Volume 43
Number 16
August 15, 2008

Newspaper of the
American
Psychiatric
Association

PSYCHIATRIC NEWS

inside

PERIODICALS:
TIME-SENSITIVE MATERIALS

Credit: David Hathcox

Darrel Regier, M.D., M.P.H., director of the American Psychiatric Institute for Research and Education, tells two FDA advisory committees and the FDA to use caution in imposing a black-box warning on labeling for antiepileptic drugs.

FDA Committees Advise Against Black-Box Warning On Antiepileptics

Its advisory committees support the FDA's conclusion that antiepileptic drugs increase the risk of suicidal thoughts and behaviors, but do not favor the addition of a black-box warning.

BY JUN YAN

Experts in neurology and psychiatry agreed with the Food and Drug Administration's (FDA) assertion that antiepileptic drugs, as a class, increase the risk of suicidal thoughts and behaviors, but they were concerned about the negative consequences of imposing a black-box warning on the labeling information.

At a joint meeting on July 10, members of the peripheral and central nervous system and psychopharmacology advisory committees voted in favor of adding warnings and precautions about the suicidality risk to the package inserts of all antiepileptic drugs—but not in the form of a black-box warning.

In 2005, the agency began asking the makers of 11 drugs approved for long-term treatment of epilepsy to submit data on the drugs and suicide-related events reported in randomized, parallel-arm, placebo-controlled trials the companies conducted. Earlier this year, the FDA announced the results of its preliminary analysis and warned about a suspected increase in suicidality risk in patients taking antiepileptics (*Psychiatric News*, March 7).

The 11 drugs included in the analysis were carbamazepine, divalproex sodium, felbamate, gapapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide. Many other drugs that carry the indication for treating epilepsy were not included because they are sold in generic formulations by multiple manufacturers, which have little incentive to conduct clinical trials. Also, the original clinical trial data for these drugs may be too old, nonrandomized, without placebo control, or difficult to obtain.

Suicidality was defined as completed suicide, attempted suicide, preparatory acts toward imminent suicidal behavior, or suicidal ideation.

please see ***Antiepileptics*** *on page 23*

Senator Wants APA Records Of Drug-Industry Interactions

Sen. Charles Grassley's request of APA is part of escalating scrutiny of relationships between medicine and the pharmaceutical industry. Similar requests were sent to the American College of Cardiology and the American Heart Association.

BY MARK MORAN

The ranking Republican member of the Senate Finance Committee has asked APA to provide detailed information about its relationships with the pharmaceutical industry.

Sen. Charles Grassley (R-Iowa) last month requested in a letter addressed to APA Medical Director James H. Scully Jr., M.D., "an accounting of industry funding that pharmaceutical companies and/or the foundations established by these companies have provided" to APA, "including but not limited to grants, donations, and sponsorship for meetings or programs."

The request covers the period from January 2003 to the present.

Grassley's request is the latest instance of the rapidly escalating public interest in—and scrutiny of—financial relationships between medicine and the pharmaceutical industry. Similar letters were sent by Grassley in January to the American College of Cardiology and the American Heart Association.

Separate from the request for information from APA, Grassley has also asked Stanford University for information on its conflict-of-interest policies and on disclosures made by APA President-elect Alan Schatzberg, M.D., about his involvement with pharmaceutical manufacturers. In a detailed response, Stanford said that all of Schatzberg's earnings have been properly disclosed, and Grassley's staff later acknowledged that at least one charge he leveled against Schatzberg about undisclosed income was in error (see page 6).

In response to the request to APA for information, APA President Nada Stotland, M.D., M.P.H., said APA has nothing to hide.

"We intend to comply with the letter and spirit of Senator Grassley's request," she told *Psychiatric News*. She added that Grassley's letter, dated July 10, had asked for the information no later than July 24—a deadline she said had been impossible to meet to collect all the information he requested. APA asked for, and received, an extension of the deadline until September 2.

Upon receipt of Grassley's letter, Stotland disseminated a memo to the APA

please see ***Senator*** *on page 6*

Contents

Features

Volume 43
Number 16
August 15, 2008

Departments

Newspaper of the American Psychiatric Association
PSYCHIATRIC news

Psychiatric News, ISSN 0033-2704, is published bi-weekly on the first and third Monday of each month by the American Psychiatric Association, 1000 Wilson Boulevard, Arlington, Va. 22209-3901. Periodicals postage paid at Arlington, Va., and additional mailing offices. Postmaster: send address changes to Psychiatric News, APA, Suite 1825, 1000 Wilson Boulevard, Arlington, Va. 22209-3901. Online version: ISSN 1559-1255.

Subscriptions
U.S.: individual, $93; student, $33. International: APA member, $82; nonmember, $140; student, $33. Single issues: U.S., $19; Canada and international, $31. Institutional subscriptions are tier priced. For site licensing and pricing information, call (800) 368-5777, or e-mail institutions@psych.org.

Officers of the Association
Nada L. Stotland, M.D., M.P.H., *President*
Alan F. Schatzberg, M.D., *President-elect*
Carol A. Bernstein, M.D., *Vice President*
David Fassler, M.D., *Secretary-Treasurer*
Ronald Burd, M.D., *Speaker of the Assembly*
James H. Scully Jr., M.D., *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, Mark Moran, Aaron Levin, Jun Yan, *Senior Staff Writers*
Eve Bender, Rich Daly, *Staff Writers*
B. Alma Herndon, *Production Manager*
Sergey Ivanov, *Senior Graphic Designer*
Stephanie Whyche, *Staff Editor/Writer*
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
Francisco Fernandez, M.D., Geetha Jayaram, M.D., Mary Kay Smith, M.D., William Womack, M.D., Michael Myers, 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) 907-7868
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: Pamela Trujillo, 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.

Extent of Suicide Among Veterans Difficult to Pinpoint

Despite attention from government officials and the media, too little is known about the number of veterans who commit suicide and the risk factors associated with their actions.

BY AARON LEVIN

Suicides by veterans or members of the armed forces in recent years have resulted in public outcry and national legislation to prevent those who have served their country from taking their own lives.

However, much of the argument and outreach has rested on a thin and often contradictory base of evidence, according to a report from the Congressional Research Service.

"[T]here is not, at this time, a system of surveillance for suicide among veterans," said the report by Ramya Sundararaman, Sidath Viranga Panangala, and Sarah Lister, of the service's Domestic Social Policy Division. "The true incidence of suicide among veterans is not known."

The Centers for Disease Control and Prevention (CDC) began the National Violent Death Reporting System (NVDRS) in 2003 to collect data on violent deaths from medical examiners, law-enforcement sources, and toxicology reports that go beyond information recorded on standard death certificates. The NVDRS permits recording whether a decedent has served in the U.S. armed forces, although that information is not always known to the person who fills out the death certificate. Furthermore, only 17 states participate in the NVDRS, limiting its generalizability.

In 2005, the NVDRS recorded 1,821 suicides among current or former members of the armed forces—although the system does not distinguish between the two. Almost all were male (97 percent), and 78 percent were 45 or older.

Other CDC databases, such as the National Death Index, can be compared with Veterans Administration (VA) patient records to try to identify suicides, but only one-third of U.S. veterans receive health care from the VA, limiting the usefulness of this approach.

A 2007 study by University of Michigan researchers that examined rates of suicide among veterans treated for depression between 1999 and 2004 found that 1,683 out of 807,694 veterans studied had killed themselves, a rate of 88.25 suicides per 100,000 person-years. That rate is higher than rates in the general population, but similar to rates among individuals with depression.

Comparing the suicide rates of veterans and the general population presents additional problems, said the report authors. "Such comparisons are often made, but they are not necessarily valid," they noted.

For one thing, suicide data about the general population include suicides by veterans. Few sources present suicide data among populations excluding veterans, and no one knows the extent to which the inclusion or exclusion of veterans alters the data for the general population.

Some veterans groups have also complained that suicides have gone unrecorded among recently discharged veterans of duty in Iraq or Afghanistan who have left the military health system and who have not signed up for care at the VA.

In addition, risky behavior by former troops, such as dangerous driving, drug use, or heavy drinking, may not be seen as linked to suicide and not recorded as such on death certificates. Both of these factors may skew the data about veterans' suicide.

Both the Department of Defense and Department of Veterans Affairs have taken steps to screen troops and veterans for suicide risk factors, according to the report. Military health policy calls for screening troops upon their return from assignment in Iraq, Afghanistan, or other active fronts and again six months later.

The VA has held suicide-awareness days, hired suicide-prevention coordinators for all its facilities, opened a 24-hour suicide-prevention hotline in cooperation with the Substance Abuse and Mental Health Services Administration, and launched two research centers that study suicide and its risk factors.

However, many of the goals set forth in the VA's Mental Health Strategic Plan in 2004 are still in the pilot phase or have been implemented only partially, said the authors.

Ultimately, they concluded, better research may be more useful than comparing veterans' suicide rates with those of the general population.

"What may be more meaningful, and more important to achieve, is the establishment of data systems that support a more robust and reliable understanding of suicide among veterans," the authors said. Such systems would include baseline data, risk and protective factors, and treatment outcomes, all of which would clarify the utility and timing of interventions.

"Suicide Prevention Among Veterans" is posted at <http://assets.opencrs.com/rpts/RL34471_20080505.pdf>. ■

APA RESOURCES

- ***Psychiatric News* Web Site:** pn.psychiatryonline.org/
- **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

Psychiatry Across the Pond

BY NADA STOTLAND, M.D., M.P.H.

Credit: David Hathcox

For the past several years, the presidents of APA and the Royal College of Psychiatrists have attended, and presented at, each other's annual meetings. It was the Royal College that gave APA our presidential medallion 40 years ago. The meetings are opportunities for both mutual commiseration and mutual inspiration. With our current concerns about the rising costs and inefficiencies of health care and our national elections around the corner, this is a good time to think about the advantages and disadvantages of different kinds of health care systems.

The Royal College performs the functions of both our APA and the American Board of Psychiatry and Neurology; it is the Royal College that sets the standards and administers the examinations that qualify physicians as specialists in psychiatry. This makes nearly all the practicing psychiatrists in the country members of the college. Within the Royal College, there are faculties comprising the psychiatric subspecialties. The faculties have their own meetings and elect their own representatives to the governing body of the college, which also includes representatives of geographic areas, making for quite a large board of directors. The president of the Royal College serves for three years. At this meeting, Professor Sheila Hollins finished her term, and Professor Dinesh Bhugra commenced his.

Credit: Ken Busch, M.D.

Dr. Stotland poses with Professor Dinesh Bhugra, president of the Royal College of Psychiatrists, at the college's headquarters in July.

Professor Hollins has a particular interest in patients with little or no reading skills. She has co-written a fascinating set of booklets: "Books Beyond Words." Each of these picture booklets addresses an important life event: losing a parent; going to the doctor, hospital, or outpatient clinic; being arrested or on trial; falling in love; and dealing with abuse; as well as speaking up for oneself, personal hygiene, and general medical care: "Looking After My Breasts" and (I had to read this title twice) "Looking After My Balls." The pictures show individuals gradually coping with each challenge and provide a stimulus for discussion with family members and health care professionals. By the way, I like the terms the authors use: "service users" rather than our "consumers," and "carers" for both professionals and lay people, usually family members, who provide care.

This year the Royal College met in London, using the meeting facilities of the Imperial College. This inexpensive venue has enabled the college to experiment with a meeting without pharmaceutical company support. The only exhibits featured college programs and publications. The meeting briefcases carried only the seal of the college. There was not a free pen, umbrella, or sticky note in sight. The attendees, therefore, bore the full expense of the meeting; registration cost between $1,500 and $2,000 for three days of meetings, coffee breaks, and hot lunches. Hotel accommodations were extra. Britain has 13,000 psychiatrists; the attendance at the meeting was fewer than 1,000 psychiatrists, which included a significant number from other European countries and from the British Commonwealth, including from India, Africa, Australia, and Canada.

This year marks the 60th anniversary of the National Health Service (NHS). Although our systems of care are very different, we face similar problems. Like us, the NHS is worried about treatment of the growing elderly population and active and returning military. At the college meeting, I participated in a symposium on the integration of primary and mental health care. The college has marked the NHS anniversary by developing "Fair Deal for Mental Health: Our Manifesto for a 3-Year Campaign Dedicated to Tackling Inequality in Mental Healthcare." One frequently repeated slogan is "No health without mental health."

Some of us have a mental image of NHS facilities as dingy, dirty, and overcrowded. Professor Bhugra recently told the press that he would not like to see a family member in some NHS psychiatric facilities. But I visited a facility where I would be more than happy to have a member of my family cared for—the Chelsea and Westminster General Hospital. I have never seen a more bright, beautiful, and architecturally brilliant hospital.

Over the past 10 years, the NHS has greatly reduced waiting times and introduced standards for the care of some medical conditions. The NHS is now moving in the direction of increased patient choice. While there is some interest in privatization, most people are satisfied with the current system, which provides care for everyone.

We spend more on health care than any other country in the world, and yet we do not excel in terms of maternal and infant mortality or life expectancy. Other countries may have something to teach us as we make crucial decisions about the future of our health care system. ■

Screening Urged to Prevent Prescription Drug Abuse

One in 12 adolescents reports misusing prescription medications, with misuse of opioids and stimulants being most common.

BY JUN YAN

Risk-taking tendencies, major depression, and other substance use problems are some of the major risk factors linked to teens' misuse of prescription drugs, a study in the July *Journal of the American Academy of Child and Adolescent Psychiatry* shows.

According to data collected in the 2005 National Survey on Drug Use and Health (NSDUH), one in 12 adolescents aged 12 to 17 (8.2 percent) reported having misused at least one prescription medication in the previous year. This prevalence trailed only the use of alcohol, tobacco, and marijuana.

Misuse was defined as "any intentional use of a medication with intoxicating properties outside of a physician's prescription for a bona fide medical condition, excluding accidental misuse."

Opioids such as hydrocodone and oxycodone are by far the class of medications most frequently misused by adolescents, followed by stimulants (for example, amphetamines and methylphenidate), tranquilizers (including benzodiazepines and muscle relaxants), and sedatives (for example, barbiturates).

In this study, Ty Schepis, Ph.D., and Suchitra Krishnan-Sarin, Ph.D., from the Department of Psychiatry at Yale University School of Medicine found that prescription drug misuse among adolescents was significantly linked to poor academic performance, a major depressive episode in the past year, risk-taking tendencies, a history of mental health treatment in the past year, and the concurrent use of other substances, including cigarettes, alcohol, marijuana, cocaine, or inhalants.

Thirty-six percent of these adolescents who misused medications had symptoms that met one or more *DSM-IV* criteria for substance use disorder. "It was somewhat unexpected to see that over a third of the adolescents misusing prescription drugs have begun to develop symptoms of dependence," Schepis commented to *Psychiatric News*.

The high rate of adolescents with co-existing substance use problems is consistent with findings from other studies, the authors pointed out. They urged clinicians to screen young patients routinely for possible prescription misuse and educate parents about the high risk of such misuse.

"There is anecdotal evidence to suggest that prescription drugs are perceived to be safer or less problematic than illicit substances," Schepis said. In addition, because prescription drugs are legal, teenagers may have easier access to painkillers, stimulants, and tranquilizers than to illegal substances, especially if parents are not monitoring their medicine cabinets.

"We can combat the supply of illicit drugs, but it's a lot harder to control the supply of prescription medications because they have legitimate medical indications," he said.

Clinicians should be more proactive in educating parents and adolescents about the dangers of misusing prescription medications, Schepis suggested, especially considering the high prevalence of substance use disorder symptoms among these teenagers.

Another notable finding was that adolescent girls had a slightly higher prevalence of misusing opioids, stimulants, and tranquilizers than did their male peers. This trend is consistent with some adult surveys that found a higher rate of misusing prescription medications by women than by men.

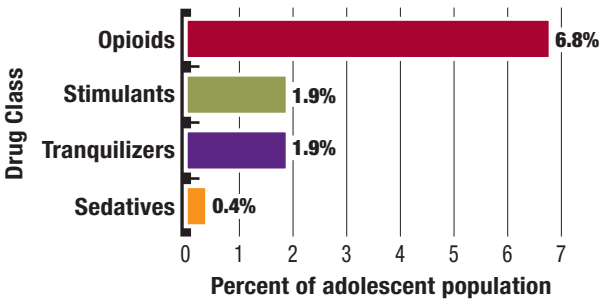
The NSDUH is an annual in-home survey sponsored by the Substance Abuse and Mental Health Services Administration that tracks trends in substance use throughout the United States. The sample used in this study comprised 18,678 adolescents, and the results were extrapolated to population estimates. This study was supported in part by a grant from the National Institutes of Health.

"Clinicians must educate adolescents about the difference between proper and improper use," said Schepis. "Adolescents may not fully understand the potential harm in misusing prescription drugs like overdose and developing addiction."

An abstract of "Characterizing Adolescent Prescription Misusers: A Population-Based Study" is posted at <www.jaacap.com/pt/re/jaacap/abstract.00004583-200807000-00006.htm>. ■

Many Adolescents Report Prescription Drug Abuse

Data from the 2005 National Survey on Drug Use and Health showed that 8.2 percent of youth between the ages of 12 and 17 reported misusing at least one prescription drug in the prior year. Opioids were the most frequently misused class. Total sample size was 18,678.



Source: Ty Schepis, Ph.D., et al., *Journal of American Academy of Child and Adolescent Psychiatry*, July 2008

Alcohol, Illicit Drug Use Vary Widely by Region

An analysis of a population-based survey on alcohol and drug use pinpoints variability in the rates of usage by specific regions of the country.

BY EVE BENDER

Although an estimated 8 percent of Americans aged 12 and older reported current use of an illicit drug, usage rates varied greatly from one state to another, and even from one county to another, according to new annual survey data from government researchers.

A June report on the survey from the Substance Abuse and Mental Health Services Administration on the illicit use of drugs and alcohol across the United States revealed that the regions with the highest rates of drug use were in Alaska, California, Massachusetts, and Rhode Island. The District of Columbia also had a high rate (see map).

When researchers looked at rates of specific drug use, they found that the highest rates of current marijuana use were reported in western Montana, with 12 percent of residents reporting current use, while the lowest rates occurred in several regions: central Utah, the Four Corners region (where Colorado, New Mexico, Arizona, and Utah meet), and San Juan, Puerto Rico, where an estimated 3 percent of residents reported current marijuana use.

The data were compiled from the combined 2004-2006 National Surveys on Drug Use and Health (NSDUH), which includes data on drug and alcohol use from 203,870 respondents from a nationally representative sample aged 12 and older. The data, featuring representative samples from all states, the District of Columbia, and Puerto Rico, are then extrapolated to population estimates.

The NSDUH is conducted annually by researchers from Research Triangle Institute in Research Triangle Park, N.C.

From 2004 to 2006, an estimated 4.9 percent of Americans aged 12 and older reported using pain relievers illicitly in the past year. Estimates ranged from 2.5 percent in Washington, D.C., to almost 8 percent in the panhandle of Florida.

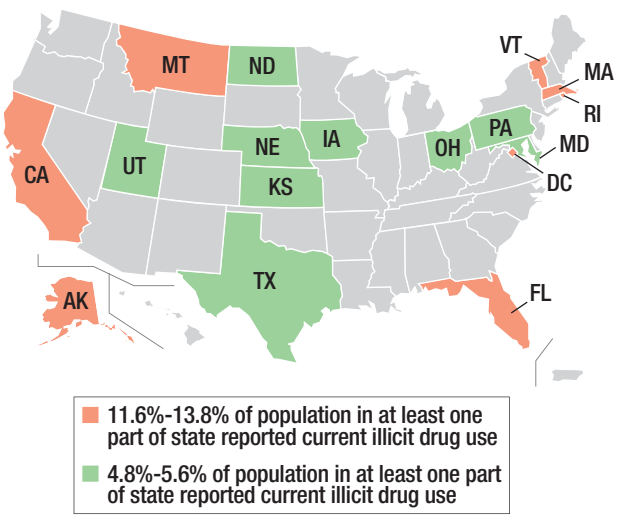
Alcohol is the most commonly used substance in the United States, with an estimated half of Americans 12 or older currently using alcohol. According to the data, the lowest rate of alcohol use was in Utah County, Utah (21 percent), and the highest was found in one section of Washington, D.C. (78.7 percent). Reports of binge drinking (defined as having five or more drinks on the same occasion) was lowest in Utah, and underage drinking was highest in D.C.

Current tobacco use was highest in West Virginia's south central region (43 percent) and lowest in Utah (17.3 percent).

"Substate Estimates From the 2004-2006 National Surveys on Drug Use and Health" is posted at <oas.samhsa.gov/substate2k8/substate.pdf>. ■

High Rates of Drug Abuse Spread Throughout U.S.

Using 2004-2006 data, the National Survey on Drug Use and Health found that the eight highest rates of illicit drug use in the U.S. were in regions in the states shown below and the District of Columbia.



Source: SAMHSA, 2008

Minority Mentors Wanted

APA members are encouraged to join the National Minority Mentors Network and become mentors to their younger minority colleagues. To facilitate membership, the Selection Advisory Committee for the minority fellowships will host a reception for mentors and current APA/SAMHSA and APA/AstraZeneca fellows during the 2008 September Component Meetings on Friday, September 5, from 7 p.m. to 8:30 p.m., in Washington, D.C. This event will provide an informal setting for fellows to network with mentors.

Mentors play an important role in the professional growth and development of beginning psychiatrists and receive great satisfaction from sharing their hard-earned wisdom and experience. Moreover, mentoring is critical to fostering successful careers in psychiatry and ensuring the field's future success.

APA members who are interested in joining or obtaining additional information about the network or who would like to attend the reception next month should contact Marilyn King at (703) 907-8653 or mking@psych.org. ■

Quality, Access to Care Heading in Wrong Direction

Prevention efforts and stepped-up screening for serious conditions, such as depression, could contribute to substantial improvements in health.

BY RICH DALY

Amid recent reports that life expectancy is falling in some parts of the nation for the first time in decades, new research concludes that overall the U.S. health care system fell short of benchmarks set in a similar report two years earlier.

The "National Scorecard on U.S. Health System Performance, 2008," a compilation of health care statistics mostly from 2007, was published by the Commonwealth Fund, a nonpartisan, health-focused think tank. The scorecard aims to provide a comprehensive measure of U.S. health outcomes, quality, access, efficiency, and equity.

Compared with the findings of the first report, released in 2006, findings in the current report indicated worsening scores in the ability of the U.S. health system to provide healthy lives, quality care, or access to care. The scores for efficiency and equity improved slightly.

"The scorecard makes a compelling case for change" in health care policy, said Cathy Schoen, senior vice president of the Commonwealth Fund.

Among the greatest concerns was that access to care had significantly declined, as shown in the finding that more than 75 million adults—42 percent of all adults aged 19 to 64—were underinsured or uninsured in 2007. That was an increase from 35 percent of adults in that age range in 2003.

One impact of the health insurance disparities was on quality of life: there was a greater percentage of uninsured working-age adults who were limited in activities because of "physical, mental, or emotional problems," compared with insured adults.

The report also stated that the U.S. system had failed to keep pace with the health gains in other advanced countries. The U.S. ranking fell from 15 to 19 in "mortality amenable to medical care" among the 19 countries tracked in the report.

Among the health care areas in which the report identified a need for improvement is access to quality mental health care. The report noted that among adults who have major depressive illness, for example, many remain untreated. Although the rate of treatment for people who have depression improved from 65 percent to 69 percent on the current scorecard, that still left nearly 1 in 3 such individuals without any care.

The researchers found that the percentage of adults who received care for a major depressive episode was greatest among Medicare, military, and veterans health beneficiaries—87 percent—and lowest among the uninsured—50 percent. The researchers found as well that about 71 percent of people with private insurance who needed depression treatment received it, as did 80 percent of Medicaid beneficiaries.

"Mental health indicators tell us this is an area where we need to improve in the United States," Schoen told *Psychiatric News*.

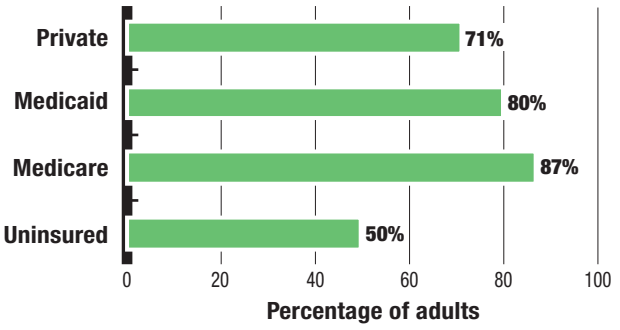
The scorecard noted that additional gaps in mental health care are created by the provision of inadequate mental health care, which the report defined as care that is not effective, well-coordinated, safe, timely, and patient centered. Improvements in mental health care would benefit not only those with mental illness but overall society as well. Improving depression care alone would increase workplace productivity by an estimated $2.2 billion annually, the researchers estimated.

Schoen said that health care research consistently indicates a reliance on crisis care to treat serious men-

please see ***Quality*** *on page 9*

Treatment for Depression Lags Among Uninsured

The percentage of adults who received treatment for a major depressive episode was lowest for uninsured Americans, according to the latest Commonwealth Fund scorecard. Such findings contributed to the poor overall U.S. health care outcomes identified in the scorecard.



Source: "National Scorecard on U.S. Health Care System Performance, 2008," Commonwealth Fund, July 2008

Schatzberg Met Disclosure Requirements, Stanford Says

Stanford University says APA President-elect Alan Schatzberg, M.D., has complied with all requirements for financial disclosure regarding financial interests in pharmaceutical companies.

BY MARK MORAN

Stanford University, responding to a request for information from Sen. Charles Grassley (R-Iowa), has said that faculty member and APA President-elect Alan Schatzberg, M.D., has properly complied with its requirements for disclosure regarding his financial interest in a pharmaceutical company he cofounded and consulting fees he earned from other companies.

Grassley's staff later acknowledged that at least one charge leveled against Schatzberg about undisclosed income was in error.

Moreover, the university is "fully aware" of the extent of Schatzberg's interest in Corcept Therapeutics Inc., the company he cofounded, and has "managed the conflict of interest to ensure that it did not influence the research he was conducting," the university said.

(According to the company's Web site at <www.corcept.com>, Corcept is engaged in development of medications for treatment of severe psychiatric and metabolic diseases believed to result from, or be negatively affected by, prolonged exposure to elevated cortisol. Schatzberg is chair of the company's scientific advisors, according to the Web site.)

The allegations and request for information made by Grassley—who is the ranking Republican member of the Senate Finance Committee—is part of a number of investigations he has launched into relationships between medicine and the pharmaceutical industry. These include requests for information from APA and at least two other physician organizations (see page 1).

In a letter to Stanford University President John Hennessy, and in comments on the Senate floor published in the June 23 *Congressional Record*, Grassley alleged that Johnson and Johnson reported paying Schatzberg $22,000 in 2002 and that in 2004 Eli Lilly reported paying him $52,000—but that neither of these payments appeared in disclosure statements made by Schatzberg.

But Stanford responded in a public statement two days later that in fact both earnings *were* reported; in the first case, the discrepancy appeared because the $22,000 was reported by Schatzberg as coming from Janssen, which is the wholly owned subsidiary of Johnson and Johnson that made the payment.

In the second instance, university documents show that Schatzberg disclosed three sources of compensation from Eli Lilly in 2004: less than $10,000 for an advisory board, $10,000 to $50,000 for consultation, and $10,000 to $50,000 for honoraria. "[S]o, together, this disclosure fully accounts for the 2004 payments from Lilly," according to Stanford.

A further charge by Grassley stated that Schatzberg had not disclosed receiving a payment from Eli Lilly in 2007. "That is simply an error," Stanford said in response. "Dr. Schatzberg did disclose that payment."

Grassley's staff later acknowledged the error, and a press officer for the senator told *Psychiatric News* that a correction would be placed in the *Congressional Record*. (At press time it was not known when that would appear.) When asked whether Grassley found Stanford's response to all of the charges satisfactory, the press officer said that "his investigation is continuing."

She added, "His investigation is not focused solely on Stanford, and it is not focused solely on psychiatry," but that at least 20 other institutions were also receiving requests for information from the senator.

Grassley also charged that Schatzberg did not disclose to the university the true value of his stock holdings in Corcept and did not disclose earnings from a sale of some of the company's stock in 2005.

(An SEC filing shows Schatzberg as owning 2,438,749 shares of Corcept as of March 30, 2007. On July 31, Corcept stock closed at $1.86 a share.)

Again, Stanford refuted Grassley's charge in its statement. In keeping with university requirements, Schatzberg "disclosed in writing his ownership of the Corcept stock and its actual value," the university stated. "As a result, Stanford was fully aware of the value of his stock based on his disclosures to the university."

Moreover, Stanford said the stock sale was publicly disclosed through filings with the Securities and Exchange Commission (SEC).

please see ***Schatzberg*** *on page 24*

Senator

continued from page 1

membership. It read, in part: "[R]ecent public focus on relationships between medicine and the pharmaceutical industry is a challenge for the whole field of medicine. APA fully endorses the concept of transparency in our relationships with pharma and other entities and has been in the forefront of the disclosure process. . . . We are proud of what we do."

Speaking to *Psychiatric News*, Stotland reiterated those points, saying that in the area of monitoring conflicts of interest, "APA is in many ways way ahead of the curve." She especially cited the processes and policies in place for vetting potential appointees to the *DSM-V* Task Force and for monitoring the content of industry-supported symposia at APA meetings.

She also noted that in March the Board of Trustees empanelled a work group charged to review all APA pharmaceutical revenues, sort them into categories, and provide the Board with options for ending pharmaceutical support in each category and the implications for the activities they currently fund.

Publicity Focuses on Psychiatry

Grassley, in his letter to APA, requested that all information be produced in a table detailing pharmaceutical income by year, company name, amount of funding, and reasons the funding was provided. He also asked for a description of "policies for accepting industry funding and whether or not the APA allows companies to place restrictions or provide guidance on how funding will be spent."

A press representative for Grassley told *Psychiatric News* that the senator's investigation was not solely focused on psychiatry. "His focus is on transparency in the relationship between medicine and the pharmaceutical industry," the press officer said.

But in June, one month before Grassley's letter, the *New York Times* featured an article alleging that psychiatric researchers at Harvard Medical School may have failed to properly report drug-industry funding they received.

Also, an analysis by the state's attorney general of pharmaceutical monies given to doctors in Vermont found that among the 100 Vermont physicians receiving the largest amount of money from drug manufacturers, 11 were psychiatrists, and they had received a total of $626,379. That total was greater than the totals for any other group of specialists on the list, according to the attorney general's report. (In 2002, Vermont became the first state in the nation to require pharmaceutical companies to disclose their gifts and cash payments to doctors, hospitals, and other health care providers.)

But Stotland and other APA leaders who spoke with *Psychiatric News* pointed out that though the 11 psychiatrists who were among the top 100 recipients of pharmaceutical funds received the largest total amount of money, it should not be inferred that psychiatrists generally in Vermont or elsewhere were receiving more money than other physicians—as the *New York Times* seemed to report on June 27.

The paper ran a correction on July 3 in which it stated that the average dollar figure the newspaper had reported for psychiatrists receiving pharmaceutical money applied only to the 11 psychiatrists in the top 100, not to all psychiatrists in the state.

"The issues of conflict of interest and relationships with industry transcend all the specialties and are by no means limited to psychiatry," said Paul Appelbaum, M.D., past chair of APA's Council on Psychiatry and Law and a past president of APA.

He added that for some specialties, such as cardiology and orthopedics, the issue of industry collaboration extends beyond pharmaceuticals to devices and technology. "I find it hard to believe that psychiatrists are any more prone to this kind of involvement than other specialties," Appelbaum said.

APA Long Sensitive to Issue

APA leaders who spoke with *Psychiatric News* generally agreed with Stotland that the Association has been diligent about monitoring conflict of interest at the organizational level well in advance of the current intense public scrutiny and that individual problems around conflict of interest are pervasive throughout medicine. (For more information about APA's relationship with the pharmaceutical industry, see "From the President" in the July 18 issue and "APA Enforces Strict Rules to Keep Bias out of CME" in the April 4 issue.)

Michael Jibson, M.D., chair of APA's Committee on Industry Relations, which is responsible for monitoring the content of industry-supported symposia at APA meetings, said APA's efforts in this area are "pretty heroic."

In keeping with requirements by the Accreditation Council on Continuing Medical Education, pharmaceutical companies are not allowed to determine the subjects for symposia—those are decided by the Scientific Program Committee—but can choose only from a menu of subjects if they want to sponsor a session.

Additionally, since 1998 APA has monitored the content of industry-supported symposia at the annual meeting and the Institute on Psychiatric Services through its Resident Monitoring Program. Psychiatry residents attend the symposia and, using guidelines developed by APA's Department of CME and Committee on Commercial Support, monitor the balance in each presentation, disclosure of conflicts of interest by faculty, use of generic vs. brand names, discussion of unapproved or investigational uses, and bias toward the supporting-company's products.

"[The process] is rigorous, and it's unusual to find anything that is objectionable," Jibson told *Psychiatric News*. "We have everything audiotaped so that if a question is raised about someone saying something that was not supported by the general literature, we can go back and review it."

But while APA's policies for monitoring conflict of interest at the organizational level may be advanced, Stotland and others agreed that standards and expectations around conflicts of interest in medicine are evolving as public scrutiny mounts and that further refinements of policy may be needed.

Appelbaum said that some organizations, such as the American Academy of Child and Adolescent Psychiatry, are moving toward developing conflict-of-interest guidelines for individual clinicians.

"There are two separate loci for monitoring clinicians in this area," he said. "One is at the medical school and hospital, where there is the greatest potential for overseeing relationships. The other is at the level of professional organizations like APA, which obviously have less leverage in terms of regulation but can certainly develop guidelines for their members. It may be appropriate for APA to do that as well," he said.

The report on Vermont physicians is posted at <www.atg.state.vt.us>. ■

Untreated Chronic Illness Blamed for High Mortality

Early mortality among people with serious mental illness can be prevented if primary care and mental health professionals take equal responsibility in caring for these patients.

BY RICH DALY

Contrary to what may be a popular belief, a person with serious mental illness is more likely to die of a heart attack or complications from diabetes than by suicide.

Misperceptions about the health care needs of people with mental illness extend even to health care professionals, which may be one of the reasons such patients are dying prematurely—25 to 30 years earlier than other Americans, according to federal health statistics. This gap in life expectancy is an increase from the 10- to 15-year mortality difference in the early 1990s between individuals with mental illness and others.

To reverse this trend, advocates for people with mental illness recently called for federal intervention, including improving the tracking of these individuals' physical and mental health; removing obstacles to their receiving quality, integrated physical and mental health care; and encouraging primary care providers to work in close proximity in the same facility with mental health clinicians to improve provision of that care.

"We have to get past the point of psychiatrists saying 'I don't do that internal medicine stuff,' and internists saying 'I don't want to take all of the time that people with mental illness need,'" said Joe Parks, M.D., medical director of psychiatric services for the Missouri Department of Mental Health.

Parks and other mental health experts briefed congressional staff in June on the need for federal efforts to reverse the declining life expectancy for people with serious mental illness. The briefing was organized by the Senate Mental Health Caucus.

It was Park's 2007 report that identified the lower life expectancy of people with serious mental illness compared with the general population and that dispelled the "suicide" stereotype behind the early deaths. Early deaths, Parks said, were largely due to untreated or undertreated nonmental chronic health conditions. Among the leading preventable medical conditions driving the increased morbidity and mortality in this population were metabolic disorders, cardiovascular disease, and diabetes mellitus.

Park's research also found a high prevalence of modifiable risk factors, including obesity and smoking. Cigarette use, he noted, is so widespread among people with serious mental illness that they now smoke about 44 percent of all cigarettes sold in the United States. "We really need to focus on smoking because it is a big opportunity" to prevent disease and death, Parks said.

The prevalence of risk factors among people with serious mental illness is exacerbated by poor health care access among this population and by the stigma they face—even from medical professionals, according to a consensus of the literature.

Similar health disparities exist even in populations with broad access to health care, such as veterans, said Barbara Mauer, a health care consultant in Seattle. Mauer, who has studied the issue, blamed both the negative attitudes of health care providers toward mental illness and a failure to educate patients to seek both needed mental and primary health care.

Research studies designed to address disparities between mental health care and general health care have found health improvements when nurse case managers coordinate both mental and physical care for each patient, while educating and giving patients new skills to better manage their own illnesses.

Analysis of one nurse case manager pilot program found that medical problems were newly detected by staff in one-third of participating patients taken to a mental health facility for evaluation and treatment. At the same time, there was an increase in disease-prevention health care provided to these patients.

Another pilot program approached the challenge of split—and therefore fragmented—mental and general health care from the behavioral health care side by placing nurse practitioners in mental health clinics. In one such program in Massachusetts, the nurse practitioners ensured that the mental health patients also received general health care services.

