to patients in acute, residential & partial setting. Salary & benefits. Position offers opportunity for administrative title & responsibilities for interested/qualified candidates. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

---

THE INSTITUTE OF LIVING
HARTFORD HOSPITAL

PSYCHIATRIST: The Institute of Living/Hartford Hospital is rapidly expanding physician employment opportunities. Boarded and Board Eligible Psychiatrists are needed to work as hospitalists in both our Adult and Child and Adolescent Inpatient Services. Available positions provide an excellent opportunity to join the medical staff of a dynamic and progressive psychiatric service. As part of a staff position, the Institute of Living supports opportunities for work within subspecialties as well as for teaching and participation in a growing research center. Some positions may include teaching responsibilities in our residency program.
Find out more about us by checking out our Web Page, www.instituteofliving.org. Applications for employment are to be submitted to Dr. Theodore Mucha, Medical Director at The Institute of Living/Hartford Hospital, 200 Retreat Avenue, Hartford, CT 06106. EEO M/F/D/V

DELAWARE

NEWARK/WILMINGTON & DOVER: General or Child Psychiatrist. Fulltime position for inpatient & partial hospital program. Also willing to consider part-time M-F schedule. Salary & benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

DISTRICT OF COLUMBIA

Well established, rapidly growing adult and child/adolescent private practice seeks ambitious and compassionate board certified/eligible psychiatrist for part to potentially full time position. Production based multidisciplinary practice has excellent national reputation, strong referral base and collegial team spirit. Full support administrative staff offers a turn key, family-friendly office environment with flexible scheduling, well-appointed offices and close proximity to Metro, shops, and restaurants. Interested candidates may visit our web site at www.rosscenter.com.
Please fax CV to 202-363-2383 or E-mail it to Jerilyn@rosscenter.com. For more information please contact Beth Salcedo, MD, Medical Director, at 202-363-1010.

FLORIDA

Staff Psychiatrist at a privatized 200 bed Forensic State Hospital in Miami. BC/BE, must possess a Florida license and at least 3 years experience in clinical psychiatry, forensic cert. not required. Experience with serious mental illness preferred. Employed position FT, benefits, 40 hours, call 1 in 4 and is by phone. Competitive salary

Send or Fax C.V. to: Debra Kirsch, MD
Chief Medical Officer
Geo Care, Inc.
dkirsch@geocareinc.com
Fax 561-999-7747
Cell 954-647-4359

Outstanding practice opportunity in Coastal Florida. Join **Top Medical Center** and hospital-based physician Group. Both Inpatient Practice Opportunity and Outpatient Practice Opportunities. Outstanding financial package, salary, bonuses and benefits. Respected Program, Collegial staff. Malpractice and Tail is covered. **Florida Coast - White Beaches, Crystal Clear Water.** Championship Golf Resorts, boating, fishing...**Excellent educational opportunities,** local Universities. Fine dining. Brian White at 1-888-339-7444 or fax cv to 1-940-234-5315 or email cv to brian@crossroadshealth.net

---

PANAMA CITY - Adult board certified or board eligible psychiatrist to join staff of comprehensive community mental health center. Salary range is: $176,000 - $183,000. Beautiful area of the country. Apply through our website www.lifemanagementcenter.org or send CV to: **Peter Hampton, Ph.D., Executive Director, Life Management Center of Northwest Florida, 525 E. 15th St., Panama City FL 32405**, EOE/DFWP. Pre-hire drug screen required.

FT. MYERS/MERBOURNE/ORLANDO/DAYTONA/MIAMI/FORT LAUDERDALE /OCALA/GAINESVILLE - Psychiatrists needed for rapidly expanding Nursing Home Service. Great support. No call. Average Salary 210K + benefits. Part-time available. Some travel required. Must have FL Medicare & FL Medicaid provider #s. Call Mike at 866-936-5250.

Miami: FL LICENSED PSYCHIATRIST; active private practice; affluent area; hosp, office, snf settings; excellent incentive plan incl salary & benefits. Dr. Carter, S. FL Psychiatric Assoc. 305-935-6060. FAX CV to 305-935-1717 or EMAIL: aventuraoffices@bellsouth.net.

Located along South Florida's east coast just minutes from the Atlantic Ocean, CARF accredited community mental health center is seeking a part-time/full-time inpatient and outpatient psychiatrists to provide comprehensive psychiatric care to children and adults. Must be Board Certified (or eligible). Excellent salary and benefits package, great staff and a lovely coastal community. Seeking applications directly from candidates. (No recruitment firms please!) Send/Fax CV: HR, New Horizons, 4500 W. Midway Rd., Ft. Pierce, FL 34981 FAX (772) 468-5606 EOE/ADA/DFWP www.nhtcinc.org

GEORGIA

WellStar Health System is seeking a Clinical Liaison Adult Psychiatrist to join an established and growing practice located in Marietta, GA. This position would consist of both inpatient and outpatient psychiatry/liaison work. WellStar offers a competitive compensation and benefits package. Please send CV to provider.positions@wellstar.org or fax to 770-792-1738. EOE.

BE/BC General Psychiatrist to join an expanding out-patient practice in St. Marys, GA, home of the Kings Bay Naval Base, a suburb of Jacksonville, FL, and listed in US News and World Report as one of the ten best retirement communities in the U.S.

Interested parties should send their CV to Bryan Warren, M.D., 235 Cardinal Circle West, St. Marys, GA, 31558.

ATLANTA: Medical Director - administrative & direct clinical care duties. Psychiatric, addiction, & dual diagnoses programs for child - geriatric patient populations. **Child Psychiatrist** for residential treatment center and/or hospital position. Salary & benefits offered. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

---

Take over a lucrative practice of a retiring psychiatrist. Practice was established in 1968. Join a group of multidisciplinary professionals in an interdenominational setting located in beautiful North Atlanta. No investment required. No In-Patient responsibilities. Weekend On-Call limited to once a month. If interested, please call 770-396-0232, ext. 232. Email your C.V. to atlantacounselingctr@yahoo.com or fax to 770-399-0007.

ILLINOIS

Opportunity for Adult and/or Child Psychiatrist at an established group practice in a western Chicago suburb. Hospital and office practice, academic and administrative involvement. Salary, productivity and benefits available. Fax resume to Medical Director at 630-850-9739 or e-mail denisehb@ameritech.net.

Greater Chicagoland area! Local group practice is looking for dedicated **Child, Addictions, & Adult** psychiatrists to work mostly **OUTPATIENT!** Highly lucrative opportunity with *competitive salary, full benefits, loan repayment, & possible sign on & relocation packages!* Partnership opportunities available as well! For more info, contact Ariana Sanjabi @ 800-735-8261 x 214, fax your CV to 703-995-0647 or email: asanjabi@medsourceconsultants.com

INDIANA

Join 10 psychiatrists in nice university community less than 90 minutes from downtown Chicago. Contact Jim Ault at St. John Associotes, 1-800-737-2001 or **jault@stjohnjobs.com. www.stjohnjobs.com**

IOWA

The North Central Iowa Mental Health Center is accepting applications for a General Psychiatrist. The Center is located on the grounds of Trinity Regional Medical Center. The doctor will treat patients on the inpatient and partial hospitalization units at Trinity Regional as well as providing out patient services. The Center also has an Assertive Community Treatment team. The Center serves an area of 120,000 people and treats about 3500 patients per year. Compensation is based on salary plus productivity bonus. Will consider applicants with J-1 Visas. Please send cover letter, CV and references to:

Jim Burr, CEO
North Central Iowa Mental Health Center
720 Kenyon Road
Fort Dodge, IA 50501
jimburr4759@hotmail.com

KANSAS

Spanish Speaking (bilingual) Child, Adolescent, and Adult Psychiatrist

Johnson County Mental Health Center (located in a suburb of Kansas City) is seeking a full-time/part-time Child, Adolescent, and Adult Psychiatrist who is fluent in Spanish. Requires a medical degree; (M.D. or D.O.); successful completion of an ACGME accredited Child and Adolescent Psychiatry Residency Program & must be eligible for licensure to practice in KS. Must have board eligibility or certification through ABPN; compensation commensurate with experience. Interested applicants should contact: Dr. Jane Lauchland, Johnson County Mental Health Center, 6000 Lamar, Suite 130, Mission, KS 66202; 913-831-2550; FAX to 913-826-1594; Jane.Lauchland@jocogov.org. EOE M/F/D.

Rainbow Mental Health Facility (RMHF) is seeking a full time board certified/board eligible **Psychiatrist** to join its in-patient staff as an Associate Medical Director. RMHF is a JCAHO accredited 50 bed psychiatric facility which provides short term psychiatric treatment to a population that includes adults, children, and adolescents. RMHF is located in Kansas City, Kansas, a large metropolitan area. Generous benefits package include paid malpractice insurance, paid holidays, vacation and sick leave, medical and dental insurance, retirement plan, opportunities for CME. For more information, contact M. Gustilo, M.D. at 913-755-7083, e-mail to: Merma@srskansas.org or send CV to Osawatomie State Hospital, Attn: Dr. Gustilo, P.O. Box 500, Osawatomie, KS 66064. SRS is an Equal Opportunity Employer committed to a diverse workforce; women, minorities, and persons with disabilities are urged to apply. Paid for by Rainbow Mental Health Facility.

LOUISIANA

Southwest Louisiana area seeks BE/BC psychiatrist for community mental health centers located in Allen and Beauregard Parishes. Generous compensation and benefits package. Please send your CV and supporting documents to the following address:

Lake Charles Mental Health Center
Attn: Laura Lyles
4105 Kirkman Street
Lake Charles, LA 70607
Telephone: (337) 475-8725
Fax: (337) 475-8054
E-mail: lalyles@dhh.la.gov

Baton Rouge, Louisiana
Capital Area Human Services

Only One Position Left for Full Time Psychiatrist in Outpatient Clinic; (1 MD retiring); Currently we have 12 psychiatrists in an Organized Med Staff; clinic serves as a teaching site for LSU Dept Psychiatry; Salary approx: $145K to 170K; paid holidays and vacation; no on-call; sick time; malpractice and benefits. Community has Excellent Quality of Life.

Also separate 1 yr position available for Katrina Mobile Outreach Effort; funded only through Aug 2007 ; applicant must be willing to do all: clinic, mobile, and/or satellite work.
Contact: David Edward Post MD, Medical Director: 225-922-2700 or: DPost@dhh.la.gov ; also visit: www.cahsd.org

---

NEW ORLEANS - General Psychiatrist - Private behavioral health hospital - general & specialty treatment programs. Primary duties in adult services. Compensation includes salary and benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

---

J-1 & F-1 WAIVER AVAILABLE

Crossroads Regional Hospital

Crossroads Regional Hospital, Alexandria, Louisiana seeks two adult and/or adolescent BE/BC psychiatrist with immediate openings. Crossroads Regional Hospital is located in the city of Alexandria in central Louisiana. Interstate 49 passes thru Alexandria.

The hospital is a 70 bed free standing psychiatric hospital, providing adult, children, and adolescent and geriatric inpatient services. The hospital is soon going to open a partial day program and intensive outpatient program.

- J-1 & F-1 waiver candidates are offered attractive salary, with benefits.
- US citizens & permanent residents can choose from several options:

1. **Minimum guaranteed net income** in excess of $150,000/year. The hospital will fund expenses to establish office practice, pay office employees, malpractice insurance, etc. All income after expenses, but at least minimum agreed amount, belongs to the physician.
2. **Full time employment**- attractive salary with benefits and bonus.

Apply with CV by fax to 225-767-8255 or email to psycheservices@bellsouth.net or mail to Attn: Dee Record 5425 Brittany Drive, Ste A, Baton Rouge, LA 70808.

MAINE

Dartmouth Faculty Psychiatrists

Dartmouth Medical School, Department of Psychiatry, in collaboration with the State of Maine Department of Health and Human Services, seeks faculty psychiatrists for the Riverview Psychiatric Center in Augusta, Maine. The Center is the flagship inpatient hospital serving central and southern Maine's system of public mental health care. A 92-bed, state of the art, replacement hospital opened in the Spring of 2004. Preference will be given to candidates with forensic training and/or experience. Maine licensure required. These are full-time Dartmouth faculty appointments with salary and rank commensurate with experience and academic accomplishments. Protected time for scholarly activities. Central and southern Maine offers exceptional opportunities to enhance your quality of life. We have safe communities, with very low crime, good schools and unparalleled four season recreational activities. Augusta is less than one hour from the Maine coast and closer to numerous crystal clear lakes and mountains. It is no wonder Maine is called "vacationland." Please send CV and three letters of reference to: **Alan I. Green, MD, Professor and Chair of Psychiatry, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756**. Dartmouth Medical School is an EOE/AA Employer and encourages applications from women and members of minority groups.

Maine's First Magnet Hospital and the World's First Free-Standing Psychiatric Magnet Hospital Seeking Adult and Child/Adolescent Psychiatrists

We are seeking BC/BE psychiatrists for both our adult and child/adolescent inpatient and outpatient programs. Acadia Hospital is a thriving, non-profit, private community-based hospital offering acute psychiatric care for adults and children, as well as chemical dependency programs. One of the only two private psychiatric hospitals in Maine. The Acadia Hospital offers physicians clinical practice in a highly collaborative, multi-disciplinary setting. Competitive salary and benefit package. Send resume to: Vice President of Medical Affairs, The Acadia Hospital, P.O. Box 422, Bangor ME 04402-0422. **www.acadiahospital.org**

