

PSYCHIATRIC NEWS

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Dual Eligibles Find Part D Rollout Problem Plagued

Numerous states have undertaken emergency plans to continue financing prescription coverage for beneficiaries who run into trouble receiving medications under the Medicare prescription drug program.

BY MARK MORAN

Many of the worst fears about the new Medicare Part D prescription drug plan appear to have materialized, at least in the first week of the program.

Throughout the country, the program has endured a tidal wave of complaints including reports that patients were being charged inappropriate copayments, pharmacies were unable to confirm eligibility in the program, and drug plans were failing to have transition policies in effect for the 6 million "dual eligibles" who ceased having their prescription drugs paid for by state Medicaid programs and began coverage under the new Medicare program on January 1.

So severe were the problems that at press time about half the states and Washington, D.C., had taken emergency action to continue prescription drug coverage under state financing until problems with the new federal program could be fixed.

Psychiatrist Andrea Stone, M.D., told *Psychiatric News* that problems with the transition have created near pandemonium at the community mental health center where she works in Westfield, Mass. She is medical director at Carson Center for Human Services.

"On Wednesday [January 4] I got my first call about a patient who could not get insulin supplies," she said. "Then we had an onslaught of patients going to the pharmacy being told they couldn't receive medications or being told they could have their meds but would have to pay \$80 or \$90.

"Their copayments were much more than they were supposed to be," she continued. "A lot of our patients can't pay that kind of money."

Stone also told *Psychiatric News* that many patients were informed that they needed prior authorization for medications, even though prescription drug plans were supposed to have transition plans for dual eligibles to circumvent the need for prior authorization. In other cases, patients were informed that the pharmacy could not confirm their enrollment in a plan.

"So far it has been stress, confusion, and pandemonium," Stone said.

She said the problems have been particularly acute for patients being treated with clozapine. Those patients are typically on clozapine because they have not responded to other medications, yet are being told they cannot get their prescription without prior authorization.

"I don't think these [pharmacy benefit] companies understand about severe and persistent mental illness, and I don't think they understand the issues around [clozapine]," she said. "They just don't seem to understand that our patients are not in a position to do all this phone calling and negotiation."

To ensure that patients continued receiving medications, please see **Part D** on page 27

What's Your Part D Experience?

APA's Office of Healthcare Systems and Financing (OHSF) is monitoring how Medicare's new prescription drug benefit, known as Medicare Part D, is working for you and your patients. OHSF wants to pinpoint problems as soon as possible so they can be brought quickly to the attention of the Centers for Medicare and Medicaid Services and remedies sought. Your experiences are vital to letting OHSF know how Part D is really working. Share your comments by calling APA's PartD Line at (866) 882-6227 or sending them by e-mail to partd@psych.org.



SAMHSA volunteer doctors and nurses pause for a moment in the infirmary aboard the cruise ship Holiday. The ship served as a shelter for evacuees following Hurricane Katrina. Top row, from left: Sharon Muelle, R.N., Catherine May, M.D., and Karen Weersing, R.N. Bottom row, from left: Fran Hudson, R.N., and Lorna Mayo, M.D.

Post-Katrina Volunteers Learn To Expect the Unexpected

Volunteer psychiatrists find that a flexible, informal approach to storm evacuees works best.

BY AARON LEVIN

Volunteer psychiatrist Catherine May, M.D., flew into Gulfport, Miss., with only a Mapquest printout to guide her to the place where she would care for Hurricane Katrina's displaced victims. For Jeff Stovall, M.D., two weeks in Louisiana meant practicing psychiatry by walking around. Leslie Gise, M.D., found that improvisation and flexibility were the keys to getting medical work done.

All three were among 50 APA members who answered a call to serve in the Gulf Coast area in the four months following the devastating hurricane and flood.

An initial request to APA members on behalf of the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) produced 56 volunteers, 28 of

whom were sent to the Gulf region under the direction of SAMHSA contractor Westover Consultants Inc. For its efforts in finding the psychiatrists on such short notice, APA received \$112,000, which was placed in an escrow account to reinvest in the organization's disaster response efforts, said Darrel Regier, M.D., M.P.H., executive director of the American Psychiatric Institute for Research and Education and director of APA's Division of Research.

A second round of requests produced an additional 37 volunteers, of whom 12 were deployed to the region. Many of the total number of volunteers were unable to serve because they could not rearrange their schedules on short notice, according to

please see **Volunteers** on page 31

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As a psychiatrist, Carolyn Spiro, M.D., found it difficult to face the fact her twin was struggling daily with symptoms of serious mental illness.

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Antidepressant prescriptions for people who have had a heart attack increased substantially from 1992 to 2003, but did so for everyone else as well.

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A fear molecule has been identified, and it may signal a major advance in understanding the molecular basis of fear.

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Supreme Court's Changing Makeup Worries Disability Advocates

The rights granted by the Americans With Disabilities Act face growing threats, and disability rights advocates mince no words as they explain their concerns about the newest members of the Supreme Court.

BY RICH DALY

Disability rights advocates say that the new members of the Supreme Court will soon have a decisive role in defining a range of rights for those with mental illness and other disabilities.

The rights of disabled individuals have been challenged in numerous circuit court cases in recent years, and many of those are expected to move on to the Supreme Court. How new Chief Justice John Roberts and Samuel A. Alito Jr., who at press time was awaiting the Judiciary Committee's vote on his nomination, view disability rights under Medicaid and the Americans With Disabilities Act (ADA) will be decisive in determining which rights are kept and which are cut, said advocates. They are not optimistic that either justice will support the rights of those with mental and physical disabilities.

Jennifer Mathis, senior staff attorney at the Bazelon Center for Mental Health Law, said there are areas in which Roberts's presence on the court may make a significant difference. She said the high court is likely to take up the issue of private enforcement of Medicaid provisions because several such cases have been considered by lower courts in recent years. At issue is whether Medicaid beneficiaries can get court enforcement of benefit rights created by Congress or “whether [Medicaid] is a meaningless entitlement,” she said.

Roberts has a record on private enforcement of statutes, she said, through memos he wrote while an attorney at the Department of Justice and in cases he argued. “[He] has been focused all along on limiting people's ability to seek enforcement of those laws, including Medicaid,” Mathis said.

In an analysis of Roberts's legal career, the National Senior Citizens Law Center highlighted a 2001 argument that he made in *Gonzaga University v. Doe* to prevent enforcement of statutes like the Medicaid Act. The Supreme Court agreed with Roberts's argument that individuals could not sue to enforce their rights under the Family Educational Rights and Privacy Act. The ruling has been used in numerous cases to thwart Medicaid recipients' ability to enforce their rights under the Medicaid Act.

The position Roberts took on behalf of his client was “consistent with positions he has advocated [for himself or the government] on other occasions going back to 1982.” The arguments raised the question of whether Roberts's advocacy of judicial modesty and judicial restraint is a way of signaling his disdain for the courts' role in enforcing federal laws that protect individ-

uals, according to the center.

Roberts, in his confirmation hearing testimony before the Senate Judiciary Committee, said rulings—such as in *Gonzaga*—had put the onus on Congress to spell out rights, instead of the courts' deciding which rights were implied by laws that did not explicitly create rights.

“This is not a good thing for the courts to be doing—deciding whether a particular right of action should be implied or not,” Roberts said.

In trying to gauge Alito's approach to this issue, disability rights advocates cite his opinion in *Sabree v. Houston*, in which he questioned court rulings that allow individuals who have been denied services under Medicaid to sue to enforce their rights. Alito supported beneficiaries' rights at the time of the ruling, noting that there was “binding precedent” but expressed discomfort with those rights.

Alito supported a decision of the circuit court on which he sat that reversed a lower court ruling barring court enforcement of Medicaid beneficiaries' rights. At issue was whether the state had to provide certain Medicaid services it had promised. In his separate opinion Alito said that he was bound by precedent, but that the Supreme Court was likely to head in a different direction.

“He seems to think that the Supreme Court is likely to go in the direction of the trial court that found no one has any rights under Medicaid,” Mathis said.

As with most disability-rights cases, it is unclear how Justice Sandra Day O'Connor would have ruled, but Mathis said that dire situations in which great mental or physical harm was involved tended to sway her in favor of the plaintiff's argument.

In his testimony before the Judiciary Committee, Alito said his experiences helped shape his decisions. “When I have a case involving someone who's been subjected to discrimination because of disability, I have to think of people who I've known and admire very greatly who've had disabilities, and I've watched them struggle to overcome the barriers that society puts up often just because it doesn't think of what it's doing.”

One of the biggest questions for Alito's critics is how much he supports congressional power. Alito's record often questions whether Congress had the power to pass laws such as the ADA.

In one case, Alito dissented when the federal appeals court on which he was sitting upheld Congress's power to ban possession of machine guns. He reasoned that if the

please see Supreme Court on page 30

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New Task Force Will Address Early Childhood Violence

BY STEVEN SHARFSTEIN, M.D.

Interpersonal violence, especially violence experienced by children, is the largest single preventable cause of mental illness. What cigarette smoking is to the rest of medicine, early childhood violence is to psychiatry. Writing in the April 22, 2005, *Science*, Frank Putnam and colleagues summarized the estimated prevalence of childhood sexual abuse and the association between childhood sexual abuse and serious mental and physical health problems, including substance abuse, and criminality in adulthood.

It is estimated that more than one-third of the U.S. population may have suffered a serious interpersonal trauma such as crime victimization, physical or sexual abuse, or assault. As much as 15 percent of the general population may have suffered multiple traumatic violent events, frequently beginning in early childhood. High-risk groups, such as inner-city youth, have even higher rates of trauma related to poverty, frequent violent crime, family dysfunction, and pervasive substance abuse.

Current estimates of posttraumatic stress disorder (PTSD) in the United States make it among the most common psychiatric disorders, but violence transcends PTSD. In children and adolescents, interpersonal violence is the leading risk factor for psychiatric hospitalization.

Interpersonal violence is also the major risk factor for a host of other serious problems among youth, including running away, conduct disorders, high-risk sexual behaviors, early pregnancy, suicidal behaviors, depression, and substance abuse. Research documents the biological effects of early trauma on brain development, intelligence, and neuroendocrine systems, which contribute to the severe behavior problems in childhood, as well as later in life.

Long-term health outcomes of childhood abuse are also highly adverse. Writing in the October 2003 *General Internal Medicine*, Springer and colleagues demonstrate that a variety of somatic symptoms is consistently found to be higher in adults with a history of physical abuse compared with those without an abuse history; these somatic symptoms include back pain, nightmares, fatigue, and other pain syndromes. The mental health effects of abuse are also well established and include a strong link to depression.

The lifetime prevalence of major depression in women with a history of childhood abuse is about three to five times greater than in women without such a history. In addition to depression, there is a higher incidence of anxiety disorders and personality disorders, especially borderline personality disorder, associated with a history of childhood abuse. Compared with other prevalent health problems, child maltreatment has been the focus of limited federal research funding. One recent positive development is the creation of the National Child Traumatic Stress Network, which is looking at the impact of trauma in a federally funded network of 54 sites providing



community-based treatment for children and their families exposed to a wide range of trauma.

I have decided to appoint a special component—the Presidential Task Force on the Biopsychosocial Consequences of Early Childhood Violence—cochaired by former APA President Paul J. Fink, M.D., and Richard Loewenstein, M.D. This task force will bring together

clinicians, researchers, public policy advocates, and others with relevant expertise to develop an integrative strategy for the prevention and treatment of violence and trauma-related disorders. The task force will review relevant research, epidemiology, demography, best practices, and theoretical formulations regarding prevention and interventions to decrease interpersonal violence.

My hope is that the task force will develop a series of action steps to inform clinical care and treatment, future research, parenting and family concerns, and community strategies. This task force will also look at the need for better education of psychiatrists and mental health professionals with an emphasis on trauma and trauma-related affective disorders as part of the routine history and differential diagnosis of psychiatric patients.

I have asked the task force to maintain a biopsychosocial approach throughout its deliberations to provide and integrate understanding of the many factors that lead to poor outcome, as well as to the relative resilience in trauma survivors. The task force will have two meetings in the coming months, and I expect its report by the May annual meeting in Toronto. ■

Nominations Invited For Disaster Psychiatry Fellowship

District branches are invited to nominate one member to receive APA's 2006 Disaster Psychiatry Fellowship. The fellowship consists of the reimbursement of the advance registration course fee for the Committee on Psychiatric Dimensions of Disasters' annual course, "Psychiatric Interventions in Disasters and Public Health Emergencies: Theory to Practice." It will be held at APA's 2006 annual meeting in Toronto on Sunday, May 21, from 1 p.m. to 5 p.m.

Up to 10 nominations will be accepted on a first-come, first-served basis, with one nomination being accepted from each district branch.

Nominations must be received no later than March 15. They should be sent to Erin Dalder-Alpher by mail to Disaster Psychiatry Fellowship, Division of Research, APA, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209; by fax to (703) 907-1087; or by e-mail to edalder@psych.org. ■

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Twins Find Common Cause After Illness Divides Them

Twin sisters put a new spin on mental health advocacy as they tour the country to share a history affected by serious mental illness but also characterized by mutual love, respect, and unfaltering support.

BY EVE BENDER

Psychiatrist Carolyn Spiro, M.D., was sleeping in the on-call room at Massachusetts Mental Health Center in Boston one night in 1981 when an urgent call came from a nurse working at the state psychiatric hospital in Connecticut.

It wasn't one of Spiro's patients who'd been admitted, but her twin sister, Pamela Wagner.

Like many twins, the two shared many of the same attributes and life experiences: dark eyes and slight builds, quick intellects, undergraduate years at Brown University, and even admission into medical school.

But after Spiro made her way to the hospital, where her sister was frozen in a cataleptic stance with one arm extended into the air, the similarities between them seemed to fall away. "This can't be my twin," Spiro remembered thinking at the time.

In a recent interview with *Psychiatric News*, Spiro said that although she knew

her sister had emotional problems and engaged in self-injurious behavior, she had denied any possibility that Wagner had serious mental illness. "Psychiatrists use the same defense mechanisms that others do," she noted. "I defended against the realization that a family member was actually suffering from the same illness I treated on the very wards where I learned how to be a psychiatrist," said Spiro.

The truth could no longer be avoided when hospital staff told Spiro that her sister had schizophrenia.

Was She Psychiatrist or Sister?

Spiro said it was difficult to know how to behave during the trip to the state hospital.

"I knew I was there to support Pammy as my sister, but I didn't know what to do with the part of myself that had been on call in a very similar hospital the night before and taking care of patients just like her," she said.



Carolyn Spiro, M.D. (left), and Pamela Spiro Wagner sign copies of the book they co-wrote, *Divided Minds*, at the West Hartford, Conn., Town Hall in August of last year.

As it turned out, Wagner ended up hospitalized because she had stopped taking her antipsychotic medications; she required multiple hospitalizations over the next two decades.

"All those drugs made me feel horrible—dull and dead—everything I didn't want to be if I was going to write poetry," Wagner told *Psychiatric News*. When she went off her medications, she'd be in "seventh heaven," she recalled, "until the paranoia and obsessions hit."

Over the years, Wagner wrote poetry and award-winning articles pertaining to mental health. In addition, she wrote a memoir about her experiences with mental illness and treatment, which would later be integrated into *Divided Minds*, a book the sisters wrote together between 2000 and 2003.

St. Martin's Press published the book last year.

Twins' Lives Diverge

The book tells the story from the alternating perspectives of Wagner and Spiro as they recount their lives and sometimes profoundly different experiences of certain events.

For instance, when the twins were in the sixth grade and President Kennedy was assassinated, Spiro felt shocked, as did many of her peers. Wagner, however, became crippled by terror and felt that she was to blame for the tragedy. "I believed that I killed Kennedy," she said.

As the twins matured, their relationship became characterized in part by rivalry as they struggled to distinguish themselves from one another.

"If Pammy did something first, I always felt like she owned it," Spiro said. "I was doomed to be in the position of imitator." Spiro never blamed her sister for being in front, she explained. "It was my fault that wherever I looked, I saw her back."

Though Wagner was plagued by increasingly threatening auditory hallucinations throughout high school, she excelled academically and managed to keep the psychosis a secret, even from her sister.

When the twins began attending Brown University, Wagner became increasingly isolated and spent a great deal of energy trying to seek refuge from the voices and nonsensical thoughts that flooded her mind. She swallowed a bottle of sleeping pills in her freshman year and was hospitalized.

Though both Wagner and Spiro attended medical school, Wagner dropped out in her second year.

Spiro explained that when her sister became ill, "she left the door open for me, and when I walked through, the horizon was clear." By this she meant that when Wagner became incapacitated by mental illness, Spiro was free of the rivalry that existed between them. "I began to try new things because I no longer assumed that I would fail," she said.

Spreading Message of Hope

Spiro embarked upon a career in psychiatry, which she believes is the "most fascinating area of medicine," but also admitted that her sister's illness gave her "an excuse to be a psychiatrist." She is now in private practice in Wilton, Conn.

Over the past several years, Wagner has found a successful combination of medications and has been "coping and doing well," she said.

Wagner remarked that writing the book has brought them closer together, and though they were "perfectly attuned to one another" toward the end of the writing process, the going was sometimes rough.

"Pam was in and out of the hospital more times than I can count," Spiro said. "I was carting notes and manuscripts back and forth to a number of different hospitals around the state."

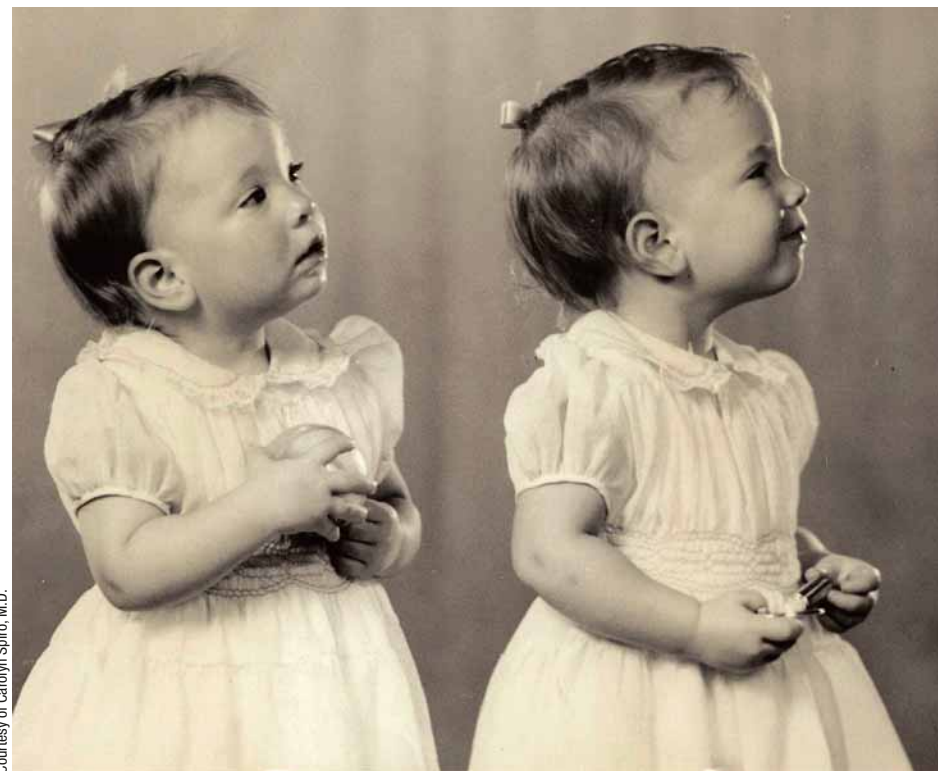
During this time, Spiro was having her own difficulties. "I was going through a divorce, but Pam was still able to be emotionally supportive," she noted.

Since the book's release, Spiro and Wagner have been traveling around the country to share their experiences at book signings and meetings of the National Alliance on Mental Illness. "Our main message is that mental illness should not be pushed into the closet," said Spiro. "We encourage people to seek treatment and know that there is hope for recovery."

Spiro noted that their speaking engagements have opened up new worlds for Wagner.

Before the book tour, Wagner had never spent a night in a hotel and had seldom dined in restaurants. "Here is this incredibly bright woman who reads everything and knows a lot from books, but hasn't experienced a lot of things," remarked Spiro.

Though public speaking can be a daunting task for anyone, Wagner said that it is "absolutely worth it to stand in front of crowds and speak if I can help people like me hang onto hope for a better tomorrow—to put one foot ahead of the other and keep walking." ■



As twins growing up in New England, Carolyn (left) and Pamela Spiro had unremarkable childhoods. Pamela began to experience the first symptoms of schizophrenia in early adolescence.

Side Effects Must Be Addressed

Pamela Wagner knows a thing or two about medication side effects.

When she was first prescribed haloperidol to combat symptoms of schizophrenia, her head felt like it was "full of cotton, my brain an emotionless blank. . . . At the same time, every motor neuron in my body urges me to pace back and forth in my room," she wrote in the book *Divided Minds*.

Though one of the newer antipsychotic medications helped her immensely, she reported, it caused her to gain 80 pounds, and she decided to stop taking it.

Wagner urged psychiatrists to take medication side effects seriously. Patients who complain about debilitating side effects "are not lying, and they do not prefer the symptoms of their illness over medication," she said in an interview with *Psychiatric News*.

Psychiatrist Carolyn Spiro, M.D., said her patients have indirectly benefited from her twin sister's experiences.

"My patients know that I will listen to them and believe them when they tell me their side effects are real," she said. "They also know I will work with them to resolve the problem."

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For more information, call 1-888-440-7903 or visit www.concerta.net

CONCERTA® (methylphenidate HCl) Extended-release Tablets

BRIEF SUMMARY: Please see full prescribing information.

DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect.

CONTRAINDICATIONS

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

Hypersensitivity to Methylphenidate: CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma: CONCERTA® is contraindicated in patients with glaucoma. **Tics:** CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors: CONCERTA® is contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO-inhibitor (hypertensive crises may result) (see PRECAUTIONS, Drug Interactions).

WARNINGS

Depression: CONCERTA® should not be used to treat severe depression. **Fatigue:** CONCERTA® should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may cause suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis: Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Seizures: There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Potential for Gastrointestinal Obstruction: Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.

Hypertension and other Cardiovascular Conditions: Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, eg, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA®, especially patients with hypertension. In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.

Visual Disturbance: Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

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

DRUG DEPENDENCE

CONCERTA® 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 withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

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

Information for Patients: Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Drug Interactions: CONCERTA® should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors). Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents. Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate. Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an

increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown. Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. In a 24-week carcinogenicity study in the transgenic mouse strain p53^{+/+}, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate. Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay. Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC. The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA® is administered to a nursing woman.

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

ADVERSE REACTIONS

The development program for CONCERTA® included exposures in a total of 2121 participants in clinical trials (1797 patients, 324 healthy adult subjects). These participants received CONCERTA® 18, 36, 54, and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. 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 tables and listings 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 receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with CONCERTA®: Adverse Events Associated with Discontinuation of Treatment: In the 4-week placebo-controlled, parallel-group trial in children (Study 3) one CONCERTA®-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively). In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no CONCERTA®-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability). In the two open-label, long-term safety trials (Studies 5 and 6: one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with CONCERTA®) 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of ≥0.5% included: insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%). **Treatment-Emergent Adverse Events Among CONCERTA®-Treated Patients:** Table 1 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA® where the incidence in patients treated with CONCERTA® was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1
Incidence of Treatment-Emergent Events* in a 4-Week
Placebo-Controlled Clinical Trial of CONCERTA® in Children

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract Infection	8 %	5 %
	Cough Increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Table 2 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at CONCERTA® doses of 18, 36, 54 or 72 mg/day.

Table 2
Incidence of Treatment-Emergent Events* in a 2-Week
Placebo-Controlled Clinical Trial of CONCERTA® in Adolescents

Body System	Preferred Term	CONCERTA® (n=87)	Placebo (n= 90)
General	Accidental injury	6 %	3 %
	Fever	3 %	0 %
Digestive	Headache	9 %	8 %
	Anorexia	2 %	0 %
	Diarrhea	2 %	0 %
	Vomiting	3 %	0 %
Nervous	Insomnia	5 %	0 %
Respiratory	Pharyngitis	2 %	1 %
	Rhinitis	3 %	2 %
Urogenital	Dysmenorrhea	2 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Tics: In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with CONCERTA®. In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Post-Marketing Experience with CONCERTA®: Additional very rare undesirable effects were reported during the marketing experience: difficulties in visual accommodation, blurred vision, abnormal liver function tests (e.g., transaminase elevation), palpitations, arrhythmia, leucopenia, and thrombocytopenia.

Adverse Events with Other Methylphenidate HCl Products: Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: hepatic coma; isolated cases of cerebral arteritis and/or occlusion; anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation. **Abuse, Dependence, and Tolerance:** See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

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

Recommended Treatment: Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory efficacy, external cooling procedures may be required for hyperpyrexia. Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CONCERTA® overdose has not been established. The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

Poison Control Center: As with the management of all overdose, 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 overdose with methylphenidate.

Rx Only.

For more information call 1-888-440-7903 or visit www.concerta.net. Manufactured by ALZA Corporation, Mountain View, CA 94043. Distributed and marketed by Specialty Pharmaceuticals Division of McNeil-PPC, Inc., Fort Washington, PA 19034.



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New Study Puts Spotlight on Post-MI Antidepressant Use

While a steady rise in the use of antidepressants among heart attack victims should be an encouraging sign, it does not outpace the use of antidepressants among non-MI patients.

BY AARON LEVIN

Heart attack victims in Ontario were twice as likely to be treated with antidepressants in 2002 as they were in 1993, but so was a group of matched controls, a pattern reflecting general population trends rather than an increased concern about depression in cardiac patients, according to a study of more than 137,000 elderly Ontario residents.

Moreover, although the use of selective serotonin uptake inhibitors (SSRIs) increased as a percentage of prescriptions, the percentage of patients taking tricyclic antidepressants (TCAs) remained the same.

"Despite the higher rates of SSRI prescribing on a population basis, we don't see that evidence demonstrating a strong connection between depression and reinfarcts and deaths among MI patients is yet translating into clinical practice," said lead author Nili Benazon, Ph.D., of the Centre for Addiction and Mental Health and the Sunnybrook and Women's Health Sciences Centre in Toronto, in an interview with *Psychiatric News*.

Prior epidemiological research has found a strong association between depression and heart disease, but the issue of causality remains unconfirmed by prospective studies (*Psychiatric News*, August 5, 2005).

Benazon and her colleagues, Muhammad Mamdani, Pharm.D., of Toronto's Institute of Clinical Evaluative Sciences, and James Coyne, Ph.D., of the University of Pennsylvania Health System in Philadelphia, drew on four databases for the study: provincial prescription claims, health insurance, and a population registry, as well as the Canadian Institutes of Health Information's hospital discharge abstract database. The study was published in the November-December 2005 *Psychosomatic Medicine*.

The researchers identified 68,870 patients who had had heart attacks and an equal number of age- and sex-matched controls. Antidepressants in the study included tricyclic and heterocyclic antidepressants, monoamine oxidase inhibitors, and SSRIs.

The percentage of heart attack patients getting antidepressants edged upward consistently over the study period, going from 7.8 percent (n=128 of 1,637 subjects) in 1993 to 15.7 percent (350/2,231) in 2002, and in matched control patients who had not had a heart attack, increasing from 6.4 percent (105/1,637) to 12.2 percent (273/2,231).

The initial results of the study showed that post-MI patients were more likely than controls to be prescribed an antidepressant (odds ratio=1.34). However, adjusting for the number of prescriptions for any medications paradoxically shifted that relationship, so that those who had had heart attacks were actually less likely to receive antidepressants than matched controls (odds ratio=0.81).

Why would having more prescriptions reduce the chances of being prescribed an antidepressant?

Drawing on previous research by others, Benazon and colleagues suggested that the

total number of prescriptions reflects medical comorbidity or physician visits, and that management of a chronic disease interferes with treatment of unrelated conditions.

"It is therefore plausible that the likelihood that an elderly post-MI patient will receive a prescription for an antidepressant increases with the number of medical visits, but the competing demands of managing the cardiac condition decrease the likelihood that antidepressants will be prescribed in a given visit," they wrote. "Health care following an MI might thus be characterized by more visits but less likelihood of a prescription for an antidepressant in any given visit, yielding the contrast between higher unadjusted odds of receiving an antidepressant and lower adjusted odds."

In short, patients who had heart attacks were prescribed more medications but relatively fewer of those prescriptions were for antidepressants.

The study results also reflected the increasing availability and use of SSRIs. In 1993, 23 percent of all antidepressant prescriptions for post-MI patients were for SSRIs, rising to 62 percent in 2002. Prescriptions for TCAs fell over the same time, from 83 percent to 36 percent. (A small number of patients received heterocyclic antidepressants or monoamine oxidase inhibitors.)

Despite this general reversal in percentage of prescriptions, there was no corresponding drop in the percentage of patients prescribed TCAs. Six percent of

post-MI patients and 5 percent of controls got TCAs in 1993, figures that were unchanged in 2002 and left the researchers puzzled.

"That there has been no reduction in the proportion of patients receiving TCAs over the last decade suggests that there is a problem in continued prescription for depression, and presumably at cardiotoxic dosages, but we cannot establish the magnitude of the problem," the authors noted.

"The difficulty in unambiguously interpreting the TCA data is that some represent low dosage for pain and sleep," added Benazon. "Also, our first observations in this dataset were from a decade earlier, when there was less evidence about toxicity and fewer alternatives to treat depression."

"I would agree that SSRIs are safer, but that information may not be well known to physicians unless it's publicized or included in guidelines," said David Sheps, M.D., editor of *Psychosomatic Medicine* and a professor of medicine and associate director of the division of cardiovascular medicine at the University of Florida. "People have a hard time changing their prescribing habits. But at least we see a gradual rise in the percentage of patients getting antidepressants. That's probably a good thing."

The growing suspicion of excessive and inappropriate prescription of antidepressants, even in the face of persistent undertreatment and inadequate treatment of depression, also concerned the researchers, said Benazon.

She cited unpublished data indicating that at least 25 percent of primary care

patients receiving antidepressants for depression had never experienced two consecutive weeks of mood disturbance.

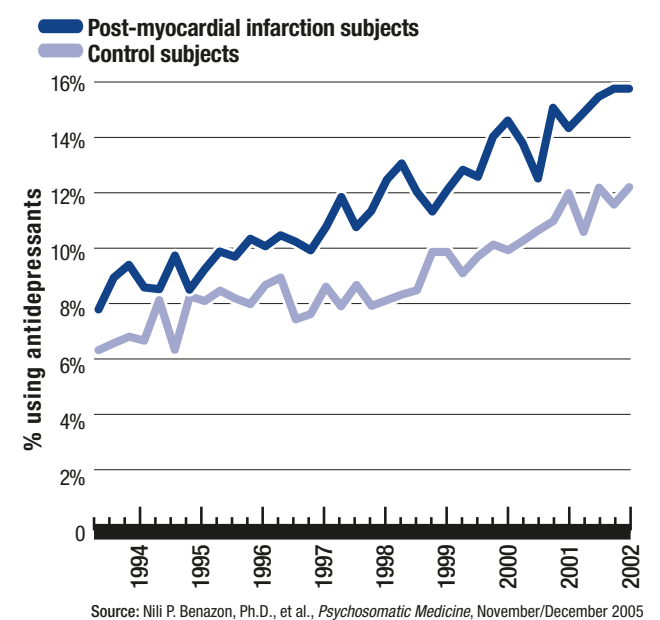
The bulk of treatment with antidepressants occurs in general medical rather than specialty mental health care, and only 20 percent to 30 percent of patients receiving treatment for depression in general medical care obtain adequate care, she said.

"Questions of the specificity and adequacy of treatment being provided for depression are important in evaluating the progressive increase in the prescription of antidepressants to post-MI patients and elderly patients more generally, but answering these questions requires going beyond the data available in our integrated dataset."

"Trends in the Prescribing of Antidepressants Following Acute Myocardial Infarction, 1993-2002" is posted at www.psychosomaticmedicine.org/cgi/content/full/67/6/916. ■

Antidepressant Use Up for All

The proportion of both post-MI subjects and matched controls receiving prescriptions for antidepressants doubled in a population-based study of elderly Ontario residents from 1993 to 2002.



Hepatitis, TB Rates Found 'Alarming' Among State Hospital Patients

In a state psychiatric hospital sample, patients were as much as 12 times as likely as the general population to test positive for hepatitis C antibodies and four times as likely to test positive for tuberculosis.

BY EVE BENDER

Patients with serious mental illness in one state hospital sample had "alarmingly" high rates of positive tuberculin tests, as well as hepatitis B, C, and HIV serology tests, prompting researchers to call for screening and vaccinating inpatients with serious mental illness.