A Colorado pilot program that is addressing health care providers' negative attitudes toward mental illness and improv-

please see ***Mortality*** *on page 24*

Competence Ruling's Impact Could Be Far Reaching

The Supreme Court ruling on competence standards could have implications for other areas of the law and for government interactions with people who have a mental illness.

BY RICH DALY

A recent Supreme Court ruling that allows state courts to limit legal self-representation by people with mental illness strengthens their legal protections, contrary to the conclusions of some media reports of the case, according to forensic psychiatry experts.

In the case *State of Indiana v. Ahmad Edwards*, the Supreme Court ruled that a defendant with mental illness who has been deemed competent to stand trial is not then automatically competent to represent himself or herself (*Psychiatric News*, July 18). Courts can set stricter standards for defendants who want to act as their own attorney.

Some media accounts of the ruling and the dissenting opinion of two justices described the establishment of a separate standard of competency for self-representation for people with mental illness as a loss of rights. Experts in mental health law disagree.

"This represents a further protection that [ensures] those with mental illnesses would not necessarily be disadvantaged in a criminal proceeding," said Patricia Recupero, M.D., J.D., chair of APA's Council on Psychiatry and Law.

The decision overturned a ruling by the Indiana Supreme Court that had found that a man with schizophrenia was entitled to a new trial on a charge of attempted murder, because the trial judge had improperly denied his request to represent himself. The defendant, Ahmad Edwards, appeared alternately coherent and markedly incoherent during the court proceedings over charges that he fired a gun at a department store security officer while trying to steal a pair of shoes. The bullet injured a bystander.

Edwards had wanted to act as his own attorney, while his trial judge insisted on putting a defense attorney in charge of his case because of Edwards' diagnosed psychosis. The decision by the lower court followed the finding of mental health expert witnesses that Edwards was competent to stand trial after two psychiatric hospitalizations in the three years between the shooting and the trial.

Ruling Promotes Trial Fairness

"We see it as essentially protecting the rights of persons with disability to have a fair trial," Recupero said.

The Court's ruling cited a brief by APA and the American Academy of Psychiatry and the Law and quoted a passage on the practical impact of serious mental illness on higher level mental functioning.

The Court made an appropriate decision, according to Howard Zonana, M.D., a forensic psychiatrist at Yale and a member of APA's Council on Psychiatry and Law. He noted that court-appointed mental health evaluators already include in their competency reports an assessment of mental ability when defendants want to represent themselves.

"Some people are marginal in that they can work with an attorney, but if you leave them all on their own, it's a whole other ball game," Zonana said.

The decision is consistent with earlier high-court rulings, including the 1975 case *Faretta v. California*, which established self-representation as a basic constitutional right, Recupero said, because it reaffirms the right to represent oneself but clarifies that defendants may now be required to show a level of competence that will allow them to do so. Mental competence is required for the legal system to provide a fair trial because it is an adversarial system that pits "two competent adversaries" against each other in an effort to find the truth, she said.

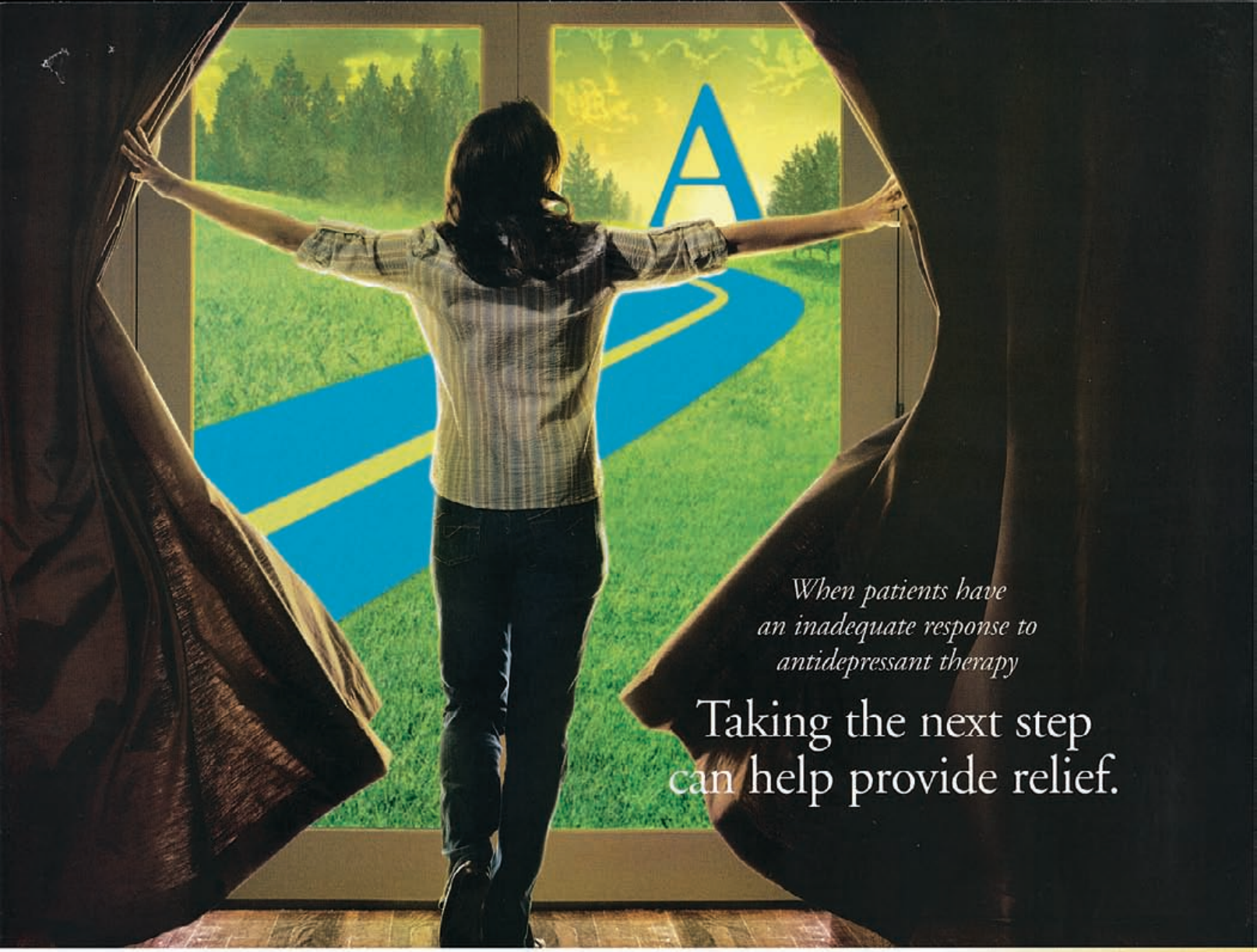
The ruling stood out as one of the better decisions the justices have made for people with mental illness in recent years, said Paul Appelbaum, M.D., past chair of APA's Council on Psychiatry and Law and a former APA president.

"Sometimes this court and other courts have treated people with mental illness as if they had focal impairments but were otherwise rational and capable," Appelbaum said. "That's not what happened here. The justices truly recognized the tremendous impact that a severe mental disorder can have."

Additional Impact Described

Critics of the ruling said it will likely have unintended consequences, such as lower-court judges' frequently appointing

please see ***Competence*** *on page 16*



The **first and only** adjunctive therapy to antidepressants for Major Depressive Disorder in adults.[1]

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

HELP ILLUMINATE THE PERSON WITHIN

ABILIFY is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults.

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. ABILIFY is not approved for use in pediatric patients with depression (see Boxed WARNING).

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

www.abilify.com

IMPORTANT SAFETY INFORMATION and INDICATION for ABILIFY® (aripiprazole)

INDICATION

- ABILIFY (aripiprazole) is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults

IMPORTANT SAFETY INFORMATION

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis and Suicidality and Antidepressant Drugs

See Full Prescribing Information for complete boxed warning

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. ABILIFY is not approved for use in pediatric patients with depression.

Contraindication–Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke–Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY.

Neuroleptic Malignant Syndrome (NMS)–As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation is recommended.

Tardive Dyskinesia (TD)–The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely.

Hyperglycemia and Diabetes Mellitus–Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be monitored 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 should also undergo fasting blood glucose testing. There have been few reports of hyperglycemia with ABILIFY.

Orthostatic Hypotension–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.

Seizures/Convulsions–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.

Potential for Cognitive and Motor Impairment–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.

Body Temperature Regulation–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.

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

Dysphagia–Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY; use caution in patients at risk for aspiration pneumonia.

Physicians should advise patients to avoid alcohol while taking ABILIFY.

Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly, except when used as adjunctive treatment with antidepressants in adults with MDD.

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly.

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo for adjunctive ABILIFY vs adjunctive placebo, respectively):

- Adult patients (with Major Depressive Disorder): akathisia (25% vs 4%), restlessness (12% vs 2%), insomnia (8% vs 2%), constipation (5% vs 2%), fatigue (8% vs 4%), and blurred vision (6% vs 1%)

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Reference:

1. *PDR® Electronic Library™* (n.d.). Greenwood Village, CO: Thomson Micromedex. http://www.thomsonhc.com. Accessed October 16, 2007.

Please see BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION, including **Boxed WARNINGS**, on adjacent pages.

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

Bristol-Myers Squibb | Otsuka Otsuka America Pharmaceutical, Inc.

570US08AB16201 May 2008 0308A-1030 Printed in USA Printed on recycled paper.

HELP ILLUMINATE THE PERSON WITHIN

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

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

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS

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. ABILIFY is not approved for the treatment of patients with dementia-related psychosis *[see WARNINGS AND PRECAUTIONS]*.

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. ABILIFY is not approved for use in pediatric patients with depression *[see WARNINGS AND PRECAUTIONS]*.

INDICATIONS AND USAGE

ABILIFY (aripiprazole) is indicated for use as an adjunctive treatment to antidepressants for Major Depressive Disorder in adults *[see CLINICAL STUDIES (14.3) in Full Prescribing Information]*.

CONTRAINDICATIONS: Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis *[see ADVERSE REACTIONS]*.

WARNINGS AND PRECAUTIONS: Use in Elderly Patients with Dementia-Related Psychosis - Increased Mortality: 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]*.

Cerebrovascular Adverse Events, Including Stroke: 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 (eg, 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]*.

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 lethargy (placebo 2%, aripiprazole 5%), somnolence (including sedation) (placebo 3%, aripiprazole 8%), and incontinence (primarily, 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]*.

Clinical Worsening of Depression 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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with Major Depressive Disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) were reported as: **Increases compared to placebo:** <18 (14 additional cases); 18-24 (5 additional cases); and **Decreases compared to placebo:** 25-64 (1 fewer case); ≥65 (6 fewer cases)

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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 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 ABILIFY should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 ABILIFY is not approved for use in treating depression in the pediatric population.

Neuroleptic Malignant Syndrome (NMS) - A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the 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 (eg, pneumonia, systemic infection) 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 (aripiprazole) 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.

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 *[see ADVERSE REACTIONS]*. 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 (eg, 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.

Orthostatic Hypotension - Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral ABILIFY (n=1894) included (aripiprazole incidence, placebo incidence): orthostatic hypotension (1.2%, 0.3%), postural dizziness (0.6%, 0.4%), and syncope (0.6%, 0.5%).

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).

Seizures/Convulsions - In short-term, placebo-controlled trials, seizures/convulsions occurred in 0.2% (3/1894) of adult patients treated with oral aripiprazole. 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, eg, 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 - ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=1894) treated with oral ABILIFY (11%, 7%). Despite the relatively modest increased incidence of these events compared to placebo, 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, (eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see ADVERSE REACTIONS]*.

Suicide - The possibility of a suicide attempt is inherent in psychotic illnesses, Bipolar Disorder, and Major Depressive 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 *[see ADVERSE REACTIONS]*.

In two 6-week placebo-controlled studies of aripiprazole as adjunctive treatment of Major Depressive Disorder, the incidences of suicidal ideation and suicide attempts were 0% (0/371) for aripiprazole and 0.5% (2/366) for placebo.

Dysphagia - Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. 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 WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS]*.

Use in Patients with Concomitant Illness - Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited *[see USE IN SPECIFIC POPULATIONS]*. 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 *[see WARNINGS AND PRECAUTIONS]*.

ADVERSE REACTIONS: Overall Adverse Reactions Profile - The following are discussed in more detail in other sections of the labeling *[see Boxed WARNING and WARNINGS AND PRECAUTIONS]*: Use in Elderly Patients with Dementia-Related Psychosis; Clinical Worsening of Depression and Suicide Risk; Neuroleptic Malignant Syndrome (NMS); Tardive Dyskinesia; Hyperglycemia and Diabetes Mellitus; Orthostatic Hypotension; Seizures/Convulsions; Potential for Cognitive and Motor Impairment; Body Temperature Regulation; Suicide; Dysphagia; Use in Patients with Concomitant Illness.

The most common adverse reactions in adult patients in clinical trials (≥10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.

Aripiprazole has been evaluated for safety in 12,925 adult patients who participated in multiple-dose, clinical trials in Schizophrenia, Bipolar Disorder, Major Depressive Disorder, and Dementia of the Alzheimer's type, and who had approximately 7482 patient-years of exposure to oral aripiprazole. A total of 3338 patients were treated with oral aripiprazole for at least 180 days and 1898 patients treated with oral aripiprazole had at least 1 year of exposure.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience - *Adult Patients Receiving ABILIFY as Adjunctive Treatment of Major Depressive Disorder:* The following findings are based on a pool of two placebo-controlled trials (up to 6 weeks) of patients with Major Depressive Disorder in which aripiprazole was administered at doses of 2 mg to 20 mg as adjunctive treatment to continued antidepressant therapy.

Adverse Reactions Associated with Discontinuation of Treatment: The incidence of discontinuation due to adverse reactions was 6% for adjunctive aripiprazole-treated patients and 2% for adjunctive placebo-treated patients.

Commonly Observed Adverse Reactions: The commonly observed adverse reactions associated with the use of adjunctive aripiprazole in patients with Major Depressive Disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were: akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision.

Less Common Adverse Reactions: The following treatment-emergent reactions reported at an incidence of ≥2%, rounded to the nearest percent, with adjunctive aripiprazole (doses ≥2 mg/day), and at a greater incidence with adjunctive aripiprazole than with adjunctive placebo during short-term (up to 6 weeks), placebo-controlled trials (aripiprazole + ADT n=371, placebo + ADT n=366), respectively, were: akathisia (25%, 4%), restlessness (12%, 2%), fatigue (8%, 4%), insomnia (8%, 2%), somnolence (6%, 4%), upper respiratory tract infection (6%, 4%), blurred vision (6%, 1%), tremor (5%, 4%), constipation (5%, 2%), arthralgia (4%, 3%), dizziness (4%, 2%), sedation (4%, 2%), increased appetite (3%, 2%), weight increased (3%, 2%), disturbance in attention (3%, 1%), feeling jittery (3%, 1%), myalgia (3%, 1%), and extrapyramidal disorder (2%, 0%). ADT= Antidepressant Therapy.

Dose-Related Adverse Reactions:

Extrapyramidal Symptoms: In the short-term, placebo-controlled trials in Major Depressive Disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for adjunctive aripiprazole-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 25% vs. 4% for adjunctive placebo-treated patients. 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 Major Depressive Disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.31; placebo, 0.03 and aripiprazole, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive aripiprazole and adjunctive placebo groups.

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities: In the 6-week trials of aripiprazole as adjunctive therapy for Major Depressive Disorder, there were no clinically important differences between the adjunctive aripiprazole-treated and adjunctive placebo-treated patients in the median change from baseline in prolactin, fasting glucose, HDL, LDL, or total cholesterol measurements. The median % change from baseline in triglycerides was 5% for adjunctive aripiprazole-treated patients vs. 0% for adjunctive placebo-treated patients.

Weight Gain: In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive aripiprazole or placebo in addition to their ongoing antidepressant treatment. The mean weight gain with adjunctive aripiprazole was 1.7 kg vs. 0.4 kg with adjunctive placebo. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was 5% with adjunctive aripiprazole compared to 1% with adjunctive placebo.

ECG Changes: Between group comparisons for a pooled analysis of placebo-controlled trials in patients with Major Depressive Disorder revealed no significant differences between oral 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 3 beats per minute compared to no increase among placebo patients.

Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole: Following is a list of MedDRA terms that reflect adverse reactions as defined in *ADVERSE REACTIONS* reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 12,925 adult patients, oral aripiprazole excluding those events already listed as adverse reactions in other parts of Full Prescribing Information, or those considered in *WARNINGS AND PRECAUTIONS*. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Adults: Oral Administration - *Blood and Lymphatic System Disorders:* ≥ *1/1000 patients and <1/100 patients* - leukopenia, neutropenia; *<1/1000 patients* - thrombocytopenia, agranulocytosis, idiopathic thrombocytopenic purpura; *Cardiac Disorders:* ≥ *1/1000 patients and <1/100 patients* - cardiopulmonary failure, bradycardia, cardio-respiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, bundle branch block; *<1/1000 patients* - atrial flutter, ventricular tachycardia, complete atrioventricular block, supraventricular tachycardia; *Eye Disorders:* ≥ *1/1000 patients and <1/100 patients* - eyelid edema, photophobia, diplopia, photopsia; *<1/1000 patients* - excessive blinking; *Gastrointestinal Disorders:* ≥ *1/1000 patients and <1/100 patients* - dysphagia, gastroesophageal reflux disease, gastrointestinal hemorrhage, swollen tongue, ulcer, esophagitis, angioedema; *<1/1000 patients* - pancreatitis; *General Disorders and Administration Site Conditions:* ≥ *1/100 patients* - asthenia; ≥ *1/1000 patients and <1/100 patients* - mobility decreased, face edema; *<1/1000 patients* - hypothermia; *Hepatobiliary Disorders:* ≥ *1/1000 patients and <1/100 patients* - cholecystitis, cholelithiasis; *<1/1000 patients* - hepatitis, jaundice; *Injury, Poisoning, and Procedural Complications:* ≥ *1/100 patients* - fall; ≥ *1/1000 patients and <1/100 patients* - self mutilation; *<1/1000 patients* - heat stroke; *Investigations:* ≥ *1/100 patients* - creatine phosphokinase increased, ≥ *1/1000 patients and <1/100 patients* - hepatic enzyme increased, blood urea increased, blood bilirubin increased, blood creatinine increased, electrocardiogram QT corrected interval prolonged, blood prolactin increased; *<1/1000 patients* - blood lactate dehydrogenase increased, glycosylated hemoglobin increased, GGT increased; *Metabolism and Nutrition Disorders:* ≥ *1/1000 patients and <1/100 patients* - anorexia, hyperlipidemia; *Musculoskeletal and Connective Tissue Disorders:* ≥ *1/100 patients* - muscle spasms; ≥ *1/1000 patients and <1/100 patients* - muscle rigidity; *<1/1000 patients* - rhabdomyolysis; *Nervous System Disorders:* ≥ *1/100 patients* - coordination abnormal; ≥ *1/1000 patients and <1/100 patients* - speech disorder, parkinsonism, cogwheel rigidity, memory impairment, cerebrovascular accident, hypokinesia, tardive dyskinesia, hypotonia, hypertonia, akinesia, myoclonus, bradykinesia; *<1/1000 patients* - Grand Mal convulsion, choreoathetosis; *Psychiatric Disorders:* ≥ *1/100 patients* - agitation, irritability, suicidal ideation; ≥ *1/1000 patients and <1/100 patients* - aggression, loss of libido, libido decreased, hostility, suicide attempt, libido increased, angor, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation; *<1/1000 patients* - psychomotor agitation, premature ejaculation, catatonia, sleep walking; *Renal and Urinary Disorders:* ≥ *1/1000 patients and <1/100 patients* - urinary retention, polyuria, nocturia; *Reproductive System and Breast Disorders:* ≥ *1/1000 patients and <1/100 patients* - erectile dysfunction, amenorrhea, menstruation irregular, breast pain; *<1/1000 patients* - gynaecomastia, priapism, galactorrhea; *Respiratory, Thoracic, and Mediastinal Disorders:* ≥ *1/100 patients* - dyspnea; ≥ *1/1000 patients and <1/100 patients* - pneumonia aspiration, respiratory distress; *<1/1000 patients* - pulmonary embolism, asphyxia; *Skin and Subcutaneous Tissue Disorders:* ≥ *1/100 patients* - hyperhydrosis; ≥ *1/1000 patients and <1/100 patients* - erythema, pruritus, ecchymosis, face edema, photosensitivity reaction, alopecia, urticaria; *Vascular Disorders:* ≥ *1/1000 patients and <1/100 patients* - hypotension, deep vein thrombosis, phlebitis; *<1/1000 patients* - shock, thrombophlebitis

Postmarketing Experience - The following adverse reactions have been identified during post-approval use of ABILIFY (aripiprazole). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

DRUG INTERACTIONS: Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally-acting drugs or alcohol.

Due to its alpha adrenergic 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 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole and Other CYP3A4 Inhibitors: 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 ketoconazole is given concomitantly with aripiprazole, the 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; moderate inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.

Quinidine and Other CYP2D6 Inhibitors: 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 quinidine is given concomitantly with aripiprazole. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and should lead to similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased. When adjunctive ABILIFY is administered to patients with Major Depressive Disorder, ABILIFY should be administered without dosage adjustment as specified in *DOSAGE AND ADMINISTRATION (2.3) in Full Prescribing Information*.

Carbamazepine and Other CYP3A4 Inducers: Coadministration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg/day) 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, the aripiprazole dose should be reduced.

Potential for ABILIFY 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 mg/day 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*.

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.

Drugs Having No Clinically Important Interactions with ABILIFY - Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40 mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate: When valproate (500 mg/day-1500 mg/day) and aripiprazole (30 mg/day) were coadministered, at steady-state the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

When aripiprazole (30 mg/day) and valproate (1000 mg/day) were coadministered, at steady-state there were no clinically significant changes in the C_{max} or AUC of valproate. No dosage adjustment of valproate is required when administered concomitantly with aripiprazole.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200 mg/day-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Coadministration of aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically significant changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with aripiprazole.

Dextromethorphan: Aripiprazole at doses of 10 mg/day to 30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphinan, a pathway dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin: Aripiprazole 10 mg/day for 14 days had no effect on the pharmacokinetics of R-warfarin and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole: Aripiprazole 10 mg/day for 15 days had no effect on the pharmacokinetics of a single 20 mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

Lorazepam: Coadministration of lorazepam injection (2 mg) and aripiprazole injection (15 mg) to healthy subjects (n=40: 35 males and 5 females; ages 19-45 years old) did not result in clinically important changes in the pharmacokinetics of either drug. No dosage adjustment of aripiprazole is required when administered concomitantly with lorazepam. However, the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone and the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone *[see WARNINGS AND PRECAUTIONS]*.

Escitalopram: Coadministration of 10 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg/day escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required when aripiprazole is added to escitalopram.

Venlafaxine: Coadministration of 10 mg/day to 20 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg/day venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required when aripiprazole is added to venlafaxine.

Fluoxetine, Paroxetine, and Sertraline: A population pharmacokinetic analysis in patients with Major Depressive Disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (37.5 mg/day or 50 mg/day), or sertraline (100 mg/day or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 10% and 36%, respectively and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole. Aripiprazole dosing was 2 mg/day to 15 mg/day (when given with fluoxetine or paroxetine) or 2 mg/day to 20 mg/day (when given with sertraline).

USE IN SPECIFIC POPULATIONS: In general, no dosage adjustment for ABILIFY (aripiprazole) is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function *[see DOSAGE AND ADMINISTRATION (2.5)* in Full Prescribing Information].

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

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 patients with Major Depressive Disorder has not been established.

Geriatric Use - In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS]*.

Of the 12,925 patients treated with oral aripiprazole in clinical trials, 1061 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. The majority (97%) of the 799 patients were diagnosed with Dementia of the Alzheimer's type.

Placebo-controlled studies of oral aripiprazole in Major Depressive Disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment - In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Hepatic Impairment - In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Gender - C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30% to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race - Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking - Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

DRUG ABUSE AND DEPENDENCE - ABILIFY 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. While the clinical trials did not reveal any tendency for any drug-seeking behavior, 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. Patients should be evaluated carefully for a history of drug abuse and closely observed for signs of ABILIFY misuse or abuse.

OVERDOSAGE: 76 cases of deliberate or accidental overdosage with oral aripiprazole alone or in combination with other substances were reported worldwide [44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal)]. Additionally, 10 of these cases were in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities. The largest known acute ingestion was 1080 mg of oral aripiprazole (36 times maximum recommended daily dose) in a patient who fully recovered. Common adverse reactions (reported in at least 5% of all overdose cases) were vomiting, somnolence, and tremor. **For more information on symptoms of overdose, see Full Prescribing Information.**

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 QT 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.

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY: [See Medication Guide in Full Prescribing Information.]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis - Advise patients and caregivers of increased risk of death *[see WARNINGS AND PRECAUTIONS]*.

Clinical Worsening of Depression and Suicide Risk - Alert families and caregivers of patients to monitor for the emergence of agitation, irritability, unusual changes in behavior, suicidality, and other symptoms as described in the *WARNINGS AND PRECAUTIONS* and to report such symptoms immediately. Advise patients and their families and caregivers to read the Medication Guide and assist them in understanding its contents *[see WARNINGS AND PRECAUTIONS]*.

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 *[see WARNINGS AND PRECAUTIONS]*.

Pregnancy - Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY *[see USE IN SPECIFIC POPULATIONS]*.

Nursing - Patients should be advised not to breast-feed an infant if they are taking ABILIFY *[see USE IN SPECIFIC POPULATIONS]*.

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 *[see DRUG INTERACTIONS]*.

Alcohol - Patients should be advised to avoid alcohol while taking ABILIFY *[see DRUG INTERACTIONS]*.

Heat Exposure and Dehydration - Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see WARNINGS AND PRECAUTIONS]*.

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.

Tablets manufactured by Otsuka Pharmaceutical Co, Ltd, Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA. Orally Disintegrating Tablets, Oral Solution, and Injection 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; 6,977,257; and 7,115,587

Bristol-Myers Squibb Otsuka Otsuka America Pharmaceutical, Inc.

Based on: 1239550A1, 0308L-0818 Rev February 2008 D6-B0001A-02-08-MDD

 570US08PBS01401 0308L-0891

Use of Substance Abuse Codes Growing Under Medicaid

The federal effort comes as physicians remain leery of screening for alcohol and/or drug addiction under private insurance, which may result in noncoverage of injuries related to substance use.

BY RICH DALY

Ten states have begun to allow physicians and other clinicians to seek Medicaid reimbursement for the first time for substance abuse screening and brief intervention (SBI). Addiction-treatment advocates said they hope the move expands access to such screening in private insurance as well.

The Centers for Medicare and Medicaid Services (CMS) added two new reimbursement codes for Medicaid claims for addiction screening and for brief-intervention services at the beginning of 2007. By July 2008, 10 states had activated the codes for SBI with Medicaid-eligible patients, according to the White House Office of National Drug Control Policy (ONDCP).

"These states have taken a historic step in transforming substance abuse in the United States," said Bertha Madras, Ph.D., deputy director for demand reduction in the ONDCP, in a written statement "By 'medicalizing' the detection and intervention of substance abuse, the 10 states recognize the need to destigmatize substance abuse and mainstream preventive services into general medical care."

The following nine states have activated the AMA's *Current Procedural Terminology (CPT)* codes or CMS's Healthcare Common Procedure Coding System codes for SBI: Iowa, Maryland, Minnesota, Montana, Oklahoma, Oregon, Tennessee, Virginia, and Washington. In addition, Wisconsin has begun to conduct SBI as part of a comprehensive package of health services for pregnant women.

More states may add SBI to their Medicaid programs later, an ONDCP representative told *Psychiatric News*, because the process for adding services to Medicaid takes longer in some states than others.

Research has shown that SBI activities have been effective in reducing substance abuse, while also saving health care dollars. For example, providing brief alcohol counseling to emergency department patients whose injuries are due to drinking saves hospitals about $330 per patient by reducing return trips for alcohol-related injuries over the following three years, according to an April 2005 study funded by the Robert Wood Johnson Foundation.

SBI an Evidence-Based Intervention

Personalized SBI procedures, according to the White House office, are designed to assess an individual's substance use along a spectrum and provide immediate interventions or referrals if necessary. These procedures can be performed in various locations and settings, including in doctors' offices, trauma centers, emergency departments, prenatal and community health clinics, college campuses, and even on the Internet.

The general applicability and benefits of SBI approaches have convinced policymakers to encourage their use. The U.S. Preventive Services Task Force—an independent panel of experts in primary care and disease prevention that reviews clinical preventive services for the federal government—recommends screening and behavioral-counseling interventions to reduce alcohol misuse by adults, including pregnant women, in primary care settings. In a 2004 review of research, the task force found evidence that screening in primary care settings, for example, can accurately identify patients whose levels or patterns of alcohol consumption do not meet criteria for alcohol dependence, but place them at risk for increased morbidity and mortality. The review also cited data showing that brief behavioral-counseling interventions with follow-up produce small to moderate reductions in alcohol consumption that are sustained over six to 12 months or longer.

Endorsement of SBI by CMS "is important because it gets the public sector to screen where there has not typically been reimbursement for it," said Alexi Greier Horan, director of government relations for the American Society of Addiction Medicine (ASAM), in an interview with *Psychiatric News*.

The society, which provides training to physicians in addiction screening and brief interventions, noted that such practices continue to gain traction in the medical and public health communities, including among many private and public health providers.

At the federal level, CMS initially approved *CPT* codes for SBI under Medicare beginning in January. The Federal Employees Health Benefits Program added coverage of SBI services for most of its beneficiaries in the spring (*Psychiatric News*, May 16).

Most of the largest health insurers, including CIGNA, Aetna, and Blue Cross and Blue Shield, also have added reimbursement for SBI services, Eric Goplerud, Ph.D., director of the Center for Integrated Behavioral Health Policy at George Washington University, told *Psychiatric News*.

Another recent change that has spurred the use of SBI was the 2007 requirement of the American College of Surgeons' Committee on Trauma that trauma centers demonstrate that they perform SBI for alcohol problems.

More widespread use of SBI has been limited by state Uniform Policy Provision Laws (UPPL), which allow insurers to deny claims if accident victims test positive for alcohol or other drugs, according to treatment advocates. Treatment of injuries related to substance abuse can be costly to insurers, say experts, and can run into the hundreds of thousands of dollars. But such laws have the unintended consequence of discouraging hospitals and other facilities from screening patients for addictive disorders.

"It penalizes physicians and hospitals for practicing good medicine," Goplerud said.

Treatment-advocacy organizations, such as ASAM, have worked to repeal UPPL laws in 10 states and the District of Columbia, which they hope will encourage more physicians to use SBI approaches. Thirty other states have UPPL laws, and the remainder never created such measures. Federal legislation sponsored by Rep. Patrick Kennedy (D-R.I.) to repeal all such laws has not advanced far in Congress.

As a result, Greier Horan said, ASAM members continue to be concerned that screening for substance abuse problems may result in private insurers' refusing to cover their patients' injury claims if their injuries are substance related. Any physician hesitancy to perform SBI for patients with SBI-restrictive insurance is worrisome in light of research that has found that drinking plays a major role in many unintentional injuries treated in emergency departments and trauma centers, but few such facilities screen for substance abuse problems.

A challenge on another front is to increase training for physicians and allied health professionals because many do not know how to provide evidence-based screening or brief interventions.

"Just because the codes exist doesn't mean that people know how to provide these services," Greier Horan said.

SBI Use Expected to Expand

A number of additional measures are expected in the near future to expand the use of SBI substantially by public and privately funded health care providers.

The Joint Commission, which accredits and certifies more than 15,000 U.S. health care organizations and programs, is examining the "desirability and feasibility" of SBI accreditation standards for hospitals, ambulatory-care centers, and mental health care providers, according to Goplerud.

In addition, an SBI measure is among the proposed physician pay-for-performance measures that are under consideration by an APA-led group developing mental health incentives for the AMA.

Further SBI usage may be spurred by grants from the Substance Abuse and Mental Health Services Administration aimed at states and medical schools. Those grants, expected to be available this fall, "will really boost interest [in SBI], especially in the medical schools, around the development of curricula on screening and brief intervention," Goplerud said.

Information on CMS's screening and brief intervention codes is posted at <www.whitehousedrugpolicy.gov/publications/pdf/screen_brief_intv.pdf>. ■

Quality

continued from page 5

tal illness. After the crisis is resolved, patients are frequently discharged with no follow-up care. This leaves providers and patients "waiting for another crisis," Schoen said.

The U.S. system could benefit from a move away from crisis mental health management and toward systematic preventative care, which is much more prevalent in other advanced countries.

For children's health, U.S. primary care providers tend to focus almost exclusively on children's physical health and ignore mental health problems that often have a serious impact on their overall health, according to the report.

Only 59 percent of children who needed mental health care received it in 2003, the last year for which data were available, the researchers found. The rate of treatment for mental illness ranged from 63 percent for children with any type of health insurance to only 34 percent for children not covered by insurance.

The scorecard is the latest research to highlight the need for changes to improve health care outcomes for Americans, said Carolyn Clancy, director of the federal Agency for Healthcare Research and Quality, during discussion in July before congressional staff regarding the scorecard. The findings illustrate that the biggest potential for savings can come from better care of chronic conditions, for example, in the 20 percent of Medicare beneficiaries who incur 72 percent of the program's treatment costs.

In the short term, however, "under the current financing system all of the players lose money [if chronic care were to be improved], so there is no incentive for change," Clancy said.

The scorecard's authors called for "bold leadership and commitment" to pursue a whole-system approach that would improve access, quality, and efficiency simultaneously. The specific steps to improving care would include a universal and well-designed coverage plan that would allow affordable access and continuity of care with low administrative expenses. Such a system would need to be organized around the patient and not around providers or insurers, as is the case in the current system.

"To secure a healthy nation, we need to come together around plans and policies that can improve health outcomes," Schoen emphasized.

The "National Scorecard on U.S. Health System Performance, 2008" is posted at <www.commonwealthfund.org/publications/publications_show.htm?doc_id=692682>. ■

government news

Young Adults Falling Into Treatment Gap

New federal initiatives aim to transition young adults with serious mental illness from treatment to productive roles in society.

BY RICH DALY

The obligation that society has felt toward children with serious mental illness has resulted in widespread state and federal programs and substantial funding to treat mental illness and provide other services to minors. But after the youth turn 18, many are left on their own.

A new effort aims to provide better support to young adults with serious mental illness. In June federal legislators introduced measures (HR 7375 and S 3195) to bolster state efforts to help young people with serious mental illness better handle the transition from childhood to adulthood.

"Too many young adults with mental illness are falling through the cracks of our fragmented mental health system," said Rep. Pete Stark (D-Calif.) in a written statement. "We have an obligation to these youth to provide appropriate and effective treatment and supports so that they can make the transition to independent and successful adults."

Introduction of the legislation followed the release of a Government Accountability Office (GAO) report in June that noted that at least 2.4 million young adults aged 18 through 26—or 6.5 percent of noninstitutionalized young adults in that age range—had a serious mental illness in 2006. The GAO also found that this group had less education and a higher rate of unemployment on average than young adults without serious mental illness.

The report used the federal definition of serious mental illness: "a diagnosable mental, behavioral, or emotional disorder of sufficient duration to meet diagnostic criteria specified within *DSM-III-R*, which resulted in functional impairment that substantially interferes with or limits one or more major life activities."

The actual number of young adults with serious mental illness is likely higher because the estimate did not include homeless, institutionalized, or incarcerated youth.

"Under the best of circumstances, the transition years from adolescence to adulthood are rarely easy," said Michael Fitzpatrick, executive director of the National Alliance on Mental Illness, in a statement about the report. "They are infinitely harder for young adults, ages 18 to 26, who live with illnesses such as schizophrenia and bipolar disorder."

The report also noted that among seriously mentally ill youth, nearly 90 percent had more than one mental disorder. About 186,000 young adults received Social Security Administration disability benefits in 2006 because of a mental illness that prevented them from engaging in substantial, gainful activity.

The difficulty in their transitioning to adulthood, according to the report, stems from the lack of available supports, including mental health care, employment, and housing services, which are not always suited to young adults with mental illness. This group also can find it difficult to qualify for adult programs that provide or pay for mental health services, which then results in disrupted treatment and worsening health.

The many young adults with multiple conditions are further challenged by the difficulty of "navigating multiple discrete programs that address varied needs," according to the GAO report.

Sen. Gordon Smith (R-Ore.) noted that young adulthood is especially difficult for people with mental illness who are trying to juggle increasing responsibilities while seeking mental health care.

"My son Garrett struggled with his transition to adulthood and in his ability to access the help he needed during this critical time," Smith said about his son, who committed suicide at age 21 in 2003. "These young adults deserve our attention, our support, and our compassion."