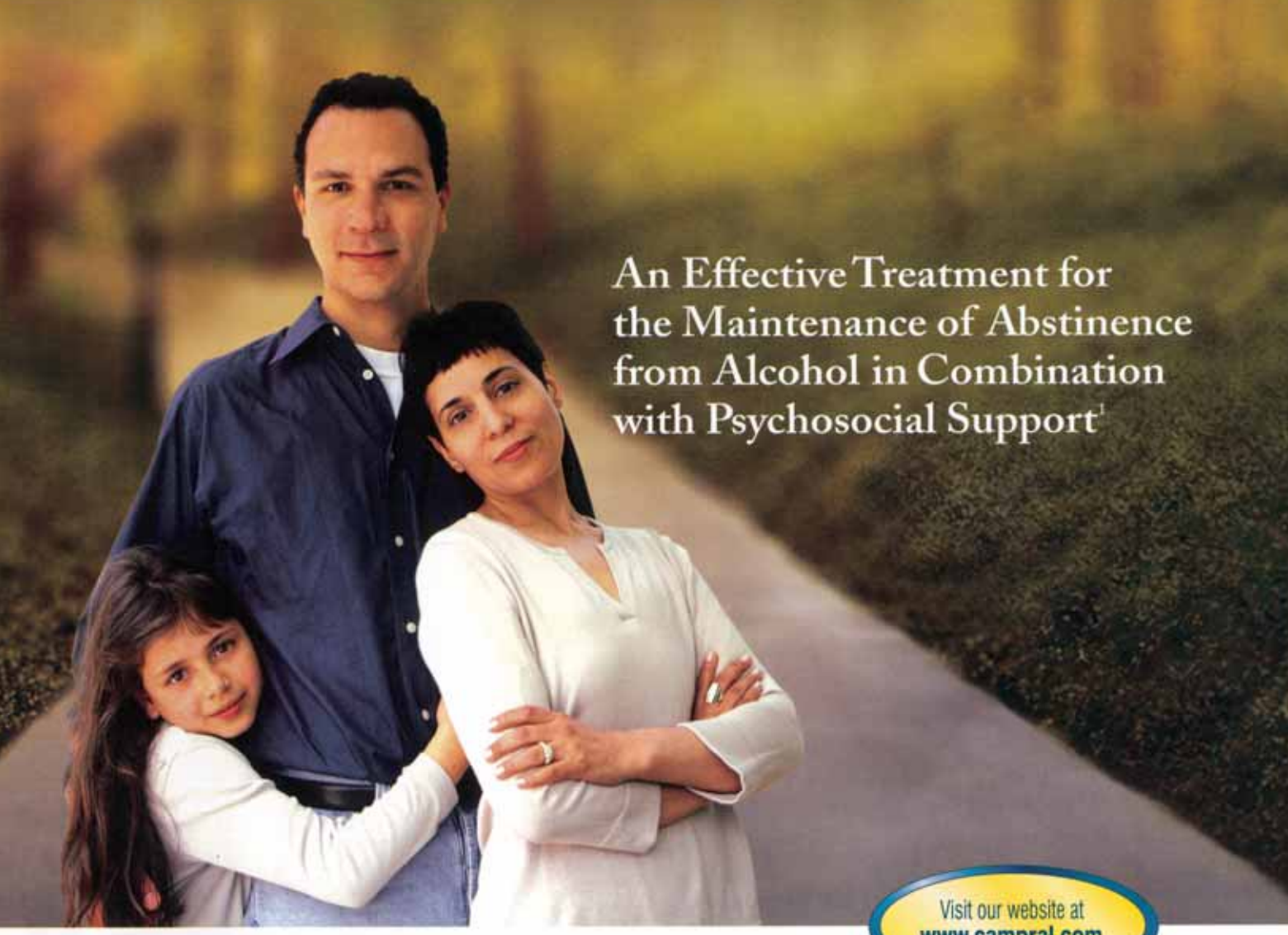
MARYLAND

Psychiatrist

Springfield Hospital Center - a 405 bed psychiatric in patient facility, operated by The Maryland State Mental Hygiene Administration seeks Maryland licensed Psychiatrists. Our rural 400 acre campus is located 22 miles west of Baltimore and convenient to Washington, DC. via routes 70 & 29. We offer full time and part time positions with comprehensive benefits, which include 27 days of paid leave, medical coverage and access to Maryland State Employees Pension at retirement. Additionally, Contractual day/night positions available. Both Board & Non-Board Certified physicians will be considered. Salary for these positions is negotiable. Please send CV to: Jonathan Book, M.D., Clinical Dir, SHC, 6655 Sykesville Rd. Sykesville, Maryland 21784. For questions call 410-970-7006 or email Jbook@dhmh.state.md.us. EOE

PSYCHIATRIST PT for fast-paced growing Geriatric Behavioral Health Practice to provide consultation services in LTC setting in Maryland. Background in medical/neurological basis for psychiatric symptoms desirable. Fax cover letter and resume to CGS, 410-832-5783, Attn.: Dr. Fitting.

Baltimore! Calling all BASEBALL FANS, GO ORIOLES! Be in the center of it all; right outside our nation's capitol! Large teaching hospital has an opportunity for an adult psychiatrist. 40 HOUR WORK WEEK, LIGHT CALL! Salaried position with full benefits & bonus incentives! Very competitive for the area! More info on this opportunity or others nationwide, contact Lindsay McCartney @ 800-735-8261 x 213, fax your CV to 703-995-0647 or e-mail: lmccartney@medsourceconsultants.com



An Effective Treatment for the Maintenance of Abstinence from Alcohol in Combination with Psychosocial Support[1]

Visit our website at **www.campral.com**

- **2 to 3 times more patients maintained abstinence vs placebo in long- and short-term studies, respectively**[2]
- **Works well with a variety of psychosocial therapies**[3-6]
- **Excellent safety and tolerability profile**[1-7]
- **Unique mechanism of action is thought to restore neurotransmitter balance***[1]
- **Used in over 1.5 million patients worldwide**[7]

CAMPRAL® (acamprosate calcium) is contraindicated in patients with severe renal impairment (creatinine clearance ≤30 mL/min). CAMPRAL is contraindicated in patients with known hypersensitivity to acamprosate calcium or any excipients used in the formulation. CAMPRAL does not eliminate or diminish withdrawal symptoms. Alcohol-dependent patients, including those patients being treated with CAMPRAL, should be monitored for the development of symptoms of depression or suicidal thinking. The most common adverse events reported with CAMPRAL vs placebo (≥3% and higher than placebo) were asthenia, diarrhea, flatulence, nausea, and pruritus.

*The mechanism of action of acamprosate in the maintenance of abstinence is not completely understood. Chronic alcohol exposure is hypothesized to alter the normal balance between neuronal excitation and inhibition. *In vitro* and *in vivo* studies in animals have provided evidence to suggest acamprosate may interact with neurotransmitter systems centrally, and has led to the hypothesis that acamprosate restores this balance. The clinical significance in humans is unknown.

References: 1. CAMPRAL® (acamprosate calcium) Delayed-Release Tablets Prescribing Information, Forest Laboratories, Inc., St Louis, Mo, 2005. **2.** Data on file, Forest Laboratories, Inc. **3.** Pelc I, Verbanck P, Le Bon O, Gievilowic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients: a 90-day placebo-controlled dose-finding study. *Br J Psychiatry.* 1997;171:73-77. **4.** Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate: results from a placebo-controlled study on alcohol dependence. *Arch Gen Psychiatry.* 1996;53:673-680. **5.** Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol Alcohol.* 1995;30:239-247. **6.** Pelc I, Ansoms C, Lehert P, et al. The European NEAT Program: an integrated approach using acamprosate and psychosocial support for the prevention of relapse in alcohol-dependent patients with a statistical modeling of therapy success prediction. *Alcohol Clin Exp Res.* 2002;26:1529-1538. **7.** Mason BJ. Acamprosate. *Recent Dev Alcohol.* 2003;16:203-215.

Please see Brief Summary of Prescribing Information on the following page.

Forest Pharmaceuticals, Inc.

 42-126187 1/05

Campral®
(acamprosate calcium)
Delayed-Release Tablets

Strengthens the will to say no

Campral
(acamprosate calcium)
Delayed-Release Tablets

Rx only

Brief Summary:
For complete details, please see full Prescribing Information for CAMPRAL

INDICATIONS AND USAGE
CAMPRAL (acamprosate calcium) is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with CAMPRAL should be part of a comprehensive management program that includes psychosocial support. The efficacy of CAMPRAL in promoting abstinence has not been demonstrated in subjects who have not undergone detoxification and not achieved alcohol abstinence prior to beginning CAMPRAL treatment. The efficacy of CAMPRAL in promoting abstinence from alcohol in polysubstance abusers has not been adequately assessed.

CONTRAINDICATIONS
CAMPRAL is contraindicated in patients who previously have exhibited hypersensitivity to acamprosate calcium or any of its components. CAMPRAL is contraindicated in patients with severe renal impairment (creatinine clearance ≤30 mL/min).

PRECAUTIONS
Use of CAMPRAL does not eliminate or diminish withdrawal symptoms. **General: Renal Impairment** Treatment with CAMPRAL in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) requires a dose reduction. Patients with severe renal impairment (creatinine clearance of ≤30 mL/min) should not be given CAMPRAL (see also CONTRAINDICATIONS). **Suicidality** In controlled clinical trials of CAMPRAL, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in CAMPRAL-treated patients than in patients treated with placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in year-long studies). Completed suicides occurred in 3 of 2272 (0.13%) patients in the pooled acamprosate group from all controlled studies and 2 of 1962 patients (0.10%) in the placebo group. Adverse events coded as "depression" were reported at similar rates in CAMPRAL-treated and placebo-treated patients. Although many of these events occurred in the context of alcohol relapse, no consistent pattern of relationship between the clinical course of recovery from alcoholism and the emergence of suicidality was identified. The interrelationship between alcohol dependence, depression and suicidality is well-recognized and complex. Alcohol-dependent patients, including those patients being treated with CAMPRAL, should be monitored for the development of symptoms of depression or suicidal thinking. Families and caregivers of patients being treated with CAMPRAL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's health care provider. **Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe CAMPRAL. Any psychoactive drug may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that CAMPRAL therapy does not affect their ability to engage in such activities. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding. Patients should be advised to continue CAMPRAL therapy as directed, even in the event of relapse and should be reminded to discuss any renewed drinking with their physician. Patients should be advised that CAMPRAL has been shown to help maintain abstinence only when used as a part of a treatment program that includes counseling and support. **Drug Interactions** The concomitant intake of alcohol and CAMPRAL does not affect the pharmacokinetics of either alcohol or acamprosate. Pharmacokinetic studies indicate that administration of disulfiram or diazepam does not affect the pharmacokinetics of acamprosate. Co-administration of naltrexone with CAMPRAL produced a 25% increase in AUC and a 33% increase in the Cmax of acamprosate. No adjustment of dosage is recommended in such patients. The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexol were unaffected following co-administration with CAMPRAL. Other concomitant therapies: In clinical trials, the safety profile in subjects treated with CAMPRAL concomitantly with anxiolytics, hypnotics and sedatives (including benzodiazepines), or non-opioid analgesics was similar to that of subjects taking placebo with these concomitant medications. Patients taking CAMPRAL concomitantly with antidepressants more commonly reported both weight gain and weight loss, compared with patients taking either medication alone.
Carcinogenicity, Mutagenicity and Impairment of Fertility A carcinogenicity study was conducted in which Sprague-Dawley rats received acamprosate calcium in their diet at doses of 25, 100 or 400 mg/kg/day (0.2, 0.7 or 2.5-fold the maximum recommended human dose based on an AUC comparison). There was no evidence of an increased incidence of tumors in this carcinogenicity study in the rat. An adequate carcinogenicity study in the mouse has not been conducted. Acamprosate calcium was negative in all genetic toxicology studies conducted. Acamprosate calcium demonstrated no evidence of genotoxicity in an *in vitro* bacterial reverse point mutation assay (Ames assay) or an *in vitro* mammalian cell gene mutation test using Chinese Hamster Lung V79 cells. No clastogenicity was observed in an *in vitro* chromosomal aberration assay in human lymphocytes and no chromosomal damage detected in an *in vivo* mouse micronucleus assay. Acamprosate calcium had no effect on fertility after treatment for 70 days prior to mating in male rats and for 14 days prior to mating, throughout mating, gestation and lactation in female rats at doses up to 1000 mg/kg/day (approximately 4 times the maximum recommended human daily oral dose on a mg/m^2 basis). In mice, acamprosate calcium administered orally for 60 days prior to mating and throughout gestation in females at doses up to 2400 mg/kg/day (approximately 5 times the maximum recommended human daily oral dose on a mg/m^2 basis) had no effect on fertility.
Pregnancy Category C Teratogenic Effects Acamprosate calcium has been shown to be teratogenic in rats when given in doses that are approximately equal to the human dose (on a mg/m^2 basis) and in rabbits when given in doses that are approximately 3 times the human dose (on a mg/m^2 basis). Acamprosate calcium produced a dose-related increase in the number of fetuses with malformations in rats at oral doses of 300 mg/kg/day or greater (approximately equal to the maximum recommended human daily oral dose on a mg/m^2 basis). The malformations included hydronephrosis, malformed iris, retinal dysplasia, and retroesophageal subclavian artery. No findings were observed at an oral dose of 50 mg/kg/day (approximately one-fifth the maximum recommended human daily oral dose on a mg/m^2 basis). An increased incidence of hydronephrosis was also noted in Burgundy Tawny rabbits at oral doses of 400 mg/kg/day or greater (approximately 3 times the maximum recommended human daily oral dose on a mg/m^2 basis). No developmental effects were observed in New Zealand white rabbits at oral doses up to 1000 mg/kg/day (approximately 8 times the maximum recommended human daily oral dose on a mg/m^2 basis). The findings in animals should be considered in relation to known adverse developmental effects of ethyl alcohol, which include the characteristics of fetal alcohol syndrome (craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor and intellectual development) and milder forms of neurological and behavioral disorders in humans. There are no adequate and well controlled studies in pregnant women. CAMPRAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects** A study conducted in pregnant mice that were administered acamprosate calcium by the oral route starting on Day 15 of gestation through the end of lactation on postnatal day 28 demonstrated an increased incidence of still-born fetuses at doses of 960 mg/kg/day or greater (approximately 2 times the maximum recommended human daily oral dose on a mg/m^2 basis). No effects were observed at a dose of 320 mg/kg/day (approximately one-half the maximum recommended human daily dose on a mg/m^2 basis).
Labor and Delivery The potential for CAMPRAL to affect the duration of labor and delivery is unknown. **Nursing Mothers** In animal studies, acamprosate was excreted in the milk of lactating rats dosed orally with acamprosate calcium. The concentration of acamprosate in milk compared to blood was 1.3:1. It is not known whether acamprosate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CAMPRAL is administered to a nursing woman. **Pediatric Use** The safety and efficacy of CAMPRAL have not been established in the pediatric population. **Geriatric Use** Forty-one of the 4234 patients in double-blind, placebo-controlled, clinical trials of CAMPRAL were 65 years of age or older, while none were 75 years of age or over. There were too few patients in the ≥65 age group to evaluate any differences in safety or effectiveness for geriatric patients compared to younger patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
The adverse event data described below reflect the safety experience in over 7000 patients exposed to CAMPRAL for up to one year, including over 2000 CAMPRAL-exposed patients who participated in placebo-controlled trials. **Adverse Events Leading to Discontinuation** In placebo-controlled trials of 6 months or less, 8% of CAMPRAL-treated patients discontinued treatment due to an adverse event, as compared to 6% of patients treated with placebo. In studies longer than 6 months, the discontinuation rate due to adverse events was 7% in both the placebo-treated and the CAMPRAL-treated patients. Only diarrhea was associated with the discontinuation of more than 1% of patients (2% of CAMPRAL-treated vs. 0.7% of placebo-treated patients). Other events, including nausea, depression, and anxiety, while accounting for discontinuation in less than 1% of patients, were nevertheless more commonly cited in association with discontinuation in CAMPRAL-treated patients than in placebo-treated patients. **Common Adverse Events Reported in Controlled Trials** Common, non-serious adverse events were collected spontaneously in some controlled studies and using a checklist in other studies. The overall profile of adverse events was similar using either method. Table 1 shows those events that occurred in any CAMPRAL treatment group at a rate of 3% or greater and greater than the placebo group in controlled clinical trials with spontaneously reported adverse events. The reported frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed, without regard to the causal relationship of the events to the drug.

Table 1. Events Occurring at a Rate of at Least 3% and Greater than Placebo in any CAMPRAL Treatment Group in Controlled Clinical Trials with Spontaneously Reported Adverse Events

Body System/ Preferred Term	CAMPRAL 1332 mg/day	CAMPRAL 1998 mg/day[1]	CAMPRAL Pooled[2]	Placebo
Number of Patients in Treatment Group	**397**	**1539**	**2019**	**1706**
Number (%) of Patients with an AE	**248(62%)**	**910(59%)**	**1231(61%)**	**955(56%)**
Body as a Whole	**121(30%)**	**513(33%)**	**685(34%)**	**517(30%)**
Accidental Injury*	17 (4%)	44 (3%)	70 (3%)	52 (3%)
Asthenia	29 (7%)	79 (5%)	114(6%)	93 (5%)
Pain	6 (2%)	56 (4%)	65 (3%)	55 (3%)
Digestive System	**85 (21%)**	**440(29%)**	**574(28%)**	**344(20%)**
Anorexia	20 (5%)	35 (2%)	57 (3%)	44 (3%)
Diarrhea	39 (10%)	257(17%)	329(16%)	166(10%)
Flatulence	4 (1%)	55 (4%)	63 (3%)	28 (2%)
Nausea	11 (3%)	69 (4%)	87 (4%)	58 (3%)
Nervous System	**150(38%)**	**417(27%)**	**598(30%)**	**500(29%)**
Anxiety**	32 (8%)	80 (5%)	118(6%)	98 (6%)
Depression	33 (8%)	63 (4%)	102(5%)	87 (5%)
Dizziness	15 (4%)	49 (3%)	67 (3%)	44 (3%)
Dry mouth	13 (3%)	23 (1%)	36 (2%)	28 (2%)
Insomnia	34 (9%)	94 (6%)	137(7%)	121(7%)
Paresthesia	11 (3%)	29 (2%)	40 (2%)	34 (2%)
Skin and Appendages	**26 (7%)**	**150(10%)**	**187(9%)**	**169(10%)**
Pruritus	12 (3%)	68 (4%)	82 (4%)	58 (3%)
Sweating	11 (3%)	27 (2%)	40 (2%)	39 (2%)

*includes events coded as "fracture" by sponsor; **includes events coded as "nervousness" by sponsor
[1] includes 258 patients treated with acamprosate calcium 2000 mg/day, using a different dosage strength and regimen. [2] includes all patients in the first two columns as well as 83 patients treated with acamprosate calcium 3000 mg/day, using a different dosage strength and regimen.

