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American
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Association

PSYCHIATRIC NEWS

inside

AP Photo/Haraz Ghanbari

Above is a detainee interrogation room in Camp V at Guantanamo Bay Naval Base, Cuba. The photograph, taken in June 2005, was reviewed by the U.S. military.

AMA Interrogation Policy Similar to APA's Position

The counsel of APA leaders in the days before the policy was approved was instrumental in moving the AMA's position to be more in line with APA's.

BY MARK MORAN

Physicians cannot ethically conduct or directly participate in the interrogation of individual detainees, according to an AMA report that closely mirrors an APA position statement on the issue approved in May.

A report by the AMA's Council on Ethical and Judicial Affairs (CEJA), which was laboriously crafted and recrafted until just days before its approval by the AMA House of Delegates last month, states that physicians must not participate in interrogations; to do so "undermines the physician's role as healer and thereby erodes trust in the individual physician-interrogator and in the medical profession."

The vote took place at the annual meeting of the AMA House of Delegates in Chicago.

The wording of the CEJA report varies somewhat from APA's statement, which says that "no psychiatrist should participate directly in the interrogation of persons held in custody by military or civilian investigative or law enforcement authorities, whether in the United States or elsewhere" *(Psychiatric News*, June 16).

The APA statement goes on to delineate specific activities that constitute "direct participation" and are thus precluded. But in the AMA report, for instance, one of the five concluding recommendations reads: "Physicians may participate in developing effective interrogation strategies for general training purposes. These strategies must not threaten or cause physical injury or mental suffering and must be humane and respect the rights of individuals" (see box on page 4).

"Because it is justifiable for physicians to serve in roles that serve the public interest, the AMA policy permits physicians to develop general interrogation strategies that are not coercive, but are humane and respect the rights of individuals," said psychiatrist Priscilla Ray, M.D., who is chair of CEJA, at a press conference after the AMA meeting.

She said an example of such strategies might include "rapport building" between interrogator and detainee. When asked if the language could be interpreted to mean that physicians could participate in developing rapport building or other strategies for specific individual detainees—as is prohibited by the APA statement—Ray said it should not be. And she reiterated that the CEJA report was closely in line with APA's position statement.

The report went through numerous iterations and was ultimately endorsed by APA, the American Academy of Psychiatry and the Law, and the American Academy of Child and Adolescent Psychiatry (AACAP). It was also supported by military physicians who spoke at the meeting.

"I really think this is a very strong statement that closely corresponds to and reinforces the APA position that physicians, including psychiatrists, should not be participating in any way in the interrogation

please see ***Interrogation*** *on page 4*

Clinicians Urged To Better Monitor Drug-Related Side Effects

Psychiatrists have more work to do to manage complex medical comorbidities commonly seen in patients with serious mental illness.

BY JIM ROSACK

Patients with schizophrenia and bipolar disorder lose as much as 20 years off their average life expectancy compared with similar individuals in the general population without serious mental illness. According to a report from the Centers for Disease Control and Prevention released in April, the leading cause of death contributing to that shortened lifespan is not the patients' mental illness, but rather something largely preventable: cardiovascular disease.

These statistics and others were cited by an expert panel as indirect evidence that the field of psychiatry is earning a failing grade when it comes to managing medical comorbidity in patients with schizophrenia and bipolar disorder—especially those patients who are taking second-generation antipsychotics (SGAs). This class of drugs is generally considered to be linked closely with increased risk of metabolic syndrome, a leading risk factor for cardiovascular disease.

The panel of experts, chaired by John Newcomer, M.D., a professor of psychiatry, psychology, and medicine at Washington University School of Medicine in St. Louis, held a press briefing at APA's 2006 annual meeting in May to issue the "Call to Action: Raising the Standard of Care in the Treatment of Schizophrenia and Bipolar Disorder."

"The good news about this is that we know a lot about the prevention of cardiovascular disease," said Newcomer, who also chairs APA's Subcommittee on Antipsychotics and Metabolic Risk. "The bad news is that the risk factors—the well-established risk factors for cardiovascular disease in this population—are generally occurring at very high levels. These risk factors are not being monitored and are not being attended to in this population."

Newcomer's point was supported by a series of nearly 50 new research presentations on the issue of metabolic syndrome and serious mental illness during the annual meeting. Among those presentations was an analysis of baseline data from the National Institute of Mental Health's CATIE trial (Clinical Antipsychotic Tri-

please see ***Side Effects*** *on page 34*

Contents

Features

Volume 41
Number 13
July 7, 2006

Departments

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PSYCHIATRIC NEWS

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Treatment Choices Complicated By Repeated Failures

Proving that the third time isn't always the charm, STAR*D's level 3 results show that successive antidepressant monotherapy may not be ideal.

BY JIM ROSACK

To some, the results from the third phase of the National Institute of Mental Health's (NIMH) STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial may prove to be disappointing when considered in isolation.

On the whole, however, clinicians as well as patients may view results of all three phases of the large effectiveness trial as not only instructive, but also encouraging.

Results from STAR*D's level 3 were reported in the July *American Journal of Psychiatry* by Maurizio Fava, M.D., a professor of psychiatry at Harvard Medical School and associate chief of psychiatry for clinical research at Massachusetts General Hospital, along with the other members of the STAR*D study team.

The trial was designed to answer real-world questions faced by clinicians and their patients regarding subsequent treatment choices following an antidepressant medication's failure to promote remission.

"What we now see is that if you have failed two consecutive antidepressant treatment trials," Fava told *Psychiatric News*, "switching to another antidepressant may not be as efficacious as initially thought." That conclusion, he added, "goes against the traditional thought that successive monotherapy trials of one antidepressant after another would be the best approach to take with resistant depression."

When a patient does not respond to a particular agent, Fava continued, "clinicians typically just try a drug from a different class. If that doesn't work, they just keep switching and switching until they find something that works."

Now, however, based on the level 3 results from STAR*D, that switching strategy "may not be the best approach after all."

Multilevel Approach Used

In level 1 of the protocol, more than 3,000 patients began treatment with citalopram (Celexa) at doses up to 60 mg a day. Of those patients, 27.5 percent met criteria for remission by the end of 14 weeks (with remission defined as a score of less than or equal to 7 on the Hamilton Depression Rating Scale) (*Psychiatric News*, January 20).

Level 2 of STAR*D included patients from level 1 who did not achieve remission on citalopram or who could not tolerate the drug's side effects. Level 2 participants were presented with two paths in which they could continue in the study: through either a switch protocol or an augmentation protocol.

Patients were asked to accept or decline the following possibilities: to switch from citalopram to sustained-release bupropion, sertraline, or extended-release venlafaxine or to continue taking citalopram and augment it with either bupropion, buspirone, or cognitive-behavioral therapy.

Then, based on their choice, each participant was randomly assigned to one of their "acceptable" protocols—a process termed "equipoise randomization."

In level 2, remission rates ranged from 18 percent to 25 percent for those who switched to a different medication, and were around 30 percent for those who continued citalopram and augmented with either bupropion or buspirone (*Psychiatric News*, April 21).

Level 3 included patients who did not remit during level 2 treatment or were unable to tolerate the regimen to which they were assigned. Again, patients were allowed to accept or decline randomization into a switch strategy or an augmentation strategy. On the basis of those preferences, participants were again randomly assigned using equipoise randomization.

In level 3, 113 patients were randomly assigned to switch from their level 2 medication to mirtazapine (Remeron) at doses up to 60 mg a day for up to 14 weeks of treatment. In addition, 121 patients from level 2 were randomly assigned to switch to nortriptyline (Pamelor) at doses up to 200 mg a day.

(The results reported here are from this level 3 switch protocol. A future report will describe level 3 results with the augmentation protocol.)

Remission Rates Disappointing

Of patients who switched from their level 2 antidepressant to mirtazapine, 14 of 113 (12.3 percent) achieved remission by the end of 14 weeks. Of those who switched to nortriptyline, 24 out of 121 (19.8 percent) met criteria for remission. Although there was a numerical difference in rates of remission between the two groups, the difference was not statistically significant.

The researchers also found no statistically significant difference in the response rates to mirtazapine and nortriptyline. Neither time to remission nor time to response differed between the two medication groups. For those who did achieve remission on mirtazapine, the mean time to remission was 5.7 weeks compared with 6.3 weeks for those on nortriptyline.

Overall, no significant differences were found in tolerability/adverse events between the two antidepressants.

Completion rates for level 3 also did not significantly differ between the mirtazapine (33.3 percent) and nortriptyline (30.6 percent) groups. Of note, four trial participants were hospitalized for suicidal ide-

please see ***Treatment Choices*** *on page 36*

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Reflections on Hurricanes Katrina and Rita

BY PEDRO RUIZ, M.D.

Almost a year has passed since hurricanes Katrina and Rita crippled New Orleans and nearby areas along the Gulf Coast, but the impact of these natural disasters is still fresh on our minds.

Several other natural and manmade disasters have affected this country in the past—for instance, the hurricane that devastated Galveston County in 1900 and the terrorist attacks in New York City and Washington, D.C., on September 11, 2001—but the sociopolitical and historic impact of a disaster on the scale of these hurricanes has never been observed before in the United States.

Recently, I had the opportunity to visit New Orleans to attend APA's Area 5 Council meeting. While there, I toured parts of the city affected by Katrina, including the area where Louisiana State University Medical Center and Tulane University Medical Center are located. I saw a children's clinic building totally decimated and a psychotherapy clinic building near Canal Street almost destroyed; I saw houses and other buildings that had been ruined or leveled. Incredibly, people were still living in this almost uninhabitable part of New Orleans. Most of them were African American and probably did not have many assets to fall back on. Frustration, despair, and even anger bubbled inside of me as I watched them. How could the federal government have turned its back on this struggling community?

What is the problem with being African American in this country? How can an African-American community in the strongest nation on earth be treated so inhumanely? I have never understood the intense discrimination that African Americans are still enduring in the world's most advanced and prosperous country. I grew up in rural Cuba among descendents of slaves brought to Cuba from West Africa, and I attended medical school in Paris with many African peers. Over the years, I have worked and developed strong friendships with many African-American colleagues, as well as with African Americans in many other walks of life. While I have brown skin, I have never been treated this way, and African Americans deserve the same treatment given me and my Caucasian friends and coworkers.

As I reflect on the disgraceful way in which the U.S. government has responded to the needs of Katrina and Rita victims, I feel shame for the policymakers who could and should have done so much more for these poor and disadvantaged American citizens but instead ignored them. I am positive that New Orleans will come back, but the African-American influence that gave the city its unique character will never be the same.

While our federal government failed miserably in its responsibilities to the people of New Orleans, American psychiatry did not. My respect and sincere thanks go to the many psychiatrists who volunteered their time and expertise to address the psychosocial and psychopharmacological needs of hurricane victims. This group included not only local psychiatrists—many of whom were hurricane victims themselves—but also psychiatrists from throughout the United States. APA's district branches in the regions impacted by the hurricanes also rose to the occasion: Louisiana Psychiatric Medical Association, Mississippi Psychiatric Association, Texas Society of Psychiatric Physicians, Alabama Psychiatric Society, and Florida Psychiatric Society. At the national level, APA's Office of International Activities and the Committee on Psychiatric Dimensions of Disasters provided excellent leadership and designed a series of very effective interventions to address victims' mental health needs. Psychiatry residents and medical students from Louisiana State University and Tulane University also assisted.

What happened—or more accurately didn't happen—in the wake of hurricanes Katrina and Rita is a reminder to Americans, and the rest of the world as well, that the U.S. government at times shows two faces: one for the rich and wealthy and another for the poor and disadvantaged, most of whom belong to the ethnic minority groups who reside in this country. ■

APA Invites Nominations for MIT Position

The APA Nominating Committee continues to accept recommendations for candidates for the member-in-training trustee-elect (MITTE) position for APA's 2007 election.

The resident elected in the 2007 election will serve as MITTE (without vote) from May 2007 to May 2008, and as MITT (member-in-training trustee, with vote) from May 2008 to May 2009.

Residents must have been accepted as APA members in both APA and their district branch, be in their PGY-2 or PGY-3 year in the summer of 2006, and have written permission from their training directors to fulfill the two-year commitment as MITTE and MITT as a part of their training.

Information about the MITTE/MITT positions, eligibility criteria, and submission forms are posted on APA's Web site at <www.psych.org/edu/res_fellows/rf/mitte.cfm>.

All materials must be received by August 4.

More information on the MITTE nominating process is available by contacting Carol Lewis by e-mail at clewis@psych.org or by phone at (703) 907-8527. ■

Military Looks to Psychologists For Advice on Interrogations

The Department of Defense decides that psychiatrists will have little or no role to play in detainee interrogations, and it will instead turn to psychologists for help in eliciting information from detainees.

BY KEN HAUSMAN

Pentagon officials and APA leaders appear to be on the same page, or at least a nearby one, when it comes to psychiatrists' participation in detainee interrogations.

On June 6 Department of Defense officials announced that from here on they would seek the help of psychologists, but not psychiatrists, when they want advice on how to elicit information from detainees in Guantanamo Bay, Cuba, and other places where prisoner interrogations take place. The policy distinguishes between physicians and "behavioral consultants," whom it describes as primarily psychologists, saying that psychologists traditionally fulfill the type of role the Pentagon envisions for its "behavioral consultants" during interrogations.

This follows by a just a few weeks a decision by the APA Board of Trustees and Assembly to adopt a position statement prohibiting the participation of psychiatrists in detainee interrogations (*Psychiatric News,* June 16). The statement read, "No psychiatrist should participate directly in the interrogation of persons held in custody by military or civilian investigative or law-enforcement authorities. . . . [including] being present in the interrogation room, asking or suggesting questions, or advising authorities on the use of specific techniques of interrogation."

The American Psychological Association has taken a more permissive approach to detainee interrogations that allows participation beyond that sanctioned by APA, based on the principle that preventing harm to the public is an important consideration along with the obligation to do no harm. The position of the psychological association is that its members can advise interrogators on questions and techniques and develop interrogation strategies as long as doing so does "not threaten or cause physical injury or mental suffering." Psychologists are barred from direct participation and from assisting in interrogations that use coercion.

Assistant Secretary of Defense for Health Affairs William Winkenwerder Jr. indicated at a June 7 press conference that the American Psychological Association's stance is closer to the military's than is APA's, and this difference contributed to the Pentagon's decision to use psychologists as advisors during interrogations.

The Pentagon's June announcement clarifies what it sees as the roles for behavioral health personnel in interrogations and describes acceptable and unacceptable actions on the part of these personnel. It points out that military psychiatrists are not "ordinarily" to be used as consultants to interrogators, "but may be so assigned" in limited circumstances when psychologists are unavailable to advise interrogators.

On June 12 the *New York Times* weighed in on the issue of detainee treatment, with an editorial condemning some of the controversial practices that the military has allowed during interrogations. The editorial followed the suicide of three prisoners at Guantanamo. The editorial stated that the "only role for psychiatrists at [Guantanamo] seems to be to help prepare prisoners for interrogation" and suggested that psychiatrists and other medical personnel also take part in forced feedings and other inhumane practices in detention facilities.

Steven Sharfstein, M.D., immediate past president of APA, sent a letter to the newspaper taking issue with its conclusion regarding psychiatrists. Moreover, Sharfstein explained that after touring the Guantanamo Bay detention facility at the invitation of the Pentagon last October, it was clear that psychiatrists were providing patient care.

"Since then," he wrote, " the American Psychiatric Association has passed a clear, strong statement barring psychiatrists from participating in interrogations. It is our position that the only role for psychiatrists is that of healer, including psychiatrists who are in the military."

At its June meeting, the AMA House of Delegates debated the issue, arriving at much the same conclusion as did APA (see article on page 1). ■

Interrogation

continued from page 1

of individual detainees," said APA immediate past President Steven Sharfstein, M.D. He visited Guantanamo Bay in October 2005 to urge U.S. military and defense officials to exclude psychiatrists from participating in any way in the interrogation of detainees.

Paul Appelbaum, M.D., chair of APA's Council on Psychiatry and Law, agreed. "Although there are small differences between the APA position statement and the AMA's position, there is agreement about the most important issues," he told *Psychiatric News*. "Physicians do not belong in the interrogation room, and they ought not to be involved in planning the interrogations of particular suspects."

'Unity of Medicine' Stressed

Both John McIntyre, M.D., chair of the Section Council on Psychiatry, and David Fassler, M.D., AACAP's delegate and author of the original resolution calling for the CEJA report, emphasized the unity of medicine around the issue of physician participation in interrogation.

"I'm glad to see that organized medicine will now be able to speak with one voice on this issue," Fassler said.

Previous iterations of the AMA report—especially the passage regarding the development of interrogation strategies—were much less proscriptive than the final version, and it was largely the counsel of APA leaders that was instrumental in moving the AMA's position to one that was more in line with APA's.

In a letter dated June 8, Appelbaum wrote on behalf of APA to members of CEJA to address concerns about the wording of the passage as it stood at the time, just one day prior to the opening of the AMA meeting. It read: "Physicians may participate in developing effective interrogation strategies that are not coercive but are humane and respect the rights of individuals."

"This language appeared to allow physicians to consult on the planning of interrogations of particular detainees," Appelbaum told *Psychiatric News*. "In contrast, APA's statement explicitly rules out advising authorities on the use of specific techniques of interrogation with particular detainees."

The final wording in the CEJA report was changed to emphasize that the development of strategies be for "general training purposes."

"Although not quite as explicit as APA's statement, the new language appears to clarify that legitimate involvement is limited to general training, such as teaching police how to deal with persons with mental disorders, as opposed to helping to plan a particular detainee's interrogation," Appelbaum said.

"This conforms to APA's statement that psychiatrists may provide training to military or civilian investigative or law enforcement personnel on recognizing and responding to persons with mental illnesses, on the possible medical and psychological effects of particular techniques and conditions of interrogation, and on other areas within their professional expertise," he said. "Thus, both statements now appear to concur that physicians should not be involved in the interrogation of particular detainees in either a direct or advisory role."

Subject Engages Ethics, National Security

The careful wording and substantial revisions that the report underwent before being accepted appears to reflect the diversity and passionate nature of opinions on a subject that engages issues not only of professional and medical ethics, but also of national security and the radical measures that some believe may be needed to confront modern terrorism.

"This is a totally new area of medical ethics," said Sharfstein.

Even the final version of CEJA's report fell short for some—at least at first glance—a reflection of the varying ways in which the council's carefully chosen words might be read.

During reference committee hearings (where opinions about reports and resolutions are aired before coming to the floor of the House of Delegates) Brig. Gen. (Ret.) Stephen N. Xenakis, M.C., delivered a strident speech calling for a more unambiguous prohibition on physician participation than the CEJA report provided. Xenakis is an advisor to the group Physicians for Human Rights and director of child and adolescent psychiatry at the Psychiatric Institute of Washington in Washington, D.C.

Later, Xenakis told *Psychiatric News* that after consulting with CEJA members about the intent of the wording, he came around to endorse the report. "They said that in their eyes they were crafting language that was intended to have the same meaning as the statement by APA," he said.

Following the House of Delegates meeting, Physicians for Human Rights issued a statement in support of the AMA.

"The AMA acted today to defend the basic principles of medical ethics and to protect the men and women bravely serving our country as military health personnel," Xenakis was quoted in the statement as saying. "Since 2001, the civilian leadership at the Pentagon has been engaged in a full frontal assault on the basic standards of medical and military ethics, from the Hippocratic Oath to the Geneva Conventions. All the major medical associations are now standing together to demand that this administration respect the core values of both the health professional and the soldier."

McIntyre noted that as a "big tent," the

continued on facing page

AMA Statement on Interrogation of Prisoners

These are the five concluding recommendations in the AMA Council on Ethical and Judicial Affairs' report on physician participation in interrogation:

- Physicians may perform physical and mental assessments of detainees to determine the need for and to provide medical care. When so doing, physicians must disclose to the detainee the extent to which others have access to information included in medical records and should not record or reveal any information against the wishes of the detainee, unless clearly justified by tenets of medical ethics and public health. Treatment must never be conditional on a patient's participation in an interrogation.
- Physicians must neither conduct nor directly participate in an interrogation, because a role as physician-interrogator undermines the physician's role as healer and thereby erodes trust in the individual physician-interrogator and in the medical profession.
- Physicians must not monitor interrogations with the intention of intervening in the process, because this constitutes direct participation in interrogation.
- Physicians may participate in developing effective interrogation strategies for general training purposes. These strategies must not threaten or cause physical injury or mental suffering and must be humane and respect the rights of individuals.
- When physicians have reason to believe that interrogations are coercive, they must report their observations to the appropriate authorities. If authorities are aware of coercive interrogations but have not intervened, physicians are ethically obligated to report the offenses to independent authorities that have the power to investigate or adjudicate such allegations.

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- After stopping treatment with SSRIs, SNRIs, TCAs, MAOIs, mirtazapine, bupropion; meperidine and analgesics such as: tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; and buspirone, approximately 1 week (5 weeks for fluoxetine) should elapse before starting therapy with EMSAM. At least 2 weeks should elapse after stopping EMSAM before starting therapy with buspirone or a drug that is contraindicated with EMSAM
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- **Adults** with MDD or co-morbid depression in the setting of other psychiatric illness **being treated with antidepressants** should be observed for **clinical worsening and suicidality**, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases
- Risk of **bipolar disorder** should be ruled out prior to initiating antidepressant therapy. EMSAM is not approved for the treatment of bipolar depression
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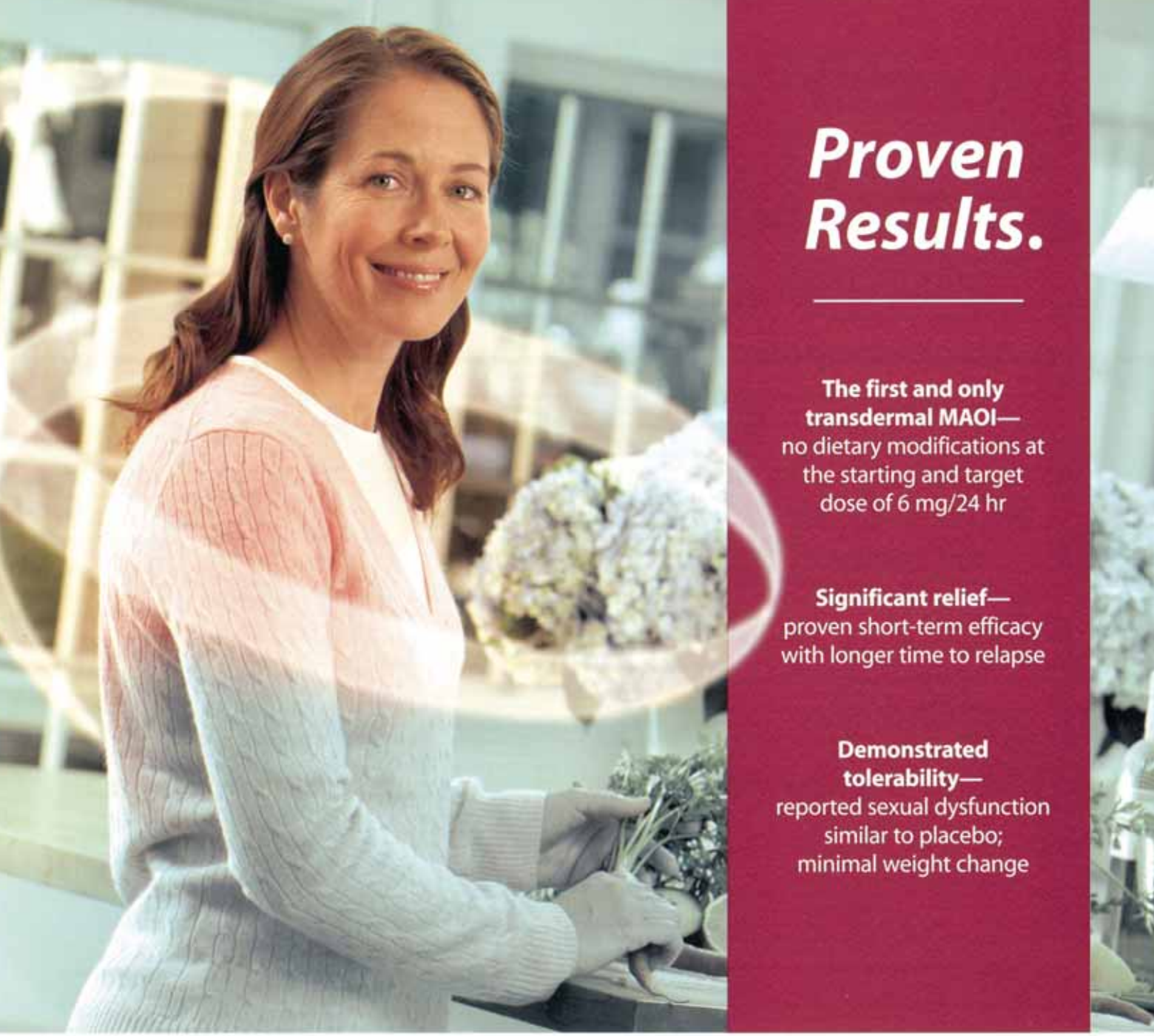

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Brief Summary of Prescribing Information. For complete prescribing information please consult official package circular.

Suicidality in Children and Adolescents

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

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

INDICATIONS AND USAGE

EMSAM is indicated for the treatment of major depressive disorder.

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

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

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

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

CONTRAINDICATIONS

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

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

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

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

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

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

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

WARNINGS

Clinical Worsening and Suicide Risk

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

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

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

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

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

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

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

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

Screening Patients for Bipolar Disorder

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

Hypertensive Crisis

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

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

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

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

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

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

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

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

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

Use With Other Drugs Affecting Monoamine Activity

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

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

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

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

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

PRECAUTIONS

General

Hypotension

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

Activation of Mania/Hypomania

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

Use in Patients With Concomitant Illness

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

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

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

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

Information for Patients

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

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

Clinical Worsening and Suicide Risk

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

General

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Drug Interactions

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

Alcohol

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

Alprazolam

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

Carbamazepine

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

Ibuprofen

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

Ketoconazole

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

Levothyroxine

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

Olanzapine

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

Phenylpropanolamine (PPA)

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

Pseudoephedrine

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

Risperidone

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

Tyramine

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

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

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

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

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

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

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

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

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

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

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

Warfarin

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In an oral carcinogenicity study in rats, selegiline given in the diet for 104 weeks was not carcinogenic up to the highest evaluable dose tested (3.5 mg/kg/day, which is 3 times the oral maximum recommended human dose on a mg/m^2 basis).

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

Mutagenesis

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

Impairment of Fertility

A mating and fertility study was conducted in male and female rats at transdermal doses of 10, 30, and 75 mg/kg/day of selegiline (8, 24 and 60 times the maximum recommended human dose of **EMSAM** [12 mg/ 24 hours] on a mg/m^2 basis). Slight decreases in sperm concentration and total sperm count were observed at the high dose; however, no significant adverse effects on fertility or reproductive performance were observed.

Teratogenic Effects - Pregnancy Category C

In an embryofetal development study in rats, dams were treated with transdermal selegiline during the period of organogenesis at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the maximum recommended human dose [MRHD] of **EMSAM** [12 mg/24 hours] on a mg/m^2 basis). At the highest dose there was a decrease in fetal weight and slight increases in malformations, delayed ossification (also seen at the mid dose), and embryofetal post-implantation lethality. Concentrations of selegiline and its metabolites in fetal plasma were generally similar to those in maternal plasma. In an *oral* embryofetal development study in rats, a decrease in fetal weight occurred at the highest dose tested (36 mg/kg; no-effect dose 12 mg/kg); no increase in malformations was seen.

In an embryofetal development study in rabbits, dams were treated with transdermal selegiline during the period of organogenesis at doses of 2.5, 10, and 40 mg/kg/day (4, 16, and 64 times the MRHD on a mg/m^2 basis). A slight increase in visceral malformations was seen at the high dose. In an *oral* embryofetal development study in rabbits, increases in total resorptions and post-implantation loss, and a decrease in the number of live fetuses per dam, occurred at the highest dose tested (50 mg/kg; no-effect dose 25 mg/kg).

In a prenatal and postnatal development study in rats, dams were treated with transdermal selegiline at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the MRHD on a mg/m^2 basis) on days 6-21 of gestation and days 1-21 of the lactation period. An increase in post-implantation loss was seen at the mid and high doses, and an increase in stillborn pups was seen at the high dose. Decreases in pup weight (throughout lactation and post-weaning periods) and survival (throughout lactation period), retarded pup physical development, and pup epididymal and testicular hypoplasia, were seen at the mid and high doses. Retarded neurobehavioral and sexual development was seen at all doses. Adverse effects on pup reproductive performance, as evidenced by decreases in implantations and litter size, were seen at the high dose. These findings suggest persistent effects on the offspring of treated dams. A no-effect dose was not established for developmental toxicity. In this study concentrations of selegiline and its metabolites in milk were ~ 15 and 5 times, respectively, the concentrations in plasma, indicating that the pups were directly dosed during the lactation period.

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

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

Geriatric Use

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

ADVERSE REACTIONS

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

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

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

Adverse Events Associated with Discontinuation of Treatment

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

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

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

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

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

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

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

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

Application Site Reactions

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

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

Male and Female Sexual Dysfunction with MAO-Inhibitors

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

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

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

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

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

Vital Sign Changes

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

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

AMA Wants Govt. to Enact Law on Insurance Coverage

The AMA House of Delegates tackled many issues of importance to psychiatry last month. Among them are mandated health insurance, direct-to-consumer advertising, and use of SSRIs during pregnancy.

BY MARK MORAN

The AMA, in a significant reversal of longstanding policy, approved a call for mandated health insurance.

Under the AMA plan, individuals and families earning more than 500 percent of the federal poverty level ($49,000 for an individual and $100,000 for a family of four) would be required to obtain minimum insurance coverage of catastrophic health care and evidence-based preventive health care, "using the tax structure to achieve compliance."

In a press conference following the action by the AMA's House of Delegates last month, AMA Trustee Ardis Hoven, M.D., told reporters that use of the tax structure meant those who neglected to buy health coverage would be subject to higher taxes.

For those earning less than 500 percent of the federal poverty level, the AMA would support a similar requirement upon implementation of a system of refundable tax credits or other subsidies to obtain health care coverage.

Though an entirely theoretical approach that has little likelihood of becoming reality anytime soon, the move marks a significant turnabout for a group that has consistently resisted mandatory health insurance in favor of voluntary incentives.

Hoven and fellow board member Edward Langston, R.Ph., M.D., emphasized the value of patient "accountability," the need for individuals to bear responsibility for their own coverage.

When asked if the new policy was a move toward government-provided health insurance, or a "single-payer" plan, Hoven replied, "This enables and encourages individuals to have their own individually owned health plan. That's not a single-payer plan."