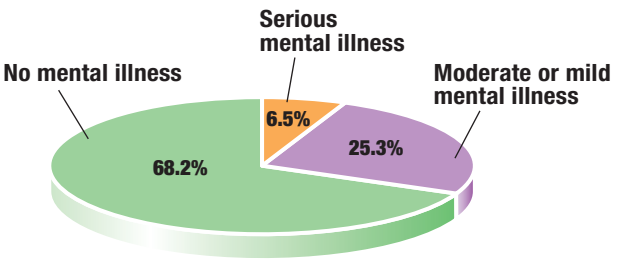
The GAO found that states provide varying levels of supports to these young adults. Among the better efforts are programs that integrate mental health treatment with employment and other services. To varying degrees, states manage to find their own and federal funding to coordinate services across multiple agencies for this population and involve young adults and their families in developing policies and aligning supports.

Past federal efforts to assist young adults with serious mental illness have included support of state demonstration projects, technical assistance, and research. Federal agencies also have established bodies to

please see ***Young Adults*** *on page 23*

Mentally Ill Youth Need Help To Transition to Adulthood

Mental health advocates say that more needs to be done to help the estimated 2.4 million young adults with a serious mental illness overcome their illness and become productive members of society. A recent report from the Government Accountability Office found a high rate of mental illness among people aged 18 to 26.



Source: "Young Adults With Serious Mental Illness," GAO, June 2008

Misunderstanding Defines Most Americans' View of Schizophrenia

Services and support are seriously lacking for people with schizophrenia and their caregivers, according to the results of a recent NAMI poll.

BY EVE BENDER

Schizophrenia is an oft-misunderstood disorder that remains shrouded in mystery, according to the results of a poll released by the National Alliance on Mental Illness (NAMI) in June.

The survey, titled "Schizophrenia: Public Attitudes, Personal Needs: Views From People Living With Schizophrenia, Caregivers, and the General Public," examined attitudes about the disorder from the perspectives of those who have firsthand knowledge of the illness as well as the general public.

NAMI contracted with Harris Interactive to conduct the poll in February among 258 people living with schizophrenia and 250 caregivers selected from a group of about 9,000 people who are registered with NAMI's Web site. The 508 respondents agreed via e-mail to complete the survey.

Representatives from Harris Interactive also polled approximately 1,000 members of the public in February. Those surveyed agreed to be on Harris's online research panel, a database of several million people who have agreed to participate in online research projects on a number of topics.

"[Americans] know schizophrenia is a medical illness affecting the brain, but it is largely misunderstood," said NAMI Executive Director Michael Fitzpatrick in a press release announcing the results. "There are gaps in knowledge and access to treatment."

In addition, less than half of those polled (46 percent) replied that they would tell a friend if they had been diagnosed with schizophrenia. Some findings on attitudes hinged on whether the person with schizophrenia was receiving treatment.

For instance, 77 percent of those surveyed reported being uncomfortable working with a person with schizophrenia who has not received treatment compared with 24 percent who would feel uncomfortable if the person with schizophrenia was receiving treatment.

Slightly more than 70 percent of those surveyed would be afraid for their own safety around a person who has not received treatment for schizophrenia, and 21 percent would be afraid for their own safety around a person who had been treated for the disorder, according to the results.

Misconceptions Mar Public Attitudes

According to the results, there are some prominent misconceptions about the nature of schizophrenia among the public: for instance, 64 percent of those polled believed that "split or multiple personalities" are a symptom of schizophrenia. However, symptoms such as drug or alcohol abuse, insomnia, or disorganized speech were not widely recognized.

About 60 percent of those polled also believed that violent behavior is a symptom of schizophrenia.

For the most part, people polled understood that schizophrenia is a medical illness (85 percent) and that with treatment, people who have schizophrenia can lead independent lives (79 percent).

Basic Supports Wanted

The survey also characterized certain aspects of the lives of those living with schizophrenia—among consumers polled, there was an average of 8.5 years between experiencing the first symptoms of schizophrenia and being diagnosed with schizophrenia.

According to the results, lack of services was a critical problem. Only 29 percent of those surveyed reported receiving vocational rehabilitation, 20 percent received job-placement assistance, and 17 percent were provided with public housing.

More than a third (39 percent) of people with schizophrenia said that their diagnosis made it more difficult to access health care for medical problems. The majority reported that crisis care (92 percent), hospital beds (83 percent), assertive community treatment (77 percent), and care managers (76 percent) were helpful services.

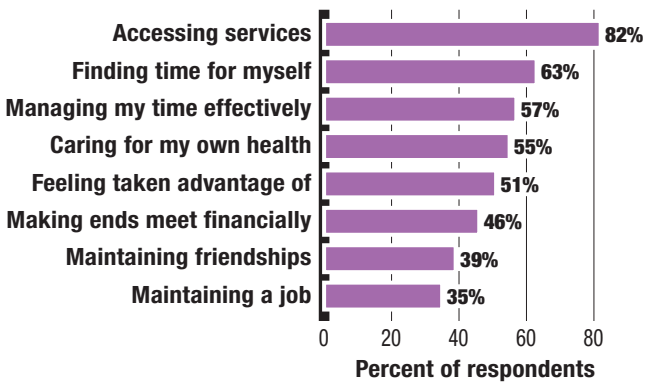
Caregivers Acknowledge Barriers

Caregivers responding to questions about people with schizophrenia were most often parents of the affected individuals (68 percent). Siblings comprised 12 percent of caregivers, and spouses or significant others 7 percent.

please see ***Schizophrenia*** *on page 23*

Caregivers Face Many Hardships

In a survey of 250 caregivers of people with schizophrenia, the majority reported having problems accessing mental health and social services that are crucial to recovery. The survey was conducted by Harris Interactive for the National Alliance on Mental Illness.



Source: "Schizophrenia: Public Attitudes, Personal Needs," NAMI, 2008

Fiscal Issues Prominent At July Board Meeting

APA Trustees vote to increase annual meeting fees amid concerns that the budget surpluses of the past few years are at an end. APA annual dues, however, will increase only for Canadian members.

BY KEN HAUSMAN

APA's finances were in the spotlight at the July meeting of the Board of Trustees in Chicago. At this early point in the year, APA is facing a potential year-end deficit of approximately $452,000, after many years of budget surpluses.

As pointed out by Secretary-Treasurer David Fassler, M.D., and Finance and Budget Committee Chair Jack Bonner, M.D., this year's budget projections may not be met in large part because of a major drop in pharmaceutical advertising in APA publications and higher than expected costs and lower than expected income from the annual meeting—these are among the major sources of income for APA. APA Medical Director James H. Scully Jr., M.D., said that there are contingency plans in place if such a deficit does exist at the end of the year.

Bonner introduced four finance-related items developed by his committee, all of which the Board passed.

The first of these actions was an increase in the rates for lump-sum dues payments, an option by which members make one payment and are then exempt from paying future dues to APA. The lump-sum amount has not changed in 15 years. About 155 members have taken advantage of the program. The rates vary by age (see table).

The second proposal the Board approved is to implement small increases in member and nonmember annual meeting course fees. Advance course registration fees will increase by $14 or $15.

In addition, the Board voted to increase registration fees for the 2009 annual meeting in San Francisco. For members, the fee will increase by $10 to $280 for advance and by $5 to $350 for on-site registration. Member-in-training registration fees will increase by $5 for both advance and on-site registration to $80 and $90, respectively. Nonmember fees were also increased.

Finally, the Board voted to increase block grants to district branches and state associations from the Board New Initiative Fund.

On a recommendation from the Membership Committee, the Board increased annual dues for Canadian members from $300 to $330. Canadians have for several years paid lower dues than U.S. members, because they benefit from fewer of the services APA provides, particularly advocacy on legislative and regulatory issues. In addition, the Canadian dollar has traditionally been worth less than the U.S. dollar, but with the latter's steady loss of value over the last few years, the two currencies are now at par.

In other actions the Board voted to

- appoint a work group to **review APA grants to district branches (DBs) and state associations** that are used to support advocacy and infrastructure improvements. Among factors to be reviewed are DB size, DB dues revenues and other member assessments, frequency with which DBs request APA grants, and how best to distinguish between advocacy and infrastructure grants.
- **add primary care initiatives to the list of priority topics for which competitive grants can be awarded** to DBs. These grants are administered by the Council on Member and District Branch Relations.
- **approve an updated edition of the Practice Guideline for the Treatment of Patients With Panic Disorder**, is scheduled to appear in the January 2009 issue of the *American Journal of Psychiatry*.
- **increase the duration of member-in-training status from six to nine years.** This reflects the fact that some residents now take consecutive fellowships in subspecialties or complete them part time.
- **endorse the Psychosomatic Medicine Core Competencies Outline** of the American Board of Psychiatry and Neurology. The competencies are divided into six topics: application of knowledge in the clinical setting, the fund of knowledge including conceptual theory and scientific literature, interpersonal and communication skills, ability to apply daily clinical practice to one's own learning, professionalism, and systems-based practice.

In addition, the Trustees heard from several speakers. Sue Bergeron, CEO of the Depression and Bipolar Support Alliance (DBSA), emphasized the consumer-led group's broad scope, with more than 1,000 groups in all 50 states. She noted that the group distributes more than 1 million brochures a year, all written in a "patient-friendly" style. The DBSA also offers several "scientifically based recovery tools," she pointed out. About 99 percent of what the group produces is free, since many of its members are on disability or can't afford to buy them, she noted.

please see ***Board*** *on page 22*

Board Increases Lump-Sum Dues

For the last 15 years APA members have had the option of making a lump-sum payment to cover their lifetime dues. The Board voted last month to increase the amounts for the first time since the program was introduced. The table shows the current and future amounts.

Age	Current lump-sum amount	Revised lump-sum amount
30-34	$11,000	$12,000
35-39	11,000	12,000
40-44	10,000	11,500
45-49	9,000	10,000
50-54	8,000	9,000
55-59	7,000	7,500
Non-life status		
60-64	5,000	5,500
65-69	3,500	4,000
70+	2,000	3,500
Life status		
60+	3,000	5,000

Congress Benefits From Psychiatrist in Its Midst

One psychiatrist gets an insider's view of how Congress crafts and passes legislation and vows to use this knowledge to be a forceful advocate for mental health issues in the future.

BY KEN HAUSMAN

Psychiatrist Daniel Bober, D.O., has had an experience of which only a handful of his colleagues can boast.

Invited to join the staff of U.S. Sen. Patty Murray (D-Wash.), Bober has been able to contribute directly to the development and advancement of mental health legislation as a Capitol Hill insider.

Bober completed a 10-month stint as APA's 2008 Jeanne Spurlock Congressional Fellow earlier this year. The fellowship, now in its sixth year, provides an opportunity for residents and early career psychiatrists in the areas of child and/or minority mental health to learn about the legislative and public-policy processes from the inside, with the goal of preparing them to be mental health advocates in the future. Bober completed a residency in child and adolescent psychiatry at the Yale Child Study Center and a forensic psychiatry fellowship at the University of Massachusetts.

Credit: U.S. Senate Photography Service

Sen. Patty Murray (D-Wash.) and 2008 Jeanne Spurlock Congressional Fellow Daniel Bober, D.O.

Murray serves on several committees that have jurisdiction over health issues, including the ones that are responsible for the mental health parity bill and veterans' health concerns. Bober praised Murray as "a true champion of veterans and people with mental illness and, by virtue of her committee assignments, is able to put her interests in mental health to direct use." He added that her positions on mental health issues made it easy for him to contribute his clinical training, experience, and knowledge.

A particularly rewarding part of his Senate experience, he said, was meeting veterans of the Iraq and Afghanistan wars, as well as their families, at Walter Reed Army Medical Center, where many of the most seriously injured combat veterans are sent. Bober noted that he was able to help Murray and her staff interpret numerous studies of veterans' mental health and discuss sequelae of serving in a war zone. In addition, he said, after meeting with veterans' service organizations and veterans' families, he was better able to "more clearly define the legislative priorities that we should focus on when trying to help veterans and their families."

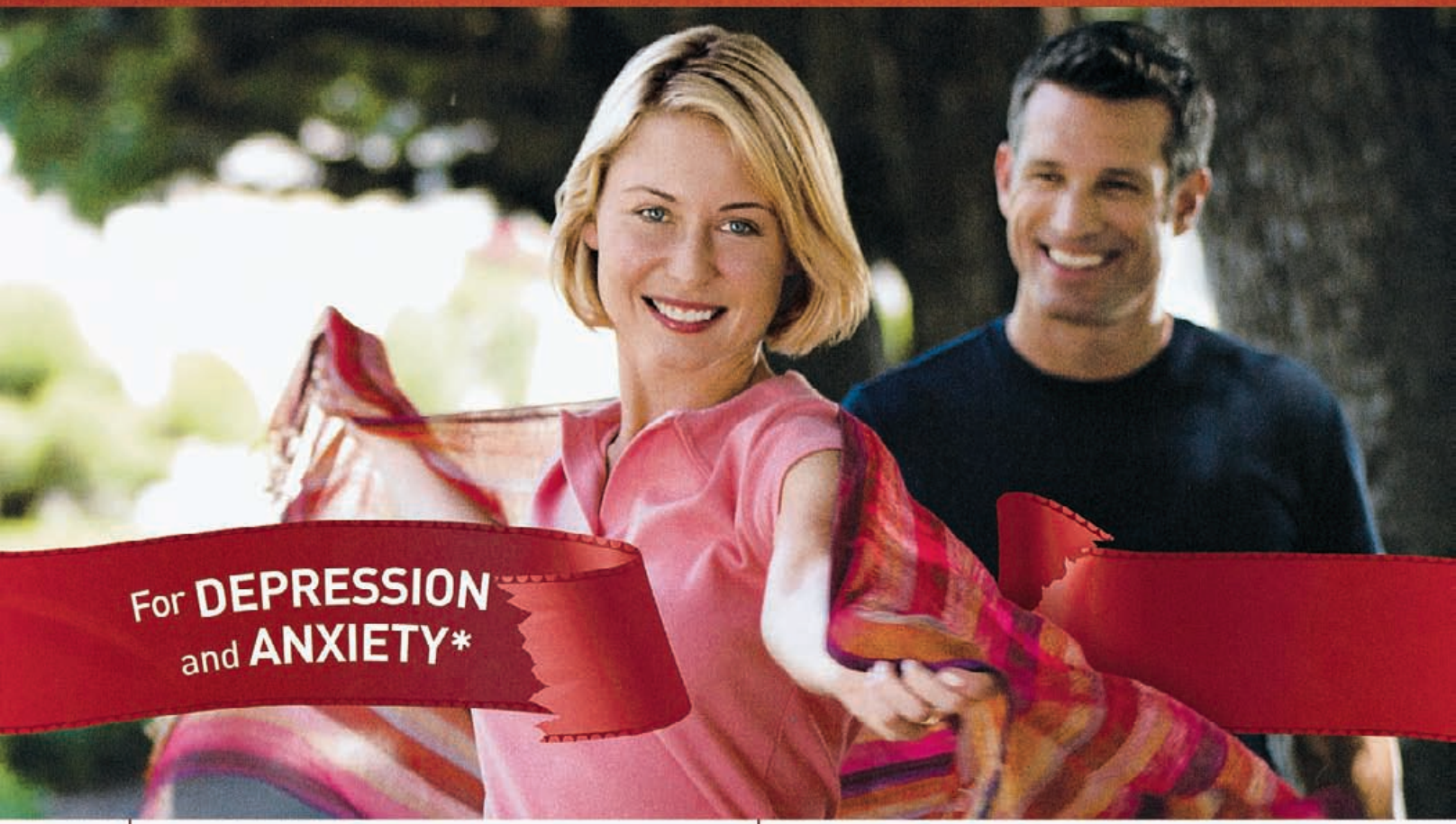
Bober also had the opportunity to brief Murray prior to the confirmation hearing for James Peake, M.D., to be secretary of Veterans Affairs. After his confirmation, Peake was the keynote speaker at APA's Advocacy Day program.

The reauthorization bill for the Substance Abuse and Mental Health Services Administration (SAMHSA) was another area on which Bober worked. "I participated in weekly working groups with the HELP [Health, Education, Labor, and Pensions] Committee staff to update and modify existing SAMHSA legislation to more clearly reflect the new challenges that we face in mental health and substance abuse treatment," he said.

The fellowship "was an experience I will never forget," he stated, "and it has emboldened me to continue to serve those who may not have a voice and need someone to fight for them."

Information about the Jeanne Spurlock fellowship and APA's other minority fellowships is posted at <www.psych.org/Resources/OMNA/MFP.aspx>. ■

A POWERFUL SSRI
that's well tolerated



UP TO 90% of depressed patients present with symptoms of anxiety[1]

Lexapro
escitalopram oxalate

*** Lexapro is indicated for Major Depressive Disorder and Generalized Anxiety Disorder**

POWER TO ENJOY LIFE™

IMPORTANT SAFETY INFORMATION – Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Antidepressants increased the risk of suicidality (suicidal thinking and behavior) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of antidepressants in children, adolescents or young adults must balance the risk to clinical need. Patients of all ages started on antidepressant therapy should be closely monitored and observed 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. SSRIs and SNRIs (including Lexapro) and other psychotropic drugs that interfere with serotonin reuptake may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to the risk. Patients should be cautioned about these risks. SSRIs and SNRIs have been associated with clinically significant hyponatremia. Elderly patients or patients taking antidiuretics or who are otherwise volume-depleted appear to be at a greater risk. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted. 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. Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry.* 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:552.

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

Forest Pharmaceuticals, Inc.

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

Rx Only

Brief Summary: For complete details, please see full Prescribing Information for Lexapro.

Suicidality and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

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 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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1. TABLE 1: Age Range and Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated:** Increases Compared to Placebo: <18 (14 additional cases); 18-24 (5 additional cases); Decreases Compared to Placebo: 25-64 (1 fewer case); ≥65 (6 fewer cases). No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and 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.** 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 (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION**—Discontinuation of Treatment with Lexapro, for a description of the risks of discontinuation of Lexapro). **Families and caregivers of 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 Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **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. *Serotonin Syndrome:*** The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Lexapro treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS - Potential for Interaction with Monoamine Oxidase Inhibitors**.) If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS - Drug Interactions**) The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS - Drug Interactions**). **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**). Abnormal Bleeding SSRIs and SNRIs, including Lexapro, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation. Hyponatremia Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Lexapro was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see Geriatric Use). Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. 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**). 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**). **Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe Lexapro. Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Lexapro and triptans, tramadol or other serotonergic agents. In a study in normal volunteers, Lexapro 10 mg/day did not impair psychomotor performance. The effect of Lexapro on psychomotor coordination, judgment, or thinking has not been systematically examined in controlled studies. Because psychoactive drugs may impair judgment, thinking, or motor skills, 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. Patients should be told that, although Lexapro has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Lexapro and alcohol in depressed patients is not advised. Patients should be made aware that escitalopram is the active isomer of Celexa (citalopram hydrobromide) and that the two medications should not be taken concomitantly. Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions. Patients should be cautioned about the concomitant use of Lexapro and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding. 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 breastfeeding an infant. While patients may notice improvement with Lexapro therapy in 1 to 4 weeks, they should be advised to continue therapy as directed. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Lexapro and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for Lexapro. 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. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Lexapro. **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 and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look 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. **Laboratory Tests** There are no specific laboratory tests recommended. **Concomitant Administration with Racemic Citalopram** Citalopram - Since escitalopram is the active isomer of racemic citalopram (Celexa), the two agents should not be coadministered. **Drug Interactions Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS-Serotonin Syndrome**). The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended (see **PRECAUTIONS - Drug Interactions**). **Triptans:** There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - Serotonin Syndrome**). 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 may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued. 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 P450206 - *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** Pregnancy Category C In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **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**). Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **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 **BOXED WARNING** and **WARNINGS—Clinical Worsening and Suicide Risk**). One placebo-controlled trial in 264 pediatric patients with MDD has been conducted with Lexapro, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Lexapro in a child or adolescent must balance the potential risks with the clinical need. **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. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS**, Hyponatremia). 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**). 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 2** 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 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 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 2**). **TABLE 2: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event (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

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(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 3** 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 3**). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event [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 4** 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 4: 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 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials** [In Males Only: **Adverse Event: 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 2 & 3**, 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 post marketing spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypotension, orthostatic hypotension, phlebitis thrombosis.

Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. St. Louis, MO 63045 USA Licensed from H. Lundbeck A/S Rev. 04/08 ©2008 Forest Laboratories, Inc.

SHAPING OUR FUTURE: SCIENCE AND SERVICE

THE *162ND* ANNUAL MEETING
OF THE
AMERICAN PSYCHIATRIC ASSOCIATION
MAY 16-21, 2009
SAN FRANCISCO, CALIFORNIA

Nada L. Stotland, M.D., M.P.H.
APA President
Josepha Cheong,
M.D.Chairperson, Scientific
Program Committee

APPLICATION OPEN	APPLICATION CLOSED	PROGRAM
05/20/08	08/28/08	COURSE
05/20/08	08/07/08	INDUSTRY-SUPPORTED SYMPOSIUM
11/04/08	12/09/08	NEW RESEARCH/YOUNG INVESTIGATOR POSTER
05/20/08	08/28/08	SCIENTIFIC & CLINICAL REPORT
05/20/08	08/28/08	SYMPOSIUM
05/20/08	08/28/08	WORKSHOP (N.B. THE COMPONENT WORKSHOP DEADLINE IS 09/19/08)

FOR MORE INFORMATION, GO TO **WWW.PSYCH.ORG/2009PROGAM** *OR CALL* **703-907-7808**

Register Early!

60th Institute on Psychiatric Services

October 2–5, 2008

Chicago

From Patient to Partner: Transforming Systems of Care

Take Advantage of Advance Registration and Save Money!

The full-time registration fee covers admission to the exhibits, including prize drawings, beverages and receptions in the exhibit hall; all scientific sessions, including Industry-Supported lunch and dinner Symposia; and other special events. The registration fee also includes the *Program Book* and *Syllabus* (for most registration categories), as well as the latest issue of the journal *Psychiatric Services*. The deadline for advance registration is **September 12, 2008.** You may still register online from September 13–October 5, at the higher, on-site rates, through APA's home page www.psych.org/IPS.

Register Early and Win Prizes

If you register before the September 12th advance registration deadline your name will be entered into a drawing to win either a one night stay at the Palmer House Hilton or your registration fee will be refunded to you. Make sure you register early and try to win one of these prizes.

60th Institute on Psychiatric Services
APA's Leading Educational Conference on Public and Community Psychiatry

For more information, please contact:
American Psychiatric Association
1000 Wilson Blvd., Suite 1825
Arlington, VA 22209-3901
Phone: 1-888-35-PSYCH
or (703) 907-7300
Fax: (703) 907-1090
E-mail: apa@psych.org
Web: www.psych.org/IPS

Drexel UNIVERSITY
Co-sponsored by Drexel University College of Medicine/ Behavioral Healthcare Education

Psychiatrist Works to Build Global Research Network

Maria Oquendo, M.D., is combining her bilingualism, multicultural background, and math skills in some ingenious ways. For instance, she is mentoring young psychiatric researchers from other countries.

BY JOAN AREHART-TREICHEL

Maria Oquendo, M.D., is pursuing a vibrant psychiatric career at Columbia University. As a professor of clinical psychiatry, she conducts full-time research and teaches courses in cross-cultural psychiatry and affective disorders. As vice chair of education, she oversees all programs for medical students, residents, and clinical and research fellows pursuing psychiatric training.

She is also making some valuable research contributions, psychiatrists who know her attest.

She is a leading authority on cross-cultural psychiatry in the United States, Deborah Cabaniss, M.D., an associate clinical professor of psychiatry at Columbia, said in an interview.

Photo courtesy of Maria Oquendo, M.D.

Maria Oquendo, M.D.: "I think perhaps the most important thing I've been able to achieve is the establishment of a very close collaboration with research groups in other countries."

Charles Nemeroff, M.D., chair of psychiatry at Emory University, told *Psychiatric News* that her major research contributions have been "identification of neurobiological markers in suicide and translational research in suicide and depression that spans the bench and the bedside."

"Her work on the basic neurobiology of bipolar disorder and the clinical implications of suicidality in mood disorders has been an important contribution to the field," Madhukar Trivedi, M.D., a professor of psychiatry at the University of Texas Southwestern Medical School, noted.

In Oquendo's opinion, one of the most important discoveries that she and her research colleagues have made is the discrepancy between the high rates of depression in Hispanics, especially Puerto Ricans, and their low rates of completed suicide.

"This finding presents an opportunity for us to learn about what kinds of things—cultural, genetic, or otherwise—protect some groups from suicide," she said.

It All Started in Spain

Oquendo's achievements are the culmination of a life's journey that started in Spain. She was born there in 1960 to a Spanish mother and a Puerto Rican father, grew up in Puerto Rico, went to college at Tufts University in Massachusetts, attended medical school at Columbia University, did her psychiatry residency at Cornell University, and became a full-fledged psychiatrist in 1988. After that, she joined the faculty of Columbia University.

Colleagues attribute her various achievements to a number of characteristics.

"She is very articulate, diligent, innovative, and a superb clinical researcher addressing some of the most important, clinically relevant topics in mood disorders," Trivedi said.

"She is persistent to the point of doggedness, able to remain calm under stress, and able to make decisions quickly," Robert Lewis-Fernandez, M.D., an associate professor of psychiatry at Columbia University, added.

"She is excellent with group dynamics," Cabaniss pointed out. "Her savvy in that area really helps her as an administrator, I think. Also, she has a hearty laugh that is infectious and wonderful. I think people really gravitate to her because of that."

Oquendo is also a risk taker in the best sense of the term. At age 35, she had what she describes as "a very interesting, comfortable, and secure job"—heading up the psychiatric community service unit at Columbia, where most of the patients were Hispanic. At this point, according to Cabaniss, she was also considered one of the leading experts on cross-cultural psychiatry in the United States. Yet Oquendo approached a psychiatric researcher at Columbia, John Mann, M.D., and said that she would like to study depression in the Hispanic population. Mann said that it was difficult to do psychiatric research only part time, but if she was willing to make a full-time commitment, she could join his research team. So she thought about it for several days; talked it over with her husband, Dana Cazzulino, Ph.D., a biochemical engineer; and then decided to take the risk.

"This was not going to be an easy path, but I decided that it was time for a change and that I was ready to take it on," she said.

Several Interests Converged

In her career, Oquendo has likewise managed to meld a number of interests.

For instance, during college she majored in math and was thinking about becoming a mathematician. Now, as a psychiatric scientist, she works closely with biostatisticians and other math types and is able to use her math skills in a very tangible way, where, she said, "I can bring about very concrete improvements in treatments and interventions for people."

Certainly, her career has had its challenges, Oquendo admitted. Probably the greatest has been balancing work and family, she said. She and her husband have two adolescent sons. "I think it is something that we female psychiatrists don't talk about enough. It's not that easy to do. It takes a lot of planning and effort."

But her career is bringing her rich dividends as well, she avowed. "I think that learning how to address scientific questions, developing mentoring relationships, and teaching are the most rewarding parts. I also get a great amount of pleasure from writing. I find it gratifying that my writing is well regarded." (Indeed, according to Cabaniss, Oquendo is "hugely prolific," having published some 160 papers in the 13 years that she has worked as a psychiatric researcher.)

Finally, where does Oquendo want to go next in her career? She would like to establish a network of collaborative psychiatric research centers around the world, she said. In fact, she is already moving in that direction.

"I have established a very close collaboration with psychiatric researchers at a university in Brazil, at a university in Austria, and at several universities in Spain," said Oquendo. "I am mentoring young investigators who come to work with me, learn how to be investigators, and then return to their own countries to start research projects. I am planning to start an international training fellowship here at Columbia, targeting psychiatric researchers in developing countries. I have been talking with potential donors and collaborators. There are many universities around this country with terrific resources and internationally oriented faculties, and we could work together to foment this type of project." ■

New Fellows Selected for APA's Minority Fellowships

APA has announced the names of the 25 new minority psychiatry residents selected to participate in the APA Minority Fellowships Program as either an APA/SAMHSA or APA/AstraZeneca fellow.

2008-2009 APA/SAMHSA Minority Fellows

Farha Abbasi, M.D., Michigan State University
Ayanna Brown, M.D., Baylor College of Medicine
Chris Esguerra, M.D., San Mateo County Mental Health Services
Arun Gopal, M.D., Cambridge Hospital
Felicia Kun, M.D., University of Massachusetts Medical School
Yunnie Lee, M.D., University of California, San Francisco
Lorraine Lothringer, M.D., Columbia University Medical Center
Kristen Ochoa, M.D., Harbor UCLA
Carlos Velez, M.D., New York University
Jacqueline Smith, M.D., University of North Carolina
Kiet Truong, M.D., UC Davis Medical Center
Donovan Wong, M.D., UCLA Neuropsychiatric Institute

Addiction Fellows

Matthew Rottnek, M.D., New York University
Carlos Suarez, M.D., Massachusetts General Hospital/McLean Hospital
Tayo Obatusin, M.D., Mount Sinai Hospital

2008-2010 APA/AstraZeneca Fellows

John Abulu, M.D., SUNY Downstate Medical Center
Vanessa Bobb, M.D., New York Presbyterian
Don DuBose, M.D., Morehouse School of Medicine
Sidney Hankerson, M.D., Emory University School of Medicine
Farah Herbert, M.D., New York University
Rex Huang, M.D., Stanford University
Gonzalo Perez-Garcia, M.D., Baylor College of Medicine
Sosunmolu Shoyinka, M.D., Maimonides Medical Center
Terri Turner, M.D., Howard University Hospital
Shaw Woods, M.D., USC/Palmetto Health Alliance ■

2009 Spurlock Fellow Selected

Kahlil Johnson, M.D., has been selected as the 2009 Jeanne Spurlock Congressional Fellow (see page 12). Johnson is a third-year psychiatry resident at George Washington University in Washington, D.C. He is also completing a master's degree in public health in the George Washington University Department of Health Policy. He plans to complete a fellowship in psychosomatic medicine after the congressional fellowship. The Capitol Hill fellowship runs from January 2009 to October 2009. ■

APA Dues Policy Payment Change

Effective with the 2008 dues year, annual membership dues must be paid by October 31 or membership in APA will lapse. If you have not already done so, please pay your dues immediately or enroll in the Scheduled Payment Plan to have your current APA and district branch dues automatically charged to your credit card in monthly installments. Act now to ensure that your membership benefits do not lapse. For more information, contact membership@psych.org or call (888) 357-7924.

It's Celebration Recovery, And Everyone's Invited

Patients and their family and friends will celebrate recovery at a lighthearted afternoon event offering food, fellowship, music, and games.

BY JILL GRUBER

In the course of their day, psychiatrists attend to the diagnosis and treatment of psychiatric illnesses and the numerous barriers to care that patients encounter that prevent them from getting well. Increasingly, psychiatrists are now focusing attention on what is the most important phase of illness to psychiatry patients: recovery. APA's Institute on Psychiatric Services will do just that this fall by holding a festive gala known as Celebration Recovery in which people who have struggled with mental illness, along with their friends and relatives, will come together with psychiatrists and others attending the institute, as well as representatives of numerous Chicago provider and advocacy groups.

Jill Gruber is APA's associate director for annual meetings.

This extraordinary event at the institute will be held on Saturday, October 4, from 5 p.m. to 7 p.m. in the Grand Ballroom of the Palmer House Hilton. The free, two-hour celebration will feature music, games, inspirational talks, dancing, food, and information booths.

The keynote speaker will be Moe Armstrong, M.B.A., M.A., the founder of the Peer Educators Project. A Vietnam veteran and self-identified consumer of mental health services, he is a former chair of the Veterans' Subcommittee for the National Alliance on Mental Illness National Board. The National Council for Community Behavioral Healthcare recently honored him for "his life-long commitment to promoting community-based and peer-support services for people living with serious psychiatric conditions."

Celebration Recovery is being presented by the Irwin Foundation in collaboration with APA and co-hosted by Thresholds Psychiatric Rehabilitation Centers. The Irwin Foundation, which receives sponsorship from a wide array of private, public, and voluntary entities, develops programs to further the vision of recovery from psychiatric illness and develops recovery-focused workshops and symposia.

Celebration Recovery event in Austin, Texas.

Celebration Recovery highlights an emerging concept in psychiatry that emphasizes person-centeredness, respect, responsibility, hope, choice, quality of life, consumer and family agency and empowerment, self-help, partnership, diversity, and community inclusiveness.

Recovery from mental disorders should be an expectation, yet the reality of recovery is too often contradicted by stigma, disempowerment, diminished expectations, custodial care instead of active treatment, and pervasive pessimism.

The recovery vision is increasingly informing mainstream psychiatric initiatives. The 2003 report of the President's New Freedom Commission on Mental Health called for a recovery-focused, consumer- and family-driven transforma-

please see ***Recovery*** *on page 24*

60th Institute on Psychiatric Services

How to Register

There are three easy ways to register for APA's 2008 Institute on Psychiatric Services, being held in Chicago from October 2 to 5:

- Register online at <www.xpressreg.net/register/iops108/regInfo.asp>.
- Use the registration form found in the preliminary program booklet and mail the completed form to APA. The booklet can be obtained by calling (888) 357-7924. Payment may be made by credit card or check payable to APA.
- Fax the completed form to (703) 907-1097. Payment must be made by credit card.

Register before September 12 and save on fees. A discounted fee is available for residents; medical students attend free.

APA's 100% Club Gains Another Member Program

All the psychiatry residents at West Virginia University have joined APA, and the program is now a member of APA's 100% Club.

The physicians enrolled in the psychiatry residency training program at West Virginia University in Morgantown kept their eyes on the prize—and it paid off. It led to the program's earning membership in APA's 100% Club.

"We are very pleased with our residents' achievements at West Virginia University," said the program's director, Ryan Finkenbine, M.D. "The APA 100% Club is a part of our commitment to educational excellence."

The doctors in Finkenbine's program follow in the footsteps and tradition of many psychiatry residency programs around the country and Canada in which all the residents joined APA.

A photo of the residents in each program that joins the 100% Club is mounted on a plaque and given to the program. 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 remain APA members.

Information about APA's 100% Club is available from Nancy Delanoche of APA's Division of Education at (703) 907-8635 or ndelanoche@psych.org. ■

Credit: Psychiatry Residency Program, West Virginia University at Morgantown

Back row, from left: Elizabeth Kane, M.D., Susanne Choby, M.D., Benjamin Lafferty, M.D., John Yarbrough, M.D., James Peykanu, M.D., Arvind Vasudevan, M.D., Patrick Marshalek, M.D., Carl Grey, M.D., Wanhong Zheng, M.D., Edward Miltenberger, M.D., and James Stevenson, M.D., professor and department chair. Front row, left to right: Cathy Layne, M.D., Melissa Albert, M.D., Michael Campbell, M.D., Derek Mongold, M.D., Muhannad Kassawat, M.D., Rajeevan Rasasingham, M.D., Chad Priestley, D.O., Saleha Abbasi, Dana Morton M.D., and Steve Neal, D.O.

clinical & research news

Obesity in Middle-Aged Adults Linked to Childhood Abuse

Childhood physical abuse may increase the risk of obesity in midlife, but having a depressed mother during childhood may help protect against it. Why this might be the case is not known.

BY JOAN AREHART-TREICHEL

As the obesity epidemic spreads throughout the world—China seems to be the latest casualty, according to the July/August *Health Affairs*—psychiatric researchers are stepping up their efforts to discover the mental health ramifications of obesity.

For example, they have found associations between anxiety, depression, and binge eating and obesity, although whether these mental disorders contribute to obesity or result from it is not clear (*Psychiatric News*, September 16, 2005; August 18, 2006). They have linked late-teen depression with early-adulthood obesity in women (*Psychiatric News*, November 21, 2003). And now Claudia Thomas, Ph.D., of University College London and colleagues have coupled physical abuse in childhood with midlife obesity. Results were published in the May *Pediatrics*.

A general population sample representative of United Kingdom adults in midlife—some 9,400 subjects born in 1958—participated in this study. At ages 7, 11, and 16, each subject was visited by a study investigator and evaluated for negative experiences such as physical or emotional neglect, domestic tension, parental alcoholism, or mother having little interest in a child's education.

At age 45 each subject provided his or her recollections about negative experiences that he or she had encountered as a child—say, verbal, physical, or sexual abuse; parental depression; an authoritarian upbringing; or parental separation or divorce. Also at age 45, each subject's body mass index was determined.

The researchers then used the prospectively and retrospectively obtained negative-experience findings, as well as subjects' body mass index at age 45, to determine whether negative childhood experiences could be linked with obesity at age 45.

They found that such a link did in fact exist. Even when possibly confounding factors were considered, a highly significant link was found between physical abuse and midlife obesity, and statistically significant links were found between verbal abuse, a strict upbringing, and a mother having little interest in her child's education and midlife obesity.

In contrast, no significant association was found between other negative childhood experiences—such as not getting along with parents, parental separation or divorce, or parental alcoholism—and midlife obesity. Intriguingly, a significant inverse association was found between maternal depression during childhood and midlife obesity.