To gather their data, researchers systematically reviewed data for the 655 patients who were admitted to the Erich Lindemann Mental Health Center in Boston between January 1, 1997, and December 31, 1999.

That state psychiatric hospital admits patients who are referred through the court system for forensic evaluations or are transferred from acute-care hospitals.

Upon admission, patients meet with an infection-control nurse who discusses risk factors for infectious diseases, coordinates disease testing, delivers the results, and counsels patients who test positive for certain infections, according to a report of the study in the December 2005 *Psychiatric Services*.

A minority of those admitted over the three-year period were deemed too psychiatrically impaired to be screened for infectious diseases or left the hospital before they could be screened.

Researchers measured the frequency of positive tests for 535 patients who received tuberculin tests, 62 who received HIV tests, and 548 who were tested for hepatitis A, B, and C.

When compared with the general population, patients in the sample had four times as many positive tuberculin tests (20.2 percent of those tested screened positive).

In addition, 33.2 percent of patients tested positive for hepatitis A, 24 percent screened positive for hepatitis B, and 21.5 percent screened positive for hepatitis C.

"The number of positive tests for hepatitis B and C among patients screened were five and 12 times as great as population estimates, respectively," the authors wrote.

Patients in the hospital sample had nine

times the number of positive HIV tests as those in the general population (almost 30 percent of those who were screened tested positive).

The authors noted that a limitation of the study was that patients were screened for markers and antibodies of the diseases rather than "active or acute disease; some patients may have had illnesses in the past or even immunization, which may result in positive tests." Patients who screened positive for infectious diseases were referred to an internal medicine specialist who examined patients further to determine whether they were actually experiencing symptoms of the disease and treated them accordingly.

However, the positive test results found during the study period prompted hospital administrators to take action; due to the high number of positive hepatitis C tests, the mental health center implemented routine screening for hepatitis C antibodies among all patients admitted since 2000. According to the report, patients who screened positive for tuberculin skin tests were more likely to be older or homeless. They were also more likely to be immigrants.

Patients with positive hepatitis B tests tended to be immigrants or have a history of drug use.

Given the relatively high proportion of positive tests for infectious diseases in the

New Manual Aids Diagnosis Of Sleep Disorders

The *DSM-IV-TR* sleep codes have been updated to be compatible with new *ICD-9-CM* codes introduced as a result of the new sleep manual.

BY LYNNE LAMBERG

Your patient reports he feels discouraged by his failure to find a job. He watches television or goes out drinking in the evening and rarely falls asleep before 3 a.m. You determine he has not only depression, but also inadequate sleep hygiene and a delayed sleep phase disorder.

This patient should receive all three diagnoses, says Michael Sateia, M.D., a professor of psychiatry and chief of sleep medicine at Dartmouth Medical School.

As this case suggests, multiple factors often contribute to difficulty sleeping, noted Sateia, who was editor of the recently published second edition of the *International Classification of Sleep Disorders Diagnostic and Coding Manual (ICSD-2)*, published in 2005 by the American Academy of Sleep Medicine. The new edition replaces *ICSD-1*, published in 1990 and revised in 1997.

Since sleep symptoms frequently accompany psychiatric illness, Sateia said, psychiatrists should find *ICSD-2* helpful in making a comprehensive assessment.

"Psychiatrists traditionally have viewed insomnia as a symptom of depression, but insomnia often has a life of its own," he said. It may persist, even after mood improves. It requires treatment beyond the standard

treatment for depression, particularly hypnotic medication and/or cognitive-behavioral therapy.

"If not treated," he added, "insomnia may boost the likelihood of the depression's recurrence."

Many sleep diagnoses outside the insomnia category also are highly relevant to psychiatry, he pointed out. As many as 50 percent of people with chronic schizophrenia have obstructive sleep apnea. Circadian rhythm sleep disorders have a high association with mood disorders. Some antidepressant medications trigger or increase periodic leg movements in sleep.

ICSD-2 represents consensus opinion from more than 100 sleep specialists worldwide. Its descriptions and criteria for sleep disorders, Sateia asserted, "are as rooted in evidence as available knowledge allows."

The 300-page manual covers more than 80 discrete disorders, organized in eight categories. Unlike *DSM-IV-TR*, *ICSD-2* does not use an axial system; it focuses only on the diagnosis of sleep disorders.

"While *ICSD-2* enables psychiatrists who specialize in the treatment of sleep disorders to make finer distinctions than is possible in *DSM-IV-TR*, *DSM-IV-TR*'s sleep disorders section continues to be useful for

the general psychiatrist," according to Michael First, M.D., cochair and editor of *DSM-IV-TR* and a research psychiatrist with the New York State Psychiatric Institute in New York City.

"The diagnostic codes in *DSM-IV-TR* were recently updated so as to be compatible with new *International Classification of Diseases (ICD-9-CM)* codes introduced as a result of *ICSD-2*," First said. The codes are posted at <www.aasmnet.org/PDF/CrosswalkCard.pdf>.

Some disorders are grouped according to a common complaint; these include insomnia, hypersomnia, parasomnia, and sleep-related movement disorder. Others, such as circadian rhythm sleep disorders, are classified by presumed etiology. Still others are classified according to the organ system from which they arise.

Separate sections deal with disorders that involve isolated symptoms, such as sleep talking, and longer and shorter than normal sleep duration. Appendices review sleep disorders associated with medical disorders, such as sleep-related epilepsy or headaches, along with psychiatric and behavioral disorders frequently encountered in the differential diagnosis of sleep disorders.

For each disorder, *ICSD-2* includes alternative names and describes essential and associated features, demographics, predisposing and precipitating factors, and familial patterns. It reports onset, course, and complications, as well as pathology and pathophysiology, and includes polysomnographic and other objective findings, diagnostic criteria, and subtypes.

Each section also addresses unresolved issues, further directions, and differential diagnosis, concluding with a concise bibli-

ography. Most pediatric presentations are incorporated into the text for individual sleep disorders; three presentations unique to childhood are listed separately.

The new code for behavioral insomnia of childhood—a disorder child psychiatrists might encounter—has sparked consternation among some pediatric sleep specialists. This *ICSD-2* disorder combines two *ICSD-1* disorders, sleep onset association disorder and limit-setting sleep disorder. Its coding was downgraded to a "V" or "problem" code usually reserved for lifestyle issues.

"A V code means insurance companies are unlikely to reimburse for this diagnosis," said Judith Owens, M.D., an associate professor of pediatrics at Brown Medical School. "That may serve as a barrier to care for families of some children with this disorder."

It also creates a pocketbook issue for practitioners, said Owens, who estimates that about 30 percent of the children in her pediatric sleep clinic have behavioral insomnia.

This disorder typically presents in the first or second year of life and probably involves a dysfunction in the child's ability to consolidate and self-regulate sleep, Owens explained, making it similar to psychophysiological insomnia in adults. Treatment involves teaching parents strategies to modify the child's behavior and improve the home sleep environment.

While pediatric sleep practitioners are campaigning to repeal this coding decision, work already has begun on *ICSD-3*. John Winkelman, M.D., Ph.D., an assistant professor of psychiatry at Harvard Medical School, chairs a task force on this issue.

Copies of *ICSD-2* may be purchased at <www.aasmnet.org>. ■

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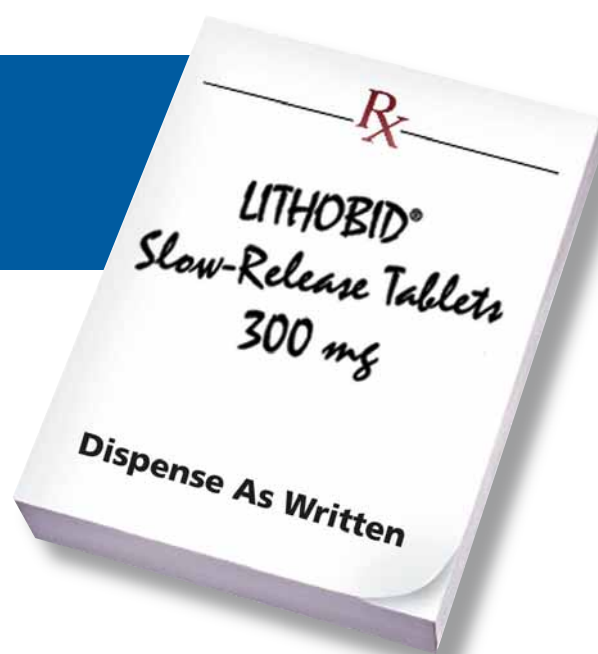


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Please see brief summary of full Prescribing Information on adjacent page.

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Employer Group Condemns Fragmentation of MH Care

The NBGH recommends that mental health specialists certify employees for disability in the case of a mental health problem and that workers be provided a treatment plan to reconnect them to the workplace.

BY MARK MORAN

Substance abuse and other mental disorders cost the nation’s employers as much as \$17 billion a year, according to a year-long study by the National Business Group on Health (NBGH).

Indirect costs associated with mental illness, including substance abuse, range between \$79 billion and \$105 billion a year, the group says.

In an interview with *Psychiatric News*, NBGH Vice President Ron Finch said the study and its recommendations emphasize the importance of integrating services and programs across employee benefits, including employee assistance programs (EAPs), disability benefits, and health insurance coverage.

The NBGH, headquartered in Washington, D.C., represents 240 mostly large

employers and advocates for their perspective on health care issues.

Care Lacks Integration

Finch said that mental health carveouts had cut costs as much as possible in the last two decades, while also fragmenting the care of workers with comorbid conditions.

“Over the last several years the cost of health care has been brought down and contained as much as it can be,” he said. “I think employers understand that they have to focus on improving and maintaining the overall health status of beneficiaries in their plans.

“But one of our major findings is that behavioral health, like general health, is fragmented and lacks integration. It is fairly rare to find employers that have well-integrated employee assistance, disability health care, and preventive health programs. Those that do have lower disability costs

and less use in general of their health care plans. They also have better outcomes with those chronic conditions where there is comorbid depression.”

Funded by the Center for Mental Health Services of the Substance Abuse and Mental Health Services Administration, the NBGH study was conducted by the National Committee on Employer-Sponsored Behavioral Health Services.

The NBGH formed that committee to review the state of employer-sponsored behavioral health services and develop recommendations to improve the design, quality, structure, and integration of programs and services. The committee also reviewed the recommendations of the President’s New Freedom Commission on Mental Health to determine how they might apply to employer-sponsored mental health benefits and programs.

The committee consisted of 25 experts including academic researchers, disability-management professionals, EAP professionals, health care benefit specialists, representatives from managed care and mental health carveout companies, and medical directors and benefit managers from member NBGH companies.

APA President Steven Sharfstein, M.D., said the group’s findings, and the promise of NBGH as a leader in promoting innovative health care strategies in the workplace, underscore the widening recognition of the value of mental health and substance abuse treatment by the nation’s employers.

“The National Business Group on Health has taken the lead in promoting access to behavioral health care as an essential component of good business practice,” he told *Psychiatric News*. “There is increased recognition that treatment works, and workplace interventions combined with good insurance coverage pay for themselves many times over.”

Chronic Conditions Require Collaboration

Finch said that the NBGH findings stress the value of collaboration between primary care and mental health specialists and of treatment by specialists where appropriate.

“Currently, the primary care and general medical system has become the default mental health system, with about 70 percent of mental health cases being seen in primary care, with the main mode of treatment being antidepressants or other psychotropic medications without concurrent psychotherapy,” he noted.

Benefit designs that favor treatment in the primary care setting are driving the phenomenon, he said. “Deductibles are much lower for primary care, and that is driving utilization to the primary care setting. But we are concerned that clinical effectiveness is much lower than when patients are being seen by behavioral health specialists,” Finch said.

He pointed out that this study underscores the need for collaboration between general medicine and mental health specialists in the care of patients with chronic conditions—such as diabetes and heart disease—in which there is significant comorbid mental illness.

“Without access to indicated treatments [in mental health care insurance coverage], patient compliance with disease management is undone,” he said. “This is costing employers dollars in terms of clinical outcome.”

Finch also highlighted the organization’s *please see **Fragmentation** on page 26*

LITHOBID® (lithium carbonate)

Slow-Release Tablets 300mg

R_x only

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

WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determination should be available before initiating therapy.

INDICATIONS

Lithium is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

Typical symptoms: of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1 to 3 weeks.

WARNINGS

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation, dehydration, sodium depletion, and to patients receiving diuretics, or angiotensin converting enzyme (ACE) inhibitors, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.

Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal function and morphologic changes and their association with lithium therapy have not been established.

Kidney function should be assessed prior to and during lithium therapy. Routine urinalysis and other tests may be used to evaluate tubular function (e.g., urine specific gravity or osmolality following a period of water deprivation, or 24-hour urine volume) and glomerular function (e.g., serum creatinine or creatinine clearance). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for re-evaluation of treatment.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic, most notably haloperidol. In some instances, the syndrome was followed by irreversible brain damage. Because of possible causal relationship between these events and the concomitant administration of lithium and neuroleptic drugs, patients receiving such combined therapy or patients with organic brain syndrome or other CNS impairment should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as Neuroleptic Malignant Syndrome (NMS).

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to the therapeutic concentrations.

Outpatients and their families should be warned that the patient must discontinue lithium therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

Usage in Pregnancy

Adverse effects on nidation in rats, embryo viability in mice, and metabolism in vitro of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palate in mice.

In humans, lithium may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised by their physician of the potential hazard to the fetus.

Usage in Nursing Mothers

Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazard to the infant or neonate. Signs and symptoms of lithium toxicity such as hypertonia, hypothermia, cyanosis and ECG changes have been reported in some infants and neonates.

Pediatric Use

Safety and effectiveness in pediatric patients under 12 years of age have not been determined; its use in these patients is not recommended.

There has been a report of transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg pediatric patient who ingested 300 mg of lithium carbonate.

PRECAUTIONS

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside.

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The elimination half-life of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2500-3500 mL) at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.

In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing thyroid disorders do not necessarily constitute a contraindication to lithium treatment. Where hypothyroidism preexists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters and/or adjustment of lithium doses, if any. If hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

In general, the concomitant use of diuretics or angiotensin converting enzyme (ACE) inhibitors with lithium carbonate should be avoided. In those cases where concomitant use is necessary, extreme caution is advised since sodium loss from these drugs may reduce the renal clearance of lithium resulting in increased serum lithium concentrations with the risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium serum concentrations is recommended (see **WARNINGS** for additional caution information).

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations and alkalinizing agents such as sodium bicarbonate.

Concomitant extended use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism.

Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea and/or tinnitus.

Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

Concurrent use of fluoxetine with lithium has resulted in both increased and decreased serum lithium concentrations. Patients receiving such combined therapy should be monitored closely.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Lithium levels should be closely monitored when patients initiate or discontinue NSAID use. In some cases, lithium toxicity has resulted from interactions between an NSAID and lithium. Indomethacin and piroxicam have been reported to increase significantly steady-state plasma lithium concentrations. There is also evidence that other nonsteroidal anti-inflammatory agents, including the selective cyclooxygenase-2 (COX-2) inhibitors, have the same effect. In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with celecoxib 200 mg BID as compared to subjects receiving lithium alone.

Lithium may impair mental and/or physical abilities. Patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

Usage in Pregnancy

Pregnancy Category D. (see **WARNINGS**)

Usage in Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants and neonates from lithium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see **WARNINGS**).

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established (see **WARNINGS**).

Geriatric Use

Clinical studies of LITHOBID® Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations and to individual patient sensitivity to lithium. They generally occur more frequently and with greater severity at higher concentrations.

Adverse reactions may be encountered at serum lithium concentrations

below 1.5 mEq/L. Mild to moderate adverse reactions may occur at concentrations from 1.5-2.5 mEq/L, and moderate to severe reactions may be seen at concentrations from 2.0 mEq/L and above.

Fine hand tremor, polyuria and mild thirst may occur during initial therapy for the acute manic phase and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration.

These side effects usually subside with continued treatment or with a temporary reduction or cessation of dosage. If persistent, a cessation of lithium therapy may be required. Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium concentrations below 2.0 mEq/L. At higher concentrations, giddiness, ataxia, blurred vision, tinnitus and a large output of dilute urine may be seen. Serum lithium concentrations above 3.0 mEq/L may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium concentrations should not be permitted to exceed 2.0 mEq/L during the acute treatment phase. The following reactions have been reported and appear to be related to serum lithium concentrations, including concentrations within the therapeutic range:

Central Nervous System: tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreoathetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes. Cases of Pseudotumor Cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs.

Cardiovascular: cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope); **Gastrointestinal:** anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion; **Genitourinary:** glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst and polydipsia;

Dermatologic: drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angioedema; **Autonomic Nervous System:** blurred vision, dry mouth, impotence/sexual dysfunction; **Thyroid Abnormalities:** euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T3 and T4. 131Iodine uptake may be elevated. Paradoxically, rare cases of hyperthyroidism have been reported. **EEG Changes:** diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm.

EKG Changes: reversible flattening, isoelectricity or inversion of T-waves. **Miscellaneous:** Fatigue, lethargy, transient scotomata, exophthalmos, dehydration, weight loss, leucocytosis, headache, transient-hyperglycemia, hypercalcemia, hyper-parathyroidism, albuminuria, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, and dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypo-thyroidism which persist after lithium discontinuation have been received. A few reports have been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of starting lithium treatment. The mechanism through which these symptoms (resembling Raynaud's Syndrome) developed is not known. Recovery followed discontinuance.

OVERDOSAGE

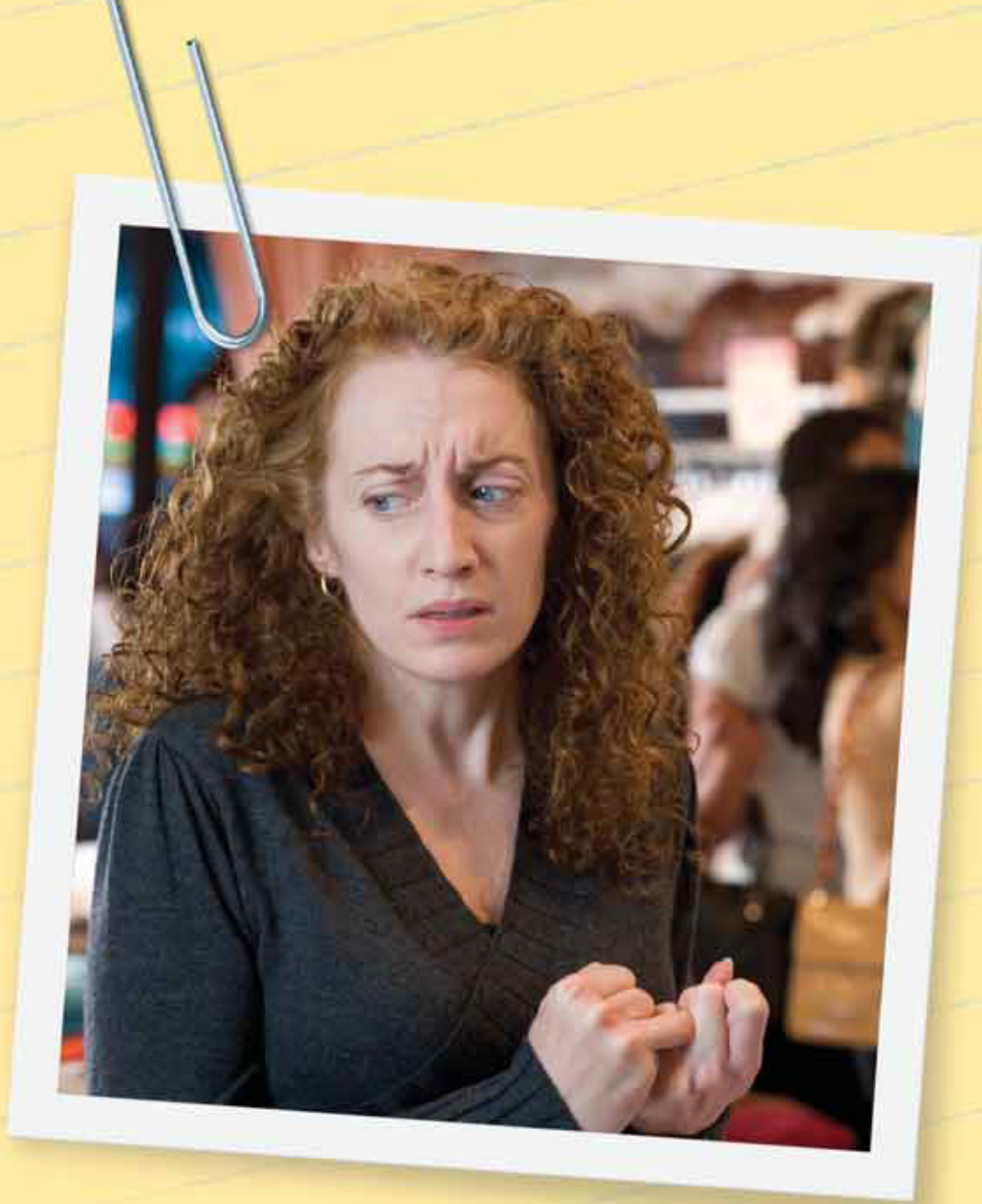
The toxic concentrations for lithium (1.5 mEq/L) are close to the therapeutic concentrations (0.6-1.2 mEq/L). It is therefore important that patients and their families be cautioned to watch for early toxic symptoms and to discontinue the drug and inform the physician should they occur. (Toxic symptoms are listed in detail under **ADVERSE REACTIONS**).

Treatment: No specific antidote for lithium poisoning is known. Treatment is supportive. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient.

Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance and, 3) regulation of kidney functioning. Urea, mannitol, and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. However, patient recovery may be slow. Infection prophylaxis, regular chest X-rays, and preservation of adequate respiration are essential.



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IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

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

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

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**

- **Adult and pediatric patients with MDD can experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressants. Patients treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy,**

Please see brief summary of Prescribing Information on adjacent page.

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- **Proven long-term (6-month) relapse[‡] prevention in panic disorder^{1§}**

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

- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.
- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence $\geq 10\%$ and $\geq 2\times$ that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

*Panic-free was defined as free from full-symptom panic attacks (ie, panic attacks with 4 or more *DSM-IV*[®] symptoms).

† Two double-blind, 12-week, placebo-controlled studies in adult patients diagnosed with panic disorder. Patients received fixed doses of 75 (n=158) or 150 (n=159) mg/day in one study and 75 (n=156) or 225 (n=160) mg/day in the other.

‡ Relapse was defined as having 2 or more full-symptom panic attacks per week for 2 consecutive weeks.

§ The cumulative probability of remaining relapse-free at 6 months was 76% with EFFEXOR XR.

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

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BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)
Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION**). Families and caregivers of pediatric patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **PRECAUTIONS: General—Discontinuation of Treatment with Effexor XR.** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. **Insomnia and Nervousness:** Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. **Changes in Weight: Adult Patients:** In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. **Pediatric Patients:** Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% vs. 3.6%; *P*<0.001). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents >12 years old. **Changes in Height: Pediatric Patients:** In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while

placebo patients grew an average of 1.0 cm (n=132); *P*=0.041. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). In a 6-month study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents >12 years old. **Changes in Appetite: Adult Patients:** Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. **Pediatric Patients:** Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. **Activation of Mania/Hypomania:** Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. **Hypонатremia:** Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. **Mydriasis:** Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **Seizures:** In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. **Abnormal Bleeding:** Abnormal bleeding (most commonly ecchymosis) has been reported. **Serum Cholesterol Elevation:** Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. **Use in Patients With Concomitant Illness:** Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide* About Using Antidepressants in Children and Teenagers is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to avoid alcohol while taking Effexor XR and to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations, they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions—Alcohol:** A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. **Cimetidine:** Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. **Diazepam:** A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. **Haloperidol:** Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol *C_{max}* increased 88%, but the haloperidol elimination half-life was unchanged. **Lithium:** A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. **Drugs Highly Bound to Plasma Proteins:** Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. **Drugs That Inhibit Cytochrome P450 Isoenzymes:** CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. **Drugs Metabolized by Cytochrome P450 Isoenzymes:** Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. **Imipramine:** Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, *C_{max}* and *C_{min}* increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. **Risperidone:** Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4:** Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. **Indinavir:** In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir *C_{max}*. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2:** Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9:** Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19:** Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). **MAOIs:** See **CONTRAINDICATIONS and WARNINGS. CNS-Active Drugs:** Use caution with concomitant use of venlafaxine and other CNS-active drugs. Based on its mechanism of action and the potential for serotonin syndrome, use caution when coadministering venlafaxine with other drugs affecting the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors, or lithium. **Electroconvulsive Therapy (ECT):** There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis:** There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. **Mutagenesis:** Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in *Salmonella* bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. **Impairment of Fertility:** No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy—Teratogenic Effects—Pregnancy Category C.** Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations

in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. **Nonteratogenic Effects:** Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General, Changes in Height and Changes in Weight**). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS: Associated with Discontinuation of Treatment**—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. **Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD**—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. **Vital Sign Changes:** Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). **Laboratory Changes:** Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. **Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR**—N=6,670. "Frequent"—events occurring in at least 1/100 patients; "infrequent"—1/100 to 1/1000 patients; "rare"—fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalciuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, breast pain, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports:** agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular

tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methyphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE:** Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE:** Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference[®] (PDR). **DOSAGE AND ADMINISTRATION:** Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS and WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C019, revised November 2005.

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Preparing for Disasters Can Minimize Disruption

Medical practices do not have immunity from the effects of a disaster, whether natural or manmade, but having an emergency response plan in place can minimize disruption and damage.

BY JACQUELINE MELONAS, R.N., J.D.

How do you prepare your practice to be ready to respond in the event of a disaster—from something small scale like a computer crash to the kind of destruction associated with hurricanes Katrina and Rita? A prompt, effective, and confident response to an emergency or emergent situation can mean the difference between considerable damages or minimal damages.

Psychiatrists and other health care professionals are accustomed to planning for and responding to medical emergencies in acute-care settings. Once in an office setting, however, many professionals fail to recognize the need for emergency planning. But injuries and damages resulting from disasters in an office setting can be just as devastating as those arising in a hospital, and advance planning, staff training, and periodic reviews can assure an effective response in even the most modest of practice settings.

The goals of an emergency plan are to minimize the probability of injury or loss related to patients, visitors, or employees; prevent or decrease risk of property loss (equipment, patient and business records, and so on), and expedite recovery from the disaster.

For most psychiatric office settings, emergency plans do not have to be lengthy, and the planning and preparation should not be time consuming. The following suggestions may assist you with planning, constructing, and implementing an emergency plan:

1. Begin by identifying and analyzing potential emergency risks.

- Think about the activities in your office and the individuals and groups involved in those activities. Some examples are patients and families, professional staff, administrative staff, visitors, individual or group therapy, acupuncture, and lab work.
- Consider specific types of emergencies that might occur, for example, medical emergencies, psychiatric emergencies, fire, bomb threats, hazmat exposure, flood, weather-related emergencies, and power outages.
- Consider other factors that might contribute to an emergency and your ability to respond. Among these are special needs and requirements for the safety of staff and patients with disabilities.

2. Weigh possible effective responses to the potential emergency situations identified and decide which responses are best for your practice setting.

For example, you have identified flooding as a potential emergency situation to plan for because your office building has experienced problems with this during severe storms.

Your analysis finds that the biggest potential risk/loss is the loss of patient and business records. After reviewing possible responses to minimize this risk, you develop a plan to

- have electronic back-up records taken weekly to a secure off-site location,
- transport active patient records to a safe location when a severe storm is imminent, and
- store inactive patient records with a medical-record storage company. You decide against purchasing file cabinets advertised as waterproof and fireproof due to cost.

3. Consider what safety features and plans may already be in place and incorporate them into your plan.

Some examples to assess include any security procedures for the building; existence of an evacuation plan, fire plan, and so on; the emergency contact person if anything goes wrong in the building or if a problem is anticipated; presence of fire and other alarms; and the regularity with which fire extinguishers are checked.

4. Prepare a written emergency plan.

The plan should be readable and stored in an easily accessible location.

5. Educate office staff about the emergency plan.

All staff should know the location of the written emergency plan. They should also review the plan and have in-service training on responding to emergencies at least yearly. Staff members should be involved in identifying potential emergencies and updating the plan.

6. Periodically review the plan and update it as needed. Keep staff informed of any changes.

7. Have a contingency plan for what staff and others should do if you are not available.

- Doctors must prepare a set of instructions for staff, family members, and willing colleagues regarding what they should do in the event of the psychiatrist's sudden incapacity. The plan need not be complex but should be documented, be readily available to those who may need to implement it, and be regularly updated. A list of suggested items to be covered in a contingency plan includes the following:
- Contact information such as the physician's pager number, cell phone number, home phone number, e-mail address, and home address.
 - Contact information for the physician's spouse, life partner, adult children, or anyone else who would likely know of the physician's whereabouts or sudden health problems.
 - A statement that staff is authorized to contact these people in the event of the physician's unexplained absence from the practice.

- Instructions regarding how long staff should wait before implementing the emergency contact plan in the event of any unexplained absence. One hour is probably the longest period of unexplained absence the plan should allow.
- Instructions regarding who is authorized to have access to patient records in the physician's unexplained absence. These instructions also should specify what information can be released from the records.
- Instructions regarding prescription refills and release of information to third parties.
- Instructions regarding how to deal with patients who become distressed, either physically or emotionally, in a crisis.
- Names, addresses, and phone numbers of psychiatrists who have agreed to act as emergency backups. There should be more than one. Staff should be trained on proper referral procedures and proper termination-of-care procedures.

The emergency plan for any practice will be unique to the needs of that practice. There is a variety of resources available to help in your planning process. Among them:

- American Health Information Management Association, <www.ahima.org> under "Practice Brief: Disaster Planning for Health Information"
- Federal Emergency Management Agency, <www.fema.gov>
- American Red Cross, <www.redcross.org/services/disaster/beprepared/busi_industry.html>
- U.S. Department of Homeland Security, <www.ready.gov/business/index.html>. The department has posted information on costs that may be expected for emergency planning and protection at <www.ready.gov/business/over-cost.html>.

(Parts of this article were excerpted from the spring 2002 issue of *Rx for Risk*.) ■

residents' forum

Residents Can Help Determine APA's Future Course

BY DANIEL MAMAH, M.D.

Although not always very apparent, individual APA members can play an important role in influencing the Association's policies and functioning. We can help shape the organization and psychiatry by communicating with APA leaders, writing articles for psychiatric publications, voting in elections, and even running for elected office. Constructive ideas can also be conveyed to APA by residents and other members who develop "action papers," documents that are formally reviewed by the APA Assembly and considered for implementation.

Processing an action paper usually requires several steps before final approval by the APA Board of Trustees.

It requires involvement of the APA Assembly, where most action papers originate. The Assembly is a legislative body made up of locally elected representatives from APA's 74 district branches and seven Area Councils (Area Councils are primarily regional links between the Assembly and the district branches). While any APA member can write an action paper, an Assembly representative is the conduit for bringing it before the Assembly.

Most APA district branches have one Assembly representative, but larger branches can have two or more, depending on the size of the membership. District branches with only one representative also have a deputy representative to the Assembly, who only has a vote in the Assembly in the absence of the representative.

In addition, a representative and deputy representative from each of APA's seven caucuses represent psychiatrists from minority/underrepresented groups. More than a

Daniel Mamah, M.D., is APA's member-in-training trustee.



dozen other psychiatric organizations also have an Assembly liaison.

The Assembly also has representatives from two key member categories—members-in-training and early career psychiatrists. Each of the seven Areas sends a member-in-training and early career psychiatrist representative and deputy representative to Assembly meet-

ings. To find out who your Assembly representatives are, you can contact your district branch. A listing of all representatives can be accessed on APA's Web site at <www.psychiatry.org> by clicking on "Members Corner" and then "Directory of Components."

Here are a few tips to help those of you who may want to write an action paper for the Assembly. When writing the paper, make sure that your language is concise, particularly when you describe the steps you would like APA to take to address the problem you raise. Your paper is more likely to be successful if you have other psychiatrists, particularly those familiar with the working of the Assembly, review it before it is introduced.

Action papers are laid out in several sections so their format is uniform. Key sections are (1) subject, (2) intent, (3) description of the problem the paper addresses, (4) alternatives and recommendations for solving the problem, (5) estimated cost (APA's Office of Finance and Business Operations can help develop the estimate), and (6) into which of APA's five strategic goals this paper best fits.

Action papers are first submitted to the APA Governance Office, where they are reviewed and shared with the Assembly Rules Committee. From here papers are assigned to Assembly reference committees or to

please see Residents' Forum on page 10

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district branches in the **news**

Physician Coalition Prepares For Scope-of-Practice Battles

Oklahoma psychiatrists are using a tried-and-true legislative tool to help them overcome their adversaries' superior numbers in the coming scope-of-practice fight: A physician alliance and a unified message.