Still, the resolution on mandatory insurance was among the most important policy measures undertaken by the House of Delegates.

"This policy is the newest addition to the AMA's plan to cover the uninsured," Hoven said. "The AMA plan now includes tax credits for the purchase of insurance, individually selected and owned health insurance, the expansion and formation of new insurance options, changes in health insurance market regulations, and individual responsibility."

More Consumer Ad Monitoring Urged

In another area relevant to all of medicine, the house approved a report calling for a temporary moratorium on direct-to-consumer advertising (DTCA) of newly approved drugs and the development of guidelines for pharmaceutical companies to follow when preparing such advertising. The time interval for this moratorium will be determined by the Food and Drug Administration (FDA), according to a report prepared by the AMA Board of Trustees.

The new AMA guidelines for DTCA state that those ads should do the following:

- Provide objective information about drug benefits that reflect the true efficacy of the drug, as determined by clinical trials.

- Show balance between the benefits and risks of the advertised drugs by providing comparable time or space and cognitive accessibility, and by presenting warnings, precautions, and potential adverse reactions in a clear and understandable way without distraction of content.

- Indicate clearly that the ad is for a prescription drug and refer patients to their physician for more information and appropriate treatment.

- Be targeted for age-appropriate audiences.

- Have pre-approval from the FDA.

"The AMA report clearly supports the need for closer monitoring of direct-

please see ***Insurance*** *on page 38*

Interrogation

continued from page 4

AMA has to accommodate a range of opinions and interests, including those of physicians in the military, to craft a document that is widely acceptable on so difficult a topic requires the ability to thread words through the eyes of some tiny needles.

"There are people on the other side of this issue," he told *Psychiatric News*. "To get a product out of the AMA that is also acceptable to APA is good work. That only occurred because we were active participants. If we didn't participate, I am certain the product would not have been something APA would favor."

A press release on the AMA's new policy to oppose direct physician participation in interrogation is posted at <www.ama-assn.org/ama/pub/category/16446.html>. ■

More Self-Reliance Urged In Disaster Planning

States, cities, and counties need a plan for dealing with the mental health consequences of disasters, train for them, and develop regional ties to back up their efforts.

BY AARON LEVIN

State emergency officials say that to cope better with the health issues resulting from future disasters, they need more training before catastrophes occur, better coordination with other state and regional bodies, and improved communication with U.S. government agencies.

Their views coalesced at a three-day meeting convened in May by the Substance Abuse and Mental Health Services Administration (SAMHSA) to discuss lessons for the mental health community from hurricanes Katrina, Rita, and Wilma. Talks at the New Orleans meeting and discussions with participants made it clear that the burden of mental health readiness for future natural or manmade disasters will fall to cities, counties, and states. Further regional coordination with surrounding jurisdictions will be needed, too, as Katrina made clear last fall.

However, an infusion of new funding is unlikely to come from the federal government. SAMHSA officials said they can offer localities only technical assistance, but only Congress can authorize new funding.

"Planning starts on the state and local levels," said A. Kathryn Power, M.Ed., director of SAMHSA's Center for Mental Health Services. "Don't rely solely on the feds."

To rely more on themselves, representatives of states and localities agreed that they must begin with explicit plans to cope with large-scale emergencies and must hold training exercises to drill public employees and volunteers in their execution.

"Identify the role of your organization in times of disaster, know those roles, and train for those roles," Michael Duffy, R.N., assistant director of the Office of Addictive Disorders in the Louisiana Department of Health and Hospitals, told the group.

"It helps to have a permanent crisis-response committee [for mental health] to set up and coordinate response around the state," added Jeff Bennett, L.C.S.W., director of the Gulf Coast Mental Health Center in Gulfport, Miss.

Last year's hurricanes taught mental health and substance abuse officials who felt the storms' impact the need for thinking across jurisdictional lines and beyond the usual short-term needs of storm victims. Agencies have to form links with emergency management bodies well before disasters strike and practice with the general disaster response team. Summed up one official: "Think horizontally."

For instance, Mississippi is planning to establish a permanent cross-agency group covering its emergency management agency; the state health department; local agencies at state, regional, local levels; and governments, volunteer organizations, and professional organizations.

Planning requires not just documents, but face-to-face contact among personnel in advance of events, said participants. Setting up protocols with nonprofit groups or religious organizations to establish a role for volunteers can help. North Carolina has agreements in place to send groups of volunteers anywhere in the state they are needed.

Planners must think beyond maps and organization charts, though.

"We tend to organize plans around a command and control structure, not around human behavior," added Dave Wanser, Ph.D., deputy commissioner for behavioral and community health in the Texas Department of State Health Services. "For instance, before Hurricane Rita we ordered an evacuation, and everybody left at once, jamming the roads. Planning needs to accommodate how people really act in disasters. Plan for people who will come to you and also for those you have to go to."

Katrina made clear the need for regional coordination, too, as storm and flood victims were evacuated to neighboring states.

Merely keeping track of hundreds of thousands of people on the move was difficult. Telephoning shelters for head counts might give wildly different numbers in a matter of a few hours. New Orleans residents camped out in a state park in Tennessee but were "lost" when they moved on without informing anyone. Alabama also sheltered many evacuees in state parks, but the evacuees were often in remote areas, away from bus lines, and didn't have easy access to services or to Federal Emergency Management (FEMA) offices. "Next time, we'll put them in parks nearer to towns," said an Alabama official.

Special populations demanded closer attention as well. Children were a special focus of psychiatrists and others after the storms (see story at left), but the seriously ill were subject to conflicting policies, sometimes left behind during evacuations.

"The federal view is to move the well populations, who have mostly transient distress, but not to move fragile people," said one participant. "We need to drop barriers to sheltering them."

Paying for behavioral health services also occupied participants. Many complained that the current emergency grant process was slow and cumbersome. Managing complex funding streams from multiple sources was further complicated by different accounting and reporting standards from various government departments.

"Expedite the hoops, procedures, and paperwork," said one. "Simplify the application process and provide help in applying. We don't have a dedicated mental health disaster person to handle it."

Others complained of the gap between short-term emergency funding and longer-term recovery funding that leaves both victims and service providers in limbo for weeks or months. Funding should also follow evacuees, so that a family sheltered and registered in a state other than their own would have access to care there.

Communication is critical both before and during emergencies. Technically, backups are needed for backups. After Katrina, land lines and cell phones were knocked out when power was lost to relay towers. Even satellite phones went out because batteries couldn't be recharged. But communication involves more than technology.

"You need an incident command structure not to command but to communicate," said Ken DeCerchio, M.S.W., C.A.P., assistant secretary for substance abuse and mental health in the Florida Department

please see ***Planning*** *on facing page*

Aaron Levin

"Plan for the fact that you won't have the capacity to handle everything," Ken DeCerchio, M.S.W., C.A.P. (center), assistant secretary for substance abuse and mental health in the Florida Department of Children and Families, tells the Spirit of Recovery conference in New Orleans. He is flanked by Lewis Gallant, Ph.D., executive director of the National Association of State Alcohol and Drug Abuse Directors, and A. Kathryn Power, M.Ed., director of the Center for Mental Health Services.

Lingering Post-Katrina MH Problems May Be 'New Normal' for Children

Only a coordinated effort by psychiatrists and mental health professionals can meet the ongoing needs of Katrina's youngest survivors.

BY AARON LEVIN

Many Louisiana children affected by Hurricane Katrina show signs of resilience today, but many others display continuing psychiatric symptoms 10 months after the storm.

"Among key issues that affect children are their ability to trust adults to keep them safe," said psychologist Joy Osofsky, Ph.D., a professor of pediatrics and psychiatry at the Louisiana State University (LSU) Health Sciences Center. She spoke at a meeting convened by the Substance Abuse and Mental Health Services Administration in New Orleans in May.

"Children's reaction mirrors their parents'. Whenever it rains, whenever there's any kind of storm, like a recent tornado, we see lots of separation anxiety."

Some kids are clingy, worry about what is going to happen, talk repeatedly about the hurricane, or are upset, afraid, or sad when thinking about the event, she said. They feel that nothing is fun and have a hard time getting along with friends and family now. The hardest-hit group may be high school students, who not only miss their friends but also worry about their ability to get into college.

Screening organized in St. Bernard Parish by Osofsky and her husband, Howard Osofsky, M.D., Ph.D., professor and chair of psychiatry at LSU, found that 54 percent of children met criteria for mental health referral, and 14 percent directly requested counseling. They also learned that 34 percent of the youngsters were separated from their primary caregiver, 14 percent had friends who had died because of the storm, 45 percent had parents who were unemployed, and 33 percent had symptoms of PTSD or depression. Even today, many students don't live with their parents because the adults are working elsewhere, said Joy Osofsky.

"We're seeing a 'slow burn' of PTSD and continuing symptoms with a slow recovery and a continued desolation," she said. "Some behavioral and emotional reactions may be 'normal' or represent a 'new normal' after such a widespread disaster with continuing anxiety."

Young people are anxious about the ongoing uncertainty in their lives, an anxiety compounded by the onset of the new hurricane season that began on June 1. Many have had trouble concentrating in school and have become disruptive. Schools that take a zero-tolerance approach to behavioral problems expel children who act out.

On the positive side, children want to resume normal life and their prehurricane activities, enjoy going back to school and being with other children, and show more resilience with support from their parents.

In her work immediately after the storm, Osofsky found that her training in trauma work was a help, but more important was just being there for young people, she said. "Listening, gathering information is a key. When they heard their own concerns, they felt better."

As part of the Louisiana Spirit program that he heads, Howard Osofsky said, children returning to schools that reopened in St. Bernard and Orleans parishes were screened, resiliency-building programs were set up, and treatment provided when needed.

Even before the storm, many children in New Orleans lived in areas of preexisting trauma, with subsistence-level poverty, crime, and bad general health, said Jay Koonce, M.S.W., L.C.S.W., clinical manager of a substance abuse treatment center in Austin, Texas. Koonce helped coor-

please see ***Children*** *on 36*

Creative Thinking Needed To Stretch Limited Budgets

Advocates are urged to work toward shifting juvenile-justice funding to mental illness prevention and treatment programs.

BY RICH DALY

David Hathcox

Rep. Patrick Kennedy (D-R.I.) advises attendees at the National Mental Health Association's annual meeting to seek more government funding for mental illness prevention efforts.

Reflecting an increasingly austere federal and state budget environment, a number of leaders at the 2006 annual meeting of the National Mental Health Association (NMHA) urged colleagues to find more cost-effective ways to spend the large sums already devoted to the various areas of mental health care.

Taking the stage at the mid-June event in Washington, D.C.—one of his first public appearances since returning from a substance abuse rehabilitation program—Rep. Patrick Kennedy (D-R.I.) urged attendees to push their elected officials for more funding to prevent mental illness, including substance abuse.

"That's where we get the biggest bang for our buck," Kennedy said.

David Shern, Ph.D., president and CEO of NMHA, said no level of treatment ever eliminated a disorder. He urged the increased use of "preventive strategies" as the only way to eliminate mental illnesses.

Another way to make better use of existing funds is through increased accountability from existing programs. Kennedy called for more research on and accountability from special-education programs, which have received steadily larger amounts of funding in recent decades without showing commensurate gains for the children in those programs.

One way to obtain more benefits from existing mental health programs is to mandate the use of evidence-based practices and increased research into the uses of cognitive-behavioral therapies that appear to be the most efficacious, he suggested.

'Smarter' Spending Urged

"How can we spend smarter?" asked Jane Knitzer, Ed.D., director of the National Center for Children in Poverty, who noted that about $4 billion is spent annually nationwide on children's mental health, excluding juvenile-justice programs.

David Hathcox

Jane Knitzer, Ed.D., tells attendees to push for a family-based mental health treatment system.

She urged the replacement of the mental health systems for both children and adults with a family treatment system to treat all of the people affected when mental illness arises.

She criticized the fact that many mental health programs "only grudgingly" focus on the emerging research on various aspects of children's mental health systems.

Another money-saving approach that Kennedy urged mental health advocates to take when approaching legislators is to highlight the low cost of the long-sought goal of mental health parity coverage in insurance. He cited the federal Office of Personnel Management's 2001 report, which found that adding the benefit of mental health parity for federal employees increased costs by just 1.3 percent, while other research has found parity's benefits exceed its costs.

Change Traditional Treatment Paradigm

Expanding mental health care beyond the traditional single-patient-focused approach was a common theme among the meeting's speakers. Knitzer said new data have identified the benefits of treating young mothers for depression as an early intervention for their children. Research also has identified benefits from cognitive-behavioral therapy for new mothers and their children.

The benefits of familial approaches to therapy often extend beyond mental health to other areas.

For example, depressed parents are less likely to buckle up their children and provide adequate care for their asthmatic children, Knitzer noted.

Comprehensive approaches can address increased use of the juvenile-justice system as a place to confine children with mental illness, Shern said. Comprehensive approaches also will benefit from increased use of community-based care, which research has shown can facilitate recovery from even the most severe mental illnesses.

A person not often cited by mental health advocates, former Speaker of the House of Representatives Newt Gingrich, urged advocates during his keynote address to push legislators to reorganize health care in ways that provide mental health care as part of a person's comprehensive care.

Comprehensive approaches should include efforts to bring entire families into planning the mental health treatment of individuals.

"More than enough" health care funding is now provided by federal and state governments, he suggested, but antiquated allocation methods squander much of the money on bureaucracy and allow fraud on a massive scale.

"When you believe that money is being wasted, it is much more difficult to get people to agree to give you new funding," Gingrich said, noting that studies have found that about 10 percent of some Medicaid programs' funding is lost to graft.

Massive savings and better care are possible only when the current budget system of program "silos" is scrapped in favor of an approach that funds health care of the long-term, overall needs of each individual, said Gingrich, founder of the Center for Health Transformation.

The major changes and reductions in Medicaid and Medicare programs in recent years will likely accelerate over the next five years. The recent controversial changes to those programs only make them more expensive and less beneficial because the changes "are all chewing around the edges of the programs." Only fundamental change will provide more care with fewer dollars, he said.

Knitzer pointed out that mental health advocates spend considerable time and money "end running the system" to get care for those in need and that both could be better spent through a system that provided mental health care regardless of the specific circumstances of those who need it.

Among the "key fiscal challenges" for mental health advocates, Knitzer said, is the ability to create new partnerships with emerging family groups that push for improved mental health care for families and children. ■

Planning

continued from facing page

of Children and Families.

More opportunities for face-to-face sharing of information in advance and ways to report relocation information across state lines during emergencies are needed, possibly using a central, easily accessible database for needs assessment, shelter occupancy, hotel use, and hospital capacity. Several attendees recalled getting different answers to the same questions, depending on when they called and who picked up the phone at FEMA. Words count, too. Even familiar terms like "treatment" may mean different things to different agencies, so development of a vocabulary common to all parties would enhance communication and speed help to disaster victims.

"There's a need for consistent, accurate information during the process of a disaster," said Duffy. "This helps the staff as well as the public."

Clinically, the conventional approach to postdisaster health care also needs revision, added Wanser. He decried a tendency among shelter directors to recommend immediate removal and hospitalization of individuals who were distraught.

Federal stockpiles of pharmaceuticals should include psychotropic drugs, which were not in the formulary last September, said Duffy.

Substance abuse requires more attention across the board, as both existing abusers seek help and stressed individuals start or increase use. Specialized professional experience is useful as well.

"Suppose a person is visiting doctors on each shift asking for pain medications," Wanser said. "Public health people don't realize this is a problem, but people who work in substance abuse treatment do."

Conference participants also argued for simplifying ways to allow outside health care professionals into states for short periods during disasters.

"Why not set up a national registry to solve credentialing and malpractice insurance problems?" said William R. Breakey, M.D., emeritus professor of psychiatry at Johns Hopkins. "Helping out after a disaster is an exciting, eye-opening learning opportunity that expands your range of skills and experiences."

Physicians and other health professionals who volunteered for the SAMHSA-coordinated program in effect after Katrina and Rita usually served for two weeks. One veteran of that experience said that the investment in learning time would give a greater payoff if deployments were longer (that is, three weeks) or a split four-week commitment. More money should be allocated for advanced training and smoother transitions to following teams or to the local health care system.

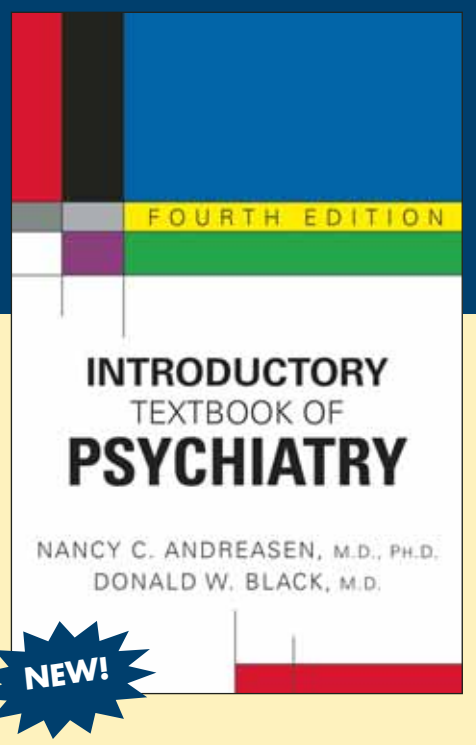
At every level, after the acute response to disasters or after disaster training, recording what worked and what did not is essential, said Florida's DeCerchio. "You have to do after-action briefings to be ready for the next season and create documentation to help the person who comes behind you."

Finally, said one participant at the end of the meeting, federal agencies should start thinking about an "all-hazards" approach to disaster. Homeland security funding has been too narrowly focused on antiterrorism efforts and not at all on the consequences of earthquakes, hurricanes, and other natural disasters. If disaster knows no geographic borders, he implied, neither is it bound by the source of the catastrophe.

Presentations from SAMHSA's "Spirit of Recovery Summit" are posted at <www.spiritofrecoverysummit.com/presentations.htm>. ■

Introductory Textbook of Psychiatry, Fourth Edition

Nancy C. Andreasen, M.D., Ph.D., and Donald W. Black, M.D.



An established resource, the *Introductory Textbook of Psychiatry* has been thoroughly revised to make it an even more effective text. This edition is more practical and easier to use. The authors continue to interweave recent advances in psychiatry with the core knowledge that students new to the field need—from grasping the neurobiology and genetics of mental illness to understanding the DSM system to assessing patients.

Hailed as a "classic text," this user-friendly volume is written in an accessible, conversational style for introductory psychiatry courses or psychiatry clerkships—or as an authoritative introduction to abnormal psychology for students of psychology, social work, or nursing.

- It introduces students to a wide range of psychiatric diagnoses—covering epidemiology, clinical features, and treatment
- Provides additional coverage of special topics such as violence and suicide, legal issues that affect psychiatry, childhood disorders, sleep disorders, and both psychosocial and somatic therapies

As a teaching resource, it boasts several benefits:

- Tools that enhance learning, such as compelling case vignettes and "clinical pearls"—even more numerous in this edition—plus self-assessment questions
- A detailed introduction to the interview process, including specific questions that the clinician might ask patients
- A critical review of DSM-IV-TR covering all disorders, arranged by diagnostic class
- Eleven chapters devoted to specific conditions, from cognitive disorders to personality disorders to impulse-control disorders, with handy tables of DSM-IV-TR diagnostic criteria, practical assessment tips, and other key points
- A single-chapter introduction to the basics of child psychiatry, covering mental retardation, autism, ADHD, and more
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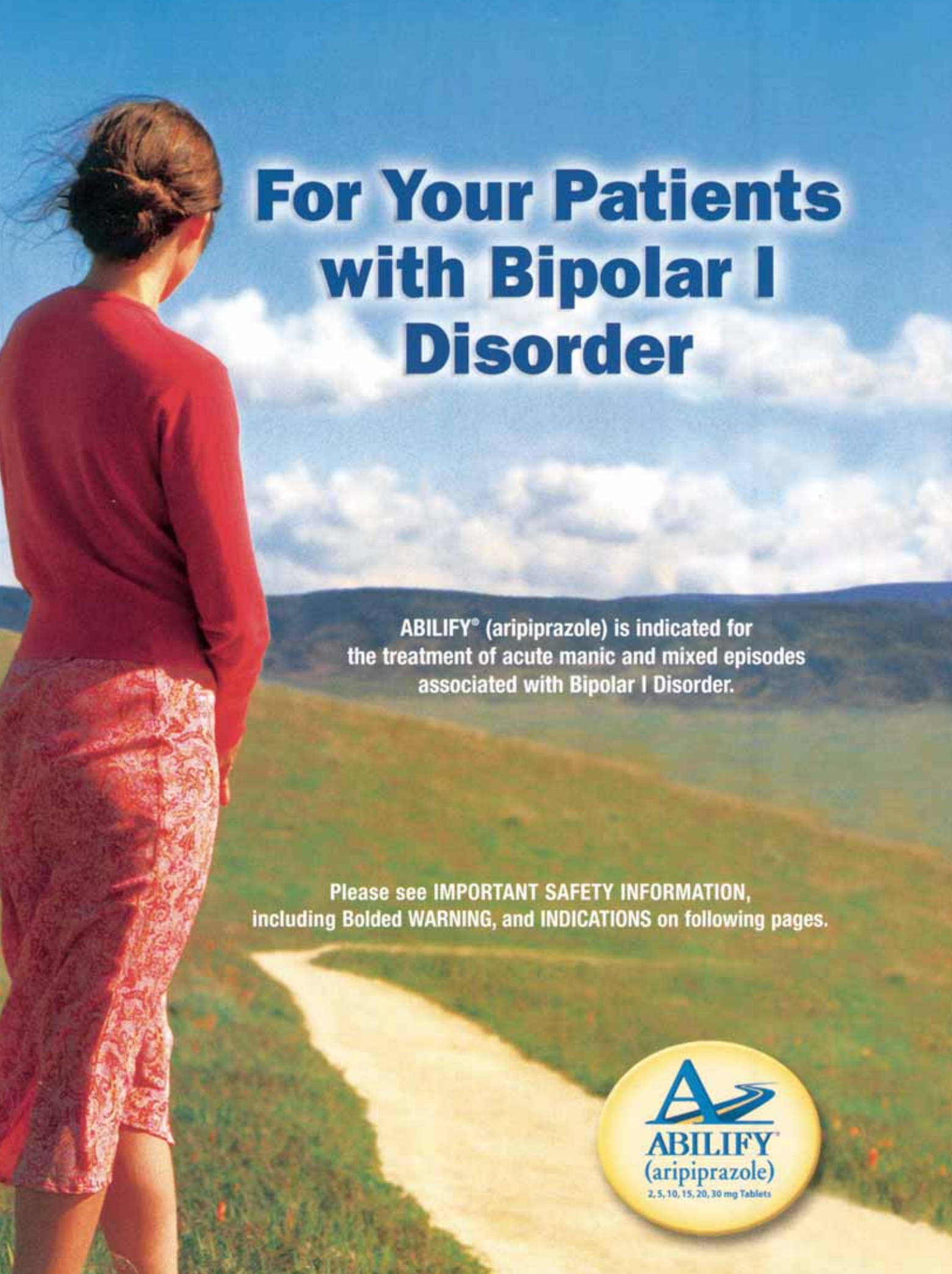

For Your Patients with Bipolar I Disorder
ABILIFY® (aripiprazole) is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder.
Please see IMPORTANT SAFETY INFORMATION, including Bolded WARNING, and INDICATIONS on following pages.
ABILIFY®
(aripiprazole)
2, 5, 10, 15, 20, 30 mg Tablets

Treating Bipolar I Disorder

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

Takes Understanding

where your patients have been

They have struggled with their symptoms and relapses. They have felt misunderstood for years before seeking treatment.

where your patients want to go

They want to move forward with treatment to help stabilize their mood swings. It starts with effective symptom control.

and how you can help them get there

ABILIFY® (aripiprazole) may be able to help. ABILIFY is indicated for **treating acute manic or mixed episodes** associated with Bipolar I Disorder and **maintaining efficacy** in patients who have been stabilized and then maintained for at least six weeks.* That means ABILIFY could help control the symptoms of bipolar mania, stabilize mood, and reduce the risk of manic relapse. In clinical trials, most patients taking ABILIFY did not gain weight or feel drowsy.†

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

***Physicians who elect to use ABILIFY for extended periods, that is longer than 6 weeks, should periodically re-evaluate the long-term usefulness of the drug for the individual patient.**

† On average, in short-term trials, patients reported: meaningful weight gain, ABILIFY 3%, placebo 2%; drowsiness, ABILIFY 12%, placebo 8%.

Please see IMPORTANT SAFETY INFORMATION, including **Bolded WARNING**, and INDICATIONS on following pages.

www.abilify.com

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole)

IMPORTANT SAFETY INFORMATION:

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

- ABILIFY is contraindicated in patients with a known **hypersensitivity** to the product.

- As with all antipsychotic medications, including ABILIFY, a rare condition referred to as **neuroleptic malignant syndrome (NMS)** has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of **tardive dyskinesia (TD)**.

- **Cerebrovascular adverse events** (eg, stroke, transient ischemic attack), including fatalities, have been reported at an increased incidence in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY, including a significant dose-response relationship in a fixed-dose trial. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

- **Hyperglycemia**, including some serious cases ranging from ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients on ABILIFY should be appropriately tested before and monitored during treatment.

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

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

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

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

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

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

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

Patients should be advised to avoid alcohol while taking ABILIFY.

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

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

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

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

INDICATIONS: ABILIFY is indicated for the treatment of:

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

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

ABILIFY is taken once daily with or without food.

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

Imagine what you could do with 2:

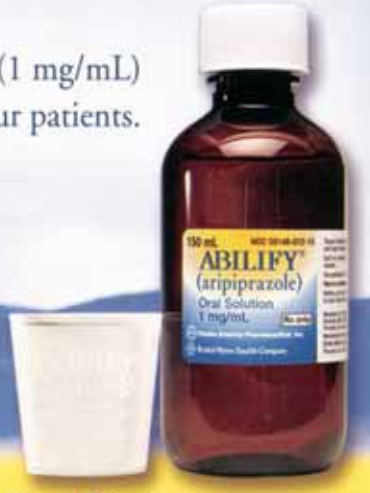
A new 2-mg tablet and a nonrefrigerated Oral Solution

A lower dosage strength of ABILIFY (aripiprazole), a **2 mg tablet,** is now available. It allows you to customize dosing for your patients by helping you cross-taper or titrate to reach a therapeutic dose.*

The **nonrefrigerated Oral Solution** (1 mg/mL) may provide convenience for your patients.

ABILIFY can be taken once daily with or without food.

All to give you more flexible dosing possibilities.



No refrigeration necessary.

*Effective dosage range: 10 to 30 mg/day for schizophrenia patients; 15 or 30 mg/day for Bipolar I Disorder patients.

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

The safety of doses above 30 mg/day has not been evaluated in clinical trials.

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

ABILIFY (aripiprazole)
2, 5, 10, 15, 20, 30 mg Tablets

Bristol-Myers Squibb | Otsuka America Pharmaceutical, Inc.

 D6-K0144 April 2006 AC444282/02-06 Printed in USA

ABILIFY® (aripiprazole) Tablets
ABILIFY® (aripiprazole) Oral Solution

Rx only

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

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

CONTRAINDICATIONS

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

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Neuroleptic Malignant Syndrome (NMS)

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

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

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

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

Tardive Dyskinesia

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

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

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

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

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

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

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

Hyperglycemia and Diabetes Mellitus

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

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

PRECAUTIONS

General

Orthostatic Hypotension

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

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

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

Seizure

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

Potential for Cognitive and Motor Impairment

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

Body Temperature Regulation

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

Dysphagia

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

Suicide

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

Use in Patients with Concomitant Illness

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

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

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

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

Information for Patients

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

Interference with Cognitive and Motor Performance

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

Pregnancy

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

Nursing

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

Concomitant Medication

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

Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Sugar Content

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

Drug-Drug Interactions

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

Potential for Other Drugs to Affect ABILIFY

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

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

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

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

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

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

Potential for ABILIFY (aripiprazole) to Affect Other Drugs

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: (Please see Full Prescribing Information.)

Pregnancy

Pregnancy Category C

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

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[f] Percentage based on gender total.

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

Dose-Related Adverse Events

Schizophrenia

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

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of

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

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

Laboratory Test Abnormalities

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

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

Weight Gain

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

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

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

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

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

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

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

ECG Changes

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

Additional Findings Observed in Clinical Trials

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

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

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

Abuse and Dependence

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

OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

Human Experience

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

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

Management of Overdosage

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

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

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

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or
Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Oral Solution manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

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Suicide Prevention vs. Aesthetics: Maine's Capital Divided

Between 1960 and 2005, 14 people in Augusta, Maine, committed suicide by leaping from a local bridge. After a suicide barrier was constructed in 1983, that grim tally dropped to zero.

BY MARK MORAN

Citizens in Augusta, Maine, have until next month to garner enough signatures to put replacement of a suicide barrier on the city's Memorial Bridge put to a citywide vote.

The city's eight-member city council voted in December 2005 and again in April of this year to rebuild the barrier—after it was taken down when the bridge was renovated—and the State Department of Transportation, which has jurisdiction over the bridge, has already agreed to reinstitute the barrier at no cost to the city.

But some citizens, including one city council member, want the question put to a citywide vote.

The 2,100 foot bridge spans the Kennebec River, which bisects Maine's capital city, and has two lanes for traffic and a sidewalk for pedestrians on each side of the roadway; at its central point the bridge is approximately 100 feet above the water.

In 1983 an 11-foot-high fence was installed on each side of the bridge to prevent people from jumping from it, but it was removed last year when the bridge was closed for renovation.

City Appears Divided

With the reopening of the bridge to auto and pedestrian traffic, a movement has emerged to scrap the suicide barrier. The controversy pits public safety and protection of people with mental illness from impulsive suicide against concerns about aesthetics and what some in the city regard as defacement of a landmark.

"People hated that fence, but they didn't know they hated it until it came down," city council member Donna Lerman, who voted against rebuilding the barrier, told *Psychiatric News*. "We didn't realize the negative impact of the fence on the city's mental well-being, but when it came down, people began to say, 'This is really a beautiful town.' The bridge is the highest point from which to view the city. We had really lost touch with what was good about our city."

Lerman said she also believes the suicide barrier diverts attention from the need for community-based services for people with mental illness in the city.

"We have a lot of people living in the community with inadequate support," she noted. "The fence on the bridge is a way people can address that problem and feel that they have no further responsibility toward making sure that people have adequate support."

She added that suicides occur in other ways—from gunshot wounds and drug overdoses—but that many of them are largely invisible to the public. "It's not so much suicide that people are concerned about as the visibility of people who jump from the bridge."