Thus, "Some childhood adversities increase the risk of obesity in adulthood," Thomas and her colleagues concluded in their study report, whereas others do not, and still others, such as parental depression, might even be protective in this regard. However, the mechanisms underlying such associations remain to be clarified, they pointed out.

The study was funded by the United Kingdom National Health Service, the United Kingdom Medical Research Council, and England's Department of Health.

An abstract of "Obesity and Type 2 Diabetes Risk in Mid-Adult Life: The Role of Childhood Adversity" is posted at <http://pediatrics.aappublications.org/cgi/content/abstract/121/5/e1240>. ■

legal news

Competence

continued from page 8

lawyers to speed up court proceedings in cases in which a defendant wants to self-represent. That was a concern raised by Justice Antonin Scalia, who wrote the dissenting opinion. It's a concern that Appelbaum shared, but he also hoped that flexibility would allow the development of legal standards and procedures to ensure that the power to appoint legal representation is not just used for a court's convenience.

The ruling is likely to have further effects in other areas of the law and society, agreed the mental health law experts.

The higher standard for self-representation in criminal cases is likely to be raised by attorneys involved in non-criminal cases, such as custody cases in which a parent with serious mental illness wants to represent himself or herself, said Recupero.

Appelbaum noted that because the Supreme Court's rulings can have a great influence with other courts and with the general public in the attitude taken toward mental illness, further consequences from the decision may include a greater realization about the disabling impact of serious mental illness and the need for comprehensive treatment.

The majority and minority opinions in* Indiana v. Edwards *are posted at <www.law.cornell.edu/supct/cert/07-208.html>. The APA amicus brief is posted at <www.aapl.org/pdf/edwardsbrief2008.pdf>. ■

Erratum

In the July 18 issue, a sentence in "From the President" was incorrectly edited. The affected area should have read, "[W]e set a limit of $10,000 a year of pharma income per participant [to be eligible to serve on the *DSM-V* Task Force or a work group]. Since we have had complaints that the limit is both too high and too low, we have probably done the best we could." ■

Buprenorphine Bests Naltrexone In Treating Heroin Addicts

Addiction research can change public health policies and make effective treatments available to more patients in more countries.

BY JUN YAN

Buprenorphine effectively prolongs abstinence and prevents relapse in the long-term maintenance treatment of heroin-dependent patients, researchers have found in a randomized, placebo-controlled, double-blind clinical trial.

This study was funded by the National Institute on Drug Abuse (NIDA) and conducted at an outpatient research clinic in Muar, Malaysia, between July 2003 and May 2004. The results were published in the June 27 *The Lancet*.

After completing a two-week residential detoxification program at baseline, 126 patients with a *DSM-IV* diagnosis of heroin dependence were randomly assigned to one of three arms of treatment—oral buprenorphine (n=44), naltrexone (n=43), or placebo (n=39) for 24 weeks. Those treated with buprenorphine had significantly longer duration of abstinence before the first heroin use (positive urine test) and duration to heroin-related relapse (three consecutive opioid-positive urine tests) than those who received naltrexone or placebo (see chart). The buprenorphine-treated group also had significantly better outcome than the placebo group in the maximum number of consecutive days of abstinence.

All patients in the study also attended weekly sessions of individual and group counseling, which included education and training on preventing relapse and reducing risky behaviors linked with HIV transmission. All patients were given urine drug tests three times a week.

The participants in each treatment group had been using heroin for an average of 14.5 to 16.4 years. Three quarters or more of the participants in each group had used injected drugs.

Retention is critical to the success of substance-dependence treatment. At the end of the six months, 36, 29, and 23 patients in the buprenorphine, naltrexone, and placebo groups, respectively, remained in the treatment. The retention rate in the buprenorphine group was higher than either the naltrexone or placebo group; however, the rate did not differ significantly between the naltrexone and placebo groups.

"This is the first randomized study, to our knowledge, that directly compares an [opioid receptor] agonist with the antagonist naltrexone," Richard Schottenfeld, M.D., a professor of psychiatry at Yale University School of Medicine and the lead author of this study, commented to *Psychiatric News*. He noted that the study revealed a consistent pattern in all of the efficacy indicators: "The buprenorphine group did the best, the placebo group the worst, and naltrexone in the middle."

In Malaysia, injected heroin abuse and associated HIV transmission pose a significant public health problem. This study was undertaken as a part of NIDA's international collaborative program that supports research in regions with drug-related HIV/AIDS epidemics.

The authors of the study examined the effects of these treatments on self-reported HIV high-risk behaviors and found that these behaviors decreased significantly from baseline in all three groups, and the difference was not significant among the groups.

"Heroin addiction is a very big problem and a major driver of HIV/AIDS epidemic in that region of the world," Schottenfeld said. "The government had been very resistant to medical treatment for drug addiction until the 1990s." The past decade saw a gradual shift in the attitude of authorities, from locking up addicts in jail and detoxification facilities to long-term maintenance medical treatment for substance dependence and abuse.

The authorities in Malaysia and many other countries have considered opioid agonists, such as buprenorphine and methadone, as a substitute addiction rather than an effective treatment.

"Stigma is what's underlying a lot of the resistance to agonist maintenance treatment," according to Schottenfeld. He said the Malaysian authorities were initially opposed to the use of any opioid agonist. However, this research and other objective evidence of the effectiveness of buprenorphine have had a significant influence on the public health policies in Malaysia. Recently, the country expanded approved treatment options to include methadone.

"The use of oral naltrexone is often an indicator of moral disapproval of substitution treatments with opioid agonists because they stabilize addicts rather than attempt to produce abstinence," wrote University of Queensland's Wayne Hall, Ph.D., and Richard Mattick, Ph.D., in an accompanying editorial. The two researchers, who work at the university's School of Population Health, recommended that "health authorities in developing countries should no longer restrict pharmacological treatment of opioid dependence to oral naltrexone. . . . The preferred oral pharmacological treatment for opioid dependence should be agonist maintenance with either methadone or buprenorphine."

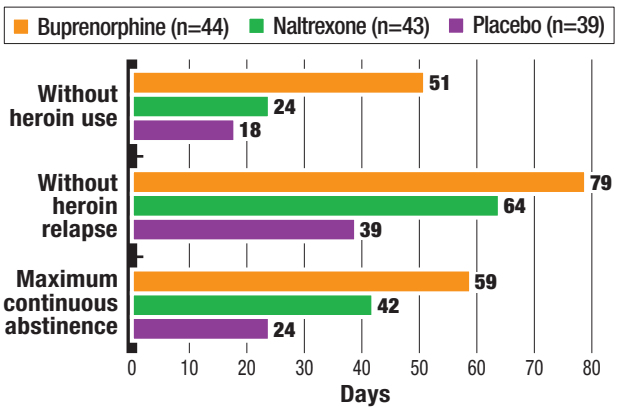
In the United States, buprenorphine with and without naltrexone is approved to treat opioid dependence. However, the stigma of and barriers to opioid agonist treatment remain in place in the United States as they do abroad, Schottenfeld pointed out. "Agonist maintenance treatments aren't as widely available as they should be. Many heroin-dependent patients do not have access to effective buprenorphine or methadone treatment."

Treatment-oriented policies are gaining ground in some countries. Schottenfeld noted that several similar NIDA research programs are currently being conducted in China and Iran and that there is a shift in many countries toward increased recognition of the need for long-term medical treatment for substance dependence as for any other chronic diseases.

An abstract of "Maintenance Treatment With Buprenorphine and Naltrexone for Heroin Dependence in Malaysia…" is posted at <www.thelancet.com/journals/lancet/article/PIIS0140673608609 54X/abstract>. ■

Buprenorphine Found Superior To Treat Heroin Dependence

In a randomized, double-blind, placebo-controlled clinical trial, heroin-dependent patients on buprenorphine had longer duration of staying in treatment without heroin use (that is, time to first positive urine test), without relapse (defined as three consecutive positive urine tests), and continuous abstinence. Buprenorphine was significantly more effective than placebo for all three outcome measures and significantly more effective than naltrexone for duration without heroin use.



Source: Richard Schottenfeld, M.D., *The Lancet*, June 28, 2008

Acute Stress Disorder Appears Poor Predictor of PTSD

While acute stress disorder may not be very predictive of posttraumatic stress disorder, it may be when trauma victims have also experienced brain injury.

BY JOAN AREHART-TREICHEL

Can acute stress disorder (ASD) predict posttraumatic stress disorder (PTSD)? Small studies have produced conflicting results. Now results of a larger study, conducted by Australian researchers, has sided with researchers who have found no predictive link.

It was headed by Richard Bryant, Ph.D., of the University of New South Wales. Results were published in the June *Journal of Clinical Psychiatry*.

Some 500 civilians admitted to four major trauma hospitals across Australia between April 2004 and April 2005 served as subjects in this study. Sixty-two percent had been admitted because of injury due to a motor-vehicle accident, 16 percent had been admitted because of injury due to a fall, 8 percent had been admitted because of injury due to an industrial accident, 5 percent had been admitted because of injury due to an assault, and the remaining 9 percent had been admitted for other reasons.

Within a month after the subjects' hospitalization, Bryant and his coworkers used *DSM-IV* criteria to determine how many of them were experiencing ASD. Thirty-three (6 percent) were. Three months later, Bryant and his coworkers used *DSM-IV* criteria to determine how many of them had PTSD. Forty-nine (10 percent) did. Bryant and his group then looked to see how many of the 49 patients who met PTSD criteria at the three-month follow-up assessment had had ASD within the month after their trauma. They found that 15 (31 percent) had.

Thus, "The majority of people who develop PTSD do not initially meet criteria for ASD," Bryant and his team concluded. "These data challenge the proposition that the ASD diagnosis is an adequate tool to predict chronic PTSD."

Nonetheless, Bryant and his coworkers did find that ASD's prognostic power tended to be somewhat stronger for subjects who had experienced a brain injury in conjunction with their trauma than for those who had not. Specifically, ASD predicted PTSD in 58 percent of this subgroup of subjects, versus 31 percent for the entire subject group. This particular finding may have relevance for the many Iraq War veterans whose PTSD is coupled with traumatic brain injury (*Psychiatric News*, March 2, 2007).

Also, since most of the subjects had been traumatized by accidental injuries, ASD might be more predictive of PTSD in patients whose trauma arises from other physical causes—say, from physical assault, sexual assault, or military combat—Bryant and his colleagues noted. Still, the rates of ASD and PTSD that they found in their subjects are similar to those that have been found in some other trauma populations, they pointed out. So their findings can probably be generalized to all trauma populations, they reasoned.

All told, since an ASD diagnosis appears to have only a limited ability to foretell PTSD, at least in persons who have been traumatized by accidental injuries, better tools than an ASD diagnosis are needed to determine which trauma victims are going to develop PTSD, Bryant and his group stated. For instance, preliminary evidence suggests that trauma patients' heart rates or moods in the wake of trauma might be good bellwethers of subsequent PTSD, they said.

The study was funded by Australia's National Health and Medical Research Council.

An abstract of "A Multisite Study of the Capacity of Acute Stress Disorder Diagnosis to Predict Posttraumatic Stress Disorder" is posted at <www.psychiatrist.com/abstracts/abstracts.asp?abstract=200806/060806.htm>. ■

Genetic Evidence Reveals Clues To Roots of Bipolar Disorder

The path leading to the genetic basis of psychiatric illnesses has more twists and turns than a strand of DNA, but that does not deter researchers.

BY AARON LEVIN

Genetic epidemiologist Peter Zandi, Ph.D., M.P.H., M.H.S., has a roadmap to the truth, but the truth is playing awfully hard to get.

Zandi, an assistant professor in the Department of Mental Health at the Johns Hopkins Bloomberg School of Public Health, is one of many researchers around the world trying to identify the specific common genetic variations that underlie the propensity of bipolar disorder to run in families.

"Bipolar disorder shows much etiological and clinical heterogeneity," said Zandi in an interview. "It presents with a variety of clinical features and comorbidities, and that probably reflects some genetic heterogeneity."

Now, he and colleagues from other institutions have published a study of genes that act on a cellular pathway known to be involved in the origins and treatment of bipolar disorder.

Their most recent efforts, published in the July *Archives of General Psychiatry*, not only represent another step along the path to understanding the genetics underlying mental illness, but also shed light on the routes researchers choose for the journey and how far they have to go. The research was supported by the National Institute of Mental Health and several private foundations.

"We started with the hypothesis that certain genes may be relevant to bipolar disorder and focused on them," said Zandi. These 34 candidate genes are associated with the Wnt signaling pathways. All genes are expressed in the brain and are located in chromosomal regions associated with bipolar disorder or schizophrenia in previous genetic linkage studies.

"We looked for genes that encode for proteins that might be important in this pathway to see if variations may be related to susceptibility in developing bipolar disorder," said Zandi.

Wnt proteins are found in species ranging from *Drosophila* to humans. They are involved in intracellular signaling pathways and in development. Several lines of research have associated Wnt proteins with bipolar disorder. For one thing, they play important roles in neuroplasticity, cell survival, and adult neurogenesis, impairments that seem related to bipolar disorder. Also, monozygotic twins discordant for bipolar disorder express Wnt signaling pathway genes differentially.

Drugs used to treat bipolar disorder interact with the Wnt pathway as well.

Lithium inhibits the enzyme GSK-3β, a critical part of the Wnt pathway, explained Todd Gould, M.D., an assistant professor of psychiatry at the University of Maryland School of Medicine in Baltimore, in an interview. That association became stronger recently when researchers found that other inhibitors of GSK-3β mimicked lithium's action and that raising levels of GSK-3β reversed lithium's effects.

"Since then, we've seen more biological evidence not only that lithium inhibits GSK-3β and activates Wnt pathways, but also that these pathways respond to valproate, antipsychotics, and some antidepressants," said Gould, who was not involved in Zandi's study. These associations have already drawn early interest from drug companies, he said.

Zandi's consortium of researchers recruited 317 families from three ongoing projects: the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder Consortium; a collaboration among the University of Chicago, Johns Hopkins University, and the NIMH Intramural Program; and the Clinical Neurogenetics collection. There were 1,118 participants, comprising 237 quads (two parents with two affected offspring) and 80 trios (two parents with one affected offspring).

They found that the single nucleotide polymorphism (SNP) producing the most significant response lay in the gene PPARD, located on chromosome 6p21. PPARD is expressed at high levels in the embryonic brain and thus may play a part in differentiating cells during neurodevelopment, wrote the authors. Furthermore, this SNP closely matched the response of another SNP identified in the bipolar cohort of the Wellcome Trust Case-Control Consortium Genome-Wide Association Study. Further genotyping of 13 additional tagging SNPs found four that were significantly associated with bipolar disorder, all lying in a single haplotype block on the gene.

"We then wanted to see if the variations in the SNPs matched clinical features of the disease," said Zandi. The two best SNPs in the PPARD gene were significantly linked to the illness with an odds ratio of 1.46. However, that risk rose to an odds ratio of 3.36 in participants with poor functioning, as measured on the GAS scale.

"The increased evidence of association for PPARD among those with poor functioning is consistent with a potential role for Wnt dysfunction in severe bipolar disorder," wrote Zandi and colleagues.

"We knew that worse functioning aggregated in families with bipolar disorder, so our findings bolster the thinking that functioning may be tied to genes," he said.

Their findings suggest that several changes along the main Wnt pathway are needed to significantly influence susceptibility to bipolar disorder, given that it is a genetically complex disease.

"I'm excited to see this paper," said Gould. "It's the best genetic evidence in humans linking Wnt to bipolar disorder."

Genome-wide studies will be useful as Zandi and other researchers try to replicate these findings.

The candidate-gene approach depends on picking the right candidates but may miss a disease-related SNP elsewhere. Genome-wide association studies look for genetic origins of disease from another direction.

"You're not looking at specific genetic variants in candidates," said Zandi. "Rather, you test throughout the genome, unconstrained by any prior hypothesis."

Both approaches will be needed to delineate the multigenetic origins of complex diseases like bipolar disorder.

"We don't know a lot about the underlying neurobiology of bipolar, so there may be genes we don't know about or won't find through candidate studies like this," said Gould. "But it is also important to interrogate genes with the candidate approach."

An abstract of "Association Study of Wnt Signaling Pathway Genes in Bipolar Disorder" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/65/7/785>. ■

Become an APA Distinguished Fellow

APA distinguished fellowship is a nationally recognized honor and is awarded to members who not only have achieved distinction in special areas of psychiatry, but also whose depth of knowledge and breadth of skills are recognized and highly respected. More information regarding the nomination and selection process is available from your district branch.

Blood Test May Identify Risk Marker for Alzheimer's

Want to find out in midlife whether Alzheimer's disease is in your future? A simple blood test might eventually give you the answer by measuring levels of an inflammatory substance.

BY JOAN AREHART-TREICHEL

It's already possible to test people in midlife to see whether they carry a well-documented genetic risk factor for Alzheimer's disease, the e4 variant of the APOE (apolipoprotein E) gene (*Psychiatric News*, October 4, 2002).

Now a blood test to see whether people in midlife are at risk of Alzheimer's later in life may soon be possible.

The reason is because a new study, conducted by University of Pittsburgh researchers and in press with *Biological Psychiatry*, has found an inverse association between levels of an inflammatory substance in the blood and the size of the brain's memory center (the hippocampus) in 76 generally healthy individuals aged 30 to 54. The substance is the cytokine interleukin-6. Moreover, this link held even when possibly confounding factors such as age, gender, education, body fat, blood pressure, and smoking were considered.

Furthermore, subjects with smaller hippocampi were found to perform worse on memory tests than those with larger hippocampi. Thus, high levels of interleukin-6 in the blood at midlife may be a marker for memory decline and possibly for risk of Alzheimer's later in life, the researchers concluded.

Exactly how elevated levels of interleukin-6 in the bloodstream at midlife might contribute to the development of later-life Alzheimer's is not known, the researchers wrote in their study report. However, animal research has revealed that interleukin-6 in the bloodstream can interfere with hippocampal function, learning, and memory, they pointed out. Also, fat tissue is a rich source of interleukin-6 in the bloodstream, and obesity in midlife and later life has been found to predict cognitive decline and the incidence of dementia, they noted. So persons who are overweight in midlife might be courting an increase in interleukin-6 in the bloodstream and then, through the interleukin-6 boost, Alzheimer's, they speculated.

The study findings might have implications for the early detection of Alzheimer's and perhaps even for its prevention, the researchers believe.

"We have just put in a grant application" to find out whether high levels of interleukin-6 in midlife indeed predict future hippocampal shrinkage and memory loss, the lead investigator, Anna Marsland, Ph.D., an associate professor of psychiatry at the University of Pittsburgh, told *Psychiatric News*.

If they find that high levels of interleukin-6 in midlife truly presage future hippocampal shrinkage and memory loss, then "a next step will be considering possible preemptive interventions," she said. In fact, there is already evidence that anti-inflammatory drugs such as ibuprofen may help prevent Alzheimer's (*Psychiatric News*, July 4).

The study was funded by the National Institutes of Health, the John D. and Catherine T. MacArthur Foundation, and the National Alliance for Research on Schizophrenia and Depression.

An abstract of "Interleukin-6 Covaries Inversely With Hippocampal Grey Matter Volume in Middle-Aged Adults" is posted at <www.journals.elsevierhealth.com/periodicals/bps> under "Articles in Press." ■

Attitude on Medication Use May Affect Severity of Illness

The results suggest that exploring negative attitudes toward medication in a patient-centered manner, based on a supportive therapeutic alliance and a strong physician-patient relationship, is likely to be beneficial.

BY MARK MORAN

Greater patient insight and positive attitudes toward medication appear to be associated with less severe symptoms and better functioning among patients with schizophrenia.

That's the finding from the latest analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The report was posted online June 26 in the Advanced Access section of *Schizophrenia Bulletin*.

Higher levels of insight at baseline were significantly associated with less severe schizophrenia symptoms at 18-month follow-up, while more positive medication attitudes were significantly associated with both lower symptom levels and better community functioning.

(Symptoms of schizophrenia were assessed by the Positive and Negative Syndrome Scale [PANSS], which yields a total average symptom score, based on 30 items rated from 1 to 7, with higher scores indicating more severe symptoms, as well as subscales reflecting positive, negative, and general psychiatric symptoms.)

Change in insight scores over time was associated with declining severity of schizophrenia symptoms, and change toward more positive medication attitudes was associated, independently of changes in insight, with significant decreases in psychopathology, improvement in community functioning, and greater medication compliance, according to the report.

CATIE was a large, 18-month, randomized, controlled trial that was designed to compare outcomes of one conventional antipsychotic medication (perphenazine) and four second-generation antipsychotics (olanzapine, risperidone, quetiapine, and ziprasidone). It was funded by the National Institute of Mental Health and conducted from January 2001 through December 2004 at 57 U.S. sites.

Insight was assessed by the Insight and Treatment Attitudes Questionnaire (ITAQ), which is designed to measure awareness of illness and insight into need for treatment in patients with schizophrenia. It consists of 11 items that are phrased as questions to elicit responses on a Likert scale. Attitudes toward medication were assessed by the Drug Attitude Inventory (DAI).

Psychosocial functioning and quality of life were assessed using the Heinrichs-Carpenter Quality of Life (HQOL) Scale and a single item from the Lehman Quality of Life Interview. Medication adherence was evaluated using monthly pill counts and information from patients, family, and clinicians.

In addition to antipsychotic treatment, participants were offered an educational plan designed to inform patients and families about diagnosis, medications, symptom self-monitoring, side effects, and change in symptoms.

Statistical analyses showed that scores on the ITAQ and DAI were significantly positively correlated, and both were correlated with lower PANSS scores and higher HQOL scores—meaning that patients who had greater insight into their illness also tended to have greater awareness of the importance of medication. Those patients tended to have fewer symptoms and higher functioning at follow-up.

Moreover, change in insight scores from baseline to follow-up was associated with decreased PANSS total scores, improvement in the HQOL total, and increased medication compliance.

"Taken together, the results suggest that increasing [patients'] insight into their illness and fostering positive attitudes toward medication may result in improved symptom and [quality of life] outcomes," wrote Somaia Mohamed, M.D., of the VA Connecticut Health Care System, and colleagues. "They suggest possible benefits of exploring negative attitudes toward medication in a client-centered manner. Such an approach should be based on the development of a supportive therapeutic alliance and a strong positive practitioner-consumer relationship. The nature of this relationship has undergone major developments in recent years, shifting from a hierarchical medical model to a recovery-oriented model that requires new ways of understanding and approaching the issue of medication choice."

An abstract of "Cross-Sectional and Longitudinal Relationships Between Insight and Attitudes Toward Medication and Clinical Outcomes in Chronic Schizophrenia" is posted at <http://schizophreniabulletin.oxfordjournals.org/cgi/content/abstract/sbn067v1>. ■

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

℞ only

BRIEF SUMMARY: Please see package insert for full prescribing information.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of paroxetine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. Paroxetine is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients in full Prescribing Information and PRECAUTIONS: Pediatric Use.)

INDICATIONS AND USAGE: Major Depressive Disorder: Paroxetine hydrochloride extended-release tablets are indicated for the treatment of major depressive disorder.

The efficacy of paroxetine hydrochloride extended-release tablets in the treatment of a major depressive episode was established in two 12 week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical 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 mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2 week period: Depressed mood, markedly diminished interest or pleasure 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, a suicide attempt, or suicidal ideation.

The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

Paroxetine hydrochloride extended-release tablets have not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to one year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials in full Prescribing Information). The physician who elects to use paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Paroxetine hydrochloride extended-release tablets are contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in paroxetine hydrochloride extended-release tablets.

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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality Per 1,000 Patients Treated
Increases Compared to Placebo	
< 18	14 additional cases
18 to 24	5 additional cases
Decreases Compared to Placebo	
25 to 64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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 (see PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets, for a description of the risks of discontinuation of paroxetine).

Families and caregivers of 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 paroxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 paroxetine is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with an 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 that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that paroxetine hydrochloride extended-release tablets not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Serotonin Syndrome: The development of a potentially life threatening serotonin syndrome may occur with SNRI sans SSRIs, including paroxetine hydrochloride extended-release tablets, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of paroxetine hydrochloride extended-release tablets with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors). If concomitant use of paroxetine hydrochloride extended-release tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see PRECAUTIONS: Drug Interactions in full Prescribing Information).

The concomitant use of paroxetine hydrochloride extended-release tablets with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS: Drug Interactions in full Prescribing Information). Potential Interaction with Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as Torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Usage in Pregnancy: ***Teratogenic Effects:*** Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS: General: *Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets*). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1 to 2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using U.S. United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8 to 2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on a mg/m^2 basis. The no effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or serotonin and norepinephrine reuptake inhibitors (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: Potential for Interaction with Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately 6-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no collaborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

There have also been post-marketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

PRECAUTIONS: General: ***Activation of Mania/Hypomania:*** During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1% of paroxetine-treated unipolar patients compared to 1.1% of active control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with paroxetine hydrochloride extended-release tablets in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, paroxetine hydrochloride extended-release tablets should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received paroxetine hydrochloride extended-release tablets in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, one patient (0.1%) experienced a seizure. Paroxetine hydrochloride extended- release tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets: Adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of paroxetine hydrochloride extended-release tablets up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for one week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for paroxetine hydrochloride extended-release tablets, at an incidence of 2% or greater for paroxetine hydrochloride extended-release tablets and were at least twice that reported for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing paroxetine hydrochloride extended-release tablets (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with paroxetine hydrochloride extended-release tablets.

During marketing of paroxetine hydrochloride extended-release tablets and other SSRIs and SNRIs, 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 and tinnitus), 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 paroxetine hydrochloride extended-release tablets. 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).

See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including paroxetine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see Geriatric Use). Discontinuation of paroxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest and death.

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 non-steroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see PRECAUTIONS: Drug Interactions in full Prescribing Information). 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 paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

Use in Patients with Concomitant Illness: Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine hydrochloride extended-release tablets in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine hydrochloride extended-release tablets are prescribed for patients with narrow angle glaucoma.

Paroxetine hydrochloride extended-release tablet or the immediate-release formulation 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 clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Pregnancy: ***Pregnancy Category D:*** See WARNINGS: Usage in Pregnancy: *Teratogenic Effects*:.

Labor and Delivery: The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when paroxetine hydrochloride extended-release tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine hydrochloride and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine hydrochloride extended-release tablets in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release paroxetine hydrochloride and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with immediate-release paroxetine hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-release paroxetine hydrochloride and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets).

Geriatric Use: In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY in full Prescribing Information and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, paroxetine hydrochloride extended-release tablets were demonstrated to be safe and effective in the treatment of elderly patients (> 60 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY: Clinical Trials in full Prescribing Information and ADVERSE REACTIONS: Table 3.)

SSRIs and SNRIs, including paroxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at great risk for adverse event (see PRECAUTIONS: General: Hyponatremia).

ADVERSE REACTIONS: The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Paroxetine Hydrochloride Extended-Release Tablets" subsection of ADVERSE REACTIONS is based on data from eleven placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, three studies were done in patients with panic disorder and one study was conducted in patients with social anxiety disorder. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies. Information on additional adverse events associated with paroxetine hydrochloride extended-release tablet and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events Observed During the Clinical Development of Paroxetine).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With Paroxetine Hydrochloride Extended-Release Tablets: ***Adverse Events Associated With Discontinuation of Treatment:*** *Major Depressive Disorder:* Ten percent (21/212) of patients treated with paroxetine hydrochloride extended-release tablets discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder. The most common events (≥ 1%) associated with discontinuation and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for paroxetine hydrochloride extended-release tablets compared to placebo) included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 212)	Placebo (n = 211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with paroxetine hydrochloride extended-release tablets discontinued due to an adverse event. Events meeting the above criteria included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 104)	Placebo (n = 109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Commonly Observed Adverse Events: ***Major Depressive Disorder:*** The most commonly observed adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a pool of two trials (incidence of 5% or greater and incidence for paroxetine hydrochloride extended-release tablets at least twice that for placebo, derived from Table 2) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Incidence in Controlled Clinical Trials: Table 2 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with paroxetine hydrochloride extended-release tablets, aged 18 to 65, who participated in two short-term (12 week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5 mg to

Page 1 of 2

50 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with paroxetine hydrochloride extended-release tablets who participated in short-term (10 week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day.

The prescriber should be aware that these figures 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 treatments, 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 side effect incidence rate in the population studied.

Table 2. Treatment Emergent Adverse Events Occurring in ≥ 1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Two Studies in Major Depressive Disorder[1,2]

	% Reporting Event	
Body System/Adverse Event	**Paroxetine Hydrochloride Extended-Release Tablets (n = 212)**	**Placebo (n = 211)**
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[9,10]	26%	1%
Female Genital Disorder[8,11]	10%	< 1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[8]	2%	< 1%
Vaginitis[3]	2%	0%

1. Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. < 1% means greater than zero and less than 1%.
3. Mostly flu.
4. A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

Table 3. Treatment Emergent Adverse Events Occurring in ≥ 5% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Study of Elderly Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System/Adverse Event	**Paroxetine Hydrochloride Extended-Release Tablets (n = 104)**	**Placebo (n = 109)**
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	< 1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	< 1%
Urogenital System		
Abnormal Ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
2. < 1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

A comparison of adverse event rates in a fixed dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

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.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of two placebo-controlled trials in nonelderly patients with major depressive disorder are as follows:

	Major Depressive Disorder	
	Paroxetine HCl Extended-Release Tablets	**Placebo**
n (males)	**78**	**78**
Decreased Libido	10%	5%
Ejaculatory Disturbance	26%	1%
Impotence	5%	3%
n (females)	**134**	**133**
Decreased Libido	4%	2%
Orgasmic Disturbance	10%	<1%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

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.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with paroxetine hydrochloride extended-release tablet or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with paroxetine hydrochloride extended-release tablets, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In a pool of two placebo-controlled clinical trials, patients treated with paroxetine hydrochloride extended-release tablets or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the extended-release paroxetine versus placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with paroxetine hydrochloride extended-release tablets and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with paroxetine hydrochloride extended-release tablets dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, 4 of 444 patients treated with paroxetine hydrochloride extended-release tablets and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of paroxetine hydrochloride extended-release tablets. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients receiving placebo.

Other Events Observed During the Clinical Development of Paroxetine: The following adverse events were reported during the clinical development of paroxetine hydrochloride extended-release tablet and/or the clinical development of the immediate-release formulation of paroxetine.

Adverse events for which frequencies are provided below occurred in clinical trials with the extended-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder and social anxiety disorder, multiple doses of paroxetine hydrochloride extended-release tablets were administered to 1,627 patients in phase three double-blind, controlled, outpatient studies. Untoward events associated with this exposure were 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 untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to paroxetine hydrochloride extended-release tablets who experienced an event of the type cited on at least one occasion while receiving paroxetine hydrochloride extended-release tablets. All reported events are included except those already listed in Tables one through four and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, 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 (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 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase two and three studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed dose and titration studies. Only those events not previously listed for extended-release paroxetine are included. The extent to which these events may be associated with paroxetine hydrochloride extended-release tablets is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, nonprotein nitrogen (NPN) increased.

Musculoskeletal System: Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*, nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Post-Marketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome like events, serotonin syndrome; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including Torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Paroxetine hydrochloride is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine hydrochloride extended-release tablets have not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. 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 history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of paroxetine hydrochloride extended-release tablets (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE: Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 nonfatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including Torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

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 paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: Drug Interactions: *Drugs Metabolized by Cytochrome CPY2D6* in full Prescribing Information).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION: Major Depressive Disorder: ***Usual Initial Dosage:*** Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25 mg dose may benefit from dose increases, in 12.5 mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least one week.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to one year with doses that averaged about 30 mg, which corresponds to a 37.5 mg dose of paroxetine hydrochloride extended-release tablets, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics in full Prescribing Information).

Special Populations: ***Treatment of Pregnant Women During the Third Trimester:*** Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose of paroxetine hydrochloride extended-release tablets is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or From a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with paroxetine hydrochloride extended-release tablets. Similarly, at least 14 days should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets: Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or paroxetine hydrochloride extended-release tablets have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine hydrochloride extended-release tablets are being prescribed. 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.

Mylan

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED SEPTEMBER 2007
BS:PRXT:R4mc

COMPILED BY JUN YAN

Research Briefs

• In a randomized, double-blind, placebo-controlled study, nursing-home residents with Alzheimer's disease saw no difference in psychotic symptoms after taking either ***aripiprazole*** or placebo for 10 weeks. The study, led by Joel Streim, M.D., a professor of geriatric psychiatry at the University of Pennsylvania, was published in the July *American Journal of Geriatric Psychiatry*. The study was supported by the makers of aripiprazole, Bristol-Myers Squibb and Otsuka Pharmaceutical. A total of 131 Alzheimer's patients aged 59 to 96 were randomized to the aripiprazole group, and 125 patients were randomized to the placebo group. Efficacy was evaluated by changes from baseline on the Neuropsychiatric Inventory–Nursing Home Version psychosis score and Clinical Global Impression severity score, and these scores were not significantly different between the two groups after 10 weeks of treatment.

"A Randomized, Double-Blind, Placebo-Controlled Study of Aripiprazole for the Treatment of Psychosis in Nursing Home Patients With Alzheimer Disease" is posted at <http://ajgponline.org/cgi/content/full/16/7/537>.

• ***Xanomeline***, a selective muscarinic receptor agonist under investigation, shows promising effectiveness in a small study that was published in *AJP in Advance* in July. Twenty patients with acute exacerbation of schizophrenia or schizoaffective disorder were randomized in a 1:1 ratio to receive either xanomeline or placebo for four weeks in a double-blind design.

The xanomeline-treated patients had significantly greater symptomatic improvement from baseline compared with placebo-treated patients. Improvement was assessed by the Brief Psychiatric Rating Scale, the Positive and Negative Syndrome Scale, and cognitive tests. The most common adverse events reported more frequently in the xanomeline group than in the placebo group were nausea, vomiting, gastrointestinal distress, salivation, diarrhea, constipation, and sweating.

The study was led by Anantha Shekhar, M.D., Ph.D., associate dean for translational research, the Raymond E. Houk professor of psychiatry, and a professor of pharmacology and neurobiology at Indiana University School of Medicine, and colleagues and supported by Eli Lilly and Co.

"Selective Muscarinic Receptor Agonist Xanomeline as a Novel Treatment Approach for Schizophrenia" is posted at <ajp.psychiatryonline.org/cgi/reprint/appi.ajp.2008.06091591v1>.

• Pharmacotherapy for smoking cessation works, a meta-analysis published in the July 15 *Canadian Medical Association Journal* concluded. Mark Eisenberg, M.D., M.P.H., and colleagues pooled 69 randomized, placebo-controlled, clinical trials of various drug therapies, which involved nearly 33,000 participants. ***Varenicline, nicotine nasal spray, bupropion, transdermal nicotine patch, nicotine tablet, and nicotine gum*** were shown to be significantly more effective than placebo, with an odds ratio of approximately 2. The efficacy results for inhaled nicotine did not reach statistical significance. Varenicline was significantly more efficacious than bupropion in a direct comparison of data from three trials of varenicline that included a comparator bupropion group.

Varenicline has recently been linked to neuropsychiatric disturbances, such as severe mood and behavior changes, vivid and strange dreams, and suicidal ideation and behaviors. At the request of the Food and Drug Administration (FDA), Pfizer has revised the drug's prescribing information and medication guide to alert health care professionals and patients about these risks.

An abstract of "Pharmacotherapies for Smoking Cessation: A Meta-Analysis of Randomized, Controlled Trials" is posted at <www.cmaj.ca/cgi/content/abstract/179/2/135>. Prescribing information for varenicline is posted at <www.fda.gov/cder/foi/label/2008/021928s008lbl.pdf>.

• ***Dimebon***, a drug being investigated for treatment of Alzheimer's and Huntington's diseases, is more effective than placebo in preventing cognitive-function decline in patients with mild-to-moderate Alzheimer's, according to a randomized, double-blind, placebo-controlled clinical trial published in the July 19 *The Lancet*. Cognition was measured with the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog). The investigators, led by Rachelle Doody, M.D., Ph.D., of Baylor College of Medicine, enrolled 183 patients with Mini-Mental State Examination scores between 10 and 24 at 11 sites in Russia, including 89 patients who were randomized to 60 mg/day dimebon and 94 who were given placebo. After 26 weeks, the improvement from baseline was statistically significantly larger in the dimebon group than the placebo group. Dry mouth and depressed mood were the most frequently reported adverse events, both by 14 percent of patients. The trial was funded by Medivation Inc.

An abstract of "Effect of Dimebon on Cognition, Activities of Daily Living, Behaviour, and Global Function in Patients With Mild-to-Moderate Alzheimer's Disease: A Randomised, Double-Blind, Placebo-Controlled Study" is posted at <www.thelancet.com/journals/lancet/article/PIIS0140673608610740/abstract>.