BY RICH DALY

Oklahoma psychiatrists have helped create a physician coalition to prevent expansions in scope of practice sought by some allied health professionals.

The PatientsFIRST Coalition, which was launched in September 2005, represents more than 7,000 Oklahoma physicians in nine medical specialties in an effort to block legislative expansion of allied health professionals' practice into areas of medical privilege.

"We're going to start educating legislators to the point where they know what is going to be asked of them [by allied health professionals], and when this legislation comes up, it won't just be psychiatrists coming to them but a united front of physicians," said Art Rousseau, M.D., cochair of the coalition.

Rousseau, Public Information/Legislative Committee chair of the Oklahoma Psychiatric Physicians Association (OPPA), said the coalition's goal is to educate legislators about the additional education and training physicians receive beyond what allied health professionals receive, so they know why medical activities, such as prescription of medications, should be entrusted to them. The educational effort is meant to preempt legislation to expand other professionals' scope of practice.

The coalition was spurred by the state legislature's recent approval of some surgical privileges for optometrists. Two years ago a bill was introduced in the state Senate to expand prescription privileges to psychologists, but the legislation never advanced. However, similar legislation was approved in recent years in Louisiana and New Mexico.

"What we're finding is that all of the medical specialties are facing the same issues," Rousseau said, about efforts by some

allied health professionals, including pharmacists and nurse practitioners, to expand their legal scope of practice.

The coalition aims to inform legislators that an issue its opponents frame as a turf war and political bullying is in reality critical to patient safety.

Ondria Gleason, M.D., president of the OPPA, said one reason that it is important for individuals with a mental health problem to be seen by psychiatrists is that psychiatrists can recognize when a patient presents with symptoms that might be due to a nonpsychiatric disorder.

"If you don't have appropriate medical training, you would not know the difference between someone who has what appears to be depression but who really has a pituitary abnormality or someone who appears to be psychotic but what they really have is an adverse reaction to a medication," Gleason said.

The coalition is based on medical coalitions in other states, including one in Texas that managed to defeat an optometrist-advocated expansion in scope of practice in 2005.

In addition to the OPPA, the coalition includes the Oklahoma State Medical Association, Oklahoma Osteopathic Association, Oklahoma Academy of Otolaryngology-Head and Neck Surgery, Oklahoma Society of Anesthesiologists, Oklahoma Academy of Ophthalmology, and the Oklahoma chapters of the American College of Physicians, American Academy of Family Physicians, and American College of Obstetricians and Gynecologists.

The coalition, which has already added two member groups since it was launched, hopes to add other medical specialty representatives.

Future efforts may include political fund raising and urging the introduction and passage of its own legislation, Rousseau said. ■

residents' forum

continued from page 9

Area Councils to review at an Assembly meeting. There are two Assembly meetings every year, one in November and one just before the APA annual meeting, usually in May.

Once presented at an Assembly meeting, action papers can be accepted as written, accepted with changes, or rejected. In addition, sometimes papers are sent to a committee or council for further discussion and then returned to the Assembly at a future meeting.

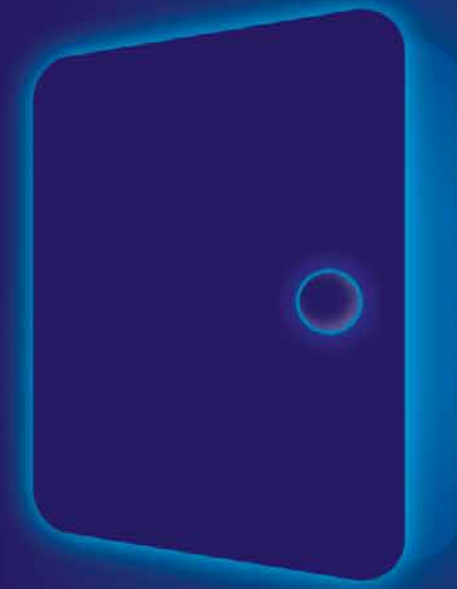
Action papers approved by the Assembly are sent to the Board of Trustees for final approval.

Psychiatry residents have been active in writing action papers for many years. During the Assembly meeting in May 2005, this was particularly evident.

Six papers were written by members-in-training; all of the papers were passed as written or with some modification. The proposals included adding free seats for residents at courses during the APA annual meeting, ensuring residents' presence on the Scientific Program Committee (which develops and implements the APA annual meeting programs), and exploring the inclusion of fetal alcohol spectrum disorders in future editions of the *DSM*.

When APA members participate in the Association's functioning, it strengthens the Association and ensures that as many voices as possible are heard. The problems facing our field are multiple and complex. It is likely that we will move faster toward solutions if the innovative ideas so many residents have are shared with the rest of the psychiatric community. ■

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Patches Won't Heal A System in Crisis

BY CHARLES ATKINS, M.D.

As I look at the literature on the last several decades in health care, I find a mountain of articles and books, which I call our history of "Crisis in American Health Care."

The central themes are that our system is the most expensive in the world, yet 45 million Americans don't have insurance coverage, 44,000-98,000 people die annually from medical mistakes in our hospitals, malpractice insurance is skyrocketing, and managed care second guesses and attempts to override physicians in medical decision making.

I don't know if I'm stating the obvious, but in the words of Kermit the Frog, "some of these things go together." In fact, they all do.

The first thing that strikes me as curi-



ous is the constant use of the word "crisis." This implies a state of affairs in which something is going to change, a flashpoint. Yet decisive change has not come. Instead, we find a series of patches—Medicare Part D being the latest in a series of these make-do repairs.

In the 20th century, as the rest of the industrialized world—excluding Japan—made the decision that access to health care was a right of citizenship, we saw the AMA lobby against a national health system. I raise this point, because our current state of affairs is multifactorial, and as physicians we need to own our piece.

While opponents of sweeping reform shot it down in years past by coining the term "socialized medicine" and tying universal coverage to the Red Scare, there was also a realization that certain groups would be unable to obtain and maintain coverage—the old, the disabled, and the very

poor. So we kind of got a national health plan with the creation of Medicare and Medicaid in the 1960s. The flashpoint was averted, and we moved forward.

Now the focus has shifted to cost. Somehow the country's annual expenditure on health care has shot up into the double digits (about 5 percent of GNP in the 1960s and over 14 percent today).

Enter managed care and exit the arguments against a national health plan. Hospital days were negotiated, tests and procedures were questioned, and we learned how to fill out new forms, get on provider panels, negotiate contracts, and do physician-to-physician reviews over the telephone.

So how do we jump from that "crisis" to the news-grabbing statistics from the Institute of Medicine about deaths from medical errors? I think the point of attachment is the truism "haste makes waste." To stay on top financially, physicians in America have to work longer hours and see more patients. The rising costs of malpractice insurance, maintaining an office, hiring staff to handle the billing, and on and on mean that you've got to pump out the volume.

If we look at the sources of medical errors, much of it comes under the heading of carelessness—indecipherable and easy-to-confuse handwriting on prescriptions and order sheets, wrong-site surgeries, uncoordinated care, drug-to-drug interactions, and inadequate time to really listen to patients.

From there, it doesn't take a brain surgeon—and are they really that smart?—to see the connection to our malpractice "crisis." Between 44,000 and 98,000 potentially preventable medical deaths a year is a whole lot of meat and potatoes for attorneys—not to mention the human tragedy those numbers represent. Malpractice premiums have skyrocketed, insurers have left the business, and we go crying to the politicians because we can't afford to stay in practice.

So, what do I take away from all of this? First, crisis or no crisis, we historically have shied away from a fundamental and sweeping overhaul of the American health care system. Instead, we've seen major changes occur, but more as reactions to the cost of health care and attempts to try and contain it. The resultant effects on quality of care and on the role and integrity of physicians have been dismal. This is not where we wanted to be.

My own career—I work for a state agency—has been one in which I have sought out situations where I don't have to spend much time thinking about payer sources and whether I can provide medically necessary treatment. In chatting with other doctors, I realize that most would prefer this. If that assumption is correct, the questions then become, and what I ask everyone who reads this to think about, what would it take to create fundamental change in the American health care system, and what role could physicians play in making those changes happen? ■

In Memoriam

APA honors the following members whose deaths were reported to APA from May through December 2005. All deceased APA members are remembered at APA's annual business meeting, held each year at APA's annual meeting.

Victor R. Adebimpe, M.D.
Pittsburgh, Pa.

Marvin Leon Adland, M.D.
Chevy Chase, Md.

James M. Bailey, M.D.
San Antonio, Texas

William E. Bakewell Jr., M.D.
Cary, N.C.

Julian I. Barish, M.D.
New York, N.Y.

Robert Galen Bowman, M.D.
Connellsville, Pa.

Charles Allan Bray, M.D.
San Angelo, Texas

Bernard Bressler, M.D.
Richmond, Va.

Vincent J. Butler, M.D.
Woodside, Calif.

Felix Cohen, M.D.
Waban, Mass.

Alan Randolph Cole, M.D.
San Francisco, Calif.

Nathan L. Comer, M.D.
Narberth, Pa.

Zarko Cuculic, M.D.
Paramus, N.J.

Irving J. Farber, M.D.
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Robert S. Garber, M.D.
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Harris S. Goldstein, M.D.
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D. Wells Goodrich, M.D.
Purcellville, Va.

Kenneth H. Gordon Jr., M.D.
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Robert Gordon Halem, M.D.
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Karl H. Hanson, M.D.
San Mateo, Calif.

Arthur R. Henderson, M.D.
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William Gray Hollister, M.D.
Chapel Hill, N.C.

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Frederick D. Jarvis Jr., M.D.
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Elwood L. Jones, M.D.
Seattle, Wash.

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Park Forest, Ill.

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David A. Lanham, M.D.
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Harold L. Levitan, M.D.
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Charles Amos Neff, M.D.
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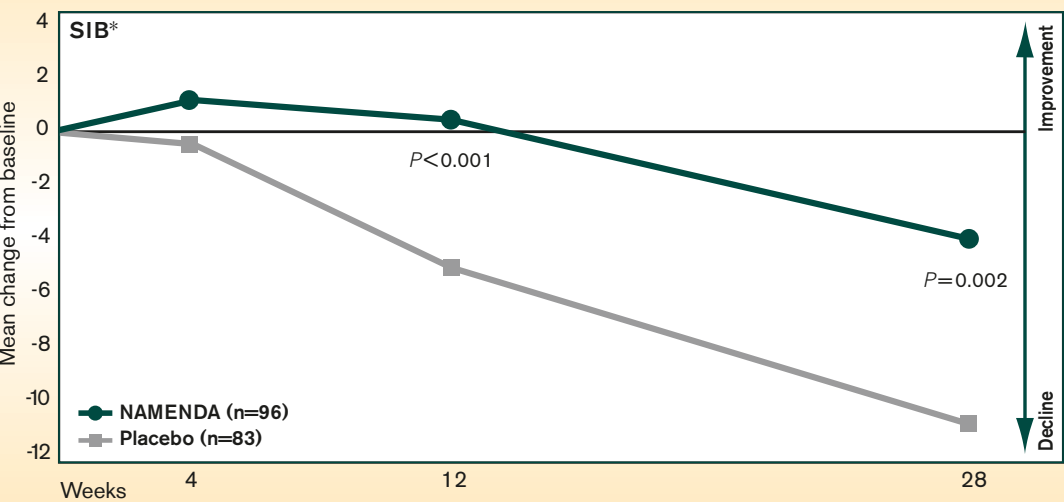
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*SIB=Severe Impairment Battery. Evaluates cognitive performance in moderate to severe AD. It is a 40-item scale that assesses attention, language, praxis, visuospatial ability, construction, memory, orientation, orienting to name, and social interaction. The test is scored from 0 (greatest impairment) to 100.³

[†] Separate placebo-controlled cost analysis.

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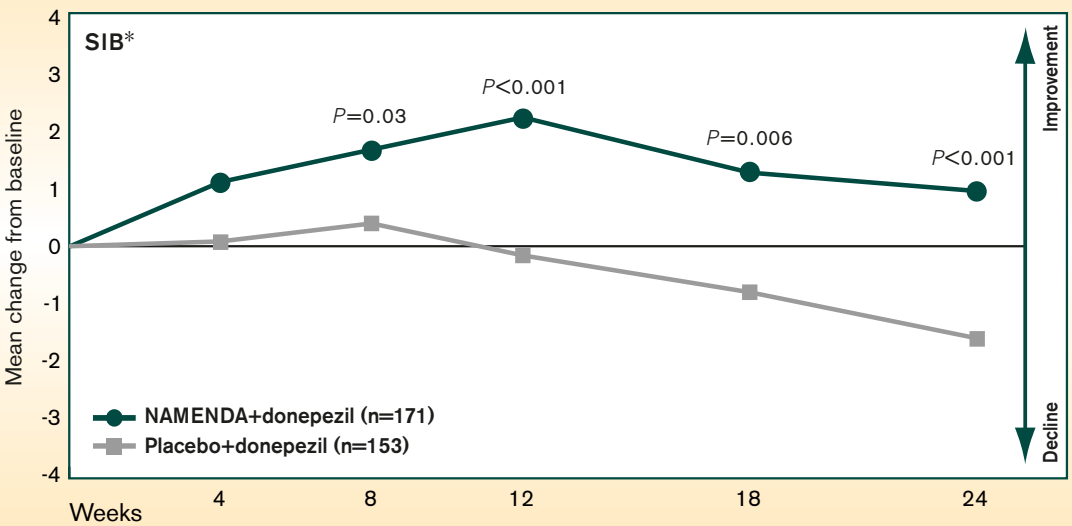


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‡ Donepezil therapy could have been 6 months or longer.

§ Alzheimer's Disease Cooperative Study Activities of Daily Living₁₉ (ADCS-ADL₁₉) Inventory. Autonomy subscale included: using a telephone, watching television, traveling, and being left alone; higher-level functions subscale included: conversing, finding belongings, obtaining a beverage, and turning a light off.²

★ NAMENDA in combination with donepezil significantly improved and sustained cognitive performance above baseline for 6 months vs progressive decline seen with donepezil+placebo ($P<0.001$)^{5‡}

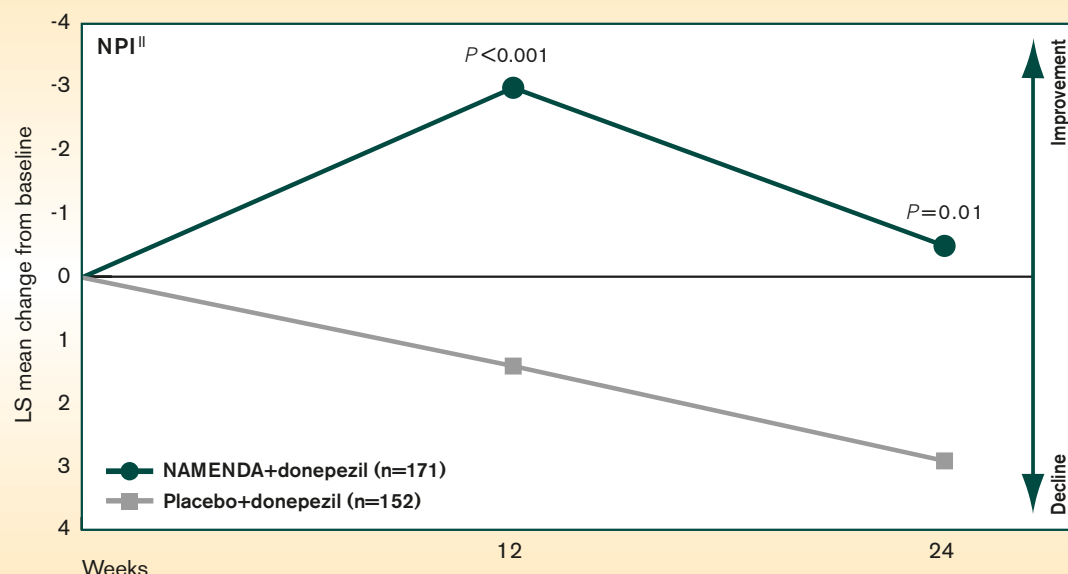
NAMENDA-treated patients also maintained significantly more autonomy and higher-level functioning than patients taking donepezil+placebo ($P<0.05$)²

★ Autonomy and higher-level function are subscales derived from the ADCS-ADL₁₉[§]

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^{II} NPI=Neuropsychiatric Inventory. The NPI is designed to assess behavioral disturbances occurring in patients with Alzheimer's disease or other dementias. It is particularly relevant because it is based on scripted questions administered to caregivers.⁷

✦ As measured by caregivers, NAMENDA+donepezil significantly improved behavioral function for 6 months compared with the progressive decline seen with patients taking donepezil+placebo ($P=0.01$)^{5,6}



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References: 1. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ, for the Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333-1341. 2. Data on file. Forest Laboratories, Inc. 3. Saxton J, McGonigle KL, Swihart A, Boller F. The Severe Impairment Battery. Bury St Edmunds, England: Thames Valley Test Company; 1993. 4. Wimo A, Winblad B, Stöffler A, Wirth Y, Möbius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics*. 2003;21:327-340. 5. 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. 6. Cummings JL, Schneider E, Tariot PN, Graham SM, for the Memantine Study Group. Effect of memantine on behavioral outcomes in moderate to severe Alzheimer's disease. Poster presented at: Annual Meeting of the American College of Neuropsychopharmacology; December 12-16, 2004; San Juan, Puerto Rico. 7. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308-2314.

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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).

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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.

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

Special Populations

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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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Brain Chemicals May Retreat, But Love Lingers On

A brain protein—nerve growth factor—seems to jump-start the altered mental state called “falling in love,” yet it takes a back seat once the romance is established.

BY JOAN AREHART-TREICHEL

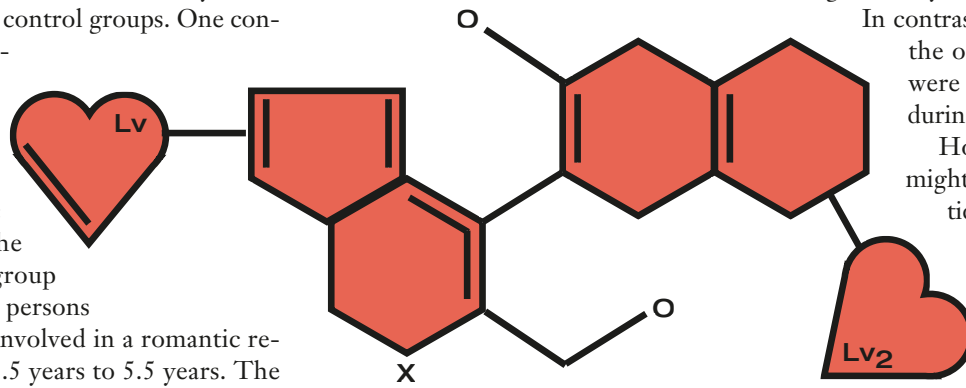
When early February comes around, many people’s thoughts turn to Valentine’s Day and romance. The biological substrate of romantic love, however, has been mostly uncharted territory.

Now some researchers, appropriately from a country associated with romance—Italy—have explored the subject. And as they report in a study in press with *Psychoneuroendocrinology*, falling in love appears to be associated with elevated levels of nerve growth factor in the bloodstream.

Enzo Emanuele of the University of Pavia and colleagues suspected that a diversity of biological mechanisms might be involved in precipitating the mental state called “falling in love,” a state characterized by obsessive thinking about one’s beloved, craving for union with him or her, euphoria, and increased energy. And one of the mechanisms that the researchers thought might be implicated are neurotrophins—brain chemicals that nourish nerves and that have been increasingly recognized as potential mediators of anxiety and other emotions.

The researchers measured blood levels of four kinds of neurotrophins—nerve growth factor, brain-derived neurotrophic factor, neurotrophin 3, and neurotrophin 4—in 58 subjects who had recently fallen in love and two control groups. One control group consisted of 58 individuals who were not engaged in a romantic relationship; the other control group consisted of 58 persons who had been involved in a romantic relationship for 2.5 years to 5.5 years. The subjects in love were likewise assessed for anxiety and depression with the State-Trait Anxiety Inventory and the Beck Depression Inventory and for the intensity of their romantic feelings with the Passionate Love Scale. This association held even when some potentially confounding variables such as age, gender, anxiety scores, and depression scores were taken into consideration.

Thus, “our data demonstrate for the first time that circulating levels of nerve growth factor, but not of other neurotrophins, are elevated among subjects in love,” Emanuele and his team concluded in their study report, “suggesting an important role for this molecule in the ‘social chemistry’ of human beings. The specificity of nerve growth factor increase during early-stage love, which was independent from anxiety and/or depression scales, as well as from other neurotrophins, seems to suggest that this neurokinine could be involved in the formation



higher in the subjects who had recently fallen in love than in the subjects who were not engaged in romantic relationship or long engaged in one.

Moreover, among subjects who had recently fallen in love, a significant positive link was found between blood levels of nerve growth factor and the intensity of romantic feelings as assessed by the Passionate Love Scale. This association held even when some potentially confounding variables such as age, gender, anxiety scores, and depression scores were taken into consideration.

Thus, “our data demonstrate for the first

of novel bonds. . . .”

Nonetheless, follow-up results from the study suggest that nerve growth factor does not play a major role in the maintenance of a romantic relationship.

Specifically, 39 of the 58 subjects who had recently fallen in love were still romantically involved a year or two later with the same partners with whom they had been involved at the start of the study. The researchers once again measured their blood levels of the four neurotrophins and used the Passionate Love Scale to assess their feelings of love. Results showed that both their Passionate Love Scale scores and nerve growth factor concentrations had decreased significantly from the start of the study.

In contrast, their concentrations of the other three neurotrophins were similar to those observed during the first assessment.

How nerve growth factor might help people forge romantic bonds remains to be determined. Emanuele and his group suspect it might be by influencing various hormones. For instance, nerve growth factor is

known to induce the release of the hormone vasopressin, and vasopressin in turn is known to play a pivotal role in the formation of social bonding.

The study was financed by the University of Pavia.

An abstract of “Raised Plasma Nerve Growth Factor Levels Associated With Early-Stage Romantic Love” can be accessed at <www.sciencedirect.com> by clicking on “Browse Journals,” “P,” “Psychoneuroendocrinology,” and “Articles in Press.” ■

Gene Variant May Hasten Development of Alzheimer’s

A fifth of Americans are estimated to possess the e4 variant of the APOE gene. This variant hastens development of Alzheimer’s, and how it does so may be by accelerating age-related myelin breakdown.

BY JOAN AREHART-TREICHEL

Apart from age, the e4 variant of the APOE gene on chromosome 19 is the best-documented risk factor for Alzheimer’s disease. Although possession of the variant is neither necessary nor sufficient for developing Alzheimer’s, those individuals who have the variant and develop Alzheimer’s succumb to the illness a good decade earlier than do per-

sons who have the other two variants of the gene—e2 and e3—and who develop Alzheimer’s.

The investigation was headed by George Bartzokis, M.D., director of the University of California at Los Angeles Memory Disorders and Alzheimer’s Disease Clinic. The results were published in the January *Archives of General Psychiatry*.

Myelination is arguably the most uniquely human aspect of the human brain. It results in the high processing speeds that underlie people’s cognitive functions. Myelination reaches a maximum in midlife, then declines with normal aging. Moreover, persons with Alzheimer’s are known to have more severe myelin breakdown than healthy older subjects, and the APOE gene is known to transport lipids for myelin maintenance and repair.

Thus, Bartzokis and his colleagues suspected that the means by which the APOE e4 gene variant hastens the development of Alzheimer’s might be by hastening the breakdown of myelin. They decided that

with the e4 variant, the next greatest breakdown in those with the e3 variant, and the least breakdown in those with the e2 variant.

The researchers recruited 102 healthy individuals between the ages of 55 and 75 for the study. They found that 12 had the e2 variant, 70 had the e3 variant, and 20 had the e4 variant. There were no significant differences between the three gene-variant groups in terms of age, education, gender, or Mini-Mental State Examination scores.

They then used magnetic resonance imaging coupled with a technique called transverse relaxation rate measures to assess indirectly the structural integrity of myelin sheaths in the three gene-variant groups. The areas of the brain they focused on included both early-myelinating regions—say, the visual pathway circuits of the corpus callosum splenium—and late-myelinating nerve regions—for example, the frontal lobes. They were particularly interested in the latter since they support executive functions and recent memories, are especially eroded with normal aging, and are especially degraded by Alzheimer’s.

They found that the breakdown of late-myelinating nerve circuits, but not of early-myelinating nerve circuits, was linked with APOE gene status. The greatest decline in late-myelinating circuits occurred in subjects with the e4 variant, the next greatest decline in those with the e3 variant, and the least decline in those with the e2 variant.

The investigators thus believe that by linking the e4 variant to the accelerated breakdown of late-myelinating nerves, they have partially confirmed their hypothesis that the APOE e4 variant hastens the development of Alzheimer’s by hastening the breakdown of myelin.

However, only prospective studies can explain how possession of the e4 variant might actually speed up myelin breakdown, the scientists wrote in their study report. They will now be conducting such studies, Bartzokis told *Psychiatric News*.

Also, “combining APOE status with noninvasive measures of myelin breakdown may be useful in assessing treatment strategies for the primary prevention of Alzheimer’s,” the scientists wrote.

“Funding possibilities for such novel primary-prevention strategies are being pursued,” Bartzokis told *Psychiatric News*.

Jeffrey Cummings, M.D., added, “These findings set the stage for studies that will investigate the effects of diets and medications that contribute to myelin maintenance.” Cummings is director of the UCLA Alzheimer’s Disease Research Center and was one of the study investigators.

The study was funded by the National Institutes of Health, California Department of Health Services, Sidell-Kagan Foundation, and Department of Veteran Affairs.

An abstract of “Apolipoprotein E Genotype and Age-Related Myelin Breakdown in Healthy Individuals” is posted at <<http://archpsyc.ama-assn.org/cgi/content/short/63/1/63>>. ■

“These findings set the stage for studies that will investigate the effects of diets and medications that contribute to myelin maintenance.”

sons who have the other two variants of the gene—e2 and e3—and who develop Alzheimer’s.

The e4 gene variant is suspected of putting people on the fast track for Alzheimer’s by accelerating the rate of breakdown of myelin sheaths that insulate brain nerves, a new study suggests. The greatest breakdown occurred in those

Protein Discovery May Lead To New Psychiatric Drugs

New research clearly connects alterations in a specific serotonin receptor to depressive changes in mood via one specific protein.

BY JIM ROSACK

The discovery of a novel protein and its interaction with a serotonin receptor on the surface of neuronal cells could prove to validate the fundamental biological basis of mood disorders, particularly depression.

The groundbreaking identification of the new protein, called p11, was reported in the January 6 *Science* by Nobel Laureate Paul Greengard, Ph.D., a professor of psychiatry and pharmacology and director of the Laboratory of Molecular and Cellular Neuroscience at Rockefeller University.

Greengard shared the 2000 Nobel Prize in Physiology or Medicine with psychiatrist Eric Kandel, M.D., of Columbia University and Arvid Carlsson, M.D., of the University of Goteborg in Sweden (*Psychiatric News*, November 3, 2000). Greengard received the Nobel for his work in defining the interplay of proteins and hormones with receptors on the cell surface. It was Greengard's work that defined the mechanism by which extracellular proteins cause an intracellular effect without having to enter the cell itself.

In 2002 Greengard again made headlines with his lab's determination of the cellular interactions of the antidepressant fluoxetine. At that time, Greengard and his colleagues detailed the interaction between fluoxetine and a cell surface protein known as DARPP-32 (*Psychiatric News*, May 17, 2002).

Greengard's latest contribution to advancing the understanding of the cellular mechanisms underlying depression involves the serotonin 1b receptor (5-HT_{1B}) and its interaction with the extracellular protein called p11. Simply put, when p11 levels increase, the number of 5-HT_{1B} receptors on the cell surface increases proportionately. With more 5-HT_{1B} receptors on the surface of the neuron, serotonin communication across the synapse is made more sensitive and more effective. However, when p11 levels are low, fewer 5-HT_{1B} receptors migrate from inside the neuron to the cell membrane at the synaptic cleft, leading to decreased efficiency and power of serotonin signaling.

To explore how the 5-HT_{1B} receptor functioned, Greengard and his colleagues conducted laboratory tests to determine with what proteins the receptors interacted. They found the interaction with p11 and hypothesized that p11 played a role in recruiting serotonin receptors to the cell surface, where they are functional.

Greengard and his colleagues suspected that p11 levels might be directly involved in the development of depression, anxiety, and similar psychiatric illnesses thought to involve faulty serotonin receptors. The researchers next examined p11 levels in post-mortem samples from the brains of depressed patients and a mice model of depression (called "helpless mice") and compared the levels with those found in non-depressed humans and normal mice. Levels of p11 were found to be substantially lower in depressed humans and the "helpless" mice.

"Mice deficient in this protein—p11—

display depressionlike behaviors, while those with sufficient amounts behave as if they have been treated with antidepressants," Greengard said in a prepared statement.

"This new-found protein," added Elias Zerhouni, M.D., director of the National Institutes of Health (which funded Greengard's work through grants from the National Institute of Mental Health), "may provide a more specific target for new treatments for depression, anxiety disorders, and other psychiatric conditions thought to involve malfunctions in the serotonin system."

Greengard's team next examined the effect of treatments that are used in humans and designed to boost weak serotonin systems on p11 levels in brain cells by administering two types of antidepressants—one tricyclic, the other a monoamine oxidase inhibitor. They also tested the effect of electroconvulsive stimulation in rats.

"These three different ways of treating depression all caused an increase in the amount of p11 in the brains of these mice," Greengard said. "They work in totally different ways, but in all cases they caused the same biochemical change. So, it is pretty convincing that p11 is associated with the

main therapeutic action of antidepressant drugs."

The researchers then altered the expression of the gene coding for p11 in mice. As they hypothesized, mice with increased expression of the p11 gene acted "less depressed." In addition, on examination of brain tissue from these mice, the researchers saw increased levels of 5-HT_{1B} receptors at the cell surface.

The researchers reached the opposite conclusion when they molecularly knocked out the p11 gene in mice. Compared with control mice, the knockout mice had fewer 5-HT_{1B} receptors at the cell surface, had reduced levels of serotonin signaling, had decreased responsiveness to sweet rewards, and were less active (all signs considered to be "depressionlike" in mice).

In an accompanying editorial, Trevor Sharp, M.D., an Oxford University pharmacologist, wrote, "Overall, [these findings] represent compelling evidence that p11 has a pivotal role in both the cause of depression and perhaps its successful treatment." Sharp noted that depression and the relief of its symptoms "are likely to be influenced by many different genes," and the current report adds to the list, "not just through the addition of p11, but also the large number of serotonin receptor-interacting proteins that p11 represents."

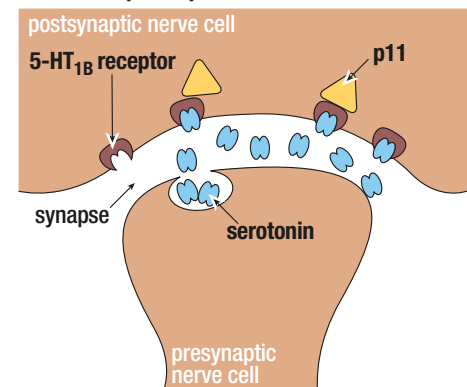
Sharp concluded, "The case for p11 as a key molecule in mood regulation is convincing, and it is now timely for translational science to take this exciting development to the next step."

An abstract of "Alterations in 5-HT_{1B} Receptor Function by p11 in Depression-

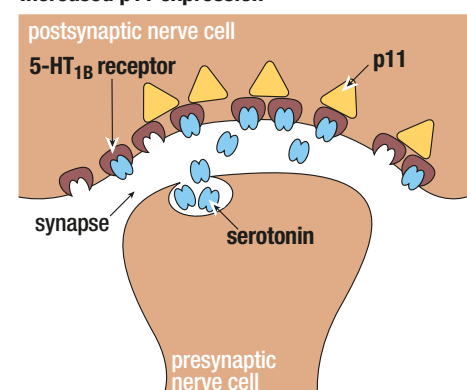
Mood and p11

Increased levels of the protein p11 increase the number of 5HT_{1B} receptors on the cell membrane, allowing for increased binding of serotonin (5HT) across the synapse.

Decreased p11 expression



Increased p11 expression



Source: *Science Magazine*, January 6, 2006

Like States" is posted at <www.science.org/cgi/content/abstract/311/5757/77>. ■

Benefits of Alzheimer's Drug Evident One Year Later

Long-term treatment with memantine may delay the inevitable decline in cognitive function, slow the loss of activities of daily living, and reduce behavioral symptoms associated with Alzheimer's disease.