Other Events Observed During the Premarketing Evaluation of CAMPRAL
Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with CAMPRAL in 20 clinical trials (4461 patients treated with CAMPRAL, 3526 of whom received the maximum recommended dose of 1998 mg/day for up to one year in duration). This listing does not include those events already listed above, events for which a drug cause was considered remote, event terms which were so general as to be uninformative, and events reported only once which were not likely to be acutely life-threatening. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the summary of adverse events in controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Body as a Whole** – *Frequent:* headache, abdominal pain, back pain, infection, flu syndrome, chest pain, chills, suicide attempt; *Infrequent:* fever, intentional overdose, malaise, allergic reaction, abscess, neck pain, hernia, intentional injury; *Rare:* ascites, face edema, photosensitivity reaction, abdomen enlarged, sudden death. **Cardiovascular System** – *Frequent:* palpitation, syncope; *Infrequent:* hypotension, tachycardia, hemorrhage, angina pectoris, migraine, varicose vein, myocardial infarct, phlebitis, postural hypotension; *Rare:* heart failure, mesenteric arterial occlusion, cardiomyopathy, deep thrombophlebitis, shock. **Digestive System** – *Frequent:* vomiting, dyspepsia, constipation, increased appetite; *Infrequent:* liver function tests abnormal, gastroenteritis, gastritis, dysphagia, eructation, gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage, liver cirrhosis, esophagitis, hematemesis, nausea and vomiting, hepatitis; *Rare:* melena, stomach ulcer, cholecystitis, colitis, duodenal ulcer, mouth ulceration, carcinoma of liver. **Endocrine System** – *Rare:* goiter, hypothyroidism. **Hemic and Lymphatic System** – *Infrequent:* anemia, ecchymosis, eosinophilia, lymphocytosis, thrombocytopenia; *Rare:* leukopenia, lymphadenopathy, monocytosis. **Metabolic and Nutritional Disorders** – *Frequent:* peripheral edema, weight gain; *Infrequent:* weight loss, hyperglycemia, SGOT increased, SGPT increased, gout, thirst, hyperuricemia, diabetes mellitus, avitaminosis; bilirubinemia; *Rare:* alkaline phosphatase increased, creatinine increased, hyponatremia, lactic dehydrogenase increased. **Musculoskeletal System** – *Frequent:* myalgia, arthralgia; *Infrequent:* leg cramps; *Rare:* rheumatoid arthritis, myopathy. **Nervous System** – *Frequent:* somnolence, libido decreased, amnesia, thinking abnormal, tremor, vasodilatation, hypertension; *Infrequent:* convulsion, confusion, libido increased, vertigo, withdrawal syndrome, apathy, suicidal ideation, neuralgia, hostility, agitation, neurosis, abnormal dreams, hallucinations, hypesthesia; *Rare:* alcohol craving, psychosis, hyperkinesia, twitching, depersonalization, increased salivation, paranoid reaction, torticollis, encephalopathy, manic reaction. **Respiratory System** – *Frequent:* rhinitis, cough increased, dyspnea, pharyngitis, bronchitis; *Infrequent:* asthma, epistaxis, pneumonia; *Rare:* laryngismus, pulmonary embolus. **Skin and Appendages** – *Frequent:* rash; *Infrequent:* acne, eczema, alopecia, maculopapular rash, dry skin, urticaria, exfoliative dermatitis, vesiculobullous rash; *Rare:* psoriasis. **Special Senses** – *Frequent:* abnormal vision, taste perversion; *Infrequent:* tinnitus, amblyopia, deafness; *Rare:* ophthalmitis, diplopia, photophobia. **Urogenital System** – *Frequent:* impotence; *Infrequent:* metrorrhagia, urinary frequency, urinary tract infection, sexual function abnormal, urinary incontinence, vaginitis; *Rare:* kidney calculus, abnormal ejaculation, hematuria, menorrhagia, nocturia, polyuria, urinary urgency. **Serious Adverse Events Observed During the Non-US Postmarketing Evaluation of CAMPRAL (acamprosate calcium)** Although no causal relationship to CAMPRAL has been found, the serious adverse event of acute kidney failure has been reported to be temporally associated with CAMPRAL treatment in at least 3 patients and is not described elsewhere in the labeling.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class Acamprosate calcium is not a controlled substance. **Physical and Psychological Dependence** CAMPRAL did not produce any evidence of withdrawal symptoms in patients in clinical trials at therapeutic doses. Post marketing data, collected retrospectively outside the U.S., have provided no evidence of CAMPRAL abuse or dependence.

OVERDOSAGE
In all reported cases of acute overdosage with CAMPRAL (total reported doses of up to 56 grams of acamprosate calcium), the only symptom that could be reasonably associated with CAMPRAL was diarrhea. Hypercalcemia has not been reported in cases of acute overdose. A risk of hypercalcemia should be considered in chronic overdosage only. Treatment of overdose should be symptomatic and supportive.

Manufactured by: Merck Santé s.a.s.
Subsidiary of Merck KGaA, Darmstadt, Germany
37, rue Saint-Romain
69008 LYON FRANCE

Manufactured for FOREST PHARMACEUTICALS, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045
07/04

Forest Pharmaceuticals, Inc.

Faculty Position
Assistant Professor (Tenure Track)
Department of Psychiatry

The Department of Psychiatry at the Uniformed Services University of the Health Sciences, Bethesda, MD is seeking to fill an Assistant Professor, tenure-track, teaching and research position with particular emphasis on biological psychiatry. The Department is comprised of twenty full-time faculty and has active research interests in the neurobiology and behavior of stress, PTSD, anxiety, depression, and substance abuse. The successful candidate will be responsible for developing a funded research program and will participate in medical student and resident education and clinical care. Individuals who hold an M.D., have completed an approved psychiatric residency and are board eligible/certified are invited to apply. Send curriculum vitae, description of current and anticipated research interests and the names and addresses of four references to: Robert J. Ursano, M.D., Chairman, Department of Psychiatry, Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20814 (rursano@usuhs.mil). Review of applications is ongoing. The University is an affirmative action/equal opportunity employer.

Inpatient psychiatry position on the bucolic Eastern Shore of Maryland. Close proximity to DC, Baltimore, and the Atlantic Coast beaches. Full-time and part-time options are available. Work on a general psychiatry inpatient unit with a team approach to patient care. For more information contact Allan Anderson, MD at 410-228-5511 ext. 2107, or e-mail at: aandersonshorehealth.org.

MASSACHUSETTS

FACULTY POSITION FOR SENIOR CLINICAL SCIENTIST: Harvard University's Department of Psychology and the Judge Baker Children's Center, affiliated with Harvard Medical School, seek a senior scientist for a joint appointment as Professor of Psychology in the Department of Psychology in the Faculty of Arts and Sciences and Director of Research at Judge Baker Children's Center. The ideal candidate will have a distinguished record of research on treatment of child or adolescent dysfunction in the disruptive, externalizing domain - preferably with an emphasis on research in clinical practice and/or school settings. Duties will include teaching and mentoring in the Department of Psychology, and directing and expanding the child and adolescent clinical research program at Judge Baker. We seek an individual who will maintain an active individual program of research while creating and leading multi-investigator collaborations in such forms as research centers, program projects, and networks. Send letter of interest, *curriculum* vitae, and representative reprints to: Chair, Search Committee, Harvard University, Department of Psychology, William James Hall 230, 33 Kirkland Street, Cambridge, MA 02138. Materials may also be sent electronically to hartford@wjh.harvard.edu. *Harvard University and Judge Baker Children's Center are Affirmative Action/Equal Opportunity Employers. Women and minority candidates are encouraged to apply.*

TRANSPLANT PSYCHIATRIST
Boston - Brigham and Women's Hospital Department of Psychiatry is seeking part to full-time consultation psychiatrist to join academic Medical Psychiatry Service to work with hospital's multidisciplinary cardiac, renal and lung transplant teams. Role includes teaching and supervision of psychiatry fellows and residents and Harvard Medical School appointment. Psychosomatic Medicine/C-L Psychiatry training or board eligibility preferred, prior transplant psychiatry experience a plus. Rank and salary commensurate with experience. Interested applicants should email letter of interest and CV to David Gitlin, MD, Director of Medical Psychiatry, dgitlin@partners.org. AA/EOE.

BOSTON
Lowell & Westwood: Child & General Psychiatrist for inpatient & partial programs. **Pembroke - Geriatric & Addiction Psychiatrists** for specialty inpatient units. **Brookline: General Psychiatrist** - adult inpatient & partial services. No call required. Salary, benefits & bonus plan offered. Part-time & fulltime positions available as well as DOC shifts. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

---

CAMBRIDGE: Child & Adolescent Psychiatry

Position available at Cambridge Health Alliance, Division of Child and Adolescent Psychiatry, Harvard Medical School. The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School with excellent residencies in adult and child psychiatry. Academic appointment up to the rank of Associate Professor, as determined by the criteria of Harvard Medical School, is anticipated. We seek candidates with demonstrated excellence in academic teaching of complex clinical assessment, child and adolescent psychopharmacology, family assessment and treatment, particular interest and experience in working with ethnic and minority populations and the underserved, and enthusiasm for the public health mission of CHA.

Outpatient Child & Adolescent Consult Liaison Psychiatrist - Part time: Exciting opportunity to develop new service providing direct clinical and consultation services at community primary care clinics. The right candidate will have excellent skills in working with clinicians of multiple disciplines and will thrive in an ambulatory medicine setting. Integrated mental health services within a primary care setting that are collaborative and patient centered will be the emphasis of the service. Position includes supervision of child psychiatry fellows, general psychiatry residents, medical students, and other trainees.

Qualifications: BC, demonstrated knowledge of clinical and research child and adolescent psychiatry, commitment to public sector populations, excellent clinical and teaching skills, leadership and management skills, team oriented, problem solver. Bilingual and/or bicultural abilities are desirable. Competitive compensation with excellent benefit package. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply.

CV & letter to: **Deborah Weidner, MD, Dept. of Psychiatry, The Cambridge Hospital, 1493 Cambridge Street, Cambridge, MA 02139. Fax 617-665-1973. DWeidner@challiance.org (email preferred)**

Psychology (Lifespan/Gerontology) Faculty - Tenure Track

The Department of Psychology at Salem State College is seeking to fill a tenure track position for the Fall of 2007. Responsibilities include a 12 hour teaching load including undergraduate and graduate courses in areas that may include general psychology, developmental psychology, and gerontology, and guiding student research. The position is advertised pending funding. Required qualifications include a Ph.D. or Psy.D. in Psychology or a closely related discipline from an accredited institution, with research interests in Gerontology. Also required are a strong commitment to teaching and research, and competency in the areas to be taught. Preferred qualifications include a Ph.D. in Lifespan Psychology. We also prefer candidates with experience in and commitment to teaching in a multiracial, multiethnic environment with students of diverse backgrounds and learning styles, as well as in distance learning and instructional technologies, and candidates who enjoy serving as role models and mentors for a diverse student body. The salary is competitive and commensurate with education and experience. Application review will begin in the fall of 2006 and continue until an adequate pool is developed.

To apply, send a letter of application, a brief statement of teaching and research interests, resume, appropriate transcripts and three letters of reference addressing teaching strengths and research potential, and selected reprints to:

Office of Human Resources & Equal Opportunity
352 Lafayette Street
Salem, MA 01970
Fax: 978-542-6163
Email: eo-hr@salemstate.edu
(Word Attachments Only)
Reference Code: 07-AA-F-PSY-LSGER

SALEM STATE COLLEGE IS AN EQUAL OPPORTUNITY / AFFIRMATIVE ACTION EMPLOYER. PERSONS OF COLOR, WOMEN AND PERSONS WITH DISABILITIES ARE STRONGLY URGED TO APPLY.

Caritas Carney Hospital
Director of Psychiatry

Caritas Carney Hospital, a Boston community teaching hospital, seeks a Director of Psychiatry for our Inpatient and Outpatient Adult/Adolescent Services. Board Certification in Child/Adolescent and Adult Psychiatry preferred. Prior experience with diverse populations including substance abusers, developmentally disabled, chronically mentally ill, geriatric clients, ECT and the medically ill is essential. Responsibilities include quality assurance, credentialing, utilization review, contracting, direct clinical service, supervision and training, administration and medical staff participation. We offer a competitive salary and excellent benefits package.

Please forward resume and cover letter to: Caritas Carney Hospital, Attn: Luis F. Lobon, MD, Chair, Search Committee, 2100 Dorchester Avenue, Dorchester, MA 02124. Fax: 617-474-3891, Direct: 617-506-4445, Email: luis.lobon @caritaschristi.org. For more information, visit our website: www.caritascarney.org.

WWW.caritas.carney.org

Psychiatrist - Southbridge/Sturbridge area. Part time adult psychiatrist needed for G.B. Wells Center, a large, friendly community mental health center and part of Harrington Memorial Hospital. Excellent working conditions, very flexible. For more information, write/call: Zamir Nestelbaum, M.D., @ G.B. Wells Center, 29 Pine St., Southbridge, MA, 01550. 508-765-9167. An AA/EOE/ADA Employer.

Inpatient Attending Psychiatrist

Position available at Cambridge Health Alliance Dept. of Psychiatry, Harvard Medical School. Inpatient attending at Whidden Memorial Hospital campus. 44 beds, multidisciplinary team approach with psychiatrist leadership, multicultural population, excellent quality services, public health oriented. Opportunities to participate in evidence based medicine implementation, QM, teaching, research.

The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School with excellent residencies in adult and child psychiatry. We are committed to improving the health of our communities and seek candidates with particular interest and experience in caring for patients with severe and persistent mental illness, as well as those with interest in health services delivery and research.

Qualifications: BE/BC, strong clinical skills, strong leadership and management skills, team oriented, problem solver. Competitive compensation, excellent benefit package. Academic appointment at a rank determined by criteria of Harvard Medical School. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply. **CV & letter to Derri Shtasel, MD, Dept. of Psychiatry, 1493 Cambridge Street, Cambridge, MA 02139. Fax 617-665-2521. Email: DShtasel@ challiance.org (email preferred).**

North Shore Medical Center
Psychiatry and Mental Health Department

NSMC is a member of Partners HealthCare, which was founded by Massachusetts General Hospital and Brigham and Women's Hospital. For more information, visit www.nsmc.partners.org

NSMC is an equal opportunity employer.