Safety Briefs

• The package inserts for all antipsychotics, including but not limited to ***quetiapine, ziprasidone, paliperidone, haloperidol,*** and ***aripiprazole,*** have been modified with a new, standard subsection on dystonia under "Adverse Reactions, Extrapyramidal Symptoms." The warning states that "symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment." It warns that "while these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups." This labeling change took effect for some of the drugs in April and others in May.

The announcement can be accessed at <www.fda.gov/medwatch/safety.htm> by clicking on the April and May lists.

• The package inserts for antidepressants such as ***paroxetine, sertraline,*** and ***fluvoxamine*** have been modified to include standard wording about potentially important drug interactions with warfarin and other drugs, such as aspirin and nonsteroidal anti-inflammatory drugs, which may increase the risk of bleeding. The warning states that "serotonin release by platelets plays an important role in hemostasis" and "epidemiological studies. . .have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding." The label now specifically warns that "SSRIs and SNRIs. . .may increase the risk of bleeding events."

The announcement can be accessed at <www.fda.gov/medwatch/safety.htm> by clicking on the March and April lists.

• The prescribing information for ***atomoxetine*** has been revised to include warnings about the drug's risks for adverse effects on blood pressure and heart rate, urinary retention and hesitation in adults, and potential interactions with drugs, such as the SSRI antidepressants, that inhibit the cytochrome P450 isoenzyme 2D6. Cardiovascular adverse events from new clinical trials in children, adolescents, and adults have been summarized in the package insert.

The updated atomoxetine prescribing information is posted at <www.fda.gov/medwatch/SAFETY/2008/May_PI/Strattera_PI.pdf>.

Regulatory Briefs

• In June the FDA approved ***methylphenidate extended-release tablets*** (Concerta) for treatment of attention-deficit/hyperactivity disorder in adults aged 18 to 65, according to an announcement by Ortho-McNeil-Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson. The approved dosages range from 18 mg to 72 mg once daily.

• The FDA has approved a generic version of ***risperidone*** for marketing in the United States. The generic risperidone tablets are manufactured by Teva Pharmaceuticals, USA. The strengths of the tablets range from 0.25 mg to 4 mg.

• The FDA will no longer issue "approvable" or "not approvable" letters in response to drug companies' new drug applications, the agency announced in July. Instead it will outline the deficiencies of the application and recommendations to resolve them in a "complete response" letter when an application is not approved. Previously, the "approvable" and "not approvable" letters implied a difference in the amount of revision or additional data required by the agency for future approval. This change was made to "help the FDA adopt a more consistent and neutral way of conveying information" when an application is not approved, according to Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research. ■

association news

Board

continued from page 12

Trustees also heard updates on activities in two DBs. Lisa Rone, M.D., president-elect of the Illinois Psychiatric Society, discussed the DB's successful advocacy efforts to convince state lawmakers to expand parity-law mandates to include anorexia and bulimia in the category of serious mental illnesses that insurance plans have to cover.

Kelda Walsh, M.D., president of the Indiana Psychiatric Society, discussed tort reform in the context of the state's Patient Care Fund, which was established in 1975 after huge increases in malpractice premiums. All physicians pay into the fund, thus keeping malpractice rates relatively low. Psychiatrists pay the lowest amount among medical specialists, she pointed out. She also noted that the DB has increased its focus on CME programs, rotating them among different regions of the state. In addition, she cited the problem of Indiana physicians dropping out of Medicaid after reforms to the program, including more prior-authorization requirements. The shrinkage of the number of participating physicians is causing an access crisis, Walsh said.

Actions taken by the Board at its July meeting are posted in the Members Corner of APA's Web site at <www.psych.org>. ■

AMA, APA Conduct Physician Practice Information Survey

APA members who receive the survey are urged to complete and return it.

Watch your mail for the Physician Practice Information survey. APA, the AMA, and more than 70 other organizations are conducting a comprehensive multispecialty survey of America's physician practices. The results will be used to positively influence national decision makers to ensure accurate and fair representation for all physicians and patients, and to articulate the challenges of running a practice that provides expert patient care, while operating a business that is sustainable. Of particular importance is the section of the study pertaining to practice expenses and the amounts that are attributable to you. The Centers for Medicare and Medicaid Services has indicated it will use the results of this study to help determine physician payment.

The survey firm, Dmrkynetec, will contact randomly selected physicians and practice managers to collect responses. Please encourage your staff to make this information available, as the survey's success depends on accurate and complete data. All responses will remain confidential. ■

Antiepileptics

continued from page 1

At this meeting, FDA staff presented updated analyses based on pooled data from 199 clinical trials involving 27,863 patients on active drugs and 16,029 on placebo. The prevalence of any suicidality event was 0.22 percent in patients on placebo and 0.37 percent in those on active drugs. The odds ratio between them was 1.80. The difference between placebo and antiepileptics was statistically significant. The pooled trial data encompassed various indications such as epilepsy, psychiatric disorders, and pain.

Based on the statistical analyses, this risk difference is equivalent to an increase of 1.9 patients with suicidality in every 1,000 patients taking antiepileptic drugs compared with those on placebo.

The FDA had enough data for analysis up to 24 weeks, and the risk of suicidality appears to persist throughout this period. The risk difference between placebo and active drugs is unknown between patients with epilepsy and bipolar disorder who may take the drugs for years.

Class Effect Questioned

At the advisory committees' meeting, Pfizer representatives vehemently argued that its two drugs, pregabalin and gabapentin, were different from the other antiepileptics in the analyses and should be exempt from carrying the suicidality warning. These two drugs, however, were not the least risky of the 11 drugs analyzed. Carbamazepine and divalproex had odds ratios below 1 in the analyses, meaning that the risk of suicidality associated with these drugs was lower than for placebo in clinical trials of these two drugs. In addition, the individual risk with felbamate could not be calculated because no suicidal behavior or ideation was reported in its trials.

Nevertheless, the FDA position is that this "signal" of increased suicidality is a class effect, even though these 11 antiepileptic drugs have different direct biological effects on the nervous system. Mark Levenson, Ph.D., the FDA reviewer who conducted the analyses, pointed out that felbamate and carbamazepine had the two smallest datasets among the 11 drugs (both under 1,000 patients), and the low risk observed may be a result of the small sample size.

While 20 of the 21 members of the advisory committees concurred with the FDA analyses and the conclusion about an elevated suicidality risk, 18 members voted "yes" to the question of whether the increased risk should be applied to all 11 antiepileptic drugs; three members voted "no."

The agency then asked the advisory committees whether they believed this suicidality risk should be extrapolated to all drugs approved for treating epilepsy, even though there are no randomized, placebo-controlled clinical data for direct analyses except for these 11 drugs.

With a 15-5 vote and one abstention, the committees agreed with the agency's recommendation, showing a growing unease with expanding the conclusion to other drugs without direct evidence to support it. This vote was, in part, driven by the worry that some clinicians may be inclined to prescribe older antiepileptics if a suicidality warning was imposed on only newer drugs, even though there is no evidence that the older drugs are safer.

To further complicate the debate, many of the drugs in this class are prescribed for a variety of indications. Carbamazepine and lamotrigene, for example, are major treatments for bipolar disorder. Pregabalin is approved for neuropathic pain, and topiramate for migraine. Off-label use is common among these drugs. The risk-benefit ratio can differ dramatically depending on the illness for which the drugs are used.

Clinicians Reluctant on Label Warning

"We are concerned about the clinical impact of reduced use of mood stabilizers," said Darrel Regier, M.D., M.P.H., director of the American Psychiatric Institute for Research and Education, in his testimony to the advisory committees and the FDA. He urged the agency to refrain from requiring the black-box warning and pointed to the substantial risk of suicide if bipolar patients go without adequate treatment.

"The data in the FDA analyses do not seem to suggest that the rate of suicidal thoughts and behaviors [linked to antiepileptics] outweighs the potential harm from possible medication discontinuation as a result of a black-box warning," he said.

Laurence Greenhill, M.D., president of the American Academy of Child and Adolescent Psychiatry, echoed Regier's concerns in his testimony. "As we have learned from previous experience, the FDA's decision to use a black-box warning significantly influenced prescribing in psychiatry and impacted patient care." Patients with serious neurological and psychiatric disorders could face life-threatening risks if they choose to stop taking these necessary treatments out of fear linked to the black-box warning, he noted.

"There is a need for prospective, systematic analysis of suicidality as opposed to relying on retrospective, spontaneous reports of suicidal events in clinical trials," Regier said.

Many members on the advisory committees expressed concerns about the unintended consequences of black-box warnings on patient care. The documented reduction in antidepressant prescribing in pediatric and adult patients with depression after the black-box warning about suicidality was issued in 2004, and the warning's impact on public health, continues to worry some clinicians.

In the end, the advisory committees voted 14-4, with three abstentions, to recommend against imposing a black-box warning for all antiepileptic drugs.

The FDA faces a difficult decision because it has limited means to communicate nuanced risk information to the public and clinicians. Russell Katz, M.D., director of the agency's Division of Neurology Products, told reporters after the meeting that the final decision on the warning for antiepileptic drugs will be announced soon. In the past, the FDA has frequently, but not always, followed the recommendations of its advisory committees. ■

government news

Young Adults

continued from page 10

coordinate programs that serve youth with mental health needs, youth with physical disabilities, and such youth in transition to adulthood.

The limited state and federal efforts are not sufficient to truly help this population, which is large and has real, demonstrated needs, said mental health advocates.

"We need a 50-state strategy to provide life skills, education, housing, supported employment, and other services that can serve as a foundation for the future of young adults in transition who live with mental illness," Fitzpatrick said.

The recently introduced federal legislation would provide grants to states to develop statewide coordination plans to assist adolescents and young adults with serious mental illness and get access to resources they need to make a successful transition to adulthood. After the Substance Abuse and Mental Health Services Administration (SAMHSA) has approved their plan, states can compete for a second round of grants to help them implement their plan.

In addition, the legislation would fund a coordinating committee among federal agencies to ensure that programs that assist adolescents and young adults with mental illness at the federal level work together and provide technical assistance to states as they implement their coordination plans. The federal group also would be required to report to Congress on the committee's progress.

"We know that we can do a better job of helping these youth," Smith said. "We can do better at ensuring they can remain stable in their communities, that they can live healthy lives, and that they can prosper as adults."

The Healthy Transition Act of 2008 can be accessed at <http://thomas.loc.gov> by searching on the bill numbers, HR 7375 and S 3195. The GAO report, "Young Adults With Serious Mental Illness: Some States and Federal Agencies Are Taking Steps to Address Their Transition Challenges," is posted at <www.gao.gov/new.items/d08678.pdf>. ■

community news

Schizophrenia

continued from page 11

Almost half of caregivers surveyed (41 percent) reported providing care to an individual with schizophrenia for more than 10 years. The vast majority (90 percent) worry about what will happen to the individual when they die.

Recommendations from the report authors, who include psychiatrists and mental health advocates, include earlier and more widespread recognition of schizophrenia symptoms, training of primary care health professionals about schizophrenia symptoms and treatment, and continued research of new treatments for the disorder.

The report, "Schizophrenia: Public Attitudes, Personal Needs," is posted at <www.nami.org/schizophreniasurvey>. ■

letters to the editor

Credibility Gap, Revisited

In the October 21, 2005, issue, *Psychiatric News* published my letter to the editor about conflicts of interest, psychiatry, and pharmaceutical and device makers. Also published was the eloquent response of Dr. Steven Sharfstein, then APA president.

At this time, I would like to revisit that issue and ask the American psychiatric community: Isn't it time that we reevaluate the ethics of accepting *any* funding from pharmaceutical companies and their surrogates? I believe that it is.

Recent articles in the *New York Times* reporting allegations of pharmaceutical payments to university researchers that were not disclosed to their universities reinforce my earlier conviction. As long as we hold dear to the morality of the worthwhile tasks of psychiatry and its subspecialties, we cannot expect, at the same time, that those values can be believed if they are mired in the millions of dollars from companies that have a vested interest in promoting themselves through us.

Our ethics should no longer be for sale. We should not be beholden to interests that are separate from honest clinical research or transparent publications. We should avoid company-funded publications that serve not to find answers to clinical questions but, instead, to expand markets for patented pharmaceuticals.

What is the short-term risk to rejecting corporate monies? Perhaps we downsize our splendid meetings and trade our glossy pages of *Psychiatric News* for newspaper print. Perhaps we curtail our ability to fund certain special projects and seminars, including repetitive ones that serve little purpose other than to add a line to an academic resume. However, what we will have is the opportunity to say to our fellow physicians, health care workers, and the public—and those who look to American psychiatry for stewardship—that we place principles before bias and integrity before price. Resolutely, we psychiatrists have one aim: to not harm and to help where and when we can to those we serve.

STEFAN KRUSZEWSKI, M.D.
Harrisburg, Pa.

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.

Schatzberg

continued from page 6

Additionally, the university stressed that Schatzberg has not "been involved in managing or conducting any human subjects research involving mifepristone, a pharmaceutical that Corcept licenses for the treatment of psychotic major depression."

Stanford acquired a patent on mifepristone in the 1990s following NIMH-funded research, for which Schatzberg was principal investigator, on the biology of psychotic depression. The patent was then licensed to Corcept. "Before the patent was issued, Dr. Schatzberg did not have any financial interest in this drug. Once he was aware he was going to have a financial interest in mifepristone, he disclosed it, and Stanford University managed the conflict of interest."

The university added, "Stanford and Dr. Schatzberg disclosed this conflict and the fact that Stanford was managing the conflict to the NIH [National Institutes of Health]. In addition, NIH reviews its data through its Data Safety and Monitoring Board structures."

Stanford also said in its statement that it had acquired "a small amount of equity in Corcept under a technology license" and that "pursuant to its policy on institutional conflict of interest, Stanford divested itself of the stock."

However, a search of university SEC filings turned up a March 31 filing that appeared to indicate that some 47,000 shares are held in the university's name. (The SEC filing is a "13F" document that, according to the SEC's Web site, "is required of institutional investment managers who exercise discretion over $100 million or more in securities." It can be found online at <www.sec.gov/Archives/edgar/data/1315828/000131582808-000002.txt>.)

When *Psychiatric News* asked the university about its filing, the university issued a statement in which it explained that the stock is individually held by the university's investment management company as part of a fund for the graduate school of business and is not related in any way to the university's research on mifepristone.

"A Stanford Graduate School of Business [GSB] investment fund, whose purpose is to benefit the school's education programs, purchased $100,000 of stock in Corcept Therapeutics in August 2007," Stanford said in a statement. "The University does not monitor the individual holdings of its investment funds managed by the Stanford Management Company, including the GSB fund, as there is an ethical wall between the University's research and operations and investment of its endowment, so that one does not influence the other. This transaction occurred more than three years after the University had divested its entire stake in Corcept, acquired through its licensing agreement with Corcept. That sale was the result of the University's institutional conflict of interest policy, enacted in December 2002, that prohibits the University from holding any stock in a company acquired through licensing of its technology if the company has a product undergoing human subjects research at the University. Investments in publicly traded companies managed by the Stanford Management Company are not required to be divested because it is believed that these circumstances sufficiently insulate University faculty and administrators from presumed biasing effects."

Additionally, information contained in Corcept filings with the SEC—and later confirmed by Stanford's press office—indicates that Stanford also receives $50,000 annually from Corcept as a nonrefundable royalty payment. The company is also obligated to pay Stanford a $50,000 "milestone" payment upon the filing of a new drug application for Corlux (the company's brand name for mifepristone) for the treatment of Alzheimer's and psychotic major depression. The company will be required to pay a further $200,000 milestone payment upon FDA approval of Corlux, according to the SEC filing.

"Stanford gets no payments for any other uses of mifepristone/Corlux," a Stanford press officer told *Psychiatric News*. "The payments are related only to the use of the patent for Alzheimer's disease or psychotic depression; all other uses are outside of the two indications covered in the Stanford patent."

In an interview with *Psychiatric News*, Schatzberg characterized Grassley's investigation as an "attack" and defended his work on developing drugs for psychotic depression.

"I don't relish the publicity," Schatzberg said. "What we have done for the last 10 years is try to develop a novel treatment for one of the most serious mental illnesses. If that is going to be impugned, then it is a sad state of where we are in terms of trying to help people with severe mental illness.

"I have nothing to hide, and I am delighted that Stanford has made it clear to the public that all is OK and there were no improprieties."

As for the money from his investments and consulting activities, he said, "Anytime someone makes a profit, it will generate a lot of conflicting feelings among people, including anger."

In addition, Schatzberg emphasized that the current system of drug development allows for—actually encourages—the kind of collaboration between academic medicine and the pharmaceutical industry that has existed between Stanford and Corcept.

Specifically, a 1980 change to a federal law known as the University and Small Business Patent Procedures Act (also known as the Bayh-Dole Act, after its sponsors Birch Bayh, a former senator from Indiana, and Bob Dole, a former senator from Kansas) gives U.S. universities and nonprofit organizations intellectual property rights over inventions—such as novel pharmaceuticals—that result from federal research funding.

The law was specifically enacted to speed the transfer of research discoveries to the marketplace by allowing universities to license their patents to private firms—just as Stanford did with its patent on mifepristone. Mifepristone is also known as RU486, a drug that acts as a progesterone antagonist and has for that reason been used to induce abortion.

But as Schatzberg explained, it is also a glucocorticoid antagonist. "We have long had the idea that psychosis seen in depression is due to excessive production of cortisol and could potentially be treated by administering antagonists for the low affinity glucocorticoid receptor," he said.

But in part because of politics surrounding the use of the agent to induce abortion, companies did not want to invest in testing it for psychotic depression.

"If we were ever going to get the drug to the market for psychotic depression," said Schatzberg, "we were going to have to do it ourselves."

Stanford's response to Sen. Grassley's charges is posted at <http://ucomm.stanford.edu/news/conflict_of_interest_schatzberg_grassley.html>. Information on stockholders of Corcept Therapeutics Inc. is posted at <http://finance.yahoo.com/q?s=CORT>. The SEC filing by Corcept is posted at <http://sec.edgar-online.com/2004/04/14/0001193125-04-061825/Section12.asp>. ■

Mortality

continued from page 7

ing access to care has found some success. The integrated care program in Summit County combined the staffs of a community health center and a mental health clinic to create "care teams" of general and mental health care providers within a facility that had previously emphasized general health care. The program provided training for the mental health staff in the common physical health care needs of people with mental illness and educated the general health care providers on signs that patients may also need mental health and substance abuse treatment.

Among the biggest impacts of the program was the improved communication it encouraged between two traditionally separate organizations, to the extent that both were comfortable referring patients and seeking additional information from the other side of the program.

"It's important to share our knowledge and share our ignorance," said Helen Royal, a nurse in the program.

Advocates at the congressional briefing said the federal government can encourage such pilot programs by including funds for them in their established grant programs.

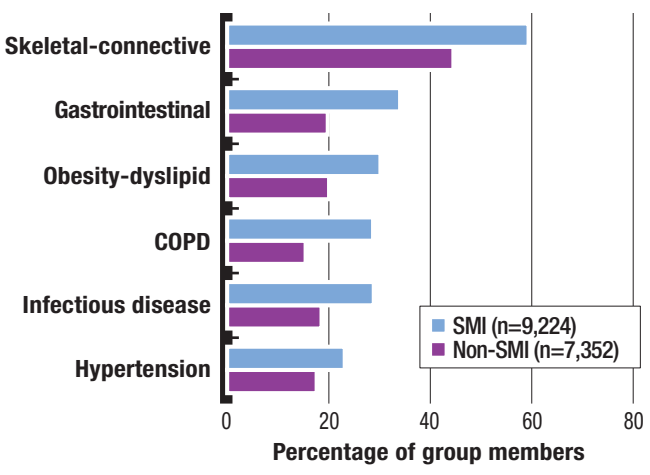
Also, the Community Mental Health Services Improvement Act (S 2182 and HR 5176) would create a new grant program through the Substance Abuse and Mental Health Services Administration (SAMHSA) to fund the co-location of primary care services within mental health organizations. The legislation, which would provide $50 million in grants for the first year of a five-year program, was included in draft legislation to reauthorize SAMHSA, but that legislation has stalled for the year.

Supporters are optimistic that the grant program will be revived in Congress next year, along with efforts to require insurers to cover smoking cessation and obesity treatment programs.

The text of S 2182 and HR 5176 can be accessed at <http://thomas.loc.gov> by searching on the bill numbers. ■

Chronic Health Problems Common In Seriously Mentally Ill People

People with serious mental illness (SMI) are more likely to have a range of chronic health conditions that contribute to life expectancies that are on average 25 years shorter than those of the general population. The conditions are treatable but often go undiagnosed.



Source: Morbidity and Mortality in People With Serious Mental Illness, National Association of State Mental Health Program Directors report, 2006

Recovery

continued from page 15

tion of mental health care in America, such that "adults with serious mental illness and children with severe emotional disturbance [can] live, work, learn, and participate fully in their communities."

The vision of recovery has been adopted by most public mental health authorities. In December 2004, more than 100 leaders, including mental health and addiction recovery experts, consumers and families, advocates, community and state officials, national-association staff, and public officials, joined forces at the consensus conference "Mental Health Recovery and Systems Transformation," sponsored by the Substance Abuse and Mental Health Services Administration. Its goal was to define recovery, reach a consensus on its key principles and elements, and identify recovery implementation strategies that work.

The Irwin Foundation was created in honor of Irwin B., who had a severe mental illness. While he eventually benefited from treatment advances, enabling him to end a relentless cycle of hospitalizations, he continued to struggle with stigma and nonacceptance. The foundation is designed to commemorate his courage and determination to eliminate stigma and to create a better future for those recovering from mental illness.

Since 2001, the Irwin Foundation has held Celebration Recovery events across the country, including at the Institute on Psychiatric Services.

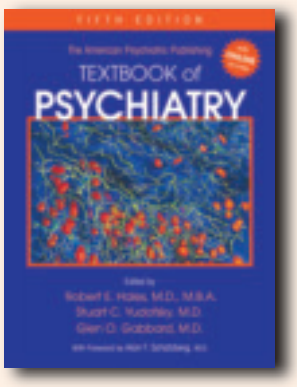
More information on Celebration Recovery is posted at <www.celebrationrecovery.org> and <www.irwinfoundation.org>. ■

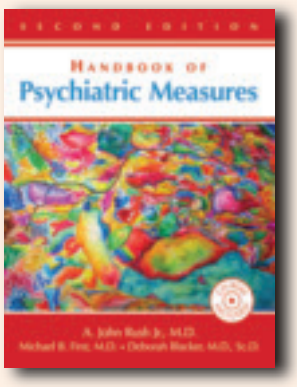
Save 10%

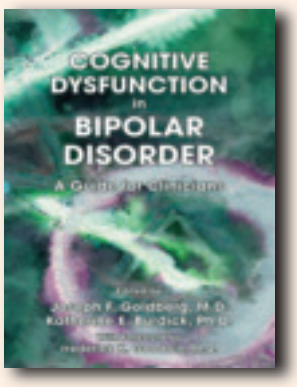
Order online at www.appi.org to receive a 10% discount off all books and journals.

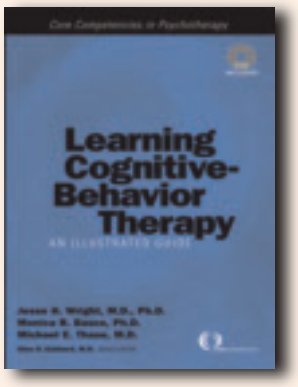
This 10% discount will be added to any existing discounts.
(For example, American Psychiatric Association Members will receive a 20% discount and APA Members-in-Training will receive a 35% discount.)

Everything is on sale including these bestselling titles:









*Discount is only available at **www.appi.org** and will be applied in the shopping cart.*
Discount valid through August 31, 2008.

American Psychiatric Publishing, Inc.

The *First* and *Last* Word in Psychiatry
Order Online: www.appi.org • Toll Free: 1-800-368-5777 • Fax: 703-907-1091 • Email: appi@psych.org
Priority Code AH850

HUTCHINGS PSYCHIATRIC CENTER

Clinical Director, Psychiatric Center, M-8

- Salary Range: $184,828 - $217,034 -

Hutchings Psychiatric Center (HPC) is seeking candidates for the position of:

CLINICAL DIRECTOR

Psychiatric Center

HPC is state-operated, Joint Commission accredited facility, which has been providing comprehensive mental health services to Onondaga, Cayuga, Cortland, Madison and Oswego counties since 1972.

New York State OMH Office of Mental Health

EQUAL OPPORTUNITY/ AFFIRMATIVE ACTION EMPLOYER

Located in the University Hill district in the heart of the Syracuse medical community, Hutchings has 105 adult inpatient beds, and provides outpatient services to 1,250 adults through a system of clinical, residential, social rehabilitation, and vocational rehabilitation services.

For more information about Hutchings Psychiatric Center, please visit our website at:

http://www.omh.state.ny.us/omhweb/facilities/hupc/facility.htm

QUALIFICATIONS:

- Board Certification in Psychiatry issued by the American Board of Psychiatry and Neurology or clearly equivalent certifying body; **and**
- A minimum of seven years of extensive professional experience providing services to people diagnosed with mental illness (two years must have been in a position comparable to a Clinical Chief of Service in the New York State Office of Mental Health); **and**
- A valid license to practice medicine in New York State or a New York State limited permit and licensure in another state or Canada; **and**
- Eligibility for full and unconditional participation in the Medicaid and Medicare programs.

Note: Employment is contingent upon maintaining a current New York State limited permit or obtaining full New York State licensure and maintaining eligibility for full and unconditional participation in the Medicaid and Medicare programs.

To apply please send curriculum vitae by September 5th, 2008 to:
NYS Office of Mental Health, Facility Personnel Services
44 Holland Avenue, Albany, NY 12229
ATTENTION: Clinical Director, Hutchings PC
PHONE: (518) 474-1251 / **FAX:** (518) 402-4086
Email: omhjobs@omh.state.ny.us

MEDICAL DIRECTOR & PSYCHIATRISTS

Southwestern Virginia Mental Health Institute (SWVMHI), located on 85 acres of tranquility in Marion, Virginia invites applications for our Medical Director and Psychiatrist openings. We are a progressive Joint Commission-accredited psychiatric hospital, with 172 beds serving adolescent, adult, geriatric and forensic patients. We offer a team oriented environment, university affiliation, and an excellent compensation and benefits package.

For our **Medical Director** position, we seek a motivated, board certified Psychiatrist with strong leadership/management skills to lead a medical staff. The Medical Director participates in facility and statewide strategic planning and improvement initiatives and is a leader in clinical improvement initiatives through membership on the SWVMHI Executive Management Committee and the Commonwealth of Virginia's system of health and quality care.

For our **Psychiatrist** positions, we seek candidates who are board certified or eligible in psychiatry to work with adult patients (ages 18-64), geriatric patients (ages 65 and older), and adolescent patients (ages 13-17).

The chosen candidates for these positions will possess or be eligible for licensure to practice medicine in Virginia and have a commitment to recovery principles as they work with multi-disciplinary treatment teams to provide active treatment for psychiatric patients. As a member of our medical staff, you will participate in the leadership of the hospital. Candidates may qualify for loan repayment with the Virginia Department of Health.

You may contact Ms. Ruby Wells, Human Resources Director, 276-783-1204 or visit our website **www.swvmhi.dmhmrsas.virginia.gov** for more information. Interested individuals, please forward a resume or complete the required employment application by visiting our website, or by visiting **http://jobs.agencies.virginia.gov.**

Southwestern Virginia Mental Health Institute
340 Bagley Circle, Marion, VA 24354

EOE

Persons with disabilities are encouraged to apply

SAVAHCS
Southern Arizona VA Health Care System

Make a difference to those who have served. Our Veterans need you – in Arizona!

You are invited to join the Professional staff at the Southern Arizona VA Health Care System (SAVAHCS) in Tucson or the Community Based Outpatient Clinics (CBOCs) in Southeast Tucson or Casa Grande, Arizona as a

PSYCHIATRIST

Our facility is seeking to fill several full-time positions with highly skilled Board Eligible/Board Certified Psychiatrists to provide outpatient, inpatient and/or consultant liaison services to a diverse patient population. Academic experience and research interest is a major plus. Responsibilities include direct patient care, supervision and education of residents and medical students from our affiliate the University of Arizona. Academic rank and tenure are commensurate with experience, education and training.

Offering competitive salary and benefits, including...

- 26 Vacation Days
- 13 Sick Days
- 10 Holidays
- Many Health Plan options
- Vision and Dental plans
- Federal Retirement
- Education Debt Reduction/Repayment program

Detailed vacancy announcements are available at http://www.vacareers.va.gov or http://www.usajobs.opm.gov . Please reference vacancy number 08-127A (Tucson), 08-121A (SE CBOC); or 08-122A (CBOC Casa Grande) on your CV/application material.
Clinical contact: Dr. David Emelity, (520) 629-1792, Chief Mental Health Care Line.

To Apply: Submit CV (include cover letter & 3 references) via email to andrea.mucha@va.gov, or via postal service to SAVAHCS, 3601 S. 6th Ave., Tucson, AZ 85723, Attn: HR/9-05.

The Department of Veterans Affairs is an Equal Opportunity Employer.

The Best Care The Best Careers HEALTH CARE CAREERS OF A LIFETIME

PSYCHIATRIST WANTED

Firelands Regional Medical Center invites you to become a member of one of the most progressive healthcare teams in the Heart of Vacationland.

Firelands Regional Medical Center is a 440 licensed-bed hospital in the final stage of a $146.9 million expansion and renovation project. The medical center serves a population of over 250,000 in a six county area.

Sandusky, located on the southern shore of Lake Erie, is one hour west of Cleveland, and one hour east of Toledo. The area is famous for its recreational facilities, which include beautiful city and state parks, fishing piers, beaches, Cedar Point Amusement Park and boating facilities. Our North Coast region is also rich in both cultural activities and educational opportunities.

For more information, call Dru Meredith, Physician Recruiter at 419-557-7885, or e-mail resume to meredid@firelands.com, fax 419-557-7886.

CHAIR, DEPARTMENT OF PSYCHIATRY

John H. Stroger Jr. Hospital of Cook County (JHSH), formerly Cook County Hospital, is seeking candidates for the Chair of the Department of Psychiatry. JHSH is a newly constructed 464-bed tertiary care general hospital, and is the flagship of the Cook County Bureau of Health Services, an integrated health care system with three major hospitals and affiliated community-based clinics.

Applicants will lead 25 staff clinicians, including psychiatrists, psychologists, mental health nurses and other professionals, delivering over 12,000 visits per year. The Chair will oversee all Psychiatric services and programs. These include adult and child outpatient services, liaison services to inpatients and emergency department, and student training programs. The applicant must possess a desire to lead by example, have strong interpersonal and consensus-building skills, excellent clinical care and teaching skills, and have at least five years of administrative/supervisory experience in Psychiatry.

Previous experience in a multicultural healthcare system and in addiction medicine is preferred. Applicants must have current licensure and specialty board certification. JHSH is an equal opportunity employer and actively solicits applications from women and underrepresented minorities. **Send CV and 3 references to:**

Maria L. Torres, M.D.
Chair, Search Committee for the Psychiatry Department Chair
Department of Anesthesiology and Pain Management
John H. Stroger, Jr. Hospital of Cook County
1901 West Harrison Street, Clinic B, Suite 1233
Chicago, Illinois 60612
Phone: (312) 864-1903 Fax: (312) 864-9536
Email: mltorres1@msn.com

Psychiatry Hospitalist Opportunity
Madison, WI

NO CALL, NO NIGHTS, NO WEEKENDS

Dean Health System, a 500+ physician owned multispecialty group, is actively seeking a board eligible or board certified General Adult Psychiatrist to function as a hospitalist at St. Mary's Hospital in Madison, Wisconsin. This is an outstanding career opportunity that offers an attractive day time work schedule of 8 a.m. to 5 p.m., Monday through Friday, with no call or weekends. Proficiency in ECT is preferred. This hospital based position averages 4 inpatients and 2 consults per day, plus follow up care to patients. Dean offers a competitive salary and benefits package with employment leading to partnership.

For more information please contact:
Kate Kaegi, Physician Services Manager
Dean Health System
1808 West Beltline Highway
Madison, WI 53713

Phone: (800) 279-9966 ext. 1071
Fax (608) 250-1020
kate.kaegi@deancare.com.

Dean Health System

www.deancare.com

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. J-1 visa applicants accepted.

Call us today regarding impending salary increases!

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.

Joginder Singh, M.D.
(559) 935-4343
JSingh@csh.dmh.ca.gov

www.dmh.ca.gov
CSH is an equal opportunity employer

CALIFORNIA DEPARTMENT OF Mental Health

Mental Health Care Professionals
Psychiatrists/Psychologists/Social Workers
Clinical Nurse Specialists/Addiction Therapists

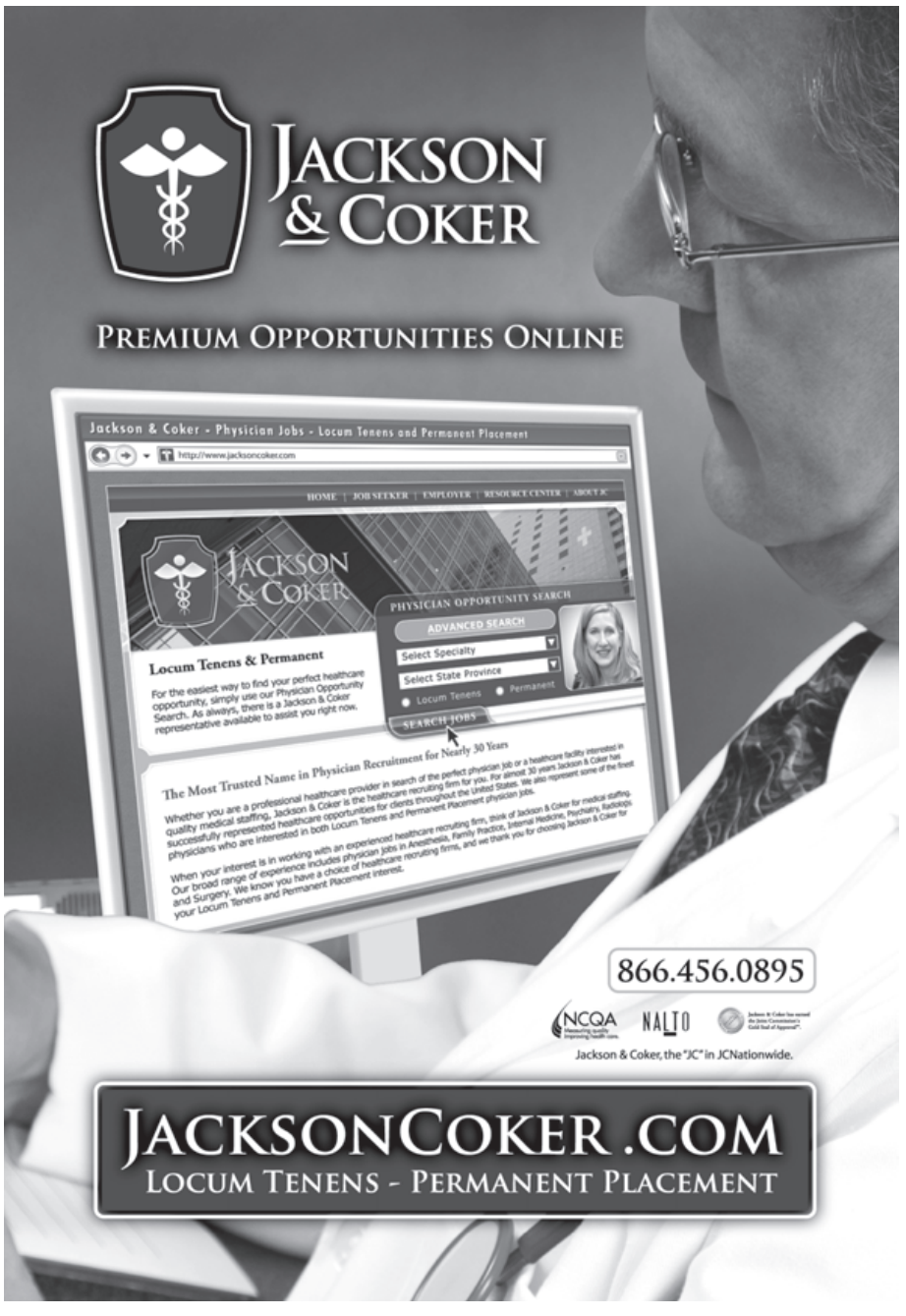
Join VA Northern California Health Care System's (NCHCS) mental health care team and support America's heroes. NCHCS is now hiring mental health care professionals to be part of our interdisciplinary care team; you'll treat patients struggling with the full range of emotional and mental disorders, including PTSD, traumatic brain injuries, mood disorders, substance abuse disorders, and sexual trauma. You'll work in an environment where innovation is encouraged and scientific evidence directs our practice.

We are now hiring for full and part time positions in Sacramento, Fairfield, Redding and Chico. Call today and be a part of VA's Mental Health Enhancement Initiative.

