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Association

PSYCHIATRIC NEWS

inside

PERIODICALS: TIME-SENSITIVE MATERIALS

Hurricane Response Often Ignored Mentally Ill People

Disaster victims who are mentally ill deserve better treatment than many got after hurricanes Katrina and Rita.

BY AARON LEVIN

Persons with psychiatric disabilities must receive the same help as other people when disasters strike and should be included in every stage of emergency planning, according to a report from the National Council on Disability, a federal advisory group.

"We hope that the report will be read by anyone concerned with disaster relief and prevention," Julie Carroll, J.D., senior attorney adviser for the council, told *Psychiatric News*.

That would include psychiatrists interested in disaster issues, said Arshad Husain, M.D., chair of APA's Committee on Psychiatric Dimensions of Disasters and director of the University of Missouri International Center for Psychosocial Trauma, in Columbia, Mo. He plans to send copies of the report to members of his committee, he said.

The report documented how Katrina and Rita caught so many agencies and organizations involved with disaster response off guard. It was based largely on media reports and firsthand accounts of persons with psychiatric disabilities derived from conference calls organized by the National Council on Disability, but did not involve any formal survey, said Carroll. The report said that relief organizations and governments at all levels mismanaged evacuations, discriminated against persons with psychiatric disabilities, and terminated recovery services prematurely.

The council used the term "people with psychiatric disabilities" to describe people who use or have used mental health or psychiatric services, including those in some phase of recovery prior to the hurricanes.

"People with disabilities were segregated from the general population in some shelters, while other shelters simply refused to let them enter," according to the report.

Even before they reached shelters, some persons with psychiatric disabilities ran into problems. Residents of group homes or other psychiatric facilities were lost to emergency officials, who were unprepared for the special requirements needed to transport or relocate them. Some ended up in state parks or other refuges that were not set up to meet the needs of persons with psychiatric diagnoses. Still others were inappropriately institutionalized because they were stereotyped with the stigma of mental illness.

"Shelters were crowded, noisy, chaotic, confusing, and sometimes violent, all inadequate circumstances for a person with psychosis, anxiety, or depression," said the report. "Many ended up living right outside the shelters, and services were not provided

please see ***Mentally Ill*** *on page 38*

Need to Prove Citizenship Could Penalize Medicaid Recipients

The impact of the tentative proof-of-citizenship rule Congress is imposing on Medicaid beneficiaries has been softened, but advocates want further steps to protect those with mental illness.

BY RICH DALY

APA hopes it can convince the federal government to modify a new rule requiring Medicaid beneficiaries to prove citizenship and identity before beneficiaries with mental illness start confronting loss of coverage.

The policy, mandated by the Deficit Reduction Act (DRA) enacted in February, was scheduled to be implemented by the Centers for Medicare and Medicaid Services (CMS) in early July. However, CMS continued to develop implementation plans after the intended start date. The final regulations were expected to be released in mid-August.

Documents that can be used to prove citizenship include a U.S. passport, certificate of U.S. naturalization, and certificate of U.S. citizenship. Other documents—such as a U.S. birth certificate or official military record of service showing a U.S. place of birth—are acceptable when accompanied by proof of identity.

In the past, most states allowed beneficiaries to attest to U.S. citizenship under penalty of perjury. Documentation was required only from those whose citizenship status was in doubt

Congress enacted the new requirement over concerns that illegal immigrants were falsely claiming citizenship to receive Medicaid benefits, although the Office of Inspector General at the Department of Health and Human Services found no substantial evidence of such problems.

APA applauded the decision by CMS in early July to allow states to exempt the approximately 8 million people already enrolled in Supplemental Security Income or Medicare programs. Most states have opted to take that less-restrictive route.

Critics of the citizenship policy, including APA, said that it endangers the health care of about 40 million recipients not included in the exemption.

Please see ***Citizenship*** *on page 38*

David Hathcox

APA Trustees (from left) William Womack, M.D., Renee Binder, M.D., and David Fassler, M.D., listen during a discussion of steps APA should take as it decides whether to develop a position statement on gender identity disorder. Binder, along with former President Lawrence Hartmann, M.D., presented recommendations on how to proceed on this issue (see page 12).

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AP Photo/POOL/KTRK

Andrea Yates is shown in this image made from a June 26 video. In the opening statements of Yates's second murder trial, prosecutor Kaylynn Williford insisted that Yates drowned her five children in a bathtub because she thought she was a bad mother and wanted to be punished.

Insanity Plea Successful In Andrea Yates Retrial

APA leaders say debate and discussion about serious mental illness and criminal responsibility generated by the first trial and its outcome may have influenced the verdict in the second.

BY MARK MORAN

Andrea Yates, the Houston woman convicted in 2002 of killing her five children, was found not guilty by reason of insanity in a retrial after her original convictions were overturned earlier this year.

Shortly after the July 26 verdict, Yates was transferred to Vernon State Hospital, a maximum-security state mental health facility in north Texas.

The now 42-year-old Yates had been sentenced to life in prison for drowning her five children in a bathtub in June 2001. Although her attorney had argued in the first trial that Yates was legally insane at the time she drowned her children, she was found guilty.

Under Texas law, the standard for a verdict of not guilty by reason of insanity hinges on whether the defendant knew that his or her behavior was wrong.

Yates petitioned for a mistrial when a forensic psychiatrist, Park Dietz, M.D., who was an expert witness for the prosecution, informed prosecutors that he had given incorrect testimony. The trial court rejected Yates' petition for a mistrial, but this ruling was overturned by the Court of Appeals for the 1st District of Texas. A new trial was ordered on January 6, 2005 *(Psychiatric News*, February 4, 2005).

The verdict from Yates's second trial was welcomed by mental health advocates, including APA leaders. "It is a great relief to hear that justice has prevailed," said APA Vice President Nada Stotland, M.D. "It's heartbreaking that she was convicted in the first place."

Stotland, who had appeared on CNN to talk about postpartum psychosis during the first trial, spoke of some of the public anxieties, perceptions, and misperceptions aroused by the sensational killings.

"It was clear that some people were swayed by their intense feelings about the sanctity of motherhood," she said. "They could not accept any excuse for a mother harming her children. So they thought it was essential that the court send a message that would convince other mothers out there that they couldn't get away with harming their children.

"Others could not grasp the possibility that a person could carry out effective plans and activities while psychotic or on the basis of psychotic beliefs," Stotland continued. "This is a recurring confusion in cases involving a psychotic defendant.

"There is also a persistent sense that society is too lenient overall, a belief that criminals are claiming insanity far more often than is the case and still far more often than this defense actually prevails. Many people simply don't believe in psychiatric conditions as genuine diseases. They feel that the punishment of those who break the rules is essential to the maintenance of a just society."

Stotland said she believes the case provided an opportunity to inform the public about postpartum psychosis and reassure many mothers who experience postpartum depression that they are not likely to harm their babies.

Paul Appelbaum, M.D., chair of APA's Council on Psychiatry and the Law, said he believes it possible that the debate and

please see ***Yates*** *on page 38*

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Foundation Spreads Message That Psychiatry Makes a Difference

BY PEDRO RUIZ, M.D.

Reaching out to the public and providing crucial information about the realities of mental illness as well as the availability of effective treatments is among APA's top priorities, as it should be for the profession and the field at large. It is really up to us, both as professionals and as an organization, to tackle the misconceptions about mental illness that still exist in our communities across the country. If we do not accept and take on this challenge, then who will?

The American Psychiatric Foundation is part of a growing and proactive effort by APA to educate the public about mental illness and the availability of high-quality care that could and should be readily accessible to all people who need these services. As APA's philanthropic arm, the foundation is uniquely positioned to bring the "voice of medicine" to the public through a mixture of programs, grant funding, and awards that touch men, women, and children of all ages, races, and ethnic, cultural, and socioeconomic backgrounds.

When I was president-elect of APA, I had the pleasure of serving on the foundation's Board of Directors for a year. This board is made up of a diverse and committed group of people including psychiatrists and nonpsychiatrists; among them are also people who have suffered from mental illness as well as family members. All directors bring unique viewpoints and a wealth of knowledge that are necessary to guide the foundation's endeavors successfully. The foundation's overall mission is straightforward and focuses on patients with mental illness and their families—that is, "Advancing public understanding that mental illnesses are real and can be effectively treated."

As I observed, the current breadth and depth of the foundation's work is growing and impressive. It addresses the need for mental health education and recognizes the particular importance of reaching out to underserved communities where the need for accurate and available information and quality care is especially urgent. The most recent grants awarded by the foundation are a good symbol of how psychiatric care can make a difference in communities where mental health services have not been a priority in the past and, thus, barriers to treatment have been very high.

For instance, one recently awarded grant went to the Merced Lao Family Community (MLFC), which serves the Southeast-Asian community in Merced County, Calif. This program currently serves 10,000 refugees who fled Laos after the Vietnam War. With the foundation's support, the MLFC is airing television talk shows and conducting mental-health-oriented workshops in the native Southeast-Asian languages in an effort to combat stigma and inform residents about the mental health resources that are locally available. Leaders of this community's seven clans are invited to attend the workshops so that they have accurate mental health information to share with the members of their clans.

Foundation funding also helped the Central Massachusetts Area Health Education Center launch its Latino Mental Health Project. This project tries to reach out to the Latino community in inner-city Worcester, Mass. Educational workshops and ads in the local Spanish-language media are helping to raise awareness about mental illnesses, enhance early detection efforts, and inform people how to find the mental health services they need within their community.

As a member of APA, I hope that you take pride in the work that our foundation is doing to make much-needed mental health information accessible to the public, particularly in underserved communities. Our foundation effectively demonstrates how psychiatry can make a difference, not just in the lives of patients, but in our broader communities as well. I urge you to become involved in your local community and spread the word about the work that our foundation is doing and about the need for early mental health intervention and the effectiveness of psychiatric treatments.

I also hope that you will join me in supporting our foundation by donating during its annual fund-raising efforts, attending its events, and spreading the word in our communities about our foundation's accomplishments. If we expect others to donate, we all need to be role models. Our foundation staff cannot effectively raise funds unless they can demonstrate that the majority of APA members have faith in the foundation and financially support it. High amounts, although welcomed, are not necessary. What is necessary is the full commitment and loyalty of you and other APA members. For more information about our foundation's programs and services, please visit its Web site at <www.psychfoundation.org>. ■

Mentors Wanted

APA members are encouraged to join the National Minority Mentors Network and become mentors to younger minority colleagues. 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.

A reception for current mentors will be held during APA's fall component meetings in Washington, D.C., on Friday, September 15, at 7 p.m.

Those interested in joining or obtaining additional information about the network or attending the reception should contact Marilyn King at (703) 907-8653 or mking@psych.org.

Report Confirms Sad State of Drug Treatment for Inmates

Only one-fifth of jail and prison inmates with drug problems receive treatment, according to a government report, even though treatment is economical and reduces crime.

BY EVE BENDER

Treating inmates who are addicted to drugs can help to reduce the costs associated with incarceration, crime, and unemployment and may slow the spread of HIV and other infectious diseases, according to a new report from the National Institute on Drug Abuse (NIDA).

The report, released last month, describes a number of principles of drug abuse treatment for criminal justice populations (see box below). A question-and-answer section addresses the needs of women and adolescents in the criminal justice system who have drug-addiction problems.

Approximately 70 percent of people incarcerated in prisons and jails have used drugs regularly during their lifetimes as compared with about 9 percent of the general population, according to the report, and for every dollar spent on addiction treatment, there is a $4 to $7 reduction in cost attributed to drug-related crimes.

The report confirms that drug abuse is costly in many ways: in 2002, costs related to drug abuse reached $181 billion, including $107 billion associated with drug-related crime. Other costs include those related to emergency room visits, unemployment, reduced productivity, and child abuse and neglect.

Inmates who are released with untreated substance use disorders are much more likely to reoffend, according to the report, which indicates that a thorough assessment of inmates should include a drug abuse history and a mental health evaluation, and services should address "issues of motivation, problem-solving, and skill-building for resisting drug use and criminal behavior."

Though the report advocates for increased treatment of inmates with drug addiction, it does not address the funding of such treatment.

Treatment must follow inmates into the community after their release, Nora Volkow, M.D., NIDA director, told *Psychiatric News*. "Before going to jail, many of these people have alienated their families, lost their jobs, eroded their social supports—so when they are released, they return to the community with little or no support, and without support, the chances of them succeeding will be very low."

Important aspects of treatment in and out of jails and prisons may combine training in problem solving, coping with stress in constructive ways, and developing cognitive skills and skills to resist the lure of drugs and engaging in criminal behavior.

Only an estimated 20 percent of U.S. inmates with substance use disorders receive some treatment while incarcerated, Volkow pointed out. Judges may decide to incarcerate drug-addicted offenders instead of sending them to treatment programs because the resources to pay for

please see ***Treatment*** *on page 37*

Courtesy of NIDA

NIDA Director Nora Volkow, M.D., discusses the importance of treating criminal offenders for substance-abuse problems at a press conference in Chicago in July. Not only do the inmates benefit, but so does society at large by, for example, reduced crime and unemployment.

NIDA's Addiction Treatment Principles For Inmates

- Drug addiction is a brain disease that affects behavior.
- Recovery from drug addiction requires effective treatment followed by management of the problem over time.
- Treatment must last long enough to produce stable behavioral changes.
- Assessment is the first step in treatment.
- Tailoring services to fit the needs of the individual is an important part of effective drug abuse treatment.
- Drug use during treatment should be carefully monitored.
- Treatment should target factors that are associated with criminal behavior.
- Criminal justice supervision should incorporate treatment planning for drug-abusing offenders, and treatment providers should be aware of correctional supervision requirements.
- Continuity of care is essential for drug abusers re-entering the community.
- A balance of rewards and sanctions encourages "pro-social" behavior and treatment participation.
- Offenders with co-occurring drug abuse and other mental health problems often require an integrated treatment approach.
- Medications are an important part of treatment for many drug-abusing offenders.
- Treatment planning for drug-abusing offenders who are living in or re-entering the community should include strategies to prevent and treat serious, chronic medical conditions such as HIV/AIDS, hepatitis B and C, and tuberculosis.

Source: "Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide," National Institute on Drug Abuse, 2006

Skepticism Required in Reading Reports From Medical Meetings

Journalists, researchers, and meeting organizers need to do a more conscientious job of presenting and reporting preliminary results of studies at medical meetings.

BY AARON LEVIN

Physicians, patients, and journalists should all be wary of news stories based on medical meeting presentations that have not yet undergone peer review and scientific publication, according to two physicians who have long campaigned for better medical reporting.

"The most direct way to improve the media coverage of scientific meetings would be to have less of it," wrote Steven Woloshin, M.D., M.S., and Lisa M. Schwartz, M.D., M.S., in the June 5 *Medical Journal of Australia*. Both authors are associate professors of medicine at the Veterans Affairs Outcomes Group of Dartmouth Medical School in White River Junction, Vt.

Presentations at scientific meetings are often big news, said Woloshin and Schwartz, although that is more often due to the combined interests of all involved. Meeting organizers like the attention that news stories bring, researchers garner academic resume builders, the public enjoys hearing about the latest discoveries, and reporters please their editors. Commercial pressures are inevitable, too.

"Journalists think they're above industry influence, but if you're not aware of industry-funded research and how positive results generate profits, you're wearing blinders," said Gary Schwitzer, director of the health journalism program at the University of Minnesota School of Journalism and Mass Communication in Minneapolis, in an interview.

Woloshin, Schwartz, and Schwitzer were faculty members at the annual Medicine in the Media program in June sponsored by the National Institutes of Health. This program is designed to help journalists better evaluate and report on medical research. Schwitzer also publishes "Health News Review," a Web site that evaluates medical news stories.

Woloshin and Schwartz looked at 174 newspaper stories and 13 television or radio stories reporting on study presen-

please see ***Reports*** *on page 32*

Cautions in Interpreting Study Results

Animal or laboratory study: Because the study was based on animals, researchers cannot be certain how well the findings will apply to people.

Small study: These findings are based on a small study population; larger studies are needed to understand how well the intervention really works.

Uncontrolled study: Everyone in this study took the drug X. By not including patients who did not take the drug, it is impossible to be sure how much (or even if) drug X accounted for the findings.

Controlled but not randomized study: Because the study was not a true experiment, researchers do not know whether it was drug X or something else about the people who happened to take drug X (for example, were they younger? less likely to smoke?) that accounted for the differences observed.

Any intervention study: The benefit observed should be weighed against the adverse effects (or other downsides such as inconvenience or cost). Important adverse effects should be specified and quantified; if there are none, this should be reported.

Unpublished scientific meeting presentations: The findings presented are from work in progress. Because a full study report has not undergone peer review, the results have yet to be independently verified and may change.

Source: Steve Woloshin, M.D., M.S., and Lisa Schwartz, M.D., M.S., *Medical Journal of Australia*, June 2006

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- After stopping treatment with SSRIs, SNRIs, TCAs, MAOIs, mirtazapine, bupropion; meperidine and analgesics such as: tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; and buspirone, approximately 1 week (5 weeks for fluoxetine) should elapse before starting therapy with EMSAM. At least 2 weeks should elapse after stopping EMSAM before starting therapy with buspirone or a drug that is contraindicated with EMSAM
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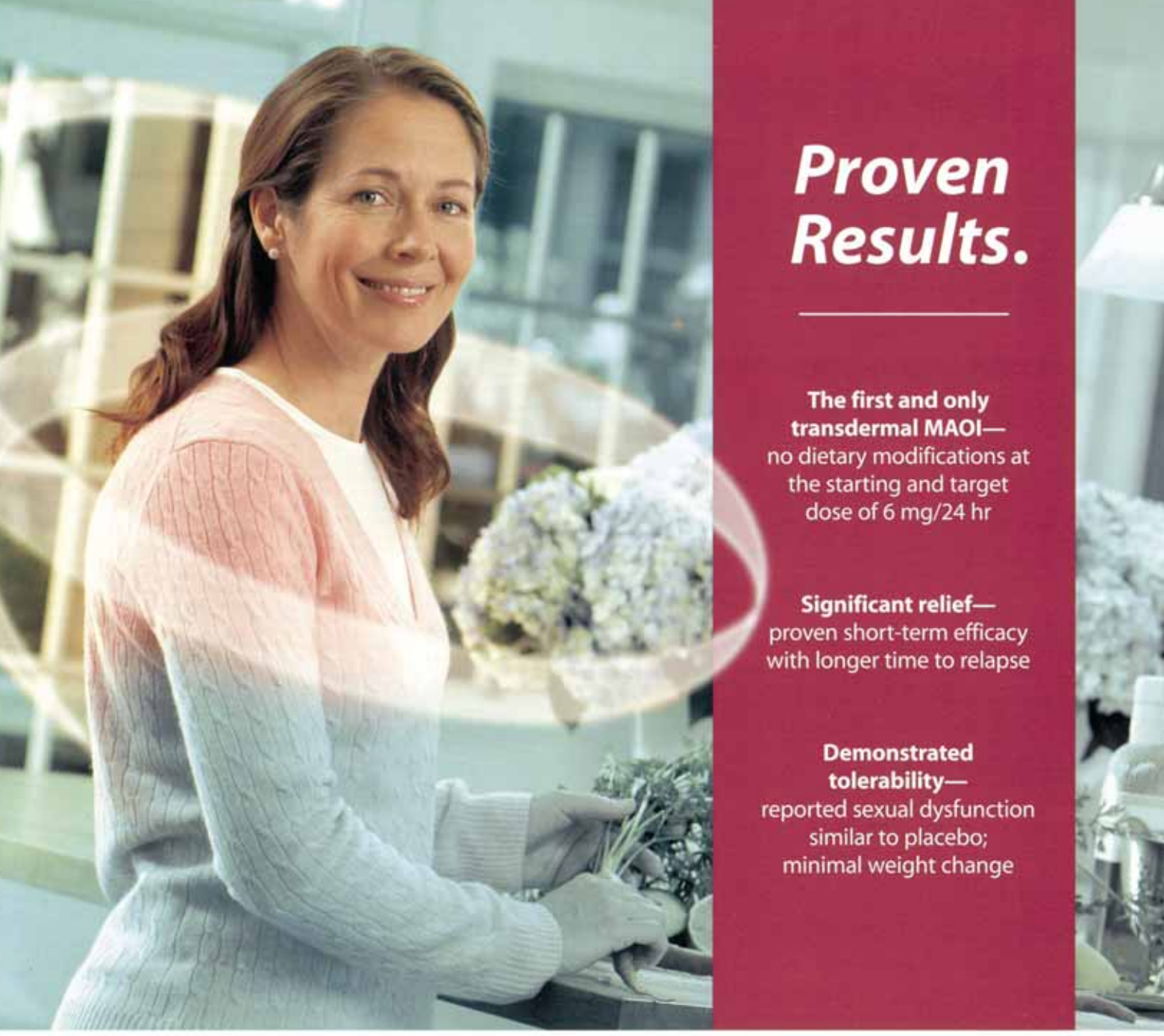

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Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders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

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EMSAM is indicated for the treatment of major depressive disorder.

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

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

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

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

CONTRAINDICATIONS

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

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

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

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

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

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

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

WARNINGS

Clinical Worsening and Suicide Risk

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

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

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

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

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

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

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

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

Screening Patients for Bipolar Disorder

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

Hypertensive Crisis

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

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

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

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

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

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

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

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

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

Use With Other Drugs Affecting Monoamine Activity

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

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

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

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

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

PRECAUTIONS

General

Hypotension

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

Activation of Mania/Hypomania

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

Use in Patients With Concomitant Illness

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

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

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

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

Information for Patients

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

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

Clinical Worsening and Suicide Risk

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

General

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Drug Interactions

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

Alcohol

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

Alprazolam

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

Carbamazepine

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

Ibuprofen

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

Ketoconazole

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

Levothyroxine

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

Olanzapine

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

Phenylpropanolamine (PPA)

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

Pseudoephedrine

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

Risperidone

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

Tyramine

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

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

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

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

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

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

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

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

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

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

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

Warfarin

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

Mutagenesis

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

Impairment of Fertility

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

Teratogenic Effects - Pregnancy Category C

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

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

Geriatric Use

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

ADVERSE REACTIONS

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

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

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

Adverse Events Associated with Discontinuation of Treatment

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

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

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

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

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

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

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

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

Application Site Reactions

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

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

Male and Female Sexual Dysfunction with MAO-Inhibitors

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

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

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

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

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

Vital Sign Changes

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

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

Multipart Strategy Urged To Reduce Medication Errors

Health care organizations should make it a standard procedure to inform patients about medication errors in their care, regardless of whether mistakes lead to harm, says the Institute of Medicine.

BY MARK MORAN

Medication errors are among the most common medical mistakes, impacting at least 1.5 million people every year, according to the Institute of Medicine (IOM).

The extra medical costs of treating drug-related injuries occurring in hospitals alone conservatively amount to $3.5 billion a year, and this estimate does not take into account lost wages and productivity or additional health care costs, the IOM states in a new report, "Preventing Medication Errors."

The report is the fourth IOM paper in its "Quality Chasm Series," begun in 1996. Previous reports include "To Err Is Human" (2000), "Crossing the Quality Chasm" (2001), and "Patient Safety" (2004).

The new report offers specific recommendations for physicians, health systems and hospitals, and patients in four broad categories: improving the patient-provider partnership; improving drug-information resources; electronic prescribing and other IT solutions; and drug naming, labeling, and packaging.

"The frequency of medication errors and preventable adverse drug events is cause for serious concern," said committee co-chair Linda Cronenwett, Ph.D., dean and professor at the University of North Carolina School of Nursing, in a statement released with the report. "We need a comprehensive approach to reducing these errors that involves not just health care organizations and federal agencies, but the industry and consumers as well."

Some of the important recommendations under each of the four broad categories are as follows:

• **Improving the Patient-Provider Partnership:** Health care organizations should make it a standard procedure to inform patients about clinically significant medication errors made in their care, whether the mistakes lead to harm or not.

The report provides consumers with a list of questions to ask health care providers, such as how to take their medications properly and what to do if side effects occur. Also included are actions consumers should take, such as requesting that their clinicians give them a printed record of the drugs they have been prescribed. Patients should maintain an up-to-date list of all medications they use—including over-the-counter products and dietary supplements—and share it with all their health care providers. This list should also note the reasons they are taking each product and include drug and food allergies.

• **Improving drug information resources:** The U.S. Food and Drug Administration (FDA) should work with other appropriate groups to standardize the text and design of medication leaflets to ensure that they are comprehensible and useful to all consumers.

The IOM called on the National Library of Medicine (NLM) to be the chief agency responsible for online health resources for consumers; it should create a Web site to serve as a centralized source of comprehensive, objective, and easy-to-understand information about drugs for consumers.

The report also recommended that NLM, FDA, and the Centers for Medicare and Medicaid Services evaluate ways to build and fund a national network of telephone helplines to assist people who may not be able to access or understand printed medication information because of illiteracy, language barriers, or other obstacles.

• **Electronic prescribing and other information technology (IT) solutions:** By 2010 all providers should be using e-prescribing systems, and all pharmacies should be able to receive prescriptions electronically. The Agency for Healthcare Research and Quality (AHRQ) should take the lead in fostering improvements in IT systems used in ordering, administering, and monitoring drugs.

All health care provider groups should be actively monitoring their progress in improving medication safety, the committee recommended. Monitoring efforts might include computer systems that detect medication-related problems and periodic audits of prescriptions filled in community pharmacies.

• **Drug naming, labeling, and packaging**: Drug naming terms should be standardized as much as possible, and all companies should be required to use the standardized terms, the report urges.

The FDA, AHRQ, and the pharmaceutical industry should collaborate with United States Pharmacopeia, Institute for Safe Medication Practices, and other appropriate organizations to develop a plan to address the problems associated with drug naming, labeling, and packaging by the end of 2007.

please see ***Errors*** *on page 37*

professional news

Nurturing an Alien Concept For Shakespeare's Mothers

Shakespeare's mothers are still shrouded in many mysteries, leaving psychiatrists and analysts with the challenge of ferreting out the answers.

BY JOAN AREHART-TREICHEL

Any psychiatrist who is a Shakespeare buff knows that the characters in Shakespeare's plays are fascinating from a psychoanalytic viewpoint. Which brings one to the subject of mothers: How many mothers are there in Shakespeare's plays? What are they like, and what motivates them? Where did he get his ideas for them?

Psychiatrist Dorothy Grunes, M.D., of Chicago was an English major in college with a special interest in Shakespeare, and she tackled these questions at the recent annual meeting of the American Psychoanalytic Association in Washington, D.C.

Joan Arehart-Treichel

A daughter-father duo—Dorothy Grunes, M.D., and Jerome Grunes, M.D.—is photographed at the annual meeting of the American Psychoanalytic Association. The two offered psychoanalytic views of the mothers in Shakespeare's plays.

Her psychiatrist father, Jerome Grunes, M.D., also contributed to the discussion, as did some other American Psychoanalytic Association members.

Anyone scrutinizing Shakespeare's plays for mothers will be struck by their paucity, Dorothy Grunes reported. For example, the mother is absent in "King Lear," and in "The Tempest," Miranda remembers only her nursemaid, not her mother.

In fact, mothers as fleshed-out characters are portrayed in only three of Shakespeare's 39 plays, Dorothy Grunes pointed out. They are the Duchess of York in "Richard III," Gertrude in "Hamlet," and Volumnia in "Coriolanus."

Moreover, she continued, the three mothers "use their sons for their own ends, for power or to play out their own intrapsychic conflicts. They are cold, neglectful, or cruel," and their relationships with their sons are tortured. For example, Volumnia exploits her son Coriolanus to fulfill her own ambitions. The Duchess of York externalizes her own failings onto her son Richard. Hamlet is unable to tolerate his mother's having married his uncle.

Indeed, these negative mother-son relationships are especially striking in view of some of the positive father-son relationships, positive father-daughter relationships, and positive sibling relationships presented in Shakespeare's plays, a session participant noted. Dorothy Grunes concurred and added, "The relationship between the father and daughter in 'King Lear' is painfully touching."

So why did Shakespeare pay mothers so little heed in his plays? Did he want to demonstrate the dominance of men over women, as one of the session speakers suggested? Perhaps, Dorothy Grunes said. But there are some strong women in his plays, she noted—for example, Portia in "The Merchant of Venice," Cordelia in "King Lear," and Lady Macbeth in "Macbeth."

When Shakespeare did depict mothers in his plays, why did he give them such unfavorable treatment? Did he have something against his own mother? Perhaps, for as one session participant indicated, the mother-son connections he depicts reflect a troubled nurturance that he probably experienced.

In contrast, another participant proposed, it is possible that the frayed mother-son bonds he describes may have come from observing other people because he obviously was keenly perceptive in some other domains. For instance, his descriptions of birds are so accurate that they could have been made by an ornithologist.

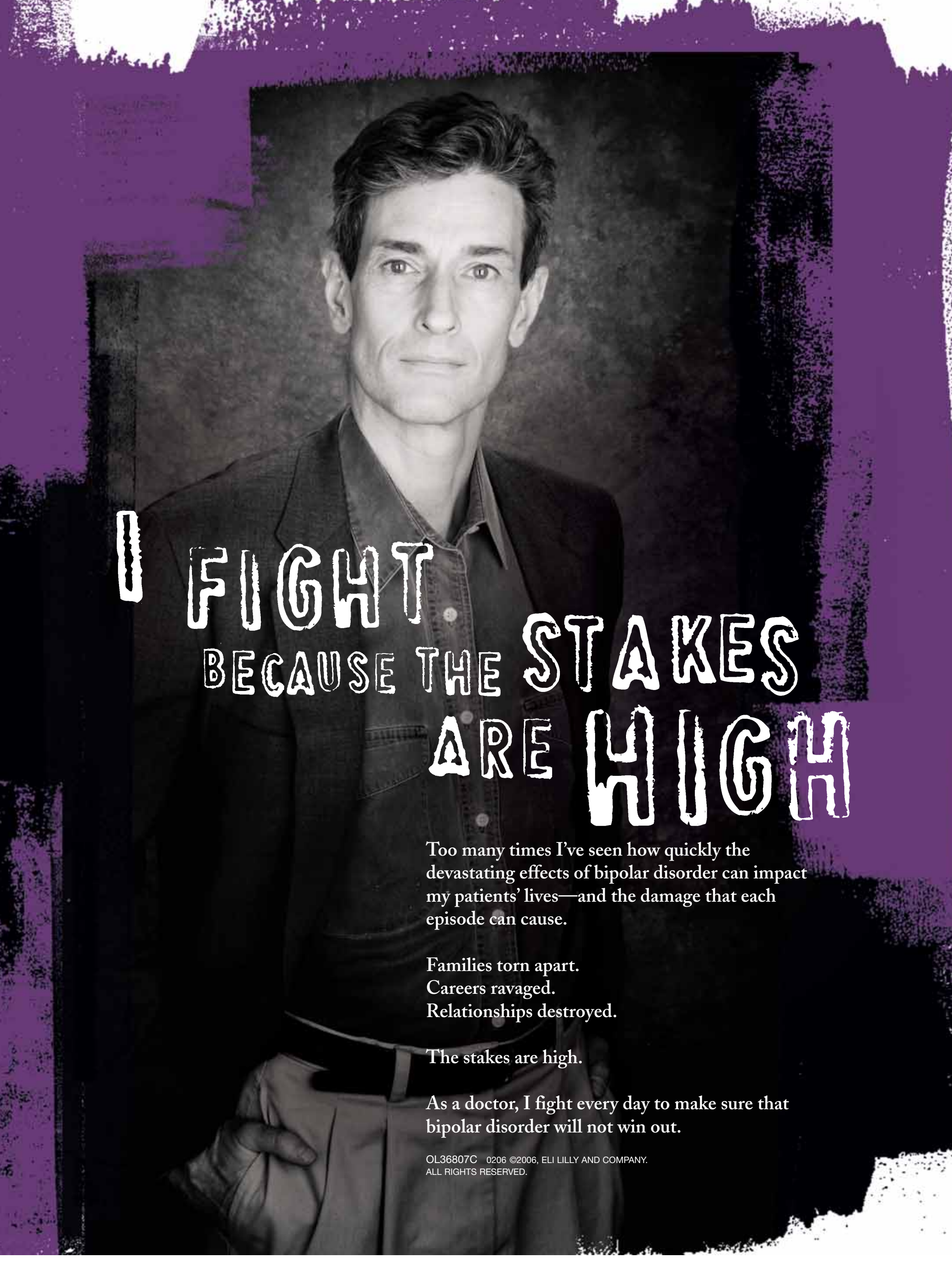
In any event, the answers to why Shakespeare portrayed so few mothers, and unflattering mothers at that, can probably be found in Shakespeare's own life. Yet unfortunately very little is known about it, Jerome Grunes reported, beyond some basic facts. For example, William's father was John Shakespeare and his mother, Mary Arden. William married Anne Hathaway at age 18, with whom he had three children. He worked as an actor, playwright, and designer of festival masks. He died at age 49, on his birthday, five years after his own mother had died.

Shakespeare's mothers (real and imagined) are still shrouded in many mysteries, leaving psychiatrists and analysts with the challenge of ferreting out the answers.

"We can see why Freud was so enamored with Shakespeare!" Jerome Grunes declared. ■

IPS Program Change

The recipient of the 2006 Alexander Gralnick Award for Research in Schizophrenia, Prof. Gerry Hogarty of the Western Psychiatric Institute and Clinic in Pittsburgh, recently passed away. Hogarty was to receive the Gralnick Award and present the Gralnick Lecture at APA's 2006 Institute on Psychiatric Services, which is being held October 5 to 8 in New York City. In his place, Shaun Eack, M.S.W., of the University of Pittsburgh will present Hogarty's work. The session will be held October 7 at 10 a.m. Thomas McGlashan, M.D., chair of the award committee, will offer perspectives on Hogarty's life and work. ■



I FIGHT BECAUSE THE STAKES ARE HIGH

Too many times I've seen how quickly the devastating effects of bipolar disorder can impact my patients' lives—and the damage that each episode can cause.

Families torn apart.
Careers ravaged.
Relationships destroyed.

The stakes are high.

As a doctor, I fight every day to make sure that bipolar disorder will not win out.

Lilly

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

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

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

Any night or every night

Leave the rest to...

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

Important Safety Information

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

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

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

Please see brief summary of complete prescribing information.

SEPRACOR

4/06

6SRZO355

Lunesta™ (eszopiclone)

1, 2 AND 3 MG TABLETS

BRIEF SUMMARY

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

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

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

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

PRECAUTIONS

General

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

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

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

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

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

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

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

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

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions

CNS-Active Drugs

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

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

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

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

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

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

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

Drugs With A Narrow Therapeutic Index

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

Pregnancy

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

Adverse Findings Observed in Placebo-Controlled Trials

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

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

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

*Gender-specific adverse event in females

**Gender-specific adverse event in males

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

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

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

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

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

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

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

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

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

Frequent: chest pain, migraine, peripheral edema.

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

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

DRUG ABUSE AND DEPENDENCE

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

Abuse, Dependence, and Tolerance

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

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

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

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

OVERDOSAGE

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

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

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

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

Rx only.

SEPRACOR 3/05

Freud's Influence Has Waned But Many Ideas Hold Sway

A number of Freud's concepts are still relevant to 21st-century psychiatry. But as scientists learn more about cognition, experience, affect, and attachment, his ideas will probably be viewed in new ways.

BY JOAN AREHART-TREICHEL

The office of Fred Hilkert, M.D., contains an etching of Sigmund Freud, a 19th-century divan, and an antique Greek bell krater (a container used for mixing wine and water). The ashes of both Freud and his wife were comingled in such a krater, the Washington, D.C., psychiatrist explained to *Psychiatric News*. The krater symbolizes what Freud felt was his greatest discovery, the Oedipus complex, derived from the play by Sophocles, "Oedipus Rex."

Although most American psychiatrists probably do not have such tangible reminders of Freud in their offices, few would dispute that Freud's concepts are still packing a powerful punch today, 150 years after his birth, regarding the practice of psychoanalysis, the practice of psychodynamic psychotherapy, and even the practice of psychiatry in general.

> **"Look at the number of people who confess to crimes they never committed! Unconscious guilt, and the need to confess, we have learned directly from Freud."**

Power of Unconscious Still Rules

Even if Freud contended that the Oedipus complex was his greatest discovery, American psychiatrists are more likely in 2006 to rate his unveiling of the unconscious as his most momentous contribution to psychoanalysis, psychodynamic psychotherapy, and psychiatry in general.

"There are certain core concepts that Freud developed and that still hold," Regina Pally, M.D., a clinical professor of psychiatry at the University of California at Los Angeles, said in an interview. "The major one is that there is an unconscious mind that influences our thoughts, emotions, and behavior. . . .And neuroscience, my particular interest, has confirmed that the unconscious is the majority of mental life, and that it runs the show."

"Freud is an icon," Sandra Walker, M.D., a Seattle psychiatrist primarily in private practice, told *Psychiatric News*. "[His] ideas about the mind have had a lasting and indelible effect. . . . So in terms of psychoanalysis and psychodynamic psychotherapy, of psychiatry, and in many other areas of life, his ideas about the unconscious, about the repression of unconscious conflict, are commonplace."

"We are motivated by many unconscious forces that are very important," Harold Blum, M.D., a clinical professor of psychiatry at New York University and executive director of the Sigmund Freud Archives at the Library of Congress, asserted. "For example, look at the number of people who confess to crimes they have never committed. Unconscious guilt, and the need to confess, we have learned directly from Freud."

Transference Also High on List

Not long ago, a patient said to Glen Gabbard, M.D.: "I can't talk to you anymore." Gabbard, chair of psychoanalysis and professor of psychiatry at Baylor College of Medicine, asked why not. "You are exactly like my father!" he replied. "You are going to humiliate me if I tell you what is bothering me."

"This is a prime example of Freud's concept of transference," Gabbard said, "where he saw me as his father, and it kept him from talking openly." And transference, like the unconscious, is high on the list of Freudian ideas that American psychiatrists still consider highly relevant to their practices.

In fact, since transference usually occurs at an unconscious level, Pally pointed out, patients may view not only their psychiatrists, but also their spouses, bosses, coworkers, and even their children as important figures from their childhood without being aware of it. And a big part of therapy, she added, may consist of helping patients realize that they possess such views and that such views might be maladaptive for their current lives.

Transference, psychiatrists tend to agree, can likewise offer important clues as to why patients do not adhere to their treatment regimens.

"You can prescribe medication for a borderline psychotic patient, but that doesn't mean that [the patient is] going to comply," said Blum, "and the reasons for the noncompliance are not strictly organic or related to the medication. They may be related to antagonism toward the doctor or profession or displaced from a host of other issues onto the treatment situation."

Transference can impact areas of medicine other than psychiatry, psychiatrists point out.

A third-year medical student rotating through a psychiatry clerkship, "Bob," had been working with a hospitalized bipolar patient nearing discharge. Then Bob missed a day with the patient because of illness. When he returned, she was unusually irritable and depressed and claimed she was not ready for discharge. She started talking about a history of being rejected by boyfriends, and finally the light went on for Bob: she viewed his absence as one more rejection, and her take on the matter was a perfect example of what psychiatrists call "transference."

Shortly after that, Bob described his

please see ***Freud*** *on page 37*

Evolved Thought

Although a number of Freud's concepts are still embraced by contemporary psychiatrists (see story at left), others appear to have fallen out of favor or to have been revised.

Oedipus complex: Freud purportedly contended that the Oedipus complex—the sexual feelings that a child develops toward the parent of the opposite sex and the rivalry that it feels as a result toward the parent of the same sex—was his greatest discovery. Today psychiatrists tend to disagree with this assessment. Moreover, they are apt to question the universality of the concept.