BY JIM ROSACK

The N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, appears to provide significant benefits to patients with moderate to severe Alzheimer's disease for as long as one year, researchers said last month.

The new data come from a 24-week open-label extension study that followed a 28-week randomized, double-blind, placebo-controlled study of memantine in 252 patients with moderate to severe Alzheimer's. The new report appeared in the January *Archives of Neurology*. Data from the double-blind, first phase of the study were published in the April 3, 2003, *New England Journal of Medicine* (*Psychiatric News*, May 2, 2003).

"This study demonstrates that it is possible to alleviate some of the cognitive and functional losses associated with the later stages of Alzheimer's, providing a basis for greater optimism on the part of caregivers," said principal investigator Barry Reisberg, M.D., in a press release. Reisberg, a professor of psychiatry at New York University (NYU) School of Medicine, was the lead author of both reports.

Both phases of the study were funded by the German company Merz Pharmaceutical GmbH, which developed the drug and markets it worldwide outside the United States. Memantine is marketed as

Namenda in the United States by Forest Pharmaceuticals.

"Our study verifies that this medication continues to be beneficial and is safe, with remarkably few side effects," added Reisberg, who is also the director of the Silberstein Aging and Dementia Research Center at NYU.

The researchers used the same primary efficacy measures during both phases of the study: change in patients' scores on the 19-item Alzheimer's Disease Cooperative Study—Activities of Daily Living Scale, modified for severe dementia (ADCS-ADL), and the New York University version of the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-Plus).

Reisberg and his colleagues previously reported that memantine significantly slowed the rate of decline in patients who took the drug for the first 28 weeks of double-blind therapy, compared with those taking placebo. In fact, ADCS-ADL scores for those taking memantine signaled a small but statistically significant improvement during the first four weeks of the first phase of the study (see chart).

During the open-label phase of the study, the patients who were switched from placebo to memantine for the remaining 24 weeks exhibited a significantly slower

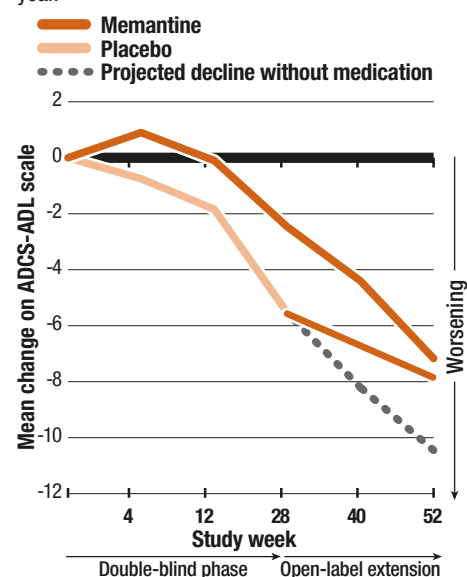
rate of decline in ADCS-ADL scores compared with their mean rate of decline while taking placebo during the double-blind phase. However, for patients who were taking memantine during the first 28 weeks and continued to take the drug for the remaining 24 weeks of open-label therapy, the rate of decline in scores on the ADCS-ADL increased, especially in the final 12 weeks (weeks 40 through 52) of the study.

Switching to memantine at week 28 was also associated with a significantly decreased rate of decline in scores on the CIBIC-Plus compared with the mean rate of decline for placebo during the double-blind period.

Overall, the most commonly reported adverse events associated with memantine during the study were dizziness and headache. *please see Benefits on page 22*

Decline Slowed

Memantine was associated with significant delays in patient decline on the ADCS-ADL scale over one year.



Source: Barry Reisberg, M.D., et al., *Archives of Neurology*, January 2006

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SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy with lithium or divalproex, and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL is not approved for the treatment of patients with dementia-related psychosis.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL.

Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Patients starting treatment with atypical antipsychotics 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.

Precautions include the risk of seizures, orthostatic hypotension, and cataract development. The most commonly observed adverse events associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.

*All atypical prescriptions: Total prescriptions. Jan. 05-Sept. 05. New prescriptions. Sept. 04-Sept. 05. IMS Health. National Prescription Audit.

†Significant improvement in all 11 YMRS items was measured at Day 21 and continued through Day 84 in monotherapy mania trials.

Please see Brief Summary of Prescribing Information on adjacent page.

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Beta-Amyloid Findings Could Be Alzheimer’s Marker

Washington University researchers find that high levels of amyloid plaques in the brain are accompanied by low levels of amyloid-42 in cerebrospinal fluid, and vice versa.

BY AARON LEVIN

The Holy Grail for researchers studying Alzheimer’s disease is an imaging system or biomarker to help diagnose the illness or at least document its progress. A new study from researchers at Washington University in St. Louis takes a step in that direction by combining PET scan imaging and cerebrospinal fluid (CSF)

analysis. The process compared the extent of beta-amyloid plaques in the brain with levels of related protein fragments in CSF or blood plasma. Using PET technology, researchers led by Anne Fagan, Ph.D., a research associate professor of neurology at the Washington University School of Medicine, scanned the brains of 24 people aged 48 to 83 to find concentrations of plaques

containing beta-amyloid. They used an amyloid-binding agent, Pittsburgh Compound B (PIB), provided by investigators at the University of Pittsburgh. Some participants were cognitively normal while others had very mild, mild, or moderate dementia.

Fagan and her colleagues from the Washington University Alzheimer’s Disease Research Center also tested CSF and blood plasma for several proteins using enzyme-linked immunosorbent assays.

They found no relation between PIB binding and the proteins amyloid-40, tau, phosphor-tau181 in CSF, and amyloid-40 and amyloid-42 in plasma. However, they did observe an inverse relationship between amyloid-42 in CSF and PIB binding at beta-amyloid plaques in the brain.

“Subjects fell into two nonoverlapping groups: those with positive PIB binding had the lowest CSF amyloid-42 level, and those

with negative PIB binding had the highest level,” wrote the researchers in an online publication of their paper in the *Annals of Neurology*.

Seven subjects showed positive PIB binding and low CSF amyloid-42 levels. Three of those subjects were diagnosed with mild or moderate Alzheimer’s-type dementia, and another with very mild symptoms.

However, three participants were cognitively normal but had high PIB binding and low CSF levels of amyloid-42, hinting that they were in such a preclinical state. If these subjects eventually develop dementia, this combined technique may indeed prove useful for identifying cases before they reach clinical status. However, if patients such as these never decline cognitively, it may show that plaque number does not always predict the disease.

Prior animal studies have suggested that amyloid plaques in the brain may bind beta-amyloid, reducing the movement of soluble beta-amyloid between the brain and the CSF, possibly accounting for the inverse relationship, said the authors. Heavy deposits of beta-amyloid plaques at autopsy are diagnostic for Alzheimer’s disease.

“These observations suggest that brain amyloid deposition results in low CSF amyloid-42 and that amyloid imaging and CSF amyloid-42 levels may potentially serve as antecedent biomarkers of preclinical Alzheimer’s disease,” Fagan said. “[They] support the hypothesis that amyloid deposition in the brain acts as a ‘sink,’ resulting in a new equilibrium between soluble and deposited amyloid-42 in the central nervous system.”

“These measures hold potential for identifying individuals with Alzheimer’s disease pathology before cognitive symptoms [appear], improving the accuracy of clinical diagnosis, and facilitating the testing of future therapies,” said Fagan in a prepared statement. “But it is important to recognize that this is still a research study, and the findings must be carefully validated before this approach can be considered for clinical use.”

“We presently don’t have fully validated imaging or biomarker measures that can help us monitor the development or progression of Alzheimer’s in living people,” commented Neil Buckholtz, Ph.D., chief of the Dementias of Aging Branch at the National Institute on Aging. “This study represents one step in the progress being made toward identifying clinically useful biological measures for AD.”

The study was supported by the National Institute on Aging and the Washington University General Clinical Research Center, which is funded by the National Institutes of Health.

An abstract of “Inverse Relation Between in Vivo Amyloid Imaging Load and Cerebrospinal Fluid A42 in Humans” is posted at <www3.interscience.wiley.com/cgi-bin/abstract/112219062/ABSTRACT>. ■

Tasman Elected

Former APA President Allan Tasman, M.D., was elected secretary for education of the World Psychiatric Association. Tasman, who will serve a six-year term, is chair of psychiatry and behavioral sciences at the University of Louisville. ■

BRIEF SUMMARY of Prescribing Information—Before prescribing, please consult complete Prescribing Information.

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

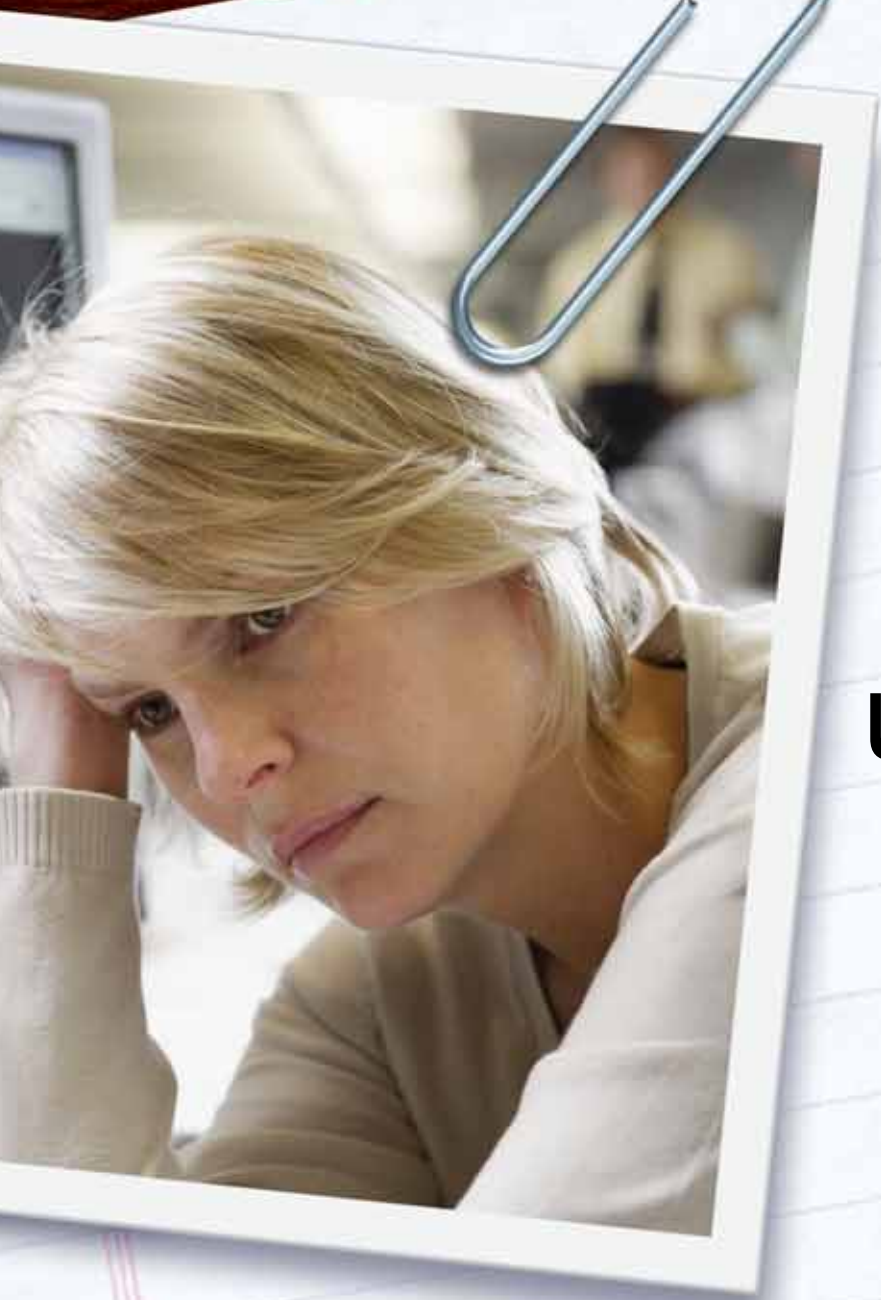
INDICATIONS AND USAGE: Bipolar Mania: SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex. The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient. **Schizophrenia:** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

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. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). **Neuroleptic Malignant Syndrome (NMS).** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude causes where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic therapy, which patients are likely to develop the syndrome. Although the syndrome can be treated with a variety of agents, its course and outcome are unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely. If antipsychotic treatment is withdrawn, antipsychotic treatment itself, however, may suppress or mask the signs and symptoms of the syndrome and the syndrome may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS: **General:** **Orthostatic Hypotension:** SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1 -adrenoceptor antagonist properties. Syncope was reported in 1% (12/731) of the patients treated with SEROQUEL compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Cataracts:** The development of cataracts was observed in association with quetiapine treatment in chronic dog studies. Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriate sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment. **Seizures:** During clinical trials, seizures occurred in 0.6% (182/732) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer’s dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Hypothyroidism:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of T4s were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free thyroxine. In patients with hypothyroidism, SEROQUEL treatment was associated with increases from baseline in cholesterol and triglycerides of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in some studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynaecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiological 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. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminase (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL

therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be exposed to conditions that may lead to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia, close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients. SEROQUEL should be avoided in patients with the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. 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Still working to
solve the problem of
unresolved depression?

residual
symptoms

sadness
low energy
anxiety

recurrence

relapse



IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

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

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

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

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EFFEXOR XR is proven to help prevent new episodes of depression up to 1 year.¹

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

- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.

- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible

Please see brief summary of Prescribing Information on adjacent page.

Reference: 1. Effexor XR® (venlafaxine HCl) Extended-Release and Effexor Immediate-Release Prescribing Information, Wyeth Pharmaceuticals Inc.

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discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.

- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence $\geq 10\%$ and $\geq 2x$ that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

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BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents

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

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

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Families and caregivers of pediatric patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **PRECAUTIONS: General—Discontinuation of Treatment with Effexor XR.** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. **Insomnia and Nervousness:** Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. **Changes in Weight: Adult Patients:** In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. **Pediatric Patients:** Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% vs. 3.6%; *P*<0.001). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents >12 years old. **Changes in Height: Pediatric Patients:** In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while

placebo patients grew an average of 1.0 cm (n=132); *P*=0.041. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). In a 6-month study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents >12 years old. **Changes in Appetite: Adult Patients:** Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. **Pediatric Patients:** Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. **Activation of Mania/Hypomania:** Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. **Hyponatremia:** Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. **Mydriasis:** Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **Seizures:** In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. **Abnormal Bleeding:** Abnormal bleeding (most commonly ecchymosis) has been reported. **Serum Cholesterol Elevation:** Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. **Use in Patients With Concomitant Illness:** Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide About Using Antidepressants in Children and Teenagers* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to avoid alcohol while taking Effexor XR and to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations, they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions—Alcohol:** A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), but did have a small effect on the psychomotor and psychometric effects induced by ethanol. **Cimetidine:** Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. **Diazepam:** A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. **Haloperidol:** Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. **Lithium:** A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. **Drugs Highly Bound to Plasma Proteins:** Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. **Drugs That Inhibit Cytochrome P450 Isoenzymes:** CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatments(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. **Drugs Metabolized by Cytochrome P450 Isoenzymes:** Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. **Imipramine:** Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. **Risperidone:** Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4:** Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. **Indinavir:** In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2:** Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9:** Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19:** Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). **MAOIs:** See **CONTRAINDICATIONS** and **WARNINGS. CNS-Active Drugs:** Use caution with concomitant use of venlafaxine and other CNS-active drugs. Based on its mechanism of action and the potential for serotonin syndrome, use caution when coadministering venlafaxine with other drugs affecting the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors, or lithium. **Electroconvulsive Therapy (ECT):** There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis:** There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m² basis. **Mutagenesis:** Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in *Salmonella* bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. **Impairment of Fertility:** No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis. **Pregnancy—Teratogenic Effects—Pregnancy Category C:** Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations

in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. **Monoteratogenic Effects:** Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General, Changes in Height and Changes in Weight**). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS: Associated with Discontinuation of Treatment**—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. **Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD**—**Body as a Whole:** asthenia, headache, flu syndrome, accidental injury, abdominal pain. **Cardiovascular:** vasodilatation, hypertension, palpitation. **Digestive:** nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. **Metabolic/Nutritional:** weight loss. **Nervous System:** dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonía, paresthesia, libido decreased, agitation, anxiety, twitching. **Respiratory System:** pharyngitis, yawn, sinusitis. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. **Vital Sign Changes:** Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). **Laboratory Changes:** Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. **Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR**—N=6,670. "Frequent"—events occurring in at least 1/100 patients; "infrequent"—1/100 to 1/1000 patients; "rare"—fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, chellitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalciuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypcholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guilaín-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, breast pain, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports:** agranulocytosis, anaphylaxis, aplastic anemia, catatonía, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular

tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methyphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE:** Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE:** Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdose, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION:** Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C019, revised November 2005.

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Increasing Use of CBT Suggests Promising Future

Cognitive-behavioral therapy will be more widely used during the next five to 10 years, predicts one of its developers. He bases his projections in part on what has occurred in Britain and Scandinavia.

BY JOAN AREHART-TREICHEL

Cognitive-behavioral therapy (CBT) is an amalgam of cognitive therapy and behavioral therapies able to help patients counter negative thoughts and behaviors underlying various mental illnesses. Science has demonstrated that it can pack quite a therapeutic wallop.

"There are more than 375 trials of cognitive-behavioral therapy in the research literature," Donna Sudak, M.D., director of psychotherapy training at Friends' Hospital in Philadelphia and a member of the APA Committee on Psychotherapy by Psychiatrists, told *Psychiatric News*. "There is

"The nice thing about CBT is that you can use it in a 15-minute appointment, a 60-minute appointment, or on an inpatient service."

very robust evidence of its efficacy in depression and in multiple anxiety disorders, particularly generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, and social phobia.

In addition, she noted, there are data to support its use as "an effective adjunctive treatment for bipolar disorder and schizophrenia—not by any means as the sole line of treatment, but in terms of increasing medication adherence, decreasing hospital days, and increasing patients' responses to medication. There is also good evidence of its efficacy in bulimia and as an adjunct in the treatment of a number of medical conditions—for example, chronic pain, chronic headache, and irritable bowel syndrome."

In fact, of all the talk therapies, CBT is "the most widely studied in controlled, clinical trials," added Bernard Beitman, M.D., chair of psychiatry at the University of Missouri and a member of the APA Committee on Psychotherapy by Psychiatrists.

Anecdotal reports from psychiatrists also underscore the value of CBT.

For example, Angela Harper, M.D., a psychiatrist in private practice in Columbia, S.C., once had a medical student as a patient. "She had a lot of false beliefs about her ability to do the work," Harper recalled during an interview. "Yet with the help of a year's worth of weekly CBT, she went from being a C+ to B student to being a B+ to A student."

H. Blair Simpson, M.D., Ph.D., an assistant professor of clinical psychiatry at Columbia University, uses CBT to help patients with obsessive-compulsive disorder. She has seen patients make remarkable recoveries as a result. "It is a very moving thing when you see someone combat their disabling anxiety and gain their life back with CBT," Blair attested. "It can not only reduce their symptoms, but also increase their self-esteem in the process."

And aside from the direct benefits that CBT brings patients, psychotherapists see other advantages.

Progress Can Be Rapid

"Generally compared with longer-term psychotherapies, we see progress pretty rapidly, which is enormously rewarding for therapists and patients," said Judith Beck, Ph.D., director of the Beck Institute for Cognitive Therapy and Research in Philadelphia and the daughter of Aaron Beck, M.D., the father of CBT. "A lot of the therapy is really oriented toward 'How can I help the patient have a better week?' So we are focusing on current problems. . . . We are also teaching the patients how to use the techniques, for example, breaking down larger problems into smaller parts. These are tools that they can use for the rest of their lives."

"The nice thing about CBT," said Harper, "is that you can use it in a 15-minute appointment, in a 60-minute appointment, or on an inpatient service. It has a lot of different utilities to it that other psychotherapies don't necessarily have."

For example, she noted, "patients tend to enjoy it because it is more interactive. They get some feedback from you as a therapist and also some helpful suggestions on what they can do when they get home and things to practice. And a lot of patients like homework for the simple reason that it gives them something to work on between appointments, and they feel like they are getting some therapeutic benefit between visits."

One of the most gratifying aspects of using CBT, Simpson pointed out, is that it provides people "with a set of skills that they can use on their own to master their own problems."

CBT Presents Several Challenges

Yet like any psychiatric treatment, CBT has its drawbacks.

"A major challenge with CBT," Beck explained, "is that the therapist has to learn the cognitive formulation for each of the specific psychiatric disorders that she'll be treating and has to learn how to vary treatment for those disorders. [For example,] treatment of panic disorder has some similarities with treatment of depression, but it is also different in important ways."

Simpson agreed: "This is one of the big research questions now, at least in anxiety disorders: Is there one generic CBT that one could teach therapists and that they could then apply to the different anxiety disorders?"

"Some of the patients don't like to do homework," said Harper. "In order to do CBT completely correctly, you really should be using homework in your therapy. . . . The other thing that may be a drawback is that some folks who are very intelligent and have a lot of insight have difficulty at first seeing the benefits of breaking things down to more simple ways of looking at things."

"One of the things that is really important early on with [CBT] is to educate the

How Many Psychiatrists Use CBT?

When it comes to getting a firm handle on the number of American psychiatrists using cognitive-behavioral therapy (CBT), the numbers are fairly elusive.

Probably the best figures come from a study conducted by Josh Wilk, Ph.D., director of workforce studies and a research scientist with APA's Practice Research Network, and in press with *Psychiatric Services*.

The results suggest that more than 50 percent of psychiatrists used CBT techniques at least some of the time during the month preceding the study. "However, the data are self-report with no validation of the types of therapy reported," Joyce West, Ph.D., director of APA's Psychiatric Research Network, told *Psychiatric News*. Also, the data were collected six years ago.

One might assume, however, that regardless of how many psychiatrists were using CBT in 1999, more are using it today. The reason is because since 2001 psychiatry residents have been required to show competency in CBT along with four other psychotherapies. "Residency programs are working hard to develop credible CBT training programs," Donna Sudak, M.D., director of psychotherapy training at Friends' Hospital in Philadelphia and a member of the APA Committee on Psychotherapy by Psychiatrists, said in an interview.

In fact, as Judith Beck, Ph.D., director of the Beck Institute for Cognitive Therapy and Research in Philadelphia, told *Psychiatric News*, "One of the things we do at the Beck Institute is help residency training programs develop much stronger programs in CBT."

"But keep in mind that there are a lot of residency programs in smaller towns, college towns, where they can't get people to teach CBT to their residents," Bernard Beitman, M.D., chair of psychiatry at the University of Missouri and a member of the APA Committee on Psychotherapy by Psychiatrists, pointed out.

Beitman also stressed that "most therapists don't rigorously follow any particular school. They adapt to the needs of the patient using what they know and from their experience, both personal and professional."

Nonetheless, "as psychiatry goes more and more toward a medication-management type practice, especially in private practice, you are going to see psychiatrists use CBT even in those brief appointments," Angela Harper, M.D., a psychiatrist in private practice in Columbia, S.C., predicted. The reason, she explained, is because "even if you are doing a 15-minute medicine check, you can still employ some of the CBT techniques with medicine management."



Judith Beck, Ph.D., and Aaron Beck, M.D.

Beck Institute for Cognitive Therapy and Research

patient in this way of thinking, in this way of understanding problems," emphasized Jesse Wright, M.D., professor and chief of adult clinical psychiatry at the University of Louisville and a CBT proponent. "And for some patients that comes very easily, . . . whereas for other people, it takes a bit of effort to educate them so that they can understand how this therapy works."

Wright added that there are some patients who just won't cooperate with the approach CBT requires. The therapy "is not a panacea that works for every patient in every situation. Some people prefer other kinds of treatment. Some people would rather just take a medication and not have psychotherapy at all."

Future Appears Bright

Even with these constraints, it looks as if CBT is not only going to continue to flourish, but to evolve.

"One of the funny, but to me expectable, evolutions of CBT," Beitman observed, "is that those who practice it are starting to recognize resistance, transference, and countertransference in what goes on. . . . [In other words,] they are realizing that some of the aspects of psychodynamic therapy have relevance for doing CBT."

"CBT techniques will be modified to make them even more effective than they are today," said Simpson. "For example, virtual reality CBT treatments and computer-interactive CBT treatments are being developed. There is also interest in using medications that might enhance the effects

of CBT itself. And what I anticipate, and what I hope, is that we'll know more and more about the brain mechanisms that underlie how CBT actually works."

"I think that what is going to happen," Beck said, "is that CBT is going to be applied more and more widely, for different diagnoses and for different populations. A huge amount of research in cognitive therapy is with medical patients who have a psychological component [to their illness]. . . . I think there will be more of an application of cognitive therapy in the primary care office. . . . And I think it will also be used more broadly not only in individual therapy, but also in group therapy."

Founder Predicts Wider Use

Finally, as Aaron Beck, M.D., university professor of psychiatry at the University of Pennsylvania and father of cognitive therapy, told *Psychiatric News*, "I think that CBT has been refined and perfected enough that the next stage is going to be dissemination. What I foresee is that it will be much more widely used by psychiatrists, who will probably integrate it into treatment of the severely mentally ill, and then by other professional groups, including psychologists, social workers, and nurses."

He explained that his projections "are based on observations, not just on wish fulfillment. In Britain and the Scandinavian countries, CBT has become the dominant form of psychotherapy and has been endorsed by the national health services of those countries." ■

Marital Strife May Keep Wounds From Healing

Marital conflict can boost proinflammatory cytokines in the bloodstream and slow wound healing. These results add to the growing evidence that marital strife can impair both mental and physical health.

BY JOAN AREHART-TREICHEL

While many studies have demonstrated the benefits of marriage in terms of promoting physical and mental health, what happens to couples who engage in verbal spats and power plays for years, maybe decades?

One study, for example, found that unhappily married subjects were 25 times more likely to experience a major depressive disorder than were happily married ones. Another found that among women with coronary heart disease, marital stress worsened their prognosis threefold. And now a new study, published in the December 2005 *Archives of General Psychiatry*, has found that marital bickering can raise, in the bloodstream, levels of proinflammatory cytokines—that is, the kind of cytokines that sabotages healing instead of promoting it.

The finding is important, the investigators believe, since sustained elevated levels of proinflammatory cytokines have in turn been linked with a plethora of age-related diseases (*Psychiatric News*, October 21, 2005).

The researchers recruited 42 married couples for their study through newspaper and radio ads, notices posted on campus and in the community, and via referral from other participants. Subjects ranged in age from 22 to 77 years and had been married anywhere from two to 52 years (on average 13 years).

Wound Healing Monitored

The couples then came to the hospital research unit at 7 a.m. on an appointed day, filled out questionnaires about themselves, had blood drawn for cytokine testing, and were administered suction blister wounds, which are an excellent model for studying the effects of early wound healing.

Each couple then engaged in a discussion where each spouse sought social support from the other in changing a personal

characteristic. In other words, one spouse was asked to “talk about something you would like to change about yourself,” while the partner was instructed to “be involved in the discussion and respond in whatever way you wish.” Roles were reversed after 10 minutes so that each spouse had the opportunity to play the role of helper.

As the couple engaged in the discussion, the research team observed and assessed their behaviors from outside the room. The instrument used to assess the behaviors was the Rapid Marital Interaction Coding System, which discriminates well between distressed and nondistressed couples.

A few hours later, each subject gave a blood sample so that his or her proinflammatory cytokine levels could be measured. His or her wound was also assessed for healing not just in the hours following the discussion, but also some days later.

At a later date the couples returned to the hospital research unit. Again, they had blood drawn to measure cytokine levels, and again they were given suction blister wounds. After that, each couple discussed a subject on which they hotly disagreed, say, money or in-laws, and tried to resolve it. The research team observed and evaluated their behaviors from outside the room. And once again, each subject gave a blood sample a few hours after the discussion to measure proinflammatory cytokine levels and was monitored over the next few hours and days for wound healing.

The investigators then rated the couples as either low in hostility to each other or high in hostility to each other during the two discussions. Twenty-nine percent were found to be highly hostile to each other. The researchers then compared levels of proinflammatory cytokines in high-hostility couples before and after a social-support discussion with their proinflammatory cytokine levels before and after a contentious discussion. They did the same for low-hostility couples. Finally, they compared the proinflammatory cytokine profiles for both groups.

Hostility Linked to Bad Cytokines

Low-hostile participants produced roughly the same increase in proinflammatory cytokine levels following a conflict discussion as after a social-support discussion. In contrast, the high-hostile participants had relatively greater increases in proinflammatory cytokines following a conflict discussion than a social-support one.

The researchers also compared blister-wound healing in high-hostile couples with that in low-hostile couples. They found that wounds healed more slowly for both groups after a conflict discussion than after a social-support one. But wound healing was especially sluggish in the high-hostile couples.

“We were surprised at how very sensitive wound healing is to even very minor stressful events,” Janice Kiecolt-Glaser, Ph.D., told *Psychiatric News*. She is chair of medicine at Ohio State University and the study’s lead investigator.

The study’s findings “have broad impli-

cations for health [since] elevated levels of proinflammatory cytokines have been linked to a variety of age-related diseases, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes mellitus, certain cancers, and frailty and functional decline. Moreover, inflammatory activation can enhance development of depressive symptoms.”

The researchers also pointed out that “couples’ fights at home are more negative and last longer than those studied in the laboratory. Unhappy couples are less likely

to volunteer for marital research than those who are more satisfied with their spouse. Accordingly, the present data are likely to underestimate the health impact of marital strife.”

The study was funded by the National Institutes of Health and the Ohio State University Comprehensive Cancer Center.

An abstract of “Hostile Marital Interactions, Proinflammatory Cytokine Production, and Wound Healing” is posted at <<http://archbpsyc.ama-assn.org/cgi/content/abstract/62/12/1377>>. ■

Multiple Prescriptions Linked to Bipolar Patients’ Hospital Visits

Patients who are prescribed two or more drugs for bipolar disorder are more likely to make use of hospitals or emergency rooms. Multiple prescriptions may reflect greater severity of illness.

BY AARON LEVIN

Polypharmacy—a term that leaves many clinicians and patients queasy—is often the rule in treating bipolar illness, yet the consequences of using more than one drug or switching between drugs are often unexamined, said psychiatrist Arthur Lazarus, M.D., M.B.A., at the annual meeting of the American Public Health Association in Philadelphia in December.

Lazarus and seven colleagues conducted a retrospective cohort study of patients with bipolar diagnoses seen at the Henry Ford Health System in Michigan and found that more than one-third had histories of switching prescriptions or receiving concomitant prescriptions. Patients prescribed at least two psychotropic medications were more likely to be hospitalized or visit the emergency room, they found. Black patients were more likely to receive at least two psychotropic medications and more likely to go to emergency departments or hospitals, compared with non-black patients. They were also more likely to be diagnosed with Axis I psychiatric disorders, to be female, and to be eligible for Medicaid, compared with non-blacks.

“I think these results demonstrate the need for more research and re-examination of treatment guidelines for bipolar disorder,” said Lazarus, senior director for neuroscience clinical research at AstraZeneca.

The need for more than one drug should not be surprising, given the need to treat different phases of bipolar disorder and to stabilize mood. Only one combination drug, composed of an existing antidepressant and antipsychotic, is now approved by the Food and Drug Administration, said Lazarus in an interview.

The researchers examined records covering continuous enrollment from one year prior to the date of the index prescription to one year after that date. Patients had to be at least 19 years old, meet criteria for bipolar disorder in the *International Classification of Diseases, Ninth Revision (ICD-9)*, and have at least one prescription for drugs in four classes: anticonvulsants, mood stabilizers, first-generation antipsychotics, and second-generation antipsychotics.

The 1,113 patients included in the study averaged 44.3 years old. About 61 percent were women, 29 percent were black, 68 percent were white, and 2.5 percent were listed as “other” by race. Patients were

stratified into black and non-black categories. Approximately one-third had cardiovascular morbidities, and 13 percent were substance abusers. Many of these patients had previously received other psychiatric diagnoses, which may indicate a high rate of misdiagnosis of bipolar disorder, said Lazarus.

About 10 percent of all patients received drugs in at least two of the four medication classes at the index date, and 36.6 percent received two or more psychotropic drugs during follow-up. However, there were statistically significant racial differences in prescribing patterns. About 12.6 percent of black patients and 8.5 percent of non-black patients received at least two drugs at the index date, and 41.1 percent of black patients and 34.7 percent of non-black patient got at least two drugs at any time.

Almost half the patients (44.2 percent) had at least one emergency department visit or hospitalization in the first year of follow-up. However, patients on multiple drug regimens were more likely to be seen in those settings than those on one or no drugs.

More than half (53.1 percent) of black patients had a hospitalization/emergency department visit during the first year’s follow-up, compared with 40.5 percent of non-black patients ($p < 0.001$). The mean total health care costs of \$11,836 per patient in the year following index date did not differ by race.