- Interdisciplinary care team model of practice
- Practice model is based on care needs, not insurance company regulations
- Your out of state license allows you to practice at any of our facilities
- Diverse professional opportunities – clinical, leadership, research, education, and national policy development
- Salary is competitive and based on credentials and experience
- Exceptional paid time off package
- Excellent health and retirement benefits
- Student loan reimbursement of up to $38,000 for psychiatrists, psychologists and psychiatric nurses

Please email Linda Nestor, Human Resources Specialist at **linda.nestor@va.gov**.

Department of Veterans Affairs an Equal Opportunity Employer



Connecticut **DMHAS**

Department of Mental Health and Addiction Services
A Healthcare Service Agency

PSYCHIATRIST POSITIONS (REFERENCE #AB1000)

DMHAS HAS CHALLENGING OPPORTUNITIES:

FULL/PART-TIME OR PER DIEM

Connecticut Valley Hospital, Middletown, Connecticut
Capitol Region Mental Health Center, Hartford, Connecticut

Whiting Forensic Division is seeking psychiatrists interested in working in a forensic psychiatric facility that is JCAHO-accredited, CMS-certified and affiliated with the Yale University Law and Psychiatry Division. Applicants must be board-eligible or board certified. Forensic Fellowship training is preferred, but not required. Yale faculty appointments are available to qualified candidates.

General Psychiatry Division, which serves a very diverse patient population in a number of specialized treatment programs, is seeking a psychiatrist for its Transitional Rehabilitation Program.

Full-time position available at **Capitol Region Mental Health Center, Hartford, Connecticut** - a community-based mental health center which provides an array of innovative clinical and community support services to individuals with a psychiatric disability, in many cases with co-occurring problems of substance abuse.

In addition to providing individuals with behavioral health services, CRMHC also collaborates with the Greater Hartford DMHAS-Funded Mental Health Programs, which are comprised of 16 non-profit agencies located in Hartford and West Hartford. These agencies work together to provide a comprehensive array of behavioral health services to nearly 3,300 individuals and families.

Salary Range: $137,314 to $168,659 (depending upon experience, licensing and certification)

The State indemnifies employees for damage or injury, not wanton or willful, caused in the performance of his/her duties and within the scope of his/her employment as provided by Sections 4-165 and 19a-24 of the C.G.S. This position provides excellent health/dental insurance and generous vacation/personal leave and licensure fee reimbursement.

Interested candidates mail/FAX a State Employment Application (PLD-1) with the DMHAS Addendum (available at www.ct.gov/dmhas/employmentopportunities) and CV to:
Audrey Bongiorno, Employment Services Division, P.O. Box 1508,
Middletown, CT 06457 Telephone: (860) 262-6740, Fax: (860) 262-6770

DMHAS is an Affirmative Action/Equal Opportunity Employer.
Members of protected classes and/or individuals in recovery are encouraged to apply.

Isn't it time
for something better?

Child/Adolescent Psychiatrist
Olympia, WA

Group Health Permanente is currently seeking a Child & Adolescent Psychiatrist. Group Health is dedicated to providing comprehensive, innovative & patient-centered care to communities throughout WA. We offer a flexible schedule with generous benefits & competitive salaries.

- Ideal candidate will have knowledge & skills in medication management and team consultation.
- 100% outpatient opportunity perfect for those with experience working with diverse patient populations.
- An unparalleled place to live, Olympia offers affordable housing, excellent schools & breathtaking views.

For additional information or to submit your CV, please contact:

Cayley Crotty – crotty.c@ghc.org
206-448-6519

EOE/AA

www.ghc.org/greatjob GroupHealth

Being a doctor just got

X20991| (06/07) ©AHC

Psychiatry

Favorable Malpractice Climate in Wisconsin

Paid Medical Liability Insurance

Aurora Health Care, a not-for-profit, integrated health care delivery system in eastern Wisconsin, has opportunities for both adult and C&A psychiatrists in Sheboygan. Aurora Sheboygan Memorial Medical Center has an inpatient psychiatric unit for the region. Models available include hospitalist, traditional practice or outpatient-only. Nestled on the shores of Lake Michigan, Sheboygan boasts the virtues of a small, safe, family-centered midwestern city. Sheboygan has been praised nationally for being one of the best places to raise a family (*Reader's Digest,* 1997).

For more information, visit ***www.Aurora.org/PhysicianOpportunities*** or contact Physician Recruitment at 1 (800) 307-7497.

Equal opportunity employer M/F/D/V

Aurora Health Care®

THE INSTITUTE OF LIVING / HARTFORD HOSPITAL

SEEKING:

ACADEMIC CHILD & ADOLESCENT PSYCHIATRIST

- Half-time support for research activities
- Academic affiliation with Yale or the University of Connecticut
- Combine with position as Director of C/A Residency Training, or providing clinical care and teaching

Located in the heart of Connecticut, Hartford enjoys easy access to diverse cultural, sporting and outdoor activities, including those in New York City and Boston.

FOR DETAILS:
www.instituteofliving.org/ChAdolPsychiatrist.pdf

Send Inquiries to:

Robert A. Sahl, M.D.
Division Chief, Child and Adolescent Services
rsahl@harthosp.org
or
Michael Stevens, Ph.D.
msteven@harthosp.org

THE INSTITUTE OF LIVING
HARTFORD HOSPITAL

www.instituteofliving.org

EOE M/F/D/V

passion + purpose = job satisfaction

This is exactly what you'll find at Remuda Ranch. Extending hope and healing to patients suffering from eating and anxiety disorders provides a sense of fulfillment rarely found in other jobs. In addition to profound satisfaction, you'll discover job security, which is a rare commodity in today's employment market. Since 1990, Remuda has experienced steady growth in Arizona and has opened a second program in Virginia.

Psychiatrists (AZ)
Psychiatric NP (AZ)
Psychiatric Supervisor (AZ)

Satisfaction and security is available right now at Remuda.
To apply go to www.remudaranch.com/careers.

REMUDA Ranch®
Hope • Healing • Life
PROGRAMS FOR EATING DISORDERS

1-800-445-1900 remudaranch.com

EOE

TOP 100 HOSPITAL EXPANDING IN CENTRAL TEXAS

ADULT PSYCHIATRISTS
SCOTT & WHITE/TEXAS A&M COLLEGE OF MEDICINE, CENTRAL TEXAS

Scott & White and Texas A&M College of Medicine is seeking outstanding candidates to join our nationally recognized Department of Psychiatry. Currently, we have openings for Adult Psychiatrists at our College Station Clinic. The division in College Station includes 2 full time Psychiatrists and 4 full-time Psychologists, offering a wide variety of preclinical and clinical teaching opportunities as the College of Medicine expands its campus in College Station. We are a full service Psychiatric Department with specialty clinics and programs. We have a diverse faculty with a close sense of collegiality.

The S&W College Station Clinic is the largest of our twenty regional clinics system, with more than 80 physicians from all specialties networked to the main campus and hospital in Temple. College Station is 90 minutes west of Houston, 90 minutes east of Austin, and 3 hours south of Dallas, and is home to Texas A&M University.

Led by physicians with a commitment to patient care, education and research, Scott & White is listed among the "Top 100 Hospitals" in America in several categories, and has been listed as a Solucient Top 15 Teaching Hospital for the past three years. All staff are full-time Texas A&M medical school faculty. The health system and medical school are investing heavily in basic, translational and clinical research, with appropriate support.

Scott & White offers a competitive salary and comprehensive benefit package, which begins with four weeks vacation, three weeks CME and a generous retirement plan. For additional information regarding these positions, please contact: Jason Culp, Physician Recruiter, Scott & White Clinic, 2401 S. 31st, Temple, TX 76508. (800) 725-3627 jculp@swmail.sw.org Scott & White is an equal opportunity employer. A formal application must be completed to be considered for these positions. For more information on Scott & White, please visit our web site at: www.sw.org

SCOTT & WHITE

TEXAS A&M HEALTH SCIENCE CENTER COLLEGE OF MEDICINE

Psychiatry Opportunity
Madison, WI

Dean Health System, a 500+ physician owned multispecialty group practice, is seeking a general adult psychiatrist for its Madison location. This is an outstanding career opportunity to work with a multidisciplinary staff providing psychiatric consultation, medication management, and solution-focused psychotherapy in a unique, collegial work environment. This is a primarily outpatient position with a call schedule of 1 in 8. Competitive salary and benefits with employment leading to partnership. Madison, population 200,000+, is the state capital of Wisconsin and the home of the University of Wisconsin (a Big 10 School). Madison consistently ranks as one of the best places to live in the U.S. due to its great lifestyle, strong economy, and excellent educational and recreational opportunities.

For more information please contact:
Kate Kaegi, Physician Services Manager
Dean Health System
1808 West Beltline Highway
Madison, WI 53713

Phone: (800) 279-9966 ext. 1071
Fax (608) 250-1020
kate.kaegi@deancare.com.

Dean Health System

www.deancare.com

What makes Maimonides

the best place to work?

Our employees' impact

Maimonides is Brooklyn's premier specialty care teaching hospital. We pioneer medical breakthroughs, boast state-of-the-art clinical and information technology, train more medical residents than anyone else in Brooklyn and regularly win awards from independent evaluators for the quality of our care. We are compassionate, patient-centered, and focused on employee participation and development.

Supervising Psychiatrist

In this role, you will work in the adult outpatient division of the Department of Psychiatry to provide clinical care and supervision of psychiatry residents. The Department's large multidisciplinary teaching program provides an extensive array of services for a multiethnic community.

Interested candidates must have a NYS license, board certification, and outstanding teaching skills. Bilingual Spanish/English or Mandarin/English is preferred. Candidates are eligible for an academic appointment.

This position is also eligible for a Loan Repayment Program.

We offer competitive compensation. Please apply on-line: **www.maimonidesmed.org** or send your resume to: **Human Resources Department, Maimonides Medical Center, via email: resumes@maimonidesmed.org or fax: 718-635-8157.** EOE.

Maimonides
Medical Center
www.maimonidesmed.org
Passionate About Medicine. Compassionate About People.

The St. Cloud VA Medical Center is growing; we continue to increase our services to veterans and we are very excited about this. To support our continued growth, we are adding new positions and have more opportunities for you to join us! Current opportunities available with the medical center include:

MENTAL HEALTH

Psychiatrist to serve as Director, Mental Health: Seeking director to oversee large inpatient, outpatient and residential psychiatric services.

Staff Psychiatrist: Outpatient and inpatient psychiatric practice.

For applications for the above position call 320-255-6301. Please reference the announcement number on your application.

The VA Medical Center offers competitive benefits and compensation packages.

VA Medical Center
4801 Veterans Drive
St. Cloud, MN 56303
Phone 320-255-6301

EOE

UNIT CHIEF (BC) OR ATTENDING (BE) INPATIENT PSYCHIATRIST

Mount Sinai School of Medicine's affiliation with Queens Hospital Center has immediate openings in the Department of Psychiatry for:

Unit Chief (BC) or Attending (BE) Inpatient Psychiatrist
Join 2nd Psychiatrist on Student
Teaching 18-bed Unit.

ACT/CPEP Psychiatrist
Full-time role to join 2nd New ACT Team.

Our Department has been recognized as a Center of Excellence and provides a full continuum of care including CPEP, PHP, CDTP, Community Satellites, ACT, Child & Adolescent, EIP/CCD, four inpatient units, and a medical detox unit.

New July 1st PAY SCALE

We offer an excellent compensation package.
Mount Sinai School of Medicine is an equal opportunity/ affirmative action employer. We recognize the power and importance of a diverse employee population and strongly encourage applicants with various experiences and backgrounds.

Send resume to:
Joseph P. Merlino, MD, MPA, Director
Department of Psychiatry
Queens Hospital Center
82-68 164th Street
Jamaica, NY 11432
fax: 718-883-6135

E mail: Merlinjo@NYCHHC.org

EOE/AA-D/V EMPLOYER

Isn't it time
for something better?

Adult Psychiatrist
Tacoma, Washington

Group Health Permanente, the Northwest's premier specialty group, is currently seeking a BC/BE Adult Psychiatrist to join our Tacoma team. Group Health is dedicated to providing comprehensive, innovative & patient-centered care to communities throughout WA.

- Ideal candidate will have knowledge & skills in medication management and team consultation.
- 100% Outpatient opportunity with limited call coverage.
- A flexible schedule, generous benefits and competitive salaries make this an opportunity worth exploring.

For additional information or to submit your CV, please contact:

Cayley Crotty – crotty.c@ghc.org
206-448-6519

EOE/AA

www.ghc.org/greatjob GroupHealth

Psychiatrists Near Coast!

McLeod Regional Medical Center

A 453 bed, tertiary care and teaching facility, located in Florence, South Carolina is recruiting a full-time BC/BE Adult Psychiatrist. Offering a competitive salary guarantee and comprehensive benefits package to include paid professional liability Insurance, CME, and relocation assistance. Call 1/4. Inpatient/ outpatient practice setting. 23 bed in-patient unit. Extensive support staff for hospital and ED consults.

The urban population of Florence is 70,000 with 130,000 in the county. Located 2 hours from historic Charleston, and 1 hour from the beach. Recent acknowledgements from Health Grades and the American Hospital Association have identified us as one of the top healthcare systems in the nation for our commitment to quality care and patient safety.

If you're interested in joining this nationally recognized hospital, please contact Tiffany Ellington @ 843-777-5169 or email tellington@mcleodhealth.org.

PSYCHIATRISTS

$174,361 TO $198,792

Ann Klein Forensic Center's Special Treatment Unit Adult facilities located in Kearny/Rahway, New Jersey invites you to join our team of professionals who are making a difference in the health and welfare of New Jersey citizens. Our inpatient units are designed to treat adult males who have been civilly committed under New Jersey's Sexually Violent Predator's Act. We seek experienced Psychiatrists to conduct detailed forensic evaluations.

Our *extraordinary* benefits include:

- **Paid Vacation**
- **Paid Holidays**
- **Sick Days**
- **Personal Days**
- **Medical Insurance**
- **Dental Insurance**
- **Life Insurance**
- **Prescription Plan**
- **Deferred Income**
- **No overnight call**
- **Potential for flexible schedule**

For immediate consideration please contact:

Director of Psychiatry **Natalie Barone Ph.D** or Clinical Director **Merrill Main, Ph.D** at **(732) 499-5534** or fax CV & letter of interest to **(732) 499-5440**.

Email inquiries may be sent to:

Natalie.Barone@dhs.state.nj.us *or* **Merrill.Main@dhs.state.nj.us**

Ann Klein Forensic Center, Special Treatment Unit/Annex
P.O. Box 905, Avenel, N.J. 07001

ANN KLEIN
FORENSIC CENTER

EOE

The American Psychiatric Association (APA) and the American Association of Psychiatric Administrators (AAPA) are seeking nominations for its jointly sponsored Administrative Psychiatry Award.

The recipient of the award is a psychiatrist who has demonstrated extraordinary competence in psychiatric administration over a substantial period and has achieved a national reputation in this area.

In addition, he or she must have directed a comprehensive program for the care of patients with mental illness and have contributed significantly to the field of psychiatric administration through activities such as teaching and research. Membership in APA and board certification are additional requirements.

Completed nominations must be received by September 1, 2008. Materials should be sent to:

CHAIRPERSON
Committee on Psychiatric Administration and Management
APA Division of Education
1000 Wilson Blvd., Ste. 1825 • Arlington, VA 22209-3091

Questions should be directed to Crystal Garner at cpam@psych.org

CLASSIFIED ADVERTISING INFORMATION

2008 RATES:
- $24 per line for orders of 1 to 2 insertions
- $22 per line for orders of 3 or more consecutive insertions, only if your written order specifies a 3 or more consecutive issue run.
- $21 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
- $35 extra for confidential blind box number
- Classified rates are non-commissionable
- Overseas and "Pratice for Sale" advertisers are required to prepay in full with a credit card.

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:

Pamela Trujillo
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.)
September 19	September 5
October 3	September 19

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

Regional

ALABAMA

ARIZONA

ARKANSAS

CALIFORNIA

UC DAVIS SCHOOL OF MEDICINE
DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

Health Sciences Assistant/Associate Clinical Professor. The University of California, Davis, Department of Psychiatry and Behavioral Sciences is recruiting for a Health Sciences Assistant/Associate Clinical Professor in the clinician/teaching series to serve as teaching attending at the Mental Health Treatment Center located next to the UC Davis Medical Center in Sacramento. The Treatment Center has a crisis unit and a 100 bed inpatient unit that is staffed by UC Davis faculty, residents, and medical students. The Center also has three dually-trained medicine-psychiatry faculty and its own primary care physician on site. Experience in teaching and supervision of medical students, residents, and other mental health professional is highly desirable. The successful candidate should be board eligible or certified in general psychiatry, be in possession of a California Medical license, and have an interest in psychiatric education and training. The successful candidate will lecture in seminars and case conferences, and provide group and individual supervision of clinical cases. The incumbent will provide clinical teaching for general psychiatry residents, psychology fellows, medical students and other mental health professionals including timely and appropriate evaluation of trainee performance.

For full consideration, applications must be received by September 30, 2008. Position is open until filled, but no later than December 31, 2008. Interested candidates should email a curriculum vitae and letter of interest in response to Position #PY-03R-08 to Kori Feinstein at kori.feinstein@ucdmc.ucdavis.edu . In conformance with applicable law and University policy, the University of California, Davis, is an equal opportunity/affirmative action employer.

http://www.ucdmc.ucdavis.edu/psychiatry/

RPS
A MEDICAL CORPORATION

FLEXIBLE SCHEDULING OPPORTUNITIES, including weekends. Provide psychiatric services in an interesting and dynamic environment. Competitive compensation. Call: (800) 882-0686 for scheduling opportunities.

The UCSD Department of Psychiatry is seeking to recruit board certified/board eligible psychiatrists to join the faculty of the UCSD Owen Clinic, the multidisciplinary adult HIV clinic at UCSD Medical Center in San Diego. Individuals must be able to become licensed in the State of California and board eligible in psychiatry and/or designated sub-specialty. Those who apply should have a strong track record in clinical, teaching and administrative expertise in clinical psychiatry settings. The successful candidate would be appointed as an Assistant Clinical professor with a career path as a clinician-educator in the Department of Psychiatry. Opportunities for scholarly activity related to HIV psychiatry and mentoring by senior faculty will be provided. Bilingual (Spanish-English) is desirable. The candidates' appointment will be determined by their individual qualifications and achievements, and salary is based on University of California staff psychiatrists pay scales. Candidates who wish to be considered for immediate employment should send curriculum vitae and other supporting documents to Search Committee K, UCSD Department of Psychiatry, 9500 Gilman Drive, La Jolla, CA 92093-0603. Attn: Dr. Lohr and Dr. Soliman. The University of California, San Diego, is an equal opportunity employer.

Faculty Positions - UCSD

The Dept. of Psychiatry at the University of California, San Diego, is currently recruiting for contracted positions at the assistant or associate clinical professor level. We are seeking board-certified or board-eligible psychiatrists with a California medical license to practice in our community outpatient clinics. Preference will be given to candidates with a strong track record in clinical care, teaching experience and an interest or experience in clinical research. The positions offer flexible scheduling, along with potential teaching and research opportunities. The appointment level will be determined by the candidate's qualifications, and the salary is based on UC staff psychiatrist pay scales. Applicants should send their curriculum vitae and other supporting documents to: Attn: Dr. Lohr and Dr. Soliman, Search Committee K, UCSD Dept. of Psychiatry, 9500 Gilman Drive, La Jolla, CA 92093-0603. UCSD is an equal-opportunity employer.

COLORADO

COLORADO COALITION FOR THE Homeless Creating Lasting Solutions

PSYCHIATRIST
DENVER

The Colorado Coalition for the Homeless seeks a part-time **PSYCHIATRIST** to work at the Civic Center Apartments, Stout Street Clinic and off-site. We are a large non-profit agency serving the homeless and those at-risk of homelessness; our activities range from street outreach to housing development. The Stout Street Clinic, located in downtown Denver, sees 10,000 patients a year. We provide primary care, dental care, laboratory and pharmacy services, an eye clinic, access to medical specialists and psychiatric and substance abuse treatment. Being co-located with a medical clinic provides a rich environment for consultation and allows our patients to get full integrated care. The psychiatric department includes 2.5 FTE's for psychiatrists as well as 5+FTE nurse prescribers. There are also opportunities to work with homeless adolescents at a youth shelter and in a public housing clinic with many Spanish speakers.

Working with homeless or near-homeless patients can be incredibly rewarding. We offer full benefits (starting on day of hire) including 403(b) deferred compensation plan. Malpractice is covered by the Federal Torts Claim Act. No call. Please forward your CV to Elizabeth Cookson MD, Director of Psychiatry, via fax: 303.293.6511, or e-mail: ecookson@coloradocoalition.org

---

University of Colorado at Denver and Health Science Center
Department of Psychiatry, Full-time Faculty

- Serves as an attending on University of Colorado Hospital Clinical Services which may include: Inpatient service, Consultation and ER Service, Outpatient clinic.
- Collaborates with and conducts research projects and/or scholarly activity.
- Full participation in residency and medical student teaching programs.

To learn more about the position please contact Marshall Thomas, MD at (303) 315-9147 or go to our website www.jobsatcu.com job posting #80387. The University of Colorado at Denver and Health Sciences Center requires background investigations for employment. The University of Colorado is committed to diversity and equality in education and employment.

CONNECTICUT

PSYCHIATRIST POSITIONS (Reference #AB1000) - DMHAS has challenging opportunities: Full/Part-Time or Per Diem: Connecticut Valley Hospital, Middletown, Connecticut; Capitol Region Mental Health Center, Hartford, Connecticut- Whiting Forensic Division is seeking psychiatrists interested in working in a forensic psychiatric facility that is JCAHO-accredited, CMS-certified and affiliated with the Yale University Law and Psychiatry Division. Applicants must be board-eligible or board certified. Forensic Fellowship training is preferred, but not required. Yale faculty appointments are available to qualified candidates. General Psychiatry Division, which serves a very diverse patient population in a number of specialized treatment programs, is seeking a psychiatrist for its Transitional Rehabilitation Program. Full-time position available at Capitol Region Mental Health Center, Hartford, Connecticut - a community-based mental health center which provides an array of innovative clinical and community support services to individuals with a psychiatric disability, in many cases with co-occurring problems of substance abuse. In addition to providing individuals with behavioral health services, CRMHC also collaborates with the Greater Hartford DMHAS-Funded Mental Health Programs, which are comprised of 16 non-profit agencies located in Hartford and West Hartford. These agencies work together to provide a comprehensive array of behavioral health services to nearly 3,300 individuals and families. Salary Range: $137,314 to $168,659 (depending upon experience, licensing and certification) The State indemnifies employees for damage or injury, not wanton or willful, caused in the performance of his/her duties and within the scope of his/her employment as provided by Sections 4-165 and 19a-24 of the C.G.S. This position provides excellent health/dental insurance and generous vacation/personal leave and licensure fee reimbursement. Interested candidates mail/FAX a State Employment Application (PLD-1) with the DMHAS Addendum (available at www.ct.gov/dmhas/employmentopportunities) and CV to: **Audrey Bongiorno, Employment Services Division, P.O. Box 1508, Middletown, CT 06457 Telephone: (860) 262-6740, Fax: (860) 262-6770.** DMHAS is an Affirmative Action/Equal Opportunity Employer. Members of protected classes and/or individuals in recovery are encouraged to apply.

FLORIDA

Adult Psychiatrist Needed
in Florida
(between Tampa and Orlando)

Excellent opportunity for a BC/BE psychiatrist to join a child psychiatrist, a psychologist and mental health therapist in well-established multi-specialty group.

- Physician-owned practice of 200 Physicians in 40 specialties
- Monday-Friday, 8:00am-5:00pm
- Exceptional suburban setting provides a varied patient mix
- Year-round outdoor activities: tennis, golf, boating, fishing; 500+ lakes, numerous parks & access to beaches, museums, sports events & attractions
- Salary guarantee + bonus the 1st year; Partnership after 2 years.
- NO STATE INCOME TAX!

WATSON CLINIC LLP
1600 Lakeland Hills Blvd.
Lakeland, FL 33805
(800) 854-7786 Fax (863) 680-7951
Email: mstephens@watsonclinic.com

The Department of Psychiatry at the University of Florida College of Medicine-*Jacksonville*, is recruiting two full-time faculty clinician teachers at its major teaching facility and urban campus, Shands Jacksonville. Primary duties include consultation/liaison, teaching, patient care, and research. Added specialty training/certification in geriatrics, sleep or pain medicine, affective disorder, or addictions would be ideal. Applicants must be MD/DO and BE/BC. Salary is highly competitive with excellent benefits package. Appointment will be offered at the tenure or non-tenure accruing level appropriate to experience and academic credentials (assistant, associate or full professor).
Please submit CV and the names/addresses of three references to:

Chair, Search Committee
Office of Steven P. Cuffe, M.D. Chair
University of Florida
Department of Psychiatry
655 West 8th Street
Jacksonville, FL 32209

Or e-mail rosetta.payne@jax.ufl.edu

The Search Committee will review applications until the positions are filled. **Please reference position numbers: 23612 & 23614**

The University of Florida is an Equal Opportunity Institution dedicated to building a broadly diverse and inclusive faculty and staff

---

DAYTONA - MELBOURNE - ORLANDO - MIAMI - FORT LAUDERDALE - PALM BEACH - OCALA - GAINESVILLE - FORT MYERS - SARASOTA - PENSECOLA - JACKSONVILLE - 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 individual provider #s. No Restrictions (H1B Candidates Considered). Call our administrator, Christy, at 866-936-5250.

Private practice opportunity in Southwest Florida. All ages seen. No multiproblematic patients. Many new referrals. Develop your own private practice under the umbrella of my practice. New patients, support, advice given ongoing. This is a genuine, non-endlessly repeating advertisement. Serious inquiries only. Call cell phone 941-374-1850 or office 239-334-1478.

Psychiatry busy solo practice for sale in South Florida Prime Location. Fee for service, no insurance with great expansion potential. Fax inquiries to: 561-482-9582.

Beautiful Coastal Location - Seeking Board Certified (or just recently finished training) Psychiatrist to work on general hospital-based psychiatric programs on the Atlantic coast. Services consist of adult, C/A and future geriatric beds and IOPs. Come be part of this friendly, top notch mental health team and live, work, play and enjoy the laid-back lifestyle of this lovely area. Please call **Terry B. Good at 1-804-684-5661**, Fax #: 804-684-5663; Email: terry.good@horizonhealth.com. EOE

GEORGIA

Psychiatrist - Metro-Atlanta

Cobb County Community Services Board, a behavioral healthcare organization in metro Atlanta (Marietta, GA), seeks a part-time BC/BE Adult Psychiatrist for Community Outpatient Behavioral Health clinic. Please send CV to cholt@cobbcsb.com or fax 770-514-2524.

Assistant Professor/Associate Professor (Inpatient/Outpatient Services) and Assistant Clerkship Director

The Department of Psychiatry and Behavioral Sciences at Mercer University School of Medicine, Macon, Georgia, is actively recruiting for a general psychiatrist at the level of Assistant/Associate Professor, tenure or non-tenure track. Primary responsibilities will include, direct patient care (in-patient and out-patient services), teaching and supervision of medical students, marriage and family therapy students and scholarly activity/research. Other interests welcomed e.g. addictions, mood disorders. Opportunities may exist for the teaching of residents in other departments. Collaboration within and across departments is encouraged. Department faculty are involved in medical and family therapy education and curriculum development and in research and clinical trials in mood disorders, psychosis and neuro-degenerative diseases, as well as other research endeavors. Applicants must have completed an approved general psychiatry residency, be board certified/eligible in general psychiatry and be eligible to obtain a Georgia medical license. Interested applicants will need to apply online at www.mercerjobs.com. AA/EOE/ADA

PSYCHIATRISTS

New Horizons Community Service Board in Columbus, Georgia is seeking one Adult and one Child and Adolescent psychiatrist for its outpatient and residential programs. This growing community offers a pleasing climate and is situated within a short distance to Atlanta and the Gulf Coast. The qualified applicant will possess or be eligible for a valid physician's license from the State of Georgia and have completed a three-year residency in an accredited facility. Excellent salary with a comprehensive benefits package. Interested parties should fax their curriculum vitae to the attention of Shannon Robertson at 706/317-5004. **No phone calls, please.**

PSYCHIATRIST

Ranked seventh among U.S. News & World Report's top public universities, the Georgia Institute of Technology is one of the nation's premiere universities and is a national and international leader in scientific and technological research and education. Year after year, Georgia Tech is consistently the only technological university ranked in U.S. News & World Report's listing of America's top ten public universities. These impressive national rankings reflect the academic prestige long associated with this premier Educational Institution.
Major responsibilities to include: providing comprehensive psychiatric health care to eligible Georgia Tech students and their spouses. Attend patient care conferences and business meetings. Attend and participate in In-Service training programs. Provide consultation to Georgia Tech clinicians. Make appropriate referrals to outside health professionals and institutions, and to other university services. Record physician encounters and prescription orders according Health Services policies & procedures. Maintain professional competence and licensure. Cooperate with other health care providers in achieving comprehensive health care. Comply with state health department regulations and Institute and Health Services regulations and procedures.
Requirements: Must hold a Medical Degree and Board Certification in Psychiatry or Recent Graduation Board Eligible (must successfully obtain Board Certification within two test cycles). Experience: Must have all current licenses to practice medicine in the state of Georgia and DEA number. Experience in a college/university environment preferred. Position requires a background check. Interested applicants must apply to: www.ohr.gatech.edu referencing job number DSM7750.
Georgia Tech is an Equal Education Opportunity Employer

ILLINOIS

Outpatient Psychiatry Opportunity

4-Day work week! Loan forgiveness available; Limited consults. Impressive base salary, signing bonus, benefits, 401K with matching; 35-days off annually. University Community with medical school and residencies. **Contact Mark Nolen 888.260.4242 x 227 mnolen@medicuspartners.com** fax 972-759-0336

Visa Sponsor!

Adult and Child Psychiatry - Bloomington/Normal Illinois. BE/BC. Join a well established behavioral health department of a multi-specialty group own by local hospital (Bromenn Healthcare). Employed position with a comprehensive benefits package with incentive compensation which includes a competitive base salary. Great Schools. Fastest growth area in Illinois outside Chicago. 2 hours to Chicago, 3 hours to St. Louis or Indianapolis.

Adult - inpatient unit of 17 beds and outpatient. 1:4 Call
Child - outpatient practice only.
Contact Thomas Kusch at
tkusch@bromenn.org
fax 309-888-0985

Vice Chair of Clinical Services Department of Psychiatry and Behavioral Sciences Northwestern University/Feinberg School of Medicine

The Department of Psychiatry at Northwestern University Feinberg School of Medicine invites applications for a full-time faculty position as Vice Chair of Clinical Affairs. The Vice Chair will develop, enhance and integrate a number of diverse clinical programs in support of the clinical mission of the Department, to achieve the very best patient outcomes and create state-of-the-art mental health care systems.

Applicants must hold an MD degree, be Board-Certified by the American Board of Psychiatry and Neurology, and eligible for an unrestricted medical license in Illinois.

The Vice Chair for Clinical Affairs will be a full-time continuing appointment with the rank of Associate or Full Professor. Proposed start date is **November 1, 2008.**

A generous salary and benefits package will be provided. The medical school and its main teaching hospital, Northwestern Memorial, are located in the heart of Chicago's magnificent "Gold Coast".

Interested applicants should submit a letter of interest, a *curriculum vitae*, and names of three references via email to **William Gilmer, M.D. at w-gilmer@northwestern.edu. Position is open until filled.**

Northwestern University is an equal opportunity/affirmative action employer. Women and minority candidates are encouraged to apply. Hiring is contingent on eligibility to work in the United States. Additional questions may be submitted to Dr. Gilmer.

IOWA

Director - Mental Health Service Line

The Department of Veterans Affairs (VA) Iowa City is seeking a highly qualified clinical leader for our Mental Health Service Line. Applicant must be a MD or equivalent (with a specialization in Psychiatry). Successful candidates must be eligible for an appointment at the operational performance level of associate professor or higher with the University Of Iowa Carver College Of Medicine. Salary will be commensurate with the applicant's qualifications and responsibilities. Please submit CV and three references to Gregory Wolff, PHR, Human Resources (05), VA Medical Center, 601 Highway 6 West, Iowa City, IA 52246. This is not a J-1 opportunity.

The Department of Veterans Affairs is an Equal Opportunity/ Affirmative Action Employers. Women and Minorities are strongly encouraged to apply.

LOUISIANA

Ochsner Health System

BC/BE Psychiatrist

OCHSNER ST. ANNE GENERAL HOSPITAL is seeking:

- A BC/BE Psychiatrist for an employed position in Raceland, Louisiana
- Located 40 miles from New Orleans with a population of approximately 40,000
- Not-for-profit critical access hospital providing inpatient & outpatient services with high quality, cost-effective emergency, medical & surgical care
- Part of nationally renowned health system of 7 hospitals, 600+ member physician group, and 33 health centers
- Very competitive salary and benefits
- Family-oriented community with year-round outdoor activities
- Favorable malpractice environment in Louisiana
- J-1 visa candidates are welcome to apply
- Ochsner Health System is an equal opportunity employer.

Please email CVs to: profrecruiting@ochsner.org or call (800) 488-2240.
Ref# APSYN4.

DEPARTMENT OF PSYCHIATRY AND NEUROLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for several general and forensic psychiatrists (clinical track) for our growing department, at the Assistant/Associate Professor level. Candidates must have completed an approved general psychiatry residency and be board certified/eligible in general psychiatry and forensic psychiatry, respectively. Responsibilities will include direct patient care, teaching of medical students and house officers (including those in our accredited forensic psychiatry fellowship program), and research (clinical and basic science) at various state hospitals, state correctional institutions, and at Tulane University Health Sciences Center. Time allocations will be based upon individual situations. Applicants must be eligible to obtain a Louisiana medical license. Applications will be accepted until suitable qualified candidates are found. Send CV and list of references to John W. Thompson, Jr., M.D., Vice Chair, Adult Psychiatry and Director, Division of Forensic Neuropsychiatry, Tulane University School of Medicine, Department of Psychiatry and Neurology, 1440 Canal Street TB53, New Orleans, LA 70112. For further information onsite, please contact Dan Winstead, MD, Chair of Psychiatry and Neurology, at 504-473-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

2008 Issue Deadlines:

Issue	Deadline
September 5	August 22
September 19	September 5
October 3	September 19
October 17	October 3
November 7	October 24
November 21	November 7
December 5	November 21
December 19	December 5

Contact: Pamela Trujilo, 703.907.7330 or classads@psych.org

The Department of Psychiatry and Neurology at Tulane University School of Medicine is recruiting a geriatric psychiatrist for a full-time faculty position. The candidate will spend part of their time at the Southeast Louisiana Veterans Health Care System (SLVHCS) and will also be involved in the new initiatives in both clinical geriatric care and special geriatric education programs at Tulane. Responsibilities include patient care as well as contributing to the various teaching and training programs of Tulane University's Department of Psychiatry and Neurology at the SLVHCS. He/she will be provided the opportunity to pursue their research interests. The person selected for this position must be professionally competent and be board eligible/certified in general psychiatry and in geriatric psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Salary will be competitive and commensurate with the level of the candidate's academic appointment. Applications will be accepted until a suitable qualified candidate is found. Applicants should send letter of interest, updated CV and list of references to Daniel K. Winstead, MD, Heath Professor and Chair, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1440 Canal Street TB48, New Orleans, LA 70112. Interested and eligible candidates may obtain further information by contacting Daniel K. Winstead, MD at 504-988-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admissions and in employment.

MAINE

OPPORTUNITY IN BAR HARBOR

A child and adolescent psychiatrist, who is interested in joining a dozen progressive, mental health clinicians doing outpatient work at the MDI Behavioral Health Center of the Mount Desert Island Hospital Health System.

Staff currently includes an adult psychiatrist, a child and adolescent psychologist and 10 therapists.

Duties will include Psychiatric evaluations, Patient medication supervision, Clinical supervision of child and adolescent therapists and furthering development and leadership of care for the youth of our community who are requesting help in ever increasing numbers.

Interested candidates will need to enjoy working with other mental health clinicians; primary care clinicians; public and private elementary, secondary, and college education systems; as well as community social service agencies.

The MDI Behavioral Health Center is one of nine ambulatory offices in the MDI system, staffed by over 40 primary care and specialty clinicians who refer their patients with behavioral problems. We maintain close contact with these referring clinicians to help integrate our patients' physical and behavioral health care.