Child Psychiatrist
Position available at Salem Campus for BE/BC Psychiatrist 20-40 hours per week. Responsibilities include Child Inpatient Psychiatry and/or Child Outpatient Mental Health. Excellent, collegial work environment, opportunities for participation in clinical research and academic appointment. Salary and benefit packages are highly competitive.

Please send cover letter and CV to: Mark Schechter, MD, Chairman, Department of Psychiatry, 81 Highland Avenue, Salem, MA 01970, Email (preferred): mschechter@partners.org, or telephone: (978) 354-4010, FAX: (978) 825-6101.

Lynn BayRidge Hospital, a non-profit psychiatric facility on Boston's North Shore, a teaching site for Boston University Medical School, has a position for an inpatient and/or partial hospitalization program psychiatrist, or for the appropriate candidate, as unit Medical Director. Experience with dually diagnosed patients is a plus. The Medical Director position includes substantial direct service; candidates for Medical Director must be board-certified, and have demonstrated skill in leadership. No required night call, but participation in a lucrative call system is optional. Full benefit package includes generous time off as well as reimbursement for malpractice insurance and CME expenses. Contact Barry Ginsberg, M.D., Medical Director, 60 Granite Street, Lynn MA 01904. Phone (781) 477-6964, Fax (781) 477-6967, email bginsber @nhs-healthlink.org.

Part/Full Time Psychiatrist - Eliot Community Human Services/Tri-City Mental Health Center, one of the area's largest providers of community mental health services minutes north of Boston, is looking for PT/FT psychiatrists to provide Outpatient services with flexible hours. No evening or weekend calls. Multiple positions are available immediately to BC/BE Psychiatrists with special interests in Child Psych and Gen. Adult Psych., positions also working with Geriatric, Subst. Abuse and Chronic Mentally Ill Services. We work in a supportive multi-disciplinary structure with an excellent team of Clinicians and support staff. Visit our website at **tcmhc.org**. Contact Medical Director Roger Greiger, MD at rgreiger@tcmhc.org. or Fax 617-387-1089.

Director, Victims of Violence Program
Department of Psychiatry
Cambridge Health Alliance

The Department seeks a clinical psychologist, psychiatrist, or other doctoral level mental health clinician with outstanding academic skills and expertise in traumatic stress to serve as director of the Victims of Violence Program (VOV). The director will maintain the philosophical and programmatic integrity of the VOV program and provide leadership, direction, and administrative oversight to the program in a manner consistent with the public health mission of the Cambridge Health Alliance. VOV services, activities, and components include hospital and community based clinical services to trauma survivors, individual and community crisis response, victim advocacy, clinical training and supervision, research, grant acquisition and management, and VOV staff development. The director will have knowledge of an ecological view of psychological trauma, commitment to multi-culturally informed clinical and community intervention, dedication to multidisciplinary staffing and staff development, and a capacity to guide ongoing program development.

The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School with excellent training programs including Harvard medical students, adult and child psychiatry residencies, APA internship, and post-doctoral fellowships. Academic appointment up to the rank of Associate Professor, as determined by the criteria of Harvard Medical School, is anticipated. The Department values scholarship, teamwork, commitment to patients and trainees, and mutual respect across clinical specialties and interests.

Demonstrated skill in teaching, clinical practice, and research activity is essential in candidates, as well as extensive mental health program development and administrative experience, scholarly contributions to the field of traumatic stress studies, and extensive grants acquisition and management experience.

Qualifications: Doctorate or board certified psychiatrist with appropriate specializations and state license. Bilingual and bicultural abilities are desirable. We offer competitive compensation and excellent benefit package. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply. **Send CV and letter to Derri Shtasel, MD, MPH; Chief, Adult Division of Psychiatry; 1493 Cambridge Street, Cambridge, MA 02139. Fax: 617-665-2521. Email: DShtasel @challiance.org (email preferred).**

UMass Memorial Medical Center, Department of Psychiatry seeks a Medical Director for the Geriatric Psychiatry Inpatient Unit/Clinton Hospital-oversees clinical care on a 20-bed unit that serves as an important referral site for the region. Supervision of Psychiatry and Family Practice residents occurs on-site. Opportunities for collaboration and teaching at Worcester Campus. Competitive compensation with complete benefit package. Faculty rank commensurate with experience. Inquiries of general interest about our many programs encouraged and applicants with specific interest in this position should send letter and CV to Alan P. Brown, MD, Vice Chairman of Clinical Services, Department of Psychiatry, UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655 or e-mail BrownA01@ummhc.org. AA/EOE

The Department of Psychiatry at the University of Massachusetts Medical School/ UMass Memorial Medical Center is seeking a BC/BE Psychiatrist for its University Hospital Outpatient Clinic. Candidates should have an interest in available academic opportunities in either training or research. Academic rank commensurate with experience. Interested applicants send CV to Alan P. Brown, M.D., Vice Chairman for Clinical Services, Department of Psychiatry, UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655 or email BrownA01@ummhc.org AA/EOE

ON call psychiatrist - Southbridge, MA. Harrington memorial Hospital has on call opportunities. Salaried position, 1 in 7 rotation, weekend rounds, very flexible. Excellent working conditions. For more information, write/call: Zamir Nestelbaum, M.D., @ G.B. Wells Center, 29 Pine St., Southbridge, MA, 01550. 508-765-9167. An AA/EOE/ADA Employer.

The Department of Psychiatry at Mount Auburn Hospital, affiliated with Harvard Medical School, is recruiting for a full time psychiatry position in our outpatient service. Responsibilities include evaluation and treatment of outpatients presenting with a wide range of psychiatric disorders, treatment planning and coordination of care with an interdisciplinary clinical staff, and consultation to primary care and specialty physicians. Teaching responsibilities include medical student teaching and teaching in our internal medicine residency program. Academic appointment, salary package. Please send inquiries and CV to: Joseph D'Afflitti, M.D., Chair, Department of Psychiatry, 330 Mount Auburn Street, Cambridge, MA 02138; tel: 617 499-5008; email; jdafflit@mah.harvard.edu.

MISSOURI

STATE CAPITOL! Great location; great opportunity! Local community hospital has an outstanding opportunity for a general psychiatrist to do **100% outpatient** work with the opportunity to do provide C&L services. Salary starting at $175,000 with an exceptional benefits plan! For more info, call Sarah McGlinnen @ 800-735-8261 x 216, fax your CV to 703-995-0647 or e-mail: smcglinnen@medsourceconsultants.com

Ozark Center
Freeman Health System
Behavioral Health Division

Adult and Child/Adolescent Psychiatrists

- Join the Behavioral Health Division for FHS which is the largest & fastest growing health system in the area.
- Eight psychiatrists working together as a group in a shared call situation
- At FHS enjoy the security and growth potential of a fully integrated delivery system with the completion of a large expansion of facilities opening in 2007.
- Join freedom and autonomy of working within a physician-driven system with 170+ employed physicians covering all specialties providing an excellent local and regional referral base for your services

EXCELLENT SALARY AND BENEFITS
JOPLIN, MISSOURI -Service Area of 450,000 + Lakes, fishing, hunting; excellent public & private schools; mild climate-four seasons; one of the lowest costs of living in the nation. Call Nancy at 800-353-6812, Fax CV to 417-347-9320.

We want to hear from you!!
njpaul@freemanhealth.com/
www.freemanhealth.com

Inpatient Psychiatry; Academic Department

UMKC Department of Psychiatry and Western Missouri Mental Health Center on the medical school campus in Kansas City seek a FT psychiatrist to provide patient care, teaching and training on an adult acute inpatient unit that is an active training site for the residency program and medical student clerkship. Typical caseload is 10 to 12. State-of-the-art facility opened in January, 2004. Thirteen psychiatrists on staff. Competitive salary and excellent benefits. Relocation costs and student loan repayment is negotiable. Send CV to Stuart Munro, MD, Chair, Department of Psychiatry, 1000 E. 24th St., K.C., MO 64108 or stuart.munro@dmh.mo.gov or call 816-512-7417.

MONTANA

PSYCHIATRIST-Seeking full-time board certified psychiatrist to fill staff position in VA Montana Healthcare System. Certifications or experience in addiction psychiatry and or pain management a plus. Responsibilities include adult outpatient treatment with urgent care/walk-in service and inpatient consultation service in a facility where state-of-the-art medicine is practiced. Fort Harrison Hospital is located in Helena, the State Capital. In beautiful western Montana, Helena has downhill and cross-country skiing, awesome fly-fishing, camping, hunting, and numerous other outdoor activities nearby. The availability of cultural activities, including concerts, annual jazz and bluegrass festivals as well as those events associated with Carroll College, a high quality educational system, is a notable asset of the community. This is also a rapidly growing community with excellent school system. It is a wonderful place to raise children. Competitive salary, benefits and liability included. Fax curriculum vitae to 406-447-7978 or call Human Resources at 406-447-7933.

NEVADA

STAFF PSYCHIATRIST

Vacancies exist for several Staff Psychiatrists at the VA Southern Nevada Healthcare System (VASNHS), Las Vegas, Nevada. Positions include Staff Psychiatrist for In-Patient and Outpatient areas, PTSD and Addiction Psychiatrist. Incumbents must be Board Certified/Eligible, Fully Licensed and have a U.S. Citizenship or proof of legal authority to work in the U.S.

VASNHS is academically affiliated with the University of Nevada, School of Medicine and involved with the premier Air Force/VA Joint Venture, with several community clinics. Compensation will be commensurate with the qualifications and experience of the applicants, including excellent benefits and no state income tax. Selectee will need to meet credentialing and privileging requirements and will be subject to random drug screening.

Las Vegas is one of the fastest growing communities in the U.S., offering a wide variety of entertainment and sports activities; i.e. golfing, camping, hiking, skiing.

Clinical inquiries may be made to Mr. Pat Duncan, LCSW, Chief, Mental Health Care Line, at 702-636-3050. Send CV and names and addresses of three references to Human Resource Management Service, VA Southern Nevada Healthcare System, P. O. Box 360001, North Las Vegas, NV 89036 or call 702-636-3033. VA IS EOE.

The University of Nevada School of Medicine, Department of Psychiatry is seeking candidates for an Assistant or Associate Professor. Duties include educational and administrative leadership of the Reno-based GME program in general psychiatry, service as medical director of a psychiatric hospital including limited practice of inpatient psychiatry with residents, and participation in the departmental teaching program. For complete position description and online application, visit http://jobs.unr.edu/professional/. Interested applicants should apply online by October 8, 2006. EEO/AA Women and under-represented groups are encouraged to apply.

NEW JERSEY

Wish to purchase fee for service practices in the Overlook, Morristown, St. Barnabas service areas. Contact Alpha Behavioral Care at (908) 273-0800.

PSYCHIATRIST - FT/PT. EVALS & MED MONITORING. NJ license. BC/BE with adults and children. No call or weekends. Team player. Resumes to: Brenda Y. Camacho, MD, NewPoint BHC, 404 Tatum Street, Woodbury, NJ 08096/Fax 856.845.0688 or email center@newpointbhc.org.

SOUTH JERSEY: General Psychiatrist. Full-time position -general psych & dual diagnoses inpatient treatment for adults. Salary & benefits offered. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

If you are a child or adult board certified psychiatrist looking to grow in a private practice that is not dependent on managed care, call us at 908.273.0800 and fax CV to 908.273.0815. We have a growing private practice in Summit, NJ, an affluent suburban community.

NEW MEXICO

Presbyterian Medical Services is a non-profit integrated healthcare network with JCHO accreditation providing medical, dental, behavioral health, children's services and supportive living services to the multi-cultural people of New Mexico. We are seeking a **Psychiatrist** who will see clients of all ages to work in our Farmington clinic. Excellent benefits. Sign-on bonus offered. For more information contact Diane Kramer at (800) 477-7633; fax (505) 954-4414; diane_kramer@pmsnet.org; P.O. Box 2267, Santa Fe, NM 87504. EOE.

NEW YORK CITY & AREA

Psychiatrists Only
locum tenens and permanent placement

PHYSICIAN OWNED AND MANAGED
www.psyonly.com
Over 400 Locum Tenens and Permanent Placement Opportunities
Don Ceniza
800-583-2256

Columbia University
College of Physicians and Surgeons
Department of Psychiatry

F/T Columbia University faculty positions available on Acute Inpatient Psychiatry Unit at Allen Pavilion for Assistant Professor of Psychiatry or Instructor in Clinical Psychiatry. Position involves medical student/resident teaching inpatient unit. Board certification in psychiatry preferred . NYS License required and ability to speak Spanish. Equal Opportunity, Affirmative Action Employer.

Please forward resumes to:
New York Presbyterian Hospital
180 Fort Washington Avenue
New York, NY 10032
Attention: Diane Looney
Fax # (212) 305-4724

PSYCHIATRIST

Mary Manning Walsh Home, a 362-bed subacute and long-term care facility in Manhattan, is accepting applications for a part-time academically-trained board certified Psychiatrist, well- versed in the care of geriatric patients and in multidisciplinary therapy, including behavioral and psycho-pharmacologic approaches.

Mary Manning Walsh Home is a member of the Catholic Health Care System & has been managed for over 50 years by the Carmelite Sisters for the Aged and Infirm. The appropriate candidate will appreciate the humanistic commitment of this faith based institution.

Please send letters of inquiry and Curriculum Vitae to: Ms. Katherine Gleaton, Medical Staff Assistant, Mary Manning Walsh Home,1339 York Avenue, NY, NY 10021. EOE

Outpatient Positions - FT & PT w/ Benefits

Nationally known mental health agency serving the **NYC** area has various positions for Adult and Child/Adolescent Psychiatrists throughout the five boroughs. Current openings include the **Bronx** and **Southern Brooklyn**. Contact us to explore your future: Richard Gersh, MD at the Jewish Board of Family and Children's Services. e-mail: rgersh@jbfcs.org or fax: 212-307-7896. JBFCS is an equal opportunity employer.

New York City!
Enjoy the many amenities of the "BIG APPLE"! Well established hospital has 4 opportunities available. 1) C&A - 100% OUTPATIENT 2) Adult - 100% OUTPATIENT but must be bilingual in Spanish 3) Adult - hospitalist 4) Unit Chief of Detox. All positions come with **NO CALL**. Very competitive salary and full benefits offered! For more info, call Carrley Ward @ 800-735-8261 x 219, fax your CV to 703-995-0647 or e-mail: cward@medsourceconsultants.com.

Director of Substance Abuse Services

St. Vincent's Hospital Westchester seeks a Board Certified psychiatrist to direct its substance abuse treatment programs and provide psychiatric management of dually diagnosed patients. Faculty appointment in New York Medical College. Send c.v. to: Richard D. Milone, M.D., St. Vincent's Hospital Westchester, 275 North Street, Harrison, NY 10528 or fax to 914-925-5158.

PSYCHIATRIST

Lincoln Medical and Mental Health Center (LMMHC) of Generations+ Network, and an affiliate of Weill- Cornell Medical College, is seeking Full/Part-time BC/BE Psychiatrists for positions in the Adult Outpatient Unit, Inpatient unit and Psych ER. Responsible for teaching, supervising residents and direct patient care. Spanish speaking pref. Excellent salary commensurate with experience.
Send CV to Melissa Schori, MD: Fax: 718-579-6060 or Email: HR@DBMAPC.ORG. AA/EOE M/F.

Psychiatrists

Full Time/Part Time/Inpatient Positions for NYS licensed, board eligible/board certified psychiatrists are available at Manhattan Psychiatric Center, an OMH facility specializing in the treatment of the refractory patient with innovative pharmacological and manualized cognitive behavioral interventions. The psychiatrist leads a multidisciplinary team, with opportunities to utilize clinical, administrative, and teaching skills on specialty units. MPC is a residency training affiliate of NYU with rotations in the STAIR program, research and outpatient clinic as well as opportunities for teaching medical students. We are conveniently located near the Triboro Bridge.