For example, "Freud believed that boys always were afraid that their fathers were going to castrate them," Regina Pally, M.D., a clinical professor of psychiatry at the University of California at Los Angeles, pointed out, "but we now realize that these things come more from a pathological environment. In the normal course of events, there doesn't have to be such heightened fears. [Also,] Freud believed that incest was a fantasy, and he kind of denied the reality that a lot of girls are molested by their fathers."

Female psychology: Certainly, Freud's theories of female sexuality and his concept of penis envy "have been controversial and often criticized," Lisa Mellman, M.D., a senior associate dean for student affairs at Columbia University College of Physicians and Surgeons, asserted.

"Freud had many good ideas, but some of them were wrong, and a good example is his view of female sexuality," Glen Gabbard, M.D., chair of psychoanalysis and a professor of psychiatry at Baylor College of Medicine, declared. "We no longer view women as having less moral conscience than men."

"His ideas about the psychology of women and women's sexuality, I think, are not considered to have any merit at this point," Norman Clemens, M.D., a clinical professor of psychiatry at Case Western Reserve University, opined. "And there are two reasons why. One is that people have studied a lot more about it, and there is a lot more information available now from subsequent research. The other is that women have become prominent in the field, and there is much more of an attitude that women have their own psychology and it is related to their biology, just as men's is to theirs."

Therapist as a blank screen: "I think Freud's way of describing psychotherapy as objective, neutral, and analogous to a biological experiment has been replaced by much more interpersonal and subjective views of what goes on between the therapist and the patient," Steven Levy, M.D., vice chair of psychiatry at Emory University, commented. "The therapist is an active psychological participant, not an objective observer."

Pally concurred: "We now realize that it is impossible, you can't be a blank screen, and it's not even good to be a blank screen."

Sex and aggression: While Freud highlighted sex and aggression as the primary motivating forces in human life, most experts today believe that motivation is more complicated.

The death instinct: Psychiatrists today do not agree with Freud that there is an instinct that leads toward death, Harold Blum, M.D., a clinical professor of psychiatry at New York University and executive director of the Sigmund Freud Archives at the Library of Congress, testified. "In fact, most of the instincts we look at from a biological viewpoint. . . are really survival instincts, instincts toward reproducing and keeping the species alive."

If Freud were alive today, how would he react to the discard or revision of the above concepts?

"Freud was a tremendously creative and innovative person, and he really changed the field of psychiatry," Clemens stated. "But he is like any great scientist who comes up with a discovery. I think he would be very happy to see that the field has progressed the way that it has rather than just being stuck in things being the way he said they were. In other words, he started something that is evolving and very alive and dynamic. That is a great tribute to anyone who opens a field."

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Assembly to Gain More Board Representation

APA's Board of Trustees takes steps to add two Assembly representatives as voting members of the Board. In addition, APA gets a top-notch report card from an independent auditing firm.

BY KEN HAUSMAN

APA Trustees acted on a broad range of issues at their meeting last month in Leesburg, Va., including increasing the Board's voting membership and endorsing several official APA position statements.

Responding to several proposals from the Assembly reflecting that body's desire to have more influence in the Association's policymaking process, the Board voted to proceed changing the bylaws to grant both the speaker-elect and immediate past speaker of the Assembly a vote on the APA Board of Trustees. The former proposal was passed unanimously, the latter by a 9-6 vote. The Assembly speaker has been a voting member of the Board for many years, while the speaker-elect has been an ex-officio member.

These proposals were forwarded by an ad hoc work group appointed by immediate past President Steven Sharfstein, M.D., to make recommendations on ways in which interactions between the Assembly and Board could be increased. The work group was appointed after the two governing bodies were unable to agree on ways to increase the influence of the Assembly in the Board's decision-making process.

David Hathcox

APA President Pedro Ruiz, M.D., discusses a report from the Membership Committee on proposed strategies to enhance efforts to recruit new members and retain current ones.

Both actions have been forwarded to the Committee on Bylaws to develop language reflecting the Board's decision. The Board will then review the wording.

Trustees also endorsed two position statements. One was a psychotherapy-related position statement emphasizing that with psychotherapy a critical component of the psychiatric care provided to many patients, discriminatory reimbursement policies for this treatment modality must end, since they discourage the use of psychotherapy and foster split therapy.

The second position statement addresses "racism and racial discrimination and their adverse impacts on mental health." Developed by the Committee of Black Psychiatrists and Council on Minority Mental Health and Health Disparities, the statement describes the multiple ways in which victims of racism can suffer deleterious mental health consequences from both overt and less-obvious forms of racial discrimination. It also notes that individual and institutional racism is a major contributor to the health care disparities that racial minorities face.

In other actions the Board voted to

• **Provide resident members with a free version** of the annual meeting online library.

• **Maintain two committees that focus on residency issues**—the Committee of Residents and Fellows and the Assembly Committee of Area Member-in-Training Representatives—as a way to maximize involvement of residents in APA, even though the committees' charges overlap.

• **Approve the creation of two components:** Task Force on Complementary and Alternative Medicine Treatments for Mental Illness and Corresponding Committee on Mental Health on College and University Campuses.

• **Extend a program that had been a pilot project** in which APA agreed to allow the California Psychiatric Association and North Carolina Psychiatric Association to add to APA dues notices a check-off box for voluntary contributions to their political action committees. It was determined that such contributions did not adversely impact voluntary contributions to APA's political action committee, APA*PAC*.

• **Approve a $5,000 contribution to preparation of an amicus curiae brief** that the Maryland Psychiatric Society intends to file in the case *Department of Mental Hygiene v. Kelly*, which involves standards for determining dangerousness before a psychiatric patient can be involuntarily medicated. The district branch is challenging a judge's ruling that a patient must show evidence of dangerousness while in a hospital, and not in the community, before he or she can be involuntarily medicated.

• Ask the Council on Minority Mental Health and Health Disparities and/or the Committee on Gay, Lesbian, and Bisexual Issues to develop a report for the Board "delineating the goals" that a proposed APA component should consider in recommending **whether APA should prepare a resource document or position statement on gender identity disorder** and its treatment.

• **Approve strategies and directions for enhancing APA's member recruitment and retention efforts** proposed by the Membership Committee. The plan's focus is on "recruiting a diverse mix of members" and increasing the number of residents, early career psychiatrists, international members, and former members, in particular. It also intends to increase the involvement of district branches, training directors, department chairs, and other members in this effort.

• **Support a moratorium on the decrease in each state** of the number of intermediate and long-term psychiatric hospital level-of-care bed (public and private) for children and adolescents with the state.

• **Support the National Association of Counties' resolution** urging the U.S. attorney general to appoint a national commission to study and make recommendation on the jailing of the non-violent mentally ill in county jails

A summary of actions the Board took at its July meeting can be accessed in the Members Corner area of APA's Web site at <www.psych.org> under "Board of Trustees." ■

David Hathcox

Board of Trustees members vote to continue a pilot project that has allowed district branches and state associations to add a check-off box to the APA dues bills that gives their members the chance to make a voluntary contribution to those organizations' political action committees.

NAMI Wants Stronger Partnership

Psychiatrist **Susan Vogel-Scibilia, M.D.,** president of the National Alliance on Mental Illness (NAMI), told APA's Board of Trustees last month that while the agendas of the two organizations may not always be identical, NAMI and APA share a commitment to several critical issues. Among these are furthering psychiatric research, increasing access to care, addressing the "encroachment of allied professions" into psychiatric care, and enhancing outreach to multicultural and other specific populations.

She also highlighted NAMI's dramatic growth from its formation in 1979 by five Wisconsin parents whose children had severe mental illness to the national organization that today has more than 200,000 members and considerable political clout at the local, state, and national levels.

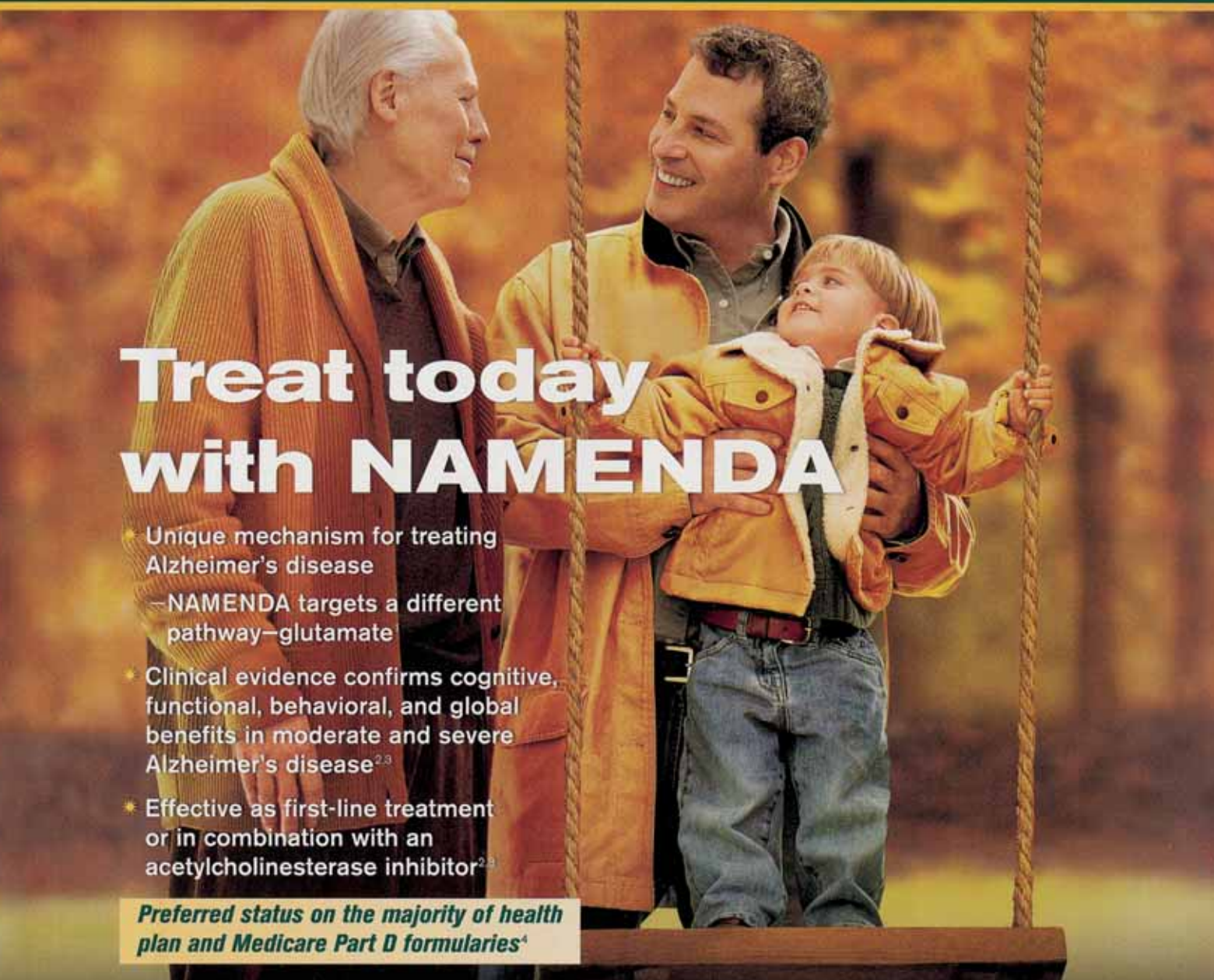
David Hathcox

She said that one of NAMI's goals is to strengthen its collaborations with APA and other organizations representing those who provide mental health care.

'Financial Position. . . Strong'

The Board of Trustees heard a report from APA's independent auditing firm, which stated that the Association's 2005 financial statements, including those of its affiliate organizations, had no "weaknesses" and are among the most solid of the nonprofit associations whose books it audits. The report stated, "The financial position of APA. . .remains strong as of the end of 2005. Assets continue to grow, primarily cash and investments. Liabilities remain steady."

At the first sign of moderate Alzheimer's disease



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References: 1. NAMENDA® (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, Mo. **2.** Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ, for the Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med.* 2003;348:1333-1341. **3.** Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, for the Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA.* 2004;291:317-324. **4.** Data on file. Forest Laboratories, Inc.

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INDICATIONS AND USAGE
Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS
Namenda (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS
Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions
Seizures: Namenda has not been systematically evaluated in patients with a seizure disorder. In clinical trials of Namenda, seizures occurred in 0.2% of patients treated with Namenda and 0.5% of patients treated with placebo.

Genitourinary Conditions
Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations
Hepatic Impairment
Namenda undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

Renal Impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment.

Drug-Drug Interactions
N-methyl-D-aspartate (NMDA) antagonists: The combined use of Namenda with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of Namenda *on substrates of microsomal enzymes: In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on Namenda: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Coadministration of Namenda with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of Namenda and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Carcinogenesis, Mutagenesis and Impairment of Fertility
There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy
Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² basis.

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

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

Pediatric Use
There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

ADVERSE REACTIONS
The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia.

Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of Namenda up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the Namenda group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of Namenda-treated patients and at a rate greater than placebo.

Adverse Events Reported in Controlled Trials: The reported adverse events in Namenda (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Namenda than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo-treated Patients.

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in Namenda-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abnormal gait, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with Namenda. A comparison of supine and standing vital sign measures for Namenda and placebo in elderly normal subjects indicated that Namenda treatment is not associated with orthostatic changes.

Laboratory Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

ECG Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with Namenda treatment.

Other Adverse Events Observed During Clinical Trials
Namenda has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: *Frequent:* syncope. *Infrequent:* hypothermia, allergic reaction.

Cardiovascular System: *Frequent:* cardiac failure. *Infrequent:* angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent:* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

Gastrointestinal System: *Infrequent:* gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: *Frequent:* anemia. *Infrequent:* leukopenia.

Metabolic and Nutritional Disorders: *Frequent:* increased alkaline phosphatase, decreased weight. *Infrequent:* dehydration, hyponatremia, aggravated diabetes mellitus.

Psychiatric Disorders: *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, neurosis, suicide attempt.

Respiratory System: *Frequent:* pneumonia. *Infrequent:* apnea, asthma, hemoptysis.

Skin and Appendages: *Frequent:* rash. *Infrequent:* skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

Special Senses: *Frequent:* cataract, conjunctivitis. *Infrequent:* macula 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: atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, claudication, colitis, dyskinesia, dysphagia, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatic failure, hyperlipidemia, hypoglycemia, ileus, impotence, malaise, neuroleptic malignant syndrome, acute pancreatitis, aspiration pneumonia, acute renal failure, prolonged QT interval, restlessness, Stevens-Johnson syndrome, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, and thrombocytopenia.

ANIMAL TOXICOLOGY
Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m² basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE
Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an overdosage with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

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Rev. 07/05

Are Payment Cuts Driving Physicians From Medicare?

While the GAO finds that the number of physicians who are Medicare providers is rising, some question whether the trend is true for psychiatrists.

BY RICH DALY

As APA and other physician organizations build momentum on Capitol Hill to halt the latest scheduled cut to Medicare payments to physicians, new research questions whether reduced or stagnating reimbursements have had much impact on physicians' willingness to participate in the program.

The Government Accountability Office (GAO) reported in late July that its study of physician participation in the Medicare program following the reduced and stagnant reimbursements allowed under the program in recent years indicated that few physicians stopped participating. Moreover, said the GAO, there was little evidence to suggest that beneficiaries had difficulty accessing care.

The study was mandated by the 2003 Medicare reform law after the Medicare physician fee formula underwent a 5.4 percent reduction to help moderate rapid spending increases. APA and other physician advocacy organizations have long been concerned that inadequate reimbursements cause physicians to drop out of the Medicare program, thereby hurting seniors' access to care.

Physicians Not Deterred

The GAO study, which used records and surveys compiled by the Centers for Medicare and Medicaid Services (CMS), found that the number of physicians billing Medicare for services and the proportion of services for which Medicare's fees were accepted as payment in full increased during the study period, from April 2000 to April 2005. Less than 4 percent of physicians said that they did not accept any new Medicare patients in that time.

In addition, the use of physician services generally increased nationwide in the study period. According to the AMA, however, this finding should not be interpreted as an improvement in access. Increases in the use of physician services could result from beneficiaries' growing sicker, the substitution of physician services for care in the hospital or other settings, or beneficiaries' taking advantage of new Medicare-covered services.

The percentage of beneficiaries reported having major difficulty in accessing care remained relatively constant over the study period at about 7 percent. Beneficiaries more likely to have difficulties accessing care were those who rated their health as poor, were under 65 and disabled, were not white, and had no supplemental health insurance or had supplemental insurance from Medicaid.

The study did not gauge the impact of future cuts, which could be significant. A recent AMA survey reported that 45 percent of physicians said they would decrease the number of new Medicare patients they accepted or stop taking them altogether if a planned 5 percent physician reimbursement cut goes into effect on January 1, 2007.

"Medicare cannot continue to provide seniors with high-quality health care while slashing reimbursements to the physicians who care for them," said Cecil Wilson, M.D., chair of the AMA Board of Trustees, in a statement.

Moreover, the study did not look at access to care by medical specialty. According to Ellen Jaffe, Medicare specialist in APA's Office of Healthcare Systems and Financing, psychiatrists seem to be opting out of Medicare participation in greater numbers than are physicians in general. Thus, while beneficiaries in general may not be experiencing an increase in access difficulties, she noted, psychiatric patients who rely on Medicare may already be confronting such problems.

The GAO findings appear to run counter to findings reported in March by MedPAC, the commission that advises Congress on Medicare. For example, MedPAC found that 25 percent of Medicare patients seeking a new primary care physician have trouble getting an appointment.

Congress Urged to Act Quickly

The GAO report was released as Congress was considering a reduction of 4 percent to 5 percent to Medicare's physician reimbursement fees. Lawmakers last year blocked a planned 4.4 percent reduction and now face a similar decision.

The annual consideration of cuts stems from the 1997 Balanced Budget Act, which created the sustainable growth rate system that sets a target for Medicare payments to doctors that factors in inflation (see story below). When spending increases exceed economic growth, payments to physicians are to be cut. Unchanged, the system will require approximately 5 percent annual cuts in physician payments through 2016 to meet program spending targets, according to federal estimates.

Those cuts are unlikely to occur, however, because lawmakers fear that payment reductions could add to the record increases in Medicare premiums and drive physicians from the program.

In late July, Rep. Michael Burgess (R-Texas), an obstetrician, introduced the Medicare Physician Payment Reform and Quality Improvement Act of 2006 that would raise Medicare physician fees about 2.8 percent next year. His proposal would rely more on the inflation measure known as the Medicare economic index.

"When I practiced medicine, I remember the financial strain when providing Medicare services cost double what I was being reimbursed," he said last month at a hearing of the Energy and Commerce Subcommittee on Health.

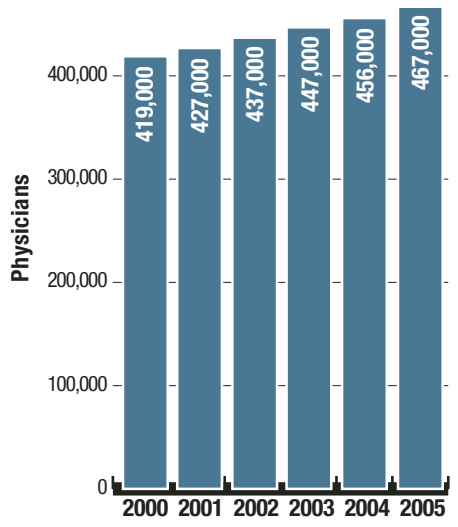
The AMA urged Congress to end consideration of the issue for the year by acting on the issue before Congress recesses in October. Observers said members of both political parties are open to a revision of the payment system to avoid the planned cuts, but there is less unity about the source of funds for a change that would cost billions of dollars.

The GAO research was based in part on reviews of Medicare claims filed from 2000 through 2004 and CMS surveys that asked patients whether finding a personal provider was "no problem," "a small problem," or "a big problem."

The GAO report is posted at <www.gao.gov/new.items/d061008t.pdf>. ■

Physicians Haven't Jumped Ship

Despite physician fee reimbursements that have been criticized for their inadequacy, the number of physicians who billed Medicare for services provided to beneficiaries rose steadily from 2000 to 2005.



Source: United States Government Accountability Office, 2006

Federal Panel Wants Reform Of Medicare Pay Formula

As a mechanism for controlling the volume of services under Medicare, the sustainable growth rate is fatally flawed because it is a national target and carries no incentive for physicians to control volume.

BY MARK MORAN

The Medicare Payment Advisory Commission (MedPAC) again has urged Congress to fix the Medicare payment formula.

In testimony before the Subcommittee on Health, Energy, and Commerce, MedPAC Executive Director Mark E. Miller, Ph.D., told representatives to scrap the sustainable growth rate (SGR) component of the Medicare payment formula.

The SGR is a projected rate of growth in Medicare expenditures calculated by taking into account medical inflation, projected growth in the domestic economy, projected growth in the number of beneficiaries in fee-for-service Medicare, and changes in law or regulation, among other factors. If actual expenditures exceed the SGR, as they have in the past several years, then the Centers for Medicare and Medicaid Services (CMS) is required to decrease doctor payments to offset the increase in volume for the next year.

APA, the American Medical Association, and MedPAC have repeatedly insisted that the SGR be scrapped and the payment formula be comprehensively revised.

"Medicare spending for physician services has been growing rapidly despite the restraint on fee increases since 2002," Miller said. "This rapid growth has created an ever-larger gap between target and actual spending. CMS estimates that by the end of 2006, actual spending will exceed allowed spending by more than $47 billion. To work off this excess. . . the SGR will call for annual updates of about negative 5 percent for nine consecutive years."

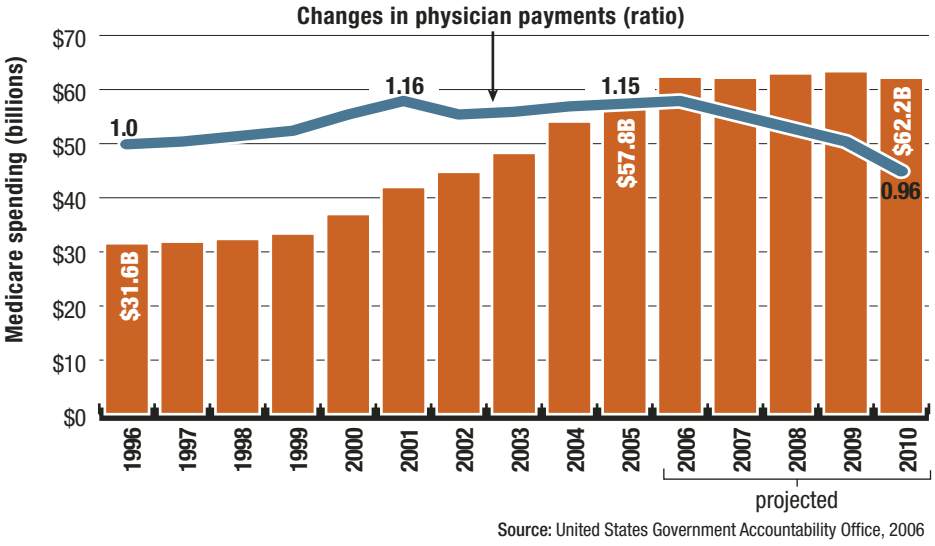
Miller said the SGR is a national target but carries no incentive for individual physicians to control volume.

"The underlying assumption of an expenditure target approach, such as the SGR, is that [it] provides physicians a collective incentive to control the volume of services," Miller told members of Congress. "However, physicians do not respond to nationwide incentives. An efficient physician who reduces volume does not realize a proportional increase in payments. In fact, such a physician stands to lose twice, receiving lower income from both lower volume and the nationwide cut in fees. Not surprisingly, there is evidence that in such circumstances physicians have increased volume in response to fee cuts.

"Instead of relying on a formula, MedPAC recommends that updates should be considered each year to ensure that payments for physician services are adequate to maintain Medicare beneficiaries' access to care." ■

Physicians to Feel Pinch

Medicare spending is exceeding targeted limits, and as a consequence payments to doctors are expected to decline. The first year in which the sustainable growth rate system was used was 1997.



Source: United States Government Accountability Office, 2006

Health Care Advocates Worry About Proposed '07 Budget

In the early stages of setting the federal health budget for 2007, Congress is willing to spend more than the president in some areas, but critics are lamenting the prospect of lower overall spending on health care.

BY RICH DALY

The Senate Appropriations Committee approved a draft Fiscal 2007 Labor-HHS-Education spending bill in late July that raised the possibility that Congress may approve the primary mental health spending measure before the next fiscal year begins.

The bill (S 3708) would provide $142.8 billion in health-related discretionary spending, which is $5 billion more than President Bush requested and $1.3 billion more than the Fiscal 2006 amount. The House version (HR 5647) would provide $141.9 billion for discretionary programs. The rest of the funding in both health budget bills is allocated for Medicare, Medicaid, and other entitlement programs.

"While [the Senate's funding level] amounts to a modest dollar increase in health spending, it is still higher than the House's version," said Nicholas Meyers, director of APA's Department of Government Relations.

The Senate bill would provide $28.5 billion for the National Institutes of Health (NIH), an increase of $220 million over Fiscal 2006 and $200 million over the president's budget request.

The House version, which also provides $28.5 billion for NIH, has been approved by that chamber's Appropriations Committee.

Congressional negotiators will reconcile differences in the two versions after both chambers pass their versions of the bill.

Rep. David Obey (D-Wis.) criticized the proposed budget for NIH as insufficient, given a "substantial" inflation in research costs. Sen. Arlen Specter (R-Pa.) said that even in the more-generous Senate version, NIH funding is $3.78 billion below the inflation-adjusted Fiscal 2006 level.

For the three mental health institutes within NIH, the Senate measure would provide $1.4 billion to the National Institute of Mental Health (NIMH), $1 billion to the National Institute on Drug Abuse, and $436 million to the National Institute on Alcohol Abuse and Alcoholism. These amounts are similar to the current year's funding levels for the three institutes.

The Senate bill would provide $3.34 billion for the Substance Abuse and Mental Health Services Administration (SAMHSA), an increase of $77 million over the president's budget request. SAMHSA is responsible for supporting mental health programs and alcohol and other drug abuse prevention and treatment services.

The Senate bill would restore the $630 million for SAMHSA's Community Services Block Grant, which was proposed for elimination in the president's budget.

Proposed Budgets for VA

The Senate Appropriations Subcommittee on Military Construction, Veterans Affairs, and Related Agencies approved a $94.3 billion Fiscal 2007 Military Construction-VA appropriations bill (HR 5385). Of that amount, $77.9 billion is earmarked for the Department of Veterans Affairs, which includes health care spending for veterans. The bill, however, does not include a proposal from the president to increase TRICARE fees for some veterans. President Bush had requested an increase in premiums for some veterans and their families in TRICARE, the program that funds health care for this population, as well as higher enrollment fees, deductibles, and prescription drug copayments for some military retirees. The House bill, which would allocate $36.5 billion for VA discretionary programs, also does not include the proposal.

Both the House and Senate bills would provide $32.7 billion for the Veterans Health Administration and $3.6 billion for VA medical facilities.

The House's allocation for the overall VA spending bill is $136.1 billion. It is dramatically higher than the Senate's $94.3 billion total because the House bill would fund some defense accounts that the Senate bill would not, including the Defense Health Program. Following Senate passage, negotiators will have to hammer out differences between the House and Senate versions of the bill.

Family Treatment Addressed

In addition to its work on a health care funding bill, the Senate passed legislation concerning children who are placed in the child welfare system because they are affected by methamphetamine use. The Improving Outcomes for Children Affected by Methamphetamine Act of 2006 (S 3525) amends the Promoting Safe and Stable Families program to reserve $40 million for grants to create regional partnerships to improve outcomes for children affected by methamphetamine abuse or addiction. This bill was sponsored by Sen. Charles Grassley (R-Iowa), and the president is expected to sign the measure.

"By emphasizing comprehensive family treatment, we are promoting a promising strategy for families to recover from meth addiction together," Grassley said at a hearing on the bill.

Information about the Labor-HHS bill is posted at <http://thomas.loc.gov/cgi-bin/bdquery/z?d109:h.r.05647:>; the Senate version of the VA spending bills is posted at <http://thomas.loc.gov/cgi-bin/bdquery/z?d109:h.r.05385:>. ■

KNOW THE FACTS

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

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

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

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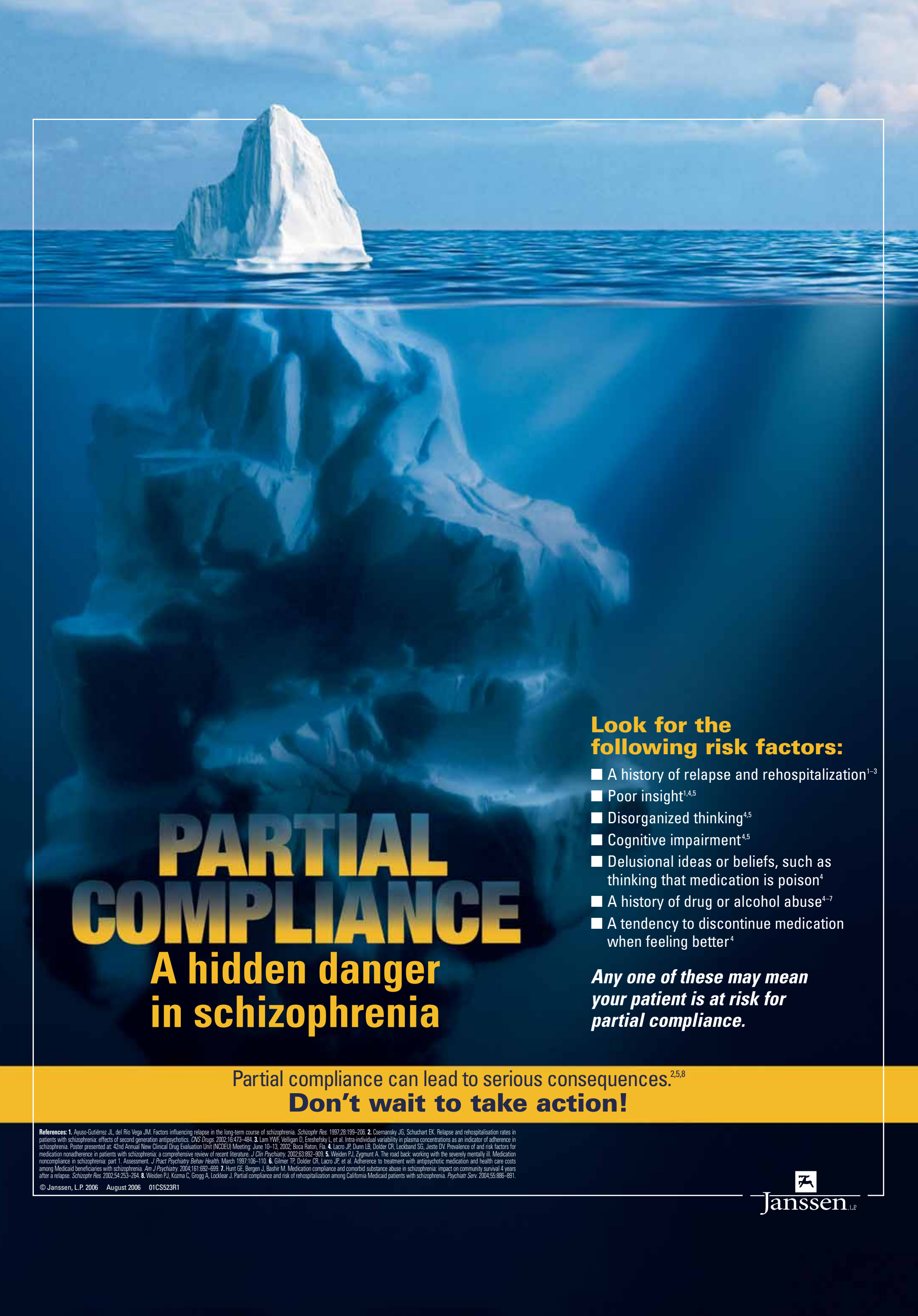

PARTIAL COMPLIANCE

A hidden danger in schizophrenia

Look for the following risk factors:

- A history of relapse and rehospitalization[1–3]
- Poor insight[1,4,5]
- Disorganized thinking[4,5]
- Cognitive impairment[4,5]
- Delusional ideas or beliefs, such as thinking that medication is poison[4]
- A history of drug or alcohol abuse[4–7]
- A tendency to discontinue medication when feeling better[4]

Any one of these may mean your patient is at risk for partial compliance.

Partial compliance can lead to serious consequences.[2,5,8]

Don't wait to take action!

References: 1. Ayuso-Gutiérrez JL, del Río Vega JM. Factors influencing relapse in the long-term course of schizophrenia. *Schizophr Res.* 1997;28:199–206. **2.** Csernansky JG, Schuchart EK. Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. *CNS Drugs.* 2002;16:473–484. **3.** Lam YWF, Velligan D, Ereshefsky L, et al. Intra-individual variability in plasma concentrations as an indicator of adherence in schizophrenia. Poster presented at: 42nd Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting; June 10–13, 2002; Boca Raton, Fla. **4.** Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry.* 2002;63:892–909. **5.** Weiden PJ, Zygmunt A. The road back: working with the severely mentally ill. Medication noncompliance in schizophrenia: part 1. Assessment. *J Pract Psychiatry Behav Health.* March 1997:106–110. **6.** Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatry.* 2004;161:692–699. **7.** Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophr Res.* 2002;54:253–264. **8.** Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv.* 2004;55:886–891.

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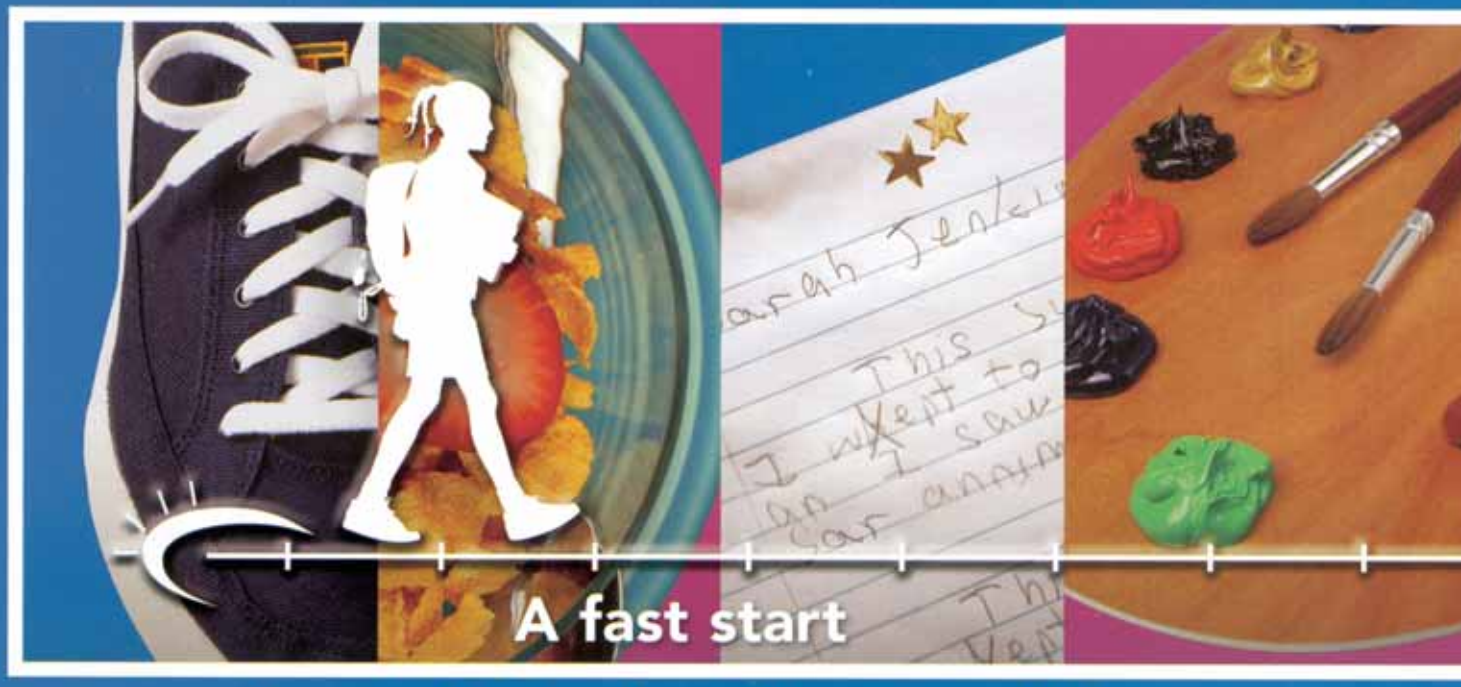

for control when they need it.

Improve ADHD symptoms with Focalin XR and give patients an early start to their day

- Proven QD ADHD treatment that starts working fast and is effective up to and including 12 hours
- Approved for children, adolescents, and adults
- Low discontinuation rates, with no discontinuations due to adverse events in a pediatric study (versus 2.1% for placebo)[1]
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12 hr

Focalin XR (dexmethylphenidate HCl) extended-release capsules is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults, adolescents, and children 6 years and older. Focalin XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (eg, psychological, educational, social) for patients with this syndrome.

Important safety information: The most common adverse events seen with Focalin XR were dyspepsia, decreased appetite, headache, and anxiety in pediatric studies; and dry mouth, dyspepsia, feeling jittery, dizziness, headache, and anxiety in adult studies.

Focalin XR is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms; in patients known to be hypersensitive to methylphenidate or other components of the product; in patients with glaucoma; in patients with motor tics or with a family history or diagnosis of Tourette's syndrome; and during or following treatment with monoamine oxidase inhibitors.

Stimulants should generally not be used in children, adolescents, or adults with known serious structural cardiac abnormalities, cardiomyopathy, serious heart-rhythm abnormalities, or other serious cardiac problems. Use with caution in treating patients with underlying medical conditions that might be compromised by increases in blood pressure or heart rate, such as those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia. Before initiating treatment, patients should have careful history and physical exam to assess for presence of cardiac disease.

Use with caution in psychosis or bipolar disorder. Discontinuation of treatment may be appropriate in the presence of treatment-emergent psychotic or manic symptoms. While aggressive behavior is often observed in children or adolescents with ADHD, patients beginning treatment should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Suppression of growth has been reported with long-term use of stimulants. Stimulants should be used with caution in patients with a prior history of seizures or EEG abnormalities. Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (See **WARNINGS**.)

For more information, visit www.FocalinXR.com.

Please see brief summary of prescribing information, including ***Boxed Warning****, on adjacent page.*

Reference: 1. Greenhill LL, Muniz R, Pestreich L, et al. Effective control of pediatric ADHD symptoms using once-daily dexmethylphenidate. Poster presented at: 51st Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 19-24, 2004; Washington, DC.