The findings may indicate that patients on two or more drugs had more severe illness and that the greater number of prescriptions was an appropriate response to that severity, said Lazarus. In contrast, they may also reflect more familiar health care disparities. The study did find that black patients were more likely to get prescriptions from emergency room physicians, an indication that they lack regular providers and continuity of care.

Currently, said Lazarus, several differing guidelines address the care of patients with bipolar disorder, which may cause confusion or undertreatment. “We need to develop practical guidelines that both physicians and patients can adhere to,” said Lazarus.

A full version of Lazarus’s APHA talk has been accepted for publication by *Psychiatric Services* and is scheduled for publication later this year. ■

Benefits

continued from page 18

ing the open-label phase of the study were consistent with what patients had experienced during the double-blind phase: agitation, insomnia, and urinary tract infection.

In an accompanying *Archives of Neurology* editorial, Jeffrey Cummings, M.D., a professor of neurology at the University of California at Los Angeles who was not involved in the study, wrote, “Overall, the data suggest that long-term memantine therapy is safe, with no excess of serious adverse events occurring in the treatment group.” Cummings added, “Two out of three measures suggest that memantine continued to exert beneficial effects for months six through 12 of therapy.”

An abstract of “A 24-Week Open-Label Extension Study of Memantine in Moderate to Severe Alzheimer’s Disease” is posted at <<http://archneur.ama-assn.org/cgi/content/short/63/1/49>>. ■

Marijuana-Induced Psychosis May Foretell Future Episodes

Few individuals who smoke marijuana experience psychosis afterward. However, when marijuana-related psychosis does occur, it may be a warning sign that more psychotic episodes could occur.

BY JOAN AREHART-TREICHEL

Reports from various researchers have suggested that marijuana-induced psychosis is generally short-lived and that total remission can be expected. Such reports, however, have been based on case studies, not on long-term follow-up data, according to the authors of a new, long-term study.

The study found that an episode of marijuana-induced psychosis is not innocuous—it often presages subsequent psychotic episodes and a diagnosis of a schizophrenia-spectrum disorder.

Mikkel Arendt, Ph.D., a fellow at the Center for Basic Psychiatric Research at

the University of Aarhus in Denmark, and coworkers used the Danish Psychiatric Central Register to identify patients treated for a first marijuana-induced psychotic episode between 1994 and 1999. There were 535 such patients. The researchers then followed those patients for at least three years to determine how many of them experienced subsequent psychotic episodes and how many could be diagnosed with a schizophrenia-spectrum disorder.

The researchers found that 77 percent of the subjects incurred subsequent psychotic episodes and that 45 percent could be diagnosed at some time within the next three years or more with a schizophre-

nia-spectrum disorder. Moreover, of the 45 percent who developed a schizophrenia-spectrum disorder after experiencing marijuana-induced psychosis, 37 percent received such a diagnosis within three years and the remaining eight after three years. Furthermore, those who developed such a disorder did so at an earlier age than did comparison subjects—individuals who developed such a disorder but who had no recorded history of mari-

“An episode of short-lived psychotic symptoms following cannabis use seems to have great prognostic value.”

juana-induced psychotic symptoms. This effect was most marked for paranoid schizophrenia.

Thus, “for the majority of patients, cannabis-induced psychotic symptoms proved to be a first step in the development of a schizophrenia-spectrum disorder or other severe psychopathology,” Arendt and his group concluded in their study report, which was published in the December 2005 *British Journal of Psychiatry*.

The results do not prove that marijuana is causally linked with schizophrenia, the researchers stated; owing to the study design, it was not possible to control for potentially confounding factors such as hereditary predisposition, socioeconomic status, or other kinds of drug use. Nonetheless, the researchers concluded, marijuana use might well hasten the onset of schizophre-

nia since the subjects who developed schizophrenia in the wake of using marijuana did so at a younger age than the comparison subjects.

“I think it is important to follow the patients treated for cannabis-induced psychosis closely and to offer them and their relatives information on risk factors for, and early signs of, schizophrenia,” Arendt told *Psychiatric News*. “Much work is going on around the world trying to find early signs of schizophrenia because the prognosis of patients improves with early intervention. An episode of short-lived psychotic symptoms following cannabis use seems to have great prognostic value.”

Eric Strain, M.D., a professor of psychiatry at Johns Hopkins University and chair of APA’s Council on Addiction Psychiatry, agreed. “The study suggests that a substance-induced psychotic episode serves as an important indicator identifying a group of patients at high risk for subsequent psychiatric needs.”

Nonetheless, Arendt stressed, “Our study does *not* show that marijuana is a risk factor for young people with a family history of schizophrenia. However, the next phase of our investigation will be a study on hereditary predispositions among those developing schizophrenia following an episode of cannabis-induced psychosis.”

An abstract of “Cannabis-Induced Psychosis and Subsequent Schizophrenia-Spectrum Disorders: Follow-Up Study of 535 Incident Cases” is posted at <<http://bjp.rcpsych.org/cgi/content/abstract/187/6/510>>. ■

Molecular Discovery Could Provide Good Reason to Fear

A fear molecule has been identified. Scientists can now see whether it plays a role in human fear and whether compounds that counter it might constitute new antianxiety drugs.

BY JOAN AREHART-TREICHEL

Although fear is known to be processed in the amygdala, an almond-shaped structure deep within the brain, as well as in some other brain areas, very little has been known about the molecular mechanisms of learned and innate fear. Specifically, glutamate receptors and major protein kinases have been implicated, but they are important for other types of memories and behaviors besides fear.

Now a fear molecule has been identified, a protein called stathmin. The identification of stathmin as a fear molecule constitutes a notable advance in understanding the molecular basis of fear, both the major investigator and senior investigator of the study told *Psychiatric News*. The major investigator was Gleb Shumyatsky, Ph.D., an assistant professor of genetics at Rutgers University. The senior investigator was Eric Kandel, M.D., a professor of psychiatry at Columbia University and a winner of the 2000 Nobel Prize in Medicine or Physiology (*Psychiatric News*, November 3, 2000).

As Shumyatsky, Kandel, and their colleagues reported in the November 18, 2005, *Cell*, they first found that the amygdala and certain other brain areas crucial to regulating fear are very rich in stathmin. Then they found that mice without the stathmin gene showed less anxiety when they heard a tone that had previously been associated with a shock than did mice with the stathmin gene. The mice without the gene were also more prone than the controls to explore novel open spaces and maze environments. Furthermore, the mice without the stathmin gene did not show deficits in a spatial task dependent on the hippocampus, where stathmin is not normally present.

“Stathmin is involved in fear function,

but not in some other types of memory,” Shumyatsky said. As the scientists concluded in their study report, stathmin is “essential in regulating both innate and learned fear.”

Also, Shumyatsky pointed out, “because stathmin is an inhibitor of microtubule formation, our study for the first time links microtubule function to memory for fear, or, for that matter, any kind of memory.” Microtubules, located in the cytoplasm of cells, are involved in cell structure and cell movement.

A challenge now is to determine whether stathmin also plays a role in fear in humans. “One has to see first if stathmin is expressed in the [human] amygdala in a way similar to that in mice,” Shumyatsky explained. “Then we can look for possible genomic mutations in the stathmin gene sequences in human patients with a history of genetic predisposition to anxiety disorders.”

If stathmin indeed turns out to be involved in fear processing in humans, it could well lead to the discovery of new types of antianxiety drugs, both Shumyatsky and Kandel believe. For example, various compounds could be tested in mice without the stathmin gene.

Shumyatsky, Kandel, and their team are planning to delineate the intricacies of stathmin function in fear and how it interacts with other proteins involved in fear behavior.

The research was funded primarily by the National Institutes of Health and the National Alliance for Research on Schizophrenia and Depression.

An abstract of “Stathmin, a Gene Enriched in the Amygdala, Controls Both Learned and Innate Fear” is posted at <www.cell.com/content/article/abstract?uid=PIIS0092867405008755>. ■

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SSRI Efficacy Reduced When Slow Psychomotor Skills Present

Depressed individuals who are slow with regard to thinking, speaking, and reacting may have a dopamine deficiency. Thus, an SSRI antidepressant might not help them.

BY JOAN AREHART-TREICHEL

In spite of the plethora of antidepressants available to patients, clinicians still have no easy way of determining whether a patient will respond to one better than another.

However, a quick test to identify patients who will not respond to the SSRI antidepressants may have been found. It is called the Controlled Oral Word Association Test FAS (FAS test for short) and reveals impaired verbal fluency.

Various lines of study have suggested that there is a link between psychomotor retardation—that is, sluggish thinking, speaking, moving, and reacting—and reduced functioning of the neurotransmitter dopamine in the brain. Moreover, psychomotor retardation exhibited by a subgroup of depressed patients also has been associated with decreased dopamine function. So Bonnie Taylor, Ph.D., an instructor in psychology at the New York State Psychiatric Institute, and coworkers suspected that depressed patients with lower psychomotor skills might not respond to an SSRI antidepressant because a dopamine deficit causes or contributes to their depression and because an SSRI would not correct their dopamine deficit. They decided to test this hypothesis.

Forty-seven subjects were recruited from an outpatient research clinic at the New York State Psychiatric Institute. All met *DSM-IV* criteria for major depressive disorder and were between 18 and 65 years old. The researchers gave neuropsychological tests to all of the subjects before they started a 12-week open trial of fluoxetine treatment. The tests concerned not only psychomotor skills, but also attention, executive functioning, verbal intelligence, and visuospatial functioning.

Of the 37 subjects who finished the study, 25 were rated as fluoxetine responders and 12 as nonresponders. The researchers found that the two groups did not perform any differently on the attention, executive functioning, verbal intelligence, and visuospatial functioning tests, but they did perform differently on the psychomo-

tor functioning ones. Specifically, even when baseline depression severity was taken into consideration, the nonresponders performed significantly worse in verbal fluency on the FAS. They also tended to perform worse than the responders on the Stroop Color and Word Test in both color naming and word reading and on the WAIS-III digit symbol subtest.

The investigators also obtained FAS test

scores for a healthy group matched to the depressed subjects by age and level of education. They found that all depressed subjects who scored above the norm responded to fluoxetine, compared with 40 percent of subjects who scored below the norm.

Thus, the results, which appeared in the January *American Journal of Psychiatry*, tended to confirm the researchers' hypothesis—that depressed patients with slow psychomotor skills were not apt to respond to an SSRI antidepressant. Also, the FAS test did a better job than the other psychomotor tests at predicting SSRI response. The FAS test could ultimately prove to be of value to clinical psychiatrists, "but we obviously need to do more work on it," Patrick McGrath, M.D., an associate professor of clinical psychiatry at Columbia University and one of the study investigators, said in an interview.

"The hope is that if we can get a sim-

ple, inexpensive test, which this is, which doesn't require fancy technology, which can be done in the office, and which takes a few minutes, it would help us better estimate people's chances of responding to antidepressant treatment."

Indeed, the FAS "is a very simple test to administer," Taylor concurred. "Patients are asked to say as many words as they can think of that start with the letters 'F,' 'A,' and 'S' for one minute each. The psychiatrist writes all of the words down and counts the total number of words produced in three minutes."

Taylor and her team will now attempt to replicate their findings.

The study was funded by Eli Lilly and Co.

"Psychomotor Slowing as a Predictor of Fluoxetine Nonresponse in Depressed Patients" is posted at <<http://ajp.psychiatryonline.org/cgi/content/full/163/1/73>>. ■

Nominations Invited For ABPN Positions

APA is seeking nominations for two American Board of Psychiatry and Neurology (ABPN) positions. The first is for a replacement for Larry Faulkner, M.D., an ABPN director for psychiatry, whose term expires next year. The second is for a board-certified child and adolescent psychiatrist to replace Sandra Sexson, M.D., on the ABPN's Child and Adolescent Committee. Both positions are effective January 1, 2007.

Applicants must submit a completed ABPN Director Nomination Form and a curriculum vitae by March 1.

Information and forms can be obtained by contacting Nancy Delanoche at (703) 907-8635 or ndelanoche@psych.org. ■



Amniotic Fluid Could Be Site Of Antidepressant Exposure

Mothers who take antidepressant medications during pregnancy may pass these compounds on to the fetus by way of amniotic fluid as well as through placental circulation.

BY AARON LEVIN

Until recently, research on a pregnant woman's transmission of antidepressant medication to the fetus focused on the placenta and umbilical cord. Now a new study asks whether amniotic fluid may also be a source of antidepressants or their metabolites for the developing fetus.

"Fetal development occurs in a continu-

ous environment of pharmacologically active drug molecules when mothers are treated with these medications," wrote Ada Loughhead, B.S., of the Emory University School of Medicine in Atlanta and colleagues in the January *American Journal of Psychiatry*.

Prior research has identified possible effects on the fetus of maternal use of antidepressants, Marlene Freeman, M.D., told *Psychiatric News*. She is director of the

Women's Mental Health Program and an assistant professor of psychiatry, obstetrics and gynecology, and nutritional sciences at the University of Arizona College of Medicine in Tucson.

Some mothers taking antidepressants late in pregnancy have had babies with a transient syndrome lasting two to four days, displaying jitteriness and trouble sleeping or eating, said Freeman. The Food and Drug Administration warned last December of increased rates (from 1 percent to 1.5-2 percent) of cardiac malformations in infants of mothers taking paroxetine in the first trimester of pregnancy.

The researchers reported on results from 27 women with confirmed exposure to antidepressants for at least four weeks prior to amniocentesis, which was performed for obstetrical reasons. Traces of antidepressants in both amniotic fluid and in maternal serum samples were recorded.

Loughhead and her team found antidepressant compounds in most of the amniotic fluid samples. All samples of amniotic fluid among women taking citalopram, escitalopram, fluvoxamine, and venlafaxine showed traces of the parent antidepressant. In addition, fluoxetine was detected in 11 of 12 fluid samples, paroxetine in one of two samples, and sertraline in two of six samples. Metabolites were found in amniotic fluid of nine of 12 fluoxetine users, four of six sertraline users, and all four venlafaxine users.

Maternal serum samples were available for 25 women. There was no consistent pattern in the proportion of parent and metabolite levels. The ratio of parent compound in amniotic fluid compared with serum ranged from 1.4 percent to 267.2 percent. The ratio for metabolites varied from 0.8 percent to 446.7 percent.

please see Amniotic Fluid on page 30

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Rozerem is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Rozerem can be prescribed for long-term use. Rozerem should not be used in patients with hypersensitivity to any components of the formulation, severe hepatic impairment, or in combination with fluvoxamine. Failure of insomnia to remit after a reasonable period of time should be medically evaluated, as this may be the result of an unrecognized underlying medical disorder. Hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Rozerem has not been studied in patients with severe sleep apnea, severe COPD, or in children or adolescents. The effects in these populations are unknown. Exercise caution if consuming alcohol in combination with Rozerem. Rozerem has been associated with decreased testosterone levels and increased prolactin levels. Health professionals should be mindful of any unexplained symptoms possibly associated with such changes in these hormone levels. Rozerem should not be taken with or immediately after a high-fat meal. Rozerem should be taken within 30 minutes before going to bed and activities confined to preparing for bed. The most common adverse events seen with Rozerem that had at least a 2% incidence difference from placebo were somnolence, dizziness, and fatigue.

Please see adjacent Brief Summary of Prescribing Information.

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Good Reasons to Retain Records; Consolidating Malpractice Policies

Q. I recently attended a seminar in which the speakers advocated retaining medical records indefinitely. I didn’t think that a patient was able to sue me for malpractice after the statute of limitations has passed. Thus, is it really necessary to retain my records beyond my state’s statute of limitations for malpractice actions?

A. Statute of limitation laws establish the period during which specific types of legal actions, such as malpractice actions, may be brought against you. Unfortunately, it is risky to rely solely on your state’s statute of limitations period when determining how long to retain your medical records, for at

least the following reasons:

The statute of limitations is not a bar to a suit’s being filed. Rather, the statute of limitations is an “affirmative defense”—it does not preclude the suit from being filed, even if the statute of limitations has passed. In fact, the statute of limitations is only relevant after a suit has been filed and only if raised as a defense by the defendant physician. Moreover, even if raised as a defense, the defendant physician may or may not be successful in having the case dismissed.

There can be many exceptions to these statutes, so that depending on the nature and wording of a complaint, an action may be brought against you even though it is not brought within the limitation periods.

For example, there are exceptions that allow for “tolling” (extending) the statute of limitations when the patient is a minor or suffers under some other legal disability or incompetence.

There is no statute of limitations for certain types of actions that may be filed against you. Your state’s statute of limitations may not limit the time for initiating litigation resulting from allegations involving fraud, conspiracy, or criminal acts, for example. Also, these laws may not be applicable to allegations involving federal laws, rules, and regulations (for example, Medicare billing complaints). Finally, statutes of limitation do not apply to disciplinary actions by licensing/medical boards or to ethics proceedings—professional complaints may be made against you at any time.

The lesson to remember is that in a legal proceeding against you, the record is the

primary means of supporting and defending the care that was given.

Q. I have incorporated my psychiatric practice, and in addition to myself, there are five psychiatrists on staff. Three are independent contractors, and two are employees. I also employ two social workers. Currently we are covered under various individual malpractice insurance policies. Is it possible to consolidate all of our insurance needs under one policy and still protect both the interests of the individual and also the corporation?

A. Yes. The Psychiatrists’ Program, the APA-endorsed Psychiatrists’ Professional Liability Insurance Program, offers professional liability insurance for behavioral health care professionals practicing in a group setting. Group members, including psychiatrists, psychologists, social workers, and independent contractors, are covered under one policy with either separate limits for each provider or one shared limit for the corporation. This type of policy helps to streamline administrative duties and allows a greater efficacy of policy management.

The many benefits and features offered through the Program for individual coverage are also available for group coverage, including discounts for part-time practice, early career psychiatrists, and risk management education. Furthermore, group participants have access to numerous risk management services, including the Program’s toll-free Risk Management Consultation Service, complimentary admission to mental health-specific risk management seminars, and subscription to a quarterly risk management newsletter.

More information about obtaining group liability coverage is available by contacting PRMS.

This column is provided by PRMS, manager of the Psychiatrists’ Program, for the benefit of members. More information about the Program is available by visiting its Web site at <www.psychprogram.com>; calling (800) 245-3333, ext. 389; or sending an e-mail to TheProgram@prms.com. ■

professional news

Fragmentation

continued from page 8

concerns about the costs of disability to employers, saying mental health problems and associated time away from work are the highest-cost item for disability plans. “We are finding that patients are being certified as disabled at the general medical setting, with initial certification of disability being up to two months, with medication as the only treatment they are receiving,” he said. “Without an active treatment plan, this initial period of disability disconnects the employee from the workplace without engaging the employee in an active treatment plan.”

For this reason, NBGH recommends that employees in these circumstances be certified by a mental health care specialist with an active treatment plan and that employees on disability be referred to the company’s EAP to ensure transition back to work.

A report on the study with its 12 findings and 18 recommendations is posted at <www.businessgrouphealth.org/pdfs/fullreport_behavioralhealthservices.pdf>. ■



Brief Summary of Prescribing Information
05-1114

ROZEREM™
(ramelteon) Tablets

INDICATIONS AND USAGE

ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS

ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

WARNINGS

Since 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 a reasonable period 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 cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine (see **PRECAUTIONS: Drug Interactions**).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depressive illness, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS

General

ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Use in Adolescents and Children

ROZEREM has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans (see **Pediatric Use**).

Information for Patients

Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.

Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

Patients should be advised that they should not take ROZEREM with or immediately after a high fat meal.

Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Laboratory Tests

No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions

ROZEREM is a highly variable inter-subject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

Effects of Other Drugs on ROZEREM Metabolism

Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the AUC_{0-24} for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ROZEREM administered alone. ROZEREM should not be used in combination with fluvoxamine (See **WARNINGS**). Other less potent CYP1A2 inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking less strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both AUC_{0-24} and C_{max}) after a single 32 mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The AUC_{0-24} and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of ROZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure (AUC_{0-24} and C_{max}) of ramelteon after a single 16 mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

Effects of ROZEREM on Metabolism of Other Drugs

Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on Rozerem

Alcohol: With single-dose, daytime co-administration of ROZEREM 32 mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically sig-

nificant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions

ROZEREM is not known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study, B6C3F₁ mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥ 100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area-under-the-curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 60, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testis at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1,429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24 hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis

Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK⁺ cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and in *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility

Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m² basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m² basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m² basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m² basis) when considering all studies.

Pregnancy: Pregnancy Category C

Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose [MRHD] on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times

higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and postnatal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m² basis).

Labor and Delivery

The potential effects of ROZEREM on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. ROZEREM has no established use in labor and delivery.

Nursing Mothers

Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Pediatric Use

Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use

A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS

Overview

The data described in this section reflect exposure to ROZEREM in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment

Five percent of the 3594 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials

The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370; % ramelteon [8 mg], n=1250) were: headache NOS (7%, 7%), somnolence (3%, 5%), fatigue (2%, 4%), dizziness (3%, 5%), nausea (2%, 3%), insomnia exacerbated (2%, 3%), upper respiratory tract infection NOS (2%, 3%), diarrhea NOS (2%, 2%), myalgia (1%, 2%), depression (1%, 2%), dysgeusia (1%, 2%), arthralgia (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

DRUG ABUSE AND DEPENDENCE

ROZEREM is not a controlled substance.

Human Data: See the CLINICAL TRIALS section, Studies Pertinent to Safety Concerns for Sleep-Promoting Agents in the Complete Prescribing Information.

Animal Data. Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotarod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotarod performance.

Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

OVERDOSAGE

Signs and Symptoms

No cases of ROZEREM overdose have been reported during clinical development.

ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

Recommended Treatment

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdose is not appropriate.

Poison Control Center

As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdose.

Rx only

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P102-0002-1

References: 1. Rozerem package insert, Takeda Pharmaceuticals America, Inc. 2. Data on file, Takeda Pharmaceuticals North America, Inc.

Part D

continued from page 1

ceiving their medications, Stone said some pharmacies agreed to supply the medications without assurance that they would be compensated. And by the end of the second week of January, some of the problems appeared to be abating, but much still needed to be resolved, she said.

Stone also expressed special appreciation to APA's Office of Healthcare Systems and Financing for its ready attention to the problems experienced in her state. "That office has been invaluable in bringing to CMS's awareness that there is a big problem," she said. "I've been very impressed with APA's advocacy."

Irvin (Sam) Muszynski, J.D., director of the Office of Healthcare Systems and Financing, urged psychiatrists to contact the office as they and their patients experience problems with Part D (see box on page 1).

"We had been very concerned that the implementation of the Part D benefit for dual-eligible beneficiaries would be very rocky," he said. "That's why we put our monitoring system in place. We can't fix the problems we don't know about."

Despite reassurances from CMS in the time leading up to January 1, many of the problems that have been encountered since then were predicted not only by mental health advocates, but by the government itself. A December 2005 report by the General Accountability Office predicted that contingency plans by CMS to ensure that beneficiaries receive medications—such as the point-of-sale fail-safe mechanism—would not be implemented in time.

"The complex process for transitioning dual-eligible beneficiaries on a single day with no overlap could create difficulties ensuring that prescriptions for some members of this vulnerable population are filled," the report concluded. "The success of the transition will largely depend on the extent to which dual-eligible beneficiaries (1) are properly identified and enrolled in PDPs [prescription drug plans], (2) do not have to change their customary pharmacy, and (3) are enrolled in PDPs that cover their medications."

In Massachusetts, for example, Gov. Mitt Romney directed the state's department of mental health to assume the cost of drugs for beneficiaries unable to receive their medications.

"Given reports about what is happening in pharmacies, Gov. Romney has made it clear that we have an obligation to make certain that MassHealth members receive their medication when they need it," said state Medicaid Director Beth Waldman. "The complexities of Part D make it a difficult program to implement perfectly. Until the program is operating as expected, we will step in to ensure that none of our members who need medication will walk away from the pharmacy without it."

There are about 190,000 Massachusetts residents eligible for both Medicare and Medicaid, according to the statement.

Waldman said pharmacies will continue attempting to bill the Medicare Part D plan as the primary payer, but as a fallback they can also bill MassHealth directly. Waldman said her agency will monitor the progress being made by the federal government and will recoup what it spends either from private insurers or the federal government.

In North Dakota, Gov. John Hoeven authorized the state Department of Human Services' Medicaid program to provide an emergency 30-day supply of medications to individuals unable to fill prescriptions through Medicare Part D until January 23, while the federal government and the prescription drug plans resolve their implementation issues.

"Medicare Part D is a federal benefit, but they are clearly having difficulty implementing this new program in a timely fashion," Hoeven said. "Going without prescriptions is not an option for our seniors and disabled, so the state of North Dakota will step up to ensure that they continue to get their medications until the federal government resolves the difficulties."

Andrew Sperling, director of legislative advocacy for the National Alliance on Mental Illness, said the problems described by Stone have been experienced nationwide. He highlighted problems experienced by enrollees in United, the prescription drug plan endorsed by AARP (formerly American Association of Retired Persons).

A spokesperson for AARP confirmed that United has experienced "database problems" affecting "a couple hundred thousand beneficiaries."

"This is something AARP is taking very seriously," the spokesperson said. "It is not isolated to United but is a global problem. We are reporting these problems to CMS,

and CMS has instructed pharmacists to fill prescriptions for at least 30 days. People should not be turned away without medications."

Information on Medicare Part D is posted on a Web site sponsored by APA and other advocacy partners at <www.mentalhealthpartd.org>.

Court Rejects Suit Seeking To Halt Part D Transition

The court rules that problems anticipated in the suit can be addressed through mechanisms provided for in the Medicare Modernization Act.

BY MARK MORAN

A federal district judge in Manhattan denied a suit filed by the Medicare Rights Center and seven other groups that sought continuation of existing drug benefits for "dual eligibles" when they were switched from Medicaid drug coverage to the new Part D Medicare prescription drug program.

The suit was filed in December 2005 in anticipation of what advocacy groups were predicting would be a logistical disaster when 6 million dual eligibles—some 2.5 million of whom have mental illness—ceased having their prescriptions paid for by state Medicaid programs and began coverage under the new Medicare program.

But U.S. District Judge Loretta A. Preska said the court had no jurisdiction to order such a continuation of drug benefits when the anticipated problems were at the time theoretical and when there was a mechanism for individuals to seek redress under the Medicare Modernization Act of 2003 (MMA), the legislation that created the new program.

"The dual eligibles whose interests Plaintiffs seek to represent are, in effect, in no different a position from individuals entitled to receive non-MMA Medicare benefits," the judge stated. "Any Medicare recipient runs the risk that he or she will seek medical services and, due to a glitch in a database, be informed, erroneously, that he or she is not in the system. The Medicare act does not contemplate that such an individual can file a complaint in federal court before even attempting to present a claim to the agency. It would be a wholesale subversion of the Medicare act's legislative intent to avoid overburdening the courts. . . if beneficiaries were able to bring federal cases where a simple phone call, e-mail, or letter might straighten out the problem. This rationale applies even more so where, as here, the alleged glitches are anticipated but have not yet occurred."

The ruling was issued in the last week of December, just before the transition to the new program was to occur on January 1, and before many of the anticipated problems were reported nationwide (see page 1).

The suit, filed against Health and Human Services Secretary Mike Leavitt, stated that he was "not taking adequate steps to meet his obligations under the statute" to ensure that dual eligibles transitioning into the new program would receive their necessary medications (*Psychiatric News*, December 16, 2005).

"Unless he does so, countless dual eligibles will fall through the cracks of this massive program transition; they will not be effectively transferred to new Medicare prescription drug coverage and may be left without needed prescription drug coverage on and after January 1, 2006," the suit alleged. "Because many of these persons need

healthpartd.org>.

The GAO report, titled "Medicare: Contingency Plans to Address Potential Problems With the Transition of Dual-Eligible Beneficiaries From Medicaid to Medicare Drug Coverage," is posted at <www.gao.gov/new.items/d06278r.pdf>. ■

prescription drug coverage to function or survive, the consequences of no longer receiving prescription drug coverage will be calamitous."

The organizations that filed the suit are Action Alliance of Senior Citizens of Greater Philadelphia, Congress of California Seniors, Massachusetts Senior Action Council, National Alliance on Mental Illness: Maine, New York Statewide Senior Action Council, Coalition of Voluntary Mental Health Agencies Inc., United Senior Action of Indiana, and Medicare Rights Center.

The organizations are represented by volunteer attorneys with the law firm Paul, Weiss, Rifkind, Wharton, and Garrison L.L.P., and the Medicare Rights Center. They have indicated that they will appeal Preska's ruling.

"Nothing in this ruling suggests that the oldest, poorest, and frailest Americans are safe," said Robert Hayes, president of the Medicare Rights Center, in a statement. "In the real world, people cut off from life-sustaining medicine cannot survive the delay of an agency appeal."

The text of the court's decision in New York Statewide Senior Action, et al, v. Michael O. Leavitt, Secretary of the U.S. Department of Health and Human Services [05 Civ. 9549 (LAP)] is posted at <www.nysd.uscourts.gov/rulings/05CV09549_opinion_122905.pdf>. ■

professional news

Hepatitis, TB

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state hospital sample, primary investigator William Pirl, M.D., emphasized that for some patients with serious mental illness, psychiatric hospitalizations may provide the perfect opportunity for screening and prevention of infectious diseases.

Pirl is an attending psychiatrist on the Psychiatric Oncology Service at Massachusetts General Hospital and an instructor in psychiatry at Harvard Medical School.

He also pointed out that for patients who are homeless or have chaotic lives, "psychiatric care may be their default primary medical care."

While hepatitis B and C vaccinations require several injections spaced weeks or months apart, Pirl suggested that inpatients receive their first vaccine during their hospitalization and arrange "outpatient medical care to complete the vaccinations."

"Screening for Infectious Diseases Among Patients at a State Psychiatric Hospital" is posted at <<http://psychservices.psychiatryonline.org/cgi/content/full/56/12/1614>>. ■

letters to the editor

Policy Doesn't Work

The front-page article titled "Psychiatrists May Soon See More Combat Veterans" in the November 4, 2005, issue begins with Col. Cameron Ritchie's cheerful news that the Pentagon is putting "lessons from other conflicts to use." But her next sentence restates one of the failed strategies of World War II, about placing treatment facilities "as close to the battlefield as possible so that troops can return to service quickly."

During that war, this doctrine, in almost the same words, was proclaimed throughout the Army Medical Corps. Its effect, according to my observations during three years in the Southwest Pacific, was to increase the number of psychiatric casualties. We Army psychiatrists soon found that a soldier returned to combat duty after convalescing from what would now be called PTSD would break down again, sooner and

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with more severe symptoms than was the case on his first admission. Many of these unhappy soldiers were rehospitalized and recycled through this process again and again until they were mercifully returned to the United States for discharge from military service.

SANFORD GIFFORD, M.D.
Cambridge, Mass.

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Please see references and Brief Summary of Prescribing Information on adjacent page.

*IMS Dataview, October 2005.

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Reach new heights

Supreme Court

continued from page 2

machine gun does not cross state lines—regardless of whether it was part of a larger regulatory scheme that affects interstate commerce—Congress can’t regulate the firearms. The implications for disability rights within states are dire because the ADA is based in part on the constitutional clause addressing interstate commerce, Mathis said.

“If machine guns can’t be seen as part of interstate commerce, then what is going to happen when we’re talking about cases where there are commerce-clause challenges to disability rights statutes?” said Daniel Davis, acting director of advocacy and public policy at the National Council on Independent Living. “Are you going to have to prove that denying an education to a person with disabilities has an impact on interstate commerce” to support constitutionally a federal law against that practice?

Alito is also thought to have a very restrictive interpretation of Congress’s au-

thority under the 14th Amendment, the other authority underpinning the ADA. “We may find that Alito is the fifth vote to say that Congress had no power under either of the sources of authority that it used to pass the ADA,” Mathis said. “If that is true, there is no ADA, at least for particular applications.”

Roberts, as the defendant’s attorney in *Toyota v. Williams*, argued for a “very restrictive interpretation of the ADA that didn’t protect a lot of people,” Mathis said. Toyota had argued that an aggrieved employee was not really disabled and so could not sue under the ADA. The Supreme Court found that a more expansive test was needed to determine disability and sent the case back to a lower court (*Psychiatric News*, August 16, 2002).

Davis said the Supreme Court’s most recent disability rights ruling in *Goodman v. Georgia* last month was a “positive decision” under the leadership of Roberts. The Court unanimously held that disabled state prisoners whose constitutional rights are violated behind bars can win damages, but it stopped short of deciding whether states can be sued

on broader grounds under the ADA.

Alito has indicated narrow interpretations of the scope of disability discrimination laws, according to disability rights advocates. Alito ruled that a medical school was allowed to flag test scores of students with disabilities who received accommodations. He found that the practice was allowed because the ADA did not explicitly prohibit such activity.