Barrier Fulfilled Its Mission

But advocates of the barrier, including the Maine Association of Psychiatric Physicians (MAPP), point out that during the 22 years in which the barrier was in place, there were no suicides from Memorial Bridge. A study completed in March by Andrew Pelletier, M.D., a medical epidemiologist at the federal Centers for Disease Control and Prevention, found that from April 1, 1960, through July 31, 2005, 14 suicides from Memorial Bridge occurred, all of them prior to construction of the suicide barrier in 1983.

"Results of this study indicated that the safety fence installed in 1983 was effective in preventing further suicides from the Memorial Bridge," Pelletier said. "The number of suicides related to jumping from other structures in Augusta remained unchanged following installation of the fence, suggesting that suicidal individuals did not seek alternative sites. The larger decline in the suicide rate for the city compared with the state further suggests that the fence was probably effective in lowering the overall suicide rate in Augusta."

Lawrence Mutty, M.D., told *Psychiatric News* that patients with mental illness come from all over Maine to be treated at the 92-bed state psychiatric hospital and various outpatient mental health clinics on either side of—and in close proximity to—the Memorial Bridge. In addition to the state hospital on the east side of the bridge, there are two other busy inpatient psychiatric services, Maine General Medical Center and the VA Medical Center Togus.

"There is a pedestrian traffic across the bridge that is uniquely at risk," said Mutty, a past president of MAPP and currently a councilor to its executive committee. He is also immediate past president of the Maine Medical Association.

He added that many of the state's medical leaders, including leaders of the Maine Medical Association, have supported reconstruction of the barrier.

The controversy over rebuilding the barrier echoes themes that surround debate about building a similar barrier on San Francisco's Golden Gate Bridge, which has for many years been a favored destination of those in the Bay area seeking to end their lives (*Psychiatric News*, April 1, 2005).

Psychiatrists with the Northern California Psychiatric Foundation have led a groundswell of support for erecting a barrier on the storied bridge in the face of public apprehension that such a barrier would deface one of the world's most extraordinary structures. Barrier design studies are under way.

In Toronto a similar debate occurred around construction of a barrier at the city's Bloor Street Viaduct. In 2003, after nearly six years of discussion, a barrier was built that has dramatically reduced the number of suicides there.

In Augusta, comments from people on both sides of the issue seem to indicate that the barrier at Memorial Bridge was less than aesthetically appealing. Mutty said the state opted for the least-costly option, a chain-link cyclone fence that had rusted over the years.

City Manager William Bridgeo told *Psychiatric News* that the state Department of Transportation has already agreed to replace the barrier with a similar one, but that if the city wants something more aesthetically appealing, it will have to pay the additional costs. He said those costs would be approximately $250,000.

Maine Department of Transportation

No suicides occurred on the Memorial Bridge in Augusta, Maine, while the suicide barriers were in place.

Bridgeo explained that in a council meeting last month, a group of citizens led by Lerman lodged a formal request for the question about the bridge barrier to be put before city voters in a referendum.

He said that under city law, if the citizens group can garner a number of signatures equal to 20 percent of the number of voters in the last gubernatorial election—or approximately 1,500 signatures—the question will be placed on the ballot. They have 60 days since last month's city council meeting to do so, or until the first week in August. ■

Government Includes Consumer Input In Seclusion, Restraint Curriculum

"Consumer-developed" guidelines aim to help mental health facilities train staff in alternatives to seclusion and restraint.

BY RICH DALY

Former patients of mental health facilities who were subjected to seclusion and restraint assisted in the development of first-of-their-kind guidelines recently released by the Substance Abuse and Mental Health Services Administration (SAMHSA).

Described as a "training curriculum" for mental health clinicians, the guidelines are designed to teach "prevention strategies" and alternative approaches to avoid and reduce the use of seclusion and restraint.

"A Roadmap to Seclusion- and Restraint-Free Mental Health Services for Persons of All Ages" emphasizes the need to create cultural change within mental health facilities to reduce the use of seclusion and restraint.

"This is the first training curriculum of its sort developed by a federal agency for direct-care staff as a means of reducing or preventing these practices," Paolo del Vecchio, SAMHSA's associate director for consumer affairs, told *Psychiatric News*.

The curriculum lays out specific strategies, including self-care approaches, peer-provided services, arts programs, and comfort rooms. Other approaches include use of advance directives, mediation, service animals, and better communication approaches.

The curriculum was developed for SAMHSA by the National Association of Consumer/Survivor Mental Health Administrators and combines input from mental health consumers and best practices described by mental health organizations nationwide. Research used to create the curriculum included that of Gayle Bluebird, R.N., who studied the use of comfort rooms as a preventive tool to reduce the need for seclusion and restraint at Atlantic Shores Hospital in Florida.

Final recommendations were pilot tested in two hospitals prior to publication. The pilot programs found that the curriculum contributes to steep reductions in the use of seclusion and restraint, to the extent that one hospital permanently removed the door of its seclusion room, said del Vecchio.

State and federal laws and regulations have increasingly aimed to curb the use of seclusion and restraint for mental health care recipients. Among these laws is the Children's Health Act of 2000, which set standards for federally funded health care facilities and nonmedical residential facilities for children.

The curriculum can be ordered in CD-ROM format through SAMHSA's National Mental Health Information Center at <www.mentalhealth.samhsa.gov> or by phone at (800) 789-2647. The curriculum is posted at <www.mentalhealth.samhsa.gov/publications/allpubs/sma06-4055/>. ■

Roadmap Outlines Other Routes

"A Roadmap to Seclusion- and Restraint-Free Mental Health Services for Persons of All Ages" has these seven modules and an online resources section:

- Teaching a personal understanding of seclusion and restraint.
- Highlighing the impact of trauma on patients and staff.
- Reviewing the cultural change and reform model for patient care.
- Illuminating resiliency and recovery from the consumer's perspective.
- Identifying strategies to reduce and eliminate seclusion and restraint.
- Outlining sustainable change through both consumer and staff involvement.
- Discussing personal and workplace action plans to reduce and eliminate use of seclusion and restraint.

government news

Law Opens MCO Panels To 'Any Willing Provider'

Mental health advocates hail the latest, and surprisingly unopposed, expansion of "any willing provider" laws into Vermont.

BY RICH DALY

Among the first "any willing provider" measures aimed specifically at mental health clinicians, a recently enacted Vermont law mandates that insurers provide identical reimbursement, regardless of whether treatment is provided by a member of its provider network.

The measure was hailed by Vermont mental health advocates as the latest refinement of the state's 1997 mental health parity law, which required insurers to provide comparable coverage for mental and other medical conditions. In the years since approval of that legislation, the state's mental health clinicians found managed care networks effectively limited mental health care for many residents by not covering the services of established clinicians for patients new to the insurance network.

"These days insurance coverage often changes when people change jobs or move, so people often lose access to their mental health or substance abuse health care provider because they are not in the new insurer's [provider] network," said Ken Libertoff, director of the Vermont Association for Mental Health. "By passing this legislation, Vermont reaffirms the right of health care consumers to receive treatment from practitioners of their choice as long as they are licensed and certified by the state of Vermont."

Research indicates that in mental health care, the relationship between the patient and clinician is an important variable in effective treatment, Libertoff said.

Patient Choice Preserved

Supporters described the bill (H 404) as part of a series of initiatives designed to preserve patient choice and ensure access to necessary and appropriate treatment options. The measure passed after a collaborative legislative push by state professional associations—including the Vermont Psychiatric Association and Vermont Medical Society—and the major patient advocacy groups.

The measure's brief language requires health insurance plans to include in their networks "any licensed mental health or substance abuse [care] provider located within the geographic coverage area of the health benefit plan if the provider is willing to meet the terms and conditions for participation established by the health insurer."

"This bill was a response to concerns about access to comprehensive treatment for people with mental illness and substance abuse disorders," said David Fassler, M.D., legislative representative for the Vermont Psychiatric Association and a member of APA's Board of Trustees. "It eliminates the use of restrictive or closed panels by insurance companies and/or their managed care intermediaries."

Supporters said the need for the measure was found in estimates that 20 percent to 30 percent of the state's population had a diagnosable mental health condition, but only 7 percent received treatment, which indicated the presence of barriers to care.

The law, effective July 1, allows psychiatrists or mental health professionals to join a network or provider panel if they are willing to accept the same terms and conditions applicable to other participants. The requirement that clinicians agree to insurers' terms related to care and fees has caused some consternation among physicians over similar laws in other states.

Short-Term Impact Unclear

The law may have some negative impact on in-network mental health care clinicians in the short term because it eliminates any clinician or insurer monopolies on who gets to treat patients, Libertoff said.

However, over the long term the measure will benefit patients, who have been forced to pay out of pocket to continue receiving care from the same clinician after they switched insurers.

The bill easily passed both chambers and faced no formal opposition from insurers, which vigorously opposed broader any-willing-provider measures in other states. The industry's opposition culminated in the 2003 Supreme Court decision in *Kentucky Association of Health Plans v. Miller*, which found any-willing-provider state laws were not barred under the federal Employee Retirement Income Security Act of 1974 (ERISA). Insurers had argued that such laws were barred by ERISA, which preempts state laws regarding employer-provided health plans.

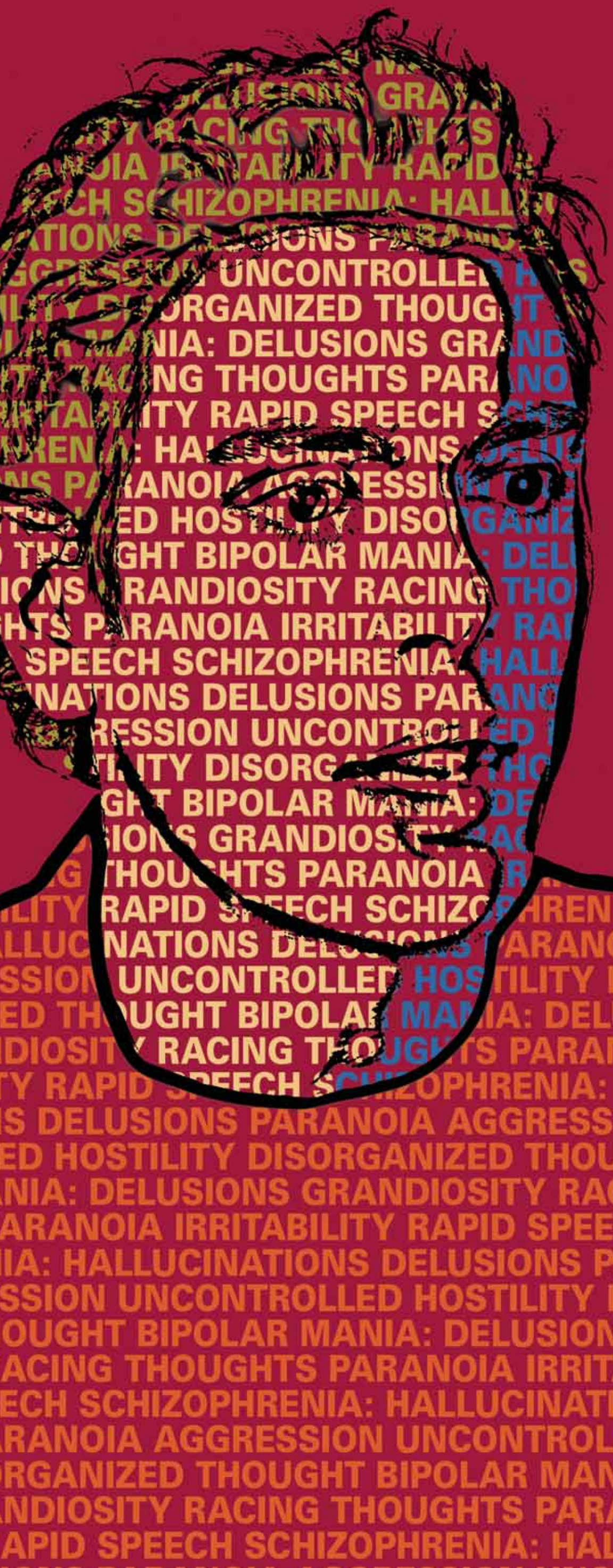
Although no Vermont insurers responded to calls from *Psychiatric News*, supporters of the law credited their lack of opposition to the broad support for the measure, the state's progressive politics, and early support from Vermont Gov. Jim Douglas (R). Douglas signed the measure on May 4.

Opponents of more general any-willing-provider laws in other states have argued that the measures would increase costs and reduce coverage options for consumers by limiting health plans' ability to negotiate with clinicians for discounted rates. Disruptions to insurers' provider networks would also disrupt their quality controls for clinicians, insurers have insisted.

Quality-control measures by insurers, Libertoff said, have been found to be largely perfunctory, with few detailed examinations of the quality of care given by individual clinicians.

Supporters of the bill highlighted statistics showing that the state's largest managed behavioral health panel represented fewer than 50 percent of licensed clinicians in the state, and other panels represent even fewer. They also pointed out that there are no comparable panel restrictions for primary care physicians.

A copy of the law is posted at <www.leg.state.vt.us/docs/legdoc.cfm?URL=/docs/2006/acts/ACT129.HTM>. ■



WHEN EFFECTIVE SYMPTOM CONTROL IS NEEDED...

For many patients, when effective symptom control is needed...

RISPERDAL

RISPERDAL is indicated for the treatment of schizophrenia.

RISPERDAL is indicated for the short-term (3-week) treatment of bipolar mania in acute manic or mixed episodes associated with Bipolar I Disorder.

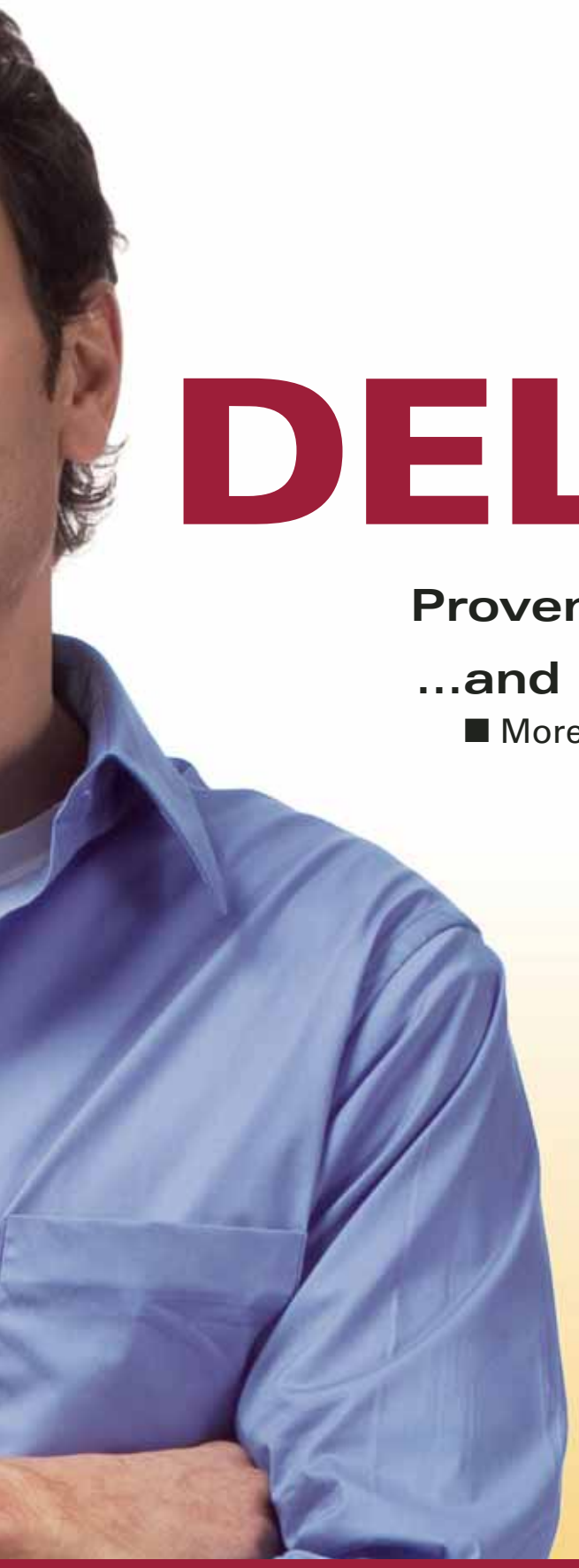
Increased Mortality in Elderly Patients with Dementia–Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these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

Commonly observed events: The most commonly observed events associated with RISPERDAL at an incidence of ≥5% and at least 2x placebo: **Bipolar Mania:** Monotherapy—somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, abnormal vision, saliva increase, and myalgia. **Schizophrenia:** anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

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

Tardive dyskinesia (TD): As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD; if its signs and symptoms appear, discontinuation of RISPERDAL should be considered. Elderly patients appeared to be at increased risk for TD.

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



DELIVERS

Proven symptom control in bipolar mania...*†[1]

...and schizophrenia‡[2]

- More than 12 years of experience[3]

Risperdal®
tablets and
oral solution 1 mg/mL
RISPERIDONE

Rx

More than 80 million prescriptions[4]

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

***All items of the Young Mania Rating Scale (YMRS) improved significantly (content, speech, irritability, sleep, disruptive/aggressive behavior, energy, elevated mood, language/thought disorder, sexual interest, and insight) with the exception of appearance.** The YMRS is an 11-item scale consisting of items intended to assess disease severity in patients already diagnosed with mania.

†The study was not powered to draw conclusions of efficacy for individual items of the YMRS. Demonstrated in a multicenter, randomized, double-blind, placebo-controlled, 3-week trial (N=259) that assessed the antimanic efficacy of risperidone relative to placebo in patients with bipolar mania in 2 parallel-treatment groups: placebo and risperidone 1- to 6-mg flexible dose daily. Starting dose for the risperidone group was 3 mg/day. Mean modal dose for the risperidone group was 4.1 mg/day.

‡Demonstrated in two 8-week, randomized, double-blind, placebo-controlled trials comparing the efficacy and safety of risperidone and haloperidol in patients with schizophrenia (N=513). Patients were randomly assigned to 1 of 6 fixed-dose, parallel-treatment groups: 2, 6, 10, or 16 mg/day of risperidone, 20 mg/day of haloperidol, or placebo. The study was not powered to show a difference between RISPERDAL and haloperidol.

References: 1. Hirschfeld RMA, Keck PE, Kramer M, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry.* 2004;161:1057–1065. **2.** Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry.* 1997;58:538–546. **3.** FDA approval 1993. **4.** IMS HEALTH, NPA *Plus*™, TRXs, 1994 through June 2005.

Please see brief summary of full Prescribing Information, including Boxed Warning, on adjacent page.

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July 2006 01RS1727TR2

Janssen, L.P.

RISPERDAL®
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TABLETS/ORAL SOLUTION

RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

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

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

INDICATIONS AND USAGE: RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia. **Monotherapy:** RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder. **Combination Therapy:** The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

CONTRAINDICATIONS: RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning). Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome. **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis:** Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

PRECAUTIONS: General: Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION in full PI). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication. **Seizures:** RISPERDAL® should be used cautiously in patients with a history of seizures. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely. **Priapism:** Rare cases of priapism have been reported. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown. **Antiemetic Effect:** Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. **Use in Patients With Concomitant Illness:** Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Increased plasma concentrations of risperidone and 9–hydroxyrisperidone occur in patients with severe renal impairment, and in patients with severe hepatic impairment. A lower starting dose should be used in such patients. **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®: **Phenylketonurics:** Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine. **Drug Interactions:** The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Carbamazepine and Other Enzyme Inducers:** In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9–hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. **Fluoxetine and Paroxetine:** Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9–hydroxyrisperidone have not been studied. **Lithium:** Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone. **Digoxin:** RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Drugs That Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9–hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY in full PI). Drug interactions that reduce the metabolism of risperidone to 9–hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9–hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. *In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY in full PI). **Drugs Metabolized by CYP 2D6:** *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. These findings are considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia). **Mutagenesis:** No evidence of mutagenic potential for risperidone was found. **Impairment of Fertility:** Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed. **Pediatric Use:** Safety and effectiveness in children have not been established. **Geriatric Use:** Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in full PI). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION in full PI). **Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis:** In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)

ADVERSE REACTIONS: Associated With Discontinuation of Treatment: Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%). In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo). **Incidence in Controlled Trials: Commonly Observed Adverse Events in Controlled Clinical Trials: *Bipolar Mania:*** In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence. *Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania:* Adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial-Monotherapy in Bipolar Mania.* **Body System/Preferred Term: Central & peripheral nervous system:** Dystonia, Akathisia, Dizziness, Parkinsonism, Hypoaesthesia **Psychiatric:** Somnolence, Agitation, Manic reaction, Anxiety, Concentration impaired **Gastrointestinal system:** Dyspepsia, Nausea, Saliva increased, Mouth dry **Body as a whole - general:** Pain, Fatigue, Injury **Respiratory system:** Sinusitis, Rhinitis, Coughing **Skin and appendages:** Acne, Pruritus **Musculo-Skeletal:** Myalgia, Skeletal pain **Metabolic and nutritional:** Weight increase **Vision disorders:** Vision abnormal **Cardiovascular, general:** Hypertension, Hypotension **Heart rate and rhythm:** Tachycardia. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial – Adjunctive Therapy in Bipolar Mania.* **Body System/Preferred Term: Gastrointestinal system:** Saliva increased, Diarrhea, Abdominal pain, Constipation, Mouth dry, Tooth ache, Tooth disorder **Central & peripheral nervous system:** Dizziness, Parkinsonism, Akathisia, Dystonia **Psychiatric:** Somnolence, Anxiety, Confusion **Respiratory system:** Rhinitis, Pharyngitis, Coughing **Body as a whole - general:** Asthenia **Urinary system:** Urinary incontinence **Heart rate and rhythm:** Tachycardia **Metabolic and nutritional:** Weight increase **Skin and appendages:** Rash. **Dose Dependency of Adverse Events:** Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation. ***Vital Sign Changes:*** RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). ***Weight Changes:*** A statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%). ***Laboratory Changes:*** A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS). ***ECG Changes:*** Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). **Other Events Observed During the Premarketing Evaluation of RISPERDAL®:** During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies and the following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it). **Psychiatric Disorders:** *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning. **Central and Peripheral Nervous System Disorders:** *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis. **Gastrointestinal Disorders:** *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis. **Body as a Whole/General Disorders:** *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing. **Respiratory System Disorders:** *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration. **Skin and Appendage Disorders:** *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria. **Cardiovascular Disorders:** *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis. **Vision Disorders:** *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation. **Metabolic and Nutritional Disorders:** *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia. **Urinary System Disorders:** *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency. **Musculo-Skeletal System Disorders:** *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain. Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage. **Liver and Biliary System Disorders:** *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage. Platelet, Bleeding, and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia. **Hearing and Vestibular Disorders:** *Rare:* tinnitus, hyperacusis, decreased hearing. **Red Blood Cell Disorders:** *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia. **Reproductive Disorders, Male:** *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure. **White Cell and Resistance Disorders:** *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly. **Endocrine Disorders:** *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder. **Special Senses:** *Rare:* bitter taste.*Incidence based on elicited reports. **Postintroduction Reports:** Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

For more information on symptoms and treatment of overdosage, see full Prescribing Information.

7503231B Revised March 2006

Janssen L.P.

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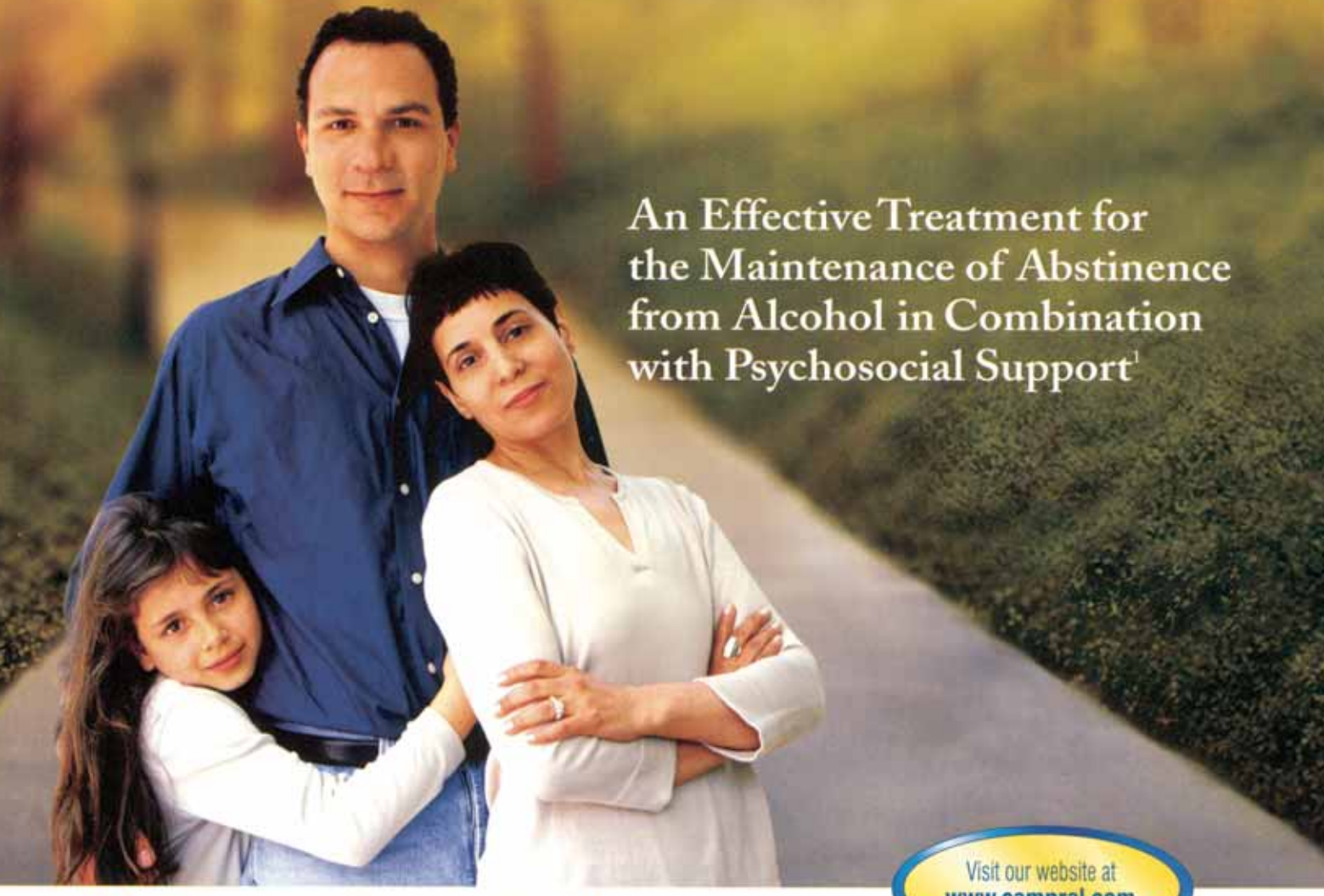

An Effective Treatment for the Maintenance of Abstinence from Alcohol in Combination with Psychosocial Support[1]

Visit our website at **www.campral.com**

- **2 to 3 times more patients maintained abstinence vs placebo in long- and short-term studies, respectively**[2]
- **Works well with a variety of psychosocial therapies**[3–6]
- **Excellent safety and tolerability profile**[1–7]
- **Unique mechanism of action is thought to restore neurotransmitter balance***[1]
- **Used in over 1.5 million patients worldwide**[7]

CAMPRAL® (acamprosate calcium) is contraindicated in patients with severe renal impairment (creatinine clearance ≤30 mL/min). CAMPRAL is contraindicated in patients with known hypersensitivity to acamprosate calcium or any excipients used in the formulation. CAMPRAL does not eliminate or diminish withdrawal symptoms. Alcohol-dependent patients, including those patients being treated with CAMPRAL, should be monitored for the development of symptoms of depression or suicidal thinking. The most common adverse events reported with CAMPRAL vs placebo (≥3% and higher than placebo) were asthenia, diarrhea, flatulence, nausea, and pruritus.

*The mechanism of action of acamprosate in the maintenance of abstinence is not completely understood. Chronic alcohol exposure is hypothesized to alter the normal balance between neuronal excitation and inhibition. *In vitro* and *in vivo* studies in animals have provided evidence to suggest acamprosate may interact with neurotransmitter systems centrally, and has led to the hypothesis that acamprosate restores this balance. The clinical significance in humans is unknown.

References: 1. CAMPRAL® (acamprosate calcium) Delayed-Release Tablets Prescribing Information, Forest Laboratories, Inc., St Louis, Mo, 2004. **2.** Data on file, Forest Laboratories, Inc. **3.** Pelc I, Verbanck P, Le Bon O, Gavrilovic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients: a 90-day placebo-controlled dose-finding study. *Br J Psychiatry.* 1997;171:73–77. **4.** Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate: results from a placebo-controlled study on alcohol dependence. *Arch Gen Psychiatry.* 1996;53:673–680. **5.** Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol Alcohol.* 1995;30:239–247. **6.** Pelc I, Ansoms C, Lehert P, et al. The European NEAT Program: an integrated approach using acamprosate and psychosocial support for the prevention of relapse in alcohol-dependent patients with a statistical modeling of therapy success prediction. *Alcohol Clin Exp Res.* 2002;26:1529–1538. **7.** Mason BJ. Acamprosate. *Recent Dev Alcohol.* 2003;16:203–215.

Please see Brief Summary of Prescribing Information on the following page.

Forest Pharmaceuticals, Inc.

 42-126187 1/05

Campral®
(acamprosate calcium)
Delayed-Release Tablets

Strengthens the will to say no

Campral
(acamprosate calcium)
Delayed-Release Tablets

Rx only

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

INDICATIONS AND USAGE
CAMPRAL (acamprosate calcium) is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with CAMPRAL should be part of a comprehensive management program that includes psychosocial support. The efficacy of CAMPRAL in promoting abstinence has not been demonstrated in subjects who have not undergone detoxification and not achieved alcohol abstinence prior to beginning CAMPRAL treatment. The efficacy of CAMPRAL in promoting abstinence from alcohol in polysubstance abusers has not been adequately assessed.

CONTRAINDICATIONS
CAMPRAL is contraindicated in patients who previously have exhibited hypersensitivity to acamprosate calcium or any of its components. CAMPRAL is contraindicated in patients with severe renal impairment (creatinine clearance ≤30 mL/min).