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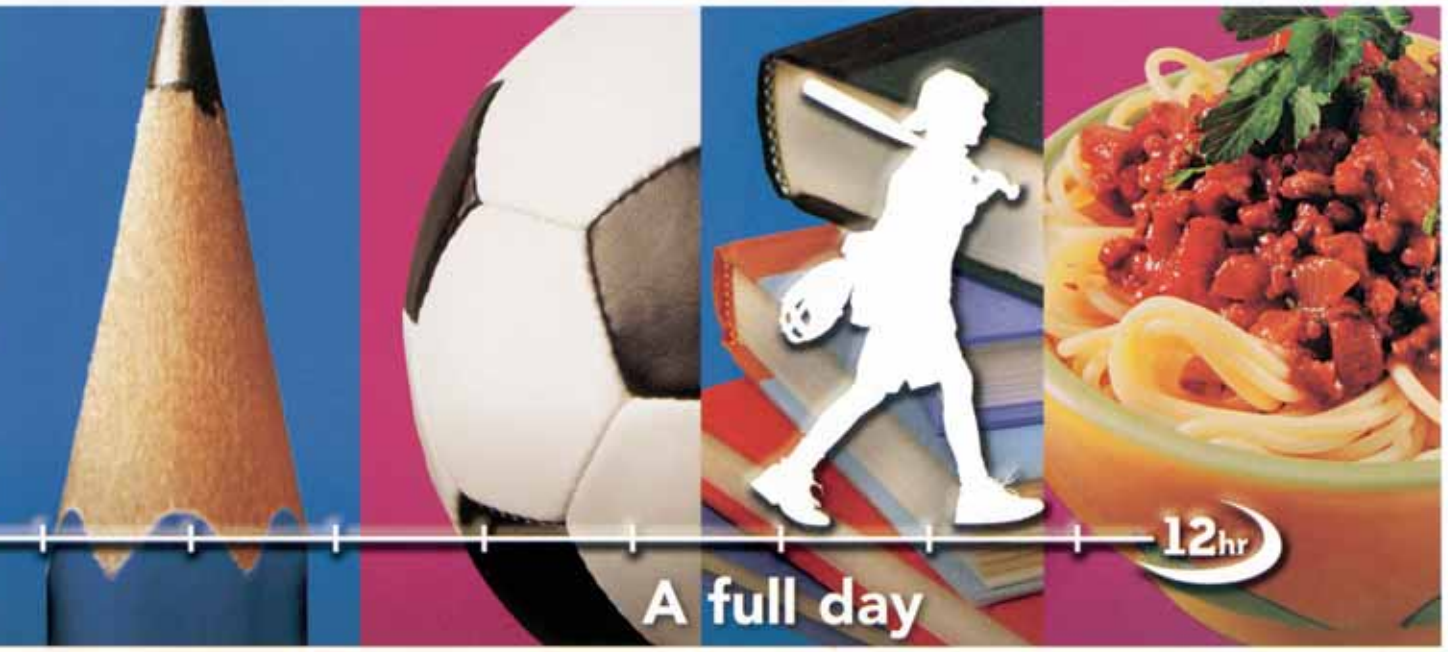

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Deliver 12-hour ADHD symptom improvement with Focalin XR and help patients get the most out of their day

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

Please see the following brief summary of prescribing information, including ***Contraindications*** *and* ***Boxed Warning****.*

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Focalin® XR

(dexmethylphenidate hydrochloride)
extended-release capsules
Rx only

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

INDICATIONS AND USAGE
Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.

The effectiveness of Focalin XR in the treatment of ADHD in patients aged 6 years and older was established in two placebo-controlled studies in patients meeting DSM-IV criteria for ADHD *(see CLINICAL STUDIES in the full prescribing information).*

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined Types requires both inattentive and hyperactive-impulsive criteria to be met.

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

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

Long-Term Use
The effectiveness of Focalin XR for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Focalin XR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient *(see DOSAGE AND ADMINISTRATION in the full prescribing information).*

CONTRAINDICATIONS
Agitation
Focalin® XR (dexmethylphenidate hydrochloride) extended-release capsules is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate
Focalin XR is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of the product.

Glaucoma
Focalin XR is contraindicated in patients with glaucoma.

Tics
Focalin XR is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. *(See ADVERSE REACTIONS.)*

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

WARNINGS
Serious Cardiovascular Events
Sudden Death and Pre-Existing Structural Cardiac Abnormalities or Other Serious Heart Problems
Children and Adolescents: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

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

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

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications
Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess

Please see adjacent page for continued brief summary of prescribing information.

Psychiatrists Don't Let Poverty Be Bar to Depression Care

What can $25 buy? A dinner in a modestly priced restaurant—or keeping a disadvantaged Chilean woman free from depression for a year.

BY JOAN AREHART-TREICHEL

Nine years ago, Greg Simon, M.D., took a sabbatical from his work as an investigator at the Center for Health Studies at the Group Health Cooperative in Seattle. He went to live in Chile. There, he came to know Chilean psychiatrist and researcher Ricardo Araya, M.D., Ph.D.

What Simon and Araya did not anticipate at the time was that they, along with other Chilean colleagues, were going to alter dramatically the delivery of depression treatment in Chile.

It all started with Simon and Araya discussing the plight of depressed, low-income women in Chile. They wondered whether a depression-treatment program introduced into government-funded primary-care clinics might help these women since such clinics are the major source of health care for the poor in Chile. And because these clinics are underfunded and underresourced, such a program, they envisioned, would be a simple add-on to operation as usual.

Several nurses or social workers at each clinic would be trained to provide group psychotherapy and teach problem-solving techniques to depressed women visiting the clinic, as well as monitor the women's treatment progress and act as the women's care managers. If a patient were severely or persistently depressed, her care manager would consult with a clinic doctor about treatment. If the doctor decided to prescribe an antidepressant for her, it would be generic, not name brand, which is considerably cheaper in Chile. And if the doctor decided that she needed a psychiatric assessment, it would be arranged.

Simon and Araya then applied for a grant from the U.S. National Institute of Mental Health (NIMH) to study whether their conceptualized program might be clinically effective. The grant came through after Simon returned to Seattle, so it was Ricardo and his colleagues in Chile who conducted the study, with some long-distance consultation from Simon.

A total of 240 women diagnosed with major depression agreed to participate in the study. They were randomized to either the depression-treatment program or usual care in a primary-care clinic, which might include antidepressant medication or a referral for a psychiatric assessment.

Intervention Subjects Did Better

Subjects in the intervention group showed large and significantly better symptom and functional outcomes at three and six months relative to those in usual care, the investigators reported in the March 22, 2003, *Lancet*.

Although the researchers are not sure why subjects in the intervention group did better than those in the control group, they believe that it was due, at least in part, to the use of antidepressants. Antidepressants, they learned, had been prescribed more often, and for a longer duration, for the intervention group than for the control group. However, when the researchers adjusted their data for antidepressant use, subjects in the intervention group still did significantly better. The investigators suspected that group psychotherapy and systematic follow-up also contributed to the intervention group's superior outcome.

> **"The extra cost per person per year to keep them depression-free was $25."**

After that, Simon, Araya, and their group set out to conduct a study of how the costs of their program compared with the costs of the "usual" depression care offered in the government-funded, primary-care clinics. This inquiry was also financed by NIMH.

Their program turned out to be more expensive, but only marginally so, they reported in the August *American Journal of Psychiatry*. Or as Simon explained during an interview, "The extra cost per person per year to keep them depression free was 10,000 Chilean pesos—that is, on the order of $25." This compares very favorably with the costs of innovative depression-treatment programs in the United States, which usually cost a few hundred dollars extra per person per year, Simon said.

In fact, Simon explained, "You are starting in the United States with a place where people are getting moderately good care, and you are trying to change moderately good to good, but in the developing world, you are usually starting from a place where people aren't getting any care at all, so there is a lot more room for improvement. And since there is a lot more room for improvement, with a relatively modest investment, you get more out of it."

Selling the Program

Then came the biggest challenge—getting the Chilean government to implement the program in its public health care system.

"There were both scientific and political issues," Simon explained. "You have to have the evidence that it is effective,

please see ***Poverty*** *on page 37*

Patients' Spirituality Useful to Healing Process

BY VISHAL MADAAN, M.D.

Compassion, empathy, and the ability to reflect deeply and thoughtfully are the essentials of our profession, yet for many patients one often wonders how to approach the spiritual dimension, that is, the crucial link with a higher power. A recent patient of mine stimulated this discussion within myself, as I struggled to help the teenager cope while he went through an arduous wait for a cardiac transplant. We drew upon our inner beliefs, trying to explore together the meaning of life and the implications of impending despair for him.

When exploring the spiritual dimension with a patient, it is essential to understand that every individual has a value system, and these spiritual factors can become effective partners of science, bringing critical insight to assessment and treatment of various psychiatric disorders.

The key questions that need to be addressed as a psychiatrist considering the role of spirituality in a patient's life include how much does a psychiatrist support the patient's spiritual and religious practices, and what role does one's own spiritual belief play in therapy? The answers are not clear, but as psychiatrists we must not assert the primacy of our own world view, but rather should help the patient find a way to live in and with the world.

Spirituality may help some individuals by raising energy levels, inducing relaxation, and enhancing connectivity of an individual toward self, a higher power, and healing. A correlation between spirituality and better health has been suggested in prevention, coping, and recovery in a wide variety of chronic physical conditions, including hypertension, cerebrovascular and cardiac disease, increased survival time in AIDS patients, and improved coping with cancer. It is, therefore, imperative that psychiatrists and mental health professionals begin to understand the value that compassion, hope, faith, and spirituality can play in the process of healing for their own patients.

While spirituality may not be missing in the personal lives of the patients, their families, their psychiatrists, or the societal belief system, it is largely unaddressed in the modern mental health delivery system. Training in psychiatry provides limited guidance as to how to deal with spiritual matters, and often, as the trainee feels unskilled, he or she tries to evade or even dismiss these issues. Yet it is likely that many individuals with mental illness turn to spiritual beliefs to help them cope with their illness and move toward recovery.

During residency and as an early career psychiatrist, one should learn to be comfortable with taking a spiritual history. This history should address the patient's spiritual attitudes and value system, spiritual development, and sense of meaning and purpose spirituality may play in the patient's life, as well as acknowledge the role of spirituality in clinical decision making. At the same time, residents and early career psychiatrists should be aware of their own countertransference issues in response to such spiritual disclosures while maintaining sensitivity to, and tolerance of, the patient's values. This approach, along with the involvement of chaplains and pastoral care as appropriate, could constitute an effective spiritual prescription.

While the patient I mentioned earlier was fortunate enough to undergo a successful cardiac transplant, he said that the experiences he had as a sufferer and then as a beneficiary completely changed his view of life and strengthened his belief in humility, hope, faith, and compassion. As the treating team, we were left watching spirituality in action and pondering what Einstein had once so aptly said: "The most beautiful experience we can have is the mysterious—the fundamental emotion which stands at the cradle of true art and true science." ■

Vishal Madaan, M.D., is a child and adolescent psychiatry fellow at the Creighton University/University of Nebraska Medical Center in Omaha.

We Need to Pay More Heed to Eating Disorders

BY DENISE SENYK, M.D.

I have noticed that over the past five years in my practice, I am seeing increasing numbers of patients who suffer from eating disorders, often comorbid with other serious psychiatric illness.

For most psychiatrists, unless they have chosen a specialty elective in this field, residency training addressing anorexia nervosa, bulimia nervosa, binge-eating disorder, or the nebulous eating disorder NOS is relatively spare. Though there are opportunities for postresidency training in the field of eating disorders, since formal ABPN certification does not exist as it does for geriatric or forensic specialization, for example, there are few fellowships available.

This is not surprising given the small number of *DSM-IV-TR* diagnoses available to psychiatrists in this category.

The new APA Practice Guideline for the Treatment of Patients With Eating Disorders, Third Edition, was released in July. It highlights the potential leadership role for psychiatrists "within a program or team that includes other physicians, psychologists, registered dietitians, and social workers."

If the standing-room only crowd at Dr. Joel Yager's "*Focus* Live" session on eating disorders at this year's APA annual meeting in Toronto is any indication, I would deduce that many of my colleagues are already being called upon or are ready to offer leadership and expertise in this field. Yager chaired the work group that developed the eating disorders practice guideline.

Like many of us outside of academia, I practice in a variety of settings (outpatient, inpatient, residential). In the residential treatment setting for serious and persistent mental illness, I have discovered that close to 25 percent of my patients have a comorbid eating disorder, often with a complex presentation. For example, a woman with schizoaffective disorder, anorexia nervosa, and borderline personality disorder stopped purging, but proceeded to cut her abdomen in an attempt to "cut the ugly fat out" of her body.

In an article in May/June issue of *Psychosomatic Medicine*, Dr. Barton Blinder, founder and chair of the APA Caucus of Psychiatrists Treating Patients With Eating Disorders, reported that 97 percent of patients at an inpatient eating-disorders program had a comorbid Axis I diagnosis. In this sample there were more diagnoses of psychosis in patients with anorexia than those with bulimia.

Beyond the traditional eating-disorder diagnoses, we now have the epidemic of obesity with which to contend. The advent of second-generation antipsychotics has added not only an effective addition to our pharmacologic tool chest for both psychotic and bipolar spectrum disorders, but also an additional responsibility to monitor our patients for metabolic syndrome. This increased monitoring of our patients' weights, BMI, lipids, and glucose tolerance is helping us to identify and manage weight-related pathology more effectively. In fact, many, including Dr. Renu Kotwal, believe that obesity should be considered a psychiatric disorder. He found that 87.2 percent of bipolar patients treated at a weight-management program had an eating disorder, compared with 71.3 percent of patients without bipolar disorder. The relationship between obesity, binge-eating disorder, and severe and persistent mental illness is fertile ground for new research.

There are several excellent professional organizations that focus on eating disorders; however, they are primarily for either researchers or are interdisciplinary in nature. As the leaders of eating-disorder treatment teams, it is imperative that, as psychiatrists, we continue to organize around the issues of residency and fellowship training in this important area, encouraging and supporting psychiatrists in eating disorders research, access to care, diagnostic and treatment advances, clinical excellence, and advocacy for our patients.

The APA Caucus of Psychiatrists Treating Patients With Eating Disorders will meet at the 2006 Institute of Psychiatric Services on Saturday, October 7, from 1:30 p.m. to 3 p.m. in the Jolson Room on the ninth floor of the Marriott Marquis. Please join us. ■

Denise Senyk, M.D., is in private practice in Bucks County, Pa., and medical director of Project Transition.

Residents Selected For 2006-2008 Fellowships

APA has announced the names of the psychiatry residents selected for the 2006-2008 APA Fellowship in Public Psychiatry (APA/BMS Fellowship). The fellowship provides experiences that will help to prepare residents for leadership roles within the public sector and to heighten awareness of the activities and career opportunities in the public sector. Since the program's founding in 1980, the fellowship has been awarded to approximately 350 outstanding residents.

Ryan Bell, M.D., J.D., University of Washington
Elisa Blankstein, M.D., St. Luke's-Roosevelt Hospital
Anthony Cariño, M.D., Montefiore Medical Center/Albert Einstein College of Medicine
Trina Chang, M.D., M.P.H., MGH/McLean Hospital
Marcy Forgey, M.D., M.P.H., Cambridge Health Alliance
Sarah Guzofski, M.D., University of Massachussetts
Allison Nitsche, M.D., Baylor College of Medicine
Ilana Nossel, M.D., Columbia University
Patrick Runnels, M.D., Mount Sinai School of Medicine
Sonali Sharma, M.D., M.Sc., Cornell University/New York Presbyterian Hospital

More information about the APA Fellowship in Public Psychiatry is posted at <www.psych.org/edu/med_students/bmsfellow/index.cfm>. ■

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

GZ274981T

Printed in USA/May 2006

Poor Intra-Brain Synchrony May Underlie Autism

People with autism are apt to think in pictures even if what they are trying to comprehend is not visual. It may be because their prefrontal cortex and parietal regions do not work simultaneously.

BY JOAN AREHART-TREICHEL

A decade ago a woman with autism wrote: "I think in pictures. Words are like a second language to me. I translate both spoken and written words into full-color movies, complete with sound, which run like a VCR tape in my head."

Thanks to neuroimaging, scientists are starting to confirm what this woman and others with autism have claimed—that they tend to think visually.

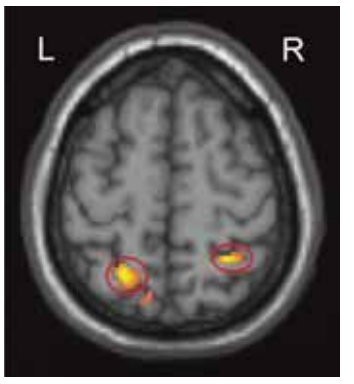
Last year, for example, an fMRI study headed by Nancy Minshew, M.D., a professor of psychiatry and neurology at the University of Pittsburgh, and Marcel Just, Ph.D., a professor of psychology at Carnegie Mellon University, showed that when individuals with autism attempt to recall letters of the alphabet, their brains process the stimuli differently from the brains of nonautistic individuals. The former rely more on the parietal regions, which are involved in visuospatial processing, whereas the latter depend more on the left prefrontal cortex, which is involved in language processing (*Psychiatric News*, February 4, 2005).

Now a new fMRI study conducted by the same group, and published on the *Brain* advance-access Internet site on July 10, reveals that when persons with autism attempt to comprehend sentences, they rally visual centers in their brains to do so even if the sentences do not contain visual images.

For example, one of the low-imagery sentences used in the experiment was "Addition, subtraction, and multiplication are all math skills." As the control group comprehended this sentence, their left prefrontal cortex was activated. But as the autism group comprehended this sentence, not only their left prefrontal cortex, but their parietal regions were switched on as well.

Moreover, as the autistic prefrontal cortex and parietal regions process language or engage in other cerebral challenges, they may be out of step with each other, another investigation has found. It was conducted by the same research team and was published on the *Cerebral Cortex* advance access Internet site on June 13.

In this inquiry, fMRI was used to examine the brains of both autism subjects and control subjects as they performed the Tower of London test. This task involves moving three balls into a specified arrangement. It requires planning and goal-management ability, using both the prefrontal cortex and the parietal regions. In the control group, the prefrontal cortex and parietal regions tended to function in synchrony—that is, increasing or decreasing their activity at the same time—whereas in the autism group, these two brain areas were less likely to do so.



Study participants with autism showed greater activation in areas near the intraparietal sulcus (circled regions) than normal control participants during the processing of low-imagery sentences. The areas near the intraparietal sulcus are associated with visual imagery.

Source: Marcel Just, Ph.D., *Brain* advance-access Internet site.

Out of Sync Due to Faulty Connections

This lack of synchronization between the prefrontal and parietal regions, in turn, implies that it may be due to faulty white matter fiber connections between them. The *Cerebral Cortex* study supports this supposition. The largest white matter fiber tract in the brain is the corpus callosum, which allows communication between the two sides of the brain. One part of the corpus callosum is the genu. The genu was found to be smaller in the autism group than in the control one, and the smaller the genu in the autism subjects, the more out of sync their frontal and parietal regions were.

Of all their new findings, Just considers this to be the most important, he told *Psychiatric News*. "The reason that this finding is important—and rare—is that it makes a crucial link between [the synchronization of activity between different brain areas] and the anatomical white matter brain structure—corpus callosum—that carries the communication between the areas. It is a crucial link between brain activation and brain tissue in autism."

Autism: Lack of Brain Communication?

Indeed, when all of these findings are considered together, they make Minshew, Just, and their group wonder whether a reduced white fiber connectivity might underlie the neurological, psychological, and behavioral symptoms that constitute the syndrome of autism. And if autism is truly due to a failure of various brain regions to communicate with each other, it "may one day provide the basis for improved treatments for autism that stimulate communication between brain areas," Duane Alexander, M.D., envisions. He is director of the National Institute of Child Health and Human Development. That institute, as well as the National Institute on Deafness and Other Communication Disorders, funded the two studies.

Meanwhile, Minshew told *Psychiatric News* that these study results help explain why individuals with autism can be so bright in specialized ways, yet have trouble with problem-solving and understanding the gist of things—they have the local brain connections to perform the former, but not the widespread brain connections to carry out the latter.

"So in dealing with patients with autism," Minshew advised, "say whatever you have to say as simply as possible. Don't give a lot of examples and expect them to extract the concept [because the circuits that handle these functions may not be working properly]. Also, don't expect them to generalize from one experience to the next [for the same reason]. Use facts, details, and their favorite interest to motivate them."

An abstract of "Sentence Comprehension in Autism: Thinking in Pictures With Decreased Functional Connectivity" is posted at <http://brain.oxfordjournals.org/cgi/content/abstract/awl164v1>. An abstract of "Functional and Anatomical Cortical Underconnectivity in Autism: Evidence From an fMRI Study of an Executive Function Task and Corpus Callosum Morphometry" is posted at <http://cercor.oxfordjournals.org/cgi/content/abstract/bhl006v1>. ■

PTSD Not Sufficient to Explain Responses to Trauma

Consider resilience as a better paradigm than posttraumatic stress among persons exposed to trauma, experts advise.

BY AARON LEVIN

Resilience rather than pathology should become the standard expectation in the aftermath of trauma, according to a leading researcher on posttraumatic stress.

"PTSD may not be the best model in the face of disaster," Arieh Shalev, M.D., professor and head of the Department of Psychiatry at Hadassah University Hospital in Jerusalem, Israel, said at a conference on early response to PTSD at the New York Medical College in Valhalla, N.Y. "The preferential use of PTSD emphasizes the psychopathological consequences of events. This has led to costly and ineffectual efforts toward systematic prevention of PTSD, with less attention or resources devoted to other outcomes."

A traumatic event alone is not a sufficient cause of PTSD, and PTSD is not the most frequent response to traumatic events, said Shalev. Studies after the terrorist attacks of September 11, 2001, found a limited prevalence of PTSD after six months.

"We need to define and study the non-PTSD outcome," said Shalev. To him, that means exploring the meaning and utility of resilience.

Psychological resilience means the ability to "bounce back," to adapt and function in the face of serious threat or adversity, much the way an engineer observes the ability of some material to return to is original shape after deformation, he said.

"We've gone from nonrecognition to overrecognition of PTSD," said Matthew Friedman, M.D., Ph.D., executive director of the National Center for PTSD in White River Junction, Vt.

Friedman said he could remember when the struggle was to persuade the psychiatric community and the public to understand that PTSD sometimes happens to people who were in the wrong place at the wrong time. But this idea may have become oversimplified with time. Today, although a significant minority of people exposed to war or disaster develop PTSD, there may be other psychiatric sequelae to trauma—or nothing at all may happen to the person involved, he said.

"Eventually people came to see trauma only through the lens of PTSD, and that was not good either," said Friedman. "The response to trauma is not an either-or thing. Trauma can cause psychiatric illness but also can also be a crucible that brings out the best in people."

Resilience should be the default unless other circumstances prevent it, said Shalev. Outcomes are affected by an array of risk factors (like neglect, abuse, lower socioeconomic status, or poor education) and protective factors (social support, escape, or control). The response to trauma may have multiple contributing causes and take many routes to an outcome, and similar inputs may lead to diverse results.

Rather than automatically pathologize the response to trauma, Shalev suggested that good adaptation should be considered the norm.

"Resilience is common and usually arises from the normative functions of human adaptational systems, with the greatest threats to human development being those that compromise these protective systems," he said, quoting Ann Masten, Ph.D., of the Institute of Child Development at the University of Minnesota.

"A bad outcome occurs when adaptive processes cannot take place," said Shalev. Exposure to trauma has different phases, he said. The initial event sparks an acute stress response and a focus on survival. The rescue phase marks an adjustment to the reality of the event, while the immediate postevent period calls for an appraisal of the event. The final stage involves the attempt to return to normal activities, with greater or lesser difficulty.

Preventive measures, then, are mainly concerned with overcoming barriers to normal adaptation. Dramatizing, pathologizing, or catastrophizing the traumatic event can undermine resilience from the start, as can creating negative expectations about outcome, hiding or manipulating information, and showing emotional distance or indifference to those who have experienced trauma. Adaptation can occur by simply allowing stage-related processes to proceed while not undermining resilience, said Shalev.

"We need to understand what are the qualities—genetic, molecular, cognitive, social—that help people cope," agreed Friedman. "Shalev's views exemplify where the field has gone in the last five years. Since September 11, the focus has turned to understanding people who cope successfully. We have to think about the aftermath of trauma exposure in two contexts: We still need to recognize that some people will not recover on their own. However, we also have to ask: What makes resilience? What are the protective factors that allow people to cope, that prevent the onset of PTSD, and facilitate or even accelerate recovery?" ■

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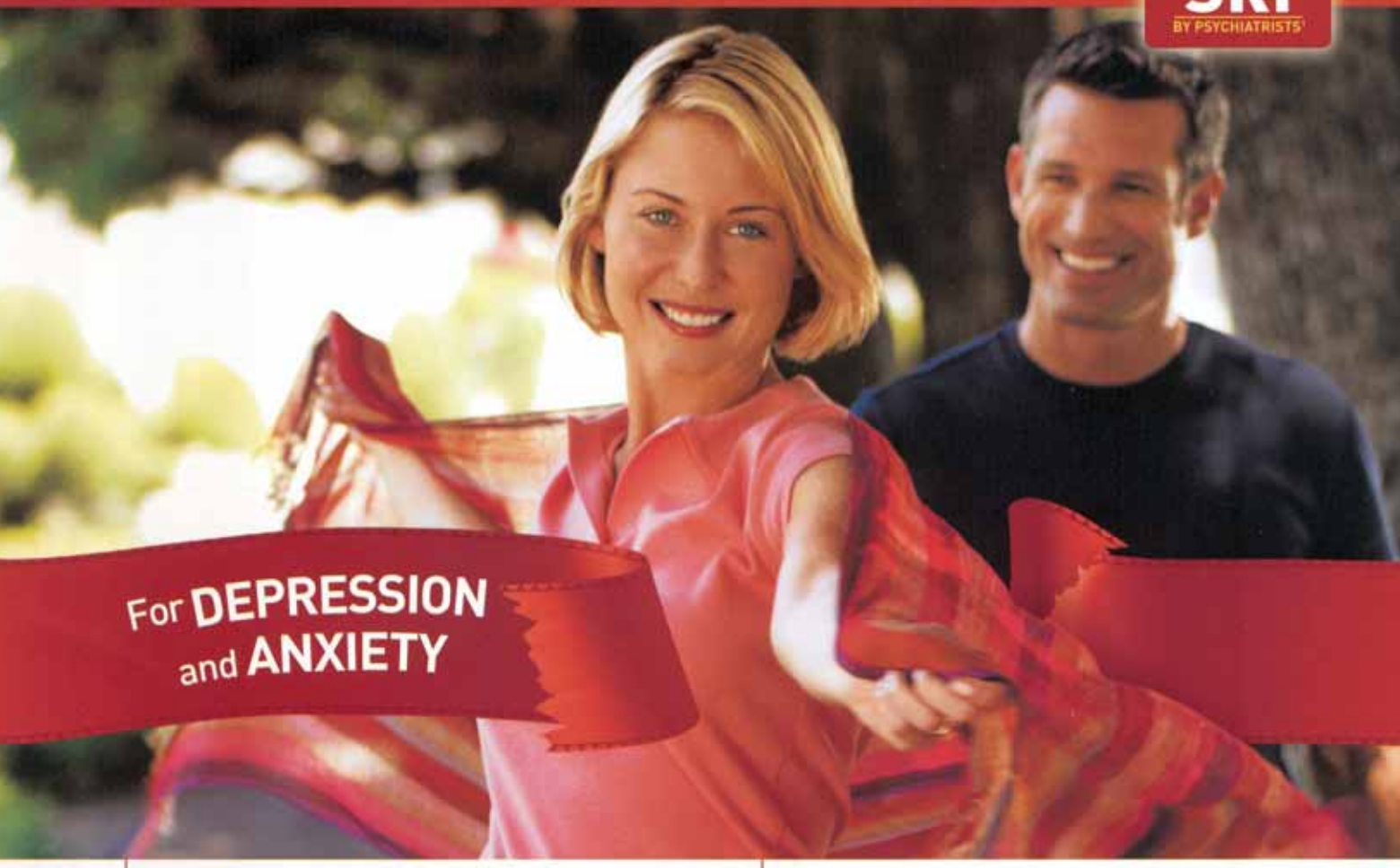

UP TO 90% of depressed patients present with symptoms of anxiety[2]

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

Lexapro escitalopram oxalate

POWER TO ENJOY LIFE™

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

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

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

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

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

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

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

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

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Has Schizophrenia Evolved Into Less Serious Illness?

Emil Kraepelin and forebears described a very high degree of phenotypic diversity in schizophrenia patients, with reproductive capacity varying inversely with phenotypic severity.

BY MARK MORAN

Michael Marsland / Yale University

Thomas McGlashan, M.D. , observes that recovery is an expectable goal for many patients with schizophrenia today, unlike decades ago.

Is the schizophrenia typically seen by clinicians today milder than the disease described by Emil Kraepelin in the 19th century or even that commonly seen by clinicians in the middle of the 20th?

And might natural selection be at work, progressively thinning the population of the most sorely affected patients while allowing a less-severe form of disease to survive into our day?

That's the intriguing idea floated by Thomas McGlashan, M.D., in an editorial in the July *Schizophrenia Bulletin*.

In an interview with *Psychiatric News*, McGlashan acknowledged that the notion hardly occurs to clinicians busy treating a disease no one would describe as mild. And credible research comparing the disease as it presented 100 years ago with today's malady is nonexistent.

But McGlashan suggests it may be reasonable for contemporary researchers and clinicians to look up, so to speak, from their work and ponder why it is that "recovery" is advanced as an expectable goal for many patients today, when 60 years ago such a notion would never have been considered.

He noted that the subjective experience of clinicians whose careers have spanned several decades seems to confirm that the severity of schizophrenia has ameliorated over the years.

"The question occasionally comes up with older colleagues about how many catatonic patients they've seen recently," McGlashan said. "And the answer is that we haven't seen any, or any of the really deteriorating cases that as a medical student I can recall seeing in the early 1960s. I can remember some of us had a trip to a state hospital then and went to the infamous building where they had the worst cases. They were really vegetative and scary, and even though they were medicated—this was in the early days of antipsychotic medication, and all of them were on Thorazine—they were often mute."

Remembering Different Disorder

Those impressions are bolstered by writings from Kraepelin on describing a schizophrenia that might seem to be a thing of the past. In his editorial, McGlashan cites two clinicians writing in the 1970s and 1980s who remember seeing a different disease earlier in their career.

"I believe that schizophrenic illnesses today are milder and that one rarely sees patients experiencing an acute, unremitting catastrophic course," wrote John Romano, M.D., in the *Bulletin* in 1977.

And in 1987 John Ellard, M.D., writing in the *Australian-New Zealand Journal of Psychiatry*, concluded a reminiscence about 40 years of treating schizophrenia with the remarkable comment: "Whereas then my patient and I struggled to communicate at all, now we are likely to finish up discussing the dopamine hypothesis."

Better treatment, including release from the back wards of state hospitals, surely has contributed to the impression that patients are less severely ill. But McGlashan believes it is possible that natural selection is at work.

Is Schizophrenia Recent Phenomenon?

It is a notion that is overlooked, he said, in part because it implies that schizophrenia is a relatively recent phenomenon. That theory, and the possibility that schizophrenia may not have existed before the 17th century, has been advanced by schizophrenia researcher Fuller Torrey, M.D., in *The Invisible Plague* (Rutgers University Press, 2001). Moreover, most people are accustomed to thinking of natural selection as a process that occurs over many centuries, rather than over one or two.

But McGlashan believes there may be something to Torrey's theory and compelling reasons for considering natural selection as one cause for the amelioration of the disease: a very high degree of phenotypic diversity is described by Kraepelin and his forebears, and it may be that reproductive capacity varies inversely with phenotypic severity.

As he writes in the *Bulletin*, "If such a process were active, we would expect to see a marked reduction in the reproductive capacity of those afflicted and to see selection against the most debilitating forms of the disorder. The former has been documented many times, and the latter appears to match the longitudinal data."

McGlashan told *Psychiatric News* that he is currently working with Danish researchers to look at the reproductive capacity of patients and their family members. Preliminary research confirms existing data: patients with schizophrenia from the latter decades of the 20th century produced

please see ***Schizophrenia*** *on page 28*

Those With Serious Mental Illness Need General Health Monitored

Individuals' health status on different indicators is relatively independent, suggesting that multiple health indicators should be assessed to ascertain overall health status in persons with serious mental illness.

BY MARK MORAN

The overall health of people with serious mental illness is well below the suboptimal level found in the general population.

A comparison of patients with either schizophrenia or major mood disorder with a sample matched for age, gender, and race in the general population found that only 1 percent of those with serious mental illness met the criteria for five selected health indicators. The study appeared in the July *Schizophrenia Bulletin*.

Those indicators included smoking status, exercise, good dentition, absence of obesity, and absence of serious medical co-occurring illness. A sixth item, absence of injury requiring medical treatment in the previous 90 days, was also compared but was not included in the composite, according to researchers at Sheppard Pratt Health System, the University of Maryland School of Medicine, and Johns Hopkins University School of Medicine.

At the same time, only 10 percent of those in the general population met criteria for all five health indictors.

"The general population in the U.S. is hampered by health problems, but our patients are even more so," co-author Faith Dickerson, Ph.D., M.P.H., told *Psychiatric News*. "We found that a very small percentage of our patient group actually met the healthy criteria for each of the items."

She is director of psychology at Sheppard Pratt Health System in Baltimore. The study was funded by the National Alliance for Research on Schizophrenia and Depression, and the principal investigator was Lisa Dixon, M.D., of the University of Maryland.

In the study, a sample of 100 adults with schizophrenia and 100 with major mood disorder were recruited from randomly selected outpatients receiving community-based psychiatric treatment. Participants were surveyed about health indicators using items from the National Health and Nutrition Examination Study III (NHANES III) and the National Health Interview Survey (NHIS). Their responses were compared with those of matched samples from the general population surveys.

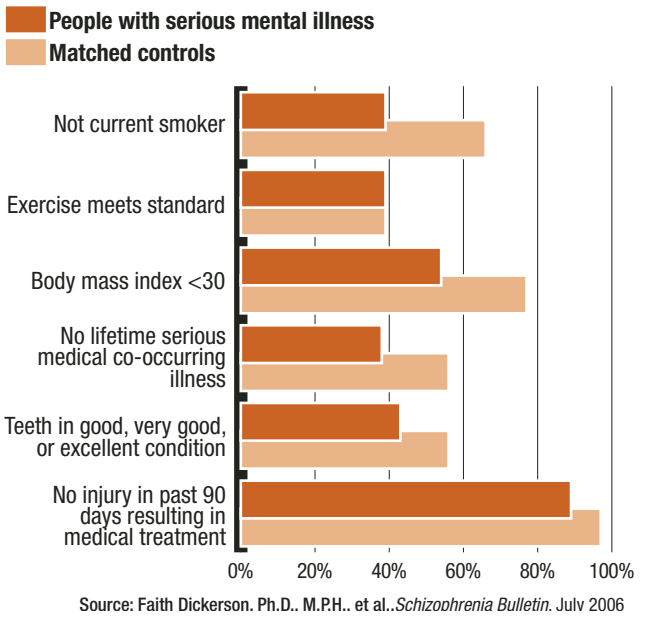
The researchers focused on survey items consistent with the leading health indicators for the U.S. population as identified by the Healthy People 2010 program of the Centers for Disease Control and Prevention. Specifically, they included being a nonsmoker (not smoking a cigarette in the previous 30 days); engaging in exercise meeting recommended standards (defined as at least 20 times a month); not being obese (a body mass index with a score of less than 30); being free of a co-occurring lifetime serious medical illness defined as arthritis, asthma, chronic bronchitis, emphysema, diabetes, congestive heart failure, hypertension, stroke, and cancer; having teeth in good, very good, or excellent condition; and not requiring medical treatment for an injury in the previous 90 days.

Items 1 to 5 were from the NHANES III, and item 6 from the NHIS. The differences between the two groups were statistically significant (with the mentally ill group reporting worse health) on all indicators except for exercise meeting recommended standards. On that score, 39 per-

please see ***Health Status*** *on page 27*

Overall Health Suffers Too

Study subjects with either schizophrenia or major mood disorder were found to be less healthy than matched controls on the six health indicators shown below. Health status on the different indicators was relatively independent. The findings point to the need to assess the overall health status of people with serious mental illness.



Source: Faith Dickerson. Ph.D.. M.P.H.. et al..*Schizophrenia Bulletin*. Julv 2006

Don't Sleep on Decision To Start Insomnia Treatment

As sleep specialists assess links between insomnia and depression, the evidence suggests that both insomnia and depression need specific treatment.

BY LYNNE LAMBERG

Is "disturbed sleep a cause of serious mental illness, or simply an antecedent to it?"

"My answer is yes!" said Ruth Benca, M.D., Ph.D., a professor of psychiatry at the University of Wisconsin School of Medicine.

Despite her jest, Benca and others weighed evidence supporting links between troubled sleep and troubled minds at the annual meeting of the Associated Professional Sleep Societies in Salt Lake City, Utah, in June.

Since diagnostic criteria for primary insomnia and major depressive disorder overlap, it often is hard to tell in clinical settings where a sleep disorder ends and depression begins, said Benca, a past president of the Sleep Research Society. Nonetheless, people with major depression generally report more severe depression and more highly disturbed sleep than do people with primary insomnia.

Sleep disturbance is the most common refractory symptom in treated major depressive disorder, she said. Fatigue ranks second. Sleep disturbance also is the first symptom to appear in recurrence. These findings, Benca said, suggest sleep disruption is a core symptom in mood disorders.

More than 50 published epidemiological studies of insomnia using data collected from representative community-dwelling samples or populations consistently show an association between insomnia and major depressive episodes, noted Maurice Ohayon, M.D., D.Sc., Ph.D., director of the Sleep Epidemiology Research Center at Stanford University School of Medicine.

Longitudinal studies show that people who report insomnia at a first evaluation are more likely than people without insomnia to have depression at their next evaluation, Ohayon said. People with insomnia at two separate evaluations have a higher risk of depression than those without persistent trouble sleeping.

In a cross-sectional and retrospective study of a community-based sample of 722 adults aged 20 to 89, Daniel Taylor, Ph.D., an assistant professor of psychology at the University of North Texas in Denton, and colleagues found that people with insomnia were 9.82 times and 17.35 times more likely to have clinically significant depression and anxiety, respectively, than people without insomnia. The researchers excluded people with other sleep or medical disorders from their study.

About 20 percent of people with insomnia had clinically significant depression, and 19.3 percent had clinically significant anxiety, the researchers reported in the November 2005 *Sleep*.

The relationship between insomnia and depression and anxiety likely is reciprocal in some cases, Taylor said. A diathesis-stress model may trigger these associations, he suggested. People who develop insomnia at times of stress may find that lying in bed awake in the dark intensifies feelings of failure or worries about the future.

"If we can rapidly address their insomnia," Taylor said, "maybe we can bring them down to a subthreshold state."

Research now under way aims to see whether cognitive-behavioral therapy for insomnia lowers the risk of depression, said Daniel Kripke, M.D., a professor of psychiatry emeritus at the University of California at San Diego. Some hypnotic medications may boost the risk of depression as compared with placebo, he said. He examined manufacturers' prescribing information for four recently approved hypnotics, finding depression reported as an adverse event in 109 of 5,535 subjects who took the medication, and in 21 of 2,318 who took the placebo, a roughly twofold increased risk (unpublished data).

While even clinicians sometimes quip, "Insomnia doesn't kill," insomnia is far from trivial, said Douglas Moul, M.D., M.P.H., an assistant professor of psychiatry at the University of Pittsburgh School of Medicine. He cited a man who developed trouble sleeping and depression after his brother died. Six months later, the man committed suicide. While in treatment for his depression, the man frequently told his physician, "All I need is for my sleep to be right."

One can imagine an underlying genetic risk in this individual, modified by exposure to life events, with pathology building up over time, Moul said, and worsened by the brother's death.

Studies of circadian rhythms support a causal role for insomnia in depression, said Fred Turek, Ph.D., a professor of neurobiology and physiology and director of the Center for Circadian Biology and Medicine at Northwestern University.

Some people with depression experience early morning awakening, he noted. This phenomenon is hypothesized to represent an advance of the body's sleep/wake cycle and cortisol rhythms, he said, and suggests that disordered circadian timekeeping may contribute to depression.

A genetic animal model for depression, the Wistar-Kyoto rat, exhibits sleep fragmentation and sleep-wake cycle disturbances similar to those in people with depression, he said.

"No one would say insomnia causes all major depression," he said, "but it may have that effect in some people. We have to think about whether temporal disorganization in the brain is playing a contributory role in these individuals and figure out how to identify them and treat them."

Most psychiatrists have been trained to treat a primary disorder, with the expectation that accompanying insomnia will improve, too, said Benca, who reviewed the diagnosis and treatment of persistent insomnia in the March 2005 *Psychiatric Services*.