“The idea that the ADA has to specifically identify every single practice that is prohibited is not what Congress intended,” Mathis said. “It intended to write a very broad law.”

Alito, in his committee testimony, pointed out that there were cases where he ruled as a judge on the 3rd U.S. Circuit Court of Appeals to uphold disability rights and was reversed by the Supreme Court, such as in *Thomas v. Commissioner of Social Security*. Alito ruled that the plaintiff was eligible to receive Social Security disability benefits because the only job she was able to perform—elevator operator—no longer existed in “substantial numbers in the national economy.”

References: 1. Faraone SV, Biederman J. A controlled study of functional impairments in 500 ADHD adults. Presented at: 157th Annual Meeting of the American Psychiatric Association; May 5, 2004; New York, NY. 2. Data on file, Shire US Inc., 2006. 3. ADDERALL XR® [package insert], Shire US Inc., 2005. 4. Claxton AJ, Cramer J, Pierce C. A systematic review of the association between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296-1310.

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

ADDERALL XR® CAPSULES

Cil Rx Only

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY. MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

INDICATIONS

ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV® criteria for ADHD, along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. **Long-Term Suppression of Growth:** Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted. **Sudden Death and Pre-existing Structural Cardiac Abnormalities:** Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR® generally should not be used in children, adolescents, or adults with structural cardiac abnormalities.

PRECAUTIONS

General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose.

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension.

Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication. In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving ADDERALL XR® 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥ 8 mmHg were observed in 18/64 (25%) placebo-treated patients and 22/100 (22%) ADDERALL XR®-treated patients. Similar results were observed at higher doses. In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg ADDERALL XR®, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.

Tics: Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Effects on Weight: Amphetamines have been associated with decreased appetite. Absolute weight increases in treated children over time, but the increases are smaller than expected based on CDC normative values. These reductions in expected weight attenuate over time and are greatest in the heaviest children. In the controlled trial in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and -2.8 lbs., respectively, for patients receiving 10 mg and 20 mg ADDERALL XR®. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents*—Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines.

Urinary acidifying agents—These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers—Adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents—Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR® and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Antidepressants, tricyclic—Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors—MAO inhibitors, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines—Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives—Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine—Chlorpromazine blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide—Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol—Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate—The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Mepredine—Amphetamines potentiate the analgesic effect of mepredine.

Methamphetamine therapy—Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine therapy.

Norepinephrine—Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital—Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytin—Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene—In cases of propoxyphene overdose, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids—Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This effect is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility: No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m² body surface area basis. Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release) (d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (enantiomer ratio of 1:1) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release) (d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis).

Pregnancy: Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m² body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m² basis) or greater to pregnant animals. Administration of amphetamine to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m² body surface area basis. Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release) (d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (enantiomer ratio of 1:1) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release) (d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis).

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Use in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: ADDERALL XR® is indicated for use in children 6 years of age and older.

Use in Children Under Six Years of Age: Effects of ADDERALL XR® in 3-year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: ADDERALL XR® has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for ADDERALL XR® included exposures in a total of 1315 participants in clinical trials

(635 pediatric patients, 350 adolescent patients, 248 adult patients, 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N=40). Safety data on all patients are included in the discussion that follows. 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 tables and listings 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.

Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR® in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

Adverse event	% of pediatric patients discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7

In a separate placebo-controlled 4-week study in adolescents with ADHD, eight patients (3.4%) discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=233). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headaches, light-headedness, and anxiety. In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and, 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adolescents and adults, respectively, treated with ADDERALL XR® or placebo are presented in the tables below. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing estimating the relative contribution of drug and non-drug factors to the adverse event incidence in the population studied.

Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR® (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Events Reported by 5% or more of Adolescents Weighing ≤ 75 kg/165 lbs Receiving ADDERALL XR® with Higher Incidence Than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=233)	Placebo (n=54)
General	Abdominal Pain (stomachache)	11%	2%
	Loss of Appetite [‡]	36%	2%
Digestive System	Diarrhea	12%	4%
	Nausea	6%	6%
Metabolic/Nutritional	Weight Loss [‡]	9%	0%

* Appears the same due to rounding

[‡] Dose-related adverse events

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adolescent patients receiving ADDERALL XR with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting. [‡] Included doses up to 40 mg

Table 3 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=191)	Placebo (n=64)
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
	Vomiting	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following events did not meet the criterion for inclusion in Table 3 but were reported by 2% to 4% of adult patients receiving ADDERALL XR® with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence. [‡] Included doses up to 60 mg.

The following adverse reactions have been associated with amphetamine use: Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

ADDERALL XR® is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There have been reports of patients who have increased the dosage to many times that recommended. Amphetamine association following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted in the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms: Manifestations of acute overdose with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps.

Fatal poisoning is usually preceded by convulsions and coma. Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard.

Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdose, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of mixed amphetamine salts from ADDERALL XR® should be considered when treating patients with overdose. Dispense in a tight, light-resistant container as defined in the USP. Store at 25° C (77° F). Excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

Manufactured for: **Shire US Inc.**, Wayne, PA 19087 Made in USA For more information call 1-800-828-2088, or visit www.adderallxr.com. ADDERALL® and ADDERALL XR® are registered in the US Patent and Trademark Office. Copyright ©2005 Shire US Inc.

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The high court deferred to the judgment of the Social Security Administration.

Opponents of Alito counter by highlighting *ADAPT v. United States Department of Housing and Urban Development*, in which Alito ruled that people with disabilities could not sue the federal housing department for failing to enforce its own requirements for accessible housing. HUD regulations require that 5 percent of federally funded public housing units are accessible for people with mobility impairments, and 2 percent are accessible for people with sensory impairments. A later decision by a different court also removed any right to sue the housing authority.

“If the law and regulations call for accessible housing and no one is doing anything about it, and if the judiciary is not going to hold [housing agencies] accountable on it, who will?” David said. “That is an example of a narrow view on justice that frankly concerns us.”

Other cases challenging the ADA’s community-integration mandate that the Supreme Court established in *Olmstead v. L.C.* are moving through the lower courts. A three-judge panel of the larger appellate court Alito sat on decided in a similar case that the ADA outlawed unnecessary institutionalization. After its case was rejected, Pennsylvania asked the entire circuit court to reconsider the ruling, but it refused to do so. Disability rights advocates noted that Alito voted to rehear the case, presumably because he wanted to reverse the decision.

Online analyses of Roberts’s and Alito’s court decisions are posted at <www.bazelon.org/takeaction/alerts/11-13-05-AlitoAlert.htm>, <www.nslc.org/news/05/07/NSCLC statement—roberts.pdf>, and <www.ncil.org/advocacy/alerts/2005/alito.html>. ■

clinical & research news

Amniotic Fluid

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Amniotic fluid can be swallowed by the fetus and is inhaled at rates of 7 ml/day at 16 weeks gestation to 210-760 ml/day at term, said Loughhead and colleagues. “The significance of respiratory exposure to antidepressants in the fetus is unknown but can theoretically be both significant and efficient and would bypass fetal hepatic metabolism before [central nervous system] exposure.”

Deciding whether to treat pregnant women with antidepressants or other psychotropic medications is complicated, said Freeman.

“You must carefully weigh the risks of exposing babies to medications with the consequences of untreated maternal depression,” she said. “We know there are also serious negative consequences of untreated maternal depression on infant outcomes.”

Both Freeman and Loughhead called for more research to study the effects on the fetus and routes of exposure of drugs taken by pregnant women. Such research and development might lead to new medications that less readily enter amniotic fluid, fetal circulation, or breast milk and thus raise fewer concerns for pregnant women and their physicians, wrote the study authors.

The study was funded by grants from Pfizer Pharmaceuticals, GlaxoSmithKline, and a National Institute of Mental Health Specialized Center of Research grant.

“Antidepressants in Amniotic Fluid: Another Route of Fetal Exposure” is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/1/145>. ■

Volunteers

continued from page 1

Edna Davis-Brown, project manager for Westover, speaking on behalf of SAMHSA. “It was hard to find psychiatrists to send over the holidays, and it was also hard to find local people, since they were trying to restart their lives like everyone else in the area,” said Davis-Brown.

Reactions Varied by Setting

May, who is in private practice in Washington, D.C., and on the clinical staffs of George Washington and Howard University hospitals, stayed at a reform school while serving first at a tent city of evacuees and then on board an anchored cruise ship pressed into service as a shelter. The two settings could not have been more different, she said in an interview.

The people in the tents had lived in rural areas around nearby Pass Christian, Miss., “tied to the earth,” said May. Many had evacuated before the storm, and their houses had been wiped out. “Yet ask them how they’re doing and they’d talk about getting by on faith, prayer, God, and family. They were tied into a support system and were better able to tap into social and spiritual resources.”

Evacuees on the ship came from more varied backgrounds, farther from their current refuge, she said. Many had ridden out the storm in attics, watching their possessions float away. On board the ship, people seemed more guarded and socially isolated, she said. People arrived at the ship with their medications but soon ran out, leaving doctors to juggle ways of substituting drugs from an inadequate supply.

Planning to assure adequate supplies of medications and licensing and insurance for out-of-state physicians ought to be addressed before future disasters strike, said May. Louisiana’s temporary law allowing outside doctors to practice in the state expired at the end of the year. They were not covered by federal insurance since that applied only to unpaid volunteers, and the psychiatrists received a stipend of \$200 a day.

“All of these are solvable problems,” she said. “You have to go down expecting the unexpected and just roll with it.”

At both sites, she and her colleagues had to develop case-management systems and help people reintegrate into their recon-

structed communities. That was not easy, given that many local psychiatrists had not yet returned to work, patients lacked transport to get to doctors, and many had lost both their livelihoods and the health insurance that went with them.

With a delay of five or six weeks before patients could be seen at the nearest mental health center, May identified those who had to be seen soonest and arranged for the rest to get sufficient medications to tide them over the wait.

Toward the end of her two-week stay, May and fellow psychiatrist Lorna Mayo, M.D., who is researching medical quality at the Veterans Affairs Medical Center in White River Junction, Vt., went through charts on the ship looking for high-risk patients, patients with no planned follow-up, and patients with multiple prescriptions and left a list for the doctors who would succeed them to offer some continuity of care.

“I had an overwhelmingly positive experience despite some of the logistical and systemic difficulties,” said May. “It reaffirms my faith in the power of the human spirit to transcend adversity.”

Adaptability Is the Key

Leslie Hartley Gise, M.D., a community psychiatrist in Kula, Hawaii, and a clinical professor of psychiatry at the University of Hawaii at Manoa, worked in a shelter housing 300 people from New Orleans’ Lower Ninth Ward for her two weeks, beginning September 30, 2005, one month after the hurricane. On some days she had a heavy clinical load, but at other times she, too, practiced psychiatry by walking around. People were reticent at first but soon enough told her their stories of living through the storm and flood.

Logistics were sometimes problematic, said Gise. The team was placed together in a hotel at first, but later had to split up to sites more than an hour’s drive from the shelter. Orientation consisted of a brief video. She had no contact with the team that succeeded hers in the shelter and little contact with local medical or mental health professionals.

Still, adaptability was essential for accomplishing the mission, said Gise. “You had to think on your feet when labs could not fax you back results because there were no phones or when some patients had none of their prescriptions filled while others got the same one three times over.”

Basketball + Psychiatry = Help

Stovall, who is medical director of adult outpatient services at Community Health-Link in Worcester, Mass., served as part of a 16-member team, along with two other psychiatrists and social workers, psychologists, pastoral counselors, and a nurse.

Stovall’s work took him to several Red Cross shelters in the parishes north of New Orleans, caring for evacuees from the city.

“We provided daily rounds of psychiatric services plus a little general medicine,” he said, echoing the experience of other volunteers. “On many days, I was the only physician in the shelter.”

He tried to involve himself broadly in the daily life of each shelter he visited—playing basketball with the children, helping them with homework, even serving food occasionally. As he became a familiar sight to shelter residents, they felt better about approaching him to talk about their mental conditions.

“Once they got to know me, people would talk to me about their pre-existing mental illness,” he said. “They had been afraid to say anything before for fear of being kicked out of the shelter or being de-



Damaged roads and bridges slowed travel for medical volunteers and other aid workers.

nied relocation. But when I approached them in an open, confidential, and trusting way, they understood that I was a person who could help them.”

Help included identifying and assessing people with mental illness, restarting their medications, helping them sort out the next step in their lives, and trying to link them to an ongoing source of psychiatric care, if those other services were available.

“I was surprised at the level at which people were able to survive in spite of their mental illness,” he said.

The volunteer program offered lessons for everyone concerned.

“Overall, it was a successful project, but it had its challenges, and SAMHSA has learned a lot,” said Davis-Brown. “Everyone involved needs to be flexible because needs will change constantly. You have to get to the area, find out what’s being done, and decide how best to support and coordinate efforts with others like state officials, the Red Cross, and FEMA.”

Even as all parties learned from their experiences, the presence of visiting psychiatrists and mental health professionals was “very helpful,” said David Edward Post, M.D., medical director of the Capital Area Human Services District in Baton Rouge.

Some volunteers were undeterred by any bumps in the road. In mid-January May and Mayo returned on their own to the Mississippi tent clinic to observe the transition from a crisis-intervention program to a sustained community setting in a local family practice. May also found that the reconstruction of lives proceeds slowly.

“In the tent city, the population has shifted a little,” she said on her return to Washington. “Those with strengths and resources are starting to be able to pull ahead, but for many of those with limited financial, personal, or spiritual resources, life remains extremely challenging.”

More information on APA’s hurricane response efforts and resources is posted on APA’s homepage at <www.psych.org>. ■

Accounts From the Front Lines

Among those volunteering to provide mental health services after Hurricane Katrina was the Massachusetts husband-and-wife team of psychiatrist Jay H. Holtzman, M.D., chief of psychiatry at Cooley-Dickinson Hospital, part of the Dartmouth-Mary Hitchcock Alliance, and psychotherapist Rorry Zahourek, Ph.D., A.P.R.N., B.C., who served in both New Orleans and Baton Rouge at an evacuation center. Below are edited excerpts from the e-mailed diary they sent to friends.

New Orleans—Everywhere we saw people looking at or going through their houses, actually, their rubble. We stopped and offered them water, snacks, masks to prevent inhaling crud, and just made some small talk. Don’t know whether we helped, but most of them seemed happy to talk with us, share their stories and sometimes their photos, and expressed real gratitude that we had come down to help out where we could. We realized after a few days of this, that this was “Disaster Psychiatry.”

—Holtzman

Baton Rouge—People who had mental health problems before are really suffering now—many don’t have their meds, and others are so traumatized they are not doing well. The three I saw today were remarkable. One woman with a long history of psychosis said this was the first crisis of her life that she didn’t go back into the hospital. Another schizophrenic woman who just had had a mastectomy for breast cancer the beginning of August was doing relatively well. A severely drug-addicted, alcoholic woman said this was the closest she has been to her children in many years, and so, in a crazy way, the storm may be a blessing.

—Zahourek

New Orleans—One thing that I don’t see written about is the degree of trauma and destruction to the mental health infrastructure in New Orleans. Not only have the clinics and hospitals been destroyed, but also the staffs have been displaced and made homeless. Many are still living in hotels and are themselves struggling with FEMA and insurance.

—Zahourek

Baton Rouge—It is frustrating to know that we could be doing more if the local agencies weren’t so battered that they are having trouble using us efficiently, but that’s part of the devastation. I believe that understanding that, going with it, and being flexible and creative about how you can best function and contribute is essential to feeling positive about disaster work.

—Zahourek



A little pharmaceutically incorrect humor lightens the décor around the makeshift clinic on board the M.S. Holiday, a floating shelter for storm evacuees.

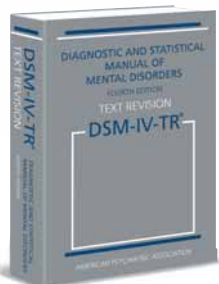
Courtesy of Lorna Mayo, M.D.

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The Department of Psychiatry is seeking a Professor or Associate Professor of Psychiatry to lead the Child and Adolescent Psychiatry Section. The successful candidate will be a board certified child and adolescent psychiatrist who has demonstrated skills as an academic/clinical leader.

The Child Section Chief role will include conceptualizing and developing clinical services, promoting and facilitating research at all clinical sites, and supporting the teaching and training functions of the section. The Child Section Chief will recruit, mentor, and support high-quality child-focused faculty members. The Child Section Chief will work as part of the Children's Hospital at Dartmouth (ChaD) to develop a sustainable model of pediatric mental health services for the region. The ideal candidate will also either be directly engaged in research or have experience nurturing research in child psychiatry.

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Please send Curriculum vitae and three letters of reference for either position to:

William C. Torrey, M.D., Chair, Search Committee
Dartmouth-Hitchcock Medical Center
Department of Psychiatry
One Medical Center Drive
Lebanon, NH 03756
e-mail: William.C.Torrey@Dartmouth.EDU

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The Department of Psychiatry is located near the southern shore of Lake Erie where the University district includes the affordable and historic neighborhoods of Shaker Heights, University Heights, and Cleveland Heights, an outstanding public school system, a world class orchestra, and abundant recreational activities. University Hospitals of Cleveland and Case Western Reserve are Affirmative Action/Equal Opportunity Employers. Women and minorities are strongly encouraged to apply. The University is an equal-opportunity/affirmative action employer. Visit us on the web at www.case.edu/med/psychiatry.

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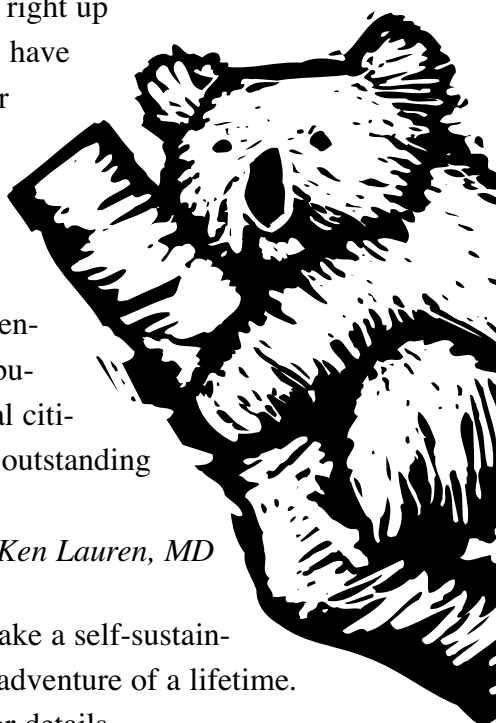
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Interested candidates should contact

Thomas Smith, MD, Chair, Department of Psychiatry, St. Vincent's Medical Center and Medical Director, Hall-Brooke Behavioral Health Services,
Phone: 203-221-8804, Fax: 203-226-8616, Email: tsmith@svhs-ct.org. EOE

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MINIMUM QUALIFICATIONS: License to practice medicine in New York State and certification in psychiatry by the American Board of Psychiatry and Neurology; eligibility for full and unconditional participation in the Medicaid and Medicare programs and five (5) years of post degree research experience.

RESEARCH SCIENTIST 7 Grade 38 (2 positions) - JOB CODE RS7 Salary: \$111,016 - \$133,978 + \$1,264 Location Pay

Two vacancies for this position exist. The incumbent will serve as part of a team, which will be headed by a Psychiatrist 2 Research.

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RESEARCH SCIENTIST 2 Grade 22 - JOB CODE RS2 Salary: \$53,080 - \$65,502+ \$1,264 Location Pay

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Associate Personnel Administrator
ATTENTION: NKI Job Code:
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Gregory W. Dalack, MD
Associate Professor and Vice Chair, Department of Psychiatry
Associate Chair for Education and Academic Affairs,
Department of Psychiatry, University of Michigan
Staff Psychiatrist
VA Ann Arbor Healthcare System
2215 Fuller Road 116A
Ann Arbor, Michigan 48105-2300

Clinical Research Faculty Positions Available

The Department of Psychiatry of the University of Rochester Medical Center is recruiting psychiatrists with strong interests in developing clinical research careers to complement growing skills as clinicians and educators. Positions are available at the Assistant Professor and Senior Instructor levels. Potential clinical areas of focus include: bipolar and other mood disturbances in children and youth; mood disorders in adults; substance use disorders; emergency psychiatry; schizophrenia and other psychotic disorders; and geriatric disorders including dementia and depression. The Department emphasizes three broad investigative themes: mind-body research; therapeutics, interventions, and health services research; and public health and preventive psychiatry involving issues such as the prevention of suicide, intimate partner violence, early life behavioral disturbances, later-life depression, and the creation of related community-partnered prevention research endeavors. The Department provides very well established mentoring programs, and NIMH-funded fellowships, with an outstanding record of successfully fostering the development of junior faculty as clinical researchers having support from NIH and comparable sources. Internal pilot project funds are available.

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University of Rochester Medical Center
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Issue	Deadline (Friday, 2 p.m. E.T.)
March 3	February 17
March 17	March 3

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ARIZONA

Maricopa County Government - Correctional Health Services, Department of Psychiatry has immediate full time positions for general and forensic psychiatrist(s). Candidates must be Board Certified or eligible in Psychiatry and have current credentials to practice in the State of Arizona. We offer a competitive salary and excellent benefits package. For more complete information about the position(s) and to apply, please visit our web site at **www.maricopa.gov/jobs**

Assistant/Associate Professor, Clinical Psychiatry Director of Inpatient Services, Department of Psychiatry, University of Arizona Health Sciences Center

The University of Arizona's Department of Psychiatry is seeking a Director of its Inpatient Psychiatry Service at the University Medical Center. This is a full-time academic appointment at the Assistant Professor level or above at a progressive and growing academic department located in the beautiful southwest. Applicants must be Board certified or eligible in Psychiatry and must have current credentials to practice medicine in the United States. Other duties include the supervision and teaching of Psychiatry residents and medical students. Competitive salary and excellent benefits package offered. For more complete information about the position, and to apply, go to <http://www.uacareertrack.com> and reference job #32585. If you have questions, please contact Lesley Bailey, Assistant to the Head of the Department of Psychiatry, 1501 N. Campbell Ave., P. O. Box 245002, Tucson, AZ 85724-5002, lbailey@email.arizona.edu or 520-626-8021. Review of applications is ongoing until position is filled.

The University of Arizona is an EEO/AA Employer—M/W/D/V.

PHOENIX - GENERAL ADULT, FORENSIC AND ADOLESCENT PSYCHIATRISTS

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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.

Salary is negotiable 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 Jerry L. Dennis, MD @ dennisj@azdhs.gov.

Arizona State Hospital
2500 East Van Buren Street
Phoenix, Arizona 85008
www.azdhs.gov/azsh

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Assistant Professor, Clinical Psychiatry University of Arizona (Kino)

The University of Arizona's Department of Psychiatry is offering a full-time academic appointment for an Adult Psychiatrist at the Assistant Professor level to join a progressive and growing academic department located in the beautiful southwest. 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 position, and to apply, go to <http://www.uacareertrack.com> and reference job #33731. If you have questions, please contact Lesley Bailey, Assistant to the Head of the Department of Psychiatry, 1501 N. Campbell Ave., P. O. Box 245002, Tucson, AZ 85724-5002, lbailey@email.arizona.edu or 520-626-8021. Review of applications is ongoing until position is filled.

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San Francisco Bay Area One Adult Psychiatrist One Child Psychiatrist

The Palo Alto Medical Foundation has been providing community based medicine since 1930, in the heart of Silicon Valley within minutes of San Francisco. As we expand to six campuses and more than three hundred physicians we maintain the collegial partnership environment that is the hallmarks of our success. Join an established team of well trained psychiatrists and LCSWs. As an outpatient physician you will do medication management, evaluations, and some psychotherapy. ADD and ADHD evaluations are needed. A full benefits package is provided.

For more information send your CV or contact Martha Elle, Director of Physician Placement, 795 El Camino Real, Palo Alto, CA 94301 650 853-6070 ellem@pamf.org

Be sure to visit our website at www.pamf.org

University of California San Francisco Department of Psychiatry Basic Scientist/Psychiatrist

THE DEPARTMENT OF PSYCHIATRY AT THE UNIVERSITY OF CALIFORNIA SAN FRANCISCO invites applications for a Psychiatrist with established skills in laboratory research in areas of basic science generally relevant to psychiatric problems. This position is at the Assistant Professor level and can begin on July 1, 2006 or thereafter. Applicants must be board eligible or certified in Psychiatry and have a California medical license at time of appointment and have a Ph.D. and/or postdoctoral training in a laboratory science. A joint appointment in the UCSF Neuroscience Program will be offered if appropriate. Applicants should submit their CV, brief statement of research interest, three letters of reference and three representative journal articles by March 1, 2006 to: **John Rubenstein, M.D., Ph.D., Search Committee Chair, c/o Astrid Prackatzsch, Department of Psychiatry, 401 Parnassus Ave., San Francisco, CA 94143-0984** 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 Vietnam era veterans and special disabled veterans.

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Outstanding Adult Psychiatrist and C & A Psychiatrist positions are available in one of California's fastest growing communities. It is located 45 minutes south of Sacramento with a population of over 260,000. **The positions are highly sought after employed outpatient opportunities with no call!** You can have a flexible schedule while you care for the full range of psychiatric cases. Work in an environment of collegiality with other highly trained Adult and C & A Psychiatrists along with their superb team of therapists, social workers, nurses, and case managers. These are perfect positions to balance your personal and professional life! **Send your CV to Tina Wilkins at wilkinstina@earthlink.net; fax to 916-482-1154; call 1-888-229-9495.**

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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.

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 or send curriculum vitae by email to tahodge@co.riverside.ca.us or by mail to:

County of Riverside
Human Resources Department
Tammy Hodge, Human Resources
Technician II
P.O. Box 7549
Riverside, CA 92513-7549

For additional information you may visit our website at www.hr.co.riverside.ca.us.

Scenic California Central Coast
Atascadero State Hospital

Atascadero State Hospital now pays board certified psychiatrists \$159,000, plus a generous year-end retention bonus. Atascadero is the nation's premier center for the treatment of forensically committed mentally ill patients. Our hospital is a teaching site affiliated with the University of California, accredited by JCAHO, and recipient of the prestigious Codman Award. All of our psychiatrists are board eligible and most are board certified. Many of our psychiatrists have forensic subspecialty boards. **We are located midway between San Francisco and Los Angeles** on the scenic central California Coast, south of Big Sur. We offer a spectacularly beautiful environment in San Luis Obispo County with temperate climate, beaches, world class wineries, cultural activities, golfing, sailing, riding, clean air, and excellent schools through the University level. **Our benefit package is valued** at an additional 30%, which includes retirement plans (including safety retirement), health plans, professional liability coverage, paid holidays, educational leave, and generous annual leave. On-call duty is compensated hour for hour over and above the base salary. Applicants must hold a current California license, or have pending application with the Medical Board of California. **For a prompt and confidential review**, send CV to Jeanne Garcia, M.D., P. O. Box 7001, Atascadero, CA 93423-7001; (805) 468-2005 or fax (805) 468-2138; or e-mail us at jgarcia@dmhash.state.ca.us. We are an equal opportunity employer.

COALINGA STATE HOSPITAL

Get in on the ground floor!

Coalinga State Hospital, in conjunction with the 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; one of the largest in the nation. It is closely affiliated with the University of California at Irvine Medical School and will train medical students and residents. A forensic fellowship program is being developed.

This is an opportunity for a psychiatrist interested in being on the forefront to explore the sexually violent predator and forensic fields within a leading national organization. Not only is Coalinga State Hospital's salary package competitive, we offer job security, flexible work schedules, and an excellent California State benefit package, including paid leave, medical insurance, and CalPERS Retirement.

Staff Psychiatrist (Safety)* \$162,792 - \$172,572
****(Includes Recruitment & Retention incentives. Candidates must be Board Certified.)***

We invite you to come and visit our astounding new facility and witness the possibilities for professional growth. 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: Stephen Wyman, M.D., at (559) 935-4079, or Erica Weinstein, M.D., at (559) 935-4343, or E-mail SWyman@csh.dmh.ca.gov or EWeinstein@csh.dmh.ca.gov. For more information, visit our website at www.dmh.ca.gov/Statehospitals/Coalinga. CSH is an equal opportunity employer.

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COLORADO

Opening for staff psychiatrist (inpatient work) in the Institute for Forensic Psychiatry in Pueblo, Colorado. The Institute for Forensic Psychiatry is the only Forensic Hospital in the State of Colorado and accepts patients from the judicial system (competency and sanity exams, ITP, NGRD), jails, and the prison system. University of Colorado medical appointments with good benefits. Four-day workweek option. Absolutely no mandatory call. Substantial incentive pay for taking call or doing court-ordered forensic evaluations. Full vesting in retirement plan in one year. Competitive salary. We are not an underserved area. Located in Southern Colorado with easy access to Colorado Springs, Denver, and Boulder as well as Northern New Mexico (Taos and Santa Fe). Affordable housing as well as recreational activities. For further information, contact A.O. Singleton, III, M.D. at (719)546-4637 or Mark Diamond, D.O. at (719)546-4891. Email: al.singleton@state.co.us Fax: (719)546-4484.

CONNECTICUT

PUTNAM, CT - ATTENDING PSYCHIATRIST/Faculty Position. UMass Memorial Medical Center, Department of Psychiatry, is seeking a full-time psychiatrist for an inpatient position with our affiliate, Day Kimball Hospital in Connecticut. Multiple career opportunities exist! Work in a collegial setting where clinical care, education and research are valued. A competitive salary, excellent benefits and progressive incentive plan. 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@ummmc.org AA/EOE

University of Connecticut
Health Center

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Seeking board certified and board eligible psychiatrists to provide care to patients in the Connecticut Department of Correction. Opportunities include patient care, research, teaching, and leadership in both an academic and public health care setting. Opportunities exist throughout the state. Exciting employment, excellent state benefits, regular working hours, and competitive salaries. Please contact Noreen Logan, Human Resources, for information and an application at (860) 679-7691 or e-mail at logan@uchc.edu.

AA/EEO M/F/PWD/V

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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

SOUTHEAST CT: Child Psychiatrist - Directorship position - new adolescent residential treatment program. Program development & clinical care responsibilities. Competitive salary & benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

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Outpatient Medical Director

The Department of Psychiatry of the Georgetown University Hospital seeks a psychiatrist at the Assistant or Associate Professor level to direct our expanding outpatient clinical programs. We seek a highly motivated academic physician with outstanding teaching, administrative, and clinical psychopharmacologic skills. We are particularly interested in a candidate who has expertise in Mood and Anxiety Disorders. Candidates must be board certified and eligible for a D.C. medical license. EOE.

Qualified candidates should send a letter of interest and CV to:

Steven A. Epstein, M.D., Professor and Chair
Dept. of Psychiatry,
Georgetown University Hospital
3800 Reservoir Road NW
Washington, D. C. 20007
epsteins@gunet.georgetown.edu

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Join psychiatric staff at hospital less than an hour from Tampa and Orlando. A diverse, family-oriented community with lots to do. Contact Jim Ault at St. John Associates, 1-800-737-2001 or jault@stjohnjobs.com. www.stjohnjobs.com

Gainesville - Position for Adult/Child psychiatrist available. Candidate must be BE/BC. Call is optional. Community Mental Health Facility looking for team player who is interested in working in a community mental health care setting. Our facility offers comprehensive treatment including crisis as well as outpatient management. Gainesville is an academic city that offers much of the culture of North Florida and is regarded as one of the best cities to live and raise a family. Competitive salary offered as well as benefit package. Please fax your CV to Human Resources (352) 374-5608 or contact us directly at (352) 374-5600 ex. 8522. I am looking forward to speaking with you.

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Practice in Paradise. Solo O.P. practice in beautiful Key West, FL. Ideal for the psychiatrist who wishes to relocate from a colder climate but doesn't wish to have to establish a patient base. Numerous referrals from therapists and MD's, other practitioner's in suite are a psychologist, nurse practitioner & MSFT. Inquiries please call (305) 292-6999 FAX (305) 292-6133.

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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.