Our community is a unique blend of island and coastal towns that surround Acadia National Park in Downeast Maine. The position is full time with competitive salary and benefits for outpatient work with no scheduled on call responsibilities. In interested, please send your C.V. to:

MDIH Behavioral Health Center
Diehl Snyder MD, Medical Director,
322 Main Street, 3rd floor
Bar Harbor, ME 04609
Email: sue.rouleau@mdihospital.org

MARYLAND

FT Salaried Psychiatrist needed for private practice in Baltimore. Duties are rotating between inpatient geropsych, PHP/IOP, and general hospital C-L rotating every 4 months. Also, there will be several nursing homes assigned that will be ongoing throughout the year. Salary will be up to $191,000 per year with 2 weeks paid vacation the first year, simple IRA with 3% match, and a health care plan with an HSA account. Also there may be extra income holiday bonus and there is ownership opportunity after 2 years allowing additional profit sharing. Baltimore is an attractive area with sports, culture and nature. Great for families and has excellent schools. Call 410-825-2281 or email suite309@aol.com

---

Faculty Opportunity
DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE, BALTIMORE

The University of Maryland School of Medicine, Department of Psychiatry, is seeking a full-time faculty psychiatrist for its **Geriatric Division**. The position carries a full-time faculty appointment at the University of Maryland School of Medicine and offers exciting opportunities for clinical care (of adults 50 years and older), mentorship, teaching, and research (with protected time). Candidates must be ABPN certified or eligible with training or clinical experience in Geriatric Psychiatry. Academic rank and salary are commensurate with experience. Send letter of introduction and CV to: Anthony F. Lehman, M.D., M.S.P.H., Professor and Chair, Department of Psychiatry, University of Maryland, Baltimore, 701 West Pratt Street, Baltimore, Maryland 21201. The University of Maryland is an AA, EOE, ADA employer. Minorities and women are encouraged to apply.

MASSACHUSETTS

STAFF PSYCHIATRIST

Opportunity for a Board-Certified/Board-Eligible Psychiatrist to join the expanding Mental Health Service at the Northampton VA Medical Center. Northampton is an active, diversified Medical Center, with 3 satellite outpatient clinics, a 16-bed substance abuse/compensated work therapy Psycho-social Residential Rehabilitation Treatment Program, 85 psychiatric inpatient beds, and 66 nursing home care unit beds. Specialized programs include PTSD, substance abuse, chronically mentally ill, and acute psychiatry. Opportunities are currently available for teaching residents as well as psychology and social work interns. Congenial work atmosphere, stimulating colleagues, and minimal night and weekend duties make this a very pleasant place to work. Northampton is located in the heart of the "five college" area of Western Massachusetts and abounds in cultural attractions. Two hours from Boston, three hours from Times Square, yet in its own cultural base, the area is ideal for raising a family. This Medical Center is affiliated to the Dartmouth Medical School. Competitive salary and federal benefits. EOE employer.

Send CV to: Michelle Zehelski, Human Resource Staffing Clerk (05-HR), Northampton VA Medical Center, 421 North Main Street, Leeds, MA 01053, (413) 584-4040, ext. 2124; FAX (413) 582-3146.

PSYCHIATRIST to join busy, large, established private psychiatric group practice. Work consists of outpatient psychiatric treatment, both psychopharmacology, and some hospital consultations. A lot of flexibility in terms of job and schedule. Partnership opportunity available. Email: afarley@glpaonline.org

---

Director, Center for Mental Health Services Research, University of Massachusetts Medical School

The UMass Department of Psychiatry is recruiting a Director of its Center for Mental Health Services Research at the Associate Professor or Professor rank. Individuals should have outstanding leadership skills, an established track record in NIH funded mental health and / or addiction health services and / or psychosocial research, and experience building teams, mentoring, and administering research programs. The position requires demonstrated ability in program evaluation, community engagement and a commitment to bridging health services and clinical research to improve service delivery.

The Center includes over 20 outstanding faculty members with funded health services in psychosocial rehabilitation, child and adolescent, family, transitional age youth, multi-cultural, addiction, co-occurring disorders, law and psychiatry, ethics, organizational change, etc. The Center has been well funded for many years. For more information about the Center visit www.umassmed.edu/cmhsr/.

The UMass Department of Psychiatry has about 200 full-time faculty and a strong public sector mission with active basic science, clinical and health services research. There is a strong commitment to faculty and staff development and diversity. Salary and fringe benefits are competitive.

Those interested in applying for the position should send their letter of interest and cv to: David Smelson, Psy.D, Vice Chair for Clinical Research, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA 01655 or via email to: David.Smelson@umassmed.edu. Nominators should submit the name, telephone number and address of prospective candidates. Review of applications will begin upon receipt.

The University of Massachusetts Medical School is an equal opportunity/affirmative action institution.

The Edith Nourse Rogers Memorial Veterans Hospital (ENRMVH) in Bedford, Massachusetts is looking for psychiatrists for newly authorized positions in order to address the needs of veterans returning from Iraq and Afghanistan. We have new positions for two outpatient psychiatrists interested in treatment of PTSD, substance abuse, depression and other disorders. We also have a new position for an innovative psychiatrist who would like to assume leadership of our 30 bed acute inpatient unit and help lead a reconfiguration of that unit to a best practice inpatient milieu. This inpatient unit already has two psychiatrists assigned as well as a full complement of experienced mental health staff. Residents from Boston University School of Medicine Division of Psychiatry rotate on the unit for their PGY1 and 2 experiences. The ENRMVH is a teaching hospital with research in Mental Health, Alzheimers Disease and Health Services Outcomes. It has a highly supportive and collegial environment in a delightful suburban setting. Academic appointments available commensurate with qualifications. ENRMVH is an Equal Opportunity Employer. Applicants are subject to an employment physical examination and drug testing.

Interested candidates please contact
Gregory K. Binus, M.D.
Mental Health Service Line Manager
Edith Nourse Rogers Memorial Veterans Hospital
Bedford, MA 01730
781 687-2363
Gregory.Binus2@med.va.gov

Child/Adult Psychiatrists

CHILD & FAMILY SERVICES is a private non-profit agency with a 164 year history of providing quality community-based mental health and child welfare services within Southeastern Massachusetts & on Cape Cod. Great area to live and work. Excellent schools, beautiful beaches. Thirty minute drive to Cape Cod.

Child & Family is looking for a full-time BE/BC child and adult psychiatrists to work as part of a solid and dedicated team of professionals providing quality services to those in need. Participate on our multi-disciplinary treatment team. Supportive work environment.

Excellent salary and benefits (medical, dental, life, LTD) 4 weeks vacation, CME leave, and generous 401k employer match. J-1 VISA WAIVER ASSISTANCE.

Letter of interest and C.V. to:
Gabriela Velcea, M.D., Medical Director
Child & Family Services, Inc.
1061 Pleasant Street
New Bedford, MA 02740
Cell: (508)567-8865
FAX: 508-991-8618
EOE/AA
Email: gvelcea@cfservices.org

The Department of Psychiatry at Mount Auburn Hospital, affiliated with Harvard Medical School, is recruiting for a half-time position in our Outpatient Psychiatry Service. Responsibilities include evaluation and treatment of adult patients with a variety of psychiatric disorders, including dual diagnosis patients, and coordination of care with other psychiatric clinicians and with primary care and specialty physicians. There are opportunities to work with our Dept. of OB/GYN and the women's mental health program. Position includes participating in the teaching activities of the Department. Academic appointment to the clinical faculty at Harvard Medical School is anticipated. Mount Auburn Hospital and Harvard Medical School are an Equal Opportunity Employer. Women and minorities are particularly encouraged to apply.
Please send letter of interest and CV to: Joseph D'Afflitti, M.D., Chair, Department of Psychiatry, Mount Auburn Hospital, 330 Mount Auburn Street, Cambridge, MA 02138; tel: 617 499-5008; email: jdafflit@mah.harvard.edu.

Child and Adult Psychiatrists, Board Eligible or Certified, for 20 to 40 hr. positions to work at North Suffolk Mental Health Association at our Revere or Chelsea Clinic Sites. Candidate will be lead psychiatrist for a Multidisciplinary Team at one or more Community Counseling Centers. Job entails psychiatric evaluations and medication follow-up appointments, and will provide and consultation to weekly multidisciplinary team meetings. S/he will have the opportunity to supervise a prescribing CNP and clinical staff, and may supervise MGH/McLean Residents. An MGH/Harvard appointment is possible with the right credentials. Excellent Pay based on background and experience; generous benefit package. Please contact Nancy McDonnell, MD at nmcdonnell@northsuffolk.org

Equal Opportunity Employer

The Edith Nourse Rogers Memorial Veterans Hospital (ENRMVH) is recruiting for a Mental Health Service Line Manager to oversee our Mental Health clinical, research and teaching program. The Mental Health Service Line provides an exceptionally comprehensive continuum of psychiatric services which include but are not limited to acute inpatient, long term inpatient, a Domiciliary for Homeless Veterans, a crisis stabilization program, a full spectrum Substance Abuse Treatment Program, a Transitional Housing Program for veterans in vocational rehabilitation treatment, standard outpatient clinic services at the facility and in four Community Based Outpatient Clinics, a Day Activities Center, a Veterans Community Care Center, an Intensive Case Management Program, a Community Residential Care Program, and a comprehensive program offering a variety of services to homeless veterans. There is a major emphasis on treatment of PTSD, psychosocial rehabilitation and recovery. ENRMVH conducts approximately $10 million in bench to bedside research each year in Mental Health, Alzheimers and Health Services Outcomes. It is a major teaching facility for Boston University School of Medicine Division of Psychiatry, its main academic affiliate, for PGY 1, 2 and 4 residents as well as 3rd year medical students in psychiatry. The facility also has a new academic affiliation with University of Massachusetts School of Medicine. ENRMVH has an outstanding, supportive and collegial staff in all disciplines and is situated in a pleasant suburban environment in Bedford, Massachusetts 25 miles northwest of downtown Boston, next to Lexington and Concord. An academic appointment commensurate with qualifications is expected. The Veterans Health Administration is an Equal Opportunity Employer. Applicants are subject to a physical examination and drug testing. Please direct inquiries and CV by June 2, 2008 to:

Gregory K. Binus, M.D.
Edith Nourse Rogers Memorial Veterans Hospital
Bedford, MA 01730
781 687-2363
Gregory.Binus2@med.va.gov

MICHIGAN

FULL-TIME, PART-TIME AND PER DIEM POSITIONS AVAILABLE
OUTPATIENT PSYCHIATRISTS NEEDED
DETROIT MICHIGAN

Management company seeks physicians for Outpatient Programs within a Community Mental Health Center. Currently offering full-time, part-time and per diem assignments for board-eligible or board-certified Adult and Child Psychiatrists that offer a high level of collaboration within a multidisciplinary team. Competitive compensation. Progressive and rapidly growing management company also has locum and/or temporary assignments. Forward/send CV to: Management Company, churskin@bhrcorp.org or FAX to: (925) 520-0010. Or call us at: (925) 520-0005, ext 102. Visit us **www.bhrcorp.org**

MONTANA

APRN or MD

Intermountain Children's Home is an accredited, nationally-recognized MT non-profit agency that provides nurturing therapeutic environments for children under severe emotional distress. Intermountain is nestled at the foot of the mountains on a 40 acre campus in beautiful Helena Montana and has dedicated the past 99 years to serving children throughout the country. Our outpatient clinic, serving children and adolescents, ages 5-21, is recruiting for a dynamic, highly-motivated, APRN or MD to provide outpatient assessments and psychotropic medication management. This is a PT position with an excellent benefit package included; salary is dependent upon experience.
If you interested in restoring hope for these kids, please submit a resume to: Intermountain, 500 South Lamborn, Helena, MT 59601 or e-mail: mardieg@intermountain.org.
Please visit our web site for further information: www.intermountain.org Position is open until filled.

NEBRASKA

Alegent Health
This is your healthcare

Excellent Psychiatry Opportunity In Omaha and Council Bluffs area

Psychiatric Associates is the premier network of highly skilled professionals in the Omaha/Council Bluffs Metro area offering the full continuum of mental health care. We are currently looking for **General & Child/Adolescent Psychiatrists** to join our group of 15 Psychiatrists.

- Guaranteed Salary plus bonus incentive
- Malpractice insurance, license fees & dues provided
- Generous CME & relocation allowances
- Top-of-the-line benefits package & more!

For Info contact: Jen McCune, 877-244-8027 or jen.mccune@alegent.org

NEW HAMPSHIRE

FORENSIC PSYCHIATRISTS
Concord, New Hampshire 03302

Join the Forensic Health Services, Inc. team in the rewarding field of mental health services with the New Hampshire Forensic Examiners Office/NH Department of Corrections. We are seeking a fellowship trained Forensic Psychiatrist for FT or PT employment. Prior experience in an inpatient forensic setting or in court evaluation services is preferred. Guide the delivery of mental health services to this diverse population of incarcerated individuals. Holley Schwieterman, (866) 204-3920 or hschwieterman@mhm-services.com Visit our website: www.forensichealthservices.com EOE

FHS
FORENSIC HEALTH SERVICES

New Hampshire - Medical Director - Full-time BE/BC Geriatric psychiatrist, fellowship-trained. Program includes 10-bed inpatient unit, an outpatient clinic, and nursing homes. Physician will be a hospital employee and will enjoy a four-day work week with light call. Salaried position with comprehensive benefits. Contact Bob Bregant at bbregant@hortonsmithassociates.com or call 800-398.2923.

NEW JERSEY

Child/Adol. or Adult Psychiatrists

Child/Adol. or Adult Psychiatrists - needed for multi-disciplinary group in affluent community in North/Central N.J. NO Managed Care! Call Dr. S. Reiter at 908-598-2400 x1 and fax CV to 908-598-2408.

NEW YORK CITY & AREA

Grants Director for national non-profit foundation promoting and funding suicide prevention research. Primary duty will be to oversee expanding grants program; 100+ grants/year. MD or PhD in psychology or related field; research methods and data management experience; publications; familiarity w/ suicide research; strong writing skills. Salary commensurate w/ experience.

Send CV and cover letter to:
Dr. Paula Clayton
American Foundation for Suicide Prevention
120 Wall Street, 22 Floor
New York NY 10005
or pclayton@afsp.org

Psychiatrists
Inpatient/Consultation Liaison/Emergency Department Psychiatrists, P/T & F/T B/E, B/C to work with 6 other Psychiatrists in a Community Hospital. Excellent benefits and desirable location with opportunity for private practice. Contact: BSposato@hunthosp.org or fax to B. Sposato @ 631-351-2064. EOE
HUNTINGTON HOSPITAL

Busy private practice seeking BE/BC PSYCHIATRIST for lucrative P/T office med mgt and/or hospital or SNF C/L Brownstone Brooklyn location. Flexible hours including evenings and weekends available. Potential for clinical research. Respond with cv to Fax # 718-625-6735

NEW YORK STATE

Psychiatrists

BryLin Hospitals, Upstate New York's only private psychiatric hospital, is looking to hire NYS BE/BC psychiatrists. Located in Buffalo, NY, BryLin is a licensed 88 bed inpatient psychiatric hospital that provides acute mental health care for ages five and up.

We have dedicated programs for children, adolescents, adults and older adults. Specialized programs include: Dual diagnosis treatment (MICA); Inpatient and ambulatory Electroconvulsive Therapy (ECT); outpatient substance abuse care; and soon to open, an outpatient mental health program.

The applicant should be interested in working half time as an inpatient psychiatrist and half time in private practice. The private practice, Niagara Frontier Psychiatric Associates (NFPA), is one of the largest groups in the region. This unique hospital/practice model allows for flexibility in one's schedule while providing a diversified work day.

Please email or fax your letter of interest and CV to:
Mark Nowak
Director of Marketing & Physician Recruitment
mnowak@brylin.com
Phone: 716-886-8200 ext. 2201
Fax: 716-886-1986
BryLin Hospitals has a history of providing quality compassionate care for over 50 years.

Well established three person private practice group in Western Suffolk County with strong referral base seeks full time, BC/BE psychiatrist to join busy inpatient and outpatient practice. Work at local community hospital and new office suite. Office accepts no managed care; creative agreement allows high income potential even before full partnership. Fax CV and cover letter to 631-265-0757.

Practice In the Perfect Place: Saratoga Springs, NY

Saratoga Hospital: Medical Director - Inpatient Unit

Saratoga Hospital seeks a Board Eligible/Certified, NYS licensed psychiatrist for the Medical Directorship and clinical oversight of a 16-bed adult inpatient unit and consultation service that includes an ECT program.

The unit is staffed with a close-knit multi-disciplinary care team. The Medical Director would supervise a staff physician who works half time, and a social worker. Responsibilities would also include assuring compliance with regulatory requirements; participation in the budget development and monitoring; as well as identification, planning and implementation of new programs. The compensation package will be competitive. Call is 1:5, shared with County Mental Health Physicians. The hospital and County are working to increase the call pool of providers through recruitment of additional County Mental Health psychiatrists who may also apply at the address below.

Located three hours from NYC, Montreal, and Boston, and a half-hour from Albany, Saratoga Springs is an historic community with lovely neighborhoods, fine restaurants, shops and entertainment including Thoroughbred horse racing and Saratoga Performing Arts Center.

For outdoor enthusiasts, Saratoga Springs is in close proximity to skiing, hiking, sailing and other sports venues.

For more information, contact: Denise Romand, Medical Staff Recruiter, Saratoga Hospital, 211 Church Street, Saratoga Springs, NY 12866. Phone: (518) 583-8465: docfind@saratogacare.org

---

Forensic Psychiatry/Child Psychiatry/Adult Psychiatry: St. Lawrence Psychiatric Center, a fully accredited EO-AAE, seeks BC/BE Psychiatrists licensed to practice medicine in NYS (or eligible to obtain NYS license) to work either full or part time at our 80-bed Civil Management, Sexual Offender Treatment Program (additional training in forensic psychiatry is helpful, but not required); Child Psychiatrists to work in a Children and Adolescent Inpatient or Outpatient Unit; and Adult Psychiatrists to work in an Adult Inpatient or Outpatient Clinic. We are designated by Federal Government as M.H.P.S.A. In addition to salary ($158,893 to $169,707 pending contract ratification) and guaranteed additional compensation by voluntary participation in an on-call program, we offer an excellent benefit package including: malpractice insurance, health insurance, paid vacation, holiday and sick time, an excellent retirement plan and educational and professional leaves.

Situated on the scenic St. Lawrence Seaway in northern New York, St. Lawrence Psychiatric Center is located in Ogdensburg, NY, an idyllic rural community offering many cultural, educational and economic opportunities. Historic and international metropolitan cultures are a reasonable driving distance away in Ottawa and Montreal, Canada, and Syracuse, NY. Ogdensburg's location on the St. Lawrence River and its close proximity to the Adirondack Mountains and Canada offers easy access to a wide variety of unspoiled natural areas and rich cultures and provides abundant recreational opportunities throughout the year.

Submit letter of interest to: Geri Kentner-Rausch, DIHRM, St. Lawrence Psychiatric Center, One Chimney Point Drive, Ogdensburg, NY 13669 or at slpogek@omh.state.ny.us. If you have questions, please call (315) 541-2182.

Ulster County Mental Health, an outpatient clinic with a wide range of services, has two full or part-time (28 hours minimum) psychiatry positions in the Kingston clinic. We are looking for recovery-oriented board certified or board-eligible community psychiatrists to treat adult patients. Kingston is located in the beautiful Hudson Valley, two hours north of NYC. Competitive salary, good benefits, on-site psychopharmacology supervision and collegial atmosphere. No on-call or weekends. Full time 35 hours. Send CV to JuLita Adamczak, MD, Medical Director, FAX #845-340-4094. Telephone #845-340-4173.

Treat today with NAMENDA

Proven efficacy with excellent tolerability

- Improves function, delays onset of behavioral symptoms, and provides benefits in cognition[1-3]
- Excellent safety and tolerability with low risk of gastrointestinal side effects may improve therapy persistence[4,5]
- Proven to reduce caregiving time, cost and caregiver distress[3,6,7]
- Proven effective first-line and in combination with an acetylcholinesterase inhibitor[1,2]

Broad patient access–covered on 98% of Medicare Part D formularies[4]

Namenda® memantine HCl

Extending memory and function

NAMENDA® (memantine HCl) is indicated for the treatment of moderate to severe Alzheimer's disease.

NAMENDA 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. 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. **2.** 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. **3.** Cummings JL, Schneider E, Tariot PN, Graham SM, for the Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology.* 2006;67:57-63. **4.** Data on file. Forest Laboratories, Inc. **5.** NAMENDA® (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, Mo. **6.** Wimo A, Winblad B, Stöffler A, Wirth Y, Möbius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics.* 2003;21:327-340. **7.** Winblad B, Poritis N. Memantine in severe dementia: results of the 'M-BEST Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry.* 1999;14:135-146.

For more details, please visit **www.namenda.com**.

Please see brief summary of Prescribing Information on the adjacent page.

Forest Pharmaceuticals, Inc.

62-1012588R 03/08

Namenda
memantine HCl

Tablets/Oral Solution
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%). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Namenda should be administered with caution to patients with severe hepatic impairment.

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 (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in Full Prescribing Information).

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/m^2 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/m^2 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/m^2 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/m^2 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/m^2 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 lutea 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: aspiration pneumonia, asthenia, atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST and hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lethargy, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged QT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, thrombocytopenia, and hallucinations (both visual and auditory).

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/m^2 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
Signs and symptoms associated with memantine overdosage in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

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.

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Licensed from Merz Pharmaceuticals GmbH

Rev. 04/07

NORTH CAROLINA

Central Regional Hospital is a new state, psychiatric hospital located in Butner, NC which is convenient to Raleigh/Durham/Chapel Hill. Central Regional Hospital is recruiting for general adult psychiatrists, and we offer competitive salary and benefits packages. We are a major teaching site of Duke University and the University of North Carolina departments of psychiatry. Academic appointments with Duke University and UNC-Chapel Hill are possible. Requires graduation from an accredited medical school, completion of an accredited psychiatric residency and board certification or eligibility.

Please contact Dr. Stephen Oxley at 919-764-7230 or the Human Resources Office at 919-764-7200. Submit state application (PD-107) and vitae to CRH; 300 Veazey Road; Butner, NC 27509. EEO/AA Employer

---

Private Practice Opportunities in North Carolina.

Carolina Partners in Mental HealthCare, PLLC is seeking BE/BC psychiatrists for our practices in Raleigh, Chapel Hill and Wake Forest, NC. Child/adolescent and/or adult psychiatrists welcome. Private outpatient practices, full partnership from day one - no investment required. FT, PT flexible. Carolina Partners has seven offices in Raleigh, Durham, Chapel Hill , Pitt sboro and Wake Forest, North Carolina. Good opportunity to control your life and clinical practice, while making a good income! Contact Executive Director or send CV to: Carolina Partners in Mental HealthCare, 1502 W. Hwy 54, Suite 103, Durham, NC 27707. Phone 919-967-9567; Fax 801-729-9867; EMail carolinapartners@bellsouth.net.

Practice in North Carolina's highest rated coastal city as an all-inpatient psychiatric hospitalist in an employed group of four. Strong package, great location. Contact Jim Ault at St. John Associates, jault@stjohnjobs.com or 800-737-2001. Visit www.stjohnjobs.com for more opportunities nationwide.

PENNSYLVANIA

PITTSBURGH - Assertive Community Treatment and Outpatient Opportunities. Mercy Behavioral Health is experiencing tremendous growth with starting our fourth ACT program, development of new residentials and expansion of outpatient. MBH offers competitive compensation and an excellent benefits package, all with a flexible schedule that will fit your needs. 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

---

Medical Director & Staff Psychiatrist Erie, PA

Horizon Health, in partnership with **St. Vincent Health Center**, a 436-bed tertiary care hospital in **Erie, PA**, seeks a **Medical Director** and **Staff Psychiatrist** for a **32-bed** Adult and Geriatric Inpatient Psychiatric Program and Outpatient Services.

Medical Director of Behavioral Services (responsibilities include 10-15% administrative with outpatient oversight and remainder is inpatient work including consultation liaison services). Three to five years experience desired. Interest in ECT would be welcomed. **Outpatient position** includes psychiatric evaluations and medication management, crisis services, consultation liaison services and contracted to community programs. Call is 1:5.

Located on the shores of Lake Erie with 7 miles of beaches, Erie is the fourth largest city in Pennsylvania with a metropolitan population of 280,000 and a referral base of 750,000.

Contact: Mark Blakeney, Horizon Health, 972-420-7473, fax CV: 972-420-8233, or email mark.blakeney@horizonhealth.com. EOE.

CAREER OPPORTUNITY - GENERAL PSYCHIATRIST

Dickinson Mental Health Center (DMHC), a community based provider headquartered in Ridgway, PA, has an opening for a full time psychiatrist interested in a general practice. DMHC is a very dynamic organization with a strong multidisciplinary clinical team. The Center is located in one of the more scenic, rural communities in NW PA and offers an array of outdoor and recreational amenities. It is located 2 hours from Buffalo, NY; 3 hours from Pittsburgh; 1 ½ hours from Erie; and 1 ½ hours from State College (home of the Pennsylvania State University).

Board certified is preferred although board eligible candidates will be given serious consideration. Travel will be required to nearby office locations in Coudersport and Emporium as well as Ridgway, PA. The area is designated as a federal mental health shortage area and qualifies for federal loan repayment.

The patient population to be served will include a small percentage of children with the remaining caseload comprised of adolescents, adults, and consumers with serious mental illness. Treatment of out-patient and partial hospitalization consumers will represent the principle service lines.

DMHC offers a very competitive salary and benefit package including 403b Thrift and Defined Contribution Retirement Plans.

For confidential consideration, please forward Curriculum Vitae to: Michael A. Galluzzi, CEO, Dickinson Mental Health Center, 110 Lincoln Street, Ridgway, PA 15853; or FAX information to (814) 776-1470; or e-mail to michael.galluzzi @dmhc.org. EOE

WellSpan Health in south central Pennsylvania has adult and child psychiatrist opportunities. Join a team of 28 psychiatrists, with an excellent call schedule. Outpatient offices are easily commutable from Baltimore and Frederick, Maryland, York or Harrisburg region. Above average compensation and benefits, including retirement, relocation, medical malpractice and tail included. WellSpan Health is a not-for-profit, community-based health care system with than 8,000 employees, including a Medical Group with more than 400 employed providers. For more information or to apply, please contact Carol Stowell at 1-866-230-1477 or e-mail at cstowell@wellspan.org.

Pittsburgh PA Metro

Armstrong County Memorial Hospital and P.B.S. Mental Health Associates, P.C. are recruiting a psychiatrist to lead our 26 bed general psychiatry unit.

Be part of a physician owned psychiatric group with opportunities for outpatient, clinic and nursing home practice. First year salary guarantee; 1:4 call; excellent benefits; productivity with robust earning potential.

J-1 available

For further information please contact Debby Solari, Practice Administrator at 724-282-1627.

Psychiatrists:

Currently we have exciting full- and part-time positions in a rapidly expanding department. Opportunities include responsibilities in and outside our five-hospital health system. There are immediate openings for child/adolescent, adult and addictions psychiatrists.

In addition, there are private practice options in a traditional psychotherapy model. Evening and weekend positions available. Excellent salaries, no on-call nor rounding responsibilities ever and exceptional benefits package offered. Send CV to Kevin Caputo, M.D., Vice President and Chairman, Department of Psychiatry, Crozer-Keystone Health System, One Medical Center Blvd., Upland, PA 19013 or contact the department manager, Kathy Waring at 610-619-7413

RHODE ISLAND

LIFESPAN PSYCHIATRY

Rhode Island Hospital
The Miriam Hospital

Affiliated Hospitals of the Brown University Department of Psychiatry & Human Behavior

These full-time clinical positions are part of an academic medical center program. These positions are eligible to be considered for Clinical Faculty appointments at Brown University. There are possibilities for some research participation for applicants with appropriate background and interests.

Outpatient (Adult): Interests should include working with medical populations as well as general psychiatry patients. The position includes a component of inpatient consultation-liaison as a member of a teaching service.

Emergency: Assistant Director (Adult) of a comprehensive regional psychiatric emergency program in a new hospital-based facility.

Inpatient (Adult): General psychiatry, inpatients. Some other clinical component may be combined with inpatient work.

Applicants must be Board Certified in Psychiatry or Board eligible (within three years of training completion). Salary and benefits commensurate with level of training and experience. 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 Street, Providence, RI 02903 and/or email: rjgoldberg@lifespan.org.

TENNESSEE

Board-certified/eligible psychiatrists needed for full time positions in a large Psychiatry Service at Mountain Home VAMC in Johnson City, Tennessee. Primary responsibility will be managing outpatients with a variety of psychiatric disorders. One position will include some administrative duties as Assistant Chief of the Outpatient Mental Health Clinic. Join staff of 30 prescribers, including 18 psychiatrists at ETSU-affiliated residency training program with medical students, adult and med-psych residencies. Clinical appointment potential and some teaching expected. Research a plus. On-call is backup to residents and shared amongst staff psychiatrists. One position is 7:45-4:30 M-F, one is for evening and Saturday clinics with no weekend call and Sunday-Monday off duty. **NO STATE INCOME TAX, LOW COST OF LIVING, BEAUTIFUL MOUNTAINOUS REGION, LOTS OF PARKS, GOLF COURSES, LAKES, NATIONAL FOREST.** Inquiries: Deborah Burchfield, 423-979-3465, or Deborah.Burchfield@va.gov applications and/or CVs to: James H. Quillen VA Medical Center P.O. Box 4000 (05), Mountain Home, TN 37684 or Fax: (423) 979-3443 or E-mail: mtnhomehrm-service@med.va.gov

---

VANDERBILT UNIVERSITY FACULTY POSITION

Vanderbilt University Department of Psychiatry (Nashville, TN) is recruiting a BE/BC full-time Adult Psychiatrist with subspecialty training in Psychosomatic Medicine to provide psychiatric consultation-liaison services to patients in the Vanderbilt University Hospital. Teaching activities include the ACGME-approved psychosomatic fellowship, adult psychiatry residents and medical students. Participation in clinical research will complement the clinical work. Appointment will be at the Assistant Professor level or above. Salary is negotiable dependent upon qualifications and experience.

For further information, please contact: Sherron Buchanan, Assistant to Chair, 1601 23rd Avenue South, Suite 3060, Nashville, TN 37212 - Phone: 615-322-2665; Fax: 615-343-8400

EAST TENNESSEE STATE UNIVERSITY JAMES H. QUILLEN COLLEGE OF MEDICINE DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES

DIRECTOR OF CHILD & ADOLESCENT DIVISION

Full-time position available for Director of Child & Adolescent Division. Position includes leadership, administration, teaching and outpatient clinical care. Responsibilities include training of psychiatric residents and medical students and research activities and creation of a child fellowship program. 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. Qualifications: Board certified in both general psychiatry and child psychiatry and experience in academic psychiatry. Applicants should submit an ETSU application, CV and two letters of reference to Merry N. Miller, M.D., Chair, Department of Psychiatry and Behavioral Sciences, ETSU, Box 70567, Johnson City, TN 37614-1707. Telephone inquiries should be made at (423) 439-2235 or e-mail at lovedayc@etsu.edu. AA/EOE.

TEXAS

MEDICAL DIRECTOR, ADDICTION TREATMENT PROGRAM

Join us as Medical Director of an innovative and growing VA addiction program. Administrative leadership will be shared and supported by the team co-leader, Dr. Stacy McCord, Ph.D. The Amarillo Veterans Health Care System (AVAHCS) addiction program currently includes intensive outpatient care and a more intensive day treatment program coordinated with a therapeutic half-way house. The program is a training site for Texas Tech Health Sciences Center School of Medicine medical students and residents, with strong potential for academic development. A residential treatment program is under development. The addiction program is moving into a new state-of-the-art facility next year. AVAHCS is nationally recognized for high levels of patient satisfaction and a culture of compassion and caring among the staff and administration.

Amarillo is a pleasant surprise - a warm friendly city with progressive cultural and artistic offerings including a fine symphony orchestra and one of the best established community theatres in the country. The VA sits in the best part of town, 5 minutes from the finest schools and residential neighborhoods. Amarillo is near incredible outdoor spectacles including Palo Duro Canyon (25 minutes) and the Rocky Mountains (3.5 hours).

Requirements:
- Unrestricted licensure as a physician in any state or territory
- Board Certified/Eligible in Psychiatry
- Excellent communication and interpersonal skills

Contact:
Ms. Helen Jefferson
Amarillo VA Human Resources (05)
6010 Amarillo Blvd. West
Amarillo, Texas 79106
Fax: (806) 354-7828

The University of Houston Health Center is seeking a Psychiatrist. Diagnoses and treats patients with psychiatric conditions by providing psychiatric evaluations and follow-ups for students; prescribes psychiatric medication and orders lab work as needed; provides consultation for professional staff at the Health Center and Counseling and Testing as needed; assists in the hospitalization of students as necessary; and, responds to emergency situations on campus and is available for crisis intervention at all times. Requires a minimum of one year of directly job-related experience and professional licensing, certification or registration directly related to the job, as specified on a job description addendum. Apply online to http://jobs.uh.edu. Refer to job posting #062948. The University of Houston is an EEO/AA institution.

Associate Professor

The Department of Psychiatry & Behavioral Sciences at the University of Texas Medical Branch in Galveston is seeking an Associate Professor.

Responsibilities include direct patient care, 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, Galveston, TX 77555-0188.

The University of Texas Medical Branch at Galveston is an equal opportunity, affirmative action institution which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

Come to beautiful San Antonio, Texas!!

Psychiatrists

The Center for Health Care Services, a 2006 APA Gold Award winner, is actively seeking full-time/part-time/contract psychiatrists for our Adult & Child Programs. The Center Psychiatrists are at the leading edge of the delivery of community mental health service, providing assessment and treatment of clients, and leadership of a team of skilled and dedicated mental health professionals. Must be board eligible or board certified.

The Center offers:
- *Attractive salary*
- *Excellent benefits package, including retirement benefits*

San Antonio offers:
- *Great climate year round*
- *Ranked among the best value cost of living*
- *Arts, Theatre, Sports and Entertainment, Amusement parks and more*
- *Easy access to beaches, Mexico, the Texas Hill Country, more*

If you are interested in learning more about service at The Center, please submit your C.V. in confidence to:

The Center for Health Care Services
Attn: HR Director
3031 IH 10 West
San Antonio, Texas 78201
Fax: 210-731-1310
staffing@chcsbc.org

EOE

VERMONT

Middlebury, VT - Psychiatrist

Psychiatrist to join our innovative interdisciplinary practice. Our highly regarded non-profit community mental health center is centrally located in Middlebury, a unique New England small college community. Our diverse practice includes consultation with Middlebury College. Responsibilities include shared back-up outpatient coverage of our experienced Emergency Team. This position is full time with excellent benefits. Qualifications: BC/BE. Child/adolescent psychiatry experience would ideally complement adult expertise. The Middlebury-Burlington area offers excellent schools and outstanding cultural and four season recreational resources.

We are people helping people.

Please submit cover letter and resume to Cheryl Huntley via email at chuntley@csac-vt.org, fax at (802) 388-8183, or mail to 89 Main Street, Middlebury, VT 05753. For more information you may call her at (802) 388-0302 ext. 493. Visit our website: www.csac-vt.org.

VIRGINIA

Virginia Commonwealth University is recruiting a BE/BC psychiatrist for a faculty position to direct the ECT Program and develop a brain stimulation therapies program. Candidates should have had one year fellowship or hands-on experience in ECT, or 2-5 years experience post-residency and an interest in developing the ECT and other stimulation therapies program at VCU. The selected candidate will have community outpatient or teaching clinic responsibilities and will be expected to teach medical students, psychiatric residents and other trainees. The VCU, Department of Psychiatry employs over 80 fulltime faculty and has 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, and top public/private schools. The internet provides comparative cost of living. Send CV to Marie Roach, Human Resources, Department of Psychiatry, VCU, Box 980710, Richmond, VA 23298. VCU is an Equal Opportunity/Affirmative Action employer. Women, minorities, and persons with disabilities are encouraged to apply.

ACADEMIC AMBULATORY PSYCHIATRY: VA Commonwealth University recruiting BE/BC Psychiatrist with community psychiatry and academic career interests to provide outpatient clinical care and supervise/teach residents/medical students. The clinical experiences include: City community psychiatry clinic and hospital-based teaching clinic. VCU Department of Psychiatry employs over 80 fulltime faculty and has 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. J-1 applicants welcome. Send CV to Marie Roach, Human Resources, Department of Psychiatry, VCU, Box 980710, Richmond, VA 23298 (Fax 804-828-1472). VCU is an Equal Opportunity/Affirmative Action employer. Women, minorities, and persons with disabilities are encouraged to apply.

Virginia Beach, Virginia

Outstanding opportunity for full time out-patient private practice in secure well established psychiatric practice of 25 yrs.

Board certified or board eligible psychiatrist can do full time out-patient care with opportunity for child and adolescent care, in-patient care and consultation-liaison care.

Guaranteed 120K base plus solid incentives, partnership opportunity after three years. Fax reply to: (757) 425-1389

Virginia Licensed Psychiatrist to join a large multi-disciplinary group of providers w/ several locations in the Virginia Beach area. Excellent compensation & benefits. Fax Resume to: Christian Psychotherapy Service, 757-497-1327 or call 757-490-0377.