Recent findings, she said, "imply that we should treat insomnia from the get-go—that along with depressive symptoms, insomnia should be a primary target of treatment."

Treatment of insomnia today is akin to that of pain in years past, she said, asserting, "Sleep problems deserve the same attention as other pathology." ■

Few Borderline-Personality Patients Eventually Develop Bipolar Disorder

The finding refutes a common expectation that borderline patients will in time develop bipolar disorder, as if borderline personality were a form of bipolar disorder that hadn't yet fully matured.

BY MARK MORAN

Only a modest association appears to exist between borderline personality disorder (BPD) and bipolar disorder, seeming to refute the notion that BPD is a variant of bipolar.

A four-year longitudinal study at four institutions found that patients with BPD had a significantly higher co-occurrence of bipolar disorder than did patients with other personality disorders. But it was only modestly higher, and this co-occurrence did not appear to affect the subsequent course of BPD, according to a report in the July *American Journal of Psychiatry*.

"Our study shows that some borderlines go on to develop bipolar disorder, but it's a minority," lead author John Gunderson, M.D., told *Psychiatric News*. "Bipolar illness occurs only modestly more frequently in BPD than in people with other types of personality disorder."

He said the finding refutes the expectation, common among some clinicians, that many borderline patients will in time develop bipolar disorder, as if BPD were a form of bipolar disorder that hadn't yet fully matured. The study appears also to challenge more generally the notion that BPD is not a distinct clinical entity, but a variant of bipolar disorder.

Gunderson said some researchers and clinicians have proposed that bipolar illness is much more common in the general population than is commonly thought, occurring in a spectrum of symptoms including those that have been classified as BPD.

He added that the notion of BPD as a variant of bipolar illness has been seized upon by managed care because bipolar—in contrast to BPD and personality disorders generally—is perceived as a straightforward, biological disorder easily treatable with mood stabilizers. But Gunderson emphasized that mood stabilizers are liable to be "modestly helpful, but never dramatically helpful" for patients with BPD, and that psychotherapies, such as dialectical behavior therapy, appear to be much better.

"Our findings don't refute the idea that there is a spectrum of bipolar disorder in the population, but it does suggest that BPD is not a real close cousin," Gunderson told *Psychiatric News*. "That's big news because modern psychiatry has been highly influenced by managed care and the biological perspective on illness. That has meant that anyone who has mood shifts is likely to be bipolar and treated with mood stabilizers, with an unrealistic expectation that it is going to be helpful."

In the study, 192 patients with BPD and 433 patients with other personality disorders were followed for four years and reassessed at six months, one year, and every year after. All the patients were treatment-seeking individuals in a variety of treatment settings at the following institutions: Columbia University and the New York State Psychiatric Institute, Yale University and Yale Psychiatric Research, Brown University, and Texas A&M.

To examine the relationship of bipolar disorder to borderline personality disorder, researchers divided the borderline personality disorder group on the basis of presence (38 subjects) or absence (158 subjects) of lifetime co-occurring bipolar I or bipolar II disorder. As a comparison group, the patients with other personality disorders were likewise divided on the basis of presence (34 subjects) or absence (399 subjects) of lifetime co-occurring bipolar I or bipolar II disorder.

Comorbid bipolar I or bipolar II disorder occurred significantly more frequently in borderline personality disorder than in other personality disorders.

But the co-occurrence of bipolar and BPD did not appear to affect clinical course, global assessment of functioning, or number of hospitalizations. It also had no significant effect on use of SSRIs, other antidepressants, neuroleptics, or anticonvulsants over the four years.

Patients with borderline personality disorder without lifetime bipolar disorder had more new onsets of bipolar illness than other personality disorder patients, but the difference was not significant.

"Six new bipolar onsets followed significant stressful life events, two followed significant neurobiological changes, one followed both stressful life events and neurobiological change, and no precipitants were observed in three," Gunderson and colleagues wrote in their report. "Clearly, the new onsets of bipolar disorder did not represent an evolution from borderline personality disorder psychopathology; rather, they most often followed stressful neurobiological or life changes. It remains to be determined whether a neurobiological disposition toward onsets of bipolar episodes was created due to the fact that our borderline personality disorder patients received far more medications than our patients with other personality disorders."

In an interview with *Psychiatric News*, Gunderson said the clinical import of these findings is that clinicians should not jump to the conclusion that their patients who are impulsive and have mood changes have bipolar disorder. Instead they should "consider carefully" whether those changes are

please see ***BPD*** *on page 29*

In patients with schizophrenia who have been discharged…

50%
are not fully compliant with their antipsychotic medication within 1 year[1]

Up to

25%
are not fully compliant with their antipsychotic medication within 7–10 days[2]

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Commonly observed events: Treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL CONSTA groups (25 mg or 50 mg) and at least twice that of placebo were: somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, and weight increase.

Hyperglycemia and diabetes: Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics (APS), including RISPERDAL CONSTA. Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Tardive dyskinesia (TD): As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD; if its signs and symptoms appear, discontinuation of RISPERDAL CONSTA should be considered. In the integrated database of multiple-dose studies, the incidence of TD was 0.6% (9/1499 patients).

Neuroleptic malignant syndrome (NMS): NMS has been reported rarely with this class of medications, including RISPERDAL CONSTA, and appropriate management should be employed.

Cerebrovascular adverse events (CAEs): CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking oral risperidone in clinical trials. The incidence of CAEs with oral risperidone was significantly higher than with placebo. RISPERDAL CONSTA is not approved for treating these patients.

References: 1. Weiden PJ, Zygmunt A. The road back: working with the severely mentally ill. Medication noncompliance in schizophrenia: part 1. Assessment. *J Pract Psychiatry Behav Health.* 1997;3:106–110. **2.** Lam YWF, Velligan D, Ereshefsky L, et al. Intra-individual variability in plasma concentrations as an indicator of adherence in schizophrenia. Poster presented at: 42nd Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting: June 10–13, 2002; Boca Raton, Fla.

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BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

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

INDICATIONS AND USAGE: RISPERDAL® CONSTA® (risperidone) is indicated for the treatment of schizophrenia.
CONTRAINDICATIONS: RISPERDAL® CONSTA® (risperidone) is contraindicated in patients with a known hypersensitivity to the product or any of its components.
WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning). Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL® CONSTA®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® CONSTA® despite the presence of the syndrome. **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:** Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with oral risperidone compared to patients treated with placebo. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.
PRECAUTIONS: General: Orthostatic Hypotension: RISPERDAL® CONSTA® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499 patients) of patients treated with RISPERDAL® CONSTA® in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). RISPERDAL® CONSTA® should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral RISPERDAL® and antihypertensive medication. **Seizures:** During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with RISPERDAL® CONSTA®. Therefore, RISPERDAL® CONSTA® should be used cautiously in patients with a history of seizures. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® CONSTA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Osteodystrophy and Tumors in Animals:** RISPERDAL® CONSTA® produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks. RISPERDAL® CONSTA® produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL® CONSTA® produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. **Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone**. Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study. The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail under PRECAUTIONS, Carcinogenicity, Mutagenesis, Impairment of Fertility. The relevance of these findings to human risk is unknown. **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Potential for Cognitive and Motor Impairment:** Somnolence was reported by 5% of patients treated with RISPERDAL® CONSTA® in multiple-dose trials. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL® CONSTA® does not affect them adversely. **Priapism:** No cases of priapism have been reported in patients treated with RISPERDAL® CONSTA®. However, rare cases of priapism have been reported in patients treated with oral RISPERDAL®. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown. **Antiemetic Effect:** Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. **Use in Patients with Concomitant Illness:** Clinical experience with RISPERDAL® CONSTA® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL® CONSTA®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms. Caution is advisable when using RISPERDAL® CONSTA® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Increased plasma concentrations of risperidone and 9–hydroxyrisperidone occur in patients with severe renal impairment. Patients with renal or hepatic impairment should be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL® CONSTA® is initiated (see DOSAGE AND ADMINISTRATION in full PI). **Drug Interactions:** The interactions of RISPERDAL® CONSTA® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® CONSTA® is administered in combination with other centrally-acting drugs or alcohol. Because of its potential for inducing hypotension, RISPERDAL® CONSTA® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® CONSTA® may antagonize the effects of levodopa and dopamine agonists. Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety. Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Carbamazepine and Other Enzyme Inducers:** In a drug interaction study in schizophrenic patients, 11 subjects received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9–hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL® CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of RISPERDAL® CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9–hydroxyrisperidone. For patients treated with the lowest available dose (25 mg) of RISPERDAL® CONSTA®, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with RISPERDAL® CONSTA®. **Fluoxetine and Paroxetine:** Fluoxetine (20 mg QD) and paroxetine (20 mg QD), which inhibits CYP 2D6, have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosage of RISPERDAL® CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. For patients treated with the lowest available dose (25 mg), it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with RISPERDAL® CONSTA®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9–hydroxyrisperidone have not been studied. **Lithium:** Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone. **Digoxin:** RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Drugs that Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9–hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY in full PI). Drug interactions that reduce the metabolism of risperidone to 9–hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9–hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. *In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY in full PI). **Drugs Metabolized by CYP 2D6**: *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® CONSTA® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis - Oral:** Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the oral MRHD (mice) or 0.4, 1.5, and 6 times the oral MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas in female mice at doses 0.75 and 3 times the oral MRHD on a mg/m^2 basis. There was a significant increase in endocrine pancreatic adenomas in male rats at doses 1.5 and 6 times the oral MRHD on a mg/m^2 basis. Mammary gland adenocarcinomas were significantly increased in female mice at all doses tested (0.2, 0.75, and 3 times the oral MRHD on a mg/m^2 basis), in female rats at all doses tested (0.4, 1.5, and 6 times the oral MRHD on a mg/m^2 basis), and in male rats at a dose 6 times the oral MRHD on a mg/m^2 basis. **Carcinogenesis - IM:** RISPERDAL® CONSTA® was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with IM injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m^2 basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m^2 basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m^2 basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m^2 basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS - Hyperprolactinemia). **Mutagenesis:** No evidence of mutagenic potential for oral risperidone was found. In addition, no evidence of mutagenic potential was found in the *in vitro* Ames reverse mutation test for RISPERDAL® CONSTA®. **Impairment of Fertility:** Oral risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the oral maximum recommended human dose. No mating and fertility studies were conducted with RISPERDAL® CONSTA®.
Pregnancy: Pregnancy Category C: The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the oral MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m^2 basis. No studies were conducted with RISPERDAL® CONSTA®. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to oral RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® CONSTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® CONSTA® on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women should not breast-feed during treatment with RISPERDAL® CONSTA® and for at least 12 weeks after the last injection. **Pediatric Use:** RISPERDAL® CONSTA® has not been studied in children younger than 18 years old. **Geriatric Use:** In an open-label study, 57 clinically stable, elderly patients (≥65 years old) with schizophrenia or schizoaffective disorder received RISPERDAL® CONSTA® every 2 weeks for up to 12 months. In general, no differences in the tolerability of RISPERDAL® CONSTA® were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern (see PRECAUTIONS, DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY in full PI). **Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis:** In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with oral placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of oral risperidone regardless of concomitant use with furosemide. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis. (See **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)
ADVERSE REACTIONS: Associated with Discontinuation of Treatment: In the 12-week, placebo-controlled trial, the incidence of schizophrenic patients who discontinued treatment due to an adverse event was lower with RISPERDAL® CONSTA® (11%; 22/202 patients) than with placebo (13%; 13/98 patients). **Incidence in Controlled Trilas: Commonly Observed Adverse Events in Controlled Clinical Trials:** Spontaneously reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® CONSTA® groups (25 mg or 50 mg) and at least twice that of placebo were: somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, weight increase. **Dose Dependency of Adverse Events:** ***Extrapyramidal Symptoms:*** The overall incidence of EPS-related adverse events (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL® CONSTA® was comparable to that of patients treated with placebo; the incidence of EPS-related adverse events was higher in patients treated with 50 mg RISPERDAL® CONSTA®. **Vital Sign Changes:** RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). In the placebo-controlled trial, orthostatic hypotension was observed in 2% of patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® (see PRECAUTIONS). **Weight Changes:** In the 12-week, placebo-controlled trial, 9% of patients treated with RISPERDAL® CONSTA®, compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint. **Laboratory Changes:** The percentage of patients treated with RISPERDAL® CONSTA® who experienced potentially important changes in routine serum chemistry, hematology, or urinalysis parameters was similar to or less than that of placebo patients. Additionally, no patients discontinued treatment due to changes in serum chemistry, hematology, or urinalysis parameters. **ECG Changes:** The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® and 98 schizophrenic patients treated with placebo in a 12-week, double-blind, placebo-controlled trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL® CONSTA®. **Pain Assessment and Local Injection Site Reactions:** The mean intensity of injection pain reported by patients using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® experienced redness, swelling, or induration at the injection site. **Other Events Observed During the Premarketing Evaluation of RISPERDAL® CONSTA®:** During its premarketing assessment, RISPERDAL® CONSTA® was administered to 1499 patients in multiple-dose studies. The conditions and duration of exposure to RISPERDAL® CONSTA® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term and long-term exposure studies. The following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. It is important to emphasize that, although the reported events occurred during treatment with RISPERDAL® CONSTA®, they were not necessarily caused by it.) **Psychiatric Disorders:** *Frequent:* anxiety, psychosis, depression, agitation, nervousness, paranoid reaction, delusion, apathy. *Infrequent:* anorexia, impaired concentration, impotence, emotional lability, manic reaction, decreased libido, increased appetite, amnesia, confusion, euphoria, depersonalization, paroniria, delirium, psychotic depression. **Central and Peripheral Nervous System Disorders:** *Frequent:* hypertonia, dystonia. *Infrequent:* dyskinesia, vertigo, leg cramps, tardive dyskinesia[a], involuntary muscle contractions, paraesthesia, abnormal gait, bradykinesia, convulsions, hypokinesia, ataxia, fecal incontinence, oculogyric crisis, tetany, apraxia, dementia, migraine. *Rare:* neuroleptic malignant syndrome. [a]In the integrated database of multiple-dose studies (1499 patients with schizophrenia or schizoaffective disorder), 9 patients (0.6%) treated with RISPERDAL® CONSTA® (all dosages combined) experienced an adverse event of tardive dyskinesia. **Body as a Whole/General Disorders:** *Frequent:* back pain, chest pain, asthenia. *Infrequent:* malaise, choking. **Gastrointestinal Disorders:** *Frequent:* nausea, vomiting, abdominal pain. *Infrequent:* gastritis, gastroesophageal reflux, flatulence, hemorrhoids, melena, dysphagia, rectal hemorrhage, stomatitis, colitis, gastric ulcer, gingivitis, irritable bowel syndrome, ulcerative stomatitis. **Respiratory System Disorders:** *Frequent:* dyspnea. *Infrequent:* pneumonia, stridor, hemoptysis. *Rare:* pulmonary edema. **Skin and Appendage Disorders:** *Frequent:* rash. *Infrequent:* eczema, pruritus, erythematous rash, dermatitis, alopecia, seborrhea, photosensitivity reaction, increased sweating. **Metabolic and Nutritional Disorders:** *Infrequent:* hyperuricemia, hyperglycemia, hyperlipemia, hypokalemia, glycosuria, hypercholesterolemia, obesity, dehydration, diabetes mellitus, hyponatremia. **Musculo-Skeletal System Disorders:** *Frequent:* arthralgia, skeletal pain. *Infrequent:* torticollis, arthrosis, muscle weakness, tendinitis, arthritis, arthropathy. **Heart Rate and Rhythm Disorders:** *Frequent:* tachycardia. *Infrequent:* bradycardia, AV block, palpitation, bundle branch block. *Rare:* T-wave inversion. **Cardiovascular Disorders:** *Frequent:* hypotension. *Infrequent:* postural hypotension. **Urinary System Disorders:** *Frequent:* urinary incontinence. *Infrequent:* hematuria, micturition frequency, renal pain, urinary retention. **Vision Disorders:** *Infrequent:* conjunctivitis, eye pain, abnormal accommodation. **Reproductive Disorders, Female:** *Frequent:* amenorrhea. *Infrequent:* nonpuerperal lactation, vaginitis, dysmenorrhea, breast pain, leukorrhea. **Resistance Mechanism Disorders:** *Infrequent:* abscess. **Liver and Biliary System Disorders:** *Frequent:* increased hepatic enzymes. *Infrequent:* hepatomegaly, increased SGPT. *Rare:* bilirubinemia, increased GGT, hepatitis, hepatocellular damage, jaundice, fatty liver, increased SGOT. **Reproductive Disorders, Male:** *Infrequent:* ejaculation failure. **Application Site Disorders:** *Frequent:* injection site pain. *Infrequent:* injection site reaction. **Hearing and Vestibular Disorders:** *Infrequent:* earache, deafness, hearing decreased. **Red Blood Cell Disorders:** *Frequent:* anemia. **White Cell and Resistance Disorders:** *Infrequent:* lymphadenopathy, leucopenia, cervical lymphadenopathy. *Rare:* granulocytopenia, leukocytosis, lymphopenia. **Endocrine Disorders:** *Infrequent:* hyperprolactinemia, gynecomastia, hypothyroidism. **Platelet, Bleeding and Clotting Disorders:** *Infrequent:* purpura, epistaxis. *Rare:* pulmonary embolism, hematoma, thrombocytopenia. **Myo-, Endo-, and Pericardial and Valve Disorders:** *Infrequent:* myocardial ischemia, angina pectoris, myocardial infarction. **Vascular (Extracardiac) Disorders:** *Infrequent:* phlebitis. *Rare:* intermittent claudication, flushing, thrombophlebitis. **Postintroduction Reports:** Adverse events reported since market introduction which were temporally (but not necessarily causally) related to oral RISPERDAL® therapy include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving oral RISPERDAL®. A causal relationship with oral RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.
DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: RISPERDAL® CONSTA® (risperidone) is not a controlled substance.
For more information on symptoms and treatment of overdosage, see full Prescribing Information.
7519506B - US Patent 4,804,663 Revised March 2006 ©Janssen 2003

Janssen L.P.

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Researchers Begin to Tease Out Obesity's Link to MH Disorders

Medicine's current bête noire, obesity, is associated with mood and anxiety disorders but not substance abuse.

BY AARON LEVIN

Mood and anxiety disorders have positive associations with obesity in the U.S. population, according to the results of a survey of 9,125 people. Unlike earlier surveys, the study found no difference between men and women in the association of obesity with psychiatric disorders, said Gregory Simon, M.D., M.P.H., and colleagues, writing in the July *Archives of General Psychiatry*.

Social and cultural factors may play a significant role in connecting obesity with depression, said Simon, of Group Health Cooperative in Seattle, in an interview. "However, we can't say from the data what the direction of causation is."

The researchers used data from the National Comorbidity Survey Replication (NCS-R) to examine connections between obesity and mood, anxiety, and substance use disorders in adults and whether these were also associated with sociodemographic factors. Interviewers used *DSM-IV* criteria and assessed participants using the World Mental Health version of the World Health Organization Composite International Diagnostic Interview. The NCS-R survey was conducted over one year beginning in February 2002 and was the U.S. element of a worldwide study coordinated by the World Health Organization.

The study concluded that obesity—defined as a body mass index (BMI) of 30 or more—was associated with about a 25 percent increase in the lifetime odds of mood and anxiety disorders and a 25 decrease in the odds of substance use disorders. These may sound like modest effects, wrote Simon and colleagues, but are important for public health reasons because of the high levels of obesity in the U.S.

The study measured only association between the two conditions and could not determine whether obesity caused mood and anxiety disorders or whether mood and anxiety disorders induced obesity.

"Many mechanisms could explain the relationship, and possibly more than one is involved," said Simon. "Some people eat more when they're depressed and some eat less, for example."

The stigma attached to being overweight might also lead to depression, as well, he said. "In social groupings where obesity is more stigmatized, it might be equally true that people who can't lose weight become depressed, or that depressed people can't lose weight."

In analyses of various sociodemographic subgroups, the association of obesity with psychiatric disorders was strongest among respondents who were younger than 30 years old, had a college education, or were of non-Hispanic white ethnicity. Simon suggested that social and cultural factors may therefore be important in understanding the connection. Similar studies in China and Poland, for instance, found that increased obesity was associated with *less* depression.

"I would imagine—although this study doesn't provide specific evidence for it—that if obesity and depression vary with educational and cultural settings, then a social environment that stigmatized obesity would produce more depression and anxiety among overweight members of that group," said Simon.

"We've seen that behavioral weight-loss interventions reduce weight and also lower depressive symptomatology," said Eric Stice, Ph.D., a senior scientist at the Oregon Research Institute in Eugene. "But there's not much evidence that treating psychiatric problems leads to weight loss.

"But there's probably a reciprocal relationship. The stress and rejection caused by obesity lead to mood and anxiety problems, while those problems lead to an increased risk of overeating."

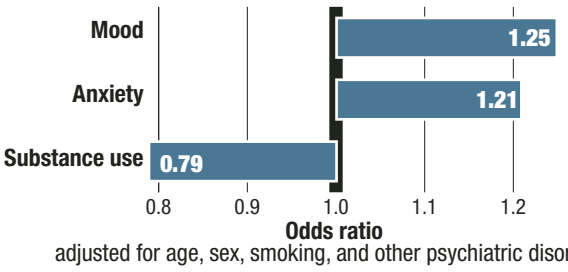
Stigma is no small concern for the overweight, said Stice, who studies risk factors that predict onset of eating disorders, obesity, and depression. "I'm amazed at what coaches, parents, and other children say about overweight kids," he said.

The results of the NCS-R study highlight the importance of sociocultural factors linking obesity and psychiatric disorders, said Simon. To explore that link, he and his colleagues are now doing a series of smaller surveys to get more information on the interaction of depression, obesity, diet, and physical activity.

An abstract of "Association Between Obesity and Psychiatric Disorders in the US Adult Population" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/63/7/824>. ■

Mood, Anxiety Disorders Tied to Obesity

In a survey of 9,125 Americans, obesity was positively associated with mood and anxiety disorders but inversely with substance abuse.



*The OR for mood disorders was adjusted for anxiety and substance use disorders, the OR for anxiety disorders was adjusted for mood and substance use disorders, and the OR for substance use disorders was adjusted for mood and anxiety disorders.

Source: Gregory Simon, M.D., M.P.H., et al., *Archives of General Psychiatry*, July 2006

SAMHSA Details Detoxification Role in Addiction Treatment

A review of detoxification procedures may benefit many patients who were originally treated for other conditions.

BY RICH DALY

The Substance Abuse and Mental Health Services Administration (SAMHSA) released a Treatment Improvement Protocol (TIP) on detoxification and substance abuse treatment in July.

The detoxification TIP, which is the 45th in the SAMHSA series of best-practice guidelines for the treatment of substance use disorders, provides information about the role of detoxification in the continuum of services for individuals with substance use disorders. It includes pharmacological advances in the management of withdrawal, patient-placement procedures, and new issues in the management of detoxification services within comprehensive systems of care.

The TIP was based on a review of clinical and health services research findings and the experiences of a panel of nonfederal researchers, clinicians, program administrators, and patient advocates.

"Detoxification is one component of the array of services that should be available to patients with substance use disorders," said Eric Strain, M.D., chair of APA's Council on Addiction Psychiatry. "This TIP provides a valuable resource guide for clinicians."

SAMHSA is the lead federal agency for improving the quality and availability of prevention and treatment services for mental illness, including substance abuse.

In addition, the TIP provides information on administrative, legal, and ethical issues commonly encountered in the delivery of detoxification services. It suggests performance measures for detoxification programs, discusses the primary goals of detoxification services, and clarifies the distinction between detoxification and substance abuse treatment.

The guidelines address issues that may affect detoxification and ensuing treatment, including evaluation procedures for patients undergoing detoxification, preparing patients for substance abuse treatment, and providing linkages to other services. Highlights include treatment regimens for specific substances and guidance on the medical, nursing, and social-service aspects of these treatments.

TIP 45 presents an overview of special conditions, modifications in protocols, and the use of detoxification medications in patients with co-occurring conditions or disorders.

Strain said that the TIP is a resource that psychiatrists should keep nearby for reference because it addresses a topic relevant to many patients.

"Even if the psychiatrist is not providing direct detoxification services, many of our patients may need such treatments at some point in their lives, and this TIP provides information that will assist the psychiatrist in treatment planning and patient care," Strain said.

A free copy of TIP 45, "Detoxification and Substance Abuse Treatment," is available from the National Clearinghouse for Alcohol and Drug Information at (800) 729-6686; the publication inventory number is BKD541. It can be ordered online at <http://store.health.org/catalog/productDetails.aspx?ProductID=17398>. ■

Health Status

continued from page 21

cent of both groups reported exercise that met recommended standards (see chart on page 21).

The researchers found that within the mentally ill group, educational level, but not diagnosis, was independently associated with a composite measure of health behaviors. There was a significant association between nonsmoking status and good dentition; between absence of obesity and absence of a co-occurring serious medical illness; and between good dentition and absence of a co-occurring medical illness. None of the other associations between individual health items was significant, nor was the association between the health behaviors and the health outcomes composites.

These findings indicate that individuals' health status on different indicators is relatively independent, Dickerson explained. The findings also argue, she said, for examining multiple health indicators to assess overall health status in persons with serious mental illness, as has been studied in the general population.

She said the study did not address whether the use of the composite indicators would be practical in everyday clinical practice, but noted that monitoring of general medical conditions in patients with serious psychiatric illness is fast becoming a major issue.

Wayne Fenton, M.D., director of adult translational research and treatment development at the National Institute of Mental Health (NIMH), has called the phenomenon of metabolic syndrome among patients with schizophrenia "an epidemic" and called for psychiatrists to be more actively involved in monitoring patients' weight and other health indicators (*Psychiatric News*, April 26, 2006).

Dickerson said that Sheppard Pratt Health System is looking at a more standardized way to collect health behavior and basic medical information, such as smoking, obesity, and lipid levels.

"There are increasing efforts to integrate routine health status checks into psychiatric care," Dickerson said. "The interest in medical illness and health behaviors among people with primary psychiatric problems is fairly recent. There is a small but growing literature on the subject. With increasing interest in smoking and obesity among the general population, there has been a growing awareness that patients with serious mental illness are even more prone to these risk factors."

An abstract of "Health Status of Individuals With Serious Mental Illness" is posted at <http://schizophreniabulletin.oxfordjournals.org/cgi/content/abstract/32/3/584>. ■

Comorbidity Study Results Called Into Question

The growing area of mental illness comorbidity research may often actually identify pseudocomorbidity, or conditions that don't exist, researchers point out.

BY RICH DALY

Frequent use in psychiatric comorbidity research of lifetime prevalence with mixed-age samples can often produce inaccurate results, several researchers maintain.

Future comorbidity studies that use lifetime prevalence should require determination of age of onset, even if only retrospectively, according to a paper published in the June *Archives of General Psychiatry* titled "Lifetime Prevalence and Pseudocomorbidity in Psychiatric Research."

One of the authors, Chris Hayward, M.D., M.P.H., an associate professor in the Department of Psychiatry and Behavioral Science and director of clinical services at Stanford University, said the article was a recognition that comorbidity in psychiatric illness is an important issue that is drawing increasing amounts of research. However, the increasing use of mixed-age samples in estimating comorbidity could lead to misleading conclusions about the extent of comorbidity.

"We have a methodological concern that applies to many current studies in which comorbidity is estimated," he told *Psychiatric News*.

The methodological concern about estimates of comorbidity applies to the use of lifetime prevalence rates for two disorders in mixed-age samples. The authors created a simulated example to demonstrate that even in cases of randomly associated disorders the use of lifetime prevalence with mixed-age samples creates the appearance of nonrandom comorbidity.

Although Hayward declined to identify specific examples of problem studies that have been published, the authors reported that the use of lifetime prevalence to estimate comorbidity is very common, which could put the results of many such studies in serious question.

'Be Suspicious'

"One of the major contributions of this article by Kraemer and colleagues is to alert investigators (and readers) to be suspicious about lifetime prevalence or lifetime history studies," James Anthony, Ph.D., professor and chair of the Department of Epidemiology at Michigan State University, said in an interview with *Psychiatric News*. "Apparently, each generation of psychiatric investigators needs to be reminded that estimation and study of 'lifetime prevalence' and 'lifetime history' are fraught with perilous difficulties and are best avoided."

Although the authors said no perfect solution for avoiding pseudocomorbidity exists, one possible way to avoid pseudocomorbidity is to estimate comorbidity in narrower age ranges.

Smaller age intervals are "the best in terms of reducing the bias, but the smaller the age grouping, the less generalizable the results are, because they become more and more narrowly applicable only to people in that age range," Hayward said.

For example, the National Comorbidity Study (NCS) used 10-year age groupings as part of its design. Although Hayward and the other paper authors found no evidence that NCS researchers used the more narrow age groupings to try to address pseudocomorbidity, the NCS approach was viewed as a good way to avoid pseudocomorbidity problems.

Solution Not Satisfactory

The pseudocomorbidity problem is further reduced with more narrow age groupings, but studies that limit participation to same-age participants are "not a very feasible solution because you can apply the estimate of comorbidity only to people of that age," Hayward said.

Other approaches could include following a group of people of the same age over time.

The use of age of onset, even in a cross-sectional study, and Kaplan-Meier sur-

Schizophrenia

continued from page 21

fewer children than the general population.

The idea that schizophrenia is a relatively recent phenomenon, a genetic predisposition that has blossomed into disease in the industrial and postindustrial environment of the last two-and-a-half centuries, is more than a midsummer fancy. For it implies new avenues for thinking about pathophysiology of the disease, something McGlashan believes is long overdue.

"We need to start thinking about schizophrenia in ways other than dopamine metabolism," he said. "That theory has generated a lot of reasonably good treatments, but it's not getting us much further. We are spending a lot of time and money trying to tweak that system, and I think we have reached a stage of diminishing returns."

"At Issue: Is Natural Selection Rendering Schizophrenia Less Severe?" is posted at <http://schizophreniabulletin.oxfordjournals.org/cgi/content/full/32/3/428#BIB17>. ■

vival curves would allow researchers to show the comorbidity at each age because they would have the age of onset for the two disorders being studied by age.

The largest obstacle to the revised approach suggested by the paper's authors, Anthony said, is that it may require a huge boost in the sample-size requirements for epidemiological research on psychiatric comorbidity.

"Necessarily, unless the goal is to produce a stratum-specific estimate only for one to five birth cohorts, the net result of the published recommendation is to move the budget for a national comorbidity survey well beyond the scope of the currently available [National Institutes of Health] budget for such research," Anthony said.

Problems can arise over the accuracy of age of onset, particularly for disorders that have early onset and when older participants are asked about the past. Hayward maintains that the age-of-onset approach is preferable to no effort to address the problem.

Good estimates of comorbidity can also be found through longitudinal studies that follow participants over time and calculate comorbidity at any given age, with estimates varying by age.

The presence of pseudocomorbidity impacts both researchers and clinicians if disorders thought to involve shared factors or to be caused by another disorder were actually unrelated.

Misinterpreting study results to find comorbidity where there is none may lead to an entire line of research that tries to explain why the disorders are comorbid, when it's very possible they are not comorbid at all.

Pseudocomorbidity also may lead clinicians to make assumptions about the risk for developing a second disorder when little or no risk actually exists.

An abstract of "Lifetime Prevalence and Pseudocomorbidity in Psychiatric Research" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/63/6/604>. ■

BPD

continued from page 22

due to reactions to interpersonal events.

"Borderline patients are hypersensitive to any kind of rejection and other interpersonal slights," Gunderson said. "Much of their psychopathology is organized around their fears that they will be hurt or abandoned. If you pay attention to that, you are likely to find that a lot of people who are impulsive and labile are borderline, and treatment recommendations should follow from that.

"Be wary of giving patients unrealistic hopes about mood stabilizers," he continued. "It's not as if the two disorders can't ever coexist or that mood stabilizers are always bad. But it encourages optimism about recovery that is disillusioning. And when their medications multiply, then the overmedication becomes the problem. That's an unfortunate byproduct of this diagnostic inaccuracy and the temper of the times."

The study was part of the Collaborative Longitudinal Personality Disorders Study funded by the National Institute of Mental Health.

"Descriptive and Longitudinal Observations on the Relationship of Borderline Personality Disorder and Bipolar Disorder" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/7/1173>. ■

Special Sessions Designed for Residents, Young Investigators

APA's fall institute expands its scientific program with a special track of sessions on health services research. The institute will be held October 5 to 8 in New York.

BY HAROLD GOLDSTEIN, PH.D.

A special track of sessions focusing on health services research has been planned for APA's 2006 Institute on Psychiatric Services, which is being held October 5 to 8 in New York City.

Harold Goldstein, Ph.D., is director of program evaluation and special projects in APA's Division of Research and the American Psychiatric Institute for Research and Education.

The goal of the new track is to highlight the implications of recent research findings on health services for psychiatric practice, introduce psychiatry residents to the field of health services research, and update clinicians on innovative and practical approaches for improving mental health care.

The track will benefit public-sector psychiatrists and those working in systems of care. Among the offerings are two symposia, two lectures, and special programming for residents and young investigators.

The track begins on Thursday, October 5, with the symposium "Monitoring Depression Severity: Clinical Applications in Psychiatry." Presenters will update clinicians on the systematic management of depression using the nine-item Patient Health Questionnaire (PHQ-9). A simple quantitative instrument, the PHQ-9 holds significant promise for improving the treatment of depression by equipping physicians with a standardized tool for monitoring severity.

On Friday, October 6, Mark Olfson, M.D., a clinical professor of psychiatry at Columbia University, will present the lecture "Antidepressant Medication and Suicidality." He will provide a clinical update of the latest research findings on this controversial issue.

Later that day, Olfson will be one of the participants in the "Meet the Experts Luncheon," a special event for psychiatry residents only.

On Saturday, October 7, the Health Services Research Breakfast will be held. The breakfast is designed to give psychiatry residents and young investigators an opportunity to interact with senior investigators in the health services research field. The recipients of the Health Services Research Early Career Award and Senior Scholar Award will be recognized at the breakfast. Attendance at the breakfast is limited to preregistered psychiatry residents and young investigators.

Following the breakfast, the Division of Services and Intervention Research (DSIR) of the National Institute of Mental Health is sponsoring a symposium on the institute's major clinical-trial studies. Presenters will review the studies' scope, methodologies, and latest findings, with emphasis on the implications for psychiatric practice and research. These studies include the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), Sequential Treatment Alternatives to Relieve Depression (STAR*D), Treatment of Adolescents With Depression Study (TADS), and Systematic Treatment Enhancement for Bipolar Disorder (STEP-BD).

The session will be chaired by DSIR Director Philip Wang, M.D. Among the presenters are, for CATIE, Jeffrey Lieberman, M.D., chair of the Department of Psychiatry at Columbia University's College of Physicians and Surgeons; for STAR*D, A. John Rush, M.D., a professor of psychiatry at Southwestern Medical Center; for TADS, Benedetto Vitiello, chief of Child and Adolescent Treatment and Preventive Intervention Branch at DSIR; and for STEP-BD, Gary Sachs, M.D., director of the Bipolar Clinical and Research Program at Massachusetts General Hospital.

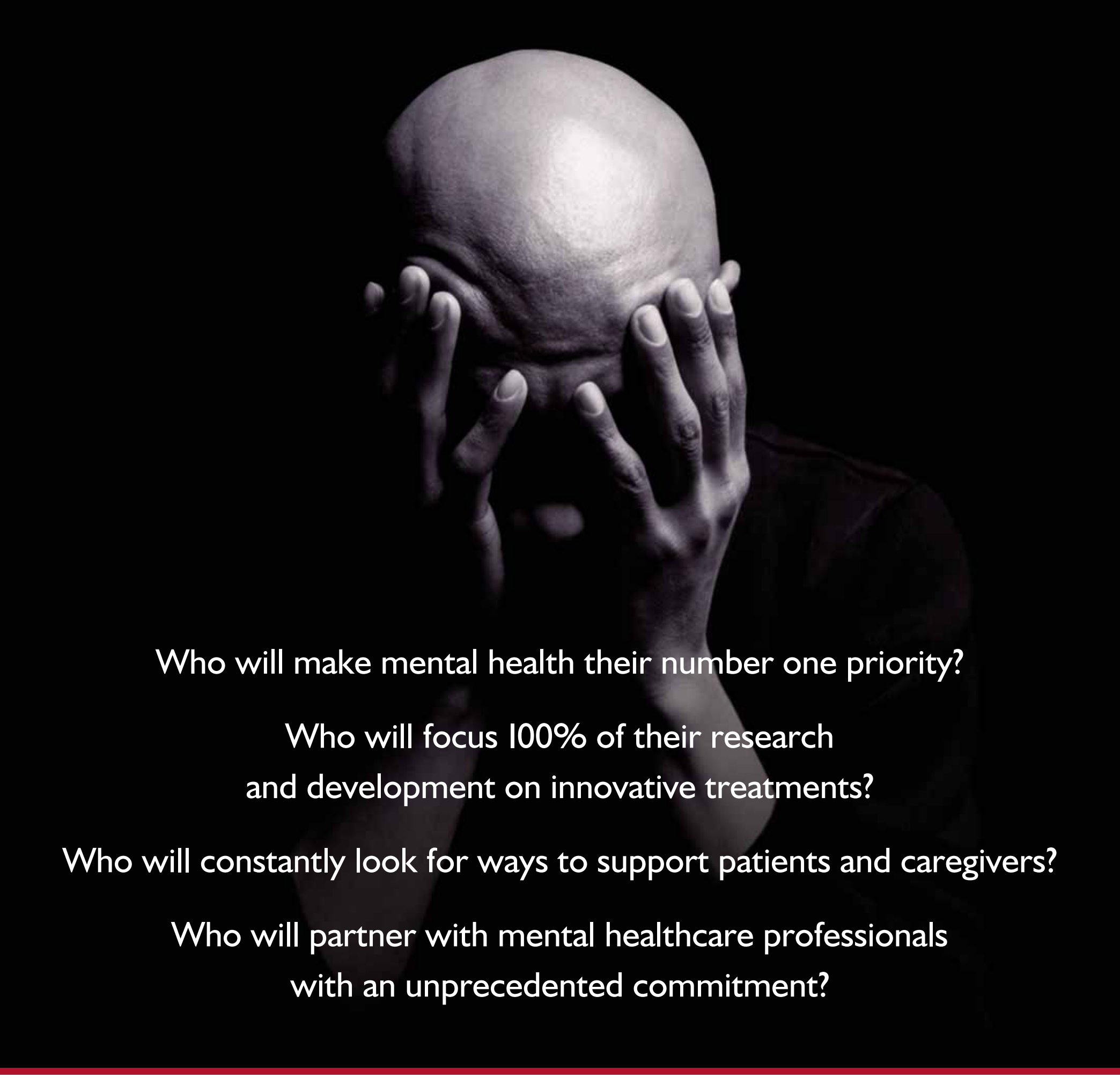
The Health Services Research Track will conclude on Sunday morning, October 8, with the lecture "Disparities in Mental Health Care: What Does Research Tell Us?," presented by Annelle Primm, M.D., M.P.H., director of APA's Office of Minority/National Affairs. She will provide an update and overview on disparities in mental health care and treatment for minority populations.

If you would like more information about the track, please contact me by phone at (703) 907-8623 or by e-mail at goharold@psych.org. ■

How to Register

- Register online for the 2006 Institute on Psychiatric Services at <www.psych.org/edu/ann_mtgs/ips/06/index.cfm>.
- Or use the registration form found in the preliminary program booklet and mail or fax the completed form to APA. The booklet can be obtained by calling (888) 357-7924.

Register before **September 7** and save on fees. A discounted fee is available for residents; medical students attend free.