PRECAUTIONS
Use of CAMPRAL does not eliminate or diminish withdrawal symptoms. **General: Renal Impairment** Treatment with CAMPRAL in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) requires a dose reduction. Patients with severe renal impairment (creatinine clearance of ≤30 mL/min) should not be given CAMPRAL (see also CONTRAINDICATIONS). **Suicidality** In controlled clinical trials of CAMPRAL, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in CAMPRAL-treated patients than in patients treated with placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in year-long studies). Completed suicides occurred in 3 of 2272 (0.13%) patients in the pooled acamprosate group from all controlled studies and 2 of 1902 patients (0.10%) in the placebo group. Adverse events coded as "depression" were reported at similar rates in CAMPRAL-treated and placebo-treated patients. Although many of these events occurred in the context of alcohol relapse, no consistent pattern of relationship between the clinical course of recovery from alcoholism and the emergence of suicidality was identified. The interrelationship between alcohol dependence, depression and suicidality is well-recognized and complex. Alcohol-dependent patients, including those patients being treated with CAMPRAL, should be monitored for the development of symptoms of depression or suicidal thinking. Families and caregivers of patients being treated with CAMPRAL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's health care provider. **Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe CAMPRAL. Any psychoactive drug may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that CAMPRAL therapy does not affect their ability to engage in such activities. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding. Patients should be advised to continue CAMPRAL therapy as directed, even in the event of relapse and should be reminded to discuss any renewed drinking with their physician. Patients should be advised that CAMPRAL has been shown to help maintain abstinence only when used as a part of a treatment program that includes counseling and support. **Drug Interactions** The concomitant intake of alcohol and CAMPRAL does not affect the pharmacokinetics of either alcohol or acamprosate. Pharmacokinetic studies indicate that administration of disulfiram or diazepam does not affect the pharmacokinetics of acamprosate. Co-administration of naltrexone with CAMPRAL produced a 25% increase in AUC and a 33% increase in the Cmax of acamprosate. No adjustment of dosage is recommended in such patients. The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexol were unaffected following co-administration with CAMPRAL. Other concomitant therapies: In clinical trials, the safety profile in subjects treated with CAMPRAL concomitantly with anxiolytics, hypnotics and sedatives (including benzodiazepines), or non-opioid analgesics was similar to that of subjects taking placebo with these concomitant medications. Patients taking CAMPRAL concomitantly with antidepressants more commonly reported both weight gain and weight loss, compared with patients taking either medication alone.
Carcinogenicity, Mutagenicity and Impairment of Fertility A carcinogenicity study was conducted in which Sprague-Dawley rats received acamprosate calcium in their diet at doses of 25, 100 or 400 mg/kg/day (0.2, 0.7 or 2.5-fold the maximum recommended human dose based on an AUC comparison). There was no evidence of an increased incidence of tumors in this carcinogenicity study in the rat. An adequate carcinogenicity study in the mouse has not been conducted. Acamprosate calcium was negative in all genetic toxicology studies conducted. Acamprosate calcium demonstrated no evidence of genotoxicity in an *in vitro* bacterial reverse point mutation assay (Ames assay) or an *in vitro* mammalian cell gene mutation test using Chinese Hamster Lung V79 cells. No clastogenicity was observed in an *in vitro* chromosomal aberration assay in human lymphocytes and no chromosomal damage detected in an *in vivo* mouse micronucleus assay. Acamprosate calcium had no effect on fertility after treatment for 70 days prior to mating in male rats and for 14 days prior to mating, throughout mating, gestation and lactation in female rats at doses up to 1000 mg/kg/day (approximately 4 times the maximum recommended human daily oral dose on a mg/m^2 basis). In mice, acamprosate calcium administered orally for 60 days prior to mating and throughout gestation in females at doses up to 2400 mg/kg/day (approximately 5 times the maximum recommended human daily oral dose on a mg/m^2 basis) had no effect on fertility.
Pregnancy Category C Teratogenic Effects Acamprosate calcium has been shown to be teratogenic in rats when given in doses that are approximately equal to the human dose (on a mg/m^2 basis) and in rabbits when given in doses that are approximately 3 times the human dose (on a mg/m^2 basis). Acamprosate calcium produced a dose-related increase in the number of fetuses with malformations in rats at oral doses of 300 mg/kg/day or greater (approximately equal to the maximum recommended human daily oral dose on a mg/m^2 basis). The malformations included hydronephrosis, malformed iris, retinal dysplasia, and retroesophageal subclavian artery. No findings were observed at an oral dose of 50 mg/kg/day (approximately one-fifth the maximum recommended human daily oral dose on a mg/m^2 basis). An increased incidence of hydronephrosis was also noted in Burgundy Tawny rabbits at oral doses of 400 mg/kg/day or greater (approximately 3 times the maximum recommended human daily oral dose on a mg/m^2 basis). No developmental effects were observed in New Zealand white rabbits at oral doses up to 1000 mg/kg/day (approximately 8 times the maximum recommended human daily oral dose on a mg/m^2 basis). The findings in animals should be considered in relation to known adverse developmental effects of ethyl alcohol, which include the characteristics of fetal alcohol syndrome (craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor and intellectual development) and milder forms of neurological and behavioral disorders in humans. There are no adequate and well controlled studies in pregnant women. CAMPRAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects** A study conducted in pregnant mice that were administered acamprosate calcium by the oral route starting on Day 15 of gestation through the end of lactation on postnatal day 28 demonstrated an increased incidence of still-born fetuses at doses of 960 mg/kg/day or greater (approximately 2 times the maximum recommended human daily oral dose on a mg/m^2 basis). No effects were observed at a dose of 320 mg/kg/day (approximately one-half the maximum recommended human daily dose on a mg/m^2 basis).
Labor and Delivery The potential for CAMPRAL to affect the duration of labor and delivery is unknown. **Nursing Mothers** In animal studies, acamprosate was excreted in the milk of lactating rats dosed orally with acamprosate calcium. The concentration of acamprosate in milk compared to blood was 1.3:1. It is not known whether acamprosate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CAMPRAL is administered to a nursing woman. **Pediatric Use** The safety and efficacy of CAMPRAL have not been established in the pediatric population. **Geriatric Use** Forty-one of the 4234 patients in double-blind, placebo-controlled, clinical trials of CAMPRAL were 65 years of age or older, while none were 75 years of age or over. There were too few patients in the ≥65 age group to evaluate any differences in safety or effectiveness for geriatric patients compared to younger patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
The adverse event data described below reflect the safety experience in over 7000 patients exposed to CAMPRAL for up to one year, including over 2000 CAMPRAL-exposed patients who participated in placebo-controlled trials. **Adverse Events Leading to Discontinuation** In placebo-controlled trials of 6 months or less, 8% of CAMPRAL-treated patients discontinued treatment due to an adverse event, as compared to 6% of patients treated with placebo. In studies longer than 6 months, the discontinuation rate due to adverse events was 7% in both the placebo-treated and the CAMPRAL-treated patients. Only diarrhea was associated with the discontinuation of more than 1% of patients (2% of CAMPRAL-treated vs. 0.7% of placebo-treated patients). Other events, including nausea, depression, and anxiety, while accounting for discontinuation in less than 1% of patients, were nevertheless more commonly cited in association with discontinuation in CAMPRAL-treated patients than in placebo-treated patients. **Common Adverse Events Reported in Controlled Trials** Common, non-serious adverse events were collected spontaneously in some controlled studies and using a checklist in other studies. The overall profile of adverse events was similar using either method. Table 1 shows those events that occurred in any CAMPRAL treatment group at a rate of 3% or greater and greater than the placebo group in controlled clinical trials with spontaneously reported adverse events. The reported frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed, without regard to the causal relationship of the events to the drug.

Table 1. Events Occurring at a Rate of at Least 3% and Greater than Placebo in any CAMPRAL Treatment Group in Controlled Clinical Trials with Spontaneously Reported Adverse Events

Body System/ Preferred Term	CAMPRAL 1332 mg/day	CAMPRAL 1998 mg/day[1]	CAMPRAL Pooled[2]	Placebo
Number of Patients in Treatment Group	**397**	**1539**	**2019**	**1706**
Number (%) of Patients with an AE	**248(62%)**	**910(59%)**	**1231(61%)**	**955(56%)**
Body as a Whole	**121(30%)**	**513(33%)**	**685(34%)**	**517(30%)**
Accidental Injury*	17 (4%)	44 (3%)	70 (3%)	52 (3%)
Asthenia	29 (7%)	79 (5%)	114(6%)	93 (5%)
Pain	6 (2%)	56 (4%)	65 (3%)	55 (3%)
Digestive System	**85 (21%)**	**440(29%)**	**574(28%)**	**344(20%)**
Anorexia	20 (5%)	35 (2%)	57 (3%)	44 (3%)
Diarrhea	39 (10%)	257(17%)	329(16%)	166(10%)
Flatulence	4 (1%)	55 (4%)	63 (3%)	28 (2%)
Nausea	11 (3%)	69 (4%)	87 (4%)	58 (3%)
Nervous System	**150(38%)**	**417(27%)**	**598(30%)**	**500(29%)**
Anxiety**	32 (8%)	80 (5%)	118(6%)	98 (6%)
Depression	33 (8%)	63 (4%)	102(5%)	87 (5%)
Dizziness	15 (4%)	49 (3%)	67 (3%)	44 (3%)
Dry mouth	13 (3%)	23 (1%)	36 (2%)	28 (2%)
Insomnia	34 (9%)	94 (6%)	137(7%)	121(7%)
Paresthesia	11 (3%)	29 (2%)	40 (2%)	34 (2%)
Skin and Appendages	**26 (7%)**	**150(10%)**	**187(9%)**	**169(10%)**
Pruritus	12 (3%)	68 (4%)	82 (4%)	58 (3%)
Sweating	11 (3%)	27 (2%)	40 (2%)	39 (2%)

*includes events coded as "fracture" by sponsor; **includes events coded as "nervousness" by sponsor
[1] includes 258 patients treated with acamprosate calcium 2000 mg/day, using a different dosage strength and regimen. [2] includes all patients in the first two columns as well as 83 patients treated with acamprosate calcium 3000 mg/day, using a different dosage strength and regimen.

Other Events Observed During the Premarketing Evaluation of CAMPRAL
Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with CAMPRAL in 20 clinical trials (4461 patients treated with CAMPRAL, 3526 of whom received the maximum recommended dose of 1998 mg/day for up to one year in duration). This listing does not include those events already listed above; events for which a drug cause was considered remote; event terms which were so general as to be uninformative; and events reported only once which were not likely to be acutely life-threatening. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the summary of adverse events in controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Body as a Whole** – *Frequent:* headache, abdominal pain, back pain, infection, flu syndrome, chest pain, chills, suicide attempt; *Infrequent:* fever, intentional overdose, malaise, allergic reaction, abscess, neck pain, hernia, intentional injury; *Rare:* ascites, face edema, photosensitivity reaction, abdomen enlarged, sudden death. **Cardiovascular System** – *Frequent:* palpitation, syncope; *Infrequent:* hypotension, tachycardia, hemorrhage, angina pectoris, migraine, varicose vein, myocardial infarct, phlebitis, postural hypotension; *Rare:* heart failure, mesenteric arterial occlusion, cardiomyopathy, deep thrombophlebitis, shock. **Digestive System** – *Frequent:* vomiting, dyspepsia, constipation, increased appetite; *Infrequent:* liver function tests abnormal, gastroenteritis, gastritis, dysphagia, eructation, gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage, liver cirrhosis, esophagitis, hematemesis, nausea and vomiting, hepatitis; *Rare:* melena, stomach ulcer, cholecystitis, colitis, duodenal ulcer, mouth ulceration, carcinoma of liver. **Endocrine System** – *Rare:* goiter, hypothyroidism. **Hemic and Lymphatic System** – *Infrequent:* anemia, ecchymosis, eosinophilia, lymphocytosis, thrombocytopenia; *Rare:* leukopenia, lymphadenopathy, monocytosis. **Metabolic and Nutritional Disorders** – *Frequent:* peripheral edema, weight gain; *Infrequent:* weight loss, hyperglycemia, SGOT increased, SGPT increased, gout, thirst, hyperuricemia, diabetes mellitus, avitaminosis, bilirubinemia; *Rare:* alkaline phosphatase increased, creatinine increased, hyponatremia, lactic dehydrogenase increased. **Musculoskeletal System** – *Frequent:* myalgia, arthralgia; *Infrequent:* leg cramps; *Rare:* rheumatoid arthritis, myopathy. **Nervous System** – *Frequent:* somnolence, libido decreased, amnesia, thinking abnormal, tremor, vasodilatation, hypertension; *Infrequent:* convulsion, confusion, libido increased, vertigo, withdrawal syndrome, apathy, suicidal ideation, neuralgia, hostility, agitation, neurosis, abnormal dreams, hallucinations, hypesthesia; *Rare:* alcohol craving, psychosis, hyperkinesia, twitching, depersonalization, increased salivation, paranoid reaction, torticollis, encephalopathy, manic reaction. **Respiratory System** – *Frequent:* rhinitis, cough increased, dyspnea, pharyngitis, bronchitis; *Infrequent:* asthma, epistaxis, pneumonia; *Rare:* laryngismus, pulmonary embolus. **Skin and Appendages** – *Frequent:* rash; *Infrequent:* acne, eczema, alopecia, maculopapular rash, dry skin, urticaria, exfoliative dermatitis, vesiculobullous rash; *Rare:* psoriasis. **Special Senses** – *Frequent:* abnormal vision, taste perversion; *Infrequent:* tinnitus, amblyopia, deafness; *Rare:* ophthalmitis, diplopia, photophobia. **Urogenital System** – *Frequent:* impotence; *Infrequent:* metrorrhagia, urinary frequency, urinary tract infection, sexual function abnormal, urinary incontinence, vaginitis; *Rare:* kidney calculus, abnormal ejaculation, hematuria, menorrhagia, nocturia, polyuria, urinary urgency. **Serious Adverse Events Observed During the Non-US Postmarketing Evaluation of CAMPRAL (acamprosate calcium)** Although no causal relationship to CAMPRAL has been found, the serious adverse event of acute kidney failure has been reported to be temporally associated with CAMPRAL treatment in at least 3 patients and is not described elsewhere in the labeling.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class Acamprosate calcium is not a controlled substance. **Physical and Psychological Dependence** CAMPRAL did not produce any evidence of withdrawal symptoms in patients in clinical trials at therapeutic doses. Post marketing data, collected retrospectively outside the U.S., have provided no evidence of CAMPRAL abuse or dependence.

OVERDOSAGE
In all reported cases of acute overdosage with CAMPRAL (total reported doses of up to 56 grams of acamprosate calcium), the only symptom that could be reasonably associated with CAMPRAL was diarrhea. Hypercalcemia has not been reported in cases of acute overdose. A risk of hypercalcemia should be considered in chronic overdosage only. Treatment of overdose should be symptomatic and supportive.

Manufactured by: Merck Santé s.a.s.
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Forest Pharmaceuticals, Inc.

Member of Famously Troubled Clan Ensures Own Mental Health

Mariel Hemingway's quest for wellness arose partly out of a childhood spent trying to survive a family fraught with dysfunction and "a lot of pain."

BY EVE BENDER

Years after growing up in a family in which dysfunction and mental illness were "swept under the carpet," actress and author Mariel Hemingway told APA annual meeting attendees that it is crucial to make suicide part of a national dialogue.

The topic of suicide is something with which Hemingway is all too familiar. Her grandfather, author and Nobel laureate Ernest Hemingway, committed suicide in July 1961 at age 61, four months before her birth. Ernest's grandfather, father, and great uncle also took their own lives.

Hemingway said she believes that her grandfather's alcoholism and suicidal tendencies were related to a fear of not being able to sustain the level of creativity and literary genius for which he had gained fame.

In 1996 suicide struck even closer to home for Hemingway when her 41-year-old sister, actress and model Margaux, died from an overdose of a sedative. At first the family was told that her death was accidental, but after a two-week investigation, officials ruled it a suicide.

"For years, I could not wrap my head around this," Hemingway told APA past president Richard Harding, M.D. "I did not want to accept that this was the case."

Hemingway sat down with Harding to discuss her upbringing and career as an actress and author for the fifth annual Conversations event of the American Psychiatric Foundation in May at APA's 2006 annual meeting in Toronto. Each year AstraZeneca provides an educational grant to support the event.

It was only a few years later while attending a suicide-prevention function that Hemingway was able to admit—to herself and others—that her sister had committed suicide. "I realized there was no shame in it—it didn't make me bad, and it didn't make my family bad. . . . I think it's very important to talk about suicide, and know that it's not your fault if you are a survivor."

Hemingway grew up in a small town in Idaho as the youngest of three sisters in a somewhat chaotic environment. "My parents were alcoholics," she said. "There was a lot of pain, a lot of yelling and screaming."

In addition, one of her older sisters, Muffet, experienced frequent bouts with psychosis and was in and out of psychiatric institutions when Hemingway was growing up.

Due to her father's strained relationship with his father, there was little mention of the famed writer in the household.

Hemingway noticed that something was different about her family when she realized that her elementary school carried the family name and the teachers and children treated her differently.

"When I handed in a kid's paper that was just kind of average, they looked at me as if to say, 'Oh, that's too bad,' " Hemingway said with a laugh.

Her sister Margaux left Idaho for New York City as a teenager for a screen test and "literally became an overnight success," Hemingway said.

Margaux helped her younger sister embark on a film career as well. In 1976 She debuted in the film "Lipstick," alongside her sister, and three years later Mariel was nominated for an Academy Award for her role as Woody Allen's teenage lover in the movie "Manhattan."

Hemingway said she moved to New York City during the filming of the movie "to free myself of this somewhat difficult family I was in."

In the meantime, her sister's life was beginning to become increasingly complicated. Symptoms of mental illness became more pronounced as time went on, and she experienced psychotic symptoms in the months before she took her life, Hemingway noted.

Hemingway's life took a different direction. "Everything I did was to create better health for myself," she acknowledged. "I come from addiction and was clearly addicted to health and wellness."

David Hathcox

Mariel Hemingway: "The ability to calm my body and mind [through yoga and meditation] has been very powerful for me.".

Though her obsession with health bordered on the unhealthy—she admitted to having an eating disorder at one point in her life—she has now found the balance she's long searched for, Hemingway said.

About 20 years ago, she began practicing yoga and meditation. In what is a cross between a memoir and a guide to yoga and meditation, *Finding My Balance*, Hemingway described the benefits she has derived from the practice of yoga. She has written another book about tools for wellness, which will be published next year.

"I am a big believer in the fact that if my grandfather were to do it all over again, he would be healthy," she said. ■

Toronto Blue Jays

APA President and baseball lover Steven Sharfstein, M.D., had nothing on Blue Jays starting pitcher Josh Towers when Sharfstein threw out the first ball in the club's game against the Tampa Bay Devil Rays on May 24. The game was a fundraiser for the American Psychiatric Foundation.

Fundraiser Hits One out of the Park

APA members and their baseball-loving president were taken out to a ballgame during APA's 2006 annual meeting in Toronto in May. The occasion was a double play: not only did members and their guests get to see a competitive match-up between the Toronto Blue Jays and Tampa Bay Devil Rays, but also part of the purchase price of their tickets went toward the team's CAN $3,400 donation to the American Psychiatric Foundation.

The idea for the APA–Blue Jays fund-raising collaboration began when Harry Einbinder of the Blue Jays organization approached Michele Werner, the foundation's development director. The foundation agreed to handle all of the promotion through *Psychiatric News* and mailers to annual meeting attendees, and a ticket booth was set up during the meeting at the Toronto Convention Centre. Baseball caps bearing the American Psychiatric Foundation's logo were made available to all APA ticket holders.

"This event was a major hit with attendees, and we are exploring a similar collaboration with the Padres for next year's annual meeting in San Diego," said Werner. "We received much favorable feedback and interest and look forward to future events that are both entertaining and support the foundation's philanthropic mission."

The evening's only disappointment was that the Blue Jays lost to the Devil Rays, 10-8 ■.

Toronto Blue Jays

Altha J. Stewart, M.D. (left), president of the American Psychiatric Foundation, and Michele Werner, director of development for the American Psychiatric Foundation, hold a ceremonial check presented by a Blue Jays' third-base coach on center field before the Toronto Blue Jays–Tampa Bay Devil Rays game on May 24. Almost 500 game tickets were purchased, increasing the final amount of the Blue Jays' donation to CAN $3,400.

Bylaws Change

At its December 2005 and March 2006 meetings, the Board of Trustees approved amendments to the APA Bylaws, and, in accordance with Bylaws Chapter 11.2, which states that amendments to the Bylaws by the Board of Trustees require (1) the approval of a two-thirds majority of the voting members of the Board present at a meeting at which a quorum is present, and (2) subsequent ratification by a two-thirds vote by strength of Assembly members present at a meeting at which a quorum is present, forwarded the amendments to the Assembly for action at its May 2006 meeting.

The Assembly ratified amendments to Bylaws in Chapter 5.5 and Chapter 5.10 to change the name of the Budget Committee to the Finance and Budget Committee and to change the name of the Reference Committee to the Joint Reference Committee.

The Assembly also ratified an amendment to Chapter 2.5 that updates the language of the existing dual-membership requirement. As amended, Chapter 2.5 states: "No person, except as exempted by the Board or as otherwise provided in these Bylaws, shall become or remain a member of the Association unless that person is a member of a District Branch and participates in continuing education according to the standards of the Association."

Nondrug Depression Treatments Show Promise for Certain Patients

Advances in existing and novel brain stimulation therapies are aimed at providing significant relief to the 4 million Americans with treatment-resistant depression.

BY JIM ROSACK

Finding effective therapeutic options for patients with difficult-to-treat, or treatment-resistant, depression remains a significant challenge. Yet encouraging progress with two nonpharmacologic treatment options—vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS)—may soon offer more choices of safe and effective treatments that represent substantial improvements over traditional electroconvulsive therapy and/or polypharmacy.

A series of presentations during APA's 2006 annual meeting in May gave attendees a firsthand look at new data from company-sponsored research on the efficacy and safety of VNS in patients with treatment-resistant depression who have failed at least four adequate trials of antidepressant therapy, as well as company-sponsored clinical trials data submitted to the FDA in support of the efficacy and safety of TMS.

Indeed, both Cyberonics Inc., which markets the VNS system, and Neuronetics Inc., which hopes to win FDA approval to market the TMS system, were highly visible at the annual meeting. Both companies had representative clinicians and researchers working with each system at the meeting and presented new data on short-term as well as longer-term efficacy of each of the "therapeutic neuromodulation" techniques, along with safety data, during new research poster presentations, symposia, and workshops.

According to Cyberonics, the company has trained more than 5,000 psychiatrists in the use of the VNS system, and more than 10,000 patients have been identified as potentially appropriate candidates for VNS therapy. About 180 different payers have approved coverage of VNS therapy, on a case-by-case basis, for about 1,100 patients. The company also estimates that about 4,700 patients have been denied coverage for VNS therapy since its July 2005 approval.

FDA approval of VNS therapy quickly became controversial when the director of the FDA's Center for Devices and Radiological Health overruled subordinates and approved the VNS system for use. FDA reviewers had recommended that the system not be approved, while the FDA advisory board voted narrowly to recommend approval. In the end, VNS was approved "for the adjunctive long-term treatment of chronic or recurrent depression" in adult patients who "have not had an adequate response to four or more adequate antidepressant treatments" (*Psychiatric News*, August 19, 2005).

Pacemaker-Like Device Used

The VNS system requires the surgical implantation of a pacemaker-like nerve stimulator under the skin in the abdomen or shoulder and the "tunneling" of stimulation wires into the neck, where they are wrapped around the vagus nerve. When turned on, the computer-driven stimulator delivers periodic electrical stimuli of a predetermined intensity to the vagus nerve.

Results from several analyses were released during the annual meeting, including an analysis of suicidality and worsening depression during two years of VNS therapy as an adjunct to pharmacotherapy. That analysis, by William Burke, M.D., a professor and vice chair of psychiatry at the University of Nebraska Medical Center, followed 235 patients over 24 months. In the overall group 205 received VNS therapy, while 30 patients received "treatment as usual."

Researchers compared data on suicides, attempted suicides, suicidal ideation, and hospitalizations due to worsening depression comparatively in the two groups. Suicidality (a composite of all three suicide measures) and hospitalizations for worsening depression declined over the 24-month study in those on VNS therapy. In comparison, those receiving treatment as usual saw slight increases in the tracked outcomes or no change over time.

The two-year study was one of several indicating that the therapeutic effects of VNS occur over time. A second analysis presented data from a pilot study in which positron emission tomography (PET) images were obtained three months after implantation of the VNS system, then again at six, 12, and 24 months after initiation of VNS therapy. Eight patients stayed in the small study through their six-month scans, six patients completed the 12-month scan, and four patients completed all scans, including the 24-month scan.

Brain Changes After Several Months

Charles Conway, M.D., an assistant professor of psychiatry at St. Louis University School of Medicine, who led the imaging study, said that the images revealed that it takes between three and 12 months before VNS appears to change brain activity. These changes "roughly parallel" the significantly delayed improvements that study psychiatrists observed in the patients' mood, Conway noted in a press release.

The study also showed, however, that "about 70 percent of patients who get better from VNS at one year stay better at two years," Conway added. "That is unheard of in a depressed population this severe and suggests that the brain changes induced by this treatment appear to be long-lasting."

Cyberonics also announced at the annual meeting that it is initiating a study to evaluate long-term clinical and economic outcomes for patients with treatment-resistant depression who receive VNS therapy. The study will include a comprehensive review and analysis of existing data on clinical and economic

please see ***Treatments*** *on page 30*

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

*IMS Dataview, October 2005.

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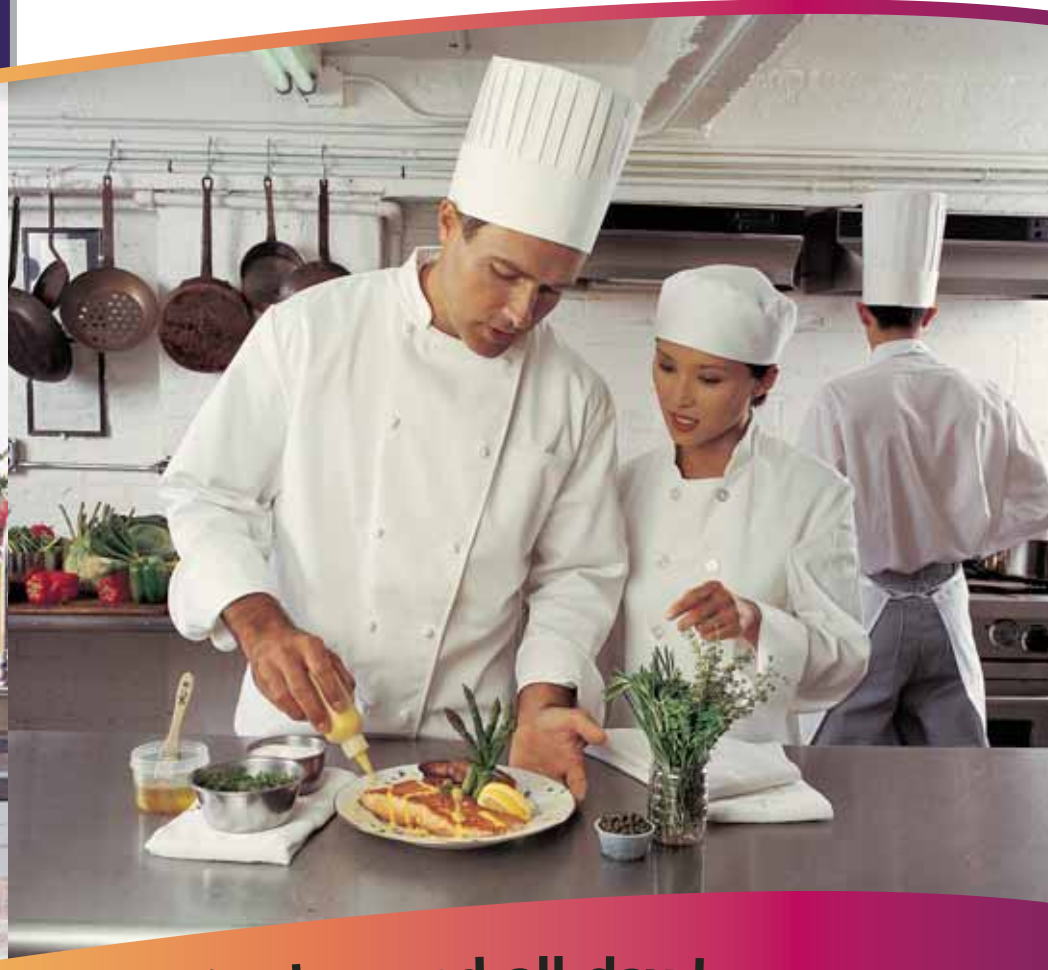

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Reach new heights

Treatment Reduces Violence In Some Offenders

Are violent offenders treatable? Three forensic psychiatrists attempt to answer this question by examining the characteristics of violent offenders and relating clinical success stories.

BY EVE BENDER

On the big screen, murderers are often portrayed as psychotic maniacs who cannot be deterred from harming their targets. The reality is somewhat less dramatic but more reassuring: some people who kill or commit violent acts exhibit symptoms of mental illness that can be mitigated with medication and psychotherapy.

Three forensic psychiatrists scoured the data to learn more about the relationship between mental illness and violent crime and discovered a relatively high prevalence of certain personality traits and behaviors among violent offenders. They discussed their findings at APA's 2006 annual meeting in Toronto in May.

"Homicide is not specifically associated with one psychiatric disorder," said Renée Sorrentino, M.D., director of forensic psychiatry at the Erich Lindemann Mental Health Center and an instructor at Harvard Medical School.

Sorrentino presented data from a study conducted by Jenny Shaw, Ph.D., of 1,594 people convicted of homicide in the United Kingdom that found that 34 percent had been diagnosed with a mental disorder during their lives, but only 10 percent of them were experiencing symptoms at the time of the offense.

In another study by the same researcher, 44 percent of those convicted of homicide in the United Kingdom had been diagnosed with a mental disorder. Of those, 11 percent had a mood disorder, 9 percent a personality disorder, and 6 percent schizophrenia. More than 63 percent had been out of contact with the mental health system at the time of the crime, she pointed out.

Eve Bender

Renée Sorrentino, M.D., tells psychiatrists that they have the ability to reduce the risk of future violence among violent offenders by treating certain symptoms such as emotional dysregulation.

Sorrentino also cited a 2004 study in which Seena Fazel, M.D., and colleagues examined the records of all individuals convicted of homicide and attempted homicide in Sweden from 1988 to 2001. The presence or absence of psychiatric diagnoses was ascertained for 1,625 (81 percent) of the homicide offenders; of these, 1,464 (90 percent) had a psychiatric diagnosis, including 20 percent with a psychotic illness. Fifty-four percent of a subgroup of 1,091 offenders about whom there was information on secondary diagnoses had a personality disorder. Only 10 percent of the offenders for whom psychiatric diagnostic information was available had no psychiatric diagnosis.