Staff Psychiatrist at a 325 bed newly built, privately operated State Hospital in Broward County, BC/BE, must possess Florida license and 3 years experience in clinical psychiatry. Employed position FT, 40 hours, competitive salary, benefits, great work setting. Experience with serious mental illness preferred. Send or Fax C.V. to: Debra Kirsch, MD dkirsch@geocareinc.com Fax 561-999-7747

COASTAL FLA! CMHC needs 1-2 adult psychs. One position is to work 100% outpatient at two of their local clinics. The other is to head up the assertive community treatment team. Salary 150K + d.o.e. plus full bene. Call Ken Pruchnicki @ 800-575-2880 x 319. CV to: kpruchnicki@medsourceconsultants.com

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, competitive salary. Send or Fax C.V. to: Debra Kirsch, MD dkirsch@geocareinc.com Fax 561-999-7747

Located along South Florida's east coast just minutes from the Atlantic Ocean, CARF accredited community mental health center is seeking a part-time/full-time inpatient and outpatient psychiatrists to provide comprehensive psychiatric care to children and adults. Must be Board Certified (or eligible). Excellent salary and benefits package, great staff and a lovely coastal community. Seeking applications directly from candidates. (No recruitment firms please!) Send/Fax CV: HR, New Horizons, 4500 W. Midway Rd., Ft. Pierce, FL 34981 FAX (772) 468-5606 EOE/ADA/DFWP www.nhtcinc.org

GEORGIA**ATLANTA: PSYCHIATRY POSITIONS**

SOUTHERN BEHAVIORAL HEALTH-CARE is looking for two full-time psychiatrists, one child and one adult. We are located in the Atlanta area, 10 minutes from the airport. Salary range: **Adult: \$165,000-170,000, Child: \$175,000-180,000. Plus an additional productivity bonus.** H-1 visa and foreign graduates are welcome. Generous benefit package. For more information, contact the medical director at 678 358 6065, e-mail to heal650@bellsouth.net or fax CV to 678 610 7111.

ATLANTA: General or Addiction Psychiatrist - Talbott Recovery Campus is nationally recognized for outstanding assessment & treatment programs. Intensive outpatient multidisciplinary setting. Ideal candidate is BC with special interest & proven skills in treating patients with substance abuse and psychiatric disorders. Comprehensive salary & benefits will be offered. **Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com**

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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.

INDIANA

Join 10 psychiatrists in a thriving university community less than two hours from downtown Chicago. Contact Jim Ault at St. John Associates, 1-800-737-2001 or jault@stjohnjobs.com. www.stjohnjobs.com

Great College Town Opportunity! Community Hospital recruiting for two Adult psychiatrists. Enjoy an employed position with an excellent benefits package. **Competitive salary with bonus incentives** to earn additional income! **Opportunities to teach first and second year Med Students!** For more info, call Sarah Mcglinnen @ 800.375.8261 ext. 216, fax your CV to 703.385.0016 or e-mail: smcglinnen@medsourceconsultants.com.

General Adult / Forensic

Liberty Healthcare is seeking a BC/BE General Adult Psychiatrist and Forensic Psychiatrist for a residential psychiatric setting in north central Indiana. Work as part of a sophisticated interdisciplinary treatment team. No Managed Care issues. Enjoy an excellent quality of life working M/F 40 hour work week with generous paid time off; competitive compensation; *additional on-call compensation*; \$2,000 sign-on bonus; paid malpractice insurance; relocation/CME allowance. Contact Carol Wertley 800-331-7122 or cell 610-389-7437; carolw@libertyhealth.com. EOE.

LOUISIANA**IMMEDIATE OPENING FOR PSYCHIATRISTS -**

J-1 Visa holders qualify - Attractive salary w/benefits. Other candidates - Guaranteed net income or attractive salary w/benefits. Board Certified or board eligible. Louisiana license required.

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MAINE

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.acadahospital.org



Your resource for life.

MaineGeneral Health

Augusta & Waterville, ME

The MaineGeneral Medical Center is recruiting for **two adult psychiatrists** in Augusta and **one child-adolescent psychiatrist** in Waterville. One adult psychiatrist will serve as Medical Director of the psychiatric ACT Team, and support case management and community services. One adult psychiatrist will serve as a hospital-based psychiatrist working with two other psychiatrists to cover inpatient services, and provide consultation to primary care and specialty clinicians. The child psychiatry position will work with the Adolescent Intensive Outpatient Program and the behavioral pediatric service.

On-call is one in six at each campus. We offer a competitive salary with a full benefits package, including time off for CME and an education allowance.

We emphasize team work and quality of care. Our mission in behavioral health: *"We help people build healthy relationships and satisfying lives."*

Contact:

David G. Folks, M.D.
Chief of Psychiatry and Medical Director
MaineGeneral Medical Center
6 East Chestnut Street
Augusta, ME 04330
Phone: 207-626-1278
Email: david.folks@mainegeneral.org



Are you looking for a life of harmony? One that achieves a true balance? At Sweetser it is a reality!

As a Child & Adolescent Psychiatrist for Maine's largest non-profit child welfare / mental health facility you can achieve true balance. This outpatient position will allow you to work with an amazing team developing, implementing, and overseeing a treatment plan for each of your clients that will encompass a wide range of services. All the while keeping you closely connected to each client. Sweetser's highly skilled staff of Crisis clinicians eliminates the need for inpatient work, providing you with more of that personal and/or family time we all yearn for.

The state of Maine also offers a great balance! Here you will find beautiful change of seasons, each presenting new and exciting recreational activities. Cultural activities are also abound from amazing art galleries to renowned theater groups. Maine has bustling cities full of shopping and nightlife, as well as an incredible countryside with farmers markets and talented craftsmen.

Sweetser is as dedicated to its employees and their families as they are to their clients. For the security of you and your family, Sweetser offers a competitive salary and a wide range of benefits, inclusive of generous retirement programs.

If you are a licensed Child & Adolescent Psychiatrist with the appropriate board certifications and want to achieve "True Balance", check out our website at www.sweetser.org or submit letter and C.V. to Sweetser Human Resources, 50 Moody St., Saco, ME 04072, Fax (207) 294-4420, or jobs@sweetser.org (text files only). Please state referral source.

Strengthen your recruitment effort through the APA Job Bank! Post your career opportunity online, receive candidate responses instantly, and access APA's resume database of psychiatrists.

Call 703.907.7330 for more info

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.

MARYLAND**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 twenty-eight (28) hours per week and a targeted start date of July 2006. 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

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@dhhm.state.md.us.)

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.

The VA Maryland Health Care System (VAMHCS) is actively seeking a Director, Mental Health Clinical Center. The VAMHCS is a tertiary care facility and is classified as a Clinical Referral Level I Facility, and affiliated with the University Of Maryland School Of Medicine. The VAMHCS has a large research. The health care system consists of two Maryland VA Medical Centers located at Baltimore and Perry Point and a 120-bed Rehabilitation and Extended Care Center on the Loch Raven campus located in Baltimore City. The VAMHCS also has five Community Based Outpatient Clinics throughout the state of Maryland.

The Mental Health Clinical Center is the largest Clinical Center within the VAMHCS, which includes allied health and administrative positions in the areas of Acute Inpatient Mental Health; Sustained Inpatient Treatment; Residential Treatment; Community (Outpatient) Mental Health; and Special Programs: Addictions and Trauma. Mental health activities are conducted at both the Baltimore and Perry Point Divisions and 5 Community Based Outpatient Clinics across the state of Maryland. VAMHCS is also the home to the VISN 5 Mental Illness Research Education and Clinical Center (MIRECC), one of only 8 national MIRECCs funded across the VA system.

The incumbent is responsible for the management and operations of the Mental Health Clinical Center and its programs, residency supervision, and services. Duties include responsibility for meeting all applicable Mental Health regulatory and accrediting body requirements within the Department of Veterans Affairs, meeting and exceeding performance measure goals, improving and monitoring access to care while predicting and absorbing demand. The incumbent works as a member of the Medical Staff Management Team, which is responsible for overall leadership, policy, planning, budget, operations, and performance of the Mental Health Clinical Center. The Director, Mental Health Clinical Center fosters and maintains relations with the affiliate university, educational programs, and contracting services.

Qualified candidates must be citizen of the United States; must be proficient in spoken and written English as required by 38 U.S.C. 7402(d) and 7405(f); must be a mental health professional who meets VHA qualification standards for their respective discipline with relevant work experience (examples include: psychiatrists, psychologists, psychiatric social workers and psychiatric nurses); and preferred applicant should have an extensive history of significant leadership, mentoring, and management experience in a mental health environment; strong business acumen for managing health care operations; demonstrated expertise in the academic missions of education and research in an affiliated environment; and credentials warranting academic appointment in the School of Medicine at the University of Maryland School of Medicine.

Interested candidates should send C.V. and cover letter, by mail or electronically to Kathleen Barney, Executive Assistant to the Chief of Staff, VA Maryland Health Care System, 10 North Greene St., Baltimore, Maryland 21201; e-mails Kathy.Barney@med.va.gov; telephone (410) 605-7008. Contact for professional questions, Dorothy A. Snow, M.D., Acting Executive Chief of Staff 410-605-7019. The Department of Veterans Affairs is an equal opportunity employer.

Psychiatrist

Springfield Hospital Center - a 405 bed psychiatric inpatient 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@dhhm.state.md.us. EOE

Easy access to Baltimore and D.C.! Enjoy big city amenities without the hassles or expense! Adult and C/A psychiatrists needed. **40 HOUR WORK WEEK!** Enjoy the security of an employed position with a lucrative salary & an excellent benefits package. Possible opportunity for private practice model if interested. For more info, call Ariana Sanjabi @ 800.735.8261 ext. 214, fax your CV to 703.378.0016 or e-mail: asanjabi@medsourceconsultants.com.

PSYCHIATRIST. Full-Time Medical Director Position for minority owned practice in Baltimore, MD. Excellent salary & benefits package. Ownership potential in fabulous psychiatric practice. Contact John Fisher at 410.779.3102 or fax 410.230.2687.

MASSACHUSETTS

CAMBRIDGE: Psychiatry Positions

Positions available at Cambridge Health Alliance Department of Psychiatry, Harvard Medical School. Full and part time opportunities in adult services. The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School. Our public health commitment to improving the health of our communities, coupled with a strong academic tradition, make this an ideal opportunity for candidates interested in caring for underserved populations in a rich clinical environment. We have strong adult and child residency training programs which provide opportunities for teaching. Inpatient, outpatient, and psychiatry emergency service positions are available. Academic appointment, as determined by the criteria of Harvard Medical School, is anticipated.

Qualifications: BE/BC, demonstrated commitment to public sector populations, strong clinical skills, strong leadership and management skills, team oriented, problem solver. Bilingual and/or bicultural abilities are desirable. Interest and experience with dual diagnosis and/or substance use disorders preferred. Competitive compensation, 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 Derri Shtasel, MD, Dept. of Psychiatry, 1493 Cambridge Street, Cambridge, MA 02139. Fax 617-665-2521. Email: DShtasel@challiance.org** (email preferred).

Child and/or Adult Psychiatrist to join busy, large, established private psychiatric group practice. Work consists of outpatient psychiatric treatment, both psychotherapy and psychopharmacology, and some hospital consultations. A lot of flexibility in terms of job and schedule. Please send C.V. to Paul Menitoff, M.D., Greater Lowell Psychiatric Associates, LLC 9 Acton Road Suite 25 Chelmsford, MA 01824.

WORCESTER - Director of Outpatient Psychiatry Service
Excellent opportunity for outstanding clinical psychiatrist at large multidisciplinary university hospital clinic. Position involves supervisory, teaching and direct care responsibilities, with opportunities for research. Faculty rank commensurate with experience. Applicants should send letter of interest and CV to Alan Brown, MD, Vice Chairman for Clinical Services, Department of Psychiatry, UMass Memorial, 55 Lake Avenue North, Worcester, MA 01655 or e-mail BrownA01@ummhc.org AA/EOE

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.

Cooley Dickinson Hospital is seeking a Medical Director of Inpatient Services. Applicant must be Board Certified in Psychiatry, have at least 2 years of inpatient experience.

Maximum call 1 week in 7, with less call possible. An extremely competitive compensation complimented by a full benefits package, is offered with the position.

Cooley Dickinson Hospital is at the heart of a vibrant, five-college community that offers residents extraordinary educational opportunities and unlimited cultural amenities. Northampton, MA, an exciting arts and college community was voted the #1 small arts town in the country by the Boston Globe and also ranked in the top 100 places to live in the U.S., according to *Money* magazine.

For more information, contact Erin Wertheim, Physician Recruiter at 413-582-2720 or erin_wertheim@cooley-dickinson.org.

CENTRAL MASSACHUSETTS - UMass Memorial Medical Center, Department of Psychiatry is seeking a psychiatrist for our affiliated hospital Health Alliance, in Fitchburg, Massachusetts. The position involves primarily inpatient and partial hospital responsibilities. Academic opportunities and faculty rank commensurate with experience and interests. Candidates must be BE/BC in Psychiatry. Applicants should send letter of interest and CV to Alan Brown, MD, Vice Chairman for Clinical Services, Department of Psychiatry, UMass Memorial, 55 Lake Avenue North, Worcester, MA 01655 or e-mail BrownA01@ummhc.org AA/EOE

CENTRAL MASSACHUSETTS - UMass Memorial Medical Center, Department of Psychiatry seeks a Psychiatrist for our Geriatric Psychiatry Inpatient Unit at Clinton Hospital. Clinical care on a 20-bed unit that serves as an important referral site for the region. Psychiatry and Family Practice resident, medical student teaching occurs on-site. Opportunities for collaboration and teaching at Worcester Campus. Competitive compensation with complete benefit package. Faculty rank commensurate with experience. Candidates should be BC/BE in general psychiatry. Added qualifications in Geriatric Psychiatry and/or previous experience working with geriatric patients is preferred. Applicants should send letter of interest and CV to Tatyana Shteinlukht, MD, Medical Director, Geri/Psych Unit, Clinton Hospital, 201 Highland Street, Clinton, MA 01510 or e-mail Shteintl@ummhc.org AA/EOE

BOSTON BROOKLINE - General Psychiatrist - new 20 bed adult intermediate services unit.
JAMAICA PLAIN - Child Psychiatrist for inpatient & partial service serving predominantly Latino patient populations.
LOWELL - Child Psychiatrist for Inpatient & Partial program - multidisciplinary setting with outstanding services. Medical Director Opportunity!

Positions offer very competitive salary/benefits package. **NO CALL.** Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

CONSULTATION-LIAISON PSYCHIATRIST

Mount Auburn Hospital, affiliated with Harvard Medical School, is seeking a full-time consultation-liaison psychiatrist. This clinical position involves working closely with our medical and surgical services, including residents in our internal medicine residency program. Academic appointment, salary package. Please send 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.

MINNESOTA

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. Employed position. Full Benefits. Competitive compensation package. For immediate consideration, call Chris Maslyn @ 800.735.8261 ext. 221, fax your CV to 703.378.0016 or e-mail: cmaslyn@medsourceconsultants.com.

MISSOURI

Inpatient Psychiatry; Academic Department

UMKC Dept. of Psychiatry and Western Mo. 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 through DMH. Relocation costs and student loan repayment is negotiable. Send CV to Rob Hornstra, MD, Medical Director at 1000 E. 24th St., K.C., MO 64108 or rob.hornstra@dmh.mo.gov or call 816-512-7504.

Provide psychiatric services to long-term inpatients. No acute unit, no ER. Modern facility with electronic medical record, dictated progress notes. Salary range up to \$165,000 depending on experience. Moving expenses, student loan repayment available. Benefits and malpractice coverage provided by employer. Small city community, one hour from Kansas City, half hour from major airport. Medical school affiliation. Pharmacy residency program on site. Training site for Certified Forensic Examiners.

James B. Reynolds, M.D.
Medical Director
(816)387-2501

MONTANA

ST. PATRICK HOSPITAL & HEALTH SCIENCES CENTER

PSYCHIATRIC HOSPITALIST

MISSOULA, MONTANA

St. Patrick Hospital, located in Missoula, Montana, is home to the International Heart Institute of Montana and the Montana Neuroscience Institute Foundation. We are a 213-bed, acute care, JCAHO accredited, Sister's of Providence, regional referral center for W. Montana and N. Idaho. Missoula is home to the University of Montana and offers an abundance of beauty & recreational opportunities. Close to Glacier and Yellowstone National Parks, you can live and recreate in beautiful country and work for a stable and well-respected hospital. We currently have a full-time Psychiatric Hospitalist opportunity for our co-occurring 26-bed inpatient unit. The co-occurring unit consists of 60-70% psychiatric patients and 30-40% addiction patients including acute detoxification. Position will also include call.

****We offer a competitive wage & benefit package.**

For a Big Sky Welcome!!
Contact: Jan Van Fossen
Vanfoss@saintpatrick.org
Human Resources Department
St. Patrick Hospital
P.O. Box 4587
Missoula, MT 59806
1-800-325-7271 ext#5627
Job line: 406-329-5885
Fax: 406-329-5856
www.saintpatrick.org

BIG OPPORTUNITY UNDER THE BIG SKY

BE/BC PSYCHIATRIST, MONTANA - You've earned it. Things are different here. The Great Falls Clinic seeks a BE/BC Psychiatrist to join the Neurosciences Department of a rapidly expanding 125-physician multi-specialty group. Successful candidates will have strong skills in both adult and geriatric psychiatry as well as a medical management approach to patient care.

Great Falls is a warm and safe community perfect for a physician interested in making a home for themselves and/or their family. Access to world-class recreational venues, outdoor activities, scenic vistas and regional culture are right outside your practice door. This opportunity does not qualify as a J-1 waiver site. For more information about this wonderful opportunity, contact Kate Bogue, Physician Recruitment Coordinator at (406) 771-3332 or kate.bogue@gfclinic.com. You may also visit our website at www.gfclinic.com

NEVADA

Southern Nevada Adult Mental Health Services (SNAMHS); Las Vegas, NV JCAHO accredited; Active Resident training; System expanding; Hiring BE/BC psychiatrists October 2005; hospital and outpatient. New Acute Hospital opens May 2006. Limited call responsibilities; Relocation assistance; Salary up to \$163,000; Good Benefit and Retirement packages. No State income tax. Contact David A. Rosin, MD; 6161, W. Charleston Blvd, Las Vegas, NV, 89146 mddirect@snamhs.nv.gov or psmith@snamhs.nv.gov; Phone 702-486-6050

Adult psychiatrist sought in the gaming capital! Private non-profit, substance abuse & addictions mental health facility. Inpatient duties for crisis stabilization unit, to 150K salary & bene. Very light call. Supplemental income possible. Call Dave Featherston @ 800-575-2880 x314 dfeatherston@medsourceconsultants.com

NEW HAMPSHIRE

ADULT PSYCHIATRIST

Riverbend Community Mental Health, Inc. a large community mental health center with a staff of over 200, including six full-time psychiatrists, seeks a BE/BC psychiatrist with expertise (fellowship training) or experience in **geropsychiatry** to provide elder outpatient and nursing home care several days a week. This position also includes practice in a general psychiatric outpatient office and an opportunity to provide consultation and supervision to family practice residents in a family practice clinic. Experience or a willingness to learn ECT is required. Shared on-call responsibilities in a 15 bed psychiatric unit located in a general hospital are part of this position.

We are part of the N.H. mental health system that is currently rated #2 among community mental health systems nationally. Concord is a family-oriented small city located one hour from Boston, the White Mountains, and the Seacoast. This position is full-time, salaried with excellent benefits including medical, dental, life, disability, retirement plan, paid malpractice insurance, continuing medical education, and reimbursement for professional expenses. Interested applicants should send a CV to Riverbend CMHC, Attn: Human Resources, P.O. Box 2032, Concord, NH 03302-2032. For more information about this opportunity, contact Elvira Downs, MD, at (603) 228-1551. EOE www.riverbendcmhc.org

NEW JERSEY

If you are a child or adult board certified psychiatrist looking to grow in a private practice that is not dependent on managed care, call us at 908.273.0800 and fax CV to 908.273.0815. We have a growing private practice in Summit, NJ, an affluent suburban community.

New Jersey Psychiatrists - Rapidly expanding behavioral health organization has immediate positions available in Newark and Cranford locations. Seeking adult and child Psychiatrists for partial hospitalization and outpatient services. Spanish speaking a plus. Full and part-time positions available. Excellent employment package including competitive salary, benefits and malpractice insurance. Fax CV to (732) 212-0061 or e-mail hr@ppenet.com.

Child/Adol. Psychiatrist

Child/Adol. Psychiatrist- needed for growing multi-disciplinary group in affluent community in North/Central N.J. Expertise in psychopharmacology required. No Managed Care! Please fax CV to (908) 598-2408

Free Online Advertising

All line classified ads are posted on the
Psychiatric News web site:

pn.psychiatryonline.org

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

Premier Multi-Site Family Medicine Not for Profit (www.INSTITUTE2000.org) seeking P/T BC/BE Adult, Child, and C-L Psychiatrists for Bronx and Manhattan O/P locations. \$100/hr, Flexible Schedule, willingness to work collaboratively with family practitioners, SW staff, and very diverse patient population. Please send CV to: Ms. Virna Little, LCSW-R, SAP, V.P. PSYCHOSOCIAL SERVICES 16 E. 16 St. NY, NY 10003. FAX 212 627 2958, TEL 212 924 7744 ext 337. Equal Opportunity and Diversity Employer.

PSYCHIATRIST

Downtown Bronx Medical Associates, the Faculty Practice of Lincoln Medical and Mental Health Center, a major teaching facility in NYC and part of the Health and Hospital Corporation is seeking FT/PT BC/BE Psychiatrists - the Adult Outpatient Unit Psychiatrists - Inpatient Unit and Director of Psychiatry - ER Services Responsible for teaching and supervising residents, and direct patient care. Spanish speaking pref. Academic Appt. with Weill-Cornell Med. College.

Send CV to A. John Pellowe, MD: Fax: 718-579-6060 or Email: somwarub@dbmapc.org. AA/EOE M/F.

PSYCHIATRISTS

Lutheran HealthCare, a sweeping system of inpatient and ambulatory services across Southwest Brooklyn, is seeking NYS licensed psychiatrists for a variety of positions in its expanding Department of Psychiatry.

Ambulatory Care Psychiatrists-Full-time openings are tailored for psychiatrists with expertise in psychopharmacology, but also multidisciplinary team participation, staff supervision and teaching. General adult and child/adolescent positions available, including special interest areas in HIV behavioral health, treatment of child/family victims of trauma, and substance abuse treatment. 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.

Moonlighting Psychiatrists-Opportunities available on inpatient ED/CL/Detox services for a variety of shifts 24/7.

We are conveniently located for travel from all of NYC Boro's. For consideration, please email: ghartman@lmcmc.com, fax (718) 630-8594, or send your CV to: Grace Hartman, Department of Psychiatry, Lutheran Medical Center, Suite 2-45, 150 55th Street, Brooklyn, NY, 11220. EOE/AA/M/F/D/V

LUTHERAN HEALTHCARE

Psychiatrist
Child/Adolescent & Adult

YAI/Premier Healthcare is a nationally recognized, well-established NYC diagnostic & treatment center for people with disabilities and their families. We are currently seeking full and part-time psychiatrists for our outpatient facilities in the Bronx.

This is an opportunity to work with a professional team of doctors and nurses in a multi-cultural, team environment. Send CV to: Karen Meyers, Clinical Recruiter, Premier HealthCare, 460 West 34 Street, N.Y., N.Y. 10001 Fax 212-563-4836 Email: kmeyers@yai.org

PSYCHIATRISTS

MANHATTAN
BH Clinic-22 hrs
Development Disabilities Clinic-21hrs

DOWNTOWN BROOKLYN
Continuing Day Treatment-33 hrs
Home Visits-Bilingual Russian-10hrs

BRONX
MH Residence- 5hrs

COPIAGUE, LONG ISLAND
BH Clinic-12hrs

FEGS, a leading provider of behavioral health services in the New York metropolitan area, seeks Board Certified/Eligible Psychiatrists for psychiatric evaluations and treatment. Competitive salary, no on-call, malpractice insurance covered by agency. Send CV to our HR consultants: HR Dynamics, Inc. (DEPT: SB/PSY) 345 Hudson Street, New York, NY 10014 or e-mail sboyle@hr-dynamics.com EOE

Westchester Suburb- 1 Child/Adol MD

PT or FT Child & Adol IP. Easy 35 minute Manhattan drive. Strong child grp, little mang'd care. No call, no evenings, no weekends! Why do OP? PT job has flex hrs for kids or priv practice. 917-710-2456 or toacp@aol.com. Also, 1 ADULT MD for OP -daily PT flex daytime hrs!

New York City! Numerous opportunities available in the "Big Apple"! All positions have **NO CALL!** 1) Two Outpatient Forensics Needs 2) Unit Chief of Inpatient Unit 3) Unit Chief of Detox Unit 4) Child Outpatient 5) Adult Inpatient. Enjoy the stability of an employed position with a competitive salary & full benefits package! For more info, call Carrley Ward @ 800.735.8261 ext. 219, fax your CV to 703.378.0016 or e-mail: cward@medsourceconsultants.com.

NEW YORK STATE

The Department of Psychiatry of the State University of Buffalo School of Medicine and Biomedical Sciences has openings for two newly ACGME-accredited PGY 5 Geriatric Psychiatry fellows to begin July 2006. The Geriatric Psychiatry fellow will have clinical experiences in geriatric dedicated home-health care, outpatient, day hospital, acute inpatient, consultation-liaison, long-term care, ECT and hospice. The fellows will participate in a clinical milieu emphasizing understanding the psychiatric aspects of medical conditions along with the medical aspects of psychiatric conditions. Fellows will have the unusual opportunity through collaborative consultation-liaison work to develop clinical expertise and professional relationship skills working closely with trainees and faculty in geriatric medicine and neurology. They will participate in a comprehensive didactic program in preparation for the ABPN geriatric psychiatry certification. Contact the Geriatric Psychiatry Division for additional information or submit an application including your CV, your letter of interest, three letters of reference including one from your residency training program director to: **Marion Zucker Goldstein M.D. ECMC Dept of Psychiatry, Division of Geriatric Psychiatry, 462 Grider Street, Buffalo, New York 14215**

The Geriatric Psychiatry Program Coordinator Sandra Gilliam can be reached at: Tel. 716-961 6955 email gilliam3@buffalo.edu

GREATER BINGHAMTON HEALTH CENTER
ADULT PSYCHIATRISTS
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 Behavioral Health Center (outpatient only, no inpatient, no call). 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

Exceptional Professional Opportunity

for psychiatrist to provide high quality care as part of a well-respected multi-disciplinary private group practice. Located in the bucolic mid-Hudson Valley about 2 hours north of NYC. Flexible hours - inpt/outpt.

Excellent salary package \$180,000+.
email CV to **qualitydocsearch@yahoo.com** or call 1-518-668-6065 for more information.

Academic Psychiatrist with
Expertise in Informatics

The Department of Psychiatry, school of Medicine and Biomedical Sciences, State University of New York at Buffalo is seeking a psychiatrist with an international reputation in informatics, decision making or a related field to develop collaborative research and educational activities with the University's School of Informatics. The successful candidate should meet criteria for Professor of Psychiatry with tenure in the University. Salary will be negotiated with the University.

Women and minorities are encouraged to apply. The University of Buffalo is an Equal Opportunity/Affirmative Action Employer. Send cover letter and resume to: Steven L. Dubovsky, M.D., Professor and Chair, UB Dept. of Psychiatry, Erie County Medical Center, 462 Grider Street, Room 1182, Buffalo, NY 14215.

P/T CHILD/ADOLESCENT PSYCHIATRIST WANTED. Outpatient position with leading LI Children and Family Mental Health Agency. Fax Resume: HR-(516)626-8403.

Excellent opportunity for BC/BE Psychiatrist in Central New York. Fast paced environment. Dedicated Psychiatry ER at St. Joseph's Hospital Health Center in Syracuse, NY. Full or Part-Time, 8-hour shifts. No beeper call. Excellent salary/benefits incl. malpractice, CME, health, 401(k). Contact: Joseph Gross - phone: (315) 448-2783; fax: (315) 703-2198; e-mail: Joseph.Gross@sjhsyr.org.

CHILD AND ADOLESCENT PSYCHIATRIST
Section on Child and Adolescent Psychiatry
Westchester Medical Center
New York Medical College

Clinical academic position available as chief of inpatient adolescent unit. The Section on Child and Adolescent Psychiatry is a growing program at a major regional medical center with a new children's hospital, and has the only accredited child psychiatry fellowship program between NYC and Albany. The adolescent unit is undergoing reconstruction as a short term, acute unit, integrating therapeutic interventions and programming, collaboration with community mental health programs, and new clinical and support staff positions. Responsibilities include supervision of social work, psychology, medical student, and physician trainees, involvement in didactics of the medical college, administrative and clinical oversight of the unit, implementation of staff training, and direct clinical care. Salary and benefits are competitive, and academic rank is commensurate with qualifications. WMC and NYMC are Affirmative Action/Equal Opportunity Employers. Women and minorities are encouraged to apply.

Please send inquiries to:

Flemming Graae, MD
Chief, Child and Adolescent Psychiatry
95 Grasslands Road
Valhalla, NY 10595-1646
Fax: 914 493-1076
E-mail Graaef@wcmc.com

Psychiatrists Needed

Comprehensive Neuroscience, Inc., a national clinical research organization specializing in CNS research is seeking part-time, board certified psychiatrists to assist in conducting clinical trials for our sites in Northern New Jersey, Washington, DC, Northern Virginia, Chicago, IL and Southern California (LA area). Position responsible for acting as sub-investigator for outpatient studies with various CNS investigational compounds.

E-mail resume to hr@cnsmail.com or fax to 914-997-4024. EOE

NORTH CAROLINA

Coastal North Carolina Residential Treatment Center seeks BC/BE child or general psychiatrist with child experience for Clinical Director of a 46 bed RTC. This employed position offers generous base salary, great benefits and a lucrative performance bonus. For info call S. Wiltgen, CEO at (910) 577-1400 or email sarah.wiltgen@psysolutions.com

SENIOR FACULTY POSITION

The University of North Carolina School of Medicine is seeking a senior psychiatrist at the Associate or Full Professor level (fixed-term) for the position of Clinical Director for a new, modern public psychiatric facility which is under construction in nearby Butner, North Carolina. This 432 bed hospital will provide psychiatric services for the central region of the state, and will include vibrant academic, teaching, and research programs in partnership with both the UNC School of Medicine and Duke University Medical Center. The Clinical Director will be responsible for medical leadership and the planning and organization of clinical, research and teaching functions. Candidates must have an M.D. from an accredited university, be Board Certified/Eligible, and able to obtain medical licensure in North Carolina. A strong track record of administrative leadership in a public academic setting is highly desirable.

Candidates should submit a letter of application, current CV, and the names and contact information of three professional references to: David Rubinow, M.D., Meymandi Professor and Chair of Psychiatry, Campus Box #7160, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7160. UNC is an Equal Opportunity/ADA Employer.

PSYCHIATRISTS (\$124,620 - \$179,068)

John Umstead Hospital, a state psychiatric hospital located in Butner, NC seeks psychiatrist for the Adult Admissions and Alcohol & Drug Abuse Treatment units. Convenient to Raleigh/Durham/Chapel Hill and has close ties with Duke University and UNC-Chapel Hill. Competitive salary and benefits package. Requires graduation from an accredited medical school, completion of an accredited psychiatric residency, and board certification or eligibility. Selected employees may qualify for the education loan repayment program authorized by Section 332 of the Public Health Service Act. Send state application (PD-107) and/or vitae to JUH, Human Resources Office, 1003 12th St., Butner, NC 27509 or contact Dr. Lou Ann Crume, Clinical Director at 919-575-7233. FAX 919-575-7550. EEO/AA Employer

Child Psychiatrist (Assistant or Associate Professor)
Department of Psychiatric Medicine
The Brody School of Medicine at
East Carolina University

The Department of Psychiatric Medicine at Brody School of Medicine at ECU is now accepting applications for a full-time faculty position (Assistant or Associate Professor). The position offers an excellent opportunity to work in an outpatient community-based mental health setting, working with multidisciplinary staff. There are opportunities for teaching medical students and residents and participating in collaborative research. Requirements include MD or equivalent degree, completion of accredited child and adolescent psychiatry residency training, preferably board certification, eligible for NC medical licensure. This is not a HPSA site. Salary and academic rank commensurate with experience and academic background. Applications accepted until position is filled. East Carolina University is the 3rd largest public university in the state, located near many recreational areas, including the Atlantic Ocean coastal resorts. **Please send a letter of interest and CV to: John Diamond, M.D., Chair Search Committee, Department of Psychiatric Medicine, the Brody School of Medicine, 4E-94B Brody Building, 600 Moye Blvd., Greenville, NC 27834, telephone 252-744-2673, e-mail: diamondj@mail.ecu.edu. East Carolina University is an AA/EO Employer.**

1 hr to Raleigh! Hospital seeks an adult psych for a lucrative private or group practice opportunity. Mix of in and out-patient work. Shared call @ 1 in 4. 2-yr income guarantee & superb bonus incentives.
Call Susan Springer 800.574.2880 ext. 315
CV to sspringer@medsourceconsultants.com.