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Psychiatrists Show Creativity In Annual Art Exhibit

The 37th APA Art Exhibit gives annual meeting goers a glimpse into the psyches and creative talents of their colleagues.

BY WILLIAM ALVAREZ, M.D.

The setting for the APA Art Association exhibit at APA's 2006 annual meeting in Toronto was as close to ideal as one can get: centrally located and conspicuously eye-catching. The artist-exhibitiors lovingly nurtured their displayed art work and were available to share their insights with the people who inquired about the "meaning" of these creative endeavors.

This year's entries evoked an incredibly wide spectrum of media and expression. Especially dazzling was the vibrancy and variety of everyday life depicted in paintings, photographs, poems, and sculptures. The pieces moved freely from the humorous and secular to holy icons, from a dignified, jewel-like radiance to depiction of hostility.

They were an inspiration on the ordinary stuff of American culture, the discovery of how art, science, and the wonders of technology have structured human perception. We may have values, knowledge, and even wealth, yet there is something missing. It could be that woman, the most passionate I have ever known. . . .40 years ago, or that grant that was denied because of my height, or my sexual fantasies. May I urge my colleagues to shed that cumbersome, protective armor that often surrounds us and keeps us from expressing our passions and rush to join the APA Art Association.

All APA members are eligible to join, as are their spouses and partners. Members of the APA staff are also invited to join. To join or learn more about the association, contact the new president of the APA Art Association, Gail Barton, M.D., M.P.H. She can be reached by mail at 29 Main Street, Windsor, Vt. 05089 or e-mail at gbarton@vermontel.net. ■

David Hathcox

Exhibit coordinator Sonia Pawluczyk, M.D., shares the finer points of her prize-winning entry in the color photography category, "Patagonian Globalization."

David Hathcox

Gail Barton, M.D., the new president of the APA Art Association (center), is flanked by Philip Margolis, M.D., and his wife, Nancy Margolis.

Exhibit Winners

Computer Art
- First: "Anachronous Dimension," Thomas Capuccio

Fiber—Basketry
- First: "Bread Basket," Gail Barton, M.D.

Graphics
- First: Deep in Thoughts," Wilma Rosen, M.D.
- Second: "The End of Summer Bouquet," Gail Barton, M.D.
- Third: "Mental Health Care: What a Zoo!" Carl Segal, M.D.

Painting—Mixed
- First: "This, My Village, Might Offer Some Love," William Alvarez, M.D.
- Second: "Four Villages Where One Won't Find Love," William Alvarez, M.D.
- Third: "Untitled #5," Bohdan Sirant

Painting—Oil
- First: "Betty," Wilma Rosen, M.D.
- Second: "Forest and Mountain View," Ellen Ugur

Painting—Waterbased
- First: "I Cor 15:22," Margot Fass, M.D.
- Second: "Job 14:10," Margot Fass, M.D.
- Third: "Docked Boats," Aydogan Ugur, M.D.

Photography—Color
- First: "Patagonian Globalization," Sonia Pawluczyk, M.D.
- Second: "Western Temples," Robert Feder, M.D.
- Third: "Church and State—Bogota Style," Robert Feder, M.D.

Poetry
- First: "McCach's Poesils," William Alvarez, M.D.
- Second: "I Cor 13:12," Margot Fass, M.D.
- Third: "Spring," Aydogan Ugur, M.D.

Best of Show
- "Patagonian Globalization," Sonia Pawluczyk, M.D.

Other
- First: "Cindy's Front Garden," Gail Barton, M.D.
- Second: "Heritage Days Clothier," Gail Barton, M.D.
- Third: "Mathew 23:33," Margot Fass, M.D.

Special awards were given to the exhibit's coordinator, Sonia Pawluczyk, M.D., and to the APA Art Association's treasurer, Linda Logsdon, M.D., in recognition of their outstanding service to the APA Art Association.

Reports

continued from page 4

tations given in 2002 and 2003 at meetings of the American Heart Association, International AIDS Conference, American Society of Clinical Oncology, Society for Neuroscience, and Radiological Society of North America.

The news stories often omitted basic facts about the studies, they said. About one-third didn't mention the study size, for instance, and more than half failed to state the study design or were so unclear that even clinical trials experts could not say what they were. About 40 percent of the stories failed to quantify results, and while 21 percent quantified the main result, they used only relative change without a base number or rate. Two-thirds presented only interim outcome measures (like blood pressure or tumor size) rather than patient outcomes. Only a minority made any mention of study cautions, like side effects or other risks, small study size, or the possible lack of applicability of animal studies to human beings.

The preliminary nature of meeting reports was rarely noted, said Woloshin and Schwartz. In fact, 173 of the 187 stories failed to state that the findings were unpublished, had not gone through peer review, or might change as the study continued.

Aside from having fewer such stories, all parties could take steps to improve coverage of meeting reports, said the authors. Researchers could include appropriate caveats in their presentations and in interviews. Meeting organizers could do the same with their press releases, as well as including data tables and absolute risks of outcomes. Presenters and organizers could both indicate the preliminary nature of the work and the need to wait for peer review. Reporters and editors should be aware of these trouble spots, too, and press for more detail when it is needed and write with more circumspection.

Of course, not all early research reports present findings that turn out to be inaccurate as the research continues or as study data undergo more analysis.

"Often they let people know about negative trials," she said. "However, physicians should approach preliminary news reports with skepticism. Often, it's better to wait until we see more data."

Physicians should also steel themselves for the all-too-common moments when patients arrive waving news clippings based on research not yet peer reviewed, added Schwitzer. Doctors need to point out that such stories are reporting on findings that are still preliminary and that evidence for benefits or side effects isn't all in yet, he said.

Researchers, journalists, and clinicians should all understand basic aspects of study design to avoid misconstruing results. Studies and the news stories based on them should make clear the strength of the evidence presented, its relation to prior work, and its relevance for readers. Reports of intervention studies should note both clinical benefits and downsides, and possible alternative treatments.

Providing that information should go a long way toward more accurate and more useful coverage of medical meetings, said the authors.

"Media Reporting on Research Presented at Scientific Meetings: More Caution Needed" is posted at <www.mja.com.au/public/issues/184_11_050606/wol10024_fm.html>. "Health News Review" is posted at <www.healthnewsreview.org>. ■

There are almost 4,000,000 children with ADHD in the U.S.[1*] Can you meet the needs of this one?

ADHD is a widespread and complex disorder. This patient, like all patients with ADHD, presents with a unique set of symptoms and circumstances and has a unique response to any given treatment.

In order for physicians to better manage the needs of individual patients, research needs to bring more treatment options to clinical practice. When physicians can more closely tailor therapy to individual needs and responses, they will be able to manage the array of symptoms associated with ADHD more effectively. This helps more patients achieve better outcomes.

At Cephalon, we're working hard to help physicians help this child—and 3,999,999 others.

*Children and adolescents, ages 3-17 years.

Reference: 1. Dey AN, Bloom B. Summary health statistics for U.S. children: National Health Interview Survey, 2003. National Center for Health Statistics. 2005. *Vital Health Stat 10*. (223):4.

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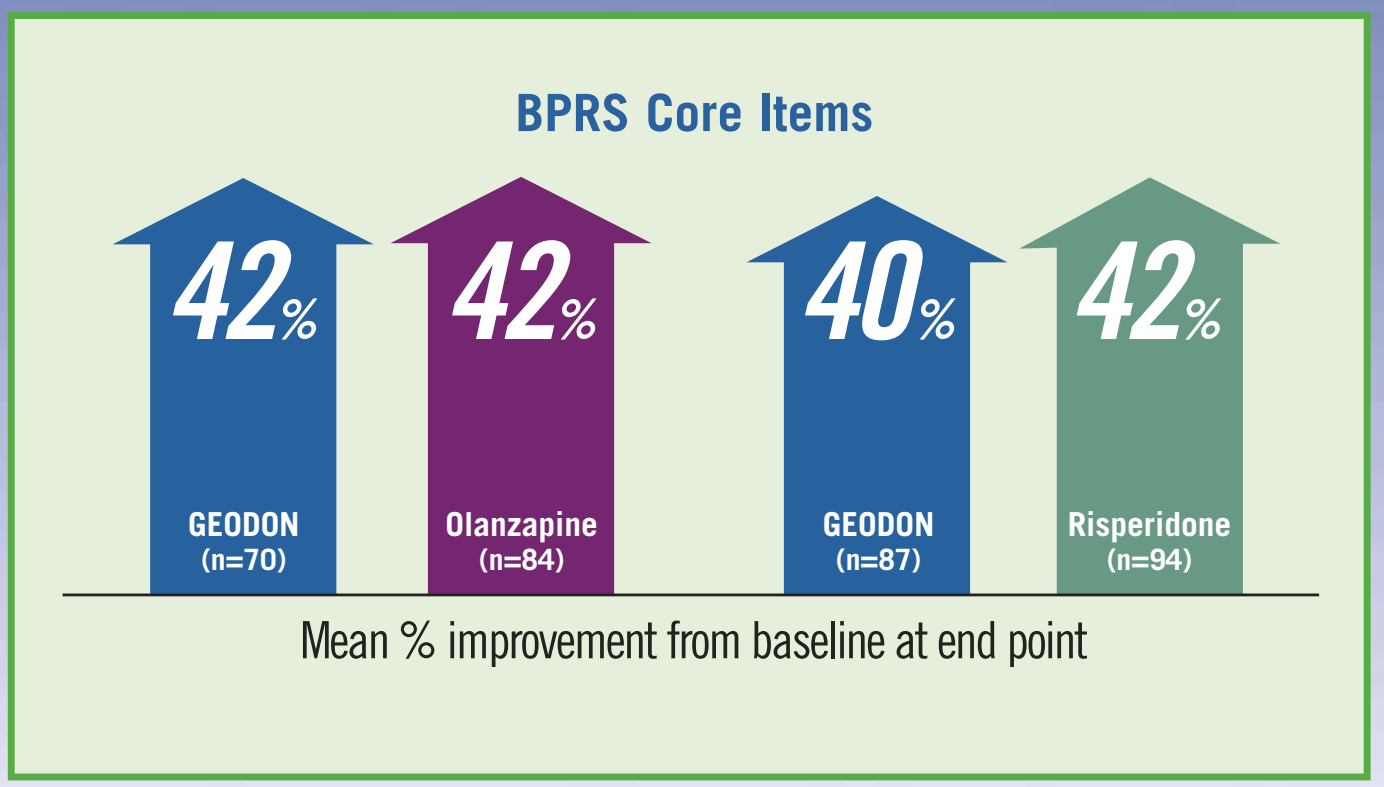
Consistent results in head-to-head studies[1-3]



A 6-week, double-blind, randomized study of GEODON vs olanzapine and an 8-week, double-blind, randomized study of GEODON vs risperidone.

- BPRS core items include hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness
- Comparable efficacy was maintained in double-blind extension studies
  —up to 1 year vs risperidone[1]
  —up to 6 months vs olanzapine[4]

GEODON is indicated for the treatment of schizophrenia and of acute manic or mixed episodes associated with bipolar disorder.

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

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_C interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

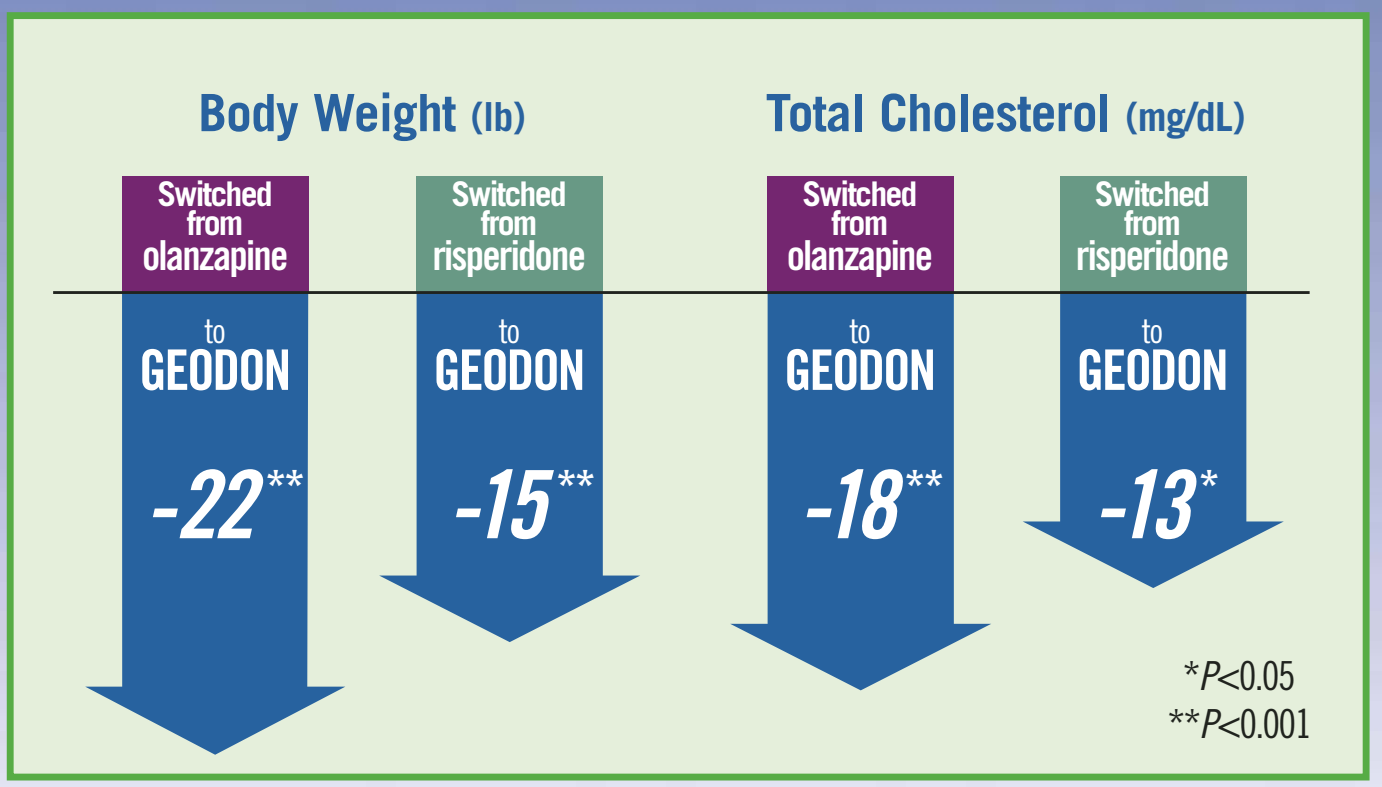
Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

In short-term schizophrenia trials, 10% of GEODON-treated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo. In the same short-term trials, the most common adverse events were somnolence (14%) and respiratory tract infection (8%).

with the body in mind

WITHOUT COMPROMISING METABOLIC PARAMETERS

Significant results in switch studies[1,5]



Two 1-year open-label extensions of 6-week, open-label switch studies in patients suboptimally controlled due to partial response or poor tolerability.

- Patients switching to GEODON from olanzapine and risperidone also experienced reductions in triglycerides[5]

In the acute head-to-head studies...

- In the GEODON vs olanzapine study, olanzapine significantly increased body weight (8 lb vs 2 lb for GEODON, $P<0.0001$)[1,2]
- In the GEODON vs risperidone study, risperidone increased body weight (2 lb vs 0 lb for GEODON, $P<0.01$)[1,3]

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Please see brief summary of prescribing information on adjacent page.

Pfizer NEUROSCIENCE

Focus on Evidence

Thank you for reporting on the results of a survey concerning the California Medicaid program in the March 17 article "Antipsychotic Polypharmacy: Value for Money?" The survey found that antipsychotic polypharmacy costs three times as much as monotherapy.

The scope of the polypharmacy problem is widespread especially in state psychiatric facilities. Even though cost is an important aspect of management in this era of managed care, experience has shown that doctors are usually defensive about their prescribing practices when the challenge is based on cost.

Considering that a significant number of patients in state psychiatric facilities may be treatment resistant, global condemnation of antipsychotic combination may be misdirected. While regular audit and individual comparison with anonymous peers is critical to monitor practices as compared with existing standards, it must be coupled with regular educational programs.

Unlike the broad-based programs that were found to be ineffective by some of the hospitals featured in the article, however, effective educational programs must be specifically focused on evidence-based prescribing practices. Such programs must also include evidence-based practical algorithms in cases in which rational combination is justified. For example, augmentation might be necessary under these conditions: when a patient fails to respond to adequate antipsychotic trials, especially with clozapine; in some instances of failed cross-taper of antipsychotics; and the addition of a first-generation antipsychotic to a second-generation antipsychotic when a patient is experiencing agitation during acute treatment of psychosis.

BABATUNDE ADETUNJI, M.D.
Philadelphia, Pa.

Faulty Logic

I find it ridiculously funny that the collective wisdom of seven psychiatrists from the United States and Canada is to stop using bags with drug company logos because it offends some people.

The idea that our professional integrity and public image are somehow tarnished by carrying a bag with a Pfizer or GSK logo on, as expressed in the letter titled "Bring Your Own Bag" in the April 21 issue, is overblown. (Though I must say something does occur: At APA's 2005 annual meeting, a passerby on the street said to me, "Hey doc, can't you afford a Neiman-Marcus bag?")

I imagine some people will buy into the faulty logic that because I have pens and bags with drug names on them, I'm a pawn of the pharmaceutical industry and/or endorse the escalating cost of health care. By that line of thinking, I should stop wearing my San Francisco Giants baseball cap least someone think I endorse anabolic steroid use in sports.

To my well-meaning colleagues who can't bring themselves to participate in a free-market society, I suggest giving your bags imprinted with drug company logos to poor school kids. That is what I do.

ETHAN KASS, D.O., M.B.A.
Coral Springs, Fla.

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.

Compromised Care

I am writing in response to the president's column in the May 5 issue titled "How Will Psychologists Practicing Medicine Affect Psychiatry?"

While I applaud Dr. Steven Sharfstein's acknowledgement that "prescriptive authority" is the practice of medicine, I have a different view and a different answer to his rhetorical question.

First, the campaign is for parity. The mislabeled prescription bills authorize state boards of psychology to define, license, and grow a practice of medicine for psychologists. Psychologists in California and elsewhere have also initiated legislation, regulation, and litigation to expand independent authority to manage medical care for people at the office, in hospitals, and in jails and prisons. The recent manifesto by Division V of the California Psychological Association specifically identifies medical, economic, and career parity with psychiatrists as the campaign goal (see <division55.org/Pages/RxPBenefitsAll.htm>).

Second, this is a public policy debate, not an argument with psychologists. Here is the issue: Shall there be a separate, second-class standard for the medical care of people with mental illness?

Third, economics will determine the consequence, not quality. If legislatures permit two standards of care, institutional buyers—governments and healthcare plans—will go for the cheaper standard. Medical education will be priced out of the mental health care market.

Fourth, it's about the future. Medicalized psychologists will replace, not add to, the psychiatric workforce. Future mental health providers will take the less expensive, more lucrative career path. Future medical students will seek careers that value fundamental medical education. Mental, like dental, will be referred out of medical curricula and medical practices.

please see ***Letters*** *on facing page*

Treatment

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treatment are lacking or there are no programs available in the community.

For treatment to be successful, treatment providers and criminal justice supervisors must work together closely to ensure that treatment plans meet correctional-supervision requirements and the inmate's needs. For instance, the report states, "abstinence requirements may necessitate a rapid clinical response such as more counseling, a targeted intervention, or increased medication to prevent relapse. Ongoing coordination between treatment providers and courts or parole and probation officers is important in addressing the complex needs of these re-entering individuals."

In addition, the report acknowledges that many inmates with substance abuse problems also have comorbid mental disorders and recommends that inmates with either a substance abuse or other mental disorder be assessed for the presence of the other and treated appropriately.

Treatment adherence can sometimes be problematic for inmates with drug problems so implementing a system of rewards can motivate them to continue with treatment, according to the report.

Said Volkow, "We tend to do things that are positively reinforced. These reinforcements don't have to be large—even a ticket to the movies can have an impact."

Volkow recalled visiting a drug court in Pennsylvania where the presiding judge acknowledged the success of offenders who had been participating in substance abuse treatment programs. "Everyone, including the treatment providers who were present, applauded," she noted, and some of the inmates who received the recognition were moved to tears.

"One of the most powerful reinforcers of humans is acceptance by a group," she observed.

"Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide" is posted at <www.nida.nih.gov/drugpages/cj.html>. There is also a companion guide for inmates who are addicted to drugs and their families. ■

Errors

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The report also recommends studies to evaluate the impact of free drug samples on overall medication safety.

Responding to the report, APA immediate past President Steven Sharfstein, M.D., emphasized the importance of the physician's relationship with patients in the reduction of medication errors.

"I do believe that health care organizations, including hospitals, should inform patients of all errors, including medication errors, even if there is no harm," he said. "It is important that patients and families are part of a safety-first culture, and patient-family education is very high on the priority list these days. Including patients and families in the formation of a treatment plan is increasingly seen as critical to its success."

Al Herzog, M.D., chair of APA's Patient Safety Committee, told *Psychiatric News* that studies of errors across medical specialties suggest psychiatry is not different from other areas of medicine.

"Serious errors that cause true patient harm happen when treating patients with multiple diagnoses and involve matters such as wrong dose and wrong medicine with medications whose names look and sound alike," he said. "Insulin and coumadin orders on inpatient units present special challenges because of the close relationship between dose and effect. Arrhythmias with some of the antipsychotics and older antidepressants also need to be watched."

Herzog emphasized especially that a "systems analysis" perspective on errors—which regards medication and other medical errors as occurring in the context of a system of care—should replace the current adversarial approach to blaming individual physicians.

"I can't overestimate the importance of looking at this as a system issue rather than 'you are a bad doctor/nurse' issue," he said. "Hopefully, all of us are taking a time-out when a mistake is made to learn from our root-cause analyses. The IOM report makes that point over and over again."

The IOM study was sponsored by the U.S. Department of Health and Human Services and Centers for Medicare and Medicaid Services. Established in 1970 under the charter of the National Academy of Sciences, the Institute of Medicine provides independent, objective, evidence-based advice to policymakers, health professionals, the private sector, and the public.

A prepublication copy of "Preventing Medication Errors" is available from the National Academies Press by phone at (202) 334-3313 or (800) 624-6242 or online at <www.nap.edu>. ■

Freud

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experience to Lisa Mellman, M.D., a senior associate dean for student affairs at Columbia University College of Physicians and Surgeons. She reminded him that "although we are trained in psychodynamic teaching to recognize transference, transference is ubiquitous, and your patients will engage in it regardless of the specialty you choose to practice."

Mind-Body Link Still Crucial

A third Freudian concept that American psychiatrists today tend to consider crucial for their work is the mind-body relationship.

"The mind-body dilemma—psychiatry remains preoccupied with the issue, and so did Freud 100 and some years ago," Steven Levy, M.D., vice chair of psychiatry at Emory University, said.

"Freud's early studies on hysteria were very rich accounts of how emotional conflicts can influence bodily processes," said Pally. "So while I might not see patients suffering from the same bodily symptoms that Freud did, like psychogenic blindness or paralysis, I can see that conflicts can lead to digestive problems, headaches, and what have you."

In fact, an experience Pally had with one patient illustrates how helping patients divest themselves of unconscious conflicts can also relieve them of bodily symptoms. The patient, "Leila," had not been able to grieve fully the loss of her mother early in childhood, but eventually, with psychotherapy, Pally helped her do so. And after that, Leila told Pally about the disappearance of a skin problem she long had had. "Yes, just like that," said Pally, "even though we really hadn't talked about it."

Indeed, numerous other Freudian concepts are still resonating with American psychiatrists today as well—for example, countertransference; projection; dream interpretation and free association unmasking unconscious conflicts; the influence of early experiences on lifelong patterns of behavior; and the impact of fantasy, both normal and pathological, on mental life.

Freud and the Future

Just as American psychiatrists are apt to concur that a number of Freud's concepts are still swaying analysis, psychodynamic psychotherapy, and psychiatry in general, they also tend to concur that his ideas will continue to pervade these fields.

"Certainly, Freud's concepts will continue to have a dominant influence on psychiatry during the next few years," Robert Michels, M.D., a university professor of medicine and psychiatry at Cornell University, predicted.

"Oh yes, Freud will continue to have a prominent influence," Gabbard added, "because he basically tells us that if we sit with [people] long enough and listen to them, they will start to reveal some of the conflicts that cause misery in their lives."

"I think Freud will be there for the foreseeable future, unless our genome changes!" Blum asserted. "This is part of the way we are, we have an unconscious mind as well as a capacity for consciousness and self-reflection."

Yet, "as people understand more about the mind, cognition, experience, affect, attachment, all of those things that are psychoanalytic. . . ," Walker predicted, "I think we will understand Freud's ideas in different ways and more sophisticated ways." ■

Poverty

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but you also have to establish connections with people who have the decision-making power. So Ricardo and I were really working both of those issues—doing the study to generate the scientific evidence, but also working with people in the ministry of health to develop relationships there, to make it happen."

And it did. The program is now being implemented in the Chilean public primary-care system, which serves about a third of the Chilean population, Simon said.

Flush with victory, Simon, Araya, and their colleagues are asking: Might the same program also prove to be clinically effective in Chile's privately funded health care sector? "We're trying to get some funding to find out," he said.

Finally, might the same program also benefit depressed women in other Latin American countries? Simon, Araya, and their team would like to determine that as well.

An abstract of "Treating Depression in Primary Care in Low-Income Women in Santiago, Chile: A Randomized Controlled Trial" is posted at <www.thelancet.com/journals/lancet/article/PIIS0140673603128255/abstract>. "Cost-Effectiveness of a Primary Care Treatment Program for Depression in Low-Income Women in Chile" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/8/1362>. ■

letters to the editor

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Answer: The ultimate mental health carveout—bad for psychiatry, disaster for people with mental illness.

RONALD C. THURSTON, M.D.
Chair, California Psychiatric
Political Action Committee

What Happened To Ethics?

I am writing this letter after much thought and anguish. The last straw was the recent news reported in the *New York Times* that a senior scientist was found to have sold his laboratory's CSF fluid samples to a drug company for profit.

Hippocrates must be turning over in his grave over the state of affairs of medicine in all specialties. I am sure there are honest physicians, but many appear to be in the silent majority.

Physicians are doing procedures with no regard for indication, treatments are recommended without adequate consideration of alternatives, and the lecture circuit is getting crowded by people who call themselves "experts." In psychiatry, I encounter such problems as overmedication, inadequate time for evaluation, quick med checks with no regard for outcome, and administration of ECT on even the most demented elderly with the hope it will keep them well. A new option—the vagus nerve stimulation system—and another one expected to be approved soon—transcranial magnetic stimulation—will probably be overused as well.

Where is the limit? What happened to medical ethics and the Hippocratic Oath? I am sure I will encounter the wrath of my colleagues as I raise these questions, but I am willing to accept the consequences. Having resigned from managed care panels and Medicare, I am free as a bird doing the work I enjoy, albeit with meager remuneration since fees figured on a sliding-scale basis have been declining along with the economy.

There are many reasons for the trends I described, and most important is the financial crunch created by managed care organizations and physicians who want to make the most money in the least amount of time. Procedures come in handy to boost income. The patient's psyche gets scant attention, and sometimes patients are advised to seek therapy elsewhere. This is a sad situation, but I have hope it can be rectified if enough physicians speak up.

SREENIVASA R. DESAI, M.D.
Binghamton, N.Y.

Mentally Ill

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to people living outside the shelters."

"Sad to say, people with mental illness are far down on the totem pole in the best of times, but they are even farther down in the worst of times," said Ron Honberg, J.D., legal director of the National Alliance on Mental Illness (NAMI). "Denying access to shelter to persons with psychiatric disabilities is almost like sentencing them to death."

These inadequacies were visible right after Katrina, said Honberg. Two weeks after the storm, NAMI sent a letter to the acting director of the Federal Emergency Management Agency (FEMA) asking for expansion of the agency's crisis counseling program to include help for persons with serious mental illness, both preexisting and triggered by the hurricane.

The lack of preparation affected even the most routine aspects of evacuation. A police officer's knock on the door could be easily misinterpreted by a mentally ill person if it raised the image of an earlier involuntary commitment episode.

Longer-term relief measures raised new problems, said the report. FEMA forms or applications for housing were often difficult to fill out with assistance. Untrained FEMA representatives often denied housing to persons with psychiatric disabilities after incorrectly assessing their disabilities. FEMA or the Stafford Act may cover short-term mental health services but were not designed for people who might remain displaced for months or years.

"FEMA mental health resources were designed only for 'normal reactions to abnormal situations,' but not for people with serious mental illnesses separated from their own services," said Honberg.

In its report, the National Council on Disability urged a range of policy changes at all levels of government. Relief services like FEMA housing, HUD housing waivers, and Medicaid coverage should continue for at least two years after a disaster, argued the report. Medicaid mental health services should include conditions worsened by the disasters as well as caused by them. Federal agencies such as the departments of Homeland Security (the parent of FEMA) and Health and Human Services should adopt policies and regulations that reflect the requirements of the Americans With Disabilities Act and Section 504 of the Rehabilitation Act to provide relief services that don't discriminate against those with mental illness. State and local officials should rethink evacuation procedures, select one person to be responsible for disaster disability questions, and simplify procedures to allow out-of-state health professionals to work during an emergency. Trained peer advocates should be allowed to provide counseling under the Crisis Counseling Assistance and Training Program. The American Red Cross should train its personnel to better identify and work with people with psychiatric disabilities. Finally, the report urged that people with disabilities be included in planning for disasters and allowed to participate in relief and recovery efforts.

Thus far, many localities have been incorporating similar recommendations for handling people with disabilities, but not many have yet included people with psychiatric disabilities, said Carroll.

"All of us should have been better prepared," said NAMI's Honberg. "Now we are less interested in making accusations and more interested in learning the lessons, correcting the problems, and making sure it doesn't happen again."

"The report should be viewed as a beginning of a healthy dialogue," said David Post, M.D., medical director of the Capital Area Human Services District in Baton Rouge, La., in an interview. "Certainly there are many lessons to be learned, especially that we all should be mindful of the specific needs of those with disability."

"The Needs of People With Psychiatric Disabilities During and After Hurricanes Katrina and Rita" is posted at <www.ncd.gov/newsroom/publications/2006/peopleneeds.htm>. ■

Yates

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discussion about serious mental illness and criminal responsibility generated by the first trial and its outcome may have influenced the verdict in the second.

"It's rare that public opinion directly shapes the outcome of a criminal trial," he told *Psychiatric News*. "But I think this was one of those cases. After the first trial, in which a jury was so horrified by the crime that they gave short shrift to Yates' insanity plea, there was a tremendous public outcry and discussion of the issues. This included extensive discussion of the nature of postpartum psychiatric disorders, and of their potential impact on criminal responsibility, even in states like Texas with narrow insanity standards. And the general view in the media was that an injustice had been done.

Appelbaum also emphasized that the insanity plea, contrary to what many among the public are reported to believe, is very rare. "The best study of the use of the insanity defense was done by Henry Steadman and colleagues in the 1980s," he said. "They showed that the defense was considered in under 1 percent of felony cases, successful in only about one-quarter of those cases, and its success usually due to all parties—prosecution and defense—agreeing to an uncontested insanity plea."

APA did not issue an official statement following last month's not-guilty verdict. But during the first trial, the Association issued a press release saying it hoped the Yates case would lead to broad public discussion about the treatment of severely mentally ill individuals in the legal system.

"Advances in neuroscience have dramatically increased our understanding of how brain function is altered by mental illness and how psychotic illness can distort reality in very subtle ways, to the degree that black becomes white," APA stated at the time of the first trial. "Research also has led to development of more effective treatments. Unfortunately, public understanding has not kept pace with these advances.

"A failure to appreciate the impact of mental illness on thought and behavior often lies behind decisions to convict and punish persons with mental disorders. The victims of mental illness are sick—just as sick as if they had cancer or chronic heart failure—and, as human beings, deserve humane and effective treatment for their illness. Prisons are overloaded with mentally ill prisoners, most of whom do not receive adequate treatment.

"Defendants whose crimes derive from their mental illness should be sent to a hospital and treated—not cast into a prison, much less onto death row," APA said. ■

Citizenship

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"Requiring paperwork for people who are seriously and persistently mentally ill is not very realistic," said Lizbet Boroughs, deputy director of APA's Department of Government Relations. "Someone who has been in and out of homeless shelters for years probably does not have a driver's license, has long since lost his Social Security card, and I'm sure is not walking around with a copy of his high school diploma."

Among the categories of beneficiaries with which mental health advocates are most concerned are foster children, who are generally eligible for Medicaid and have high rates of both medical and mental health problems but have difficulty documenting citizenship. Others at risk of losing their benefits are applicants who are found eligible for the Social Security Disability Income or Medicare programs, but who are still in the waiting period for those programs.

The regulations require states to help applicants with an "incapacity of mind or body" to locate citizenship documents when applicants cannot comply quickly and lack a representative to assist them. Such individuals include those who have amnesia, mental illness, or physical incapacity.

According to CMS, states also can document citizenship and identity through data matches with state-government agencies, such as with school records, to establish the identity of children. If documentation is unavailable, CMS may accept signed affidavits from two citizens—one of whom cannot be related to the applicant—who "have specific knowledge" of a beneficiary's citizenship status.

The agency noted that current beneficiaries should not lose benefits while making "a good-faith effort to provide documentation to the state."

APA has urged modifications of the rule through its partnership with the Campaign for Mental Health Reform. In a letter in May to CMS, the campaign urged the agency to allow "a broad list of other documents that may be used to demonstrate citizenship, particularly those accepted by other federal agencies, including the Social Security Administration and the Department of Justice."

William Emmet, interim director of the campaign, said CMS's decision to give states some discretion in determining which applicants meet the proof-of-citizenship standard was a positive step and that he hoped for similar latitude in the agency's final rules.

"Our concern all along was that people with mental illnesses and other disabilities—people who are aged and infirmed with mental illness, for example—are the most at risk, but the feds have left the door open for the states to provide the kinds of assistance that those folks may need," Emmet told *Psychiatric News*.

> **"It is critically important that remedial action occurs quickly. . . so that Medicaid beneficiaries don't lose their health lifeline."**

APA also is coordinating with the bipartisan National Governors Asssociation, which is engaging in talks with federal officials responsible for implementing the law.

Opponents of the documentation requirements have filed a class-action lawsuit challenging the change from previous requirements.

"It is critically important that remedial action occurs quickly, either by the Congress repealing the law or the federal district court enjoining it, so that Medicaid beneficiaries don't lose their health lifeline," said Ron Pollack, executive director of Families USA, which is assisting with the lawsuit.

Opponents of the requirement estimate that approximately 3 million to 5 million low-income people may lose their Medicaid benefits because they are unable to produce the required documents. Hospitals are still required to provide emergency care regardless of whether individuals meet the documentation requirement.

The CMS letter is posted at <www.familiesusa.org/assets/pdfs/Fact-Sheet-Citizenship.pdf>. The proof-of-citizenship requirements are posted at <www.cms.hhs.gov/MedicaidEligibility/05_ProofofCitizenship.asp#TopOfPage>. ■

Job Bank Web Site Launches New Features

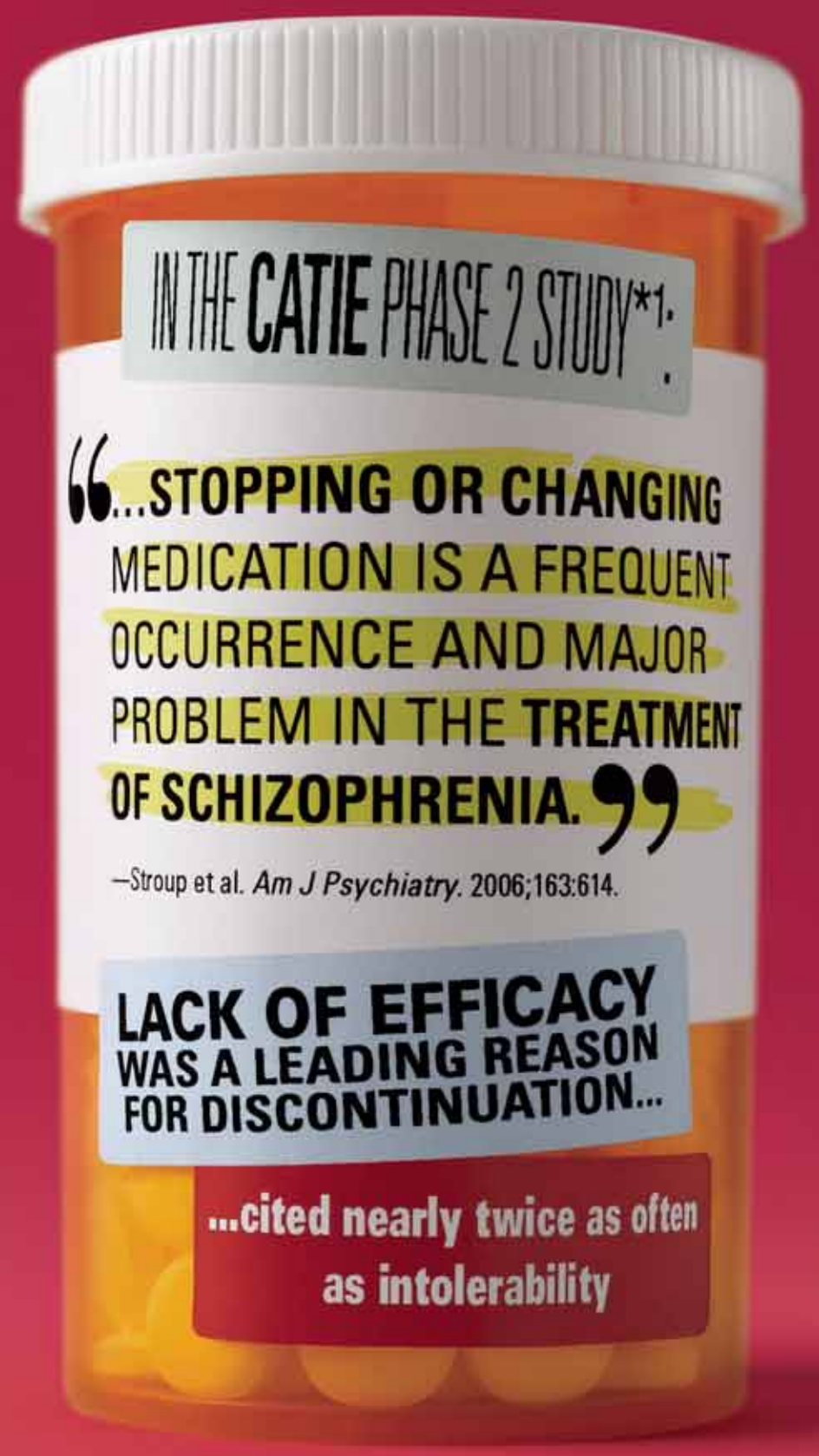
APA's online Job Bank, accessible at <www.psych.org/jobbank>, has launched several helpful new features for job seekers that will improve job-search efficiency and quality with state-of-the-art tools and technology. All features are free to job seekers and easy to use with simple instructions and templates.

The site has a new design and is easier to use. The registration process has been streamlined, allowing job seekers to register quickly with minimal information. The Job Search and Conference Connection features have also been streamlined and are intuitive to users.

In addition to the new site design, users will appreciate a new tool—"Résumé Builder"—that can be used to create a professional résumé or upload an existing professional résumé in Microsoft Word or Adobe PDF format while maintaining its formatting. "Résumé Builder" offers a variety of design and formatting options, including the ability to customize fonts and color schemes. While "Résumé Builder" recommends sections to be included in a professional résumé, job seekers have the flexibility to select the specific sections they wish to include, reorder sections, and add information. Additionally, job seekers can save multiple résumés, as well as choose which versions to make searchable by employers and to post on personal Web sites.