Please fax resume to:
Manhattan Psychiatric Center
Ward's Island Complex
Ward's Island, NY 10035
Samuel J. Langer, M.D., Chief of Psychiatry
646 672 6386
MPC is an equal opportunity employer
A Bridge to Recovery

PSYCHIATRISTS

LUTHERAN HEALTHCARE is currently seeking full-time NYS-licensed ambulatory care psychiatrists for positions in the Sunset Terrace Mental Health and Substance Abuse Treatment Center, in the Sunset Park area of Brooklyn.

Openings include a **FT Adult Psychiatrist** with interest/expertise in HIV and addiction treatment, and a **FT Child/Adolescent Psychiatrist.** Both positions offer opportunity for interface with primary care and family support settings. Bilingual Spanish, Chinese, or Arabic strongly desirable. Psychiatrists will offer treatment in facilities that have a Federal Mental Health HPSA (Health Profession Shortage Area) designation for loan repayment purposes. Minimal call responsibility.

Conveniently located for travel from all NYC Boro's. For consideration please email: bgoff@lmcmc.com, fax (718) 630-8594 or send CV to: Bradford M. Goff, M.D., Department of Psychiatry, Lutheran Medical Center, Suite 2-45, 150 55th Street, Brooklyn, NY, 11220. EOE/AA M/F/D/V

LUTHERAN HEALTHCARE

Consulting Psychiatrist

BC/BE - Psychiatrist to provide consultation services in long term care setting. (NH, SNF) PT/FT. Above average salary, flexible hours. Recent graduates encouraged to apply.

Psychologists

FT/PT - NY State licensed, to provide IQ testing for MRDD population, excellent compensation.

Please contact: Carlos Rueda, M.D. at Tel: 718-920-9093 or via fax - 718-920-9217, e-mail - crueda@olmhs.org

---

CHAIR POSITION: NEW YORK CITY BOROUGH!!! Head psych department for prestigious multi-specialty group. Department Mgmt & Admin; Clinical Oversight; Co-ord & Oversight Res. program. 180K-200K! Must be BC, 10 yrs exp. Susan Springer 800.575.2880 ext. 315 sspringer@medsourceconsultants.com

NEW YORK STATE

Child and Adolescent Psychiatrist
Ellis Hospital
Schenectady, NY 12308

Ellis Hospital, ranked in the top 5% of hospitals in the nation and a respected leader in mental health in the capital region of New York State, has an opening for a full time NYS licensed, BC/BE Child and Adolescent Psychiatrist. The position offers a highly competitive salary and benefits package, opportunities for continuing education and a stimulating, physician friendly work environment. The position offers combined inpatient and outpatient practice opportunities and minimal call requirements.

Ellis hospital is located in Schenectady, NY, in the Mohawk Valley at the foothills of the Adirondack Mountains. The area is well-known for its beautiful lakes, including scenic Lake George, numerous parks, ski resorts, golf courses, and the famous Saratoga Raceway, all within an hours drive. Major cities are within a three hour drive including New York and Boston.

For further information on this excellent opportunity, contact Anthony Yacona, M.D., Chairman, Department of Psychiatry, Ellis Hospital, 1101 Nott St., Schenectady, NY, 12308. Phone (518) 243-4154, e-mail yaconaa@ellishospital.org.

GREATER BINGHAMTON HEALTH CENTER
ADULT PSYCHIATRIST
And
CHILD/ADOLESCENT PSYCHIATRISTS

GBHC, (JCAHO-Accredited New York State Office of Mental Health facility) is seeking full time, board certified/board eligible **ADULT PSYCHIATRISTS** for its 140 bed adult inpatient facility and **CHILD/ADOLESCENT PSYCHIATRISTS** for its Child/Adolescent unit. Abundant on-site CME. Salaried, permanent positions with excellent New York State benefits.

Submit CV to: Personnel Office, Greater Binghamton Health Center, 425 Robinson St., Binghamton, NY 13904. Fax: (607) 773-4117. EOE/AAE.

Inpatient/ Outpatient Psychiatrists
Ellis Hospital
Schenectady, NY 12308

The Ellis Hospital Department of Psychiatry, a respected leader in mental health in the Capital Region of New York State, has openings for full-time NYS licensed, BC/BE inpatient and outpatient psychiatrists. The hospital offers a generous salary and benefit package, opportunities for continuing education, and a stimulating work environment.

Ellis Hospital is located in Schenectady, NY, in the Mohawk Valley at the foothills of the Adirondack Mountains. The area is well-known for its beautiful lakes, including scenic Lake George, numerous parks, ski resorts, golf courses, and the famous Saratoga Raceway, all within an hour's drive. Major cities within a three-hour drive include New York and Boston.

For further information, contact Anthony Yacona, M.D., Chairman, Department of Psychiatry, Ellis Hospital, 1101 Nott St., Schenectady, NY 12308 at (518)-243-4154 or e-mail yaconaa @ellishospital.org.

Practice In the Perfect Place!

Consider this opportunity to practice a combination of inpatient and outpatient psychiatry in beautiful Saratoga Springs, NY. Saratoga Hospital seeks a BE/BC psychiatrist to provide care as part of a close-knit multi-disciplinary care team on a 16-bed adult inpatient unit. This position is full time when combined with an outpatient position at the Saratoga County Mental Health Center. Call is 1:8, shared with the unit Director and County Mental Health physicians. Interest in ECT is required to provide backup to Director. Compensation is competitive.

Located a half hour from Albany, and less than three hours from NYC, Montreal and Boston, Saratoga Springs offers lovely neighborhoods and a downtown with fine restaurants and specialty shops. The city is known for world-class entertainment including thoroughbred racing and the Saratoga Performing Arts Center. Nearby mountains, lakes and rivers beckon outdoor enthusiasts for year-round recreation. Contact: Denise Romand, Medical Staff Recruiter, Saratoga Hospital, 211 Church St., Saratoga Springs, NY 12866. Phone: 518-583-8465; Fax: 518-580-2605; docfind@saratogacare.org

---

Looking for a Psychiatrist with New York State License and completed psychiatric residency to join a busy practice in Forest Hills with good return and flexible schedule. PT or FT. Please call (718) 268-1100.

Well established practice for sale in Nassau County-North Shore, New York. About thirty hours per week currently, with good referral base for expansion. Very reasonable terms and flexible on offers. Fax inquiries to: 516-997-8402 or call 516-997-4610.

NORTH CAROLINA

Psychiatrist (Assistant or Associate Professor)
Department of Psychiatric Medicine
The Brody School of Medicine at
East Carolina University

The Department of Psychiatric Medicine at the Brody School of Medicine at ECU is now accepting applications for a full-time faculty position (Assistant or Associate Professor). The position offers an excellent blend of clinical care, teaching, and scholarly activities in this growing, multi-disciplinary, and collegial Department. Requirements include MD or equivalent degree, completion of accredited psychiatric residency training in psychiatry, and preferably board certification in Psychiatry. Salary and academic rank commensurate with experience and academic background. Tenure-track is available. Applications accepted until position is filled. Greenville is the hub of Eastern NC and the home of East Carolina University, the 3rd largest public university in the state. Located near many recreational areas, including the Atlantic Ocean coastal resorts, Greenville is university town, rich in cultural activities with charm and an easy pace of life. **The position is open until filled. Please send letters of interest and a CV to: Dr. Diana J. Antonacci, Chair Search Committee, Department of Psychiatric Medicine, the Brody School of Medicine, Room 4E-98A Brody Building, 600 Moye Blvd., Greenville, NC 27834, telephone 252-744-2660, e-mail: antonaccid@ecu.edu. The East Carolina University is an AA/EO Employer.**

NORTH DAKOTA

MeritCare Health System of Fargo, ND is seeking an Adult Psychiatrist to join its 32-member multi-disciplinary Psychiatry Department. Faculty appointment and teaching of psychiatry residents is available through University of North Dakota School of Medicine. MeritCare is an integrated 384-physician multi-specialty group practice, 583-bed Level II tertiary/trauma hospital with 26 primary care clinic sites in two states. Sister cities, Fargo, ND and Moorhead, MN are a tri-college community of 200,000 located near the heart of Minnesota's lake country. Fargo-Moorhead offers excellent educational systems, recreation and sporting activities as well as a variety of entertainment and cultural events. This is an excellent opportunity with a competitive compensation and benefits package being offered. Drug-free workplace. AA/EOE. This is not a designated HPSA site.

To apply send CV to:

Jill Gilleshammer, Physician Recruiter
MeritCare Health System
P O Box MC
Fargo, North Dakota 58122
Phone: (800) 437-4010, ext. 280-4851
Email: Jill.Gilleshammer@meritcare.com

PRAIRIE ST. JOHN'S

We have an exciting opportunity for a talented and dynamic **Child and Adolescent Psychiatrist** to join a growing, well-respected, mission-focused organization that Offers Hope and Healing to Those Suffering From Psychiatric Conditions and Addictions.

Prairie St. John's, a Catholic Psychiatric and Addictions Health Care Organization, based in Fargo, ND is seeking a Child & Adolescent Psychiatrist to join our group of 10 Psychiatrists (including eight C&A trained). Prairie provides mental health, chemical dependency and dual diagnosis treatment programs in a continuum of care that includes inpatient, partial hospital, residential, intensive outpatient and clinic services to children, adolescents, and adults. Starting salary up to $210,000 dependent on site of practice and qualifications, plus productivity compensation. Excellent benefits. Fargo is a great place to live, raise a family, work and do business. Prairie is a great place to practice Psychiatry. View us on-line at www.prairie-stjohns.com.

Send CV and letter of interest to: Karen Frigen, Development Specialist, Prairie St. John's, 510 4th St. S., Fargo, ND 58103 or via e-mail to kfrigen@prairie-stjohns.com.

OHIO

FACULTY POSITION: The MetroHealth System, an affiliated teaching hospital of Case Medical School, is seeking a board certified (or board eligible) psychiatrist at the Instructor level. The psychiatrist will provide psychopharmacological services in an urgent care setting. Other duties involve resident and medical student teaching. Benefits include competitive salary, incentive plan, liability and health insurance, and an academic appointment. Please send letters of interest, CV, and two references to RT Segraves, M.D., Department of Psychiatry, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, Ohio 44109. Inquiries can be sent to rsegraves@metrohealth.org. In employment, as in education, MetroHealth System and Case Western Reserve University are committed to Equal Opportunity and World Class Diversity.

---

15 Minutes to Downtown Cleveland! Reputable Mental Health Provider seeks Adult and Child Adolescent Psychiatrist to join 7 others. Position is outpatient based, with a call schedule of 1-8. Salary and full benefits. Call Ken Pruchnicki @ 800-575-2880 x 319 kpruchnicki@medsourceconsultants.com

OKLAHOMA

Community MH Center currently seeks an adult psychiatrist commutable to Tulsa, OK region! Flexible duties for mix IP/OP work involving PACT team effort; J1 visas & loan repayment. Great benes, salary to $150k+, light travel. Call Dave Featherston @ 800-575-2880 x314 dfeatherston@medsourceconsultants.com

OREGON

Oregon State Hospital

Oregon State Hospital is currently recruiting for Psychiatrists with interest and/or experience in adult and forensic programs. A strong benefits package complements salary. Opportunities for additional on-call work can increase your income substantially.

Oregon State Hospital provides specialized mental health services, including general adult, geriatric, and forensic treatment programs with campuses in Salem and Portland. Oregon State Hospital currently employs approximately 1,200 staff, including 30 Psychiatrists.

Located in the beautiful Willamette Valley, the area offers a great diversity of recreational activities. Within an hour's drive one finds the Cascades, the Coastal Range, and the Pacific Ocean. Oregon is justifiably famous for its world-class fishing, hunting, skiing, golfing, windsurfing, white water rafting, camping, and mountaineering opportunities.

Contact:
Becky Hawkins, Office of Human Resources
Oregon State Hospital
2600 Center Street NE
Salem, OR 97301-2682

Phone: (503) 945-2822
Fax: (503) 945-9910
E-Mail: Becky.Hawkins@state.or.us

PENNSYLVANIA

PENNSYLVANIA - The Psychiatry Department at 800-bed Lehigh Valley Hospital has a position available for a 7th BC/BE consultation/liaison psychiatrist. We are looking for someone with fellowship training or a strong interest in C/L work to join our salaried group which currently has a total of 14 psychiatrists. Our new partner will share responsibilities for the consults we do on med/surg, ob/gyn, oncology, cardiology, trauma and burn unit. In addition to our C/L work, our practice offers a mix of outpatient psychiatry, opportunities for clinical research as well as teaching medical students and residents in several disciplines. Faculty appointment at Penn State/Hershey. Generous compensation package includes paid medical malpractice insurance, paid health insurance for self and family, life insurance of two times salary, four weeks vacation, one CME week with a $3,000 stipend and more. Location is 60 miles north of Philadelphia and 90 miles west of NYC. Email CV to Ralph A. Primelo, Chief, Section of C/L Psychiatry, c/o Pamela.Adams@lvh.com. Fax 610-969-0214. Phone (610) 969-0208.

STATE COLLEGE area: Child and/or General Psychiatrist. Inpatient & outpatient.
CLARION: General or Child Psychiatrist - inpatient & partial programs. Admin/clinical position.
SHIPPENSBURG: General or Geriatric Psychiatrist for admin/clinical position. All positions offer salary, bonus potential, & benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

---

UNIQUE CAREER OPPORTUNITY
FOR ADULT PSYCHIATRIST

This is a superb opportunity for a BC/BE psychiatrist interested in a combination of emergency psychiatry and inpatient care. Establish a close working relationship with our psychiatric emergency service and our inpatient behavioral science unit. You will work with a large salaried hospital-based group who practice at LVH, an 800-bed academic community hospital where opportunities exist to teach medical students and residents and pursue career advancement. The successful candidate will also be eligible for faculty appointment at Penn State/Hershey. We are offering an excellent call schedule and a favorable lifestyle so that you can enjoy the beautiful Lehigh Valley where more than 700,000 people appreciate safe neighborhoods, good schools and easy access to major metropolitan areas. Philadelphia is 1 hour south and NYC is 1.5 hours east. For more information, call 610-969-0213. Email CV to Pamela.Adams@LVH.com or fax to (610) 969-0214.

Pennhurst Medical Group, P.C. Various Pennsylvania locations BC/BE, Excellent Salary, Benefits, No Billing, Full Time, Part Time and Locums Positions. Send CV to bp@pennhurstmedical.com or by fax 610-524-0952. Call Bob Plunkett at 610-524-2400 x 160 with any questions or for more information

---

PITTSBURGH - Mercy Behavioral Health, part of the Pittsburgh Mercy Health System, is seeking an adult psychiatrist to start in December or January. We offer competitive compensation and an excellent benefits package, all with a schedule that will fit your needs. The position is flexible, which may include combinations of outpatient, inpatient, residential and other possibilities. Please contact Jim Jacobson, M.D., Medical Director, Mercy Behavioral Health, 330 S. 9th St., Pittsburgh, PA 15203.
Phone 412-488-4927, Fax: 412-488-4929, e-mail: JJacobson@mercybh.org

Child/Adolescent Psychiatry
The best of both worlds - flexible scheduling and high-end care!

Geisinger Health System's Division of Psychiatry in Danville, PA, is seeking a child/adolescent psychiatrist. This position offers an excellent quality of life and an opportunity to work part-time or full-time depending on the needs of the candidate.