NORTH DAKOTA

MeritCare Health System of Fargo, ND is seeking an Adult Psychiatrist to join its 32-member multi-disciplinary Psychiatry Department. Faculty appointment and teaching of psychiatry residents is available through University of North Dakota School of Medicine. MeritCare is an integrated 384-physician multi-specialty group practice, 583-bed Level II tertiary/trauma hospital with 26 primary care clinic sites in two states. Sister cities, Fargo, ND and Moorhead, MN are a tri-college community of 200,000 located near the heart of Minnesota's lake country. Fargo-Moorhead offers excellent educational systems, recreation and sporting activities as well as a variety of entertainment and cultural events. This is an excellent opportunity with a competitive compensation and benefits package being offered. Drug-free workplace. AA/EOE. This is not a designated HPSA site.

To apply send CV to:

Jill Gilleshammer, Physician Recruiter
MeritCare Health System
P O Box MC
Fargo, North Dakota 58122
Phone: (800) 437-4010, ext. 280-4851
Email: Jill.Gilleshammer@meritcare.com

OHIO

TENURE TRACK: The MetroHealth System, an affiliated teaching hospital of Case Western Reserve University, is currently seeking an outpatient consult liaison psychiatrist at the instructor or assistant professor level. This psychiatrist will provide clinical care and teaching of residents and students at MetroHealth Medical Center. Benefits include a competitive salary, incentive potential, health insurance, paid time off, liability insurance, an academic appointment and CME opportunities. Please submit a letter of interest and curriculum vitae to R. T. Segraves, M.D., Ph.D., Chairperson, Department of Psychiatry, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109-1998 or rsegraves@metrohealth.org. In employment, as in education, The MetroHealth System and Case Western Reserve University are committed to Equal Opportunity and World Class Diversity. The Psychiatry Department at MetroHealth has HPSA designation.



THE 1ST CHOICE IN
PSYCHIATRIC RECRUITMENT

Northeast Ohio
MEDICAL DIRECTOR - Clinical and leadership duties. Exceptional Opportunity
For more information contact: **BOB TOTH**
(800) 783-9152 FAX (270) 782-1055
www.fcspsy.com

OREGON

Physician Specialist needed: Must have M.D. & completion of residency in Psychiatry, Internal Medicine, or General Medicine. Must be BE/BC in Psychiatry, Internal Medicine or General Medicine and eligible for OR Medical License. Location: Pendleton, OR. If interested, mail resume to: Charles E. Wood, Manager Human Resource at the State of Oregon, Eastern Oregon Training Centers, 2575 Westgate, Pendleton, OR 97801.

PENNSYLVANIA

Lehigh Valley Hospital has immediate openings for 3 psychiatrists - Join 14-member psychiatry practice at largest hospital in Pennsylvania, based on admissions. LVH is an 800-bed tertiary care hospital with a freestanding psychiatric facility that has 52 adult and 13 adolescent beds. Psych services include continuum of care from emergency evaluation to intensive care, partial hospital and outpatient follow-up, home-care and skilled nursing facility consultation. Faculty appointment at Penn State/Hershey is offered along with a very competitive salary, excellent benefits that include paid medical malpractice and paid health insurance for self and family.

WE SEEK THE FOLLOWING
Child and Adolescent Psychiatrist
Adult Psychiatrist
Consultative Liaison Psychiatrist

Lehigh Valley Hospital is located 60 miles north of Philadelphia and 90 miles west of NYC in one of the fastest growing areas on the Atlantic Seaboard. For more information, call 610-402-7013. Email CV to Pamela.Adams@lvh.com or fax to 610-402-7014.

SOUTH CENTRAL PENNSYLVANIA — BE/BC Psychiatrist needed to join thriving psychiatry department at Chambersburg Hospital. Position flexible based upon physician preference. Excellent salary with bonus program and outstanding benefits package. Local colleges and universities. Family-oriented lifestyle with very affordable housing and abundant outdoor and cultural activities yet an easy drive to Harrisburg, Baltimore or DC. Email CV to mroyce@summithealth.org Mail CV to Marie Royce, Director of Physician Relations, Summit Health, 112 N. 7th Street, Chambersburg, PA 17201. Call 1-800-758-8835. Fax 717-267-7769. Visit us at www.summithealth.org

Outstanding Private Practice - Seeking BC/BE psychiatrist for successful, established private group practice in southeastern Pennsylvania's Lehigh Valley. Great earning potential, option to teach and do clinical research. In and outpatient responsibilities, weekend call is 1 in 6. Beautiful suburban area 1 hour from Philadelphia, 1.5 hours from NYC. Email CV to Dr. Paul Gross at pkgmd@yahoo.com, Fax to (610) 820-3835.

STATE COLLEGE area: The Meadows Psychiatric Center provides behavioral health services to varied patient populations - inpatient, partial hospitalization & outpatient. Rewarding practice opportunities work with multidisciplinary treatment teams in all services. Very competitive salary, bonus potential & full benefits. Interested candidates contact **Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com**

PSYCHIATRISTS... BE/BC excellent salary, benefits, no billing, upscale working environment, Inpatient or Outpatient. Full time and Part time available. Pennsylvania locations send CV bp@pennhurstmedical.com or fax to 610-524-0952 **Pennhurst Medical Group, P.C.** Some LT also!

RHODE ISLAND

Rhode Island Hospital

Psychiatrist Adult, Inpatient and Outpatient (Mood Disorders)

The Department of Psychiatry, Rhode Island Hospital, a Lifespan partner and Brown University affiliated program, is seeking a psychiatrist to share inpatient and outpatient responsibilities with an established fulltime hospital-based group. The inpatient component involves treating patients with a wide range of acute conditions. The outpatient component involves assessing and treating patients with mood disorders as a member of a specialized multidisciplinary clinical research team. 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

Rhode Island Hospital
Director of Substance Abuse

The Department of Psychiatry, Rhode Island Hospital, Providence, RI, is seeking a full-time Psychiatrist for Director of Substance Abuse of the Division of Adult Psychiatry, Department of Psychiatry, at Rhode Island Hospital. Must be an M.D. and Board certified in General and Addiction Psychiatry. Must have successfully completed training in Adult Psychiatry in an accredited program, with residency served in Adult Psychiatry. Also responsible for education and research, as agreed upon. Candidates should have a record of clinical research or scholarly activity in the area of Substance Abuse. The candidate should also have a record of teaching and supervision of psychiatry residents. Five years post-training in staff capacity in a teaching-training environment experience preferred. Candidate must be eligible for academic appointment at Brown University at the Assistant, Associate, or Full Professor level, Teaching or Research Scholar Track. Demonstrated clinical research productivity is necessary for appointment at the Assistant Professor level. If hired at the Associate Professor level in the Teaching Research Scholar Track, or the Associate Professor level of the Research Scholar Track, the candidate will have to demonstrate a national reputation in his or her field. If hired at the Full Professor level in the Research Scholar Track, candidate must demonstrate international reputation in his or her field. Rhode Island Hospital is a EO/AA employer, and encourages applications from minorities, women, and protected persons. Review of applicants will begin immediately and will continue until the position is filled or the search is closed. Send letter and CV to: Martin B. Keller, M.D., Chairman, Department of Psychiatry and Human Behavior, Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906.

SOUTH CAROLINA

Psychiatry
100% OUTPATIENT PRACTICE
Central South Carolina

An established 120+ bed acute care hospital is actively seeking a General Psychiatrist for a 100% Outpatient Practice Only. The practice will be comprised of both Adult and Pediatric patients.

- Solo opportunity
- Currently no Psychiatrists in the county
- 100% outpatient practice only
- Excellent built-in referral base
- NO Inpatient Psychiatric beds

BE/BC Psychiatrists are encouraged to respond, as an excellent income guarantee is being offered. *Sorry, this is not a Visa opportunity.*

Please contact:
Mary Ellen Scaturro
Boone-Scaturro Associates, Inc.
1-800-749-1884
Fax: 770 475 5055
MES@boone-scaturre.com

TENNESSEE

EAST TENNESSEE STATE UNIVERSITY
JAMES H. QUILLEN COLLEGE OF MEDICINE
DEPARTMENT OF PSYCHIATRY &
BEHAVIORAL SCIENCES

CHILD PSYCHIATRIST

Full-time position available for Child Psychiatrist. 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 area, rated #1 place in North America in cost-of-living, crime rate, climate and health care. Applicants should submit a CV and two letters of reference to Merry N. Miller, M.D., Chair, Department of Psychiatry and Behavioral Sciences, ETSU, Box 70567, Johnson City TN 37614. Telephone inquiries should be made at (423)439-2235 or e-mail at lovedayc@etsu.edu. AA/EOE.

TEXAS

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.

Nacogdoches and Livingston - The Burke Center, a multi-site, JCAHO accredited community mental health center, currently has a full time Adult Psychiatrist position available in Nacogdoches, and a full time Child Psychiatrist (or General Psychiatrist with child experience) position available in Livingston to see a mix of child and adult patients. Physician Assistants and Advanced Nurse Practitioners will be considered as well. Both positions are outpatient only, 40 hour weeks, with no on call. Enjoy a comfortable lifestyle in the beautiful, piney-woods/lakes area of East Texas. Recreational opportunities abound in national forests nearby. Houston less than 2 hours away; Dallas 3 hours; major state university nearby. Excellent benefits and competitive salary. 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.

THE 1ST CHOICE IN
PSYCHIATRIC RECRUITMENT

San Antonio
C & A Psychiatrist for lucrative private practice. For more information contact:
RICHARD SIMPSON
(800) 783-9152 FAX (270) 782-1055
www.fcpspy.com

Psychiatrists for Adult Mental Health Outpatient Programs (Full Time or Part Time for at least 20 hrs.) for a progressive and comprehensive community mental health center in San Antonio, TX. The center is evolving into a national model for the integration of primary and behavioral healthcare. Duties will be performed under the clinical supervision of the Medical Director, include: psychiatric examinations and reviews, prescribing psychotropic medications, and direct face to face service with clients and families. Very competitive salary and benefits, paid malpractice insurance, moving expenses, CME's offered at no charge and admin time to acquire. Applicant should have: current TX Physician's Permit, TX Dept. of Public Safety Controlled Substance Registration Cert., a US Drug Enforcement Agency Substance Registration Certificate (DEA), completed an Accredited Psychiatric Residency Program, Board Certification (or be eligible for Certification) in Psychiatry, and Medicaid/Medicare provider numbers. Must have a current TX driver's license, have auto liability insurance and be insurable under Center's insurance carrier (for malpractice). Apply through the Center for Health Care Services web site, www.chcsbc.org.

AMARILLO: Private Practice group seeking associate/partner. Inpatient & outpatient care with diverse patient population. Community need & great income potential.

MCALLEN: Child Psychiatrists for combination inpatient/outpatient private practice.

SAN ANGELO: BE/BC General or Geriatric Psychiatrist. Must have interest working with diverse patient population of adult - senior adults. Established practice - will offer employment.

Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

VIRGINIA

ADULT or GERIATRIC PSYCHIATRISTS

Catawba Hospital is accepting applications from BE/BC Psychiatrist's, interested in joining an outstanding medical staff in a 110-bed, JCAHO accredited, psychiatric hospital. Academic affiliation exists with the Residency Program of the University of Virginia School of Medicine's Department of Behavioral Medicine & Psychiatry. Teaching medical staff have academic faculty appointment. Experience with acute and chronic adult and/or geriatric psychiatry is desired. Applicants must be licensed or eligible for licensure in Virginia. No call required of attending psychiatrists.

Located just minutes from the metropolitan community of Roanoke, VA, the area provides excellent recreational, educational, and cultural opportunities:

- one of the ten best places to raise a family in the United States (*Parenting magazine*);
- ranked among the least stressful locations in the United States (*Zero Population Growth, Inc.*);
- 7th healthiest place to live (*Kiplinger's Personal Finance Magazine*);
- one of the nation's top 20 cities for quality of life (*recent University of Kentucky study*).

An excellent competitive salary with a generous benefit package, including a bonus for Board Certification, awaits the best candidate.

On grounds housing in a two or three bedroom house or a two bedroom apartment is available on a temporary or permanent basis.

For telephonic/e-mail inquiries contact:

Gary Hiler, HR Programs Mgr.
(540) 375-4368

gary.hiler@catawba.dmhmr.sas.virginia.gov

Submit CV to:

**Human Resource Office
CATAWBA HOSPITAL
P.O. Box 200
Catawba, VA 24070-0200**

**TDD(540)375-4385
FAX(540)375-4359**

EOE M/F/H/V

**PACT Psychiatrist
(Program for Assertive Community Treatment)**

New River Valley Community Services in Blacksburg, VA is seeking an outstanding individual to join our growing community mental health services team. Live in a dynamic university city in the beautiful Blue Ridge Mountains. Work full or part-time with a multi-disciplinary team in a 100% outpatient CARF accredited program. The successful candidate will provide psychopharmacology services, crisis intervention, and consultation to PACT Team clients. Virginia license is required. Position is open until filled. Please submit VA state application and CV to New River Valley Community Services, Attn: Human Resources Dept., 700 University City Blvd., Blacksburg, VA 24060, or fax to 540-961-8466. State applications are available on our website at www.nrvcs.org. For more information call 540-961-8421. EOE

**Deadlines:
Mar 3 issue - Feb 17
Mar 17 issue - Mar 3**

CONSULTATION/LIAISON PSYCHIATRY - PSYCHOSOMATIC MEDICINE
FACULTY POSITION:

VA Commonwealth University at the Medical College of Virginia campus recruiting faculty position in large, exciting, well-established C/L Division in major academic medical center (750 bed university hospital). Clinical, liaison, and research opportunities abound in primary care, organ transplantation, oncology, HIV program, etc. Help train and supervise senior residents and our nationally recruited C/L fellows. We are seeking BE/BC candidates with demonstrated potential as clinicians, teachers and scholars. C/L fellowship training preferred. Community offers excellent location and lifestyle. Please call or write James Levenson, MD, Chair, Div. of C/L Psychiatry, VCU, Box 980268, Richmond, VA 23298 (804-828-0763). VCU is an Equal Opportunity/Affirmative Action employer. Women, minorities, persons with disabilities are encouraged to apply.

PSYCHIATRIST: Roanoke/Salem: Board Certified/Board Eligible in psychiatry. Position is predominately outpatient telemental health services to rural areas via videoconferencing; some outpatient mental health clinic services; and some inpatient PTSD. Excellent salary and benefits, including vacation and sick leave.

Active Psychiatry Residency Program and medical student training affiliated with University of Virginia School of Medicine, and the Via College of Osteopathic Medicine. Facility appointment and research opportunities. No overhead or malpractice premium. Licensed in any state. All American City with metro population 250,000, low cost of living, numerous activities, rated top 10 best places to raise a family by Parenting Magazine. Excellent schools. Contact Delmar Short, MD, Chief, Mental Health Service Line, Veterans Affairs Medical Center, Salem, VA 24153, or call (540) 982-2463, ext. 2515. EOE.

WASHINGTON

BC/BE PSYCHIATRIST

Seeking a BC/BE Psychiatrist with an interest in geriatrics (*fellowship training a plus*), to join a *collaborative practice affiliated with a comprehensive medical center. Mostly outpatient with some inpatient. Competitive base salary guarantee, good benefits plus potential additional compensation for productivity.* Located just 20 minutes from downtown Seattle and the shores of Puget Sound. This area is consistently rated as one of the best places to live. For more information send CV to Gail Mumma, gmumma@HighlineMedical.org or Fax to 206-242-4625 or Call: (206)431-0785

WEST VIRGINIA

200K in Medical School Loans Paid Off! Relaxed working environment with excellent clinical support team. Facility needs a Child Psychiatrist due to expansion. Work a mix of inpatient & outpatient. 1 in 6 call. **Contact Karen Brennan at 800-575-2880 x307. E-mail CV to kbrennan@medsourceconsultants.com.**

WISCONSIN

FOND DU LAC COUNTY
DEPARTMENT OF COMMUNITY PROGRAMS

PSYCHIATRIST

Looking for B/E or B/C Psychiatrist to join 3 other Psychiatrist at the Fond du Lac County Department of Community Programs. Medical, model, flexible hours, general medical, retirement and vacation benefits. Opportunities to work outside hours.

Contact:
JR Musunuru
459 East First
Fond du Lac, WI 54935
920-929-3502

AN EQUAL OPPORTUNITY EMPLOYER

CHILD-ADOLESCENT/ADULT PSYCHIATRIST -
LA CROSSE, WI

Board certified/eligible child-adolescent psychiatrist needed to join the Psychiatry Department/Behavioral Health Program at Franciscan Skemp Healthcare-Mayo Health System in La Crosse, WI. At least 50% of the position will be devoted to outpatient child-adolescent psychiatry patients. Remainder of the practice will be a mix of inpatient and outpatient adult psychiatry. Position will include sharing in the general Psychiatry call schedule with five adult psychiatrists. Competitive salary & comprehensive benefits. Franciscan Skemp Healthcare, part of Mayo Health System, is a multispecialty group/healthcare network with 200+ providers, serving a primary care population of 240,000 in WI, MN & IA. La Crosse, city of 52,000 with metro area of 120,000, located on the scenic Upper Mississippi River, offers an ideal family environment with unlimited, four-season recreational & cultural activities. Excellent schools, including two universities and technical college.

Contact Bonnie Guenther or Mike Hesch, Physician Services
Franciscan Skemp Healthcare-Mayo Health System
700 West Avenue South, La Crosse, WI 54601
800-269-1986 / fax 608-791-9898
guenther.bonnie@mayo.edu /
hesch.michael@mayo.edu
www.franciscanskemp.org

SPECTACULAR OPPORTUNITY
FOR INPATIENT MEDICAL DIRECTOR

Gundersen Lutheran, a multidisciplinary 400 member group practice in La Crosse, WI, is seeking an experienced BC/BE Psychiatrist to perform the functions of the Medical Director of an existing Inpatient Unit and to develop a day hospital program.

This candidate will join 9 general and 4 child psychiatrists, 7 psychologists and more than 40 therapists in providing outpatient/inpatient care for a broad range of clinical disorders.

Psychiatric outpatient care is offered on our main campus and at several sites in the Gundersen Lutheran healthcare system. Inpatient care is provided in a 27-bed unit, which is adjacent to the medical center. Call will be 1:12.

Located in a city of 52,000 with a metropolitan area of 120,000 and a service delivery area of more than 500,000, Gundersen Lutheran provides the opportunity to practice metropolitan-scale medicine in a context of small town character and comforts. Nationally recognized schools, three universities, safe neighborhoods, affordable housing and extensive recreational and cultural activities make La Crosse, on the Mississippi River, an outstanding place to live and work. Our compensation package, pension plan and continuing education opportunities are exceptional.

Interested candidates are invited to call Gale Kreibich, Medical Staff Development, Gundersen Lutheran, at 1-800-362-9567, ext. 56863, 1900 South Ave., La Crosse, WI, 54601, or e-mail grkreibi@gundluth.org

We support a safe, healthy and drug-free work environment through background checks and controlled substance screening.
EOE/AA

WYOMING

CASPER - General or Child Psychiatrist for combination practice of outpatient, partial & inpatient services. Multidisciplinary treatment team support. Great compensation plan offering salary, benefits & bonus potential. Open to J1 candidates. **Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com**

**To advertise contact
Joel Nepomuceno
703-907-7330,
classads@psych.org**

Fellowships

Clinical Psychopharmacology Research Fellowship

The Bipolar Disorder Research Program at Emory University is seeking a PGY-5 clinical research fellow. Fellowship provides clinical and research experience, specializing in bipolar disorder, with extensive individual supervision by Dr. Nassir Ghaemi. Fellows will gain expertise in diagnosing and treating bipolar disorder, and in functioning as investigators in clinical trials. Fellows will learn statistical method methods, and write research papers. Ideal for those who want more clinical expertise and for those interested in an academic psychiatry career. Competitive salary with full benefits package. Send CV and letters of reference to: Dr. Nassir Ghaemi, 1365 Clifton Rd NE., Bldg B, Suite 6100, Atlanta, GA 30322, nghaemi@emory.edu

PUBLIC PSYCHIATRY FELLOWSHIP CMHC - YALE

The Connecticut Mental Health Center - Yale University School of Medicine is offering a one-year Fellowship in Public Psychiatry beginning July 2006. CMHC is a major site for training, research and clinical service within the Yale and State systems. As a state-funded, academic, urban mental health center it provides a unique setting for psychiatrists to obtain advanced training as they pursue careers as leaders in the field. Fellows will spend 50% time in seminars, supervision, and administrative/policy meetings of CMHC and the CT Dept. of Mental Health and Addiction Services; and 50% effort providing direct clinical service and/or consultation within public mental health settings in New Haven. Candidates must be eligible for board certification and CT licensure. Minority applicants are encouraged to apply. For further information contact Jeanne Steiner, D.O. Medical Director, CMHC - Yale Univ., 34 Park St New Haven, CT 06519 or Jeanne.Steiner@yale.edu.

Vanderbilt University Medical Center Addiction Psychiatry Fellowship

The Psychiatry Department at Vanderbilt University Medical Center is seeking applicants for our PGY-5 Addiction Psychiatry Fellowship Program starting July 1st, 2006. Fellows have an opportunity to develop expertise in diagnosis and management of addiction in inpatient and outpatient settings, including a general hospital consultative service. Teaching goals provide qualification for subspecialty certification and development of specific clinical and/or research interest areas. An opportunity exists to extend the fellowship by up to 2 years by participating in a training program in translational addiction research in neuroimaging, pharmacotherapy, genomics, and bioinformatics. Contact Peter R. Martin, M.D., Director, 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

Forensic Psychiatry Fellowship

ACGME-accredited fellowship program (PGY-5) sponsored by the SUNY Upstate Medical University in Syracuse, NY. One position is available beginning July 1, 2006. This is a one-year program with training at multiple clinical sites in the Medical University and at Central New York Psychiatric Center; the JCAHO accredited psychiatric hospital of the New York State prison system. There is a substantial component at the Syracuse University College of Law. Dedicated research support is available. Candidates must be eligible for licensing or limited permit in New York State. For information, please contact Jonathan Kaplan, M.D., SUNY-Upstate Medical University Department of Psychiatry, 750 E. Adams Street, Syracuse, NY 13210, 315-464-3104, fax 315-464-3141, e-mail address cn00025@omh.state.ny.us.

PSYCHODYNAMIC PSYCHOTHERAPY PROGRAMS. Two year training includes coursework, case conferences, and supervision with experienced analysts. **NEW CHILD-ADOLESCENT PROGRAM.** The New York Psychoanalytic Institute, 247 East 82nd Street, NY NY 10028, (212) 879-6900 www.psychoanalysis.org

PSYCHOSOMATIC MEDICINE FELLOWSHIP - VIRGINIA COMMONWEALTH UNIVERSITY

One year exciting, well established, fellowship program, one of the first approved by the ACGME, in a 750-bed university hospital, accepting applications for July 1, 2006. Advanced training offered to psychiatrists who have completed residency. Please write or call: James L. Levenson, M.D., Chairman, C-L Division, VCU Health System, Department of Psychiatry, Box 980268, Richmond, VA. 23298-0268; jlevens@vcu.edu (804) 828-0762 or Yaacov R. Pushkin, M.D.; ypushkin@vcu.edu

Psychosomatic Medicine Fellowship

Harborview Medical Center (HMC) at University of Washington School of Medicine is seeking a one-year Psychosomatic Medicine Fellowship applicant entering as a PGY-5 after completion of a General Psychiatry Residency Program. Our mission is to provide excellent, multidisciplinary subspecialty training in Consultation-Liaison Psychiatry by integrating broad clinical experiences with: comprehensive didactic training; close clinical supervision; and scholarly time which allows a fellow to pursue an area of interest. We also intend to provide leadership and organizational skills together with solid clinical teaching in order to develop qualified, competent, compassionate and ethical academic and community-based clinical leaders in the area of Psychosomatic Medicine.

The Department of Psychiatry at the University of Washington is a major research, training and clinical care leader in Consultation-Liaison Psychiatry. The HMC Consultation Service, which consists of psychiatrists, residents, PhD psychologists, social workers and clinical nurse specialists sees approximately 60 to 80 patients each month and provides an excellent interdisciplinary training setting for a PGY-5 fellow.

As a county hospital and part of the University of Washington network of hospitals serving 5 states (Washington, Wyoming, Alaska, Montana, and Idaho), HMC has a diverse population in terms of age, ethnic/cultural and socioeconomic mix. HMC is the only Level I adult and pediatric trauma center and regional burn center serving 4 states and has Centers for Emphasis in the areas of: neurosciences; trauma; burns; reconstruction and rehabilitation; the mentally ill, chemically dependent and medically vulnerable; and AIDS/HIV/STD treatment.

For more information please contact:

Melissa H. Hanbey
Administrative Assistant,
HMC Consultation-Liaison Psychiatry
Department of Psychiatry and
Behavioral Sciences
University of Washington School of Medicine
Harborview Medical Center Box 359910
325 9th Avenue
Seattle, Washington 98104-2499
206-731-5923
206-731-3455

Research Fellowships for Young Psychiatrists and Advanced Residents: The Yale University Department of Psychiatry and the Connecticut Mental Health Center are pleased to offer NIMH funded fellowships that provide two years of research support and training for psychiatrists who have recently completed residency or are in their PGY-4 training year. Fellows will choose a mentor from among over 20 Yale faculty researchers, and develop and carry out their own research project. A formal didactic program provides seminars on research design, statistics and review of the current evidence base regarding key clinical questions. Program focus is on adding to the evidence base to guide treatment of people with chronic and recurrent psychiatric illnesses, especially during the 95% of their lives when they are not in periods of acute symptom exacerbation. Fellowships are designed for psychiatrists interested in academic careers in clinical, psychosocial, epidemiological or translational neuroscience research. To apply send CV, statement of research interests and two letters of recommendation to: Bruce E. Wexler, MD, Professor of Psychiatry, Yale University School of Medicine, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519, or bruce.wexler@yale.edu.

INFANT PSYCHIATRY FELLOWSHIP. The Section of Child and Adolescent Psychiatry at Tulane University Health Sciences Center is seeking a full-time Fellow in Infant Psychiatry. This one or two year fellowship includes clinical and research experiences with the multidisciplinary Infant Mental Health group at Tulane. Completion of a fellowship in Child and Adolescent Psychiatry preferred. Faculty appointment at the Instructor level is possible. Applications will be accepted until a suitable qualified candidate is found. Applicants should send letter of interest, updated CV and list references to Charles Zeanah, MD, Vice Chair and Director of Child and Adolescent Psychiatry, 1440 Canal Street TB52, New Orleans, LA 70112. Interested eligible applicants may obtain further information regarding this position by contacting Dr. Zeanah at 504-988-5402 or czeanah@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

ANXIETY & FUNCTIONAL NEUROIMAGING. The University of California San Diego (UCSD) in La Jolla, CA, is seeking applicants for a PGY-5 Anxiety & Functional Neuroimaging Fellowship starting July 1, 2006. Fellows have an opportunity to develop expertise in anxiety disorders outcomes research and functional magnetic resonance imaging (fMRI) task design and analysis. Dual mentorship by Martin Paulus MD and Murray B. Stein MD, MPH. Competitive salary. Two-year commitment preferred. Applicants must be board-eligible in psychiatry and eligible for California medical licensure. Interested candidates should send a CV and statement of interest by e-mail to Dr. Stein (mstein@ucsd.edu) and/or Dr. Paulus (mpaulus@ucsd.edu).

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The Department of Psychiatry and Behavioral Science at Stony Brook University announces the availability of an innovative ACGME-accredited geriatric psychiatry fellowship position starting July 2006 with the option for special emphasis on consultation-liaison psychiatry. With eight board-certified geriatric psychiatrists on the faculty, the geriatric psychiatry fellow will have dedicated experiences in geriatric inpatient, long-term care, outpatient, ECT, and consultation-liaison psychiatry at both the University Hospital as well as several community settings. Located within the new Stony Brook Division of Medical and Geriatric Psychiatry, fellows in geriatric psychiatry will participate in a clinical milieu emphasizing understanding the psychiatric aspects of medical conditions along with the medical aspects of psychiatric conditions. Fellows have the unusual opportunity through collaborative consultation-liaison work to develop added clinical expertise and professional relationship skills working closely with trainees and faculty in geriatric medicine, neurology, and family medicine. To apply for the position, send by U.S. mail, fax (631) 444-7534, or e-mail steven.cole@stonybrook.edu, your letter of interest, your CV, and three letters of reference to Steven Cole, M.D., Head, Division of Medical and Geriatric Psychiatry, Health Sciences Center, 10th Floor, Room 042, Stony Brook NY 11794-8101. AA/EOE.

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BRIEF SUMMARY. See package insert for full prescribing information.

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

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS — *QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). ***QT Prolongation and Risk of Sudden Death:*** GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see **CONTRAINDICATIONS**, and see *Drug Interactions* under **PRECAUTIONS**). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. ***Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. ***PRECAUTIONS—General:*** In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. ***Orthostatic Hypotension:*** GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1 -adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). ***Seizures:*** In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. ***Dysphagia:*** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also Boxed WARNING, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**). ***Hyperprolactinemia:*** As with other drugs that antagonize dopamine D₂ receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. ***Potential for Cognitive and Motor Impairment:*** Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. ***Priapism:*** One case of priapism was reported in the premarketing database. ***Body Temperature Regulation:*** Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. ***Suicide:*** The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. ***Use in Patients with Concomitant Illness:*** Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and ***Orthostatic Hypotension*** in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the

information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. ***Effect of Other Drugs on GEODON:*** ***Carbamazepine,*** 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. ***Ketoconazole,*** a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. ***Cimetidine,*** 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. ***Effect of GEODON on Other Drugs:*** In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with ***lithium*** 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrophan. There was no statistically significant change in the urinary dextromethorphan/dextrophan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see ***Hyperprolactinemia***). ***Mutagenesis:*** There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. ***Impairment of Fertility:*** GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m² basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m² basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. ***ADVERSE REACTIONS—Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: ***Body as a Whole***—asthenia, accidental injury, chest pain. ***Cardiovascular***—tachycardia. ***Digestive***—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. ***Nervous***—extrapyramidal symptoms, somnolence, akathisia, dizziness. ***Respiratory***—respiratory tract infection, rhinitis, cough increased. ***Skin and Appendages***—rash, fungal dermatitis. ***Special Senses***—abnormal vision. Bipolar Mania: ***Body as a Whole***—headache, asthenia, accidental injury. ***Cardiovascular***—hypertension. ***Digestive***—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. ***Musculoskeletal***—myalgia. ***Nervous***—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. ***Respiratory***—pharyngitis, dyspnea. ***Skin and Appendages***—fungal dermatitis. ***Special Senses***—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonía, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: ***Body as a Whole***—*Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. ***Cardiovascular System***—*Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. ***Digestive System***—*Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. ***Endocrine***—*Rare:* hypothyroidism, hyperthyroidism, thyroiditis. ***Hemic and Lymphatic System***—*Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. ***Metabolic and Nutritional Disorders***—*Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. ***Musculoskeletal System***—*Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. ***Nervous System***—*Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonía, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. ***Respiratory System***—*Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. ***Skin and Appendages***—*Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. ***Special Senses***—*Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. ***Urogenital System***—*Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. ***Adverse Finding Observed in Trials of Intramuscular GEODON:*** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). ***Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:*** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. ***Body as a Whole***—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. ***Cardiovascular***—postural hypotension, hypertension, bradycardia, vasodilation. ***Digestive***—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. ***Nervous***—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonía, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. ***Respiratory***—rhinitis. ***Skin and Appendages***—furunculosis, sweating. ***Urogenital***—dysmenorrhea, priapism. ***DRUG ABUSE AND DEPENDENCE—Controlled Substance Class:*** GEODON is not a controlled substance. ***OVERDOSAGE***—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/75).

References: 1. IMS Health, July 2005. 2. Data on file. Pfizer Inc., New York, NY. 3. Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M, and the Ziprasidone Study Group. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:491-505. 4. Potkin SG, Keck P, Giller E, Ice K, Warrington L, Mandel FS. Ziprasidone in bipolar mania: efficacy across patient subgroups. Presented at: American Psychiatric Association Annual Meeting; May 1-6, 2004; New York, NY.

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GEODON is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder, with or without psychotic symptoms



Steady state of mind™

Effective control of symptoms

*In schizophrenia*³

- Irritability
- Suspiciousness
- Disorganized thoughts
- Agitation
- Hallucinations

*In acute mixed episodes of bipolar disorder*⁴

- Irritability
- Psychomotor agitation
- Depressive symptoms

*In acute manic episodes of bipolar disorder*⁴

- Grandiosity
- Elevated mood
- Flight of ideas

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

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

In short-term schizophrenia trials, the most commonly observed adverse events associated with GEODON at an incidence of ≥5% and at least twice the rate of placebo were somnolence and respiratory tract infection. The most common adverse events associated with GEODON in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.

GEODON®
Oral Capsules (ziprasidone HCl)
and Injection (ziprasidone mesylate)
Power to restore potential™

Please see brief summary of prescribing information on next page.