Other studies have linked homicide with certain symptoms or behaviors that can be managed when treated by a psychiatrist, Sorrentino noted.

"Some of the risk we can attenuate, such as paranoid delusions, command hallucinations, and suicidality," she said, adding that some suicidal people may be at risk for violence "because they feel they have nothing to lose."

She cited data from a study of 48 people who committed homicide in which there was a clear sexual component that found they were more likely than nonhomicidal incest offenders to have been removed from their homes during childhood. Homicidal sexual offenders were also more likely to score higher on psychopathic and antisocial personality scales and have neuropsychological impairment.

Other studies have found that people who commit homicides that are sexual in nature were more likely than nonhomicidal sexual offenders to belong to gangs, have a history of being cruel to animals, collect pornography, abuse drugs, and exhibit sadism, fetishism, or voyeurism.

According to Joy Stankowski, M.D., "the strongest predictor of violence is not an Axis I disorder, but personality disorders and substance use disorders." She is a senior instructor in psychiatry at Case Western Reserve University in Cleveland.

She noted that studies of jail detainees have found high rates of antisocial personality disorder and substance abuse.

Violent individuals may benefit from targeted forms of treatment depending on their personality traits, Stankowski said. For instance, people with emotional dysregulation, a common symptom of borderline personality disorder, may benefit

please see ***Violence*** *on page 36*

Depression can recur many times...

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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.

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Zoloft® (sertraline HCl)	✔	✔	*
Paxil® (paroxetine HCl)	✔	✔	†

✔ = demonstrated relapse/recurrence prevention at end point.

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

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

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

- 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, or at the time of increases or decreases in dose.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.
- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

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

Please see brief summary of Prescribing Information on adjacent page.

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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. ***Mydriasis***: Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **PRECAUTIONS**: **General**—***Discontinuation of Treatment with Effexor XR.*** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness***: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. ***Changes in Weight***: ***Adult Patients***: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients***: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; $P<0.001$) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Height***: ***Pediatric Patients***: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled SAD study, both the Effexor XR (n=109) and the placebo (n=112) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Appetite***: ***Adult Patients***: Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide About Using Antidepressants in Children and Teenagers* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 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; 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**— ***Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. 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, hypercalcinuria, 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, vesiculobulious rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease (including pulmonary eosinophilia), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C023, revised April 2006.

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Psychiatrists Search for Links Between Religion, Illness

Could substance abuse be viewed as a spiritual quest? Could a spiritual vacuum underlie personality disorders? Psychiatrists propose these bold concepts at APA's 2006 annual meeting.

BY JOAN AREHART-TREICHEL

Many people—psychiatrists and others—believe that psychiatry has not been religion friendly. After all, Freud was an avowed atheist, and only about one-third of American psychiatrists say they carry religious beliefs into their everyday lives, according to a study cited at APA's 2006 annual meeting in the symposium "A Research Agenda for *DSM-V* Concerning Religious and Spiritual Issues in the Diagnostic Process."

Nonetheless, during the past decade or so, the possible impact of religion and spirituality on mental health has sparked interest among psychiatrists (*Psychiatric News*, March 19, 2004; June 18, 2004; November 4, 2005). And material presented at the symposium, which was sponsored by the APA Corresponding Committee on Religion, Spirituality, and Psychiatry, should kindle interest further.

Little research has been conducted on the possible influence of religion and spirituality on mental health, symposium speakers agreed—at least compared with the extensive research that has been conducted on other mental health topics. For example, information about the influence of religion and spirituality on psychopathology among youth is limited to only a few studies, Mary Lynn Dell, M.D., an associate professor of psychiatry at Emory University, noted.

In addition, studies that have been conducted have produced results that often conflict. For instance, at least 76 studies have been conducted on the relationship between religion and anxiety, Gerrit Glas, M.D., Ph.D., a professor of psychiatry and philosophy at Leiden University in the Netherlands, reported. Of these, 35 found less anxiety among religious people; 10 found more, and the rest found either no link or produced mixed results. As for studies exploring the possible influence of religion on obsessive-compulsive disorder, including religious obsessions, contradictory outcomes have also emerged, he said.

Role in Depression Uncertain

The role of religion and spirituality in depression is likewise in question. One study, Dell pointed out, suggested that religious involvement might shield adolescents against depression. In contrast, Dan Blazer II, M.D., Ph.D., a professor of psychiatry at Duke University, and his colleagues found, in a community-based study, that subjects who identified their religious affiliation as Pentecostal had a higher rate of major depression than did the overall population. However, the Pentecostal subjects came from a lower socioeconomic background. So other factors related to psychological stress may have contributed to their depression more than their religious beliefs did, Blazer explained.

Also unclear is whether religious belief can help people cope with trauma, said Samuel Thielman, M.D., Ph.D., director of the Office of Mental Health Services at the U.S. Department of State. Studies have produced both positive and negative results in this domain. For example, one investigation found that trauma made people more religious; another found that it did not.

Even with the paucity of research on religion, spirituality, and mental well-being, and in the face of conflicting research results, one symposium speaker—Marc Galanter, M.D., a professor of psychiatry at New York University—tapped research he has conducted on the subject to make a provocative suggestion.

Mary Lynn Dell, M.D.: We need to think about the value of religion and spirituality to youth coping with illness, death, or other stressors.

Joan Arehart-Treichel

William Narrow, M.D.: Religion and spirituality might be viewed as complementary or alternative medicine.

He and his group have found that substance-abuse patients tend to score high in spiritual needs—that is, in a thirst or reaching out for a God, the arts, humanism, nature, or something that is transcendent for them. He and his team have also learned that physicians recovering from alcoholism rated Alcoholics Anonymous, which is spiritually oriented, very highly. So substance abuse and its treatment might be viewed, at least in certain circumstances, as a spiritual quest, he maintained.

Daring Proposal Offered

Another speaker, C. Robert Cloninger, M.D., a professor of psychiatry and genetics at Washington University and director of the university's Sansone Center for Well-Being, made an even more audacious hypothesis—that a spiritual vacuum

please see ***Religion*** *on page 20*

Speakers Find Symposium Enlightening

After a symposium on religion, spirituality, and mental health (see article above), *Psychiatric News* asked several of the speakers what aspects of the symposium had impressed them the most. Here are some replies:

"The main thing that impressed me," Dan Blazer II, M.D., Ph.D., a professor of psychiatry at Duke University, said, "was the upsurge in interest in spirituality among a group of fairly senior psychiatrists—psychiatrists who have watched the field evolve over many years. . . . In addition, the type of conversation that is emerging regarding spirituality and psychiatry is much more mature, much more critical in a positive and constructive sense, and much less combative than in the past. We are witnessing real progress in expanding the conversation and serious scholarly pursuits."

"I was most impressed with the diversity of the psychiatrists in attendance—ethically, religiously, geographically," Mary Lynn Dell, M.D., an associate professor of psychiatry at Emory University, commented. "There was also equal interest from early career, mid career, and seasoned psychiatrists."

As for Samuel Thielman, M.D., Ph.D., director of the Office of Mental Health Services at the U.S. Department of State, and who stressed that the views expressed are his own, not those of his employer, he "was impressed by the professional stature of the presenters, given that the presentation was on a topic that is sometimes considered to be of peripheral interest to many psychiatrists. I was also encouraged by the expressions of interest in 'protective factors' in contradistinction to risk factors—religion and spirituality being seen by most of the presenters as having the potential for being protective in some circumstances. Finally, I was impressed by the fact that, as psychiatrists, we are moving toward a more broadly based fund of knowledge, one that looks more at human beings in all their complexity, and moves away from biological reductionism and an excessive interest in pharmaceutical agents."

Cultural Beliefs Can Be Harnessed To Aid Outcome

Several examples of using cultural beliefs to enhance treatment are relaxing boundaries, getting the family involved, and enlisting help of native healers.

BY JOAN AREHART-TREICHEL

Not long ago, David Henderson, M.D., an associate professor of psychiatry at Harvard University, treated a Japanese student from the Massachusetts Institute of Technology (MIT) for depression.

Yet after he gave the student a prescription for an antidepressant, the student did not return for a follow-up visit. Concerned about the student, Henderson contacted the dean at MIT. The reason the student failed to come for the follow-up, it turned out, was that he had decided that he was not very depressed because he had been given only one prescription, not multiple ones, which would have been the case in Japan.

Joan Arehart-Treichel

Shamsah Sonawalla M.D., chaired the symposium on ethnic and cultural aspects of mood and anxiety disorders.

In other words, no matter how much psychiatrists know about cultural differences among patients, there is still more to learn, Henderson indicated in a symposium at APA's 2006 annual meeting in Toronto in May.

"It makes our lives as clinicians challenging, that's for sure," symposium discussant Gregory Fricchione, M.D., declared. Fricchione is director of the Division of International Psychiatry at Massachusetts General Hospital.

To speed psychiatrists on their journey of learning more about cultural differences among patients, speakers presented some valuable insights gleaned either from their personal experiences or from studies that they had conducted. For example:

- **Keeping appointments.** Patients from a Hispanic background may arrive early or late for appointments because Hispanics sometimes have a different conception of time than many non-Hispanic Americans do, David Mischoulon, M.D., Ph.D., reported. Mischoulon, an assistant professor of psychiatry at Harvard University, is originally from Argentina.
- **Depression.** When depressed Chinese-American patients visit clinicians, they tend to talk about physical symptoms, not their depression, Albert Yeung, M.D., Sc.D., an assistant professor of psychiatry at Harvard University, noted. The reason, he said, is that they do not seem to realize what the illness of depression is, but if you ask them directly whether they are sad, they will acknowledge it.
- **Culture-bound syndromes.** Indian

please see ***Cultural Beliefs*** *on page 20*

Religion

continued from page 19

underlies personality disorders. Harm avoidance, novelty seeking, and the search for social approval are some of the emotional needs that people have, Cloninger explained, and they activate more primitive parts of the human brain such as the amygdala.

Yet these emotional needs have to be regulated by certain character traits that activate the rational part of the brain, the prefrontal cortex. These traits include being self-directed (responsible), cooperative (flexible, helpful), and self-transcendent (compassionate).

Furthermore, people with personality disorders tend to lack self-regulation of these character traits and thus can be irritating and unlikable. This lack of self-regulation, Cloninger asserted, can be characterized as "a deficit in their spiritual perspective, which leads to patterns of thought, feeling, and behavior that can be described as vices like pride, lust, and greed."

Some 19th-century psychiatrists also held the same view, he pointed out. At the beginning of the 19th century, the antisocial personality was referred to as "moral insanity" or "loss of self-government." Benjamin Rush said that people with personality disorders are "insensitive to the suffering of others."

Cloninger, in fact, proposes that if psychiatrists helped individuals with personality disorders develop a fuller spiritual perspective, it might "expand their awareness of the intangible connections among people. . . ." Such an expanded awareness may not only lead to improvement in their character and behavior, but also "make their lives more meaningful and satisfying."

"This is fascinating, a totally different approach," audience member Carl Bell, M.D., commented. Bell is president and C.E.O. of the Community Mental Health Council in Chicago.

And in a sense, spirituality might be viewed as a complementary or alternative treatment, William Narrow, M.D., the symposium discussant, pointed out. Narrow is associate director of APA's Division of Research and director of research for *DSM-V.*

Yet there is no doubt, Narrow added, that much more research needs to be conducted to determine the roles that religion an information might eventually bolster psychiatrists' efforts to diagnose, treat, and even prevent various mental illnesses. ■

Your Input Invited

APA members are invited to comment on a draft of the Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias of Late Life, Second Edition. The draft is posted in the Members Corner area of APA's Web site at <www.psych.org/members/assembly/pg/pgdraft_reviewmembers.cfm>. Comments should be submitted by July 31 to guidelines@psych.org. More information is available by contacting Amy Albert at (703) 907-8605 or aalbert@psych.org.

Cultural Beliefs

continued from page 19

men sometimes believe that they are losing semen in urine, but actually they are anxious and depressed, said Rajesh Parikh, M.D. Parikh is a consultant neuropsychiatrist at the Jaslok Hospital and Research Center in Bombay. Hispanic patients sometimes experience an "attack of nerves," Mischoulon noted. It is similar to a panic attack, but often involves fainting or shouting. Some two-thirds of individuals who experience this syndrome are anxious or depressed, studies have shown.

- **Psychotic symptoms.** Psychotic symptoms expressed by Hispanic patients may differ from those often seen in Americans patients of other ethnic backgrounds, Mischoulon said. For example, their auditory hallucinations may consist of hearing a knocking at the door, a doorbell ringing, or children's voices calling one's name. Visual hallucinations might consist of "black" thoughts flying across one's vision.

The symposium speakers also suggested ways of deploying patients' cultural beliefs and expectations to bolster the therapeutic process. Among them:

- **Involving the family.** With patients from India, it is crucial to involve family members in treatment, Parikh asserted, because family in their culture is very important. The same is the case with Hispanic patients, Mischoulon stressed. Also, bringing in family members can give a clinician more perspective on a patient's issues, he said.
- **Relaxing boundaries.** Many Hispanic patients expect clinicians to divulge a lot of personal information about themselves, which American psychiatrists usually do not do, said Mischoulon. Thus, providing a little personal information might further therapy with Hispanic patients.
- **Countering fatalistic beliefs.** When Hispanic patients resist treatment because they hold fatalistic beliefs such as "the good Lord willing" or "Que sera, sera" (what will be, will be), Mischoulon might admonish them to "do the necessary legwork to help God."
- **Enlisting native healers.** For some Hispanic patients, for example, it may help to enlist the assistance of traditional healers, Mischoulon asserted. The reason is that patients may respect the psychiatrist for being open to their ways.

These "practical tips for harnessing an individual's cultural beliefs, support systems, et cetera, toward treatment" were some of the symposium highlights, co-chair Shamsah Sonawalla, M.D., an assistant professor of psychiatry at Harvard University, told *Psychiatric News.*

"The most impressive notion [of the symposium]," Fricchione believes, "was that modern psychiatry in the United States must become more sophisticated in its evaluation and management of diverse populations that increasingly seek treatment in our centers. This is because, while there are certainly psychiatric conditions that all groups share, with common symptom clusters and treatment responses, there are also important differences that will impact on patient access, compliance, and response to treatment." ■

KNOWTHEFACTS

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

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

GZ274981T

Printed in USA/May 2006

APA's 159th annual meeting

Together in Toronto

Approximately 18,000 psychiatrists and others decided that the friendly, cosmopolitan city of Toronto was an excellent place for APA to hold its 2006 annual meeting in May.

An even greater lure than Toronto's sophisticated, international flavor—complete with cuisine from all parts of the globe—was a scientific program full of cutting-edge research findings and clinical information. Many of the presentations, large and small, centered around the theme "From Science to Public Policy: Advocacy for Patients and the Profession." The theme was chosen by APA President Steven Sharfstein, M.D., whose term ended at the close of the annual meeting on May 25.

During his last formal presidential address, Sharfstein highlighted the importance of advocacy. "Advocacy is not just calling on others to do what we want; it is a shining light for others to follow."

Incoming President Pedro Ruiz, M.D., described ambitious goals he hopes APA can achieve in the next year. "In recent decades," he said, "the mental health care system of the United States, our profession, and the field of psychiatry at large have confronted challenges that have never been faced before."

It's not too early to begin making plans to be part of next year's annual meeting, which will move to sunny San Diego.

Two members of the Royal Canadian Mounted Police stand guard at the opening session.

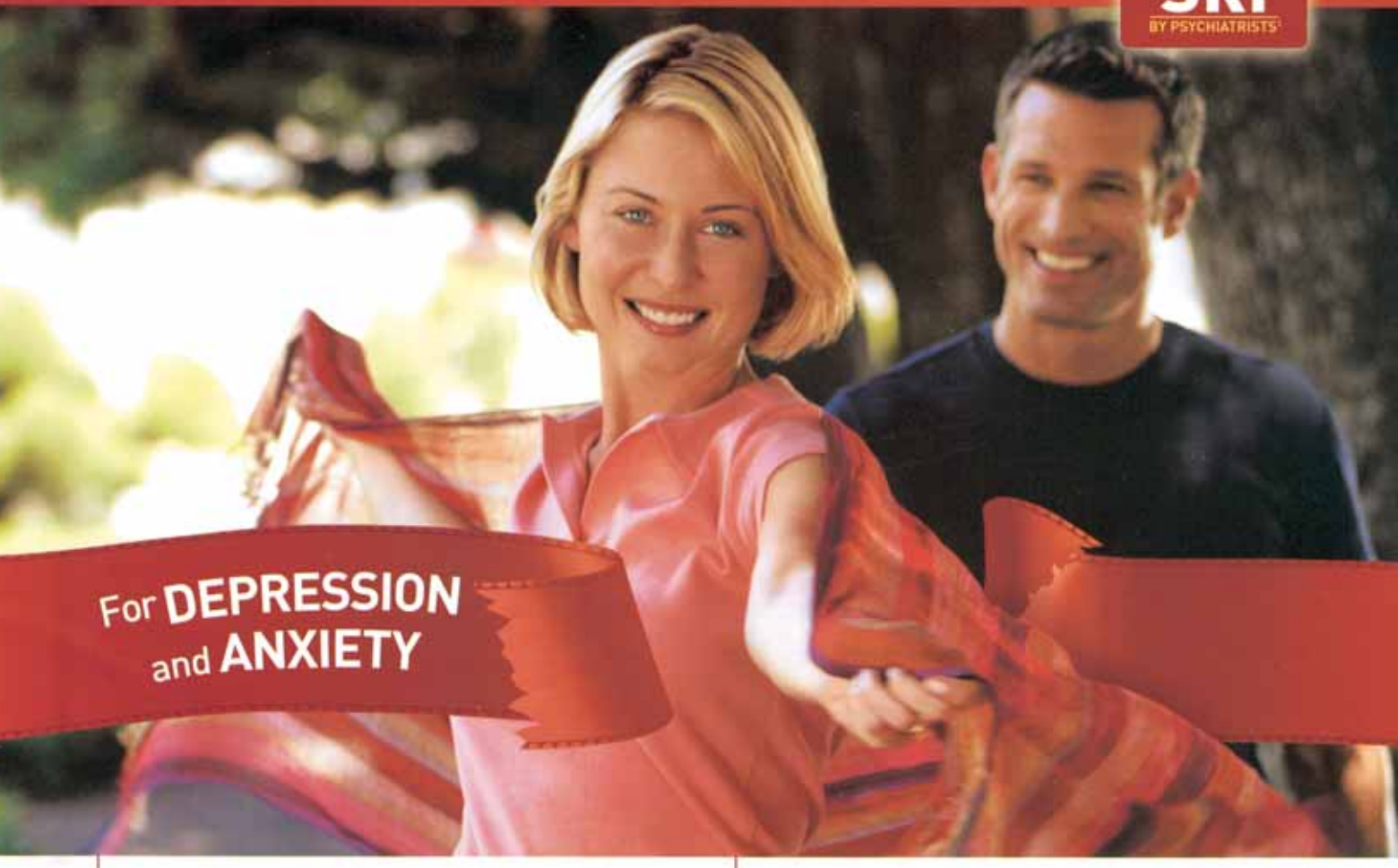
The Toronto Welsh Male Voice Choir performs at a benefit for the Disaster Relief Fund for Psychiatrists.

Shakeeb Hussain, M.D., of Grand Forks, N.D., made the annual meeting a family affair. With him are his wife, Albina, and their sons.

"Our advocacy in favor of access to effective pharmacopeia should never have been seen as mere marketing on behalf of industry; it must come from a dispassionate reading of the science, access to all clinical trial data, and our clinical experience."

A POWERFUL SSRI that's well tolerated

#1 PRESCRIBED SRI BY PSYCHIATRISTS[1]



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

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

Lexapro escitalopram oxalate

POWER TO ENJOY LIFE

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

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

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

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

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) **TABLETS/ORAL SOLUTION**

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

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

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

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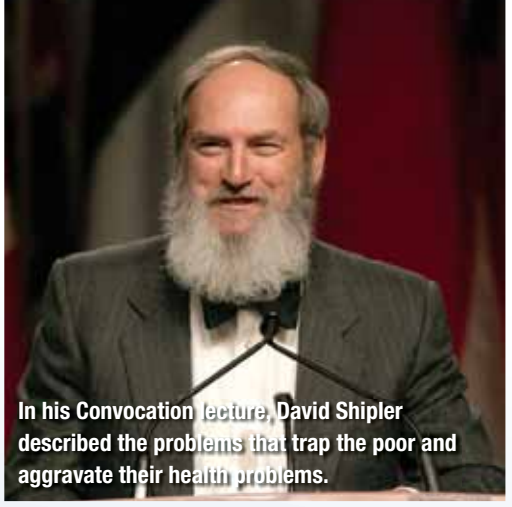
Julius Masskola of Embrach, Switzerland, tries out a virtual reality program in the main exhibit hall.

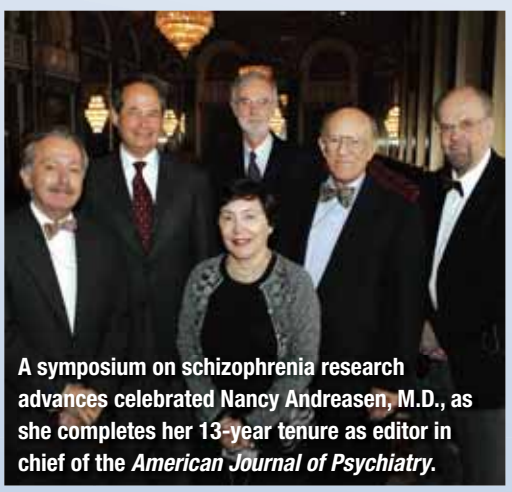


In his Convocation lecture, David Shipler described the problems that trap the poor and aggravate their health problems.

Antonio Mautone of Bologna, Italy, takes advantage of one of the many interactive displays in the Exhibit Hall.

The new section of the Toronto Convention Centre featured open spaces bathed in natural light and expansive views of Lake Ontario.

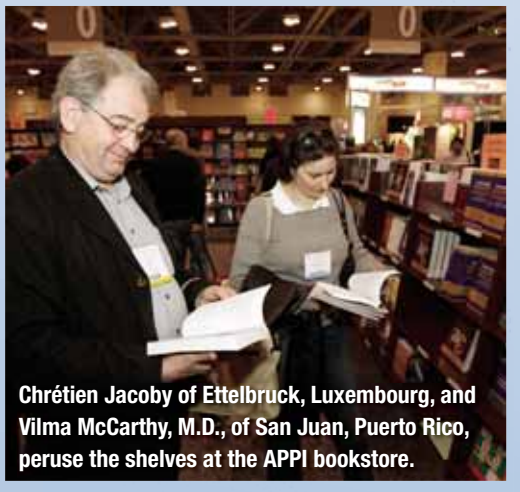
Robin Stone, M.D., of Huntersville, N.C., writes to one of her federal legislators at a kiosk set up by the Department of Government Relations.



A symposium on schizophrenia research advances celebrated Nancy Andreasen, M.D., as she completes her 13-year tenure as editor in chief of the *American Journal of Psychiatry*.

APA President Steven Sharfstein, M.D., stands with the winners of this year's APIRE/Kempf Fund Research Award.

A packed hall left some sitting in the aisles to hear Aaron Beck, M.D., present his lecture, "New Advances in Cognitive Therapy."



Chrétien Jacoby of Ettelbruck, Luxembourg, and Vilma McCarthy, M.D., of San Juan, Puerto Rico, peruse the shelves at the APPI bookstore.

Annelle Primm, M.D., recieves a presidential commendation for "inspiring a generation of psychiatrists to serve the needs of underserved patients."

"I wish that all of you, together with your families, join me in making a dream become a reality: this dream is that organized medicine, under the leadership of APA, and in full partnership with advocacy and patient-oriented groups, secures for our patients universal access to psychiatric care, comprehensive parity of mental health services, and, above all, humane care, not only in the United States but in all corners of the world."

Interpersonal Relationships Predict Course of BPD

The quality of their relationships with children may help predict how patients with borderline personality disorder will fare in treatment. This is in line with reports indicating that for some patients motherhood leads to positive self-esteem, while others can be immobilized by the difficulties of childrearing.

BY MARK MORAN

The quality of a patient's current interpersonal relationships and history of childhood trauma are factors that can aid clinicians in rendering a prognosis for treatment of borderline personality disorder (BPD).

That was a new finding from the study "Predictors of Two-Year Outcome for Patients With Borderline Personality Disorder" published in the May *American Journal of Psychiatry*.

Somewhat more predictably, the longitudinal follow-up of 161 patients with BPD found that the strongest predictor of two-year outcome was severity of baseline psychopathology as measured by the number of BPD diagnostic criteria and functional disability.

But the finding that an assessment of interpersonal stability can aid in the prediction of outcome was something of a surprise. "Interpersonal relationships have not been examined very often as prognostic variables," lead author John Gunderson, M.D., told *Psychiatric News*. "In our study, we looked at interpersonal relations alongside the other two factors—impulsivity and affective instability. These other two factors have often been looked at in prior research.

"The overall quality of the borderline patients' interpersonal relationships proved to be a stronger predictor of course than either their affective instability or impulsivity," said Gunderson, a professor of psychiatry at Harvard Medical School and director of the Center for Treatment and Research on Borderline Personality Disorder at McLean Hospital. "That interpersonal relations have predictive value is clinically useful and adds to prior research. This means that clinicians should recognize that their patients with the most chaotic, stormy, and frequent interpersonal disturbances are not likely to get well soon."

Impulsivity Data Surprising

Gunderson added that the finding that impulsivity was not predictive was surprising, since it had emerged as a solid predictor in other studies. "We don't really understand why it wasn't here," he said. "Our sample was pretty representative, and our assessments were reliable and used standard measures. Perhaps longer-term follow-up will tell us more."

In the study, 160 patients were recruited from four clinical sites of the Collaborative Longitudinal Personality Disorders Study. Patients were assessed at baseline and at six, 12, and 24 months with the Structured Clinical Interview for *DSM-IV* Axis I disorders; the Diagnostic Interview for *DSM-IV* Personality Disorders, a modified version of that instrument; the Longitudinal Interval Follow-Up Evaluation; and the Childhood Experiences Questionnaire–Revised.

Three Categories Assessed

The patients were assessed for a range of variables, grouped into three categories—psychiatric history, developmental experiences, and presenting phemonenology.

Psychiatric history variables found to be predictive were length of previous hospitalizations and early age of psychiatric contact. Developmental experiences predictive of poor outcome included childhood abuse, parental underinvolvement, being a victim of father-daughter incest, parental divorce, parental brutality, childhood separations or losses, and disturbed maternal relationships.

Predictor variables within presenting phenomenology traits were of three subtypes: severity, comorbidity, and personality. Severity variables previously reported to predict poor outcome include having low Global Assessment Scale scores, meeting a greater number of bipolar disorder criteria, and presenting a greater number of Axis II diagnoses at follow-up.

Comorbidity variables found to be predictive of poor outcome include substance abuse and depression or "dysphoria." Comorbid personality predictor variables of poor outcome include those related to schizotypal, antisocial, and paranoid personality disorders. Better outcome was related to comorbid obsessive-compulsive personality disorder.

Personality trait variables that predicted outcome were impulsivity and affective instability.

Two-year outcome was assessed according to measures of global functioning and number of borderline personality disorder criteria.

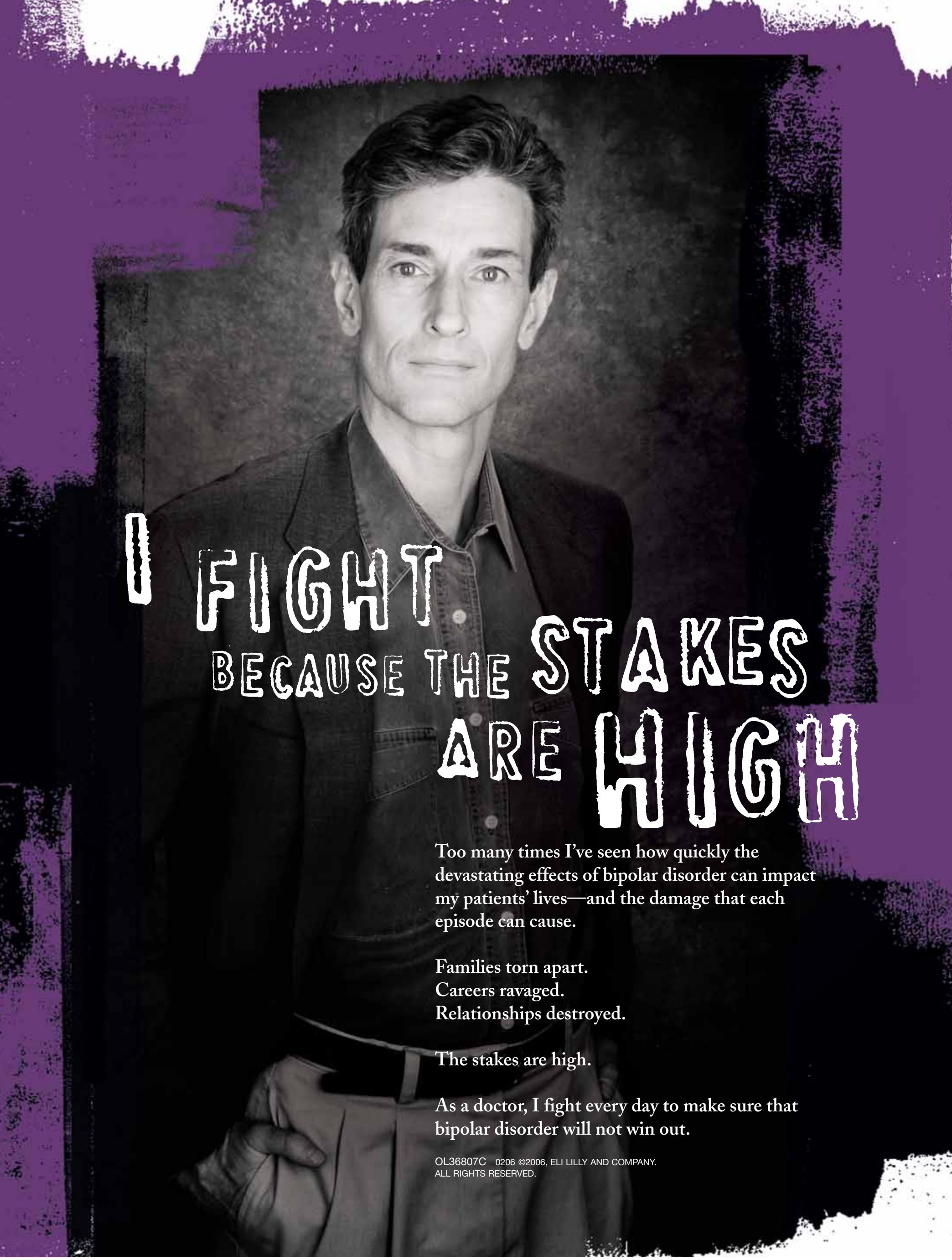
The clearest and strongest finding from the study was that the greater the severity level of dysfunction and psychopathology at baseline, the worse the outcome. Yet Gunderson drew attention to the fact that the study did not yield overwhelmingly conclusive results for any of the predictors.