This position offers:
- A flexible schedule - start/end times are negotiable.
- A collaborative team of psychiatrists/psychologists with experience and expertise in a variety of psychiatric specialties.
- The support of multiple PAs, a nurse specialist and masters-level therapists.
- An excellent call schedule (1 in 7).
- The opportunity to work in a comprehensive academic practice that sees a wide variety of clinical activity from pediatric to geriatric patients and diagnostic types (including ECT).
- Research opportunities through the Weis Center for Research and the Center for Health Research and Rural Advocacy (both located on the campus of Geisinger Medical Center). Current research projects include studies on genomic schizophrenia, adolescent depression and improving the delivery of adult depression through primary care.
- An accredited Clinical Psychiatry Internship and the opportunity to teach pediatric and emergency medicine residents.
- An established referral base through Geisinger Health System's 40 community medical groups, 3 hospitals, local/community physicians and broad-base of third party contracts.

Pediatric specialty services include:
- A comprehensive program dedicated to treating kids with bedwetting problems
- Disruptive behavior
- Asperger's Group
- Adolescent treatment
- In-school services
- Community psychiatry
- Neuro-psych services

Last year, more than 100 physicians joined Geisinger Health System. And it's no wonder. While many healthcare organizations are struggling, Geisinger and the Division of Psychiatry is experiencing unprecedented growth. In the past two years they have added a 10-bed Adolescent Inpatient Unit at Geisinger South Wilkes-Barre, the neuro-psychiatry practice has doubled and added 2 post-doctoral fellows and Pediatric Psychiatry has experienced significant growth. At Geisinger, you'll experience the support, camaraderie and professional challenges of a leading practice while discovering the charms of Pennsylvania living...all while having the time and flexibility to enjoy your new quality of life.

To discuss this opportunity, contact:
Kathy Kardisco, Recruiter
Geisinger Department of Professional Staffing,
100 North Academy Avenue, Danville, PA 17822-2428
Phone: 1-800-845-7112 o
Fax: 1-800-622-2515
e-mail: kkardisco@geisinger.edu

RHODE ISLAND

PSYCHIATRIST

The Providence Center, a JCAHO facility, is recruiting a Psychiatrist to join a medical staff of 11 other full-time Psychiatrists in a well respected community mental health center. The Center provides a wide spectrum of outpatient and residential services, and is a training site for residents and medical students from Brown University. Center Psychiatrists also provide inpatient care for its patients at Butler Hospital. Job responsibilities are varied. Board certification or eligibility is required. Experience working in a multidisciplinary setting is preferred as is Spanish speaking capacity. The Center can be a J1 site.
Contact:

Michael A. Silver, M.D.
The Providence Center
530 North Main Street
Providence, RI 02904
Phone: 401-276-6359
Fax: 401-276-4034
Email: msilver@provctr.org

Outstanding opportunity for enthusiastic psychiatrist interested in a clinical faculty position in the admitting service of Butler Hospital, a private psychiatric facility located on the beautiful East Side of Providence, RI. Butler is a major psychiatric teaching facility for Brown Medical School. Strong interest/experience in educating medical students and residents required. Salary commensurate with experience. Please reply with CV and letter of interest to Steven_Rasmussen@Brown.edu.

Rhode Island Hospital

Psychiatrist, Adult Outpatient and Mood Disorders

The Department of Psychiatry, Rhode Island Hospital, a Lifespan partner and Brown University affiliated program, is seeking a psychiatrist with interests in adult outpatient responsibilities within an established fulltime hospital-based group. The outpatient component involves assessment and treatment of patients as a member of a specialized multidisciplinary team. Interest and expertise in mood disorders is desirable. We offer an opportunity for both teaching as well as clinical research involvement to complement clinical practice. The candidate must be Board Certified or eligible, and may be eligible for a clinical appointment at Brown University School of Medicine. Salary and benefits commensurate with level of training. Please send CV's along with a letter of interest to Richard J. Goldberg, M.D., Psychiatrist-in-Chief, APC-9, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903 and/or e-mail to rjgoldberg@lifespan.org.

SOUTH CAROLINA

AIKEN - minutes from Augusta GA - General or Geriatric Psychiatrist - inpatient & partial programs. **BENNETTSVILLE - East Carolina**. Medical Director for 8 bed adult-geriatric unit. Some call, ER consults & staff supervision. Salary, benefits and bonus plan offered. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

TENNESSEE

EAST TENNESSEE STATE UNIVERSITY
JAMES H. QUILLEN COLLEGE OF MEDICINE
DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES

DIRECTOR OF RESIDENCY TRAINING

Full-time position available for Director of Psychiatry Residency Training. Position may include inpatient and/or outpatient. Responsibilities include training of psychiatric residents and medical students and research activities. Salary is competitive with funding available through the Medical School, faculty private practice, and extramural contracts. ETSU is located in the Tri-Cities Tennessee/Virginia region, which was the first region in the nation to be designated as an "All-American City" with attractive cost-of-living, crime rate, climate, and health care. Applicants should submit a CV and two letters of references to Merry N. Miller, M.D., Chair, Department of Psychiatry and Behavioral Sciences, ETSU, Box 70567, Johnson City TN 37614. Telephone inquiries should be made at (423) 439-2235 or e-mail at lovedayc@etsu.edu. AA/EOE.

TEXAS

Texas Forest Country - The Burke Center, a multi-site, JCAHO accredited community mental health center, has an immediate opening for either a **general psychiatrist or child psychiatrist** willing to treat some adults. The position is outpatient only, primarily located in Livingston, although there may be some work in other locations or by telemedicine. Enjoy an excellent lifestyle with a 40-hour work week, no call, competitive salary, and fantastic benefits. Physician Assistants and Advanced Nurse Practitioners will be considered as well. Recreational opportunities abound in national forests nearby. Houston is less than 2 hours away; Dallas 3 hours; major state university nearby. Please send CV to Mark Janes, M.D., Medical Director, Burke Center, 4101 S. Medford Drive, Lufkin, TX 75901. Fax: (936)634-8601. Email: markj@burke-center.org. Check out the details on our website: *www.burke-center.org*.

Psychiatrists needed in Houston, Texas. Full-time employee, very competitive salary and benefits package. Seeking two (2) psychiatrists: Position 1 is for provision of physician services to psychiatric patients in an inpatient setting. Position 2 is for provision of physician services to psychiatric patients primarily in an outpatient setting, with some inpatient and possible psychiatric research services. Must have current Texas Medical License. Current Medicare number preferred. **Please email resume and references to: dgafford@dapaprograms.com**

AMARILLO: Private Practice opportunity. Inpatient & outpatient. Community need - great income potential. **SAN ANGELO**: General /Geriatric and Child Psychiatrist to join an established private practice - will offer employment, benefits & program directorship. **MCALLEN**: Child Psychiatrist - inpatient/outpatient private practice. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

Assistant Professor

The Department of Psychiatry and Behavioral Sciences at the University of Texas Medical Branch in Galveston is seeking an Assistant Professor.

Responsibilities include inpatient care, outpatient clinics, resident supervision and teaching. Research opportunities are available. Successful candidates must be board certified/board eligible in Psychiatry.

Candidates with interest and skills in this area should send a curriculum vitae and cover letter to: **Robert M.A. Hirschfeld, M.D., The University of Texas Medical Branch, Department of Psychiatry and Behavioral Sciences, 301 University Boulevard, Galveston, TX 77555-0188**.

The University of Texas Medical Branch is an equal opportunity, affirmative action institution which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

Denton, Texas

Mayhill Hospital located in **Denton, Texas** is currently seeking a Psychiatrist to serve as Assistant Medical Director for its 30-bed inpatient program as well as to provide comprehensive outpatient services. For additional information, please contact Rhonda Ashley-Dixon at 1-800-786-6211, ext. 313. CVs may be faxed to (615)-230-3149 or emailed to rad@seniorhealthinc.com.

UTAH

LICENSED PSYCHIATRIST- Bear River Mental Health Services, Inc., serving northern Utah. Duties: medical assessments; medication management; coordination of medical care with PCP's; hospital rotation; psychiatric emergency consultation. Team model of service delivery. Must maintain hospital privileges. Computer literacy. Specialty in child/adolescent psychiatry preferred but not required. Salary negotiable. Competitive benefits. Potential for student loan repayment program. EOE. Send resume and cover letter to: **HR Dept., Bear River Mental Health Services, Inc., 90 E. 200 N., Logan, UT, 84321; Email: sharons@brmh.com**

VERMONT

Central Vermont

Washington County Mental Health Services, a CMHC located in Montpelier, is seeking a full time psychiatrist to join its high quality, dedicated psychiatric staff. Opportunities exist for outpatient work with geriatic and adult patients suffering from a wide range of mental illnesses, developmental disorders, and mental retardation. Particularly needed is a psychiatrist for a newly developing, innovative, recovery oriented and trauma informed, highly staffed, ten bed, residential program providing a level of services not previously available outside of a hospital setting in Vermont. Competitive salary and benefits; EOE. Applicant must be BE/BC. Please send cover letter and CV to: Stuart Graves, MD, 9 Heaton Street, Montpelier, VT, 05602, or e-mail to Stuartg@wcmhs.org.

PSYCHIATRISTS - Northeast Kingdom Human Services, Inc. a CMHS located in St. Johnsbury, is seeking two Full-Time Psychiatrists. Opportunities exist for outpatient work with adult patients suffering from a wide range of serious mental illnesses, and for consultation to primary care practices at the primary care office. This position is perfect for someone who enjoys outdoor activities in a rural environment. You will find mountains and lakes as well as the urban lifestyle less than an hour away. NKHS provides community-based, consumer-sensitive mental health, substance abuse and developmental services for residents of Caledonia, Essex & Orleans counties of Vermont. Our agency offers an outstanding benefits package. Please apply with cover letter and resume to bbrenk@nkhs.net or Bianca Brenk, NKHS, POB 724, Newport, VT 05855. For further information please visit our web site at www.jobsinvt.com or www.nkhs.net.

VIRGINIA

Academic Chair & Medical Director of Psychiatry
Roanoke, VA

Carilion Health System has an opening for Academic Chair and Medical Director of Psychiatry. As the Associate Director of the Psychiatry Residency Program based on the campus of Carilion Roanoke Memorial Hospital, this individual is responsible for excellence in graduate psychiatric medical education and will work collaboratively with the Director of Carilion's Psychiatry Residency Program (based at Salem-VAMC) and Carilion's Director of Medical Education.

The Chair develops and manages the research program, faculty development needs, and strategic growth of medical education within the department. The physician will have a leadership role in creating strategic plans for the growth of regional clinical services in all aspects of psychiatry. The Medical Director actively supports and promotes patient safety, continuous performance and quality improvement, risk management, and efficient resource utilization linked highly to evidence-based medicine. The physician will also demonstrate responsiveness to the concerns and needs of faculty and organized medical staff and fosters a close relationship between and among physicians, management and clinical staff.

MINIMUM QUALIFICATIONS:
- MD/DO
- ABMS/AOA-BC in Psychiatry
- 5 years clinical experience

In addition to the above, 3 years progressive administrative/leadership experience is required, along with an established track record of excellence in clinical care, medical education and research. Management training and degree desirable, as well as expertise in process improvement and data analysis and the use of information systems to develop and support outcome meaurement and management. To apply, submit cover letter, CV and references to Rhonda Creger, Physician Recruiter, Carilion Health System, POB 40032, Roanoke, VA 24022-0032, or email rhondac@carilion.com , or call 540-224-5189. Minorities and women are encouraged to apply.

CHILD PSYCHIATRIST-Virginia Commonwealth University/Medical College of Virginia Hospitals, Division of Child & Adolescent Psychiatry in the Department of Psychiatry, recruiting Virginia licensed BE/BC child psychiatrist faculty as attending for Day Treatment Unit. Position located in professional shortage area; J-1 candidates welcome to apply. Will be responsible for administration and clinical care as well as teaching and supervision of medical students, residents and child fellows. In addition, consultation work with community agencies will be available. Interest in teaching and academic work, as well as ability to work on interdisciplinary team, required. Department has nine fulltime child psychiatrists and child research institute, over 80 fulltime faculty and well-funded research in genetics, addictions, child and women's mental health and psychopharmacology. VCU is a large urban university with robust health science campus and 750-bed university hospital. Richmond, the State Capital, has moderate climate and rich mix of history with modern facilities, excellent suburban housing, public/private schools. Internet provides comparative cost of living. Send CV to Bela Sood, MD, c/o Mary Swartz, VCU, Box 980710, Richmond VA 23298. Virginia Commonwealth University is an Equal Opportunity/Affirmative Action employer. Women, minorities, and persons with disabilities are encouraged to apply.

VA COMMONWEALTH UNIV: Dept. of Psychiatry recruiting two BE/BC psychiatrist faculty positions: 1) Director of Mood Disorders Program - 50% Inpatient and 50% outpatient responsibilities to include teaching rounds on 10-bed team, supervision of teaching clinic and faculty practice or city mental health clinic services. Fellowship in mood disorders or post-residency experience preferred. 2) Director of Crisis Intervention Services. Duties include attending on psychiatric triage team, 23-hour Obs unit and short-term inpatient team, and training/supervision of residents and medical students. Experience in emergency psychiatry & crisis interventions preferred. Opportunities for collaborative and independent research available for both positions. VCU is a large urban university with robust health science campus and 750-bed university hospital. Department of Psychiatry employs over 80-full time faculty and is nationally ranked in federally funded research. Richmond, the State Capital, has moderate climate and rich mix of history with modern facilities. Excellent suburban housing and quality public/private schools. Send CV to Mary Swartz, Human Resources, Department of Psychiatry, VCU/MCV, Box 980710, Richmond, VA 23298. VCU is an EEO/AA employer. Women, minorities, persons with disabilities encouraged to apply.

Christiansburg, VA - General Adult Psychiatrist needed in Virginia's New River Valley region for state-of-the-art inpatient facility with office suite contiguous to the inpatient unit. Position provides for a combination of inpatient/outpatient psychiatry, including administering ECT; on-call an average of 6-7 days/month, including 1-2 weekend days. Virginia's New River Valley region comprises the localities of Blacksburg, home of Virginia Tech, and Radford, home of Radford University, plus the town of Christiansburg and surrounding communities, a population of 175k. Carilion Health System is a nonprofit regional healthcare system comprised of several acute-care hospitals including teaching/tertiary referral center nearby, medical education programs, and 70+ multispecialty clinics. Base salary with bonus incentive plan based on quality outcome and scorecard measures. Requirements: Minimum of 3 years experience post-residency, and/or other professional experience prior to completing residency; ABMS-BC ideal, or BE acceptable with plan in place to receive certification in 2 years; excellent interpersonal and communication skills. Positions available immediately. To apply, submit CV with references and cover letter to:

Rhonda B. Creger, Physician Recruiter
Carilion Health System
POB 40032
Roanoke, VA 24022-0032
Office 540-224-5189
FAX 540-985-5329
Email: rhondac@carilion.com
Website: www.carilion.com

Faculty, Addictions Psychiatry,
Virgina Commonwealth University
The Department of Psychiatry invites applicants for tenured or tenure-eligible faculty positions as faculty and/or Chair of the Division of Addiction Psychiatry. The successful applicants will be expected to have an MD, PhD or equivalent doctoral-level training with appropriate research and leadership experience. Rank is open, depending on the qualifications and experience of the selected applicant. The ideal candidate should have substantial research experience in basic, treatment and/or services research focused on problems of substance abuse. Candidates are not required to be qualified as treatment providers, although such candidates would be preferred as applicants. Funded ACGME accredited Fellowship Program. Strong department with over 90 fulltime faculty. Opportunities exist for faculty to interact with the multi-disciplinary group of over 45 faculty in the Institute for Drug and Alcohol Studies, who conduct research in such areas as neuroscience, pharmacology, medications development, prevention, treatment, women's health and psychiatric genetics. For very strong candidates, there may be opportunities to identify significant other resources, including additional faculty and/or post-doctoral positions. Virginia Commonwealth University is an Equal Opportunity/Affirmative Action employer. Women, persons with disabilities, and minorities are encouraged to apply. Send applications to Joel J. Silverman, M.D., Chairman, Department of Psychiatry, MCV/VCU Box 980710, Richmond, VA 23298 (jsilverm@vcu.edu).