WASHINGTON

The University of Washington and Harborview Medical Center (HMC) in Seattle, WA is accepting applications for a psychiatrist at the rank of Instructor or Assistant Professor (without tenure). This position is 1.0 FTE and will do a combination of hospital consultation work, and inpatient psychiatric attending duties, working with an interdiscliplinary team consisting of an adult psychiatrist, psychologist, nurse and social worker. Two half days a week will be spent working in psychiatry outpatient service settings. The position requires an MD and includes responsibility for teaching residents and medical students. University of Washington faculty engage in teaching, research, and service. Please send application and CV to Peter Roy-Byrne MD, Chief Psychiatry, Harborview Medical Center 325 9th Ave. Box 359911, Seattle, WA 98104. The UW is building a culturally diverse faculty and strongly encourages applications from females and minority candidates. The UW is an EOE/AA employer.

The University of Washington and Harborview Medical Center (HMC) in Seattle, WA is accepting applications for a geriatric psychiatrist at the rank of Acting Instructor or Assistant Professor (without tenure). This position is 1.0 FTE and will work half time doing hospital consultation work with an interdisciplinary team consisting of an adult psychiatrist, psychologist, nurse and social worker. The other half time will be spent working in geriatric psychiatry outpatient service settings that include nursing home and mental health center programs. The position requires an MD and includes responsibility for teaching residents and medical students. University of Washington faculty engage in teaching, research, and service. Please send application and CV to Peter Roy-Byrne MD, Chief Psychiatry, Harborview Medical Center 325 9th Ave. Box 359911, Seattle, WA 98104. The UW is building a culturally diverse faculty and strongly encourages applications from females and minority candidates. The UW is an EOE/AA employer.

Western Washington State: Adult/Geriatric/Forensic Psychiatrist (BE/BC with a WA state license) applications considered. Western State Hospital is a fully accredited (JCAHO) and certified (CMS) 997 bed hospital serving adult, geriatric and forensic populations. Annual salary up to $158,304 DOQ. Excellent benefits, including hospitalization/medical insurance, retirement and vacation leave, plus optional deferred income plan. Send CV to Leah Muasau, Medical Staff Coordinator; Western State Hospital; 9601 Steilacoom Blvd. SW; Lakewood, WA 98498-7213. E-Mail: MUASALL@DSHS.WA.GOV.

COLUMBIA RIVER MENTAL HEALTH SERVICES
6926 Northeast Fourth Plain Avenue
Vancouver, Washington 98661
360 993 3039 FAX 360 993 3047

FULL-TIME STAFF PSYCHIATRIST
An Opportunity in Vancouver, Washington

Columbia River Mental Health Services, a not-for-profit mental health services provider located in Vancouver, Washington, is recruiting for a full-time **STAFF PSYCHIATRIST** to provide psychiatric services to adult consumers in acute need of medical detoxification or mental health services. Serves as Inpatient Facility Medical Director. We offer a collegial work culture. **MINIMUM QUALIFICATIONS:** Current Washington physician licensed to practice psychiatry, board eligible, board certified preferred. Two years experience practicing psychiatry. Experience in community mental health center preferred. The ideal candidate will believe wholeheartedly that people can and do recover from mental illness, that services must be culturally competent, and that diverse staff are necessary to serve a diverse community.

Rapidly growing Vancouver WA is located just across the river from Portland OR. The two cities are among the most desirable urban areas in the nation. Mountains and ocean beaches are only an hour away. The cities have world-class shopping and dining, and thriving cultural, educational, and entertainment scenes.

WE FREQUENTLY HAVE OPENINGS FOR REGISTERED NURSES AND ARNP WITH MENTAL HEALTH/PSYCHIATRIC EXPERIENCE. PLEASE INQUIRE.

APPLICATION INSTRUCTIONS: Provide a letter of interest and resume:

1. E-mail to recruiter@crmhs.org or
2. FAX materials to 360 993 3047, or
3. Mail materials to: COLUMBIA RIVER MENTAL HEALTH SERVICES, P.O. Box 1337, Vancouver, Washington 98666.

We encourage bilingual individuals to apply.
AFFIRMATIVE ACTION/EQUAL OPPORTUNITY EMPLOYER

WISCONSIN

Madison, WI - noted as "U.S. Best City", two years, seeks a BC/BE child psychiatrist. *Capitol Associates*, well-recognized for more than 20 years, is Madison's largest, independent, licensed mental health clinic and is dedicated to comprehensive inpatient/outpatient care. CA boasts 14 mental health professionals, including 2 psychiatrists. A university town surrounded by many lakes, Madison has abundant recreational activities, high educational standards and support for the arts. Please consider joining our caring, energetic team. Capitol Associates, LLC, Attention: Johna Gerasch, PhD (Managing Partner), 440 Science Dr., Suite 200, Madison, WI 53711. (608) 238-5176, ext. 314. No recruiting companies please.

Wisconsin - Seeking a BE/BC psychiatric hospitalist to join established behavioral health practice. Hospital based position. 14-bed adult unit. Excellent salary and benefit package. Lakefront living, year round recreation, and excellent schools. An easy drive to Madison, Milwaukee, Chicago, or Minneapolis/St. Paul. It's worth checking out! Contact Bob Bregant at bbregant@hortonsmithassociates.com or call 800.398.2923. Job #1185

International

AUSTRALIA & NEW ZEALAND
PSYCHIATRY JOBS
Gen. Adult - Child & Adoles. - Forensics
Locum Tenens or Permanent Jobs
Salary = $250-350,000 per annum
www.IMRpsychiatry.com

Fellowships

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 board eligible/board certified graduates of approved psychiatric residency programs. The fellowship seeks psychiatrists with outstanding clinical and academic records as evidenced by publications, presentations, teaching experience, and exceptional letters of recommendation, who are interested in an academic career in Psychosomatic Medicine (consultation-liaison psychiatry). Spanish speaking a plus. 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 2009-2010 academic year. To apply, please submit a personal statement, three letters of recommendation, and a C.V., no later than October 15, 2008. 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.

ADDICTION PSYCHIATRY FELLOWSHIP UNIVERSITY OF MICHIGAN

The Addiction Psychiatry Fellowship Program is a one-year, post-residency, clinical training program for psychiatrists interested in addiction psychiatry, available July 1, 2009. The program is accredited by the Accreditation Council for Graduate Medical Education, and successful completion of the 1-year clinical track qualifies psychiatrists to apply for subspecialty certification in addiction psychiatry from the American Board of Psychiatry and Neurology. Qualified applicants will have completed (before starting the fellowship) an accredited psychiatry residency in the U.S. and have passed all necessary examinations to obtain a physician's license in the State of Michigan. Training licenses will not be accepted. Applicants with J1 visas will be considered. Excellent salary and benefits.

Contact: Carol Skala, Program Coordinator, 734-232-0294. Web: http://www.med.umich.edu/psych/education/addiction/

The University of Michigan is an equal opportunity/affirmative action employer.

PSYCHOSOMATIC MEDICINE FELLOWSHIP

One year exciting, well-established, fellowship program, one of the first accredited by the ACGME, in a 750-bed university hospital, accepting applications for July 1, 2009. 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, jlevenson@mcvh-vcu.edu (804) 828-0762; Yaacov R. Pushkin, M.D. ypushkin@mcvh-vcu.edu, or Sherif Meguid, M.D. aabdel-meguid@mcvh-vcu.edu

PSYCHOSOMATIC MEDICINE FELLOWSHIP UNIVERSITY OF MICHIGAN

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 education, administration, and research, 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, 2009. Candidates must have completed an approved U.S. residency in Psychiatry and must have passed USMLE Step III prior to entry into program. Excellent salary and benefits.

Contact: Michelle Riba, MD, Associate Director, Psychosomatic Medicine Services, Department of Psychiatry, University of Michigan Health System, 1500 E. Medical Center Drive, Room F6327A MCHC, Ann Arbor, MI, 48109-0295. Tel: (734) 764-6879; FAX: (734) 936-1130; Email:gacioch@umich.edu; web: http://www.med.umich.edu/psych/education/psychosomatic/.

The University of Michigan is an equal opportunity/affirmative action employer.

Geriatric Psychiatry Fellowship with Emphasis on Integrated Consultation-Liaison Psychiatry

The Department of Psychiatry and Behavioral Science at Stony Brook announces the availability of an innovative ACGME-accredited geriatric psychiatry fellowship position starting July 2009 with the option for special emphasis on consultation-liaison psychiatry. With eight board certified geriatric psychiatrists on the faculty, the geriatric psychiatry fellow will have dedicated experience in geriatric inpatient, long-term care, outpatient, ECT, and consultation-liaison psychiatry at the University Hospital as well as several community settings. Located within the new Stony Brook "Division of Medical and Geriatric Psychiatry," fellows in geriatric psychiatry will participate in a clinical milieu emphasizing understanding of the psychiatric aspects of medical conditions, along with the medical aspects of psychiatric conditions. Fellows have the unusual opportunity, through collaborative consultation-liaison work, to develop added clinical expertise and professional relationship skills working closely with trainees and faculty in geriatric medicine, neurology, and family medicine. To apply for the position, fax (631) 444-7534 or email *steven.cole@stonybrook.edu* your letter of interest, your CV, and three letters of reference. Or send by mail to Steven Cole, MD, Head, Division of Medical and Geriatric Psychiatry Health Sciences Center, 10th Floor, Room 042, Stony Brook NY 11794-8101. Equal opportunity/affirmative action employer.

FELLOWSHIP PUBLIC PSYCHIATRY at YALE

The Connecticut Mental Health Center - Yale University School of Medicine is accepting applications for a one-year Fellowship in Public Psychiatry for July 2009. 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 spend 50% time in seminars, supervision, and administrative/policy meetings of CMHC and the CT Dept. of Mental Health and Addiction Services; and up to 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.

GERIATRIC PSYCHIATRY FELLOWSHIP UNIVERSITY OF MICHIGAN

ACGME-accredited Geriatric Psychiatry Fellowship at the University of Michigan and Ann Arbor VA Healthcare System (VAHS) available July 1, 2009. 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. Excellent salary and benefits.

Contact: Susan Maixner, MD, Director, Geriatric Psychiatry Fellowship, University of Michigan, 1500 E. Med. Ctr. Drive, F6327A MCHC, Ann Arbor, MI, 48109-0295; Tel: (734) 764-6879; FAX: (734) 936-1130; Email: gacioch @med.umich.edu; Web: http://www.med.umich.edu/psych/education/GERIAT/.

The University of Michigan is an equal opportunity/affirmative action employer.

Addiction Psychiatry Fellowship - This is a PGY 5 position, to begin July 1, 2009, at the University of Illinois at Chicago, Department of Psychiatry. Fellow will acquire expertise in treating addictions through comprehensive training in a variety of inpatient, outpatient, and consultative settings. Teaching and research opportunities included in fellowship. Rodney Eiger, M.D., Fellowship Director.

PRIME Residency - This is a PGY 4 position, to begin July 1, 2009 at the Jesse Brown VA Med Ctr/University of Illinois at Chicago, Department of Psychiatry. The trainee will receive psychiatric consultation-liaison training as a member of a primary care team (PRIME) and will educate primary care team about identification and management of common psychiatric disorders. Resident will participate in ongoing didactic programs and provide care in community-based outpatient clinics. Opportunities for clinical research, electives in ECT, home care, addiction and geriatric psychiatry available. Supervision is provided by faculty from the Depts of Psychiatry and Medicine at JBVA Medical Center and the University of Illinois at Chicago.

Women's Mental Health Fellowship - This is a one-year, PGY 4 or 5 position, to begin July 1, 2009 at the University of Illinois at Chicago, Department of Psychiatry. We are seeking an exceptional candidate who wants to develop expertise in reproductive and gender-linked psychiatric disorders. Our program has received the ACP Award for Creativity in Psychiatric Education, and the APA Gold Award in recognition of our pioneering work in women's mental health.

USMLE Step 3 required for PGY 4 and above positions. For the above 3 positions contact: Robert W. Marvin, MD, Director Residency Training, by mail: 912 S. Wood St., MC 913, Chicago, IL 60612; by e-mail: recruit@psych.uic.edu; or by phone: (312) 996-3583, on or before December 31, 2008. Detailed descriptions are posted on the Residency web site: http://www.psych.uic.edu/education/residents/fellowships. The UIC and JBVA are AA/EOE.

Psychosomatic Medicine Fellowship, Portland, Oregon. Recruiting for 07/01/09 ACGME-accredited PGY5 level, at Oregon Health & Science Univ and Portland VA Med Center. Flexible program with clinical and research opportunities. Training sites include ambulatory care, specialty services, and consultation to inpatient med/surg. Research and clinical strengths in health services, mental disorders in primary care, pain, end-of-life/palliative care, ethics, mood disorders, Parkinson's disease, and substance abuse. Contact Dr. Steven Dobscha, Portland VA Med. Ctr., PO Box 1034 (R&D 66), Portland, OR 97207; at steven.dobscha@va.gov or (503) 220-8262, Ext. 56444. EOE.

Residencies

Unexpected Opening

Dartmouth Medical School's Department of Psychiatry based at Hitchcock Medical Center located in Lebanon, NH, has an unexpected immediate opening for a PGY-1 in our Adult Psychiatry Residency Program.

To learn more about the program, faculty, and residents see our website.

http://dms.dartmouth.edu/psych/training/adult_residency/

To inquire further about the position please e-mail our ProgramDirector: Ronald.L.Green@Dartmouth.EDU

Practice for Sale

Excellent, financially successful Psychiatric private practice for sale in San Antonio, Texas. CALL: 210-877-1473

Software

POMIS - PRACTICE MANAGEMENT SOFTWARE by PerfectByte

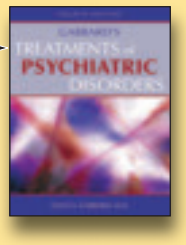
Comprehensive/User Friendly/Affordable. Billing, Scheduling, Collections Module, Recalls, Electronic Medical Records, Image Storage, Customizable Documents, Rx Writer, Interoffice Messaging and more...**FREE TRIAL www.pomismedical.com 877.767.7007**

PsychiatryOnline.com

Online access to a premier collection of psychiatric resources

Two additional resouces added to PsychiatryOnline

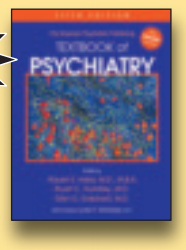
NEW!



Gabbard's Treatments of Psychiatric Disorders, Fourth Edition

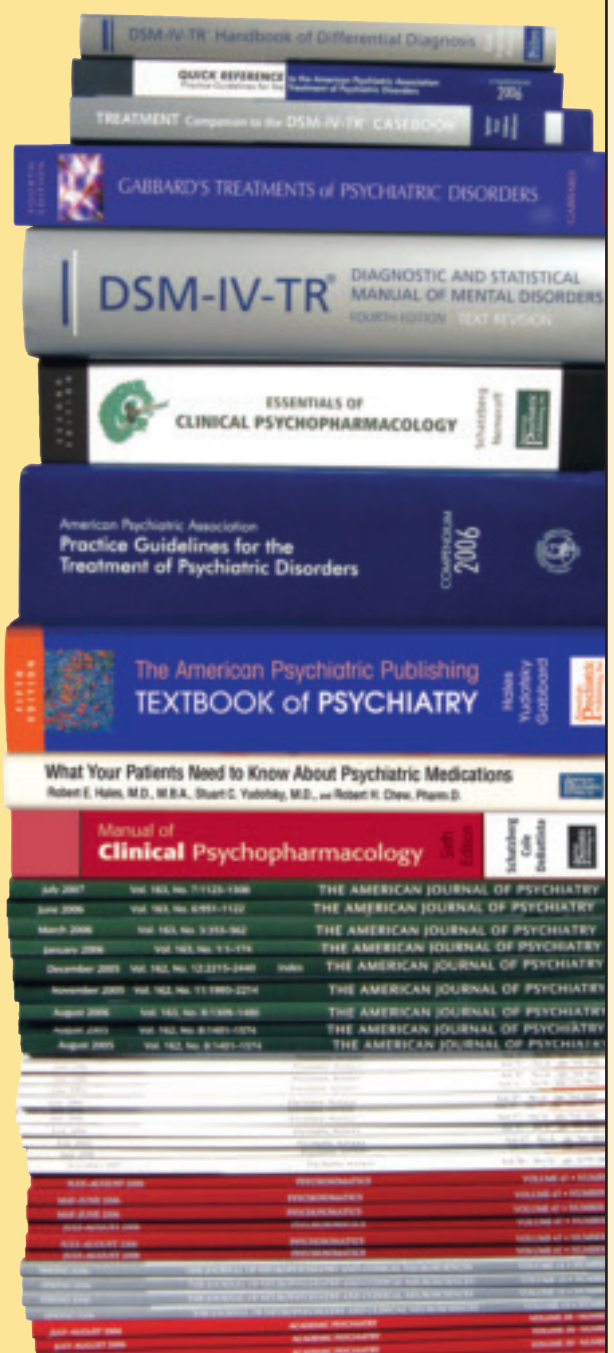
Edited by Glen O. Gabbard, M.D.

Coming May 2008!



The American Psychiatric Publishing Textbook of Psychiatry, Fifth Edition

Edited by Robert E. Hales, M.D., M.B.A., Stuart C. Yudofsky, M.D., and Glen O. Gabbard, M.D.



PsychiatryOnline.com is a powerful website that features *DSM-IV-TR*® and *The American Journal of Psychiatry* as the cornerstones of an unsurpassed collection of psychiatric references, including books, journals, and self-assessment tools. Much more than simply books and journals presented online, **PsychiatryOnline.com** features sophisticated searching and indexing tools that enable you to quickly target all the information you need.

Whether your needs are clinical, learning, or research, **PsychiatryOnline.com** provides access to the information critical to your work and everyday practice with convenient features such as:

- Search and linking tools that let you find relevant book chapters and journal articles quickly.
- Unlimited downloads to PDA so you can take book sections with you wherever you go.
- Copy and paste functions for easy creation of tables and presentations.
- Citation exports to most reference manager formats.
- Printer-friendly views that mean no reformatting when you need a hard copy.
- Saved searches and bookmarked chapters to make it easy to return to topics of interest.
- Email page feature that allows you to share the information with colleagues.

Other subscriber benefits include:

- Book of the Month—You'll get access each month to a FREE PDF version of a featured book from American Psychiatric Publishing, Inc.
- The most up-to-date versions available including NEW *American Psychiatric Association Practice Guidelines* as they are released.
- PLUS Guideline Watches and DSM-IV-TR Coding Updates, as soon as they are available.
- American Psychiatric Association Members receive **$110 discount** off a regular priced subscription. APA Members-in-Training (MITs) can save even more!

Subscribe TODAY, visit
www.PsychiatryOnline.com.

Please enter priority code AH818 when completing your request.

Interested in an institutional subscription? Please contact us at institutions@psych.org or call 1-800-368-5777 ext. 8538 or 703-907-8538 for more information and a subscription rate quote.

American Psychiatric Publishing, Inc.

The *First* and *Last* Word in Psychiatry

American Psychiatric Foundation
Advancing public understanding of mental illnesses™

2008 Annual Benefit "Windows on Washington"

Saturday, May 3, 2008 • 7:00 – 10:00 p.m. • East Hall of Union Station • 50 Massachusetts Ave. NE, Washington, D.C.

The American Psychiatric Foundation invites you to "Windows on Washington" a special evening at the East Hall of the magnificent Union Station. Enjoy tasty cuisine and live music in the historic building that has played host to 17 presidents and countless foreign dignitaries. The evening's program includes a silent auction and a presentation of the Awards for Advancing Minority Health. Event proceeds support the foundation's grants, programs, research funding and awards that advance public understanding that mental illnesses are real and treatable. It will be a time to network with new friends and old.

Union Station is accessible by the Red line of the Metro rail or is a short taxi ride from the Washington Convention Center and most of the core APA hotels.

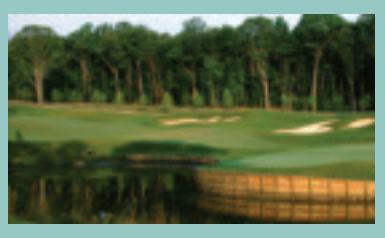
Tickets:
$150 per person if purchased by April 1 or $175 per person thereafter. To order tickets, please call (703) 907-8512 or visit www.psychfoundation.org.

Benefit Program Ads:
Honor your colleagues or celebrate a special milestone with an advertisement in the foundation's benefit program and auction catalogue. For more details, call (703) 907-8512 or e-mail apf@psych.org.

Pitch in for Mental Health! – Nationals Park

Saturday, May 3, 1:05 pm • Washington Nationals vs. the Pittsburgh Pirates
Friday, May 9, 7:35 pm • Washington Nationals vs. the Florida Marlins
(Ticket prices will vary based on seating)

Experience the inaugural season at Nationals Park! Enjoy springtime at the ball park while supporting the work of the foundation. The Washington Nationals will play the Pittsburgh Pirates and the Florida Marlins while the APA is in town. For every ticket sold a portion of the sale will be contributed to the foundation. To order tickets, call Michael Benko, Account Executive, Group Sales – Washington Nationals Baseball Club at (202) 541-1617 or email at michael.benko@nationals.com. More information is available at www.psychfoundation.org.



Golfers of the APA (GAPA) 2008 Annual Golf Tournament

Monday, May 5, 2008 • Shotgun Start at 8:00 a.m. • Old Hickory Golf Club

Enjoy a round of golf at Old Hickory Golf Club, located only 26 miles from downtown D.C. This 7,190-yard, Par-72 Championship layout features stunning tree-lined and striped fairways, sculpted mounds and bunkers with bent grass from tee to green. $145 includes transportation to the course, greens fees, carts, lunch, awards banquet, and prizes. Club rental is an additional $30. Event proceeds will benefit the foundation. For more information on the course, visit http://www.golfoldhickory.com. To learn more, or to enter the tournament, please contact Stan Jennings, M.D., at mbears@comcast.net or (804) 320-7881.

"Conversations" featuring Patty Duke

Tuesday, May 6, 2008 • 5:30 – 6:30 p.m. • Washington, D.C. Convention Center, Hall D
Free to all annual meeting attendees (Seating is limited, early arrival is suggested)

Don't miss our 7th annual *"Conversations"* event, an interactive series that offers meeting attendees an opportunity to hear unique perspectives on mental illness. Academy award winning actress and author Patty Duke will share her personal story of living with bipolar disorder.

"Conversations" is supported by a charitable contribution from AstraZeneca to the American Psychiatric Foundation. AstraZeneca

CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. Cymbalta is not approved for use in pediatric patients. *[See Warnings and Precautions and Use in Specific Populations.]*

INDICATIONS AND USAGE: Major Depressive Disorder—Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD).

Generalized Anxiety Disorder—Cymbalta is indicated for the acute treatment of generalized anxiety disorder (GAD).

Diabetic Peripheral Neuropathic Pain—Cymbalta is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.

Fibromyalgia—Cymbalta is indicated for the management of fibromyalgia (FM).

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors—Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include 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 serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome *[see Warnings and Precautions]*.

Uncontrolled Narrow-Angle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: 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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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 discontinuation can be associated with certain symptoms *[see Warnings and Precautions, Discontinuation of Treatment with Cymbalta]*.

Families and caregivers of 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 Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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 Cymbalta (duloxetine) is not approved for use in treating bipolar depression.

Hepatotoxicity—There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (85/7,632) of Cymbalta-treated patients compared to 0.2% (13/5,578) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Warnings and Precautions and Drug Interactions]* and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Serotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated *[see Contraindications]*.

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*.

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*.

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

During marketing of 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, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. 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.

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP, GAD, or fibromyalgia placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/9445) of patients treated with duloxetine and 0.01% (1/6770) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions, Vital Sign Changes]*.

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta—*CYP1A2 Inhibitors*—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions]*.

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions]*.

Potential for Cymbalta to Affect Other Drugs—*Drugs Metabolized by CYP2D6*—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered *[see Drug Interactions]*.

Other Clinically Important Drug Interactions—*Alcohol*—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions and Drug Interactions]*.

CNS Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action *[see Warnings and Precautions and Drug Interactions]*.

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations]*. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency *[see Warnings and Precautions and Use in Specific Populations]*.

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations]*.

Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma *[see Contraindications]*.

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related. In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327), GAD (N=668), DPNP (N=568) and FM (N=876). The population studied was 17 to 89 years of age; 64.8%, 64.7%, 38.7%, and 94.6% female; and 85.5%, 84.6%, 77.6%, and 88% Caucasian for MDD, GAD, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder—Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain—Approximately 14.3% (81/568) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) were nausea (duloxetine 3.5%, placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%), and fatigue (duloxetine 1.1%, placebo 0.0%).

Fibromyalgia—Approximately 19.5% (171/876) of the patients who received duloxetine in 3 to 6 month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 11.8% (63/535) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 1.9%, placebo 0.7%), somnolence (duloxetine 1.5%, placebo 0.0%), and fatigue (duloxetine 1.3%, placebo 0.2%).

Adverse Reactions Occurring at an Incidence of 5% or More and at least Twice Placebo Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled Trials for all Approved Indications—The most commonly observed adverse reactions in Cymbalta-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, hyperhidrosis, and decreased appetite.

In addition to the adverse reactions listed above, DPNP trials also included dizziness and asthenia.

Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine- Treated Patients in Placebo-Controlled Trials—The incidence of treatment-emergent adverse reactions in placebo-controlled trials **(N=4843 Cymbalta; N=3048 placebo)** for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo were: *nausea*, *headache*, *dry mouth*, *fatigue (includes asthenia)*, *insomnia** *(includes middle insomnia*, *early morning awakening*, *and initial insomnia)*, *dizziness, somnolence** *(includes hypersomnia and sedation)*, *constipation**, *diarrhea*, *decreased appetite** *(includes anorexia)*, *and hyperhidrosis*. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine- Treated Patients in Placebo-Controlled Trials—Pooled MDD and GAD Trials—Table 3 in full PI gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials **(N=2995 Cymbalta; N=1955 placebo)** for approved indications that

Cymbalta® (duloxetine hydrochloride) PV 5908 AMP
Cymbalta® (duloxetine hydrochloride) PV 5908 AMP

occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Investigations—weight decreased*; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Nervous System Disorders—dizziness, somnolence (includes hypersomnia and sedation), tremor; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, decreased libido (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); Reproductive System and Breast Disorders—erectile dysfunction, ejaculation delayed, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); Respiratory, Thoracic, and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot flush. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Diabetic Peripheral Neuropathic Pain—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPNP placebo-controlled trials **(N=115 Cymbalta 20 mg once daily; N=228 Cymbalta 60 mg once daily; N=225 Cymbalta 60 mg twice daily; N=223 placebo)** with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; General Disorders and Administration Site Conditions—fatigue, asthenia, pyrexia; Infections and Infestations—nasopharyngitis; Metabolism and Nutrition Disorders—decreased appetite, anorexia; Musculoskeletal and Connective Tissue Disorders—muscle cramp, myalgia; Nervous System Disorders—somnolence, headache, dizziness, tremor; Psychiatric Disorders—insomnia; Renal and Urinary Disorders—pollakiuria; Reproductive System and Breast Disorders—erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis.

Fibromyalgia—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of FM placebo-controlled trials **(N=876 Cymbalta; N=535 placebo)** and with an incidence greater than placebo were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, dyspepsia; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Immune System Disorders—seasonal allergy; Infections and Infestations—upper respiratory tract infection, urinary tract infection, influenza, gastroenteritis viral; Investigations—weight increased; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Musculoskeletal and Connective Tissue Disorders—musculoskeletal pain, muscle spasm; Nervous System Disorders—headache, dizziness, somnolence (includes hypersomnia and sedation), tremor, paraesthesia, migraine, dysgeusia; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), sleep disorder, abnormal dreams (includes nightmare), orgasm abnormal (includes anorgasmia), libido decreased (includes loss of libido); Reproductive System and Breast Disorders—ejaculation disorder (includes ejaculation failure and ejaculation dysfunction), penis disorder; Respiratory, Thoracic, and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis, rash, pruritus; Vascular Disorders—hot flush.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Physicians should routinely inquire about possible sexual side effects. See Table 6 in full PI for specific ASEX results.

Vital Sign Changes—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions]*. Duloxetine treatment, for up to 26-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3-4 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In fibromyalgia studies, patients treated with Cymbalta for up to 26 weeks experienced a mean weight loss of approximately 0.4 kg compared with a mean weight gain of approximately 0.3 kg in placebo-treated patients. In one long-term fibromyalgia 60-week uncontrolled study, duloxetine patients had a mean weight increase of 0.7 kg.

Laboratory Changes—Cymbalta treatment in placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients *[see Warnings and Precautions]*.

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 27,229 patients were treated with duloxetine. Of these, 29% (7,886) took duloxetine for at least 6 months, and 13.3% (3,614) for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. **Cardiac Disorders**—*Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia; **Ear and Labyrinth Disorders**—*Frequent:* vertigo; *Infrequent:* ear pain and tinnitus; **Endocrine Disorders**—*Infrequent:* hypothyroidism; **Eye Disorders**—*Frequent:* vision blurred; *Infrequent:* diplopia and visual disturbance; **Gastrointestinal Disorders**—*Frequent:* flatulence; *Infrequent:* eructation, gastritis, halitosis, and stomatitis; *Rare:* gastric ulcer, hematochezia, and melena; **General Disorders and Administration Site Conditions**—*Frequent:* chills/rigors; *Infrequent:* feeling abnormal, feeling hot and/or cold, malaise, and thirst; *Rare:* gait disturbance; **Infections and Infestations**—*Infrequent:* gastroenteritis and laryngitis; **Investigations**—*Frequent:* weight increased; *Infrequent:* blood cholesterol increased; **Metabolism and Nutrition Disorders**—*Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia; **Musculoskeletal and Connective Tissue Disorders**—*Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching; **Nervous System Disorders**—*Frequent:* dysgeusia, lethargy, and parasthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; *Rare:* dysarthria; **Psychiatric Disorders**—*Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide; **Renal and Urinary Disorders**—*Infrequent:* dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal.; **Reproductive System and Breast Disorders**—*Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms, and sexual dysfunction; **Respiratory, Thoracic and Mediastinal Disorders**—*Frequent:* yawning; *Infrequent:* throat tightness; **Skin and Subcutaneous Tissue Disorders**—*Infrequent:* cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis; **Vascular Disorders**—*Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

Postmarketing Spontaneous Reports—The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

DRUG INTERACTIONS: Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine t1/2 was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin *[see Warnings and Precautions]*.

Inhibitors of CYP2D6—Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) *[see Warnings and Precautions]*.

Dual Inhibition of CYP1A2 and CYP2D6—Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)—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 may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued *[see Warnings and Precautions]*.

Lorazepam—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption *[see Warnings and Precautions]*.

Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold *[see Warnings and Precautions]*.

Drugs Metabolized by CYP2C9—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors—Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI *[see Contraindications and Warnings and Precautions]*.

Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended *[see Warnings and Precautions]*.

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions]*.

Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol.

In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen *[see Warnings and Precautions]*.

CNS Drugs—*[see Warnings and Precautions]*.

Drugs Highly Bound to Plasma Protein—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

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

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (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 and Precautions]*.

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions]*. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2,418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1,074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1,761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPNP studies, 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 greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*.

Gender—The half-life of duloxetine is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—*[see Warnings and Precautions]*.

Severe Renal Impairment—*[see Warnings and Precautions]*.

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

Literature revised June, 13, 2008

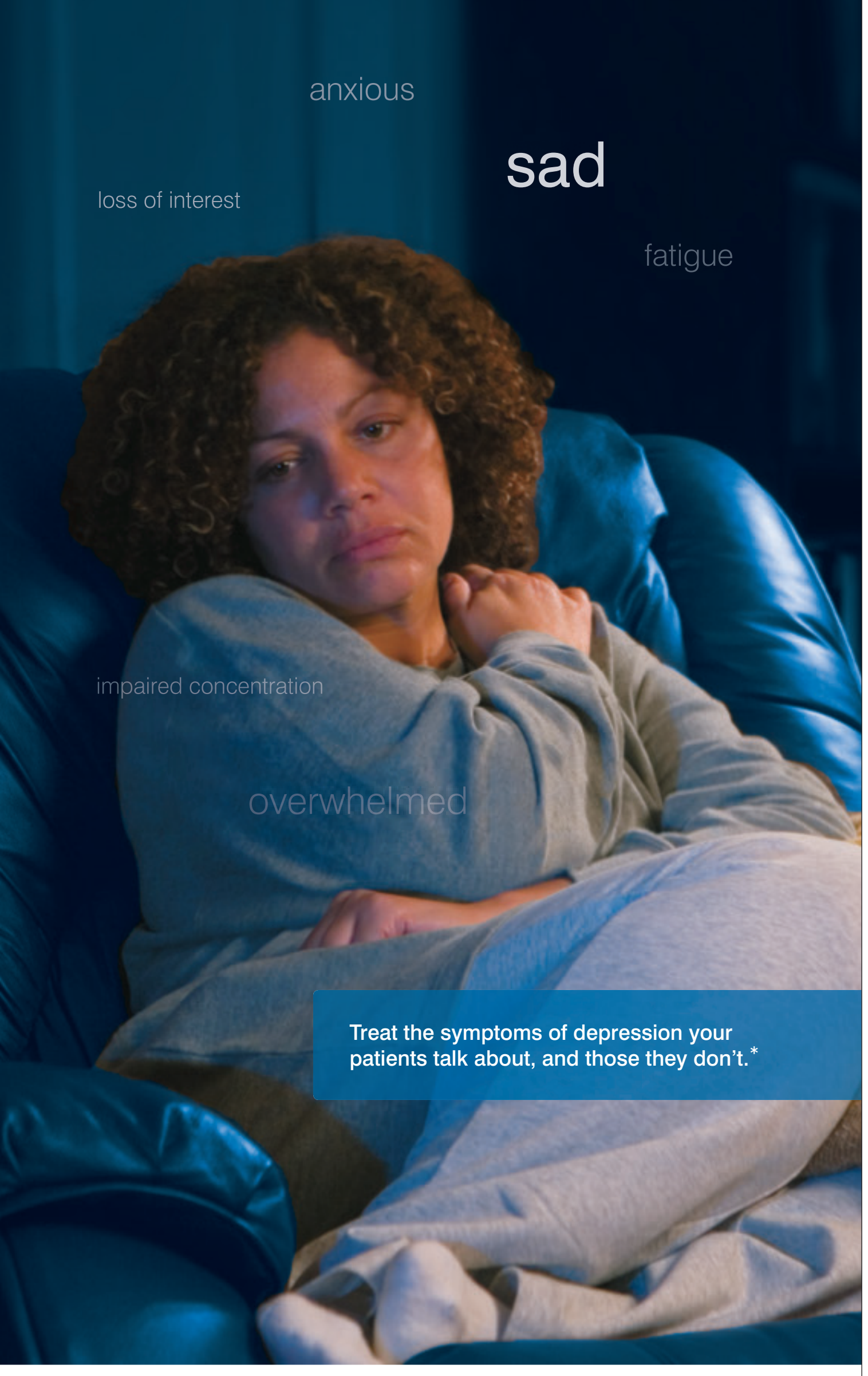
PV 5908 AMP PRINTED IN USA

Eli Lilly and Company
Indianapolis, IN 46285, USA

www.Cymbalta.com

Cymbalta® (duloxetine hydrochloride) PV 5908 AMP

Cymbalta® (duloxetine hydrochloride) PV 5908 AMP



Important Safety Information

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients of all ages started on therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.**
- **Cymbalta is not approved for use in pediatric patients.**

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or in patients with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All patients being treated with an antidepressant for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients**.

Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Cases of orthostatic hypotension and/or syncope as well as cases of hyponatremia have been reported.

Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs, including triptans. Concomitant use is not recommended.

SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.

On discontinuation, adverse events, some of which may be serious, have been reported with SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.

Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.

Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics).

Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min).

As observed in DPNP clinical trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases up to 52 weeks, an increase in HbA_{1c} in both the Cymbalta (0.5%) and routine care groups (0.2%) was noted.

If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=4843 vs 3048) were: nausea, dry mouth, somnolence,* constipation,* decreased appetite,* and increased sweating.

* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

See Brief Summary of full Prescribing Information, including Boxed Warning, on following spread.

* Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for MDD on mean change in $HAM\text{-}D_{17}$ Total Score,[1] Maier Subscale,[1] Psychic Anxiety,[1] and Visual Analog Pain Scales.[2]
Full antidepressant response may take 4-6 weeks.
MMRM=Mixed-effects Models Repeated Measures analysis

References: 1. Data on file, Lilly Research Laboratories: CYM20070220C.
2. Fava M, et al. *J Clin Psychiatry*. 2004;65(4):521-530.

www.insidecymbalta.com

Cymbalta® duloxetine HCl DELAYED RELEASE CAPSULES

Lilly