"A rather sobering message is that none of the predictors is very strong," he told *Psychiatric News*. "The heterogeneous and often quite positive course of borderline patients remains hard to predict with confidence."

Nevertheless, the relevance of the quality and stability of current interpersonal relationships is a finding that will aid clinicians in determining prognosis and treatment. Related to this was a finding that among BPD patients who are parents, the quality of relationships with their children was also predictive.

This is consistent with clinical reports that some patients with BPD find mother-

please see ***BPD*** *on page 30*



I FIGHT BECAUSE THE STAKES ARE HIGH

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

Families torn apart.
Careers ravaged.
Relationships destroyed.

The stakes are high.

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

Lilly

Understanding Personality Disorders Requires New Way of Thinking

A psychiatric researcher maintains that drugs are "vastly" overused in the treatment of personality disorders and that the system for diagnostic classification of personality disorder is ripe for change.

BY MARK MORAN

Personality disorders—like the patients who suffer from them—are complex phenomena, stubbornly resisting the trend in medical and psychiatric nosology toward simplification and standardization.

Much about them, including prevalence, etiology, biology, course, and treatment, remains to be learned or better elucidated, and their diagnostic classification is badly in need of refinement or overhaul, said Joel Paris, M.D., in a lecture at APA's 2006 annual meeting in Toronto in May.

Paris, who has published extensively on the subject of personality disorders, especially borderline personality disorder (BPD), said there have been repeated efforts to redefine personality disorders as variants of Axis I disorders—especially bipolar disorder and posttraumatic stress disorder—a move toward simplification that he said should be resisted.

"People want to have simple, well-defined diagnostic entities with specific treatments using drugs," Paris said. "Some Axis I diagnoses fit that model, but personality disorders don't. People try to explain them away in other ways. But what this is really about is the fact that the world is complicated, and personality disorders are complicated, even if no one wants it to be that way."

Paris noted, for instance, that some in the field have focused on the mood instability characteristic of BPD and have tried to suggest that BPD is really an expression of bipolarity.

"I think that's wrong, but it's a very popular idea," Paris said. He cited fellow BPD researcher John Gunderson, M.D., of McLean Hospital in Belmont, Mass., who has noted that it is difficult to find a BPD patient who has not been diagnosed with bipolar disorder and treated with a mood stabilizer. Yet mood stabilizers do not work as well with patients with BPD.

"This is more of a hope than evidence-based medicine," Paris said.

Another group has argued that BPD is a form of posttraumatic stress disorder, based on a belief in the prevalence of childhood trauma in patients' lives. Yet research findings have shown that this isn't the case.

"Patients are assumed to have had a childhood trauma when they haven't," Paris said. The effects of childhood abuse are broad and nonspecific, he said, citing community research showing that most people who experience some form of abuse never develop any mental illness.

"Most children are resilient, so abuse and trauma are risk factors but not causes," he said.

Paris is a professor and chair of the Department of Psychiatry at McGill University in Montreal and editor in chief of the *Canadian Journal of Psychiatry*. He is also a past president of the Association for Research in Personality Disorders.

Paris said recent research is helping to clarify issues around personality disorders, including diagnostic specificity, treatment outcome, and long-term course. A substantial body of knowledge has accumulated on some of the disorders, especially borderline and antisocial personality disorders. But much more about personality disorders remains to be learned and reconceptualized, and much of Paris's lecture was a catalog of the challenges to understanding, diagnosing, and treating these patients.

Especially problematic is the widespread overuse of drugs in the treatment of patients with personality disorders. "These patients are clinically difficult and noncompliant, and drugs don't have predictable results," Paris said. "They are vastly overused. Several patients have told me that when they learned they had a personality disorder, they were relieved. They said, 'I thought I was just a bad patient because I didn't get better on Prozac like everyone else.' "

Paris said it is not uncommon for patients with a personality disorder to be treated with as many as five drugs: a combination of multiple antidepressants, mood stabilizers, and benzodiazepines. "The problem is that there is no science to support polypharmacy, and it's probably bad for patients," he said.

Because comorbid depression is frequently a component of personality disorders, and clinicians are familiar with depression, they often opt to treat that aspect of a patient's condition with an antidepressant. But Paris said comorbidity is an artifact of the *DSM* system of classification, common to almost every condition in the manual.

"The response to medications is different," he said of patients with BPD and other personality disorders. "When you give patients with classical depression an antidepressant, they may be cured in a few weeks. But you never see that in patients with borderline personality. It might take the edge off, but patients never go into remission."

He added that several psychotherapies have been shown to be effective, though all

are lengthy and expensive. For BPD, Marcia Linehan's dialectical behavior therapy is the most extensively researched model; also promising are schema therapy, mentalization-based therapy, and the transference-focused therapy pioneered by Otto Kernberg, M.D.

Paris expressed dissatisfaction with guidelines for BPD that he said support polypharmacy and hospitalization. He said that hospitalization is "toxic" for BPD patients and has not been shown to prevent suicide.

He was critical as well of the commonly cited prevalence figure of 10 percent for personality disorders. "I don't believe this figure; I think it's much too high," he said. "By *DSM* criteria, it may be 10 percent, but we are cutting too broad a swath in thinking about personality disorders. We need to narrow down the concept. I would like to reserve the diagnosis for more severely affected populations."

Paris was emphatic that the system for diagnostic classification of personality disorders was ripe for change, saying it should be substantially revised in *DSM-V,* due in 2011. He was especially critical of the current categorical approach to diagnosis, whereby a patient who meets an arbitrary number of criteria has a disorder.

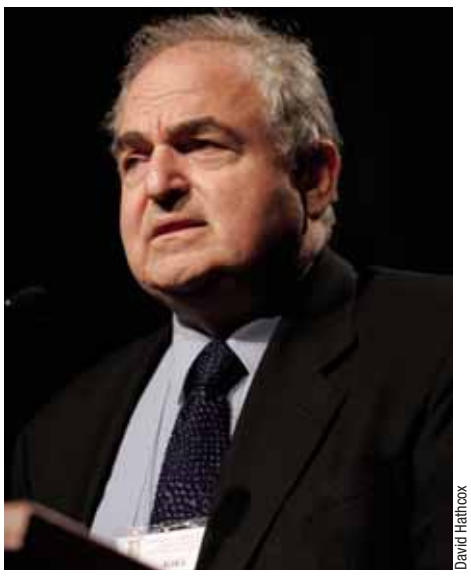
Among the more popular competing ideas for how to reconceptualize personality disorders is a "dimensional" model, whereby patients are assessed according to dimensions of personality functioning. One prominent system is the Five Factor Model in which personality traits are grouped into five encompassing dimensions: neuroticism, extraversion, openness to experience, conscientiousness, and agreeableness.

Paris cited the Collaborative Longitudinal Personality Disorders Study (CLPS), which was summarized last year in a paper in the October 2005 *Journal of Personality Disorders.* That study suggested that personality disorders may be reconceptualized as hybrids of stable personality traits and intermittently expressed symptomatic behaviors.

One intriguing finding from the study was that patients often cease to meet diagnostic criteria over time. That finding complements other studies showing that specific symptoms of personality disorders appear to diminish after age 40, though underlying personality traits persist.

"Most patients don't keep their diagnoses," Paris said at the Toronto lecture. "The question is whether they have really remitted. Even when they stop meeting

please see ***Personality*** *on page 34*



David Hathcox

Joel Paris, M.D.: "I would like to reserve the diagnosis [of BPD] for more severely affected populations."

Parents' Verbal Abuse Leaves Long-Term Legacy

Parental verbal abuse may wound children's psyches so deeply that the effects remain apparent in young adulthood. Such abuse may wreak psychological havoc greater than that caused by physical abuse.

BY JOAN AREHART-TREICHEL

With an M.B.A. degree under her belt, 24-year-old "Jaime" (not her real name) should have glowing job prospects in Chicago. But she harbors memories that erode her self-confidence and make her bristle with anger—memories of her father shouting at her, during drunken rages, that she was ugly and of little value.

Indeed, verbal abuse during childhood can scar people deeply, a new study suggests. It was headed by Martin Teicher, M.D., Ph.D., director of the Developmental Biopsychiatry Research Program at McLean Hospital, which is affiliated with Harvard Medical School. Results were published in the June *American Journal of Psychiatry*.

Although the injurious effects of child physical and sexual abuse have been the subject of considerable inquiry, not much attention has been paid to the possibly noxious effects of verbal abuse on children.

More than 500 young adults were recruited via advertisements to participate in the study. Each subject was evaluated for childhood exposure to verbal abuse, physical abuse, sexual abuse, and domestic violence. Each subject was also assessed for current anxiety, depression, anger-hostility, and symptoms of dissociation.

The researchers then looked to see if there were any associations between verbal abuse during childhood and current anxiety, depression, anger-hostility, and symptoms of dissociation; between other types of abuse during childhood and these current psychological problems; and how any associations for verbal abuse might compare with associations for other types of childhood abuse.

The strength of the association between maltreatment history and current psychological difficulties was determined by calculating the effect sizes and 95-percent confidence intervals for the differences between subjects who had no exposure to maltreatment and subjects exposed to the maltreatment categories. "Effect size is a more valuable measure for assessing the impact of an experience than the p value, which is strongly affected by group size," Teicher and his coworkers explained in their report.

Childhood verbal abuse had a relatively weak association with current anxiety, the investigators found, but it had moderate to strong links with current depression, anger-hostility, and dissociative symptoms.

Moreover, these links were stronger than those for being a victim of physical abuse during childhood. They were comparable to those for witnessing domestic violence during childhood and for being sexually abused by a nonfamily member during childhood.

The only form of child abuse that had a stronger link with current depression and dissociative symptoms than childhood verbal abuse was being sexually abused by a family member. And even it had a weaker connection with current anger-hostility than did childhood verbal abuse.

These results, of course, do not prove that childhood verbal assaults can cause psychological consequences in early adulthood since the investigation was of a retrospective rather than a prospective nature. Nonetheless, Teicher and his coworkers believe that it may well be the case. As they concluded in their report, childhood verbal abuse is "a potent form of maltreatment."

But perhaps the most interesting findings to emerge from their study came when they examined the links between more than one type of child abuse and current psychological difficulties.

They found, for example, an extraordinarily powerful link between the combination of verbal abuse and witnessing domestic violence and current dissociative symptoms. "This finding is consonant with studies that suggest that emotional abuse may be a more important precursor of dissociation than is sexual abuse," Teicher and his team said.

Indeed, the connections that Teicher and his group found between various combinations of child abuse and current psychological difficulties were so potent that they often equaled or exceeded the link between familial sexual abuse during childhood and current mental health. "This is of great importance," the researchers noted, "as it suggests that combined exposure to less blatant forms of abuse may be just as deleterious as the most egregious acts we confront."

The study was funded by the National Institute of Mental Health and the National Institute on Drug Abuse.

"Sticks, Stones, and Hurtful Words: Relative Effects of Various Forms of Childhood Maltreatment" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/6/993?>. ■

Positive Psychosis Symptoms Linked to Violence Risk

Command hallucinations and persecutory delusions are associated with episodes of violence among a large sample of people with schizophrenia, but serious violence by such individuals is infrequent.

BY EVE BENDER

Though violent behavior is the exception rather than the rule among people with schizophrenia, one large study found that positive psychotic symptoms such as persecutory ideation and grandiosity were associated with an increased risk of serious violence.

In contrast, negative symptoms such as passivity and social withdrawal were associated with a decreased risk of violent behavior.

"I think these findings reinforce the view that violence risk reduction should be an important goal and component of community-based treatment for schizophrenia and that risk reduction needs to focus on clinical as well as nonclinical factors that may contribute to violence," one of the study's investigators, Marvin Swartz, M.D., told *Psychiatric News*. Swartz is a professor and head of the Division of Social and Community Psychiatry at Duke University Medical Center.

Nonclinical factors related to violence in the sample included residing in restrictive housing (such as a halfway house, psychiatric hospital, or jail) or with family, not feeling "listened to" by family members, and a recent history of police contact.

Data came from baseline interviews of 1,410 people with schizophrenia enrolled in the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

The CATIE study was a randomized trial conducted between January 2001 and December 2004 at 56 clinical sites in 24 states to investigate treatment effectiveness and outcomes among patients with schizophrenia.

Each study site screened inpatients and outpatients for study eligibility. Those who were deemed to be appropriate for participation had adequate decision-making capacity and were receiving suboptimal treatment with antipsychotic medications due to problems with efficacy or tolerability.

During a baseline assessment and before the patients were randomized to experimental treatments for the CATIE study, lead investigator Jeffrey Swanson, Ph.D., and colleagues assessed the patients for violent behavior in the prior six months. He is an associate professor in the Department of Psychiatry and Behavioral Sciences at Duke.

To assess the generalizability of the sample, Swanson compared participants with a "quasi-random" sample of 1,413 patients enrolled in the Schizophrenia Care and Assessment Program, an observational study of schizophrenia treatment in the United States.

Though the CATIE sample had a lower proportion of minority patients, the two samples were similar in other demographic characteristics, age, and a variety of clinical characteristics.

The similarities provide "some confidence that the CATIE project's randomized, controlled-trial design did not result in a biased selection of more severely ill and impaired patients," the authors noted.

They used the MacArthur Community Violence Interview to measure minor and serious violence. Researchers defined minor violence as a simple assault without injury or weapon use (shoving or slapping another person, for example) and serious violence as assault using a lethal weapon or resulting in injury, threat with a lethal weapon, or sexual assault.

Researchers gathered information on violent acts by the subjects through patient self-reports and family collateral information (when available).

Researchers also assessed patients at baseline for factors such as available social support, severity of illness, and awareness of mental health problems, among others. They also used the Structured Clinical Interview for Axes I and II of *DSM-IV* Disorders–Patient Edition to confirm schizophrenia diagnoses and assess childhood conduct problems.

In addition, they used the Positive and Negative Syndrome Scale (PANSS) to rate severity of psychotic symptoms.

Among the 1,410 patients, the six-month prevalence of any violence was 19.1 percent: 219 patients (15.5 percent) reported minor violence, while 51 (3.6 percent) reported serious violence.

Both Clinical, Nonclinical Factors Play Role

Swanson found that serious violence was associated with several clinical and nonclinical factors.

For instance, those who scored above the median on the PANSS for positive psychosis symptoms had 2.71 times the risk for serious violence as those with lower scores.

minor violence included limited or no vocational activity, residing in "restrictive" housing with family, and not feeling "listened to" by family members.

"Studies show that when violent behavior occurs, it tends to involve family members and acquaintances much more often than strangers," Swanson noted. "People with severe mental illness may also experience emotional conflict within family relationships. . .that can contribute to the risk of violence."

He speculated that a "cause-and-effect connection" might play a role in the link between minor violence and lack of a job. "Being unemployed and having no meaningful work to do—especially over a long period of time—can be stressful and may indirectly increase risk of assaultive behavior in people with schizophrenia."

Majority Do Not Act Violently

Swanson emphasized that the majority of patients with schizophrenia have positive psychotic symptoms but do not engage in violent behavior.

He acknowledged that "serious violence [among people with schizophrenia] may be unlikely, but it's a bad thing when it happens" and that clinicians and advocates for patients' rights may have different interpretations of the study findings.

"Psychiatrists worry about patient violence not because it's especially common, but in part because of clinicians' legal liability for adverse, but rare, outcomes of their treatment decisions."

In contrast, patients' rights advocates, who often oppose involuntary treatment, may be concerned because national surveys have shown that the "majority of the public believes (erroneously) that mentally ill people are generally dangerous," and this belief could be used to justify legal strategies for overriding people's right to refuse mental health treatment, Swanson said.

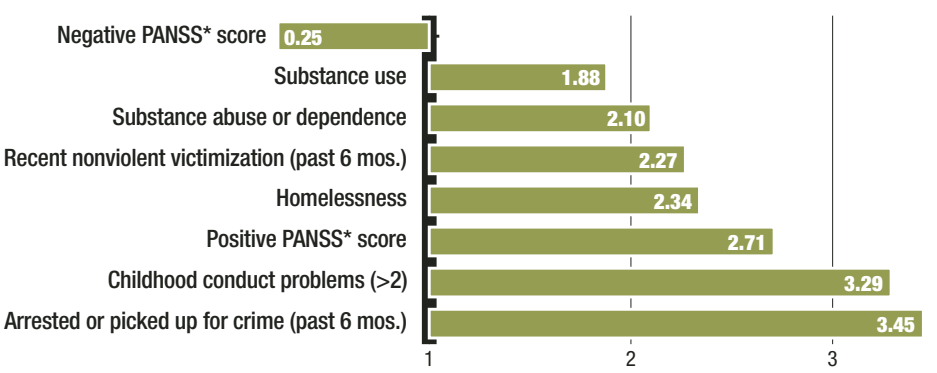
He noted that homicides or other serious violent acts committed by a person with schizophrenia usually become "banner headlines" in newspapers "even if other potential factors are involved" in the violent act. "You will not read a companion story about the thousands of other people with mental illness in the same city who never did anything violent."

The findings, he continued, "reinforce the view that violence risk-reduction should be an important goal of community-based treatment for schizophrenia"

please see ***Psychosis*** *on page 38*

Risk Factors for Committing Serious Violence

In a sample of patients with schizophrenia in a number of settings, those with positive (above the median) PANSS* scores had 2.7 times the risk of committing an act of serious violence. In contrast, those who scored above the median on the PANSS negative symptom subscale were .75 times less likely to commit an act of serious violence.



*The Positive and Negative Syndrome Scale (PANSS) is a clinical rating scale of individual psychotic symptoms on a 7-point scale from "symptom absent" to "extreme." Researchers analyzed two subscales for positive and negative psychotic symptoms.

Source: Jeffery W. Swanson, Ph.D., et al., *General Archives of Psychiatry,* May 2006

Patients who scored above the median for negative psychotic symptoms had about a quarter of the risk as those who scored below this point.

People with suspiciousness and persecutory delusions also had an increased risk of engaging in serious violence (odds ratio 1.46, p<.001), as did those who responded to hallucinations (odds ratio 1.43, p<.001).

Also, serious violence was significantly associated with grandiosity (odds ratio 1.31, p=<.001) and excitatory symptoms (odds ratio 1.30, p=.02).

In addition, the findings showed that 27.5 percent of those who committed serious violence were arrested, and 16.1 percent of those with minor violence were arrested for some crime in the previous six months. Arrest data were gathered by self-report.

Swanson told *Psychiatric News* that he thought that positive psychotic symptoms may lead to violence in several ways: "A person with a severe thought disturbance may hear voices directing him or her to attack someone else," he said. With persecutory delusions, "a person may act on a false perception of threat of harm from someone" in which case "a violent act might seem like self-defense from the distorted perspective of the person with psychosis."

Younger age, childhood conduct disorder problems, and a history of arrests were nonclinical factors associated with serious violence, the researchers found.

Nonclinical factors associated with

Can Treatment Prevent Violence?

While findings from the CATIE study on violence cannot be disputed—3 percent to 6 percent of people with schizophrenia in the sample engaged in serious violence in the six months before a baseline interview (see article above)—the issue of how those findings should be applied to people with serious mental illness is a divisive one.

Treatment Advocacy Center Director Mary Zdanowicz, J.D., and Bazelon Center for Mental Health Law Director Robert Bernstein, Ph.D., agreed that the study is important because it sheds light on the correlates of violence among people with schizophrenia.

But while Zdanowicz believes that the findings should support laws that mandate treatment for people who are a danger to themselves or others, Bernstein does not.

The Treatment Advocacy Center is a nonprofit organization dedicated to eliminating barriers to treatment; it advocates for assisted outpatient treatment. The Bazelon Center describes its mission as protecting and advancing the rights of people with mental illness.

"This study isn't designed to create an argument for legal intervention," Bernstein told *Psychiatric News*. Since the CATIE study does not establish a causal relationship between violence and patients' clinical characteristics, "any attempt to jump to a conclusion that we can prevent violence is preposterous," he said.

Zdanowicz noted that the study "helps us better understand the specific array of symptoms that increase the risk of violence," and said the study provides clinicians and others with "the hope of identifying who is at risk for violence and managing that risk by ensuring that they get the treatment they need."

Adult Separation Anxiety Often Overlooked Diagnosis

Adult separation anxiety disorder is often mistaken for fear of being in situations from which escape might be difficult, but is a surprisingly prevalent condition.

BY JOAN AREHART-TREICHEL

If the American public were asked to give an example of adult separation anxiety disorder, they might cite the classic Hollywood film "Casablanca," where Ilsa (Ingrid Bergman) clings to Rick (Humphrey Bogart) shortly before they part forever. Or they might point to the Hollywood thriller "Psycho," where lead character Norman Bates (Anthony Perkins) sleeps next to his mother long after she has died.

Adult separation anxiety disorder is more than the stuff of Hollywood, though. It afflicts some 7 percent of Americans at some point in their lives, according to a new study.

"The results did not really surprise me," Katherine Shear, M.D., a professor of psychiatry at Columbia University and the lead investigator, told *Psychiatric News*. "Our group in Pittsburgh, as well as colleagues in Australia and in Italy, have observed adult separation anxiety disorder in clinical populations for a number of years now. It is clear that this is an identifiable syndrome."

The investigation conducted by Shear and her colleagues appears to be the first to explore the prevalence of adult separation anxiety disorder in the American population. Data for the inquiry were collected as part of the National Comorbidity Survey Replication, which has already provided a treasure trove of information about the prevalence and treatment of psychiatric disorders (*Psychiatric News*, July 1 and July 15, 2005).

Still other notable insights into adult separation anxiety disorder have emerged from the study by Shear and her team. For example, the prevalence of the disorder in the United States is even greater than that of childhood separation anxiety disorder, which is 4 percent. While some Americans with the adult version first experienced it during childhood, the vast majority encountered it once they reached adulthood. Adult separation anxiety disorder often occurs along with other psychiatric illnesses, especially other anxiety conditions or mood disorders.

Further, adult separation anxiety disorder is often associated with personal and social impairment—many Americans with it are poorly educated, unemployed, and unmarried—even when other psychiatric illnesses are not present. And while 75 percent of Americans with the condition are receiving treatment, most are receiving help for comorbid conditions rather than for separation anxiety per se.

These results have implications for clinical psychiatrists, Shear believes. "They need to be aware of the occurrence, prevalence, and comorbidities of this syndrome, which could be confused with agoraphobia and which could complicate another Axis I disorder, since it is co-occurring with so many. Following the principle of measurement-based care, it will be very important to follow these symptoms in patients who are treated for adult separation anxiety and/or co-occurring conditions."

Even with the insights obtained from this study, a lot more needs to be learned about adult separation anxiety disorder, Shear and her group pointed out in their study report, which appeared in the June *American Journal of Psychiatry*.

For instance, when is the dependence of family members on each other culturally determined and acceptable, and when is it pathological? When is angst about separation from a loved one during war, natural catastrophes, or other dire circumstances to be expected, and when is it not? And what are normal and abnormal responses to the loss of a loved one? Shear, in fact, is exploring these issues (*Psychiatric News*, August 20, 2004; July 15, 2005).

The study by Shear and her team was financed by the National Institute of Mental Health, John D. and Catherine T. MacArthur Foundation, Pfizer Foundation, U.S. Public Health Service, Pan American Health Organization, Eli Lilly and Co., and GlaxoSmithKline.

"Prevalence and Correlates of Estimated* DSM-IV *Child and Adult Separation Anxiety Disorder in the National Comorbidity Survey Replication" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/6/1074?>. ■

Treatments

continued from page 16

outcomes associated with the use of VNS compared with the outcomes of treatment as usual without VNS therapy.

A second initiative is Cyberonics' launch of a patient registry of treatment-resistant patients who receive VNS therapy. The registry, which will be administered by Martin Keller, M.D., a professor and chair of psychiatry at Brown University, currently involves 22 medical centers across the country and may involve up to 100 centers that will enroll 2,000 patients in the registry. The longitudinal, prospective, observational registry will track clinical course and outcomes for patients with VNS and without.

TMS Data Look Promising

Neuronetics Inc. released results of the first multicenter, controlled clinical trial of its transcranial magnetic stimulation (TMS) therapy at a symposium at APA's annual meeting. In contrast to the invasive nature of VNS (which requires surgical implantation), TMS is noninvasive (*Psychiatric News*, July 1, 2005).

During a TMS therapy session, a patient sits in a chair similar to those found in dental offices with the TMS machine directed at the patient's skull over the left prefrontal cortex. The device looks similar to a dental X-ray machine. The TMS apparatus uses a strong, highly focused magnetic field—much like MRI technology—to create a focal electrical current in the brain tissue. The therapy does not require anesthesia or sedation, so patients can drive themselves home immediately following their 40-minute treatment.

The "NeuroStar TMS therapy system" is currently under review by the FDA, with an approval anticipated by Neuronetics sometime around early 2007, said Mark Demitrack, M.D., a vice president and chief medical officer at Neuronetics.

The company's pivotal trials of TMS therapy involved 301 patients with depression who were unresponsive to at least one previous adequate antidepressant therapy at 23 clinical research institutions in the United States, Canada, and Australia. Previously, TMS had been studied (for about a decade) in small, single-site studies with small numbers of patients.

Neuronetics completed two studies lasting four to six weeks, the first an acute efficacy and safety trial including a double-blind "sham TMS" control. In sham TMS, internal modifications were made to shield the TMS system magnet so that therapy with random patients would outwardly appear to progress normally but no magnetic stimulation could reach their brains. The system modifications were made by persons not involved in the clinical aspects of the trial. Neither the patients nor the clinicians knew whether specific patients were in the active therapy group or in the sham-control group.

A second four- to six-week study was also conducted with an open-label, crossover design with the patients who did not respond to the double-blind sham-controlled trial. Then, all patients who improved (defined as at least a 25 percent decrease from baseline in total score on the Hamilton Depression Rating Scale-17 Item at study completion) in either of the four- to six-week trials were entered into a "maintenance of antidepressant effect" trial lasting six months.

Overall, patients studied were in a recurrent episode of major depressive disorder and were roughly equal in terms of gender, averaged 48 years of age, and had a mean duration of their current depressive episode of about 13 months. The average number of verified antidepressant treatment failures per patient was 1.6 for the current depressive episode. The patients were severely depressed, with average Montgomery-Asberg Depression Rating Scale scores around 33 and Hamilton scores around 23.

Patients receiving active TMS improved significantly more than the sham patients by week 4. Response rates in the active group were generally about two-fold higher than those with sham-TMS by week 4, and remission rates were also about two-fold higher in the active group compared with the sham group by week 6. Reflecting the severity of the patients' illness, placebo response rates were low, averaging 11 percent at week 4 and 13 percent at week 6.

Importantly, in the six-month extension study, efficacy was well maintained through the end of the study. TMS, even at high-intensity administration, was safe with no seizure activity in any patients, no negative auditory or cognitive effects, and a general absence of typical side effects of antidepressant medications.

The most frequent treatment-emergent adverse events associated with active TMS, compared with sham-TMS, were pain at the application site, including facial discomfort or pain, toothache, skin pain, and muscle twitching.

Clinical Urgency Remains

While the data continue to be very favorable, the clinical urgency to help patients with treatment-resistant depression remains, Neuronetic's Demitrack said, especially in light of the recent reports from the National Institute of Mental Health's STAR*D study of pharmacotherapy of treatment-resistant depression.

Neuronetics' data show a comparable degree of efficacy with STAR*D level 2 data, "albeit with a greater degree of treatment resistance and a much reduced adverse-event burden," Demitrack told *Psychiatric News*.

TMS has broad effects on brain activity, as well as in specific areas of the brain associated with mood, Demitrack added. Most of the therapeutic effects of TMS appear to involve dopamine; however, lesser effects have been noted with serotonin and norepinephrine.

"As such, TMS may have different or added long-term effects," Demitrack concluded. "TMS may also have implications for other uses, in other psychiatric disorders such as schizophrenia, and possibly obsessive-compulsive disorder, as well as in nonpsychiatric disorders such as epilepsy, chronic pain, and poststroke rehabilitation." ■

Erratum

In the June 2 issue, the name of the residency program whose psychiatry residents have all become APA members recently was incorrectly given as the Mt. Sinai School of Medicine. The correct name is Mt. Sinai Affiliated Hospitals-Elmhurst Hospital Center, located in Queens, N.Y. ■

BPD

continued from page 24

hood a source of positive self-esteem and security, whereas others can be immobilized by the conflicts related to nurturing or disciplining their children, according to the report.

"Clinicians have often been exposed to borderline patients who found the stress of mothering overwhelming," Gunderson said. "Whenever they felt angry at their child, they felt they were bad and became self-destructive. This study sheds light on the other side of this. Many borderline patients have found the mothering experience a source of stability and self-esteem. They are less apt to reappear in treatment settings. Knowing this has made me more circumspect about advising women with borderline personality disorder whether to have children or not."

"Predictors of 2-Year Outcome for Patients With Borderline Personality Disorder" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/163/5/822>. ■

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

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

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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/m^2 basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m^2 basis, respectively) through 128 weeks.

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

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy
Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m^2 basis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Psychiatric Disorders: *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paronira, 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/m^2 basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

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

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

OVERDOSAGE
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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Trauma, Violence to Get Multidisciplinary Focus

APA's fall meeting will be held October 5 to 8 in New York. It will focus on addressing trauma and violence at the community level.

BY CHARLES W. HUFFINE JR., M.D.

It is dazzling to chair the Institute on Psychiatric Services in the year that it is being held in New York City. What glory for a Seattle boy who loves the Big Apple and would have loved to spend a year or two of my life there. This meeting will be a big one, not only because so many of our community-practice members live in, or close to, New York City, and not only because of the city's draw for the rest of us, but because we have a program that is cutting edge and relevant to your work.

When Pedro Ruiz, M.D., APA's incoming president, and I developed the theme for the institute, "Trauma and Violence in Our Communities," 9/11 was a painful memory no longer needing to be thrashed over once again at our meetings, and Katrina had not yet happened. But the buzz about disasters had persisted, and we felt that there was a sense of danger in our communities and in our world. This year's institute captures that concern in a thousand different ways, as it affects our patients, especially those with severe psychiatric illness; ourselves; and the population at large. The lineup of lecturers will touch on aspects of this theme, as will many of the symposia and workshops. They will be interspersed with solid clinical presentations and a series of medical updates.