WASHINGTON

PSYCHIATRIST, SEATTLE SUBERB

Seeking a full-time BC/BE psychiatrist to join our multidisciplinary group practice.

Ours is a collegial and professionally stimulating practice environment. Established practice base and referral source. Set our own hours, 1-6 call. We offer a one-year salary guarantee with benefits. This area is consistently rated as one of the best places to live and work. Just minutes from downtown Seattle and the shores of Puget Sound. For more information please email CV to gmumma@Highlinemedical.org or Fax to 206-242-4625.

Emergency Psychiatry Clinical Faculty Position
University of Washington, Seattle, WA

Harborview Medical Center, Department of Psychiatry and Behavioral Sciences is seeking a psychiatrist in the Psychiatric Emergency Services (PES). The coverage is shared among several psychiatrists who work under the supervision of the PES Medical Director. The position will receive a UW clinical faculty appointment. The PES attending psychiatrists provide direct evaluation, triage and acute treatment to patients, and overall supervision of the clinical team, including residents. Pay scale is highly competitive due to shift work and off-hours schedule. University of Washington faculty engage in teaching, research and service. HMC has a nationally recognized psychiatric emergency service and strives to deliver state of the art care in an academic medical setting. Please forward your letter and CV to: Peter Roy-Byrne, MD, Box 359911 Psychiatry HMC 325 9th Avenue, Seattle 98104. The UW is building a culturally diverse faculty and strongly encourages applications from females and minority candidates. The UW is and EOE/AA employer.

A Career In Psychiatry
In The Beautiful Wine Country
Of Washington State's
Walla Walla Valley

Department of Corrections
Lead Psychiatrist
Full time Staff Position
Or, Personal Contract.
All employee benefits.
96 Bed Residential Unit.
16 Bed Acute Care.
Immediate Availability.

Call or email Michael Wall
509 526 6436
mbwall@DOC1.WA.GOV

Pacific Northwest - Inpatient and Outpatient Psychiatrists

Highline West Seattle Mental Health/West Seattle Psychiatric Hospital is a large community mental health agency located in the Emerald city of Seattle. We have FT positions available in our psychiatric hospital and PT in our outpatient mental health center. Seattle offers a full, contemporary urban experience, with excellent schools and culture, surrounded by incredible mountains and outdoor recreation. Our salary is competitive; benefits include all the standard insurances, CME, approx. 1 month leave, etc. Please contact Jeff Skolnick, MD-Chief Medical Officer 206-933-7127 or JeffS@Highline.Org

WEST VIRGINIA

PSYCHIATRISTS - William R. Sharpe, Jr. Hospital, a 150-bed, JCAHO-accredited, state psychiatric hospital and winner of APA Award for state/university collaboration, is searching for BE/BC psychiatrists. The facility is unique in the region for the range of psychiatric services offered and quality of care provided. The hospital is one of the largest training sites for various clinical disciplines including psychiatric residents, medical students as well as psychology, social work and nursing trainees. These are full time faculty positions with regionally competitive salaries and excellent benefits. There is no call duty. The area has an abundance of outdoor activities, four-season climate, and one of the lowest crime rates in the country. There are several metropolitan areas within easy driving distance. West Virginia University is an affirmative action/equal opportunity employer. Women and minority candidates are encouraged to apply. Positions will be open until filled. J1 applicants are encouraged to apply. Contact Abe Adel, MD, Clinical Director, William R. Sharpe, Jr. Hospital, WVU Department of Behavioral Medicine & Psychiatry 936 William Sharpe Road, Weston, WV 26452. 304-269-1210. bettygumfoster@wvdhhr.org

WISCONSIN

Exciting opportunity for BE-BC psychiatrist to join collegial team of dedicated professionals at a premier public facility with 100-year history of community service. 32-40 hour work week, 1:6 weekend call, no billing or managed care worries. Competitive salary with benefit package valued at an additional 35%. Ideal for physician striving for balance between career and outside interests in a family-friendly small city with nationally recognized public school system, very affordable housing and an abundance of cultural activities. You'll have plenty of free time to fish our beautiful lakes and rivers, hike, mountain bike, kayak, downhill and cross-country ski. Mail or FAX your current CV and letter of interest to: Gabriel Ticho, M.D. Clinical Director North Central Health Care Facility 1100 Lakeview Dr. Wausau, WI 54403 FAX:715-842-3630; Phone:715-848-4455; Email: gticho@norcen.org

---

SPECTACULAR OPPORTUNITY
FOR INPATIENT MEDICAL DIRECTOR

Gundersen Lutheran, a multidisciplinary 400 member group practice in La Crosse, WI, is seeking an experienced BC/BE Psychiatrist to perform the functions of the Medical Director of an existing Inpatient Unit and to develop a day hospital program.

This candidate will join 9 general and 4 child psychiatrists, 7 psychologists and more than 40 therapists in providing outpatient/inpatient care for a broad range of clinical disorders.

Psychiatric outpatient care is offered on our main campus and at several sites in the Gundersen Lutheran healthcare system. Inpatient care is provided in a 27-bed unit, which is adjacent to the medical center. Call will be 1:12.

Located in a city of 52,000 with a metropolitan area of 120,000 and a service delivery area of more than 500,000, Gundersen Lutheran provides the opportunity to practice metropolitan-scale medicine in a context of small town character and comforts. Nationally recognized schools, three universities, safe neighborhoods, affordable housing and extensive recreational and cultural activities make La Crosse, on the Mississippi River, an outstanding place to live and work. Our compensation package, pension plan and continuing education opportunities are exceptional.

Interested candidates are invited to call Jon Nevala, Medical Staff Development, Gundersen Lutheran, at 1-800-362-9567, ext. 54224, 1900 South Ave., La Crosse, WI, 54601, or e-mail jpnevala@gundluth.org

We support a safe, healthy and drug-free work environment through background checks and controlled substance screening.
EOE/AA

Luther Midelfort - Mayo Health System in Eau Claire, Wisconsin, seeks a **BC/BE Child & Adolescent Psychiatrist** with a developmental, biopsychosocial perspective who is comfortable treating a full range of psychiatric disorders in children and adolescents. The ideal candidate has a caring, collaborative, problem solving approach, and truly enjoys working with children and adolescents, their families, foster families, schools, and/or other support systems. Our clinic has a tiered system of care for children and adolescents with behavioral health problems in which the child and adolescent psychiatrists sees the patients with the most severe difficulties. The child and adolescent psychiatrist also provides support to family physicians, pediatricians, a pediatric neurologist, a nurse practitioner, and a psychotherapist who provide behavioral health care to children and adolescents and their families. Call would not be an expectation of this position unless the candidate would wish to see adults as well.

Luther Midelfort-Mayo Health System is a physician-directed, fully integrated multi-specialty hospital and clinic owned by the Mayo Clinic. Luther Midelfort offers a complete benefits package & salary guarantee.

A multitude of family activities are available in Wisconsin's four season climate. Eau Claire is located 90 minutes east of Minneapolis/St. Paul. For more information, contact Christine Rodman, 800-573-2580; fax 715-838-6192; or e-mail rodman.christine@mayo.edu

---

Luther Midelfort - Mayo Health System in Eau Claire, Wisconsin, seeks a **BC/BE Adult Psychiatrist** with emphasis on inpatient and outpatient work. Call is 1:5.

Luther Midelfort-Mayo Health System is a physician-directed, fully integrated multi-specialty hospital and clinic owned by the Mayo Clinic. Behavioral Health services are used by a nine county area of Western Wisconsin.

Luther Midelfort offers a complete benefits package. A multitude of family activities are available in Wisconsin's four season climate. Eau Claire is located 90 minutes east of Minneapolis/St. Paul. For more information, contact Christine Rodman, 800-573-2580; fax 715-838-6192; or e-mail rodman.christine@mayo.edu

WYOMING

The Allure of the West!

- Ranked #1 in the U.S. by "Kiplinger's" for the lowest taxes paid per household
- Ideal to raise a family, possesses great schools, and retains its western charm although only 90 minutes from Denver
- United Medical Center is a 206-bed hospital that serves Wyoming, Northern Colorado, and Western Nebraska
- 16-bed Behavioral Health Unit (12 adult and 4 adolescent) and active outpatient clinic

Adult Psychiatrists
Opportunities for both inpatient and outpatient treatment of adults. Skills and experience in treating geriatrics a plus.

Addiction Specialist
Unique opportunity to spearhead and champion the expansion of a hospital-based, outpatient addiction treatment program. Specialization in addiction treatment is required.

Both candidates must be team players with excellent communication skills. Program development a plus. Board-Certified (or-eligible). Wyoming license (or-eligible).

Contact: Lauren Maines, Physician Recruiter, 214 E. 23rd St. Cheyenne, Wyoming 82001, Office: (307) 432-2649, Fax: (307) 432-3181, LMaines@umcwy.org.

CASPER: General or Child Psychiatrist - combination outpatient, partial & inpatient services. Multidisciplinary treatment team support. Compensation plan offers salary, benefits & bonus potential. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

Fellowships

Medical Staff Fellowship
Molecular Imaging Branch
National Institute of Mental Health
National Institutes of Health
Department of Health and Human Services
Bethesda, MD, USA

The Molecular Imaging Branch at the National Institute of Mental Health, NIH will have a medical staff fellowship position available July 1, 2007, with duration of one to three years. This laboratory uses state-of-the-art PET (positron emission tomography) technology and newly developed radioligands to study molecular targets in animals and humans. The fellow will have ample opportunities to learn from multidisciplinary experts in the field and acquire all skills necessary to pursue a research career in neuroimaging. The NIH imaging facilities and our research team provide outstanding opportunities for productivity and learning. Applicants must have completed residency training (e.g., psychiatry, neurology, or nuclear medicine/radiology) and must possess a valid US medical license. Repayment of up to $35,000 per year is available for qualified college and medical school loans. Interested applicants should send their CV and the names of two references to: Robert Innis, MD, PhD; Chief, Molecular Imaging Branch, NIMH, Building 1, Room B3-10, 1 Center Drive MSC-0135, Bethesda, MD 20892-0135, Email: robert.innis@nih.gov Women and minorities are encouraged to apply. For information on the lab, see: http://intramural.nimh.nih.gov/mood/proginfo/mib/

DHHS and NIH are equal opportunity employers

UNIVERSITY OF MICHIGAN
GERIATRIC PSYCHIATRY FELLOWSHIP

ACGME-accredited Geriatric Psychiatry Fellowship at Univ. of Michigan and Ann Arbor VA Healthcare System (VAHS) available July 1, 2007. One-year fellowship program (PGY-5) provides broad-based clinical experience in inpatient, outpatient, nursing home settings, with unique multidisciplinary emphasis, in an extraordinarily rich academic environment. Two-year fellowship program (PGY-5 & 6) available to selected candidates and includes all clinical experience of one-year program, plus a research training component (available in basic, clinical and health services research) designed to prepare trainee for academic career. University has NIH-funded Geriatric Research and Training Center and Alzheimer's Disease Research Center, as well as the nation's first comprehensive academic Depression Center. VAHS has Geriatric Research, Educational and Clinical Center (GRECC). Candidates must have completed an approved U.S residency in Psychiatry, and must have passed USMLE Step III prior to entry into program. Applications accepted through November 1, 2006. Please send CV to Alan M. Mellow, M.D., Ph.D., Chief, University of Michigan Section of Geriatric Psychiatry, MHSL/116MH, Ann Arbor VA Medical Ctr., 2215 Fuller Road, Ann Arbor, MI 48105; Email: amell@umich.edu

POSITION: Geriatric Psychiatry Fellowship

SPONSOR: University of Rochester Medical Center, Department of Psychiatry, Program in Geriatrics and Neuropsychiatry

DESCRIPTION: The University of Rochester Program in Geriatrics and Neuropsychiatry offers one-year PGY-5 clinical fellowships in Geriatric Psychiatry. Ours is an ACGME accredited program, successful completion of which makes graduates eligible for the ABPN subspecialty examination in geriatric psychiatry. The fellowship offers training in the care of older patients in a variety of inpatient, long-term care, outpatient, consultation, and palliative care settings. Supervised clinical experiences are complemented by a didactic program, elective offerings, and opportunities to develop individual scholarly and research interests. In addition to the breadth of our clinical programs and patient populations, we have a large cadre of experienced and nationally recognized clinicians, teachers, and researchers serving on our faculty. We pride ourselves on providing a stimulating, rewarding educational experience in a supportive and nurturing environment.

CONTACT: For more information please contact Jeffrey M. Lyness, M.D., Director, Geriatric Psychiatry Fellowship, Department of Psychiatry, University of Rochester Medical Center, 300 Crittenden Boulevard, Rochester, NY 14642-8409 (Phone 585-275-6741; Fax 585-273-1082; E-Mail Jeffrey_Lyness@urmc.rochester.edu)

The University of Rochester is an equal opportunity/affirmative action employer. Applications from women and minority groups are encouraged.

UNIVERSITY OF MICHIGAN
PSYCHOSOMATIC MEDICINE FELLOWSHIP

A Psychosomatic Medicine fellowship position is available at the University of Michigan, Department of Psychiatry. The one-year fellowship program (PGY-5) provides a broad-based clinical experience, with a strong multidisciplinary emphasis, and opportunities to achieve skills in research, education and administration, in an extraordinarily rich academic environment, with no night or weekend on-call. Supervision is provided by full-time attendings with board certification in Psychosomatic Medicine. The fellowship begins on July 1, 2007. Excellent salary and benefits. Candidates must have completed an approved residency in Psychiatry and must have passed USMLE Step III prior to entry into program.

Applications will be accepted through January 15, 2007. Please email/mail/fax CV to Michelle Riba, MD, Associate Director, Psychosomatic Medicine Services, Department of Psychiatry, University of Michigan Health System, 1500 E. Medical Center Drive, Room F6236 MCHC, Ann Arbor, MI, 48109-0295. Tel: (734) 764-6879; FAX: (734) 936-1130; web: http://www.med.umich.edu/psych/education, Email:gacioch@umich.edu.

PSYCHOSOMATIC MEDICINE/
CONSULTATION-LIAISON PSYCHIATRY
COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS AND SURGEONS

The Department of Psychiatry at Columbia University College of Physicians and Surgeons offers a one-year fellowship in Psychosomatic Medicine at New York Presbyterian Hospital-Columbia University Medical Center for graduates of approved psychiatric residency programs. The fellowship seeks psychiatrists interested in an academic career in Psychosomatic Medicine (consultation-liaison psychiatry). This is a full-time, ACGME-approved program with clinical, research, and teaching experience at a major tertiary care center. Some call is required. Applicants are sought for the 2007-2008 academic year. To apply, please submit a personal statement, three letters of recommendation, and a C.V., no later than October 15, 2006. For further information, applicants should contact Dr. Peter A. Shapiro at Columbia University, College of Physicians and Surgeons, 622 West 168th Street, Box 427, New York, NY 10032; (212) 305-9985, or by email at mf251@columbia.edu. Columbia University is an AAEOE.