Perhaps the most exciting enhancement is the new "My Site" feature, which allows job seekers to build a personalized, password-protected Web site with a unique URL. Job seekers can create a homepage for their site and have the option to upload a personal photograph or other image. The "Site Materials" section allows users to upload or link to articles they have written or published. References can be entered on the site, and job seekers can post their résumé on their site as well. Finally, job seekers will have the option of branding their site to indicate that they are an APA member. ■

In a schizophrenia trial measuring time to all-cause discontinuation...



EFFICACY MATTERS

For many patients in the treatment of schizophrenia

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RISPERDAL is indicated for the treatment of schizophrenia.

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

Commonly observed events: In short-term trials, the most commonly observed adverse events associated with RISPERDAL at an incidence of ≥5% and at least 2x placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Hyperglycemia and diabetes: Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS), including RISPERDAL. Patients starting treatment with APS who have or are at risk for diabetes, should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Tardive dyskinesia (TD): As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD; if its signs and symptoms appear, discontinuation of RISPERDAL should be considered. Elderly patients appeared to be at increased risk for TD.

Neuroleptic malignant syndrome (NMS): NMS has been reported rarely with this class of medications, including RISPERDAL and appropriate management should be employed.

DELIVERS

of RISPERDAL—

- Proven symptom control in schizophrenia[†2]
  - —More than 12 years of experience[3]

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tablets and
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Cerebrovascular adverse events (CAEs): CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking risperidone in clinical trials. The incidence of CAEs with risperidone was significantly higher than with placebo. RISPERDAL is not approved for treating these patients.

Please see brief summary of full Prescribing Information, including Boxed Warning, on adjacent page.

Visit our Web site at risperdal.com

*Subjects with schizophrenia (N=444) who had discontinued the atypical antipsychotic randomly assigned during phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigation were randomly reassigned to double-blind treatment with a different antipsychotic (olanzapine, 7.5–30 mg/day [N=66]; quetiapine, 200–800 mg/day [N=63]; risperidone, 1.5–6.0 mg/day [N= 69]; or ziprasidone, 40–160 mg/day [N= 135]). Identical capsules (risperidone, 1.5 mg qd or bid; olanzapine, 7.5 mg qd or bid; quetiapine, 200 mg bid; ziprasidone, 40 mg bid) were flexibly dosed (within 1 to 4 capsules daily) on the basis of the study doctor's judgment. Patients were assigned to a treatment they had not received in phase 1. This phase 2 study was recommended to patients who poorly tolerated treatment in phase 1, but also included individuals who 1) discontinued previous treatment in phase 1 because of inefficacy and who did not want to consider treatment with clozapine, and 2) discontinued their previous treatment independently of their doctor's recommendation. The primary aim was to determine if there were differences among the four treatments in effectiveness, as measured by time until discontinuation for any reason.

†Demonstrated in two 8-week, randomized, double-blind, placebo-controlled trials comparing the efficacy and safety of risperidone and haloperidol in patients with schizophrenia (N=513). Patients were randomly assigned to 1 of 6 fixed-dose, parallel-treatment groups: 2, 6, 10, or 16 mg/day of risperidone, 20 mg/day of haloperidol, or placebo. The study was not powered to show a difference between RISPERDAL and haloperidol.

References: 1. Stroup TS, Lieberman JA, McEvoy JP, et al, for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry.* 2006;163:611–622. **2.** Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry.* 1997;58:538–546. **3.** FDA approval 1993.

 August 2006 01RS1845T

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Janssen L.P.

RISPERDAL®
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RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

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

INDICATIONS AND USAGE: RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia. **Monotherapy:** RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder. **Combination Therapy:** The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.
CONTRAINDICATIONS: RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.
WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning). Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome. **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis:** Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.
PRECAUTIONS: General: Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION in full PI). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication. **Seizures:** RISPERDAL® should be used cautiously in patients with a history of seizures. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely. **Priapism:** Rare cases of priapism have been reported. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown. **Antiemetic Effect:** Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. **Use in Patients With Concomitant Illness:** Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Increased plasma concentrations of risperidone and 9–hydroxyrisperidone occur in patients with severe renal impairment, and in patients with severe hepatic impairment. A lower starting dose should be used in such patients. **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®: **Phenylketonurics:** Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine. **Drug Interactions:** The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Carbamazepine and Other Enzyme Inducers:** In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9–hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. **Fluoxetine and Paroxetine:** Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9–hydroxyrisperidone have not been studied. **Lithium:** Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone. **Digoxin:** RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Drugs That Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9–hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY in full PI). Drug interactions that reduce the metabolism of risperidone to 9–hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9–hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≈70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. *In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY in full PI). **Drugs Metabolized by CYP 2D6:** *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. These findings are considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia). **Mutagenesis:** No evidence of mutagenic potential for risperidone was found. **Impairment of Fertility:** Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed. **Pediatric Use:** Safety and effectiveness in children have not been established. **Geriatric Use:** Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in full PI). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION in full PI). **Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis:** In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)
ADVERSE REACTIONS: Associated With Discontinuation of Treatment: Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%). In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo). **Incidence in Controlled Trials: Commonly Observed Adverse Events in Controlled Clinical Trials: *Bipolar Mania:*** In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence. *Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania*: Adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial-Monotherapy in Bipolar Mania*. **Body System/Preferred Term: Central & peripheral nervous system:** Dystonia, Akathisia, Dizziness, Parkinsonism, Hypoaesthesia **Psychiatric:** Somnolence, Agitation, Manic reaction, Anxiety, Concentration impaired **Gastrointestinal system:** Dyspepsia, Nausea, Saliva increased, Mouth dry **Body as a whole - general:** Pain, Fatigue, Injury **Respiratory system:** Sinusitis, Rhinitis, Coughing **Skin and appendages:** Acne, Pruritus **Musculo-Skeletal:** Myalgia, Skeletal pain **Metabolic and nutritional:** Weight increase **Vision disorders:** Vision abnormal **Cardiovascular, general:** Hypertension, Hypotension **Heart rate and rhythm:** Tachycardia. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial – Adjunctive Therapy in Bipolar Mania*. **Body System/Preferred Term: Gastrointestinal system:** Saliva increased, Diarrhea, Abdominal pain, Constipation, Mouth dry, Tooth ache, Tooth disorder **Central & peripheral nervous system:** Dizziness, Parkinsonism, Akathisia, Dystonia **Psychiatric:** Somnolence, Anxiety, Confusion **Respiratory system:** Rhinitis, Pharyngitis, Coughing **Body as a whole - general:** Asthenia **Urinary system:** Urinary incontinence **Heart rate and rhythm:** Tachycardia **Metabolic and nutritional:** Weight increase **Skin and appendages:** Rash. **Dose Dependency of Adverse Events:** Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation. ***Vital Sign Changes:*** RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). ***Weight Changes:*** A statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%). ***Laboratory Changes:*** A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS). ***ECG Changes:*** Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). **Other Events Observed During the Premarketing Evaluation of RISPERDAL®:** During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies and the following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it). **Psychiatric Disorders:** *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning. **Central and Peripheral Nervous System Disorders:** *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis. **Gastrointestinal Disorders:** *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis. **Body as a Whole/General Disorders:** *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing. **Respiratory System Disorders:** *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration. **Skin and Appendage Disorders:** *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria. **Cardiovascular Disorders:** *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis. **Vision Disorders:** *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation. **Metabolic and Nutritional Disorders:** *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia. **Urinary System Disorders:** *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency. **Musculo-Skeletal System Disorders:** *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain. Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage. **Liver and Biliary System Disorders:** *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage. Platelet, Bleeding, and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia. **Hearing and Vestibular Disorders:** *Rare:* tinnitus, hyperacusis, decreased hearing. **Red Blood Cell Disorders:** *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia. **Reproductive Disorders, Male:** *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure. **White Cell and Resistance Disorders:** *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly. **Endocrine Disorders:** *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder. **Special Senses:** *Rare:* bitter taste.*Incidence based on elicited reports. **Postintroduction Reports:** Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.
DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.
For more information on symptoms and treatment of overdosage, see full Prescribing Information.
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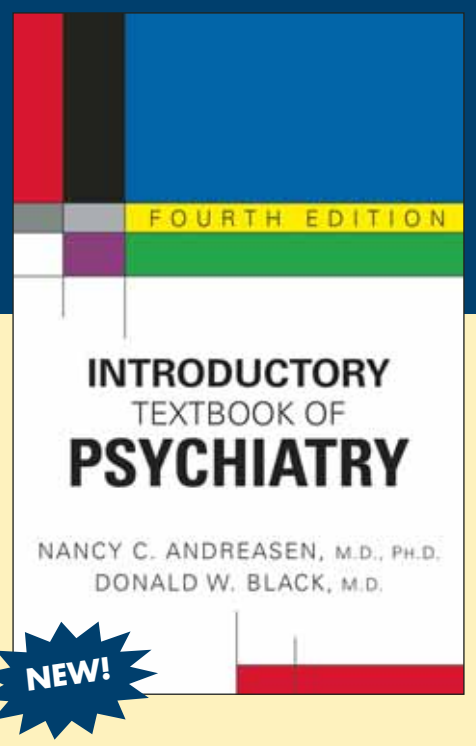
Introductory Textbook of Psychiatry, Fourth Edition

Nancy C. Andreasen, M.D., Ph.D., and Donald W. Black, M.D.



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- 6 line minimum
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- $50 extra for email and web page links
- Classified rates are non-commissionable to agencies

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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.

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ATTN.: Box P-XXX
Psychiatric News Classifieds
American Psychiatric Publishing Inc.
1000 Wilson Blvd, Suite 1825
Arlington, Virginia 22209-3901

SUBMISSIONS: Email, Fax or Mail ad copy, including issue dates desired, contact name, phone number, and billing address, to:

Joel Nepomuceno
Psychiatric News Classifieds
American Psychiatric Publishing Inc.
1000 Wilson Blvd, Suite 1825
Arlington, Virginia 22209-3901
(703) 907-7330 • Fax (703) 907-1093
classads@psych.org

All advertising copy, changes and cancellations received after the deadline will be placed in the next available issue. We do not provide proofs of ads before publication.

DEADLINES: All new advertising copy, changes, and cancellations must be received *in writing* by Friday, 2 p.m. (E.T) two weeks prior to publication date. Publication dates are the first and third Fridays of every month. Specific deadline dates for upcoming issues are as follows:

Issue	Deadline (Friday, 2 p.m. E.T.)
September 15	September 1
October 6	September 22

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.

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ALABAMA

HORIZON HEALTH
MEDICAL DIRECTOR

Located 1 hour south of Tuscaloosa, Alabama. A Medical Director is needed for a 10-bed geriatric psychiatric and IOP program in southwest Alabama. Growing geriatric psych program will need a Psychiatrist who is interested in establishing a private practice in the community. Excellent Private Practice potential. Stipend/Income Guarantee! Contact Diane Odom, Horizon Health, 800-935-0099 or email CV to diane.odom@horizonhealth.com, EOE

ALASKA

Enjoy Alaska's Pacific Maritime Climate on the Inland Passage!

Bartlett Regional Hospital in Juneau, Alaska's Capital City, is seeking a BE/BC child-adolescent psychiatrist or an adult psychiatrist for an outpatient and inpatient setting. Eligible for National Health Service Corps loan repayment program. University of Washington clinical faculty affiliation. The benefit package is State of Alaska Public Employees Retirement System and City and Borough of Juneau. Salary is most competitive, with excellent fringe benefits, which include five CME days in addition to 28 leave days during the first year with subsequent increases.

Please direct questions or CV to:

Verner Stillner, MD, MPH
Medical Director for Behavioral Health
Bartlett Regional Hospital
3260 Hospital Drive
Juneau, AK 99801
PH: (907) 796-8498
FX: (907) 796-8497
Email: vstillner@bartletthospital.org

ARIZONA

Mohave Mental Health Clinic, Inc., a non-profit organization located in northwest Arizona has an opening for a Psychiatrist for its Bullhead City clinic. We offer a competitive salary, 5 weeks PDO the first year, 401k, and excellent employer paid benefits. The area offers lots of outdoor activities and is just a few hours drive from Phoenix, Las Vegas and Flagstaff. Contact: Human Resources, 1743 Sycamore Ave, Kingman, AZ 86409. Phone: 888-757-8111 Fax: 928-757-3256 or email Barbt.mohave@narbha.org.

Assistant Professor, Clinical Psychiatry
University of Arizona (UPH Hospital-Kino)

The University of Arizona's Department of Psychiatry is recruiting adult psychiatrists to join a progressive and growing academic department located in the beautiful Southwest with academic appointments as Assistant Professor of Clinical Psychiatry. Individual must be Board certified or eligible in Psychiatry and have current credentials to practice medicine in the United States. Incumbent will provide clinical care in an inpatient facility with adult and geriatric populations. Other duties may include supervising and teaching adult psychiatry residents and medical students. Competitive salary and excellent benefits package offered. For more complete information about the positions, and to apply, go to: http://www.uacareertrack.com and reference job #35321. If you have questions, please contact Betsy Pepping, Administrative Associate, Dept of Psychiatry, 1501 N. Campbell Avenue, P.O. Box 245002, Tucson, AZ, 85724-5002, peppingb@email.arizona.edu or (520) 626-3819. Review of applications begins July 15, 2006 and is ongoing until positions are filled.

The University of Arizona is an EEO/AA Employer-M/W/D/V.

PHOENIX - GENERAL ADULT AND FORENSIC PSYCHIATRISTS

Come to the beautiful and sunny southwest! Arizona State Hospital in Phoenix is recruiting for full-time board certified/qualified psychiatrists at our 338 bed JCAHO accredited hospital, including 160 beds-adult civil, 162 beds-forensic, and 16 beds-adolescent.

Phoenix offers a rich variety of cultural, sporting and recreational opportunities. The state of Arizona offers a diversity of climates and recreational opportunities all within a few hours of the sixth largest city in the U.S.

Starting salary of $160K or higher DOE with an excellent fringe benefit package and additional compensation for Officer-of-the-Day duty. Bilingual Spanish applicants are encouraged to apply. Arizona state license required for process of application. Open until filled. Apply via e-mail to John C. Cooper, CEO @ cooperj@azdhs.gov.

Arizona State Hospital
2500 East Van Buren Street
Phoenix, Arizona 85008
www.azdhs.gov/azsh
602.220.6000

The Arizona Department of Health Services is an Equal Opportunity Employer.

PSYCHIATRIST

West Yavapai Guidance Clinic, a non-profit organization with a 40-year history of providing quality service to the Prescott Arizona area, has openings for adult and child and adolescent psychiatrists to augment its current staff of five psychiatrists. The clinic is experiencing rapid growth and presently has 220 employees who provide inpatient and outpatient behavioral health services. We offer a competitive salary, excellent employer-paid benefits, a 401k plan, generous paid time off, 10 paid holidays, paid CME days and allowance, and a relocation and/or hire-on bonus. Positions eligible for National Health Services Corp loan and scholarship programs. Prescott, 96 miles north of Phoenix, is Arizona's quaint mile-high city bordered by the Prescott National Forest offering four seasons of mild weather with year round outdoor activities. Please contact: Human Resources, 642 Dameron Drive, Prescott, AZ 86301. Phone: 928-445-5211, Fax: 928-445-6542, e-mail: wygc.org. EOE.

CALIFORNIA

Dominican Hospital is offering a full-time contract position for a board eligible or board certified psychiatrist. The hospital currently contracts with five psychiatrists who provide inpatient, partial hospitalization and consultation-liaison services to a wide variety of patients. Expertise in medication management and psychotherapy skills are required. Ability to work in a multi-disciplinary team setting is essential. Dominican Hospital is a large multi-specialty hospital. Santa Cruz is a beautiful seaside community near San Francisco. Please send CV and cover letter to: Freddie Weinstein, MD, Medical Director, Dominican Hospital Behavioral Health Services 1555 Soquel Drive Santa Cruz, CA 95065, 831-462-7646 or fax 831-462-7570.

Department of Psychiatry
University of California, San Francisco
Director of Child and Adolescent Psychiatry

THE DEPARTMENT OF PSYCHIATRY AT THE UNIVERSITY OF CALIFORNIA SAN FRANCISCO invites applications for Director of Child and Adolescent Psychiatry. The position will be in the Tenure Track series at the Associate to Full Professor level, and can begin on January 1, 2007, or thereafter. Applicants must be board certified in child and adolescent psychiatry and eligible to be licensed to practice medicine in California, have an established record of research, educational, and clinical leadership, and demonstrated ability in administration. Responsibilities include development and oversight of research programs in child and adolescent mental health; oversight of education programs-including child and adolescent psychiatry residents, and adult psychiatry residents, medical students, and other mental health disciplines who are training in child and adolescent psychiatry; oversight of clinical services-encompassing outpatient services, and consultation-liaison services within the university system and with community agencies, including a strong affiliation with the pediatrics programs at the UCSF Children's Hospital and San Francisco General Hospital; and community activities. Applicants should submit their CV, brief statement of interest, brief statement describing their professional background and current research activity, three letters of reference, and three representative journal articles by September 30, 2006 to: John L. R. Rubenstein, M.D., Ph.D., Search Committee Chair, c/o Susan Yu, Department of Psychiatry, Rock Hall, 1550 4th Street, 2nd Floor South, Room RH 284C, University of California, San Francisco, San Francisco, CA 94143-2611. UCSF is an affirmative action/equal opportunity employer. The University undertakes affirmative action to assure equal employment opportunity for underrepresented minorities and women, for persons with disabilities, and for covered veterans. UCSF seeks candidates whose experience, teaching, research, or community service has prepared them to contribute to our commitment to diversity and excellence.

GREATER BAY AREA - Modesto, California

General & Child Psychiatrists needed, for unique, stable County Mental Health system in a welcoming community. Serve both public & private sector patients, in both inpatient/outpatient settings that have been benchmarked for their quality. Possibilities for Resident teaching & consultation with a full range of providers. When patients require hospitalization, inpatient & outpatient staff work **TOGETHER** to optimize care. Stanislaus County is located only 1 1/2 hours from both San Francisco and Yosemite, enjoying the best of both worlds.

Excellent salary scale, with steps from $159K to $194K; **PLUS** full benefits; **PLUS** 5% additional for each of following: Inpatient, General Boards, Child Boards; **PLUS** extra for limited On-Call; **PLUS** Union-negotiated increases already set for next few years. Negotiable hourly contract also an option. Fax CV to Marshall Lewis, MD, 209-558-8641 or call 209-558-4639.

COALINGA STATE HOSPITAL

Get in on the ground floor!

Coalinga State Hospital, in conjunction with UC Irvine, is inviting applications for psychiatrists.

Coalinga State Hospital is the first new State psychiatric hospital built in California in over 50 years. With its 1,500 beds, almost exclusively devoted to the treatment of sexually violent predators, it is a state-of-the-art facility. It is closely affiliated with the University of California, Irvine School of Medicine, and will train medical students and residents. A forensic fellowship program is being developed.

This is an excellent opportunity for a Board Certified or Board Eligible clinician interested in general adult psychiatry as well as forensic psychiatry. Coalinga State Hospital's salary package is competitive and we offer job security, flexible work schedules, and a generous California State benefit package, including paid leave, medical insurance, and CalPERS Retirement.

Staff Psychiatrist (Safety) $162,792 - $172,572*
(Board Certified) *(Includes Recruitment & Retention incentives.)

Coalinga State Hospital is a young organization with an idealistic staff. We invite you to come and visit our new facility and to meet our staff; travel expenses may be covered. Coalinga is located in the San Joaquin Valley, equidistant from Los Angeles, San Francisco, and Sacramento, and only two hours from the coast and National Parks.

If you are interested in discussing any of our psychiatric positions, please contact: Erica Weinstein, M.D., at (559) 935-4343, or E-mail EWeinstein@csh.dmh.ca.gov. For more information, visit our website at www.dmh.ca.gov/Statehospitals/Coalinga. CSH is an equal opportunity employer.

The University of Southern California Department of Psychiatry is accepting applications for anticipated openings in the Adult and Child/Adolescent Services. These are full time academic positions which include the training of residents and medical students in addition to direct patient care. Positions can be combined with clinical research (interest in genetic psychiatry a plus). Participation in our faculty private practice plan is also an option. Please fax CV to Carlos Pato, MD, Chair @ 323-226-5713. EOE

Psychiatrist Opportunities

Are you tired of managing overhead expenses or are you finishing residency and looking for a stable opportunity to practice your clinical skills? We at the Riverside County Department of Mental Health are looking for qualified psychiatrists. The department operates an inpatient facility as well as out patient clinics in multiple locations. We serve people of all ages and are staffed by knowledgeable and supportive personnel.

Our salary is very competitive. Per-diem positions include liability insurance as well as a 401(a) pension plan. **Hours are flexible with no on-call**. Full-time employment may be offered on a case by case basis.

Riverside County is one of the fastest growing counties in coveted Southern California with numerous choices of both active and leisure lifestyles along with more affordable housing and an easy reverse commute from surrounding areas.

Interested? Please call Dr. Raja at (951) 358-4610 and send resume (CV) by email to rschulte@co.riverside.ca.us or by mail to:

County of Riverside
Attn: Ryan Schulte
4095 County Circle Drive
P.O. Box 7549
Riverside, CA 92513-7549

For additional information you may visit our website at www.rc-hr.com.

SANTA BARBARA - THE AMERICAN RIVIERA

Santa Barbara County is an unrivaled natural paradise. Beautiful valleys, rugged mountains, and 50 miles of spectacular coastline make Santa Barbara County one of the most desirable locales in the world.

Live and work in Paradise! Culture, urban resources, and rural beauty - for quality of life Santa Barbara County is the place to be.

Santa Barbara County has **immediate openings** in adult outpatient psychiatry.

$136,207 - $166,723/yr including benefit allowance.

We offer a stable work schedule, competitive salary, and a **generous benefits package**, including paid holiday, vacation, and sick leave; medical, dental, and vision care coverage; and a retirement package that includes both a defined-benefit pension and an optional deferred compensation plan through your choice of several competitive investment options.

For more information, or to apply online, visit our Website at
www.sbcountyjobs.com
Or call 805-568-2800

COLORADO

Denver/Boulder

Colorado Permanente Medical Group is seeking a full time or part time BC/BE adult psychiatrist to join a large multidisciplinary behavioral health staff working within an integrated medical system. CPMG is a physician-governed group providing services for the non-profit Kaiser Foundation Health Plan, Colorado's most experienced Integrated Health Care System. Kaiser Foundation Health Plan of Colorado has received national recognition as one of the top health care plans in the nation. We offer an excellent benefit package with a competitive salary. Enjoy one of the best practice and lifestyle opportunities in the nation. EOE, M/V

Please contact:
Phone: 303-344-7838
E-Mail: eileen.t.jones-charlett@kp.org
Fax: 303-344-7818

Sol Vista - Colorado's brand new cutting edge adolescent forensic treatment center needs a well-qualified psychiatrist. Responsibilities include heading a clinic treatment team for 20 beds. Position includes full benefits from employer, University of Colorado Medical School. Adolescent fellowship preferred, but experienced psychiatrists will be considered. Complimentary interviews will be provided to qualified applicants. We are not an underserved area. If interested, contact A. O. Singleton, III, M.D. @ (719) 546-4637 or Michelle Manchester, MA, CACIII @ (719) 546-4498

CONNECTICUT

Department of Psychiatry, Yale School of Medicine, seeks a Residency Program Director. This position carries a faculty appointment at the rank of Associate Professor, Clinical Educator Track. The successful candidate will be a board certified psychiatrist with extensive experience in a major academic setting developing and directing accredited psychiatric residency training. Candidates must have a history of involvement in the education, evaluation and testing of psychiatric residents and be recognized at the local and national level for this expertise. All applicants must have extensive clinical experience in both inpatient and outpatient settings, be licensed to practice medicine in CT and legally employable in the U.S. Send CV and cover letter by September 19, 2006 to Benjamin S. Bunney, MD, Chairman, Yale Department of Psychiatry, 300 George St., Suite 901, New Haven, CT 06511. Yale University is an affirmative action, equal opportunity employer. Women and minorities are encouraged to apply.

GENERAL PSYCHIATRY— CENTRAL CONNECTICUT

Opportunity for BC/BE psychiatrist to join well established two-person successful adult psychiatric private practice. Practice is affiliated with Bristol Hospital, a leading community hospital offering a comprehensive mental health continuum, including both inpatient and outpatient settings. Our central Connecticut location offers a wide range of upscale suburban living options, including first-rate schools, many desirable cultural activities, and easy accessibility to NY and Boston. We offer a benefits package and salary. To learn more about this opportunity, call toll-free, Christine Bourbeau in the recruitment office at 800-892-3846 or fax your CV to 860-585-3086. EOE. Email address: **cbourbeau@brishosp.chime.org**

Associate Medical Director New England Area

Nationally known as one of the MOST BEAUTIFUL residential communities in America! Located in the picturesque northwest corner of Connecticut. An **Associate Medical Director** is needed for a 12-Bed Geriatric inpatient psychiatric program. Behavioral health program is part of state-of-the-art 78-bed Medical Center serving CT, MA, and NY. The best that modern medicine has to offer with a 92 year history of community service. Lucrative private practice potential. Exceptional prep schools, parks, and recreation. Enjoy all the charms of New England! Contact Mark Blakeney, Horizon Health, 800-935-0099, email CV to mark.blakeney@horizonhealth.com, fax: 972-420-8233. EOE

DELAWARE

PSYCHIATRISTS Greater Wilmington Area

Horizon Health seeks psychiatrists for hospital-based psychiatric services in greater Wilmington, DE. Specialties include: General Adult, Chemical Dependency, and Geriatric services. **Salaried positions with exceptional benefits**. Contact: Mark Blakeney, Horizon Health, 800-935-0099, fax CV: 972-420-8233, or email mark.blakeney@horizonhealth.com. Visit our web site: www.horizonhealth.com. EOE.

DISTRICT OF COLUMBIA

Well established, rapidly growing adult and child/adolescent private practice seeks ambitious and compassionate board certified/eligible psychiatrist for part to potentially full time position. Production based multidisciplinary practice has excellent national reputation, strong referral base and collegial team spirit. Full support administrative staff offers a turn key, family-friendly office environment with flexible scheduling, well-appointed offices and close proximity to Metro, shops, and restaurants. Interested candidates may visit our web site at www.rosscenter.com.
Please fax CV to 202-363-2383 or E-mail it to Jerilyn@rosscenter.com. For more information please contact Beth Salcedo, MD, Medical Director, at 202-363-1010.

The Department of Psychiatry and Behavioral Sciences at the GWU Medical Faculty Associates, an independent non-profit clinical practice affiliated with the George Washington University, is seeking a psychiatrist for a full-time academic appointment. This position will include: 1) oversight of an acute admissions team with psychiatry residents and medical students on the psychiatric unit in the GWU Hospital; 2) outpatient clinical work; and, 3) opportunities for additional medical student and resident education and clinical research. The applicant must be license eligible in the District of Columbia and Board Certified or Board Eligible in General Psychiatry. Academic rank and salary will be commensurate with qualifications. Review of applications begins on August 21, 2006 and will continue until the position is filled. Please send letter of interest and CV to Jeffrey S. Akman, MD, Chair, Department of Psychiatry and Behavioral Sciences, 2150 Pennsylvania Avenue, NW, Washington, DC 20037. Tel. 202-741-2880; fax 202-741-2891. The GWU Medical Faculty Associates is an Equal Opportunity/Affirmative Action Employer.

WASHINGTON DC-COMMUTABLE! Top-rated schools, internat'l airport nearby. 50/50 mix, In & Outpatient work. Be hospital employee in newly renovated psych unit. All adult patients. *ECT a plus. Call 1:6. Sue Springer 800-575-2880 x 315 sspringer@medsourceconsultants.com

FLORIDA

Miami: FL LICENSED PSYCHIATRIST; active private practice; affluent area; hosp, office, snf settings; excellent incentive plan incl salary & benefits. Dr. Carter, S. FL Psychiatric Assoc. 305-935-6060. FAX CV to 305-935-1717 or EMAIL: aventuraoffices@bellsouth.net.

Located along South Florida's east coast just minutes from the Atlantic Ocean, CARF accredited community mental health center is seeking a part-time/full-time inpatient and outpatient psychiatrists to provide comprehensive psychiatric care to children and adults. Must be Board Certified (or eligible). Excellent salary and benefits package, great staff and a lovely coastal community. Seeking applications directly from candidates. (No recruitment firms please!) Send/Fax CV: HR, New Horizons, 4500 W. Midway Rd., Ft. Pierce, FL 34981 FAX (772) 468-5606 EOE/ADA/DFWP www.nhtcinc.org

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Boca Raton Prestigious/Upscale Psychiatric Group in sunny seaside resort town seeks psychiatrist. Outpatient Practice. Partnership track in a friendly and collegial work environment. Must have Fl. license prior to hire. Fax Resume to 561 392 9170 or e-mail brpg7284@lycos.com

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Staff Psychiatrist at a privatized 200 bed Forensic State Hospital in Miami. BC/BE, must possess a Florida license and at least 3 years experience in clinical psychiatry, forensic cert. not required. Experience with serious mental illness preferred. Employed position FT, benefits, 40 hours, call 1 in 4 and is by phone. Competitive salary

Send or Fax C.V. to: Debra Kirsch, MD
Chief Medical Officer
Geo Care, Inc.
dkirsch@geocareinc.com
Fax 561-999-7747
Cell 954-647-4359

FT. MYERS/MERBOURNE/ORLANDO/ DAYTONA/MIAMI/FORT LAUDERDALE /OCALA/GAINESVILLE - Psychiatrists needed for rapidly expanding Nursing Home Service. Great support. No call. Average Salary 210K + benefits. Part-time available. Some travel required. Must have FL Medicare & FL Medicaid provider #s. Call Mike at 866-936-5250.

PANAMA CITY - Adult board certified or board eligible psychiatrist to join staff of comprehensive community mental health center. Salary range is: $176,000 - $183,000. Beautiful area of the country. Apply through our website www.lifemanagementcenter.org or send CV to: **Peter Hampton, Ph.D., Executive Director, Life Management Center of Northwest Florida, 525 E. 15th St., Panama City FL 32405**, EOE/DFWP. Pre-hire drug screen required.

East Coast Florida organization needs a fifth psychiatrist. Combine a strong salary with full benefits, miles of unspoiled beaches and great lifestyle options. Contact Jim Ault at St. John Associates, 1-800-737-2001 or **jault@stjohnjobs.com**. Visit **www.stjohnjobs.com**.

GEORGIA

Take over a lucrative practice of a retiring psychiatrist. Practice was established in 1968. Join a group of multidisciplinary professionals in an interdenominational setting located in beautiful North Atlanta. No investment required. No In-Patient responsibilities. Weekend On-Call limited to once a month. If interested, please call 770-396-0232, ext. 232. Email your C.V. to atlantacounselingctr@yahoo.com or fax to 770-399-0007.

WellStar Health System is seeking a Clinical Liaison Adult Psychiatrist to join an established and growing practice located in Marietta, GA. This position would consist of both inpatient and outpatient psychiatry/liaison work. WellStar offers a competitive compensation and benefits package. Please send CV to provider.positions @wellstar.org or fax to 770-792-1738. EOE.

BE/BC General Psychiatrist to join an expanding out-patient practice in St. Marys, GA, home of the Kings Bay Naval Base, a suburb of Jacksonville, FL, and listed in US News and World Report as one of the ten best retirement communities in the U.S.

Interested parties should send their CV to Bryan Warren, M.D., 235 Cardinal Circle West, St. Marys, GA, 31558.

St. Simons Island!
Staff Psychiatrist

A Board Certified or Board Eligible Staff Psychiatrist is needed for a 101-bed inpatient psychiatric and chemical dependency facility. Located in beautiful St. Simons Island, a popular vacation destination where history is enriched in every view. Offering attractive compensation (salary) and benefits package. Contact Diane Odom, Horizon Health, 800-935-0099 or email CV to diane.odom@horizonhealth.com, EOE

HORIZON HEALTH
Medical Director Needed
1 hour south of MACON, GA

Horizon Health seeks outstanding Medical Director for a 15-bed adult behavioral health program located within 99-bed hospital. Enjoy all the benefits of beautiful Georgia, a state rich in history, charm and southern hospitality. Excellent practice opportunity with solid support from hospital and staff. Stipend or Employment available. Please contact Diane Odom for more information 800-935-0099 or e-mail diane.odom @horizonhealth.com EOE

ILLINOIS

PSYCHIATRIST NEEDED!

A well established and very busy private practice, located in the Chicago area is looking to hire a full time or part time psychiatrist. Work includes hospitals, outpatients and nursing homes. Compensation package is very attractive and negotiable. For more information please call Kathy at our office between 8am and 4pm 1-312-565-2251.

Opportunity for Adult and/or Child Psychiatrist at an established group practice in a western Chicago suburb. Hospital and office practice, academic and administrative involvement. Salary, productivity and benefits available. Fax resume to Medical Director at 630-850-9739 or e-mail denisehb@ameritech.net.

INDIANA

Attention General Psychiatrists and Psychiatrists who have an interest in Forensic Psychiatry!!!

You are missing from our leading team of top Psychiatrists! Seeking B/C or B/E General Psychiatrists and Psychiatrists who have experience or interest in Forensic Psychiatry. Our Forensic team practices in the brand new, state-of-the-art, magnificent Isaac Ray Center which is connected to the beautiful main hospital where our team of General Psychiatrists practice. Both facilities lie on the well-known 20+ acre, tranquil campus in North Central, IN. Enjoy a 40 hr. M-F work-week. Excellent compensation; very generous amount of PTO; paid malpractice insurance; generous financial assistance for CME/relocation; no billing or managed care. Liberty is physician-owned and has been recognized for 30 yrs. as a leader in managing and staffing progressive employers w/ the highest quality of healthcare professionals throughout the U.S. Liberty's track record for staffing and retaining the most prominent Psychiatrists is unmatched nationally. Please contact Tina Rosner at 800-331-7122 x150; Cell 610-585-9624; Email tinar@libertyhealth.com. EOE.

IOWA

The North Central Iowa Mental Health Center is accepting applications for a General Psychiatrist. The Center is located on the grounds of Trinity Regional Medical Center. The doctor will treat patients on the inpatient and partial hospitalization units at Trinity Regional as well as providing out patient services. The Center also has an Assertive Community Treatment team. The Center serves an area of 120,000 people and treats about 3500 patients per year. Compensation is based on salary plus productivity bonus. Will consider applicants with J-1 Visas. Please send cover letter, CV and references to:

Jim Burr, CEO
North Central Iowa Mental Health Center
720 Kenyon Road
Fort Dodge, IA 50501
jimburr4759@hotmail.com

KANSAS

Spanish Speaking (bilingual) Child, Adolescent, and Adult Psychiatrist

Johnson County Mental Health Center (located in a suburb of Kansas City) is seeking a full-time/part-time Child, Adolescent, and Adult Psychiatrist who is fluent in Spanish. Requires a medical degree; (M.D. or D.O.); successful completion of an ACGME accredited Child and Adolescent Psychiatry Residency Program & must be eligible for licensure to practice in KS. Must have board eligibility or certification through ABPN; compensation commensurate with experience. Interested applicants should contact: Dr. Jane Lauchland, Johnson County Mental Health Center, 6000 Lamar, Suite 130, Mission, KS 66202; 913-831-2550; FAX to 913-826-1594; Jane.Lauchland@jocogov.org. EOE M/F/D.

KENTUCKY

An established private practice located in the Greater Cincinnati area based in Northern Kentucky is seeking a full time or part time general psychiatrist licensed and board certified in Kentucky.
Our patients range from adults, children and adolescents, with the majority of adults. Our practice includes one Psychiatrist and three Advanced Registered Nurse Practitioners. Office hours are flexible, Monday through Thursday, and closed on Fridays. Remuneration package is negotiable. Psychiatrist/owner is planning to retire and we offer the possibility for our future hire to take over the practice.
Please email CV to: bmsgen@bmscincy.com or fax to: (513) 351-8565.

PSYCHIATRIST

Horizon Mental Health, a national leader in managed psychiatric programs seeks a psychiatrist to work with our current Medical Director in Paducah, KY. Well established 20-bed inpatient psychiatric unit with excellent potential for outpatient Private Practice. Salaried position with benefits. Contact: Michael Lemos, Ph 972-420-8232, Fax 972-420-8252, or email CV: michael.lemos@horizonhealth.com EOE

LOUISIANA

Southwest Louisiana area seeks BE/BC psychiatrist for community mental health centers located in Allen and Beauregard Parishes. Generous compensation and benefits package. Please send your CV and supporting documents to the following address:

Lake Charles Mental Health Center
Attn: Laura Lyles
4105 Kirkman Street
Lake Charles, LA 70607
Telephone: (337) 475-8725
Fax: (337) 475-8054
E-mail: lalyles@dhh.la.gov

Baton Rouge, Louisiana
Capital Area Human Services

Only One Position Left for Full Time Psychiatrist in Outpatient Clinic; (1 MD retiring); Currently we have 12 psychiatrists in an Organized Med Staff; clinic serves as a teaching site for LSU Dept Psychiatry; Salary approx: $145K to 170K; paid holidays and vacation; no on-call; sick time; malpractice and benefits. Community has Excellent Quality of Life.

Also separate 1 yr position available for Katrina Mobile Outreach Effort; funded only through Aug 2007 ; applicant must be willing to do all: clinic, mobile, and/or satellite work.
Contact: David Edward Post MD, Medical Director: 225-922-2700 or: DPost@dhh.la.gov ; also visit: www.cahsd.org

MAINE

Forensic Psychiatrist

Interested in professional growth as well as personal time for you and your family? Seeking Forensic Psychiatrist to work along Maine's exquisite coastal town of Rockland. Excellent compensation; very generous amount of PTO; paid malpractice; generous relocation/CME allowance; no billing or managed care. Please contact Tina Rosner at 800-331-7122 x150; Cell 610-585-9624; email tinar@libertyhealth.com. EOE.

Dartmouth Faculty Psychiatrists

Dartmouth Medical School, Department of Psychiatry, in collaboration with the State of Maine Department of Health and Human Services, seeks faculty psychiatrists for the Riverview Psychiatric Center in Augusta, Maine. The Center is the flagship inpatient hospital serving central and southern Maine's system of public mental health care. A 92-bed, state of the art, replacement hospital opened in the Spring of 2004. Preference will be given to candidates with forensic training and/or experience. Maine licensure required. These are full-time Dartmouth faculty appointments with salary and rank commensurate with experience and academic accomplishments. Protected time for scholarly activities. Central and southern Maine offers exceptional opportunities to enhance your quality of life. We have safe communities, with very low crime, good schools and unparalleled four season recreational activities. Augusta is less than one hour from the Maine coast and closer to numerous crystal clear lakes and mountains. It is no wonder Maine is called "vacationland." Please send CV and three letters of reference to: **Alan I. Green, MD, Professor and Chair of Psychiatry, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756**. Dartmouth Medical School is an EOE/AA Employer and encourages applications from women and members of minority groups.

Maine's First Magnet Hospital and the World's First Free-Standing Psychiatric Magnet Hospital
Seeking Adult and Child/Adolescent Psychiatrists

We are seeking BC/BE psychiatrists for both our adult and child/adolescent inpatient and outpatient programs. Acadia Hospital is a thriving, non-profit, private community-based hospital offering acute psychiatric care for adults and children, as well as chemical dependency programs. One of the only two private psychiatric hospitals in Maine. The Acadia Hospital offers physicians clinical practice in a highly collaborative, multi-disciplinary setting. Competitive salary and benefit package. Send resume to: Vice President of Medical Affairs, The Acadia Hospital, P.O. Box 422, Bangor ME 04402-0422. **www.acadiahospital.org**

MARYLAND

PSYCHIATRIST PT for fast-paced growing Geriatric Behavioral Health Practice to provide consultation services in LTC setting in Maryland. Background in medical/neurological basis for psychiatric symptoms desirable. Fax cover letter and resume to CGS, 410-832-5783, Attn.: Dr. Fitting.