The institute is the home meeting of the American Association of Community Psychiatrists (AACP). Its program gives us inspiration and ideas that help our local programs and keeps us going another year. Do note the number of program items that are jointly sponsored by APA and the AACP.

In the spirit of community practice, APA has made this meeting welcoming to allied professionals. The American Orthopsychiatric Association will be offering a program element again this year, as will the Therapeutic Education Association, a regular at the institute. We are proud of the institute's large cross-professional attendance.

Recovery is a concept whose value is being increasingly appreciated throughout the treatment community, given the clear mandate for system transformation from the President's New Freedom Commission on Mental Health. Many speakers will be focusing on recovery, and we are sure that community psychiatrists will leave the institute with renewed enthusiasm for the concept.

Last year, Celebration Recovery, a consumer and family fair and celebration funded and organized by the Irwin Foundation, held one of its events at the institute. Many such celebrations have occurred all over the country in parks and halls in association with chapters of the National Alliance on Mental Illness or consumer groups. We had no idea how the event would turn out. About 200 psychiatrists came to Celebration Recovery, not having a clue what it was. It had all the magic of a 1960s "happening" —with a sense of fun, hopefulness, and creative energy reflected in a remarkable art exhibit, performances, and speeches. We estimated that nearly 600 consumers and their families came to Celebration Recovery. The amazement on their faces told the story of their appreciating what is truly meant by recovery.

Our own Michael Schwartz, M.D., Joan Clayton Ph.D., and their team from the Irwin Foundation are bringing Celebration Recovery to this year's institute. It will be bigger and more spectacular—a testament to the healing force of hope and positive expectations.

So come to this year's institute, go out on the town, and gather with friends and colleagues. It is often said that the institute is a friendly and intimate meeting, and that's not surprising—community psychiatrists know how to have fun. We are very embracing of all our psychiatric colleagues and will help them find the community psychiatrist within, yearning to be free!

I want to end by giving special thanks to Dr. Ruiz, who has been an inspiration to work with; Jay Scully, M.D., our APA medical director, who values the institute as a critical gathering for APA; and our lead staff person, Jill Gruber.

More information about this meeting, including the preliminary program, is posted at <www.psych.org/edu/ann_mtgs/ips/06/index.cfm>. The preliminary program may also be obtained by calling (888) 35-PSYCH. ■

Charles W. Huffine Jr., M.D., is chair of the Scientific Program Committee of the Institute on Psychiatric Services.

How to Register

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

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

apa institute

Medical Updates to Highlight HIV and Lung, Eye Disorders

Since mind and body affect one another, APA's institute is including updates on four medical topics of relevance to psychiatry.

BY SPENCER ETH, M.D.

While New York City is known for its world-class theatric, artistic, athletic, musical, and financial performances, it also boasts an impressive concentration of medical schools and teaching hospitals. Indeed, there are four medical schools affiliated with multiple hospitals in Manhattan, two in the other boroughs, and three in nearby counties. Drawn from this distinguished pool of medical talent are four academic physicians who will be featured in the medical update series at APA's 58th Institute on Psychiatric Services, to be held in the Big Apple October 5 to 8.

These four sessions are intended for a general medical audience, and each will cover a topic area of special significance to psychiatrists.

On Thursday, October 5, at 8 a.m., Kenneth M. Prager, M.D., will discuss pulmonary disease. This topic is especially important because of the staggering prevalence of cigarette smoking among people with mental illness. Prager will review the evaluation of pulmonary functioning, the effects of smoking and pollution, and the diagnosis and treatment of asthma, chronic obstructive and interstitial lung disease, and pulmonary neoplasms.

Prager is a graduate of Columbia University and Harvard Medical School. He was trained in internal medicine at Columbia-Presbyterian Medical Center in Manhattan and Billings Hospital of the University of Chicago. In addition to his work as a clinical professor in the Division of Pulmonary and Critical Care of Columbia University College of Physicians and Surgeons, he serves as the director of clinical ethics and chair of the Medical Ethics Committee at New York Presbyterian Hospital.

At 10 a.m. that day, Joseph Z. Lux, M.D., will discuss HIV and AIDS. Although neuropsychiatric and psychosocial issues pertaining to HIV will be addressed in an institute symposium, this presentation will focus on the medical progress in evaluating and treating patients infected with the virus and its common comorbidities.

Lux is board certified in internal medicine and infectious disease in addition to psychiatry. He completed a residency in internal medicine at New York University and an infectious disease fellowship at Columbia University College of Physicians and Surgeons before training in psychiatry at St. Vincent's Hospital in Manhattan. Lux is an attending psychiatrist in the HIV and consultation-liaison services at Bellevue Hospital and an assistant professor at New York University School of Medicine.

Also on Thursday, at 3:30 p.m., James C. Tsai, M.D., will offer an overview of ophthalmology, a topic that is particularly relevant as baby boomers—both our patients and ourselves—grow older. Tsai will discuss the latest advances in the diagnosis and medical and surgical management of glaucoma, macular degeneration, cataracts, and corneal disease.

Tsai completed his medical degree at Stanford, his residency at the University of Southern California's Doheny Eye Institute, and two clinical fellowships at Bascom Palmer Eye Institute in Miami and at the Moorfields Eye Hospital in London. He is an associate professor of ophthalmology and director of the Glaucoma Division at the Harkness Eye Institute of Columbia University College of Physicians and Surgeons.

On Friday, October 6, at 10 a.m., F. Russell Kellogg, M.D., will discuss preventive health care. Timely care provided by primary care physicians can reduce the death rate among people under age 65. Kellogg will analyze current medical evidence for common preventive interventions, including screening, immunizations, and counseling. He will also discuss the role of routine health examinations and testing for asymptomatic persons and the value of understanding each patient's risk profile.

Kellogg is a graduate of New York Medical College and is a board certified internist and geriatrician with a faculty appointment at New York Medical College. He has spent his career in the Department of Community Medicine at St. Vincent's Hospital in Manhattan. For the past five years he has served as department chair and director of the primary care adult medicine resident training program.

More information on the institute is posted at <www.psych.org/edu/ann_mtgs/ips/06/index.cfm>. ■

Spencer Eth, M.D., is the local arrangements consultant for APA's 2006 Institute on Psychiatric Services.

KNOWTHEFACTS

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

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

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Side Effects

continued from page 1

als of Intervention Effectiveness). That analysis revealed that large percentages of patients who enrolled in the 18-month comparative treatment study already had comorbid disorders that significantly increased their risk for cardiovascular disease, even before receiving any study medications. (The average patient in CATIE had been diagnosed 14 years before entering the study and had taken numerous antipsychotics previously.)

"I think this is probably the single most important finding in the CATIE study," noted Henry Nasrallah, M.D., a professor of psychiatry, neurology, and neuroscience at the University of Cincinnati College of Medicine and a CATIE investigator. CATIE allowed investigators to determine "to what degree patients were at high risk when they entered CATIE, and what happened to them when they received certain antipsychotics within the CATIE [protocol]."

Results from CATIE largely confirmed what other studies have reported over the last five to seven years, Nasrallah said. "Some antipsychotics worsened the [patients'] metabolic condition, and other [medications] helped them by lowering their weight, lowering [blood glucose levels], and lowering their lipids."

Somewhat surprising, Nasrallah said, was the finding that 42 percent of the 1,460 patients initially enrolled in CATIE met criteria for metabolic syndrome. Metabolic syndrome is a constellation of signs and symptoms that taken together signal a significantly increased risk of death by cardiovascular disease (see box).

However, Nasrallah reported at the press briefing and in a new research poster presentation that these were the truly troubling findings: 45.3 percent of the patients who had diabetes when they initially enrolled in CATIE were not receiving any treatment to help control their blood glucose levels; 89.4 percent of the patients who had hyperlipidemia at baseline were not taking a statin medication to lower blood lipid levels; and 62.4 percent of the patients who met criteria for hypertension at baseline were not receiving antihypertensive pharmacotherapy.

Missing the Forest for the Trees

Similar data were presented at APA's annual meeting by John Kane, M.D., chief of psychiatry at Zucker Hillside Hospital in Glen Oak, N.Y. Kane is leading a large international study, funded by Pfizer, that is examining cardiac risk factors in patients with schizophrenia. To date, that study—the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC)—has enrolled more than 17,000 patients who have schizophrenia and are taking a variety of antipsychotic medications. ZODIAC will attempt to determine whether ziprasidone (Geodon) can mitigate cardiovascular risk factors associated with other antipsychotic medications.

At baseline, 19 percent of ZODIAC patients had hypertension, and 16 percent met criteria for hyperlipidemia, yet less than 3 percent were taking any antihypertensive or statin medications. Nearly two-thirds of the patients met criteria for obesity, and 8.3 percent had diabetes.

"Clearly," Nasrallah said at the press briefing, "our patients with schizophrenia are subject to double jeopardy, as I like to call it. On the one hand, they have a high risk of metabolic disorders that shorten their lives and cause early heart disease. On the other hand, they are not getting appropriate and necessary treatment" for these problems.

Guidelines Not Being Followed

Nasrallah believes the most significant factor underlying the lack of treatment for cardiovascular risk factors in patients with serious mental illness is clinicians' failure to identify and monitor metabolic adverse effects.

"Are psychiatrists actually checking their patients at baseline?" Nasrallah asked. "Do they measure and follow their patients' obesity, their hypertension, their hyperglycemia and hyperlipidemia?"

In February 2004, APA joined with the American Diabetes Association in issuing a consensus statement calling for standardized monitoring of metabolic adverse effects associated with the use of SGAs (*Psychiatric News*, March 5, 2004). It was also endorsed by the American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity.

The statement included a summary review of evidence showing that not all six of the SGAs appeared to be equally associated with metabolic adverse events and recommended specific laboratory tests that should start at baseline, prior to the patients' first dose of antipsychotic medication, and continue at regular intervals through the first five years of antipsychotic therapy.

Based on data from several studies presented at APA's annual meeting, it appears that less than 10 percent of patients on the medications are being monitored using the APA/ADA consensus protocol.

New research presented at APA's 2006 annual meeting by Brian Cuffel, Ph.D., and Antony Loebel, M.D., of Pfizer revealed that after release of the APA/ADA consensus statement, only 6 percent to 8 percent of patients in their study taking SGAs completed the recommended baseline evaluation of serum lipid levels along with follow-up measurement three months after initiation of antipsychotic therapy. Similarly, only 16 percent to 23 percent of patients underwent recommended baseline and follow-up serum glucose testing.

To see whether baseline monitoring and follow-up of patients improved after the release of the consensus statement, Cuffel and Loebel compared data on 21,848 patients before the statement's release and 8,166 patients six months afterward. The researchers were surprised to find little improvement. While baseline monitoring was more common than follow-up, monitoring rates actually declined after antipsychotic treatment was initiated.

The obvious disconnect between recommended monitoring of serious adverse events and what actually occurs with patients taking antipsychotics is of "growing concern," Newcomer said.

"The good news is, there are efforts now under way" to educate doctors about the importance of monitoring, he added. "And there's a sort of groundswell of interest" in making sure recommended monitoring is performed appropriately.

The APA Subcommittee on Antipsychotics and Metabolic Risk, Newcomer added, will soon issue a white paper summarizing SGAs' differential metabolic risk and the monitoring protocols that should help to prevent or reduce serious adverse events. In addition, the National Association of State Mental Health Program Directors recently held a policy meeting and will issue a report soon.

Finally, Nasrallah noted, increasing evidence indicates that initial impressions of differential adverse effects among the SGAs exist. "There are antipsychotics that are completely metabolically weight-neutral, lipid-neutral, and glucose-neutral. There are other antipsychotics that significantly increase [all three]. We need to match the patient with the drug and get the safest medication for patients who are at the highest risk"

Newcomer agreed. "This is a variable that psychiatrists are potentially in a position to control." ■

To be diagnosed for metabolic syndrome, patients must exhibit at least three of the following five criteria:

1. Obesity as measured by a waistline exceeding 40 inches for males or 35 inches for females.
2. Fasting serum triglyceride levels above 150 mg per deciliter.
3. Serum high density lipoprotein (HDL) levels below 40 mg per deciliter for males or 50 mg per deciliter for females.
4. Hypertension defined by an increase in systolic, diastolic blood pressure, or both, above 130/85.
5. Hyperglycemia defined by elevated fasting serum glucose levels greater than 110 mg per deciliter (some use glucose levels above 100 mg/dL).

letters to the editor

STAR*D Clarification

We noted with interest that the article "For Nonremitting Depression, Add Rather Than Switch" in the April 21 issue describes the results of the NIMH Sequenced Treatment Alternative to Relieve Depression trial (STAR*D). Unfortunately, the headline gives the wrong impression of the study results.

After treatment with citalopram failed to bring patients to remission, patients and clinicians had some choice in the groups of treatments that were available for next-step randomization. They could either choose to add another medication (bupropion-SR or buspirone), they could switch to another medication (bupropion-SR, sertraline, or venlafaxine-XR), or they could accept options that included either adding cognitive-behavioral therapy (CBT) or switching to CBT (Rush et al., 2004). Another option was for patients to choose to be randomized to any one of all available treatments. This strategy is called "equipoise randomization" (Lavori et al., 2001). This design allows patient preference to be a factor in treatment allocation. Consequently, patients were not forced to a randomization to either a switching or adding strategy.

This patient preference may introduce a confounding variable, which can preclude a direct comparison of the two strategies. Indeed, in our study most patients and clinicians chose to either add or switch, but not both; consequently, the results from adding medication cannot be compared with the results from switching medications. Therefore, results do not indicate that adding is preferred over switching. Instead, we believe the results suggest that either adding or switching appears reasonable.

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For the the STAR*D Team

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clinical & research news

Personality

continued from page 27

DSM criteria, their functional scores don't change. They continue to have serious problems. Borderlines may stop cutting themselves and may stop overdosing—that's worth something—but it doesn't mean they are cured. To me the CLPS findings present an important challenge to the current criteria in *DSM* Axis II."

Despite the difficulty that the concept of personality disorder presents to clinicians and researchers, it remains a valid diagnosis and applies to up to 25 percent of most psychiatrists' patients. For this reason, he said personality disorders have been referred to as a "stepchild" of psychiatric nosology—challenging to embrace, but undeniably a member of the family.

"Psychiatry's stepchildren may have come of age," Paris said. "They are unique disorders, not simply variants of Axis I disorders, and diagnoses of personality disorders are associated with serious morbidity. Etiology and pathogenesis need a lot more research, but the prognosis is much better than we used to think. BPD does seem to improve over time, so we can tell our patients, 'Yes, you have borderline personality, but you are going to get better.' " ■

Old But New

I read with interest the article "Residency Program Combines Child, General Psychiatry" in the March 3 issue. I was surprised that this combined training seemed like a new and suddenly creative concept. Thomas Anders, M.D., wrote, "Now we have regulatory concurrence that integrated training is feasible. We are left with how to implement this."

Certainly, one place to look for proof is Duke University Medical Center. Drs. John Fowler and Ewald Busse had a four-year combined program for child psychiatry training already in place when I entered in 1970. The general residents were part of the same program, starting their child rotations in year one. Thus, this "new" concept is at least 36-plus years old.

WILIAM BEUTE, M.D.
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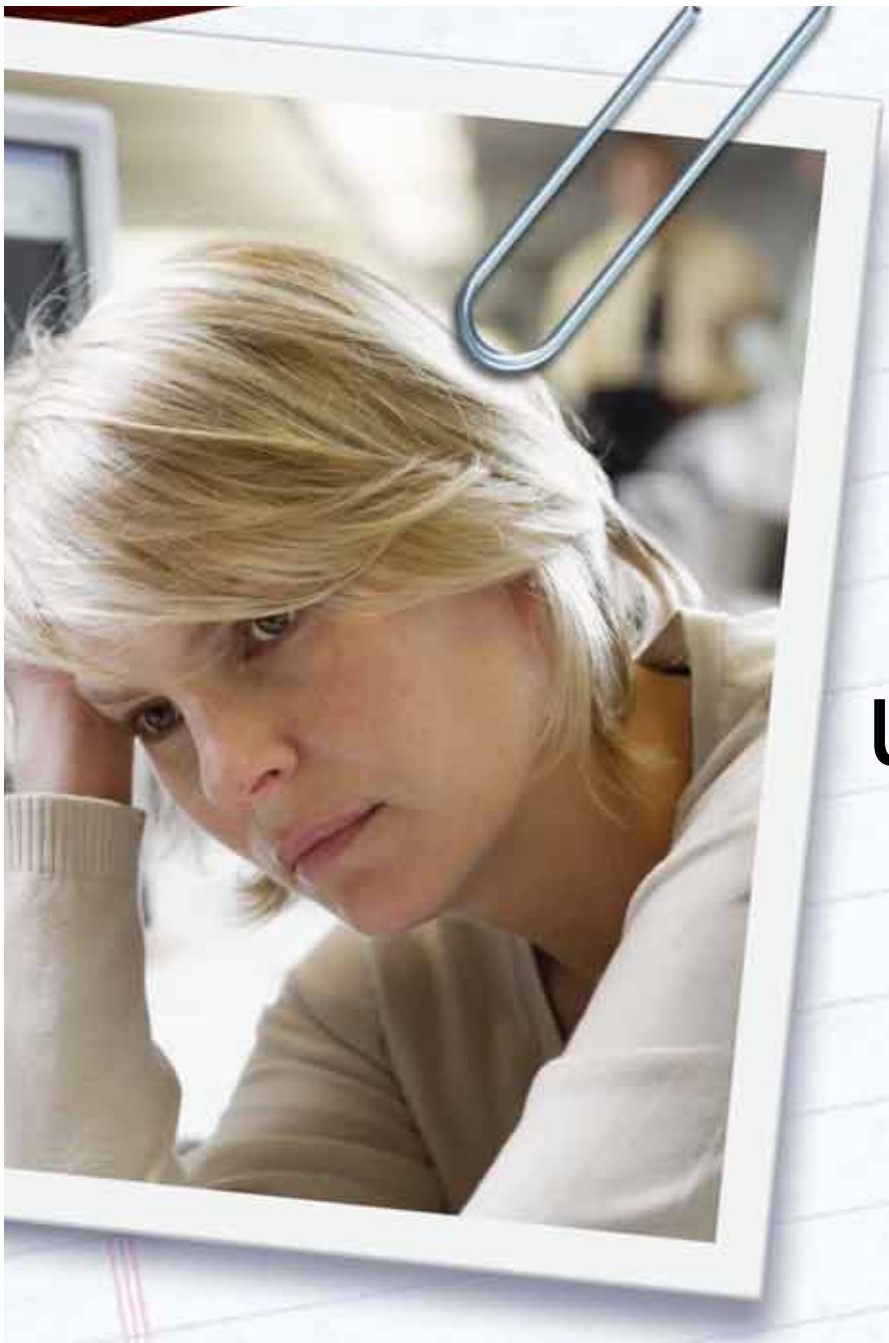

Still working to solve the problem of unresolved depression?

residual symptoms

sadness
low energy
anxiety

relapse

recurrence

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

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

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

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

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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 discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.
- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

Please see brief summary of Prescribing Information on adjacent page.

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

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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), 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, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, breast pain, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C019, revised November 2005.

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Control acute agitation with

GEODON®

*for **Injection** (ziprasidone mesylate)*

In schizophrenia…

Rapid improvement with low EPS[1,2]

- Significant control achieved between 15 and 30 minutes* after injection[1,3]
- Proven advantages over haloperidol IM
  - twice the improvement as measured on the BPRS[4†]
  - significantly lower incidence of movement disorders[2‡]
- Smooth transition, with continued improvement, from IM to oral therapy[2,4]
- May be used concomitantly with benzodiazepines

*In 2 pivotal studies vs control, significance was achieved at 15 minutes (with 10 mg dose) and 30 minutes (with 20 mg dose), respectively.

†In a 7-day, open-label IM-to-oral transition study.

‡In a 6-week, open-label IM-to-oral transition study.

GEODON®
***Oral Capsules** (ziprasidone HCl)*
*and **Injection** (ziprasidone mesylate)*

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

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

In fixed-dose, pivotal studies, the most commonly observed adverse events associated with the use of GEODON for Injection (incidence ≥5%) and observed at a rate in the higher GEODON dose groups (10 mg, 20 mg) of at least twice that of the lowest GEODON dose group (2 mg control) were somnolence (20%), headache (13%), and nausea (12%).

Please see brief summary of prescribing information on adjacent page.

Treatment Choices

continued from page 2

ation or attempts, all of whom were receiving mirtazapine.

In their report, Fava and his colleagues said that "there is no clear advantage in switching to either one of these two treatments for outpatients who have not responded to multiple treatment trials." They also concluded that "the use of successive monotherapies results in only modest remission rates, even when the antidepressants have pharmacological profiles that clearly differ from those of previous agents," as was the case in the three levels of STAR*D.

"I think the issue here," Fava told *Psychiatric News*, "is that combining agents, as in adding or augmenting strategies, should be considered as an alternative."

The overall message, he continued, is that after a first failed antidepressant trial, whatever strategy you try next—switching or augmentation—appears to work. After two [consecutive] failed antidepressant trials, what you try next may, in some ways, have greater impact."

Fava maintains that more research is needed to define more clearly the best options for particular subclasses of patients. Pending reports from the STAR*D Study Team may help address these issues.

In an accompanying editorial, Matthew Menza, M.D., an associate professor of psychiatry and director of the Affective Disorders Program at the Robert Wood Johnson Medical School, calls STAR*D "a laudable endeavor." The study's results will continue to be published, he added, "and beyond this first wave, we will continue to see results that may affect our practice."

He cautioned, however, that "clinical trials tell us how groups of patients do on average. For an individual patient, a particular treatment may or may not work. These trials do not tell us which patient will respond to which treatment; they merely suggest what treatment is most likely to be helpful."

As for the relatively small and nonsignificant difference between mirtazapine and nortriptyline in level 3, Menza wrote, "We are left wondering whether the difference was mere chance or if we really should be using tricyclic antidepressants, such as nortriptyline, more than we currently do."

"A Comparison of Mirtazapine and Nortriptyline Following Two Consecutive Failed Medication Treatments for Depressed Outpatients: A STAR*D Report" is posted at <http://ajp.psychiatryonline.org/> under the July issue. ■

clinical & research news

Violence

continued from page 18

from dialectical-behavioral therapy if they engage in an impulsive, reactive type of violence, Stankowski noted.

However, such treatment may not work for those with antisocial traits who plan a violent act in a "calculating" manner, she said.

Even violent offenders with mental illness and a history of medication noncompliance can benefit from treatment, according to information presented at the workshop.

To help attendees better understand how violent patients may be treated on an inpatient unit, Susan Hatters-Friedman, M.D., a senior instructor in psychiatry at Case Western Reserve University in Cleveland, presented the case of "Billy," a 30-year-old patient with schizoaffective disorder, borderline personality disorder, and mild mental retardation.

At a young age, he was raped by a family member and as an adult was convicted of rape. Soon after admission to an inpatient unit, Billy grabbed a female nurse and tried to pull down her pants, Hatters-Friedman said, in response to auditory hallucinations to rape her.

Clinicians treated Billy one symptom at a time, according to Stankowski. They administered IM injections of a long-acting antipsychotic medication due to his lack of insight and poor medication compliance. In addition, he received IM injections of hormones to decrease his libido. To help his symptoms of borderline personality disorder, Billy received dialectical-behavioral therapy, Stankowski noted.

"Until he learned new ways to cope with his emotions" through therapy, clinicians helped him better control his emotions through pharmacotherapy, she said.

In some cases, remarked Sorrentino, "violence is predictable and treatable." ■

professional news

Children

continued from page 6

dinate mental health services for evacuees in that city. "They endured a traumatizing experience of being victimized by nature and abandoned by society. They experienced trauma, on top of trauma, on top of trauma."

Koonce's watchword for helping evacuees was: "Meet them where they are."

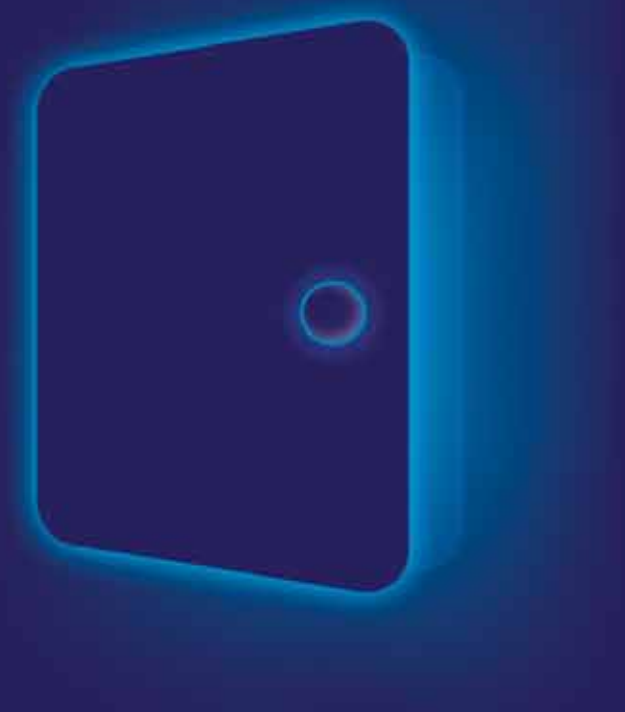
He found that mental health professionals could either wait in designated areas for guests (as he called the evacuees) to self-refer or be brought in by police or medical staff, or they could take to the shelter floor and roam about, finding people who needed help. The latter approach was much more productive, he said.

Going to those who needed help remained the favored tactic in Austin. In the months after the storm, as people moved out of shelters, students were enrolled in the city's public schools. A Communities-in-the-Schools Katrina Project was established, funded by private corporations for a year to coordinate school-based counselors and case managers.

During the school year, the school was the place to connect with families, said Koonce. Now that school is out, the home is the locus of contact.

"Asking parents if they need psychological help may meet with resistance, but we have more success if we say to them, 'Why don't you come in and let's talk about how to help your kids?' then open up the discussion to include the parents' mental health and how it affects their children," he said. ■

Investigating New ADHD Treatments…



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professional news

Insurance

continued from page 5

to-consumer advertising of pharmaceutical products," said David Fassler, M.D., the delegate to the AMA house from the American Academy of Child and Adolescent Psychiatry and author of a resolution originally calling for the report *(Psychiatric News*, July 15, 2005).

"In particular, I agree with the call for a moratorium on such advertising for a period of time after a new medication is initially approved," Fassler said. "Large-scale use by a wide range of patients is very different from carefully controlled clinical trials. Physicians need time to gain firsthand experience with new medications. In the long run, I believe the AMA's actions will improve safety without limiting access to necessary and appropriate treatment."

Other Psychiatric Issues

In other business relevant to psychiatry, the house approved a resolution seeking a report by the AMA's Council on Science and Public Health (CSPH) to clarify uncertainties surrounding the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy.

Testifying in favor of the resolution, APA Vice President Nada Stotland, M.D., put a "human face" on the clinical controversy.

"My subspecialty is the psychiatric aspects of women's reproductive health," she said. "I see women patients who are pregnant and clinically depressed. I can tell them that untreated depression poses a danger to them and to their pregnancies. I can tell those whose depression has been successfully controlled with medication that there is a 60 percent chance that their depressions will recur if they discontinue that medication. They tell me that they are reading in the popular press that antidepressants can hurt their growing fetuses. The prospect of doing anything that might harm their babies is agonizing.

"I also receive many calls from colleagues caring for pregnant women, raising these same concerns," she continued. "Patients look to their physicians for expert advice, and their physicians look to our AMA for the evidence-based guidelines on which they can base that advice. This resolution will put AMA guidelines into the hands of our colleagues so that they can offer their patients and their families the best possible information on which to make these difficult decisions."

The house also approved a report by the CSPH advocating for increased availability of mental health services for college students. The report calls on AMA to do the following:

• Evaluate insurance coverage of this high-risk population and recommend approaches to ensure mandated, full health insurance coverage for full-time undergraduate and graduate students.

• Advocate for elimination of college and university policies that discriminate against students who disclose or seek treatment for depression, substance use disorders, or other mental health problems.

• Encourage clinical staff of campus health services and campus counseling services of colleges and universities to improve their skills in screening, conducting brief interventions, and making student referrals for problem drinking.

• Continue to work to repeal state laws and insurance codes that allow denial of insurance payments to treat injuries as a result of an insured person's being intoxicated.

Three other items sponsored by APA and affiliated organizations were also approved by the house:

• A resolution requesting the CSPH to prepare an update to its 1997 report on the diagnosis and treatment of attention-deficit/hyperactivity disorder. It was sponsored by APA, AACAP, the American Academy of Psychiatry and the Law, and the American Academy of Pediatrics.

• A resolution urging the Centers for Medicare and Medicaid Services to institute and enforce regulations, policies, and guidance for Part D prescription drug plans that will ensure continuity of care for Medicare beneficiaries, eliminate access barriers for psychotherapeutic drugs, and fairly compensate physicians for additional administrative burdens imposed by the Medicare Part D prescription drug program.

• A resolution calling on the AMA to encourage state and county medical societies to advocate for initiatives ensuring all eligible children, adolescents, and young adults are enrolled in Medicaid and the State Children's Health Insurance Program (SCHIP); and that the AMA advocate for federal and state funding for Medicaid and SCHIP so that funding is sufficient to support enrollment and provision of necessary services to all eligible children, adolescents, and young adults. The resolution also asks the AMA to encourage state and county medical societies to oppose state efforts to increase Medicaid beneficiaries' premiums and other cost-sharing measures.

More information about the 2006 annual meeting of the AMA House of Delegates is posted at <www.ama-assn.org/ama/pub/category/15931.html>. ■

clinical & research news

Psychosis

continued from page 29

and that "risk reduction needs to focus on clinical and nonclinical factors that may contribute to violence."

Further research in this area, he said, should focus on studying violence in people with mental illness from a developmental perspective, "taking into account the complex interactions between social environment, features of psychiatric illness, and personal characteristics of individuals as they change over time."

The study was funded by the Foundation of Hope, an organization in Raleigh, N.C., that promotes research into causes and treatments of mental illness.

An abstract of "A National Study of Violent Behavior in Persons With Schizophrenia" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/63/5/490>. ■

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

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

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

Any night or every night

Leave the rest to...

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

Important Safety Information

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

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

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

Please see brief summary of complete prescribing information.

4/06

6SRZO355

Lunesta™ (eszopiclone)

1, 2 AND 3 MG TABLETS

BRIEF SUMMARY

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

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

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

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

PRECAUTIONS

General

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

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

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

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

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

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

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

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

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions

CNS-Active Drugs

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

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

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

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

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

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

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

Drugs With A Narrow Therapeutic Index

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

Pregnancy

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

Adverse Findings Observed in Placebo-Controlled Trials

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

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

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

*Gender-specific adverse event in females

**Gender-specific adverse event in males

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

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

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

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

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

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

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

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

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

Frequent: chest pain, migraine, peripheral edema.