BRIGHAM & WOMEN'S / FAULKNER HOSPITALS
WEST ROXBURY VA HOSPITAL - DANA-FARBER CANCER INSTITUTE
HARVARD MEDICAL SCHOOL

JULY 2007 - JUNE 2008 ACADEMIC YEAR

FELLOWHIP POSITIONS IN PSYCHOSOMATIC MEDICINE (C-L PSYCHIATRY) AND PSYCHOSOCIAL ONCOLOGY

BOSTON - Available for July 2007. ACGME-Accredited. Three PGY V Fellowship positions at Brigham & Women's/ Faulkner Hospitals; **one PGY V Fellowship position** at the Brigham and Women's/ West Roxbury VA Hospitals; **one PGY V Fellowship position** at Dana-Farber Cancer Institute/ Brigham & Women's Hospital in Psychosocial Oncology available for the July 07- June 08 academic year. These positions, which offer advanced training in consultation-liaison psychiatry and psychosomatic medicine, also include consultation-liaison experiences with OB/GYN, Neuropsychiatry and Behavioral Neurology, Burn/Trauma, Transplantation, Emergency Psychiatry, Psycho-oncology and Palliative Care. Excellent supervision, research and liaison support. Fellowship positions include Harvard Medical School appointment.

Please Contact:

For Psychosomatic Medicine or VA Fellowships:
David Gitlin, M.D.
Director, Medical Psychiatry Division
Brigham & Women's/ Faulkner Hospitals
75 Francis Street, Boston, MA 02115
617-732-6701 Fax: 617-738-1275
Email: dgitlin@partners.org

For Adult Psychosocial Oncology Fellowship:
John Peteet, M.D.
Psychosocial Oncology and
Palliative Care Service
Dana-Farber Cancer Institute
44 Binney Street, Boston, MA 02115
617-632-6181 Fax: 617-632-6180
Email: jpeteet@partners.org

RESEARCH FELLOWSHIP IN SUBSTANCE ABUSE
M.D. or Ph.D.

Columbia University/New York State Psychiatric Institute fellows receive extensive training in clinical and/or laboratory research. For interested psychiatrists, the fellowship has a two-year, ACGME-accredited training program in addiction psychiatry sponsored by Columbia University and New York Presbyterian Hospital. The addiction psychiatry program provides comprehensive clinical and research training experiences in a variety of substance abuse treatment settings. Individuals with strong research interests are encouraged to apply.

For applications:
Frances R. Levin, M.D.
Director Research Fellowship
in Substance Abuse
1051 Riverside Drive, Unit 66
New York, NY 10032
(212) 543-6105, Fax: (212) 543-6018
FRL2@columbia.edu

In accordance with Federal funding regulations, this announcement is directed to U.S. citizens, non-citizen nationals and foreign nationals with permanent resident status. Columbia University is an AA/EEO employer.

Geropsychiatry Fellowship, Portland, Oregon. Recruiting for 07/01/07 ACGME-accredited PGY5 level, at Oregon Health & Science Univ and Portland VA Med Center. Flexible program with either research or clinical emphasis. Training sites include inpatient, outpatient, nursing home and community. Research and clinical strengths in end-of-life/palliative care, ethics, mood disorders, dementias, Parkinson's disease, and substance abuse. Contact Dr. Linda Ganzini, Dir, Geriatric Psychiatry Training, Mental Health Div, P3MHDC, PO Box 1034, Portland, OR 97207; (503) 220-8262, Ext. 56492; or at Linda.Ganzini@va.gov. EOE.

FORENSICS FELLOWSHIP: One-year fellowship at Virginia Commonwealth University Department of Psychiatry in Forensic Psychiatry. PGY- 5 or higher candidates may apply. Must obtain Virginia license prior to July 1, 2007 start date. Fellow will work in either the Department of Corrections or State Forensic Hospitals, and will participate in civil and criminal clinics, consultation service, private evaluations, seminars, research meetings and supervision at VCU/MCV. Send CV to Dr. Deborah Giorgi-Guarnieri, MD, Department of Psychiatry, Box 980253, Richmond, VA 23298. VCU is an EEO/AA employer. Women, minorities and persons with disabilities are encouraged to apply.

FELLOWSHIP
PUBLIC PSYCHIATRY at YALE
2007

The Connecticut Mental Health Center - Yale University School of Medicine is offering a one-year Fellowship in Public Psychiatry beginning July 2007. CMHC is a major site for training, research and clinical service within the Yale and State systems. As a state-funded, academic, urban mental health center it provides a unique setting for psychiatrists to obtain advanced training as they pursue careers as leaders in the field. Fellows will spend 50% time in seminars, supervision, and administrative/policy meetings of CMHC and the CT Dept. of Mental Health and Addiction Services; and 50% effort providing direct clinical service and/or consultation within public mental health settings in New Haven. Candidates must be eligible for board certification and CT licensure. Minority applicants are encouraged to apply. For further information contact Jeanne Steiner, D.O. Medical Director, CMHC - Yale Univ., 34 Park St New Haven, CT 06519 or Jeanne.Steiner@yale.edu.

INFANT PSYCHIATRY FELLOWSHIP. The Section of Child and Adolescent Psychiatry at Tulane University Health Sciences Center is seeking a full-time Fellow in Infant Psychiatry. This one or two year fellowship includes clinical and research experiences with the multidisciplinary Infant Mental Health group at Tulane. Completion of a fellowship in Child and Adolescent Psychiatry preferred. Faculty appointment at the Instructor level is possible. Applications will be accepted until a suitable qualified candidate is found. Applicants should send letter of interest, updated CV and list references to Charles Zeanah, MD, Vice Chair and Director of Child and Adolescent Psychiatry, 1440 Canal Street TB52, New Orleans, LA 70112. Interested eligible applicants may obtain further information regarding this position by contacting Dr. Zeanah at 504-988-5402 or czeanah@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

ADDICTION PSYCHIATRY FELLOWSHIP: Virginia Commonwealth University seeks PGY-5 level psychiatry residents for July 2007 ACGME-accredited Addiction Psychiatry Training Program. Fellowship provides clinical experience in all aspects of addiction treatment, including addiction pharmacotherapy (buprenorphine, methadone, naltrexone), abstinence-based treatment, inpatient alcohol/drug detoxification, residential and outpatient treatment, consultation-liaison, comorbid disorders, and impaired health professionals program. Fellows gain experience in addiction research project of their choice. Current research includes addiction pharmacotherapy development, drug interaction studies, prescription opioid addiction treatment, and genetics of addiction studies. Competitive salary with full benefits package. Please send letter of interest, CV, and 3 letters of reference to: Elinore McCance-Katz, MD, PhD, Div. of Addiction Psychiatry, VCU, Box 980109, Richmond, Virginia 23298; TEL: (804) 828-5351; FAX: (804) 828-5386. Equal Opportunity/Affirmative Action employer.

PSYCHOSOMATIC MEDICINE FELLOWSHIP - VIRGINIA COMMONWEALTH UNIVERSITY

One year exciting, well established, fellowship program, one of the first approved by the ACGME, in a 750-bed university hospital, accepting applications for July 1, 2007. Advanced training offered to psychiatrists who have completed residency. Please write or call: James L. Levenson, M.D., Chairman, C-L Division, VCU Health System, Department of Psychiatry, Box 980268, Richmond, VA. 23298-0268; jlevens@vcu.edu (804) 828-0762 or Yaacov R. Pushkin, M.D.; ypushkin@vcu.edu

Positions Wanted

Psychiatrist with several years of clinical and biological research experience and leadership roles in the field of schizophrenia research, looking for a full-time position to mentor young academicians and aid the development of psychiatric research in an academic, industrial, government or private foundation setting. Currently based in NYC, but willing to relocate depending on the position. Expertise includes brain imaging and genetics. Please respond to Box P-727, Psychiatric News Classifieds, American Psychiatric Publishing, Inc., 1000 Wilson Blvd. Suite 1825, Arlington, VA 22209.

Practice for Sale

Retiring psychiatrist in upscale NJ community 1 hour from Manhattan offers sale of large psychiatric practice. Average of 50-60 private pay patients weekly. Gross income over $300,000. Over 200 active files. Affiliation with outstanding teaching hospital available. All office equipment and furnishings included. Contact Ronnie at 973-267-2748 or fax 973-278-7718.

ADULT PSYCHIATRIC PRACTICE FOR SALE

Decorator designed 2 office suite (for cross referral with therapist) in beautiful Chicago suburb. Available immediately due to retirement. Over 450 active patients, grossing over $100,000 / 20 hours per week. Furniture included. Terms of purchase will be to assume lease ($675 month per person). Web Page is www.drjuraadams.com. Contact me at cell (630) 667-7509 or fax (312) 440-8863.

FOR SALE: Large practice with two psychiatrists, a nurse practitioner, a psychologist, and a licensed professional counselor. Last year gross income was $621,000. Managing physician has to sell due to illness. Please contact 713-705-0030 if interested.

Part-time Adult Psychiatric Practice for sale. Suburban Syracuse, N.Y. location. No third party billing. Direct payment from patients. Furniture can be included. Part-time consultation position also possible. Contact me at (315) 446-3001.

Courses & Workshops

ELECTRO-CONVULSIVE THERAPY
5-DAY HANDS-ON COURSE
35 CME Credits

Weeks of: 9/11/2006; 10/2/2006; 1/8/2007
2/5/2007; 3/19/2007; 5/7/2007

Comprehensive training in modern ECT with "hands-on" treatment of patients. Exceeds APA training guidelines and provides a "new procedure" certificate for credentialing of ECT.
Course Directors: Samuel Bailine, M.D. and Georgios Petrides, M.D.

Office of CME: 516-465-2500 or
www.northshorelij.edu/cme

North Shore LIJ The Zucker Hillside Hospital
North Shore-Long Island Jewish Health System

Furniture

PSYCHOANALYTIC COUCHES

Prestige Furniture and Design is the leading manufacturer of psychoanalytic couches. For a brochure and price list, call (800) 283-9958.

Software

Diagnose Major Psychiatric and Personality disorders. Differential diagnosis, History,Treatment plans, Patient records.
Palm OS, Windows, Pocket PC
http://www.SoftPsych.com

BRIEF SUMMARY. See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS — ***QT Prolongation:*** Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).** ***QT Prolongation and Risk of Sudden Death:*** **GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec.** ***Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS —** ***General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis)**. Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine,* 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS —** ***Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients.There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole—*Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System—*Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System—*Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine—*Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System—*Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders—*Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System—*Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System—*Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System—*Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages—*Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses—*Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System—*Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE—*Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/75).

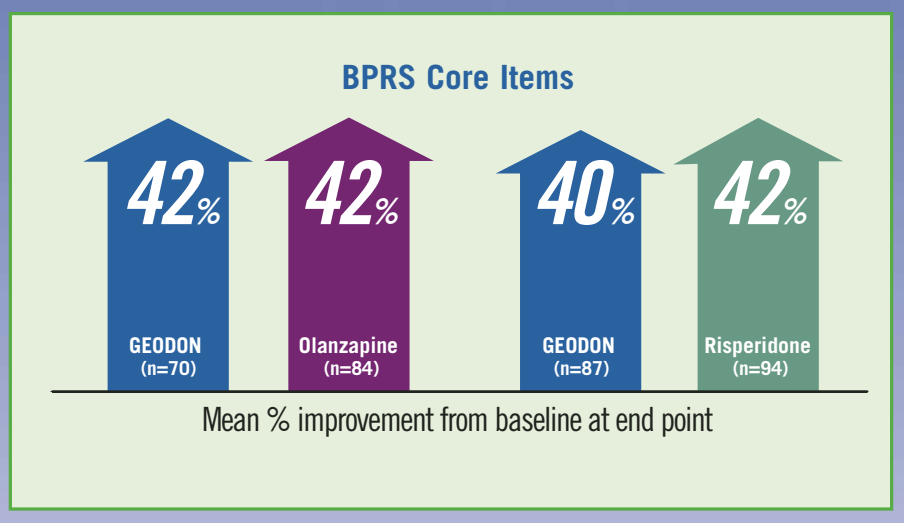
References: 1. Data on file. Pfizer Inc., New York, NY. **2.** Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry.* 2004;161:1837-1847. **3.** Addington DEN, Pantelis C, Dineen M, Benattia I, Romano SJ. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry.* 2004;65:1624-1633. **4.** Simpson GM, Weiden P, Pigott T, Murray S, Siu CO, Romano SJ. Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. *Am J Psychiatry.* 2005;162:1535-1538. **5.** Weiden PJ, Loebel A, Yang R, Lebovitz H. Course of weight & metabolic benefits 1 year after switching to ziprasidone. Presented at: American Psychiatric Association Annual Meeting; May 1-6, 2004; New York, NY.

Revised May 2005

Treat schizophrenia with the body in mind

COMPARABLE EFFICACY

Consistent results in head-to-head studies[1-3]

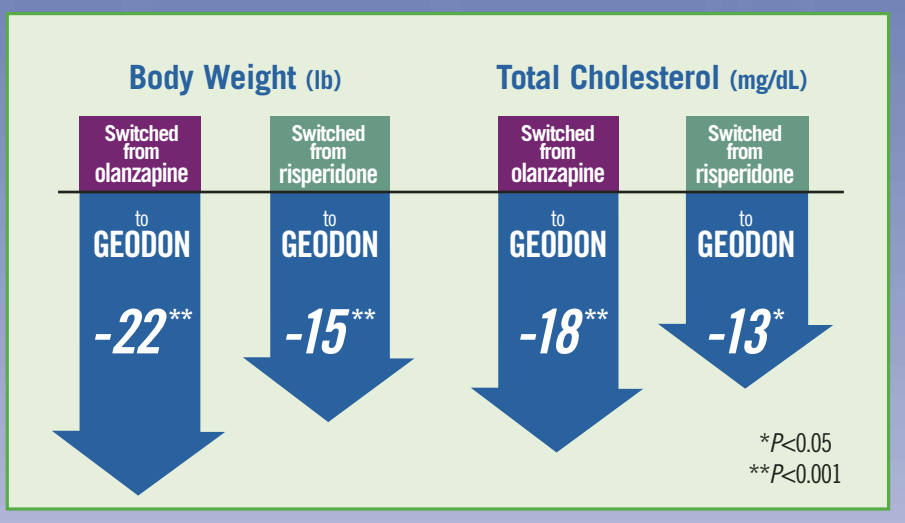


A 6-week, double-blind, randomized study of GEODON vs olanzapine and an 8-week, double-blind, randomized study of GEODON vs risperidone.

- BPRS core items include hallucinatory behavior, unusual thought content, conceptional disorganization, and suspiciousness
- Comparable efficacy was maintained in double-blind extension studies
  —up to 1 year vs risperidone[1]
  —up to 6 months vs olanzapine[4]

WITHOUT COMPROMISING METABOLIC PARAMETERS

Significant results in switch studies[1,5]



Two 1-year open-label extensions of 6-week, open-label switch studies in patients suboptimally controlled due to partial response or poor tolerability.

- Patients switching to GEODON from olanzapine and risperidone also experienced reductions in triglycerides[5]

In the acute head-to-head studies...

- In the GEODON vs olanzapine study, olanzapine significantly increased body weight (8 lb vs 2 lb for GEODON, $P<0.0001$)[1,2]
- In the GEODON vs risperidone study, risperidone increased body weight (2 lb vs 0 lb for GEODON, $P<0.01$)[1,3]

GEODON®
(ziprasidone HCl) Oral Capsules

GEODON is indicated for the treatment of schizophrenia and of acute manic or mixed episodes associated with bipolar disorder.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_C interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

In short-term schizophrenia trials, 10% of GEODON-treated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo. In the same short-term trials, the most common adverse events were somnolence (14%) and respiratory tract infection (8%).

Please see brief summary of prescribing information on adjacent page.

Pfizer NEUROSCIENCE