Psychiatrist

Pathways, Inc., the longest operating multi-service mental health agency in St. Mary's County, located on Maryland's western shore of the Chesapeake Bay, is seeking a licensed; board certified/board eligible Psychiatrist for the position of Medical Director.

St. Mary's County has been designated as an underserved area for mental health professionals so applicants with foreign visas are welcome. Assistance with moving expenses and student loan payments consistent with the underserved area designation for this county are possible. Additional benefits include a competitive wage, medical, dental, disability, and malpractice insurance, paid leave and no on-call requirement.

This position will require a minimum effort of thirty-five (35) hours per week. Salary and other terms are negotiable. If interested please submit your C.V. and letter of interest to: Jack Dent, Administrative Officer, Pathways, Inc., P.O. Box 129, Hollywood, MD 20636, 301- 373- 3065 ext. 208, Fax 301-373-3265, e-mail: jdent@pathwaysinc.org

BALTIMORE - The Walter P. Carter Center, a 51 bed adult inpatient facility on the downtown campus of the University of Maryland, is seeking a BC/BE psychiatrist. This is a full-time faculty position in the Department of Psychiatry at the U. of Md. School of Medicine, and involves direct patient care, the teaching and supervision of residents and medical students, and opportunities for research. Please contact Louis Cohen, M.D., Clinical Director at 410-209-6101; or e-mail at LCohen@psych.umaryland.edu.

Inpatient psychiatry position on the bucolic Eastern Shore of Maryland. Close proximity to DC, Baltimore, and the Atlantic Coast beaches. Full-time and part-time options are available. Work on a general psychiatry inpatient unit with a team approach to patient care. For more information contact Allan Anderson, MD at 410-228-5511 ext. 2107, or e-mail at: aanderson@shorehealth.org.

Clifton T. Perkins Hospital Center, a JCAHO-accredited institution and Maryland's only maximum security forensic hospital, is seeking candidates for the position of staff psychiatrist. Candidates with forensic interest or experience would be especially well-suited. Responsibilities include the provision of high quality psychiatric care on an inpatient unit in a state-of-the-art forensic facility. Additional opportunities include evaluations of dangerousness, competency to stand trial, and criminal responsibility.

Join a vibrant medical staff with expertise in care of the seriously mentally ill within a forensic setting. Faculty appointments are available at University of Maryland and Johns Hopkins, if eligible. The hospital is centrally located 20 minutes from Baltimore, 35 minutes from DC, and 20 minutes from Annapolis. Competitive salary with excellent benefits, flexible working hours, and the opportunity for paid overnight call.

Interested candidates should contact C. Dennis Barton, Jr., MD, MBA, at 410-724-3078 or P.O. Box 1000, 8450 Dorsey Run Road, Jessup, MD 20794 (BartonD@dhmh.state.md.us.)

Faculty Position
Assistant Professor (Tenure Track)
Department of Psychiatry

The Department of Psychiatry at the Uniformed Services University of the Health Sciences, Bethesda, MD is seeking to fill an Assistant Professor, tenure-track, teaching and research position with particular emphasis on biological psychiatry. The Department is comprised of twenty full-time faculty and has active research interests in the neurobiology and behavior of stress, PTSD, anxiety, depression, and substance abuse. The successful candidate will be responsible for developing a funded research program and will participate in medical student and resident education and clinical care. Individuals who hold an M.D., have completed an approved psychiatric residency and are board eligible/certified are invited to apply. Send curriculum vitae, description of current and anticipated research interests and the names and addresses of four references to: Robert J. Ursano, M.D., Chairman, Department of Psychiatry, Uniformed Services University, 4301 Jones Bridge Road, Bethesda, MD 20814 (rursano@usuhs.mil). Review of applications is ongoing. The University is an affirmative action/equal opportunity employer.

Psychiatrist

Springfield Hospital Center - a 405 bed psychiatric in patient facility, operated by The Maryland State Mental Hygiene Administration seeks Maryland licensed Psychiatrists. Our rural 400 acre campus is located 22 miles west of Baltimore and convenient to Washington, DC. via routes 70 & 29. We offer full time and part time positions with comprehensive benefits, which include 27 days of paid leave, medical coverage and access to Maryland State Employees Pension at retirement. Additionally, Contractual day/night positions available. Both Board & Non-Board Certified physicians will be considered. Salary for these positions is negotiable. Please send CV to: Jonathan Book, M.D., Clinical Dir, SHC, 6655 Sykesville Rd. Sykesville, Maryland 21784. For questions call 410-970-7006 or email Jbook@dhmh.state.md.us. EOE

MASSACHUSETTS

Professor of Psychiatry,
Harvard Medical School
Director of Residency Training, Department of Psychiatry, VA Boston Healthcare System

The Harvard Medical School and VA Boston Healthcare System are recruiting a Professor of Psychiatry to serve at the VA Boston Healthcare System. The individual will serve as Director of the Harvard South Shore Psychiatry Residency Training Program. Applicants should have an academic record sufficient to allow appointment as a full Professor at Harvard Medical School. We seek an outstanding psychiatrist with strong academic credentials, significant executive or program administration experience, and the energy and vision to reshape and lead this Harvard training program. The program trains a total of 30 residents over four years and is fully accredited by the ACGME. The applicant must be board certified in psychiatry with a minimum of 5 years of experience post-residency. Experience as a residency director or associate director is preferred. This Residency Program is integrated into a Mental Health Service with extensive inpatient, residential and transitional and outpatient programs. This Residency Program functions in an excellent academic environment with other nationally recognized training programs, prominent research programs and several VA Clinical Centers of Excellence. This position offers a highly competitive salary from the VA. To apply, candidates should send a letter of interest, CV, and the names of three persons to contact for references to: Dr. Robert McCarley, Chair of Search and Chair, Harvard Department of Psychiatry, VA Boston Healthcare System, 940 Belmont Street Brockton, MA 02301. Phone: 774-826-2486; email: robert_mccarley@hms.harvard.edu Harvard/VA Boston is an Affirmative Action/Equal Opportunity Employer with a strong institutional commitment to diversity in all areas.

ON call psychiatrist - Southbridge, MA. Harrington memorial Hospital has on call opportunities. Salaried position, 1 in 7 rotation, weekend rounds, very flexible. Excellent working conditions. For more information, write/call: Zamir Nestelbaum, M.D., @ G.B. Wells Center, 29 Pine St., Southbridge, MA, 01550. 508-765-9167. An AA/EOE/ADA Employer.

Psychiatrist - Southbridge/Sturbridge area. Part time adult psychiatrist needed for G.B. Wells Center, a large, friendly community mental health center and part of Harrington Memorial Hospital. Excellent working conditions, very flexible. For more information, write/call: Zamir Nestelbaum, M.D., @ G.B. Wells Center, 29 Pine St., Southbridge, MA, 01550. 508-765-9167. An AA/EOE/ADA Employer.

The Department of Psychiatry at the University of Massachusetts Medical School/ UMass Memorial Medical Center is seeking a BC/BE Psychiatrist for its University Hospital Outpatient Clinic. Candidates should have an interest in available academic opportunities in either training or research. Academic rank commensurate with experience. Interested applicants send CV to Alan P. Brown, M.D., Vice Chairman for Clinical Services, Department of Psychiatry, UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655 or email BrownA01@ummhc.org AA/EOE

CAMBRIDGE: Child & Adolescent Psychiatry

Position available at Cambridge Health Alliance, Division of Child and Adolescent Psychiatry, Harvard Medical School. The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School with excellent residencies in adult and child psychiatry. Academic appointment up to the rank of Associate Professor, as determined by the criteria of Harvard Medical School, is anticipated. We seek candidates with demonstrated excellence in academic teaching of complex clinical assessment, child and adolescent psychopharmacology, family assessment and treatment, particular interest and experience in working with ethnic and minority populations and the underserved, and enthusiasm for the public health mission of CHA.

Outpatient Child & Adolescent Consult Liaison Psychiatrist - Part time: Exciting opportunity to develop new service providing direct clinical and consultation services at community primary care clinics. The right candidate will have excellent skills in working with clinicians of multiple disciplines and will thrive in an ambulatory medicine setting. Integrated mental health services within a primary care setting that are collaborative and patient centered will be the emphasis of the service. Position includes supervision of child psychiatry fellows, general psychiatry residents, medical students, and other trainees.

Qualifications: BC, demonstrated knowledge of clinical and research child and adolescent psychiatry, commitment to public sector populations, excellent clinical and teaching skills, leadership and management skills, team oriented, problem solver. Bilingual and/or bicultural abilities are desirable. Competitive compensation with excellent benefit package. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply.

CV & letter to: **Deborah Weidner, MD, Dept. of Psychiatry, The Cambridge Hospital, 1493 Cambridge Street, Cambridge, MA 02139. Fax 617-665-1973. DWeidner@challiance.org (email preferred)**

North Shore Medical Center
Psychiatry and Mental Health Department

NSMC is a member of Partners HealthCare, which was founded by Massachusetts General Hospital and Brigham and Women's Hospital. For more information, visit www.nsmc.partners.org

NSMC is an equal opportunity employer.

Child Psychiatrist

Position available at Salem Campus for BE/BC Psychiatrist 20-40 hours per week. Responsibilities include Child Inpatient Psychiatry and/or Child Outpatient Mental Health. Excellent, collegial work environment, opportunities for participation in clinical research and academic appointment. Salary and benefit packages are highly competitive.

Please send cover letter and CV to: Mark Schechter, MD, Chairman, Department of Psychiatry, 81 Highland Avenue, Salem, MA 01970, Email (preferred): mschechter@partners.org, or telephone: (978) 354-4010, FAX: (978) 825-6101.

Lynn BayRidge Hospital, a non-profit psychiatric facility on Boston's North Shore, a teaching site for Boston University Medical School, has a position for an inpatient and/or partial hospitalization program psychiatrist, or for the appropriate candidate, as unit Medical Director. Experience with dually diagnosed patients is a plus. The Medical Director position includes substantial direct service; candidates for Medical Director must be board-certified, and have demonstrated skill in leadership. No required night call, but participation in a lucrative call system is optional. Full benefit package includes generous time off as well as reimbursement for malpractice insurance and CME expenses. Contact Barry Ginsberg, M.D., Medical Director, 60 Granite Street, Lynn MA 01904. Phone (781) 477-6964, Fax (781) 477-6967, email bginsber@nhs-healthlink.org.

Director, Victims of Violence Program
Department of Psychiatry
Cambridge Health Alliance

The Department seeks a clinical psychologist, psychiatrist, or other doctoral level mental health clinician with outstanding academic skills and expertise in traumatic stress to serve as director of the Victims of Violence Program (VOV). The director will maintain the philosophical and programmatic integrity of the VOV program and provide leadership, direction, and administrative oversight to the program in a manner consistent with the public health mission of the Cambridge Health Alliance. VOV services, activities, and components include hospital and community based clinical services to trauma survivors, individual and community crisis response, victim advocacy, clinical training and supervision, research, grant acquisition and management, and VOV staff development. The director will have knowledge of an ecological view of psychological trauma, commitment to multi-culturally informed clinical and community intervention, dedication to multidisciplinary staffing and staff development, and a capacity to guide ongoing program development.

The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School with excellent training programs including Harvard medical students, adult and child psychiatry residencies, APA internship, and post-doctoral fellowships. Academic appointment up to the rank of Associate Professor, as determined by the criteria of Harvard Medical School, is anticipated. The Department values scholarship, teamwork, commitment to patients and trainees, and mutual respect across clinical specialties and interests.

Demonstrated skill in teaching, clinical practice, and research activity is essential in candidates, as well as extensive mental health program development and administrative experience, scholarly contributions to the field of traumatic stress studies, and extensive grants acquisition and management experience.

Qualifications: Doctorate or board certified psychiatrist with appropriate specializations and state license. Bilingual and bicultural abilities are desirable. We offer competitive compensation and excellent benefit package. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply. **Send CV and letter to Derri Shtasel, MD, MPH; Chief, Adult Division of Psychiatry; 1493 Cambridge Street, Cambridge, MA 02139. Fax: 617-665-2521. Email: DShtasel@challiance.org (email preferred).**

Reverse Commute - Enjoy your drive to this well-respected community psychiatric facility in Central Mass. Need a Child Psychiatrist to work on Residential Treatment and Outpatient programs. Federal Loan Repayment Eligibility. Contact **Karen Brennan at 800-575-2880 x307**. E-mail to **KBrennan@MedSourceConsultants.com.**

Hallmark Health
INPATIENT & OUTPATIENT PSYCHIATRISTS - BOSTON AREA

Excellent Opportunities For BC/BE Psychiatrists

- Full Time Medical Director for 22 Bed Inpatient Adult Unit at Melrose-Wakefield Hospital *(Director Experience Required)*
- Weekend and Evening Call Opportunities at Melrose-Wakefield Hospital
- Full Time Staff Psychiatrist for Inpatient Geriatric Medical Psychiatric Unit at Lawrence Memorial Hospital. Includes oversight of Nursing Home Consultation Services.
- Part Time and Per Diem positions in an Outpatient Clinic providing psychopharmacology and psychotherapy services to adult and geriatric patients.

Very Competitive Salary and Benefits Package. Located a few miles North of Boston. A Financially Strong and Progressive Healthcare System with two hospital campuses and an expanding Behavioral Health Service Line.

Send CV to:

Janet Lensing, System Director of Behavioral Health Services
Hallmark Health System, Inc.
585 Lebanon St
Melrose, MA 02176
Fax: 781-979-3326

UMass Memorial Medical Center, Department of Psychiatry seeks a Medical Director for the Geriatric Psychiatry Inpatient Unit/Clinton Hospital-oversees clinical care on a 20-bed unit that serves as an important referral site for the region. Supervision of Psychiatry and Family Practice residents occurs on-site. Opportunities for collaboration and teaching at Worcester Campus. Competitive compensation with complete benefit package. Faculty rank commensurate with experience. Inquiries of general interest about our many programs encouraged and applicants with specific interest in this position should send letter and CV to Alan P. Brown, MD, Vice Chairman of Clinical Services, Department of Psychiatry, UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655 or e-mail BrownA01@ummhc.org. AA/EOE

The Department of Psychiatry at Mount Auburn Hospital, affiliated with Harvard Medical School, is recruiting for a full time psychiatry position in our outpatient service. Responsibilities include evaluation and treatment of outpatients presenting with a wide range of psychiatric disorders, treatment planning and coordination of care with an interdisciplinary clinical staff, and consultation to primary care and specialty physicians. Teaching responsibilities include medical student teaching and teaching in our internal medicine residency program. Academic appointment, salary package. Please send inquiries and CV to: Joseph D'Afflitti, M.D., Chair, Department of Psychiatry, 330 Mount Auburn Street, Cambridge, MA 02138; tel: 617 499-5008; email; jdafflit@mah.harvard.edu.

CORRECTIONAL & FORENSIC PSYCHIATRY

The University of Massachusetts Medical School seeks psychiatrists for its innovative and multidisciplinary correctional mental health program, which provides services at several locations throughout the state. We offer generous, newly enhanced salaries, excellent benefits, regular hours without call responsibilities, and a faculty appointment with the University of Massachusetts Medical School. Send letter of interest and curriculum vitae to: Kenneth Appelbaum, MD, University of Massachusetts Medical School, Health & Criminal Justice Programs, 1 Research Drive, Suite 120C, Westborough, MA 01581; Kenneth.Appelbaum@umassmed.edu; Phone: 508-475-3236; Fax: 508-475-3258. UMMS is an equal opportunity employer.

MINNESOTA

PRAIRIE ST. JOHN'S

Offering Hope and Healing to Those Suffering from Psychiatric Conditions and Addictions

Child and Adolescent Psychiatrist

Prairie St. John's, a Catholic Healthcare Organization, is looking for enthusiastic and dynamic Psychiatrists dedicated to helping others improve the quality of their lives. We are expanding services in the Mpls-St. Paul area and need Psychiatrists to provide care at Child_Adolescent PHP and Clinic.

The Prairie St. John's organization started in Fargo, ND and provides services in a continuum of care that includes inpatient, partial hospital, intensive outpatient and clinic services to adults, adolescents and children. Starting salary up to $210,000 dependent on qualifications, plus potential productivity compensation. Excellent benefits. Full or Part-time available. View us online at www.prairie-stjohns.com.

Send CV and letter of interest to: Karen Frigen, Development Specialist, Prairie St. John's, 510 4th St. S., Fargo, ND 58103 or e-mail to kfrigen@prairie-stjohns.com.

TWIN CITIES! Enjoy the big city amenities of Minneapolis-St. Paul! Not-for-profit facility is seeking an Adult psychiatrist to perform either **ALL OUTPATIENT** or **ALL INPATIENT** work. Enjoy the security of an employed position with full benefits. For immediate consideration, call Lindsay McCartney @ 800-735-8261 x 213, fax your CV to 703-995-0647 or e-mail: lmccartney@medsourceconsultants.com

MISSISSIPPI

HORIZON HEATH
Associate Medical Director

The Gateway city of Northern Mississippi, Corinth, has an opportunity for an Associate Medical Director for a 19-bed Adult psych unit. Location provides an excellent opportunity to establish your own practice with the benefit of a stipend, income guarantee and call coverage. Contact Diane Odom Horizon Health for more details, Email CV to diane.odom@horizonhealth.com, Fax: 972-420-8233. 800-935-0099. EOE

MISSOURI

MEDICAL DIRECTOR

Horizon Mental Health is seeking DYNAMIC Medical Director for it's Inpatient Psychiatric Programs in Silkeston, Sullivan, & Farmington, MO. All programs are well established with excellent potential for outpatient Private Practice. Excellent Salary and Benefits Offered. Contact: Michael Lemos, 972-420-8232, Fax: 972-420-8252 or email CV: michael.lemos@horizonhealth.com EOE.

Ozark Center
Freeman Health System
Behavioral Health Division

Adult and Child/Adolescent Psychiatrists

- Join the Behavioral Health Division for FHS which is the largest & fastest growing health system in the area.
- Eight psychiatrists working together as a group in a shared call situation
- At FHS enjoy the security and growth potential of a fully integrated delivery system with the completion of a large expansion of facilities opening in 2007.
- Join freedom and autonomy of working within a physician-driven system with 170+ employed physicians covering all specialties providing an excellent local and regional referral base for your services

EXCELLENT SALARY AND BENEFITS
JOPLIN, MISSOURI -Service Area of 450,000 + Lakes, fishing, hunting; excellent public & private schools; mild climate-four seasons; one of the lowest costs of living in the nation. Call Nancy at 800-353-6812, Fax CV to 417-347-9320.

We want to hear from you!!
njpaul@freemanhealth.com/
www.freemanhealth.com

Inpatient Psychiatry; Academic Department

UMKC Department of Psychiatry and Western Missouri Mental Health Center on the medical school campus in Kansas City seek a FT psychiatrist to provide patient care, teaching and training on an adult acute inpatient unit that is an active training site for the residency program and medical student clerkship. Typical caseload is 10 to 12. State-of-the-art facility opened in January, 2004. Thirteen psychiatrists on staff. Competitive salary and excellent benefits. Relocation costs and student loan repayment is negotiable. Send CV to Stuart Munro, MD, Chair, Department of Psychiatry, 1000 E. 24th St., K.C., MO 64108 or stuart.munro@dmh.mo.gov or call 816-512-7417.

MONTANA

PSYCHIATRIST-Seeking full-time board certified psychiatrist to fill staff position in VA Montana Healthcare System. Certifications or experience in addiction psychiatry and or pain management a plus. Responsibilities include adult outpatient treatment with urgent care/walk-in service and inpatient consultation service in a facility where state-of-the-art medicine is practiced. Fort Harrison Hospital is located in Helena, the State Capital. In beautiful western Montana, Helena has downhill and cross-country skiing, awesome fly-fishing, camping, hunting, and numerous other outdoor activities nearby. The availability of cultural activities, including concerts, annual jazz and bluegrass festivals as well as those events associated with Carroll College, a high quality educational system, is a notable asset of the community. This is also a rapidly growing community with excellent school system. It is a wonderful place to raise children. Competitive salary, benefits and liability included. Fax curriculum vitae to 406-447-7978 or call Human Resources at 406-447-7933.

NEW JERSEY

C&A psychiatrist needed for WEST OF NYC! This ideal coastal location, with research opportunities, and academic role enables one to enjoy life! 100% Outpatient duties, light call & no travel. Flexible hours too! Call Dave Featherston @ 800-575-2880 x314
dfeatherston@medsourceconsultants.com

The Garden State!
Respected free standing psychiatric hospital has 2 needs. 1) MEDICAL DIRECTOR - addictions experience or interest is a plus 2) C&A psychiatrist- 100% OUTPATIENT. **Rewarding opportunity** with competitive base salary & full benefits package! For more info, contact Ariana Sanjabi at 800-735-8261 x 214, fax your CV to 703-995-0647 or email: asanjabi@medsourceconsultants.com

NEW MEXICO

Presbyterian Medical Services is a non-profit integrated healthcare network with JCHO accreditation providing medical, dental, behavioral health, children's services and supportive living services to the multi-cultural people of New Mexico. We are seeking a **Psychiatrist** who will see clients of all ages to work in our Farmington clinic. Excellent benefits. Sign-on bonus offered. For more information contact Diane Kramer at (800) 477-7633; fax (505) 954-4414; diane_kramer@pmsnet.org; P.O. Box 2267, Santa Fe, NM 87504. EOE.

NEW YORK CITY & AREA

PSYCHIATRISTS

LUTHERAN HEALTHCARE is currently seeking full-time NYS-licensed ambulatory care psychiatrists for positions in the Sunset Terrace Mental Health and Substance Abuse Treatment Center, in the Sunset Park area of Brooklyn.

Openings include a **FT Adult Psychiatrist** with interest/expertise in HIV and addiction treatment, and a **FT Child/Adolescent Psychiatrist.** Both positions offer opportunity for interface with primary care and family support settings. Bilingual Spanish, Chinese, or Arabic strongly desirable. Psychiatrists will offer treatment in facilities that have a Federal Mental Health HPSA (Health Profession Shortage Area) designation for loan repayment purposes. Minimal call responsibility.

Conveniently located for travel from all NYC Boro's. For consideration please email: bgoff@lmcmc.com, fax (718) 630-8594 or send CV to: Bradford M. Goff, M.D., Department of Psychiatry, Lutheran Medical Center, Suite 2-45, 150 55th Street, Brooklyn, NY, 11220. EOE/AA M/F/D/V

LUTHERAN HEALTHCARE

Psychiatrists
Full time positions available at Kirby Forensic Psychiatric Center, a New York State Office of Mental Health facility specializing in the treatment of a wide range of patients with forensic concerns. The psychiatrist leads a multi disciplinary team, with opportunities to utilize clinical, administrative, and teaching skills. Prior forensic training is not expected, but opportunities exist to develop forensic skills. Kirby is affiliated with the NYU residency and forensic fellowship programs. We are conveniently located near the Triboro Bridge.

Please fax or mail resume to:
Kirby Forensic Psychiatric Center
Wards Island Complex
Wards Island, NY 10035
James Hicks, M.D.,
Associate Clinical Director
Fax 646-672-6893
Kirby Forensic Psychiatric Center is an equal opportunity employer

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Consulting Psychiatrist

BC/BE - Psychiatrist to provide consultation services in long term care setting. (NH, SNF) PT/FT. Above average salary, flexible hours. Recent graduates encouraged to apply.

Psychologists

FT/PT - NY State licensed, to provide IQ testing for MRDD population, excellent compensation.

Please contact: Carlos Rueda, M.D. at Tel: 718-920-9093 or via fax - 718-920-9217, e-mail - crueda@olmhs.org

NEW YORK STATE

Psychiatrists Only
locum tenens and permanent placement

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Don Ceniza
800-583-2256

Forensic 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 a new 80 bed Sex Offender Treatment Program. Additional training in forensic psychiatry is helpful, but is not required. We are designated by the Federal Government as M.H.P.S.A. In addition to salary ($148,922 to $154,528) 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, excellent retirement plan and educational and professional leaves.

Situated on the scenic St. Lawrence Seaway in northern New York State, SLPC is located in Ogdensburg, New York, 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, New York. 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: Teresa Dishaw, St. Lawrence Psychiatric Center, 1 Chimney Point Drive, Ogdensburg, NY 13669, or at slastad@omh.state.ny.us If you have questions, call (315) 541-2182.

Physician Clinical Research Scientist in Integrated Healthcare

The Center for Integrated Healthcare, a newly funded research, clinical and educational enterprise spanning the VA Healthcare Network, Upstate New York (VISN 2), is actively recruiting for a Physician Clinical Research Scientist with interest and experience in the integration of behavioral health and primary care services. The Center is headquartered in Syracuse and includes VA medical centers and academic affiliates in Buffalo and Albany, with numerous other regional participating VA healthcare facilities. The mission of the Center is to improve the healthcare of veterans by increasing the use of evidence-based behavioral health interventions in the primary care medical setting. The successful candidate will provide scientific leadership for a research project or projects under his/her direction through the Center. The successful candidate will join a team of doctoral level researchers, clinicians and educators working together to improve the health care of veterans. The position can be located in Syracuse, Buffalo or Albany, based upon the successful candidate's preference and best match of the professional research community.

Qualifications: The successful candidate may be a psychiatrist or primary care physician who will provide scientific leadership for a research project or projects under his/her direction through this newly created center. The successful candidate must possess an MD and will also need to possess or be eligible for a New York State medical license and be board-certified in the appropriate medical specialty. Fellowship experience is desirable. A strong background in health services research is expected. Areas of research focus are negotiable but should definitely include interest, experience and expertise in the integration of mental health services, broadly defined, in the primary care medical setting. Experience in the VA system is preferred as is current NIH or VA research funding. In the absence of current extra-mural research funding, the successful candidate's application must demonstrate a strong probability of such funding in the near future. U. S. Citizenship is required. The VA is an Equal Opportunity Employer.

Excellent salary and benefits include 13 vacation days and 13 sick days (with unlimited accrual) per year, 10 paid holidays, health/life insurance and federal retirement.

The incumbent will receive a faculty appointment at the Assistant Professor to Professor level in either the Department of Psychiatry at the State University of New York, Upstate Medical University in Syracuse, NY; the Department of Psychiatry, Albany Medical College; or the Department of Psychiatry, State University of New York at Buffalo, depending upon location. Faculty rank will be commensurate with background, professional qualifications, and contributions to the department.

Applications will be considered until the position is filled. Submit cover letter, curriculum vitae, and contact information for three references via mail, fax or e-mail to:

Stephanie Hamilton, HR Specialist
VAMC, 800 Irving Avenue
Syracuse, NY, 13210
Phone: (315) 425-4638
Fax: (315) 425-2447
E-mail: stephanie.hamilton@med.va.gov

GREATER BINGHAMTON HEALTH CENTER
ADULT PSYCHIATRIST
And
CHILD/ADOLESCENT PSYCHIATRISTS

GBHC, (JCAHO-Accredited New York State Office of Mental Health facility) is seeking full time, board certified/board eligible **ADULT PSYCHIATRISTS** for its 140 bed adult inpatient facility and **CHILD/ADOLESCENT PSYCHIATRISTS** for its Child/Adolescent unit. Abundant on-site CME. Salaried, permanent positions with excellent New York State benefits.

Submit CV to: Personnel Office, Greater Binghamton Health Center, 425 Robinson St., Binghamton, NY 13904. Fax: (607) 773-4117. EOE/AAE.

Northern New York!
Psychiatrist

A **Psychiatrist** is needed for a 28-bed adult inpatient unit located in a 159-bed community hospital and regional referral center. Positioned on the US/Canadian border, the city offers the opportunity to explore the cultures of neighboring Canada. Charming city located along the southern shore of the beautiful **St. Lawrence River**. Salaried position. **J-1 Waiver Available**. Please contact Mark Blakeney, Horizon Health, for more details. Office 800-935-0099, e-mail mark.blakeney@horizonhealth.com, fax 972-420-8233. EOE

Assistant/Associate Professor (2 Positions)

Stony Brook University has two faculty positions for Assistant/Associate Professors of Mental Health Services Research/Psychiatric Epidemiology available immediately. *Required:* Ph.D., D.P.H., or M.D. or equivalent. Doctoral degree from accredited institution. Demonstrated research experience in Mental Health Services, Psychiatric Epidemiology, or Mental Health Policy. *Preferred:* Track record of funded research in this area. Salary commensurate with experience; full benefits. Send resume to: Mark J. Sedler, M.D., MPH, Chairman, Department of Psychiatry and Behavioral Science, Health Science Center, T10-020, Stony Brook University, Stony Brook, NY 11794-8101, or fax: (631) 444-1560. Equal Opportunity/Affirmative Action Employer. Visit *www.stonybrook/cjo* for further information.

Inpatient/ Outpatient Psychiatrists
Ellis Hospital
Schenectady, NY 12308

The Ellis Hospital Department of Psychiatry, a respected leader in mental health in the Capital Region of New York State, has openings for full-time NYS licensed, BC/BE inpatient and outpatient psychiatrists. The hospital offers a generous salary and benefit package, opportunities for continuing education, and a stimulating work environment.

Ellis Hospital is located in Schenectady, NY, in the Mohawk Valley at the foothills of the Adirondack Mountains. The area is well-known for its beautiful lakes, including scenic Lake George, numerous parks, ski resorts, golf courses, and the famous Saratoga Raceway, all within an hour's drive. Major cities within a three-hour drive include New York and Boston.

For further information, contact Anthony Yacona, M.D., Chairman, Department of Psychiatry, Ellis Hospital, 1101 Nott St., Schenectady, NY 12308 at (518)-243-4154 or e-mail yaconaa@ellishospital.org.

Practice In the Perfect Place!

Consider this opportunity to practice a combination of inpatient and outpatient psychiatry in beautiful Saratoga Springs, NY. Saratoga Hospital seeks a BE/BC psychiatrist to provide care as part of a close-knit multi-disciplinary care team on a 16-bed adult inpatient unit. This position is full time when combined with an outpatient position at the Saratoga County Mental Health Center. Call is 1:8, shared with the unit Director and County Mental Health physicians. Interest in ECT is required to provide backup to Director. Compensation is competitive.

Located a half hour from Albany, and less than three hours from NYC, Montreal and Boston, Saratoga Springs offers lovely neighborhoods and a downtown with fine restaurants and specialty shops. The city is known for world-class entertainment including thoroughbred racing and the Saratoga Performing Arts Center. Nearby mountains, lakes and rivers beckon outdoor enthusiasts for year-round recreation. Contact: Denise Romand, Medical Staff Recruiter, Saratoga Hospital, 211 Church St., Saratoga Springs, NY 12866. Phone: 518-583-8465; Fax: 518-580-2605; docfind@saratogacare.org

NORTH DAKOTA

PRAIRIE ST. JOHN'S

Medical Director Opportunity

Prairie St. John's, located in Fargo, ND is seeking a talented and experienced Medical Director. This position actively directs and coordinates the activities of both Child_Adolescent and Adult Services, along with providing clinical care for an Adult inpatient caseload; primarily chemically dependent patients. The Medical Director's duties include Psychiatric personnel selection, orientation, and evaluation, overall clinical program refinement and oversight, and policy development and review. Approximately 1/3 administrative, 2/3 clinical practice. Reports to Chief Executive Officer. Requires BC in General Psychiatry and previous supervisory experience. Salary $210k - $240k depending on qualifications.

The Fargo, ND-Moorhead MN metro area has a population of 180,000 and has been named one of the best places to live, raise a family, work and do business by Forbes magazine (May 2005). We are a college community located near the beautiful Minnesota lakes country offering excellent educational systems, recreation and sporting activities as well as a variety of entertainment and cultural events.

Prairie St. John's provides an excellent compensation and benefits package. View us on-line at www.prairie-stjohns.com.

Send CV and letter of interest to: Karen Frigen, Development Specialist, Prairie St. John's, 510 4th St. S., Fargo, ND 58103 or via e-mail to kfrigen@prairie-stjohns.com.

MeritCare Health System of Fargo, ND is seeking an Adult Psychiatrist to join its 32-member multi-disciplinary Psychiatry Department. Faculty appointment and teaching of psychiatry residents is available through University of North Dakota School of Medicine. MeritCare is an integrated 384-physician multi-specialty group practice, 583-bed Level II tertiary/trauma hospital with 26 primary care clinic sites in two states. Sister cities, Fargo, ND and Moorhead, MN are a tri-college community of 200,000 located near the heart of Minnesota's lake country. Fargo-Moorhead offers excellent educational systems, recreation and sporting activities as well as a variety of entertainment and cultural events. This is an excellent opportunity with a competitive compensation and benefits package being offered. Drug-free workplace. AA/EOE. This is not a designated HPSA site.

To apply send CV to:

Jill Gilleshammer, Physician Recruiter
MeritCare Health System
P O Box MC
Fargo, North Dakota 58122
Phone: (800) 437-4010, ext. 280-4851
Email: Jill.Gilleshammer@meritcare.com

OHIO

Very Desirable Cincinnati Suburb! Reputable acute care facility seeks BE/BC Adult Staff Psychiatrist. Carry approx. 12 patients per day on an inpatient basis. Manageable call schedule, which is back up to moonlighters. Call Ken Pruchnicki @ 800-575-2880 x. 319 kpruchnicki@medsourceconsultants.com

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CLEVELAND SUBURBS! Outstanding opportunity with a local CMHC to work **100% OUTPATIENT** with **NO CALL!** Position is based on a 37 ½ hour work week & comes with an *academic appointment*! Competitive salary & benefits package offered. For more info, call Sarah McGlinnen @ 800-735-8261 x 216, fax your CV to 703-995-0647 or e-mail: smcglinnen@medsourceconsultants.com

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PSYCHIATRISTS
Greater Cleveland Area

Horizon Health seeks psychiatrists for hospital-based psychiatric services in greater Cleveland, OH. Opportunities exist for: Child/Adolescent, General Adult, Geriatric, and Eating Disorders Specialists. **Salaried positions with exceptional benefits. J-1 waiver applicants welcome.** Contact: Mark Blakeney, Horizon Health, 800-935-0099, fax CV: 972-420-8233, or email mark.blakeney@horizonhealth.com. Visit our web site: www.horizonhealth.com. EOE.

OREGON

Oregon State Hospital

Oregon State Hospital is currently recruiting for Psychiatrists with interest and/or experience in adult and forensic programs. A strong benefits package complements salary. Opportunities for additional on-call work can increase your income substantially.

Oregon State Hospital provides specialized mental health services, including general adult, geriatric, and forensic treatment programs with campuses in Salem and Portland. Oregon State Hospital currently employs approximately 1,200 staff, including 30 Psychiatrists.

Located in the beautiful Willamette Valley, the area offers a great diversity of recreational activities. Within an hour's drive one finds the Cascades, the Coastal Range, and the Pacific Ocean. Oregon is justifiably famous for its world-class fishing, hunting, skiing, golfing, windsurfing, white water rafting, camping, and mountaineering opportunities.

Contact:
Becky Hawkins, Office of Human Resources
Oregon State Hospital
2600 Center Street NE
Salem, OR 97301-2682

Phone: (503) 945-2822
Fax: (503) 945-9910
E-Mail: Becky.Hawkins@state.or.us

PENNSYLVANIA

Outpatient Child/Adolescent and Adult Psychiatrists: Positions available in the scenic Laurel Highlands of Southwestern Pennsylvania (60 minutes SE of Pittsburgh/3 hours NW of to D.C.). Join team of seven psychiatrists in a progressive community-based behavioral health program. Full-time and part-time positions available in a comprehensive outpatient service. Treatment provided in concert with a team of professional counselors and certified psychiatric nurses. Crisis Intervention team provides 24/7 on-call coverage. Competitive salary and excellent benefit package. **J-1/H-1 positions available**. Please forward CV to: Brian Eberts, M.D., Medical Director, Chestnut Ridge Counseling Services, Inc., 100 New Salem Road, Uniontown, PA 15401 FAX: 724 437-6415 EMAIL: beberts@crcsi.org

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PITTSBURGH - Mercy Behavioral Health, part of the Pittsburgh Mercy Health System, is seeking an adult psychiatrist to start in December or January. We offer competitive compensation and an excellent benefits package, all with a schedule that will fit your needs. The position is flexible, which may include combinations of outpatient, inpatient, residential and other possibilities. Please contact Jim Jacobson, M.D., Medical Director, Mercy Behavioral Health, 330 S. 9th St., Pittsburgh, PA 15203.
Phone 412-488-4927, Fax: 412-488-4929, e-mail: JJacobson@mercybh.org

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PSYCHIATRIST
Salary Plus Benefits

Horizon Health managed inpatient psychiatric program seeks psychiatrist 45 minutes north of **Pittsburgh. Salaried position with benefits**. Join a successful, thriving, well established group practice in the area as well as service a 20-bed Geropsych program or a 20-bed Chemical Dependency program. Contact: Mark Blakeney, Horizon Health, 800-935-0099 x7473, fax CV: 972-420-8233, or email mark.blakeney@horizonhealth.com. Visit our web site: www.horizonhealth.com. EOE.

UNIQUE CAREER OPPORTUNITY
FOR ADULT PSYCHIATRIST

This is a superb opportunity for a BC/BE psychiatrist interested in a combination of emergency psychiatry and inpatient care. Establish a close working relationship with our psychiatric emergency service and our inpatient behavioral science unit. You will work with a large salaried hospital-based group who practice at LVH, an 800-bed academic community hospital where opportunities exist to teach medical students and residents and pursue career advancement. The successful candidate will also be eligible for faculty appointment at Penn State/Hershey. We are offering an excellent call schedule and a favorable lifestyle so that you can enjoy the beautiful Lehigh Valley where more than 700,000 people appreciate safe neighborhoods, good schools and easy access to major metropolitan areas. Philadelphia is 1 hour south and NYC is 1.5 hours east. For more information, call 610-969-0213. Email CV to Pamela.Adams@LVH.com or fax to (610) 969-0214.

Pennhurst Medical Group, P.C. Various Pennsylvania locations BC/BE, Excellent Salary, Benefits, No Billing, Full Time, Part Time and Locums Positions. Send CV to bp@pennhurstmedical.com or by fax 610-524-0952. Call Bob Plunkett at 610-524-2400 x 160 with any questions or for more information

RHODE ISLAND

Rhode Island Hospital

Psychiatrist, Adult Outpatient and Mood Disorders

The Department of Psychiatry, Rhode Island Hospital, a Lifespan partner and Brown University affiliated program, is seeking a psychiatrist with interests in adult outpatient responsibilities within an established fulltime hospital-based group. The outpatient component involves assessment and treatment of patients as a member of a specialized multidisciplinary team. Interest and expertise in mood disorders is desirable. We offer an opportunity for both teaching as well as clinical research involvement to complement clinical practice. The candidate must be Board Certified or eligible, and may be eligible for a clinical appointment at Brown University School of Medicine. Salary and benefits commensurate with level of training. Please send CV's along with a letter of interest to Richard J. Goldberg, M.D., Psychiatrist-in-Chief, APC-9, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903 and/or e-mail to rjgoldberg@lifespan.org.

SOUTH CAROLINA

Minutes from Charlotte, NC!
Enjoy the many amenities of a growing metropolitan city! Several gorgeous lakes nearby. Sunny weather & numerous outdoor activities available! Opportunity to do a mix of inpatient & outpatient work with a very stable and lucrative facility that is expanding. 4 NEEDS - 1) ADULT 2) C&A 3) GERIATRIC fellowed/experienced 4) ADDICTIONS fellowed/experienced. Exceptional compensation offered & tons of referrals waiting in this booming area. For more info, call Carrley Ward @ 800-735-8261 x 219, fax your CV to 703-995-0647, e-mail: cward@medsourceconsultants.com.

MYRTLE BEACH!
Staff Psychiatrist OR Medical Director

Located in Conway, SC (Located 20 minutes from Myrtle Beach). A Psychiatrist is needed for a geriatric psychiatric program. Physician will be responsible for the start up of geriatric psych program. Behavioral Health program consists of 28-acute care beds; 20-bed adult psych & 8-bed geriatric psych beds. Ideal candidate will be interested in moving to the local area and starting a private practice. Medical Director position also available. Medical Director will oversee 28-bed acute care program, High Management Group Homes, and RTF: Adolescent Residential Program. Contact Diane Odom, Horizon Health, 800-935-0099 or e-mail CV to diane.odom@horizonhealth.com, EOE

TENNESSEE

EAST TENNESSEE STATE UNIVERSITY
JAMES H. QUILLEN COLLEGE OF MEDICINE
DEPARTMENT OF PSYCHIATRY
& BEHAVIORAL SCIENCES

DIRECTOR OF RESIDENCY TRAINING

Full-time position available for Director of Psychiatry Residency Training. Position may include inpatient and/or outpatient. Responsibilities include training of psychiatric residents and medical students and research activities. Salary is competitive with funding available through the Medical School, faculty private practice, and extramural contracts. ETSU is located in the Tri-Cities Tennessee/Virginia region, which was the first region in the nation to be designated as an "All-American City" with attractive cost-of-living, crime rate, climate, and health care. Applicants should submit a CV and two letters of references to Merry N. Miller, M.D., Chair, Department of Psychiatry and Behavioral Sciences, ETSU, Box 70567, Johnson City TN 37614. Telephone inquiries should be made at (423) 439-2235 or e-mail at lovedayc@etsu.edu. AA/EOE.

HORIZON HEALTH
Medical Director

Horizon Health seeks an outstanding Medical Director for the 22-bed adult psychiatric program in northwest Tennessee. State-of-the-art 142-bed hospital provides high quality patient care. Conveniently located less than two hours from Memphis and Nashville, TN. Located near Kentucky Lake where outdoor activities are plentiful. Excellent practice opportunity with solid support from hospital and staff. Competitive stipend, practice guarantee, and relocation package. Please contact Diane Odom for more information 800-935-0099 or e-mail diane.odom@horizonhealth.com EOE

Staff Psychiatrist
KNOXVILLE, TN

Horizon Health seeks an outstanding Staff Psychiatrist for a multi-disciplinary inpatient treatment program (Adult & Geriatric Psych) as well as Intensive Outpatient behavioral health programs. Program located within 500-bed full service hospital. Salaried position with complete benefits package: medical, dental, 401K, Insurance, holiday & vacation. Knoxville, a city that offers nightlife, outdoor activities, and a vibrant arts community. Contact Diane Odom for more information 800-935-0099 or e-mail diane.odom@horizonhealth.com EOE

TEXAS

Texas Forest Country - The Burke Center, a multi-site, JCAHO accredited community mental health center, has an immediate opening for either a **general psychiatrist or child psychiatrist** willing to treat some adults. The position is outpatient only, primarily located in Livingston, although there may be some work in other locations or by telemedicine. Enjoy an excellent lifestyle with a 40-hour work week, no call, competitive salary, and fantastic benefits. Physician Assistants and Advanced Nurse Practitioners will be considered as well. Recreational opportunities abound in national forests nearby. Houston is less than 2 hours away; Dallas 3 hours; major state university nearby. Please send CV to Mark Janes, M.D., Medical Director, Burke Center, 4101 S. Medford Drive, Lufkin, TX 75901. Fax: (936)634-8601. Email: markj@burke-center.org. Check out the details on our website: *www.burke-center.org*.

Psychiatrists needed in Houston, Texas. Full-time employee, very competitive salary and benefits package. Seeking two (2) psychiatrists: Position 1 is for provision of physician services to psychiatric patients in an inpatient setting. Position 2 is for provision of physician services to psychiatric patients primarily in an outpatient setting, with some inpatient and possible psychiatric research services. Must have current Texas Medical License. Current Medicare number preferred. **Please email resume and references to: dgafford@dapaprograms.com**

CHILD/ADOLESCENT PSYCHIATRIST
OPPORTUNITY

Immediate opportunity for psychiatrist to work with a supportive free-standing behavioral hospital staff, while building your inpatient practice. Padre Behavioral Hospital offers distinct units for children, adolescents, and adults with emotional, psychiatric and/or substance abuse problems. Corpus Christi is a thriving small city, a tropical paradise, with a growing cultural center, where you can determine your own career and lifestyle choice. Expected income of $200,000 to $250,000 per year with private practice. Please email CV to kathyb@padrehospital.com, or fax to Kathy Bubela at 361-986-1810.

San Antonio State Hospital is a 203 bed JCAHO accredited psychiatric hospital located within 10 minutes from the downtown Riverwalk in beautiful San Antonio, Texas. We are seeking a board certified or board-eligible full-time Adult Psychiatrist and one full-time Child/Adolescent Psychiatrist. The Child/Adolescent Psychiatrist will join our two board certified child psychiatrists and an experienced multi-disciplinary treatment team on our Adolescent Unit. The Adult Psychiatrist will join the multi-disciplinary treatment teams on our adult units. Advantages include no state income tax, paid sick leave, paid vacation, paid time off for CME, 12-14 paid holidays, retirement plan, availability of additional 401 or 457 plan, possibility of clinical faculty appointment with the University of Texas Health Science Center at San Antonio; on-call not required but option to do so for additional pay, 40 hour work week, congenial colleagues and co-workers, San Antonio, Texas has excellent schools, a myriad of cultural, educational opportunities and nationally recognized medical center and wonderful climate.

Contact: Terresa Stallworth, M.D., Clinical Director for more information
Phone (210) 531-7715 or 7716
Fax (210) 531-7876
Email Address:
terresa.stallworth@dshs.state.tx.us
San Antonio State Hospital
6711 S. New Braunfels, Suite 100
San Antonio, Texas 78223-3006
San Antonio State Hospital is an equal opportunity/drug free workplace

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BLUEBONNET TRAILS MHMR
Has openings for the following positions :

2 FULL TIME STAFF PSYCHIATRISTS to serve our adult and child population in the following counties: GUADALUPE (Seguin, TX), CALDWELL (Luling, TX), and GONZALES (Gonzales, TX). Willing to negotiate contract/part time inquiries.
PART TIME (2 days per week) CHILD AND ADOLESCENT PSYCHIATRIST available in BASTROP and BURNET counties.

Counties are beautifully located in central Texas, close to Austin and San Antonio. Please send CV to Vicky Hall, Mental Health Director, at Vicky.hall@bluebonnetmhmr.org, fax (512) 244-8401, or for additional information, visit our website at www.bluebonnetmhmr.org

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Assistant Professor

The Department of Psychiatry and Behavioral Sciences at the University of Texas Medical Branch in Galveston is seeking an Assistant Professor.

Responsibilities include inpatient care, outpatient clinics, resident supervision and teaching. Research opportunities are available. Successful candidates must be board certified/board eligible in Psychiatry.

Candidates with interest and skills in this area should send a curriculum vitae and cover letter to: **Robert M.A. Hirschfeld, M.D., The University of Texas Medical Branch, Department of Psychiatry and Behavioral Sciences, 301 University Boulevard, Galveston, TX 77555-0188**.

The University of Texas Medical Branch is an equal opportunity, affirmative action institution which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

Denton, Texas

Mayhill Hospital located in **Denton, Texas** is currently seeking a Psychiatrist to serve as Assistant Medical Director for its 30-bed inpatient program as well as to provide comprehensive outpatient services. For additional information, please contact Rhonda Ashley-Dixon at 1-800-786-6211, ext. 313. CVs may be faxed to (615)-230-3149 or emailed to rad@seniorhealthinc.com.

Well-established Private Practice - Seeking Psychiatrist for successful, established private practice in San Antonio, Texas. Physician has the option to become associate/partner. Practice has been providing Psychiatric services for 12 years. Options available - Locum Tenems - rent the practice by August 1, 2006; form a partnership with option to buy later or sell out. This position will require a minimum effort of 40 hours per week. Exclusively outpatient, dedicated to mood disorders to life span of 8 years to 100 years. No inpatient work, no on call, with annual salary potential over $200,000. Physician has option to work Saturdays and work inpatient if desired. Practice attends many up scaled patients from Mexico. Very well controlled Practice can see up to 90 patients per week. Qualifications include: Board Certified or Board Eligible in Psychiatry, Texas Medical License, DEA number, and bilingual in Spanish a plus. Submit inquiries and CV to: Isaac Ayala & Associates, 10000 IH Ten West, Suite 450, and San Antonio, Texas 78230. Call 210 697-8155, Fax 210 697-8850 or e-mail ayalai@aol.com.

VERMONT

Faculty Position - Mood and Anxiety Disorder Clinic, Mid-Level Psychiatry Service

The University of Vermont College of Medicine and Fletcher Allen Health Care are seeking two full-time faculty members at the Assistant Professor level to join an enthusiastic team of professionals to work in their Mid-Level Psychiatry Service. This service consists of a partial hospitalization program, an intensive outpatient program and intensive outpatient services for patients suffering from mood and anxiety disorders, in acute exacerbation. The methods of treatment offered include state-of -the art multidisciplinary modalities as group psychotherapy, individual psychotherapy, experienced treatment coordination and pharmacological management by licensed therapists, psychologists, psychiatric nurses and psychiatrists. The clinical approach is cognitive-behavioral with elements of dialectic behavior therapy with interdisciplinary involvement.

The selected candidate will be responsible for performing psychiatric evaluations, pharmacological management and for contributing to the interdisciplinary collaboration process in the newly created Mood and Anxiety Disorders Clinic which will be integrated to the well established partial hospitalization and intensive outpatient programs.

An appreciation of the importance of and satisfaction from performing these critical functions and an ability to work collaboratively are essential. An interest in systems of care is encouraged. Knowledge of evidence-based medical practice and prior experience in the provision of care in a partial hospitalization setting and/or high volume outpatient clinic is an asset.

Applicants must have a medical degree and be board certified (preferably) or board eligible in psychiatry. Experience in inpatient or community settings preferred. Qualifications in Addiction, Geriatric Psychiatry, Somatic Medicine a plus.

Burlington Vermont is located in the beautiful Lake Champlain region, surrounded by the Green and Adirondack Mountains. It is a great place for families with excellent public schools and year-round recreational opportunities. It is home to the University of Vermont and three independent colleges that provide an academically stimulating and culturally rich environment. Montreal and Boston are within easy driving distances.

Please apply online at www.uvmjobs.com or send a letter of interest, *curriculum vitae*, and the names, addresses and telephone numbers of three references to:

Isabelle Desjardins, M.D.
Fletcher Allen Health Care
Psychiatry Service, Patrick 4
111 Colchester Ave
Burlington, VT 05401
e-mail: isabelle.desjardins@vtmednet.org

The University of Vermont is an Equal Opportunity and Affirmative Action Employer. Women and people from diverse racial, ethnic, and cultural backgrounds are encouraged to apply. Applications will be accepted until the position is filled, but we strongly encourage submission of required materials by August 1, 2006.

Central Vermont

Washington County Mental Health Services, a CMHC located in Montpelier, is seeking a full time psychiatrist to join its high quality, dedicated psychiatric staff. Opportunities exist for outpatient work with geriatic and adult patients suffering from a wide range of mental illnesses, developmental disorders, and mental retardation. Particularly needed is a psychiatrist for a newly developing, innovative, recovery oriented and trauma informed, highly staffed, ten bed, residential program providing a level of services not previously available outside of a hospital setting in Vermont. Competitive salary and benefits; EOE. Applicant must be BE/BC. Please send cover letter and CV to: Stuart Graves, MD, 9 Heaton Street, Montpelier, VT, 05602, or e-mail to Stuartg@wcmhs.org.

VIRGINIA

Faculty, Addictions Psychiatry, Virginia Commonwealth University
The Department of Psychiatry invites applicants for tenured or tenure-eligible faculty positions as faculty and/or Chair of the Division of Addiction Psychiatry. The successful applicants will be expected to have an MD, PhD or equivalent doctoral-level training with appropriate research and leadership experience. Rank is open, depending on the qualifications and experience of the selected applicant. The ideal candidate should have substantial research experience in basic, treatment and/or services research focused on problems of substance abuse. Candidates are not required to be qualified as treatment providers, although such candidates would be preferred as applicants. Funded ACGME accredited Fellowship Program. Strong department with over 90 fulltime faculty. Opportunities exist for faculty to interact with the multi-disciplinary group of over 45 faculty in the Institute for Drug and Alcohol Studies, who conduct research in such areas as neuroscience, pharmacology, medications development, prevention, treatment, women's health and psychiatric genetics. For very strong candidates, there may be opportunities to identify significant other resources, including additional faculty and/or post-doctoral positions. Virginia Commonwealth University is an Equal Opportunity/Affirmative Action employer. Women, persons with disabilities, and minorities are encouraged to apply. Send applications to Joel J. Silverman, M.D., Chairman, Department of Psychiatry, MCV/VCU Box 980710, Richmond, VA 23298 (jsilverm@vcu.edu).

HORIZON HEALTH
INTERIM Medical Director
Southern Virginia

Horizon Health seeks a Psychiatrist to work on an INTERIM basis from September 4-October 4 2006. State-of-the-art medical center provides high quality patient care. Located in South Hill, Virginia the Psychiatrist will be responsible for the 15-bed adult psychiatric program. Physician will spend 2-3 hours on the inpatient program a day and will share call coverage with local physician. South Hill is located about an hour equal distance from Richmond, VA and Raleigh, NC. Horizon Health will pay physician a daily rate. Interim position could lead into permanent opportunity with full time Medical Director. Please contact Diane Odom for more information 800-935-0099 or e-mail diane.odom@horizonhealth.com, EOE

GEROPSYCHIATRIST: Virginia Commonwealth University, Department of Psychiatry recruiting Virginia licensable BE/BC psychiatrist in to provide clinical care, training of fellows, residents and medical students, and research activities at Piedmont Geriatric Hospital (80%) and the University campus (20%). Teaching, research experience and geropsychiatry fellowship preferred. J-1 AVAILABLE. PGH is specialty geriatric state hospital located in Burkeville, VA, 35 minutes from Richmond. VCU is a large urban university with robust health science campus and 750-bed university hospital. The Department of Psychiatry employs over 80 fulltime faculty and has well-funded research in women's mental health, genetics, addictions, child mental health and psychopharmacology. Richmond, the State Capital, has moderate climate and rich mix of history with modern facilities, excellent suburban housing, public/private schools. Internet provides comparative cost of living. Send CV to Search Committee, c/o Mary Swartz, VCU, Box 980710, Richmond VA 23298. Virginia Commonwealth University is an Equal Opportunity/Affirmative Action employer. Women, minorities, and persons with disabilities are encouraged to apply.

Christiansburg, VA - General Adult Psychiatrist needed in Virginia's New River Valley region for state-of-the-art inpatient facility with office suite contiguous to the inpatient unit. Position provides for a combination of inpatient/outpatient psychiatry, including administering ECT; on-call an average of 6-7 days/month, including 1-2 weekend days. Virginia's New River Valley region comprises the localities of Blacksburg, home of Virginia Tech, and Radford, home of Radford University, plus the town of Christiansburg and surrounding communities, a population of 175k. Carilion Health System is a nonprofit regional healthcare system comprised of several acute-care hospitals including teaching/tertiary referral center nearby, medical education programs, and 70+ multispecialty clinics. Base salary with bonus incentive plan based on quality outcome and scorecard measures. Requirements: Minimum of 3 years experience post-residency, and/or other professional experience prior to completing residency; ABMS-BC ideal, or BE acceptable with plan in place to receive certification in 2 years; excellent interpersonal and communication skills. Positions available immediately. To apply, submit CV with references and cover letter to:

Rhonda B. Creger, Physician Recruiter
Carilion Health System
POB 40032
Roanoke, VA 24022-0032
Office 540-224-5189
FAX 540-985-5329
Email: rhondac@carilion.com
Website: www.carilion.com

WASHINGTON

Emergency Psychiatry Clinical Faculty Position University of Washington, Seattle, WA

Harborview Medical Center, Department of Psychiatry and Behavioral Sciences is seeking a psychiatrist in the Psychiatric Emergency Services (PES). The coverage is shared among several psychiatrists who work under the supervision of the PES Medical Director. The position will receive a UW clinical faculty appointment. The PES attending psychiatrists provide direct evaluation, triage and acute treatment to patients, and overall supervision of the clinical team, including residents. Pay scale is highly competitive due to shift work and off-hours schedule. University of Washington faculty engage in teaching, research and service. HMC has a nationally recognized psychiatric emergency service and strives to deliver state of the art care in an academic medical setting. Please forward your letter and CV to: Peter Roy-Byrne, MD, Box 359911 Psychiatry HMC 325 9th Avenue, Seattle 98104. The UW is building a culturally diverse faculty and strongly encourages applications from females and minority candidates. The UW is and EOE/AA employer.

Pacific Northwest - Inpatient and Outpatient Psychiatrists

Highline West Seattle Mental Health/West Seattle Psychiatric Hospital is a large community mental health agency located in the Emerald city of Seattle. We have FT positions available in our psychiatric hospital and PT in our outpatient mental health center. Seattle offers a full, contemporary urban experience, with excellent schools and culture, surrounded by incredible mountains and outdoor recreation. Our salary is competitive; benefits include all the standard insurances, CME, approx. 1 month leave, etc. Please contact Jeff Skolnick, MD-Chief Medical Officer 206-933-7127 or JeffS@Highline.Org

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A Career In Psychiatry In The Beautiful Wine Country Of Washington State's Walla Walla Valley

Department of Corrections
Lead Psychiatrist
Full time Staff Position
Or, Personal Contract.
All employee benefits.
96 Bed Residential Unit.
16 Bed Acute Care.
Immediate Availability.

Call or email Michael Wall
509 526 6436
mbwall@DOC1.WA.GOV

PSYCHIATRIST, SEATTLE SUBERB

Seeking a full-time BC/BE psychiatrist to join our multidisciplinary group practice.

Ours is a collegial and professionally stimulating practice environment. Established practice base and referral source. Set our own hours, 1-6 call. We offer a one-year salary guarantee with benefits. This area is consistently rated as one of the best places to live and work. Just minutes from downtown Seattle and the shores of Puget Sound. For more information please email CV to gmumma@Highlinemedical.org or Fax to 206-242-4625.

WEST VIRGINIA

PSYCHIATRISTS - William R. Sharpe, Jr. Hospital, a 150-bed, JCAHO-accredited, state psychiatric hospital and winner of APA Award for state/university collaboration, is searching for BE/BC psychiatrists. The facility is unique in the region for the range of psychiatric services offered and quality of care provided. The hospital is one of the largest training sites for various clinical disciplines including psychiatric residents, medical students as well as psychology, social work and nursing trainees. These are full time faculty positions with regionally competitive salaries and excellent benefits. There is no call duty. The area has an abundance of outdoor activities, four-season climate, and one of the lowest crime rates in the country. There are several metropolitan areas within easy driving distance. West Virginia University is an affirmative action/equal opportunity employer. Women and minority candidates are encouraged to apply. Positions will be open until filled. J1 applicants are encouraged to apply. Contact Abe Adel, MD, Clinical Director, William R. Sharpe, Jr. Hospital, WVU Department of Behavioral Medicine & Psychiatry 936 William Sharpe Road, Weston, WV 26452. 304-269-1210. bettygumfoster@wvdhhr.org

WISCONSIN

PSYCHIATRIST - Full-time position for outpatient psychiatrist with no on-call responsibilities to work in our Wauwatosa, WI counseling office. Individual must be licensable in the State of Wisconsin. Salary range $134,000 - $200,000 and excellent benefit package. Preferably adheres to evangelical Christian belief. Send CV to Mary Schoultz, HRM, Wisconsin Lutheran Child & Family Service, PO Box 245039, Milwaukee, WI 53224-9539, or for additional information, contact Dr. R.P. Ascano, Provider Service Director, (218)643-3867, rascano@wlcfs.org.

MEDICAL DIRECTOR Wausau, WI

Horizon Health seeks a **Medical Director** for a 12-bed adult inpatient psychiatric program at our client hospital in **Wausau, WI**. Attractive **salary** with full benefits in addition to administrative **stipend** paid for Medical Director's duties. Call: **1:6, Malpractice**: 100% coverage, **Health & Dental:** 100%, **Retirement:** 403B Tax Shelter Annuity, plus Defined Contribution Plan, **Sick:** 10 Days, **Vacation:** 3 weeks 1st year, 4 weeks thereafter, **CME Time:** 1 week 1st year, 2 weeks thereafter, **CME:** $5,250, **Relocation:** 100% up to $10,000, Disability/Life Insurance, Dependent Life Insurance and Flex Spending. Contact: Mark Blakeney, Horizon Health, 800-935-0099 x7473, fax CV: 972-420-8233, or email mark.blakeney@horizonhealth.com. Visit our web site: www.horizonhealth.com. EOE.

Exciting opportunity for BE-BC psychiatrist to join collegial team of dedicated professionals at a premier public facility with 100-year history of community service. 32-40 hour work week, 1:6 weekend call, no billing or managed care worries. Competitive salary with benefit package valued at an additional 35%. Ideal for physician striving for balance between career and outside interests in a family-friendly small city with nationally recognized public school system, very affordable housing and an abundance of cultural activities. You'll have plenty of free time to fish our beautiful lakes and rivers, hike, mountain bike, kayak, downhill and cross-country ski. Mail or FAX your current CV and letter of interest to: Gabriel Ticho, M.D. Clinical Director North Central Health Care Facility 1100 Lakeview Dr. Wausau, WI 54403 FAX:715-842-3630; Phone:715-848-4455; Email: gticho@norcen.org

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SPECTACULAR OPPORTUNITY FOR INPATIENT MEDICAL DIRECTOR

Gundersen Lutheran, a multidisciplinary 400 member group practice in La Crosse, WI, is seeking an experienced BC/BE Psychiatrist to perform the functions of the Medical Director of an existing Inpatient Unit and to develop a day hospital program.

This candidate will join 9 general and 4 child psychiatrists, 7 psychologists and more than 40 therapists in providing outpatient/inpatient care for a broad range of clinical disorders.

Psychiatric outpatient care is offered on our main campus and at several sites in the Gundersen Lutheran healthcare system. Inpatient care is provided in a 27-bed unit, which is adjacent to the medical center. Call will be 1:12.

Located in a city of 52,000 with a metropolitan area of 120,000 and a service delivery area of more than 500,000, Gundersen Lutheran provides the opportunity to practice metropolitan-scale medicine in a context of small town character and comforts. Nationally recognized schools, three universities, safe neighborhoods, affordable housing and extensive recreational and cultural activities make La Crosse, on the Mississippi River, an outstanding place to live and work. Our compensation package, pension plan and continuing education opportunities are exceptional.

Interested candidates are invited to call Jon Nevala, Medical Staff Development, Gundersen Lutheran, at 1-800-362-9567, ext. 54224, 1900 South Ave., La Crosse, WI, 54601, or e-mail jpnevala@gundluth.org

We support a safe, healthy and drug-free work environment through background checks and controlled substance screening.
EOE/AA

WYOMING

The Allure of the West!

- Ranked #1 in the U.S. by "Kiplinger's" for the lowest taxes paid per household
- Ideal to raise a family, possesses great schools, and retains its western charm although only 90 minutes from Denver
- United Medical Center is a 206-bed hospital that serves Wyoming, Northern Colorado, and Western Nebraska
- 16-bed Behavioral Health Unit (12 adult and 4 adolescent) and active outpatient clinic

Adult Psychiatrists
Opportunities for both inpatient and outpatient treatment of adults. Skills and experience in treating geriatrics a plus.

Addiction Specialist
Unique opportunity to spearhead and champion the expansion of a hospital-based, outpatient addiction treatment program. Specialization in addiction treatment is required.

Both candidates must be team players with excellent communication skills. Program development a plus. Board-Certified (or-eligible). Wyoming license (or-eligible).

Contact: Lauren Maines, Physician Recruiter, 214 E. 23rd St. Cheyenne, Wyoming 82001, Office: (307) 432-2649, Fax: (307) 432-3181, LMaines@umcwy.org.

International

MAKE A DIFFERENCE! Outstanding opportunity in cross-cultural psychiatry. Work as a psychiatrist in the W Pacific with all ages and diverse settings. Competitive salary with excellent tax benefits. Also eligible for NHSC loan repayment. Contact Dr Shearer docrobin@pticom.com, or: www.dphsaipan.com & www.saipanhospitaldocs.org

Fellowships

Addiction Psychiatry Fellowship - This is a PGY 5 position, to begin July 1, 2007 at the University of Illinois at Chicago, Department of Psychiatry. Fellow will acquire expertise in 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 - These are two PGY 4 Positions, to begin July 1, 2007 at Jesse Brown VA Med Ctr/University of Illinois at Chicago, Department of Psychiatry. This is an exciting opportunity for psychiatric consultation-liaison training available as a member of a primary care team (PRIME). PGY 4 residents will receive training in providing C/L to primary care team members; educate primary care team about identification and management of common psychiatric disorders. Residents will participate in ongoing didactic programs and telepsychiatry clinic. 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, 2007 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 4 positions contact: Robert W. Marvin, MD, Director Residency Training, 912 S. Wood St., MC 913, Chicago, IL 60612 FAX 312-996-3514 on or before February 15, 2007. The UIC and JBVA are AA/EOE.

Geropsychiatry Fellowship, Portland, Oregon. Recruiting for 07/01/07 ACGME-accredited PGY5 level, at Oregon Health & Science Univ and Portland VA Med Center. Flexible program with either research or clinical emphasis. Training sites include inpatient, outpatient, nursing home and community. Research and clinical strengths in end-of-life/palliative care, ethics, mood disorders, dementias, Parkinson's disease, and substance abuse. Contact Dr. Linda Ganzini, Dir, Geriatric Psychiatry Training, Mental Health Div, P3MHDC, PO Box 1034, Portland, OR 97207; (503) 220-8262, Ext. 56492; or at Linda.Ganzini@va.gov. EOE.

POSITION: Geriatric Psychiatry Fellowship

SPONSOR: University of Rochester Medical Center, Department of Psychiatry, Program in Geriatrics and Neuropsychiatry

DESCRIPTION: The University of Rochester Program in Geriatrics and Neuropsychiatry offers one-year PGY-5 clinical fellowships in Geriatric Psychiatry. Ours is an ACGME accredited program, successful completion of which makes graduates eligible for the ABPN subspecialty examination in geriatric psychiatry. The fellowship offers training in the care of older patients in a variety of inpatient, long-term care, outpatient, consultation, and palliative care settings. Supervised clinical experiences are complemented by a didactic program, elective offerings, and opportunities to develop individual scholarly and research interests. In addition to the breadth of our clinical programs and patient populations, we have a large cadre of experienced and nationally recognized clinicians, teachers, and researchers serving on our faculty. We pride ourselves on providing a stimulating, rewarding educational experience in a supportive and nurturing environment.

CONTACT: For more information please contact Jeffrey M. Lyness, M.D., Director, Geriatric Psychiatry Fellowship, Department of Psychiatry, University of Rochester Medical Center, 300 Crittenden Boulevard, Rochester, NY 14642-8409 (Phone 585-275-6741; Fax 585-273-1082; E-Mail Jeffrey_Lyness@urmc.rochester.edu)

The University of Rochester is an equal opportunity/affirmative action employer. Applications from women and minority groups are encouraged.

UNIVERSITY OF MICHIGAN GERIATRIC PSYCHIATRY FELLOWSHIP

ACGME-accredited Geriatric Psychiatry Fellowship at Univ. of Michigan and Ann Arbor VA Healthcare System (VAHS) available July 1, 2007. One-year fellowship program (PGY-5) provides broad-based clinical experience in inpatient, outpatient, nursing home settings, with unique multidisciplinary emphasis, in an extraordinarily rich academic environment. Two-year fellowship program (PGY-5 & 6) available to selected candidates and includes all clinical experience of one-year program, plus a research training component (available in basic, clinical and health services research) designed to prepare trainee for academic career. University has NIH-funded Geriatric Research and Training Center and Alzheimer's Disease Research Center, as well as the nation's first comprehensive academic Depression Center. VAHS has Geriatric Research, Educational and Clinical Center (GRECC). Candidates must have completed an approved U.S residency in Psychiatry, and must have passed USMLE Step III prior to entry into program. Applications accepted through November 1, 2006. Please send CV to Alan M. Mellow, M.D., Ph.D., Chief, University of Michigan Section of Geriatric Psychiatry, MHSL/116MH, Ann Arbor VA Medical Ctr., 2215 Fuller Road, Ann Arbor, MI 48105; Email: amell@umich.edu

UNIVERSITY OF MICHIGAN PSYCHOSOMATIC MEDICINE FELLOWSHIP

A Psychosomatic Medicine fellowship position is available at the University of Michigan, Department of Psychiatry. The one-year fellowship program (PGY-5) provides a broad-based clinical experience, with a strong multidisciplinary emphasis, and opportunities to achieve skills in research, education and administration, in an extraordinarily rich academic environment, with no night or weekend on-call. Supervision is provided by full-time attendings with board certification in Psychosomatic Medicine. The fellowship begins on July 1, 2007. Excellent salary and benefits. Candidates must have completed an approved residency in Psychiatry and must have passed USMLE Step III prior to entry into program.

Applications will be accepted through January 15, 2007. Please email/mail/fax CV to Michelle Riba, MD, Associate Director, Psychosomatic Medicine Services, Department of Psychiatry, University of Michigan Health System, 1500 E. Medical Center Drive, Room F6236 MCHC, Ann Arbor, MI, 48109-0295. Tel: (734) 764-6879; FAX: (734) 936-1130; web: http://www.med.umich.edu/psych/education, Email: gacioch@umich.edu.

Addiction Psychiatrist Research Training Fellowship

A Joint Program of Vanderbilt University Medical Center and Meharry Medical College

We are seeking applicants for our NIDA-funded training program in translational addiction research. The goal of our program is to appropriately prepare addiction psychiatrists embarking on combined clinical and research careers to engage in multidisciplinary research across the bench to bedside continuum. Trainees will conduct an original interdisciplinary research project involving preceptors from at least two out of four conceptual frameworks (psychiatry, neuroimaging, molecular medicine, and biomedical informatics). They will also complete the required didactics for the Masters of Science in Clinical Investigation. Applicants who are board eligible in Addiction Psychiatry may enter directly into the 2-year research training program. PGY-5 trainees may qualify for our ACGME-approved clinical training program which provides expertise in diagnosis and management of addiction in inpatient and outpatient settings, including a general hospital consultation service. Contact Peter R. Martin, M.D., Director, Addiction Psychiatry Interdisciplinary Research Training Program and the Vanderbilt Addiction Center, The Psychiatric Hospital at Vanderbilt, Suite 3068, 1601 23rd Avenue South, Nashville, TN 37232-8650, (615) 322-3527; e-mail: peter.martin@vanderbilt.edu or Samuel Okpaku, MD, PhD, Chair, Department of Psychiatry and Behavioral Science, Meharry Medical College, (615) 327-6063; email: sokpaku@mmc.edu.

Positions Wanted

Psychiatrist with several years of clinical and biological research experience and leadership roles in the field of schizophrenia research, looking for a full-time position to mentor young academicians and aid the development of psychiatric research in an academic, industrial, government or private foundation setting. Currently based in NYC, but willing to relocate depending on the position. Expertise includes brain imaging and genetics. Please respond to Box P-727, Psychiatric News Classifieds, American Psychiatric Publishing, Inc., 1000 Wilson Blvd. Suite 1825, Arlington, VA 22209.

Practice for Sale

Retiring psychiatrist in upscale NJ community 1 hour from Manhattan offers sale of large psychiatric practice. Average of 50-60 private pay patients weekly. Gross income over $300,000. Over 200 active files. Affiliation with outstanding teaching hospital available. All office equipment and furnishings included. Contact Ronnie at 973-267-2748 or fax 973-278-7718.

ADULT PSYCHIATRIC PRACTICE FOR SALE

Decorator designed 2 office suite (for cross referral with therapist) in beautiful Chicago suburb. Available immediately due to retirement. Over 450 active patients, grossing over $100,000 / 20 hours per week. Furniture included. Terms of purchase will be to assume lease ($675 month per person). Web Page is www.drjuraadams.com. Contact me at cell (630) 667-7509 or fax (312) 440-8863.

FOR SALE: Large practice with two psychiatrists, a nurse practitioner, a psychologist, and a licensed professional counselor. Last year gross income was $621,000. Managing physician has to sell due to illness. Please contact 713-705-0030 if interested.

Office Space Available

Spacious treatment rooms available in office suite located in the professional building adjacent to Ridgeview Institute, a psychiatric hospital, located in Smyrna, Ga., a northern suburb of Atlanta. Full service including appointment setting, reception, billing, collections, insurance filing, transcription, prescription issues and patient record requests available, including rent, at very reasonable rates. Special incentives for child psychiatrist. **For information, please call Terry Tenenbaum, president, Janell Professional Management Services at 770-431-2354. Email terrytbaum@bellsouth.net.**

CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

WARNING

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

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

INDICATIONS AND USAGE: Cymbalta is indicated for the treatment of major depressive disorder (MDD). Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

CONTRAINDICATIONS: ***Hypersensitivity***—Known hypersensitivity to duloxetine or any of the inactive ingredients. ***Monoamine Oxidase Inhibitors (MAOIs)***—Concomitant use with Cymbalta is contraindicated (*see* WARNINGS). ***Uncontrolled Narrow-Angle Glaucoma***—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use is not recommended in patients with uncontrolled narrow-angle glaucoma.

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

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, ie, beyond several months. It is also unknown whether the suicidality risk extends to adults.

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

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

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD 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, Discontinuation of Treatment with Cymbalta).

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

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (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 is not approved for use in treating bipolar depression.

MAOIs—In patients receiving a serotonin reuptake inhibitor (SSRI) 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 SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

PRECAUTIONS: ***General***—Hepatotoxicity—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) 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 Postmarketing reports have described cases of 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. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. 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. Effect on Blood Pressure—In MDD clinical trials, Cymbalta treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes). Activation of Mania/Hypomania—In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (1/1139) of Cymbalta-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/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 MDD. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania. Seizures—Cymbalta has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with MDD, seizures occurred in 0.1% (1/1139) of Cymbalta-treated patients and 0% (0/777) of placebo treated patients. In placebo-controlled clinical trials in patients with diabetic peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder. 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, Uncontrolled Narrow-Angle Glaucoma). Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in MDD placebo-controlled clinical trials of up to 9 weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

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 (eg, 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.

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. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, 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. However, the electrocardiograms of 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes). In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (*see* ADVERSE REACTIONS, Electrocardiogram Changes). 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, small increases in fasting blood glucose were observed in Cymbalta-treated patients. HbA_{1c} was stable in both Cymbalta-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the Cymbalta and the routine care groups, but the mean increase was 0.3% greater in the Cymbalta-treated group. There was also a small increase in fasting blood glucose in the Cymbalta-treated group. Total cholesterol was increased in Cymbalta-treated patients (2 mg/dL) and decreased in the routine care group (6 mg/dL). Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.

Laboratory Tests—No specific laboratory tests are recommended.

Drug Interactions—*Potential for Other Drugs to Affect Cymbalta*—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. Inhibitors of CYP1A2—Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided. Inhibitors of CYP2D6—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) 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 (eg, fluoxetine, quinidine). *Potential for Duloxetine to Affect Other Drugs*—Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates. Drugs Metabolized by CYP2D6—Cymbalta is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (eg, 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.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. *Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs*—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* PRECAUTIONS, Hepatotoxicity). 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. Potential for Interaction with 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 (eg, 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.

Monoamine Oxidase Inhibitors—*See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, 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 daily 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.

Pregnancy—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 rats; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits). 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 rats; 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, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

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* BOX WARNING *and* WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or 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 greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: Cymbalta has been evaluated for safety in 2418 patients diagnosed with MDD who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8 or 9 week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year. Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12 to 13 week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure. For both MDD and DPN clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. MedDRA terminology was 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. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). Diabetic Peripheral Neuropathic Pain—Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials—Major Depressive Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled trials (N=1139 Cymbalta; N=777 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting; Metabolism and Nutrition Disorders—appetite decreased (includes anorexia); Investigations—weight decreased; General Disorders and Administration Site Conditions—fatigue; Nervous System Disorders—dizziness, somnolence, tremors; Skin and Subcutaneous Tissue Disorders—sweating increased; Vascular Disorders—hot flushes; Eye Disorders—vision blurred; Psychiatric Disorders—insomnia (includes middle insomnia), anxiety, libido decreased, orgasm abnormal (includes anorgasmia); Reproductive System and Breast Disorders—males only: erectile dysfunction, ejaculation delayed, ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure).

The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence ≤ placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

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 DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; 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.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence ≤ placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function—Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, 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. Sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials were: Males (N=378 Cymbalta; N=247 placebo): orgasm abnormal (includes anorgasmia), ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure), libido decreased, erectile dysfunction, ejaculation delayed. Females (N=761 Cymbalta; N=530 placebo): orgasm abnormal, libido decreased.

Because adverse sexual events 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. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Physicians should routinely inquire about possible sexual side effects. See Table 4 in full PI for specific ASEX results.

Urinary Hesitation—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. ***Laboratory Changes***—Cymbalta treatment, for up to 9 weeks in MDD or 13 weeks in DPN 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* PRECAUTIONS). ***Vital Sign Changes***—Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (*see* PRECAUTIONS). Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials and for up to 13 weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of about 2 beats per minute. ***Weight Changes***—In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9 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. ***Electrocardiogram Changes***—Electrocardiograms were obtained from 321 Cymbalta-treated patients with MDD and 169 placebo-treated patients in clinical trials lasting up to 8 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between Cymbalta-treated and placebo-treated patients. Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

Postmarketing Spontaneous Reports—Adverse events reported rarely since market introduction that were temporally related to Cymbalta therapy include: hallucinations, rash, and urinary retention. The following adverse events were reported very rarely: alanine aminotransferase increased, alkaline phosphatase increased, anaphylactic reaction, angioneurotic edema, aspartate aminotransferase increased, bilirubin increased, extrapyramidal disorder, glaucoma, hepatitis, hyponatremia, jaundice, orthostatic hypotension (especially at the initiation of treatment), serotonin syndrome, Stevens-Johnson Syndrome, syncope (especially at initiation of treatment), syndrome of inappropriate antidiuretic hormone secretion (SIADH), and urticaria.

DRUG ABUSE AND DEPENDENCE: ***Controlled Substance Class***—Duloxetine is not a controlled substance. ***Physical and Psychological Dependence***—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

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 (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: There is limited clinical experience with Cymbalta overdose in humans. In premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, were reported with none being fatal. Postmarketing experience includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures. ***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.

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MY PATIENTS DON'T WANT TO REMISSION ANOTHER FAMILY VACATION.

Cymbalta 60 mg/day provided high rates of remission (HAM-D_{17} Total Score ≤7). In 4 pooled 60 mg/day studies, the remission rate for Cymbalta was 43% vs 27% on placebo ($P \leq .001$).[1]

Cymbalta is indicated for the treatment of major depressive disorder (MDD).

Important Safety Information:

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients started on therapy should be 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 thioridazine and not in patients with a known hypersensitivity or with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All adult and pediatric patients being treated with an antidepressant for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially when initiating drug therapy and when increasing or decreasing the dose. A health professional should be immediately notified 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.

Cymbalta should 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).

Postmarketing, severe elevations of liver enzymes or liver injury with a hepatocellular, cholestatic, or mixed pattern have been reported.

Cymbalta should generally not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Most common adverse events (≥5% and at least twice placebo) in MDD premarketing clinical trials were: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating.

Reference:

1. Data on file, Lilly Research Laboratories: CYM20060101C.

See Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent page

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