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

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

DRUG ABUSE AND DEPENDENCE

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

Abuse, Dependence, and Tolerance

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

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

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

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

OVERDOSAGE

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

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

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

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

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Miramichi Regional Health Authority
500 Water Street Miramichi, NB E1V 3G5
Telephone 506 - 623-3195
E-mail sanjay@rha7.ca
or
Luc Dube, Acting Regional Director of Mental Health Service
Telephone: 506-623-3198
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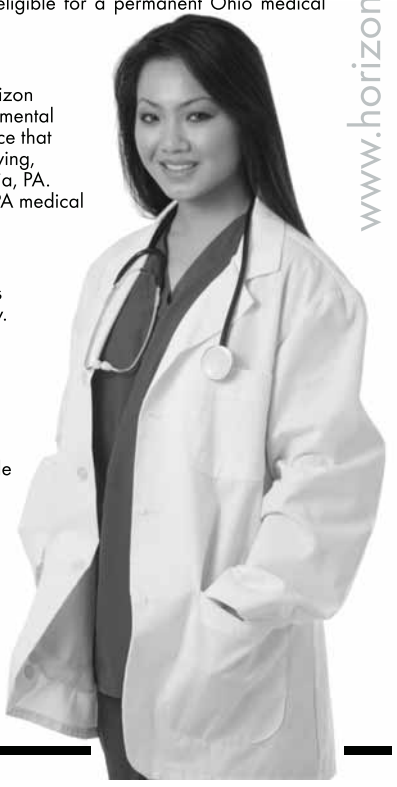

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Medical Director for Behavioral Health
Bartlett Regional Hospital
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Juneau, AK 99801
PH: (907) 796-8498
FX: (907) 796-8497
Email: vstillner@bartletthospital.org

ARIZONA

PSYCHIATRIST

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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.

The Perfect Positions in Northern California!

Outstanding Adult Psychiatrist and C & A Psychiatrist positions are available in one of California's fastest growing communities. It is located 45 minutes south of Sacramento with a population of over 260,000. **The positions are highly sought after employed outpatient opportunities with no call!** You can have a flexible schedule while you care for the full range of psychiatric cases. Work in an environment of collegiality with other highly trained Adult and C & A Psychiatrists along with their superb team of therapists, social workers, nurses, and case managers. These are perfect positions to balance your personal and professional life! **Send your CV to Tina Wilkins at wilkinstina@earthlink.net; fax to 916-482-1154; call 1-888-229-9495**.

SOUTHERN CALIFORNIA

The Department of Psychiatry at Arrowhead Regional Medical Center is seeking full time physician to assist in staffing our acute inpatient psychiatric program. Our hospital is located in Colton, CA, approximately 50 miles east of downtown LA. We are an easy reverse traffic commute from a large portion of the LA Basin. Position salary is $170,000 with additional benefits that include a fully vested 401K retirement plan, malpractice, health insurance, life insurance, 6 weeks paid vacation and an additional 13 paid county holidays. Additional income can be earned through voluntary sign up on our ER schedule.

Please contact the Dept. of Psychiatry for additional information at: (909) 580-3830.

Psychiatrist Opportunities

Are you tired of managing overhead expenses or are you finishing residency and looking for a stable opportunity to practice your clinical skills? We at the Riverside County Department of Mental Health are looking for qualified psychiatrists. The department operates an inpatient facility as well as out patient clinics in multiple locations. We serve people of all ages and are staffed by knowledgeable and supportive personnel.

Our salary is very competitive. Per-diem positions include liability insurance as well as a 401(a) pension plan. **Hours are flexible with no on-call**. Full-time employment may be offered on a case by case basis.

Riverside County is one of the fastest growing counties in coveted Southern California with numerous choices of both active and leisure lifestyles along with more affordable housing and an easy reverse commute from surrounding areas.

Interested? Please call Dr. Raja at (951) 358-4610 and send resume (CV) by email to rschulte@co.riverside.ca.us or by mail to:

County of Riverside
Attn: Ryan Schulte
4095 County Circle Drive
P.O. Box 7549
Riverside, CA 92513-7549

For additional information you may visit our website at www.rc-hr.com.

C&A Locums in Northern California!
There is an immediate need for a C&A Locum Tenens Psychiatrist to provide three months of coverage at an outpatient clinic with no call. Physician is responsible for Medication Management and Psychiatric Evaluations. There is a full staff to assist the Physician on a daily basis. The clinic is located just a short drive to the Bay Area. For more info, contact Gene Itoh @ 800-735-8261 x. 223, fax your CV to 703-995-0647 or email: gitoh@medsourceconsultants.com for this or any of our other Nationwide Locum Tenens opportunities.

THE 1ST CHOICE IN PSYCHIATRIC RECRUITMENT

California
C/A Psychiatrist-Tele-Medicine.
For more information contact:
BRIAN BROWNING
(800) 783-9152 FAX (270) 782-1055
www.fcspsy.com
fcsinfo@fcspsy.com

Central California Opportunity of a Lifetime!

Live in a lovely city in Central California with a growing population of over 100,000 and enjoy an abundance of cultural and recreational activities along with affordable housing. There are two inpatient openings in a hospitalist model at a 68-bed behavioral health facility. Work with a team of therapists, social workers, and nurses in providing consultation, pharmacotherapy, and psychotherapy to inpatients with diverse cases. The call coverage is one weekday night per week and one weekend in every four. Call 1-888-229-9495 for more information. **Send your CV to Tina Wilkins wilkinstina@earthlink.net or fax it to 916-482-1154**.

COLORADO

ADULT PSYCHIATRIST

Pikes Peak Mental Health Center, located in Colorado, blends a strong history of community mental health commitment with ideals of recovery, family systems, and community integration.

Due to significant growth over the past few years, we are actively recruiting for two full time Adult Psychiatrists to join our team of seasoned and dynamic behavioral health care professionals.

Duties include psychiatric evaluation, case consultation, supervision of medical staff, medication reviews and backup inpatient support. The right candidate must have strong clinical skills, customer service orientation, a team oriented style and a solid sense of community. Specialty interest or training in Addictions, Acute Care or Geriatrics would be helpful. Both positions have competitive salary and benefits package including 5 weeks leave, and 12 paid holidays. Relocation costs are negotiable.

Please contact Fred Michel, MD, Medical Director at 719-339-3890, or Sue Allen, Administrative Assistant at 719-572-6151 or by email at SueA@ppmhc.org.

www.ppmhc.org. EOE

Denver/Boulder

Colorado Permanente Medical Group is seeking a full time or part time BC/BE adult psychiatrist to join a large multidisciplinary behavioral health staff working within an integrated medical system. CPMG is a physician-governed group providing services for the non-profit Kaiser Foundation Health Plan, Colorado's most experienced Integrated Health Care System. Kaiser Foundation Health Plan of Colorado has received national recognition as one of the top health care plans in the nation. We offer an excellent benefit package with a competitive salary. Enjoy one of the best practice and lifestyle opportunities in the nation. EOE, M/V

Please contact:
Phone: 303-344-7838
E-Mail: eileen.t.jones-charlett@kp.org
Fax: 303-344-7818

Assistant/Associate/Professor - Medical Director

The Department of Psychiatry at the University of Colorado at Denver and Health Sciences Center is looking for a full time Medical Director for CeDAR (Center for Dependency, Addiction and Rehabilitation). The Medical Director will have a major role in planning and running CeDAR's programs for treatment, research, and teaching, as well as in attracting funds to support those activities.

The successful applicants will meet the following criteria: a physician with board certification in psychiatry and added qualifications in addiction psychiatry (or equivalent training and experience); eligible for Colorado medical licensure; a strong record in organizing programs for treatment, teaching, and research in the field of substance dependence; collegial skills for building treatment, teaching, and research collaborations.

Salary is commensurate with education and experience.

Review of applications will begin June 15, 2006 and continue until position is filled.

To Apply: Address applications (cover letter, curriculum vitae, and three references) to:

Marshall Thomas, M.D.
c/o Lois Campbell
Associate Professor and Medical Director,
University of Colorado School of Medicine
4200 East 9th Avenue, Box C249-36
Denver, CO 80262
Lois.Campbell@uchsc.edu

Please refer to position #676035 (requisition #16498)

The University of Colorado at Denver and Health Sciences Center requires background investigations for employment.

The University of Colorado is committed to diversity and equality in education and employment.

CONNECTICUT

University of Connecticut Health Center

CORRECTIONAL MANAGED HEALTH CARE

Seeking board certified and board eligible psychiatrists to provide care to patients in the Connecticut Department of Correction. Opportunities include patient care, research, teaching, and leadership in both an academic and public health care setting. Opportunities exist throughout the state. Exciting employment, excellent state benefits, regular working hours, and competitive salaries. Please contact Noreen Logan, Human Resources, for information and an application at (860) 679-7691 or e-mail at logan@uchc.edu.

AA/EEO M/F/PWD/V

ACADEMIC GEROPSYCHIATRIST

The Department of Psychiatry at the University of Connecticut is recruiting for a geropsychiatrist to join its academic faculty in the Summer/Fall of 2006. The successful candidate will be interested in building an academic career based on clinical care, teaching of residents and medical students, and research. Heading a multidisciplinary inpatient treatment team, working in both hospital and ambulatory consultation-liaison, and participating in ongoing research programs are all part of the responsibilities of this position. Candidates with a demonstrated record of scholarly work in the form of publications and grant funding will be preferred. Interested candidates should send a letter of interest and CV electronically to **Dr. Leighton Huey, Professor and Chair, Department of Psychiatry, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030-1410. Email: huey@psychiatry.uchc.edu**

Psychiatrists-CT & RI
MedOptions provides behavioral health and primary medical care services to long-term care and assisted living facilities in Connecticut and Rhode Island. We currently serve over 11,000 residents in 165 facilities and continue to grow at a dramatic rate. This growth has presented employment opportunities for FT psychiatrists to join our dynamic consultation team in RI and western CT. Enjoy a flexible work schedule and collaborate with a great team of specialists who strive to improve the physical and mental health of residents. For more information or consideration, please contact Marianne Wright, Director of Recruiting, MedOptions, Inc. at 800-370-3651, ext 164, email: mwright@medoptionsinc.com or fax your CV to 860-679-7744.

FLORIDA

Outstanding practice opportunity in Coastal Florida. Join **Top Medical Center** and hospital-based physician Group. Both Inpatient Practice Opportunity and Outpatient Practice Opportunities. Outstanding financial package, salary, bonuses and benefits. Respected Program, Collegial staff. Malpractice and Tail is covered. **Florida Coast - White Beaches, Crystal Clear Water.** Championship Golf Resorts, boating, fishing...**Excellent educational opportunities,** local Universities. Fine dining. Brian White at 1-888-339-7444 or fax cv to 1-940-234-5315 or email cv to brian@crossroadshealth.net

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FT. MYERS/MERBOURNE/ORLANDO/DAYTONA/MIAMI/FORT LAUDERDALE/OCALA/GAINESVILLE - Psychiatrists needed for rapidly expanding Nursing Home Service. Great support. No call. Average Salary 210K + benefits. Part-time available. Some travel required. Must have FL Medicare & FL Medicaid provider #s. Call Mike at 866-936-5250.

PANAMA CITY - Adult board certified or board eligible psychiatrist to join staff of comprehensive community mental health center. Salary range is: $176,000 - $183,000. Beautiful area of the country. Apply through our website www.lifemanagementcenter.org or send CV to: **Peter Hampton, Ph.D., Executive Director, Life Management Center of Northwest Florida, 525 E. 15th St., Panama City FL 32405**, EOE/DFWP. Pre-hire drug screen required.

Miami: FL LICENSED PSYCHIATRIST; active private practice; affluent area; hosp, office, SNF settings; excellent incentive plan incl salary & benefits. Dr. Carter, S. FL Psychiatric Assoc. 305-935-6060. Please FAX CV to 305-935-1717 or EMAIL: aventuraoffices@bellsouth.net.

Psychiatrists for FACT Programs

Mental Health Resource Center, Inc. (MHRC) is recruiting six **Adult Psychiatrists** for its Florida Assertive Community Treatment (FACT) Programs in the following six Florida locations: Rockledge/Cocoa area, Stuart, Naples, Tampa, Clearwater and Jacksonville.

Each position is full-time salaried with comprehensive benefits package including professional liability insurance. Florida licensure and Board Eligibility/Certification required. To apply, contact Dr. Robert Sommers, President, RBHS, P. O. Box 19249, Jacksonville, FL 32245. e-mail: rbhspres@bellsouth.net. Fax: (904) 743-5109. Phone: (904) 743-1883, ext. 219.

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

Take over a lucrative practice of a retiring psychiatrist. Practice was established in 1968. Join a group of multidisciplinary professionals in an interdenominational setting located in beautiful North Georgia. No investment required. No In-Patient responsibilities. Weekend On-Call limited to once a month. If interested, please call 770-396-0232, ext. 232. Email your C.V. to atlantacounselingctr@yahoo.com or fax to 770-399-0007.

WellStar Health System is seeking a Clinical Liaison Adult Psychiatrist to join an established and growing practice located in Marietta, GA. This position would consist of both inpatient and outpatient psychiatry/liaison work. WellStar offers a competitive compensation and benefits package. Please send CV to provider.positions@wellstar.org or fax to 770-792-1738. EOE.

ILLINOIS

The Department of Veterans Affairs Illiana Health Care System (VAIHCS), Danville, Illinois is actively seeking two board certified or board eligible psychiatrists. Mental Health Service consists of 37 inpatient beds and a large outpatient services, including Substance Abuse and PTSD Programs. VAIHCS provides primary and secondary care including various specialty services and is affiliated with U of I College of Medicine at Champaign-Urbana. Individual must be eligible for faculty appointment. Danville is located in East Central Illinois and 30 miles from Champaign/Urbana, 1 1/2 hour from Indianapolis, 3 hours from St. Louis and 3 hours from Chicago. Salary is negotiable. Qualified applicants should submit CV to: Darla Krout (05-2), Human Resources, VA Illiana Health Care System, 1900 East Main Street, Danville, IL 61832 or FAX 217-554-4585. For additional information, please contact Chief of Staff's Office at 217-554-5078. VA Illiana Health Care System is an EEO employer.

PSYCHIATRIST NEEDED!

A well established and very busy private practice, located in the Chicago area is looking to hire a full time or part time psychiatrist. Work includes hospitals, outpatients and nursing homes. Compensation package is very attractive and negotiable. For more information please call Kathy at our office between 8am and 4pm 1-312-565-2251.

Academic Forensic Psychiatrist

Northwestern University, Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences is recruiting a full-time, nontenure, Assistant Professor, Forensic Psychiatrist as Director of the Division of Psychiatry and Law. The Director would assume overall leadership and direction of Department forensic psychiatry activities. Responsibilities include: forensic psychiatry consultations to the Division's clients and agencies, case consultation and oversight to other Division experts, lead program business development and client/public relations, case assignment and forensic psychiatry education to residents and medical students. Additionally, opportunity to develop a forensic fellowship. Salary is negotiable. Please submit curriculum vitae to: Ronald F. Krasner, M.D., Interim Chairman, Department of Psychiatry and Behavioral Sciences, 446 E. Ontario St., Suite 7-200, Chicago, IL 60611. Northwestern University is an Affirmative Action, Equal Opportunity Employer. Women and minorities are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

Chicago Suburbs! Several exceptional opportunities right outside of the **Windy City!** 1) Adult opportunity for outpatient services and consults 2) Child opportunity for all outpatient or a mix if in and outpatient 3) Geriatric Psychiatrist needed for a mix of in and outpatient 4) Opportunity for a Eating Disorder Psychiatrist 5) Addictions Psychiatrist opportunity. **Rewarding opportunities** with competitive base salaries and full benefits package! For more info, contact Sarah McGlinnen at 800-735-8261 x 216, fax your CV to 703-995-0647 or email smcglinnen@medsourceconsultants.com

INDIANA

Join hospital staff in culturally-rich university town voted by *USA Today* as one of the eight most desirable places to live in the US, based on economy, climate, housing, safety and leisure activities. Enjoy a very strong salary with full benefits. Contact Jim Ault at St. John Associates, 1-800-737-2001 or jault@stjohnjobs.com. Visit our website at www.stjohnjobs.com

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Easy Access to Indianapolis & Cincinnati! DYNAMIC OPPORTUNITY! Hospital seeks C/A and Adult Psychiatrist. Both in & outpatient work available. Option to teach medical students is as well! **Very lucrative position nestled between two cities in a beautiful college town!** For more info on this opportunity or others nationwide, contact Lindsay McCartney at: 800-735-8261 x 213, fax your CV to 703-995-0647 or email: lmccartney@medsourceconsultants.com

IOWA

The North Central Iowa Mental Health Center is accepting applications for a General Psychiatrist. The Center is located on the grounds of Trinity Regional Medical Center. The doctor will treat patients on the inpatient and partial hospitalization units at Trinity Regional as well as providing out patient services. The Center also has an Assertive Community Treatment team. The Center serves an area of 120,000 people and treats about 3500 patients per year. Compensation is based on salary plus productivity bonus. Will consider applicants with J-1 Visas. Please send cover letter, CV and references to:

Jim Burr, CEO
North Central Iowa Mental Health Center
720 Kenyon Road
Fort Dodge, IA 50501
jimburr4759@hotmail.com

Join Our Psychiatric Medicine Team!
Seeking BC/BE adult psychiatrist to join multispecialty system serving patients in Southeast Iowa and Northern Missouri. Hospital managed group including one child/adolescent psychiatrist, two adult psychiatrists, nurse practitioners and therapy/counseling staff. Inpatient unit currently under remodeling scheduled to open in the summer/fall of 2006 along with outpatient practice. Department offers full spectrum of mental health services and continues to be very progressive in pursuit of innovative and evidence based delivery systems of care. Guaranteed salary, signing bonus and competitive benefits package.
Visit www.practiceyourway.com and e-mail CV to
Becky Helgerson - bhelgerson@orhc.com or call 800-933-6742 ext. 2740.
This is a great opportunity worth the call!

KANSAS

Osawatomie State Hospital (OSH) is seeking a full time board certified/board eligible **Psychiatrist** to join its in-patient staff. OSH is a JCAHO accredited 176 bed psychiatric facility which serves the adult population. Programs consist of a crisis stabilization unit, acute care units, and a continuing care unit. The hospital is adjacent to a major highway, which combines a friendly rural setting and easy access to a large metropolitan area. Generous benefits package include paid malpractice insurance, paid holidays, vacation and sick leave, medical and dental insurance, retirement plan, opportunities for CME. For more information, contact M. Gustilo, M.D. at 913-755-7083, e-mail to Merma@osh.ks.gov or send CV to Osawatomie State Hospital, Attn: Dr. Gustilo, P.O. Box 500, Osawatomie, KS 66064. SRS is an Equal Opportunity Employer committed to a diverse workforce; women, minorities and persons with disabilities are urged to apply. Paid for by Osawatomie State Hospital.

Rainbow Mental Health Facility (RMHF) is seeking a full time board certified/board eligible **Psychiatrist** to join its in-patient staff as an Associate Medical Director. RMHF is a JCAHO accredited 50 bed psychiatric facility which provides short term psychiatric treatment to a population which includes adults, children, and adolescents. RMHF is located in Kansas City, Kansas, a large metropolitan area. Generous benefits package include paid malpractice insurance, paid holidays, vacation and sick leave, medical and dental insurance, retirement plan, opportunities for CME. For more information, contact M. Gustilo, M.D. at 913-755-7083, e-mail to Merma@srskansas.org or send CV to Osawatomie State Hospital, Attn: Dr. Gustilo, P.O. Box 500, Osawatomie, KS 66064. SRS is an Equal Opportunity Employer committed to a diverse workforce; women, minorities and persons with disabilities are urged to apply. Paid for by Rainbow Mental Health Facility.

LOUISIANA

Southwest Louisiana area seeks BE/BC psychiatrist for community mental health centers located in Allen and Beauregard Parishes. Generous compensation and benefits package. Please send your CV and supporting documents to the following address:

Lake Charles Mental Health Center
Attn: Laura Lyles
4105 Kirkman Street
Lake Charles, LA 70607
Telephone: (337) 475-8725
Fax: (337) 475-8054
E-mail: lalyles@dhh.la.gov

J-1 & F-1 WAIVER AVAILABLE

Crossroads Regional Hospital

Crossroads Regional Hospital, Alexandria, Louisiana seeks two adult and/or adolescent BE/BC psychiatrist with immediate openings. Crossroads Regional Hospital is located in the city of Alexandria in central Louisiana. Interstate 49 passes thru Alexandria.

The hospital is a 70 bed free standing psychiatric hospital, providing adult, children, and adolescent and geriatric inpatient services. The hospital is soon going to open a partial day program and intensive outpatient program.

- J-1 & F-1 waiver candidates are offered attractive salary, with benefits.
- US citizens & permanent residents can choose from several options:

1. **Minimum guaranteed net income** in excess of $150,000/year. The hospital will fund expenses to establish office practice, pay office employees, malpractice insurance, etc. All income after expenses, but at least minimum agreed amount, belongs to the physician.
2. **Full time employment**- attractive salary with benefits and bonus.

Apply with CV by fax to 225-767-8255 or email to psycheservices@bellsouth.net or mail to Attn: Dee Record 5425 Brittany Drive, Ste A, Baton Rouge, LA 70808.

PSYCHIATRIST
MEDICAL DIRECTOR

Central Louisiana State Hospital, Pineville, LA, seeks Medical Director for 132 patient psychiatric hospital. Campus housing available. Community of approximately 50,000 including two colleges, music and arts, good schools, sports. Full medical benefits, retirement, generous sick and vacation leave, and tax-sheltered savings plan. Salary depends on experience and credentials. EOE. For other information call Ann Hall, HR Manager 318-484-6321; fax 318-484-6345; ahall@dhh.la.gov.

MAINE

Dartmouth Faculty Psychiatrists

Dartmouth Medical School, Department of Psychiatry, in collaboration with the State of Maine Department of Health and Human Services, seeks faculty psychiatrists for the Riverview Psychiatric Center in Augusta, Maine. The Center is the flagship inpatient hospital serving central and southern Maine's system of public mental health care. A 92-bed, state of the art, replacement hospital opened in the Spring of 2004. Preference will be given to candidates with forensic training and/or experience. Maine licensure required. These are full-time Dartmouth faculty appointments with salary and rank commensurate with experience and academic accomplishments. Protected time for scholarly activities. Central and southern Maine offers exceptional opportunities to enhance your quality of life. We have safe communities, with very low crime, good schools and unparalleled four season recreational activities. Augusta is less than one hour from the Maine coast and closer to numerous crystal clear lakes and mountains. It is no wonder Maine is called "vacationland." Please send CV and three letters of reference to: **Alan I. Green, MD, Professor and Chair of Psychiatry, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756**. Dartmouth Medical School is an EOE/AA Employer and encourages applications from women and members of minority groups.

Maine's First Magnet Hospital and the World's First Free-Standing Psychiatric Magnet Hospital Seeking Adult and Child/Adolescent Psychiatrists

We are seeking BC/BE psychiatrists for both our adult and child/adolescent inpatient and outpatient programs. Acadia Hospital is a thriving, non-profit, private community-based hospital offering acute psychiatric care for adults and children, as well as chemical dependency programs. One of the only two private psychiatric hospitals in Maine. The Acadia Hospital offers physicians clinical practice in a highly collaborative, multi-disciplinary setting. Competitive salary and benefit package. Send resume to: Vice President of Medical Affairs, The Acadia Hospital, P.O. Box 422, Bangor ME 04402-0422. **www.acadiahospital.org**

SOUTHERN MAINE

How would you like to be valued as part of a professional team for one of Southern Maine's largest mental health and community service based agencies where there is a strong commitment to staff, clients, and their agency mission?

Counseling Services, Inc. is a comprehensive and integrated community mental health center serving adults and children with serious mental health and substance abuse problems. Our programs include Complementary Therapies, Child and Family Primary Care Services, Adult and Family Primary Care Services, Primary Care Support Services, Psychiatric Services, Assessment Referral and Treatment, and Crisis Response Services.

We are currently recruiting for full-time, part-time, or contracted adult and child psychiatrists. The positions will involve direct patient care at our community mental health centers in Southern Maine. The physician will work with a multidisciplinary team providing outpatient services to a variety of programs.

We offer a generous time-off program, a comprehensive medical, dental and life insurance benefit, and other attractive incentives.

If you are aware of a qualified individual who would want to explore these exciting opportunities, please contact the Human Resources Department at 207-294-7104. A resume and cover letter may be sent to: Counseling Services, Inc., P.O. Box 1010, Saco, Maine 04072 or human.resources@csimaine.com. We are an equal opportunity employer.

MARYLAND

Psychiatrist

Springfield Hospital Center - a 405 bed psychiatric in patient facility, operated by The Maryland State Mental Hygiene Administration seeks Maryland licensed Psychiatrists. Our rural 400 acre campus is located 22 miles west of Baltimore and convenient to Washington, DC. via routes 70 & 29. We offer full time and part time positions with comprehensive benefits, which include 27 days of paid leave, medical coverage and access to Maryland State Employees Pension at retirement. Additionally, Contractual day/night positions available. Both Board & Non-Board Certified physicians will be considered. Salary for these positions is negotiable. Please send CV to: Jonathan Book, M.D., Clinical Dir, SHC, 6655 Sykesville Rd. Sykesville, Maryland 21784. For questions call 410-970-7006 or email Jbook@dhmh.state.md.us. EOE

PSYCHIATRIST PT for fast-paced growing Geriatric Behavioral Health Practice to provide consultation services in LTC setting in Maryland. Background in medical/neurological basis for psychiatric symptoms desirable. Fax cover letter and resume to CGS, 410-832-5783, Attn.: Dr. Fitting.

Clifton T. Perkins Hospital Center, a JCAHO-accredited institution and Maryland's only maximum security forensic hospital, is seeking candidates for the position of staff psychiatrist. Candidates with forensic interest or experience would be especially well-suited. Responsibilities include the provision of high quality psychiatric care on an inpatient unit in a state-of-the-art forensic facility. Additional opportunities include evaluations of dangerousness, competency to stand trial, and criminal responsibility.

Join a vibrant medical staff with expertise in care of the seriously mentally ill within a forensic setting. Faculty appointments are available at University of Maryland and Johns Hopkins, if eligible. The hospital is centrally located 20 minutes from Baltimore, 35 minutes from DC, and 20 minutes from Annapolis. Competitive salary with excellent benefits, flexible working hours, and the opportunity for paid overnight call.

Interested candidates should contact C. Dennis Barton, Jr., MD, MBA, at 410-724-3078 or P.O. Box 1000, 8450 Dorsey Run Road, Jessup, MD 20794 (BartonD@dhmh.state.md.us.)

THE 1ST CHOICE IN PSYCHIATRIC RECRUITMENT

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www.fcspsy.com
fcsinfo@fcspsy.com

BALTIMORE - The Walter P. Carter Center, a 51 bed adult inpatient facility on the downtown campus of the University of Maryland, is seeking a BC/BE psychiatrist. This is a full-time faculty position in the Department of Psychiatry at the U. of Md. School of Medicine, and involves direct patient care, the teaching and supervision of residents and medical students, and opportunities for research. Please contact Louis Cohen, M.D., Clinical Director at 410-209-6101; or e-mail at LCohen@psych.umaryland.edu.

MASSACHUSETTS

THE 1ST CHOICE IN PSYCHIATRIC RECRUITMENT

Boston Metro
Medical Director
For more information contact:
YVONNE CHAMBERS
(800) 783-9152 FAX (270) 782-1055
www.fcspsy.com
fcsinfo@fcspsy.com

CAMBRIDGE: Child & Adolescent Psychiatry

Outpatient Child & Adolescent Psychiatrist - half time position available at Cambridge Health Alliance, Division of Child and Adolescent Psychiatry, Harvard Medical School. An innovative and growing multidisciplinary team at the Center for Child and Adolescent Development seeks a half-time child psychiatrist. Must have special interest/expertise in psychopharmacology and in autism, bipolar disorder, and childhood psychosis. Opportunity to work closely with other team members including neuropsychology, pediatric neurology, social workers, psychologists and other prescribers. A half time position is available providing outpatient psychopharmacology services in a dynamic community based clinic. Position includes supervision of child psychiatry fellows, general psychiatry residents, medical students, and other trainees. Program development and research opportunities for candidate with appropriate experience.

The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School with excellent residencies in adult and child psychiatry. Academic appointment up to the rank of Associate Professor, as determined by the criteria of Harvard Medical School, is anticipated. We seek candidates with demonstrated excellence in academic teaching of complex clinical assessment, child and adolescent psychopharmacology, family assessment and treatment, particular interest and experience in working with ethnic and minority populations and the underserved, and enthusiasm for the public health mission of CHA.

Qualifications: Board Certified, demonstrated knowledge of clinical and research child and adolescent psychiatry, commitment to public sector populations, excellent clinical and teaching skills, leadership and management skills, team oriented, problem solver. Bilingual and/or bicultural abilities are desirable. Competitive compensation, excellent benefit package. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply. **Send CV & letter to: Jean A. Frazier, MD, Dept. of Psychiatry, Cambridge Health Alliance-Station Landing, 1493 Cambridge Street, Cambridge, MA 02139. Fax: 781-306-8644. jfrazier@challiance.org (email preferred)**

Lynn BayRidge Hospital, a non-profit psychiatric facility on Boston's North Shore, a teaching site for Boston University Medical School, has a position for an inpatient and/or partial hospitalization program psychiatrist, or for the appropriate candidate, as unit Medical Director. Experience with dually diagnosed patients is a plus. The Medical Director position includes substantial direct service; candidates for Medical Director must be board-certified, and have demonstrated skill in leadership. No required night call, but participation in a lucrative call system is optional. Full benefit package includes generous time off as well as reimbursement for malpractice insurance and CME expenses. Contact Barry Ginsberg, M.D., Medical Director, 60 Granite Street, Lynn MA 01904. Phone (781) 477-6964, Fax (781) 477-6967, email bginsber@nhs-healthlink.org.

Hallmark Health INPATIENT & OUTPATIENT PSYCHIATRISTS - BOSTON AREA

Excellent Opportunities For BC/BE Psychiatrists

- Full Time Medical Director for 22 Bed Inpatient Adult Unit at Melrose-Wakefield Hospital
- Weekend and Evening Call Opportunities at Melrose-Wakefield Hospital
- Full Time Staff Psychiatrist for Inpatient Geriatric Medical Psychiatric Unit at Lawrence Memorial Hospital
- Nursing Home Consultation Services at Lawrence Memorial Hospital
- Part Time and Per Diem positions in an Outpatient Clinic providing psychopharmacology and psychotherapy services to adult and geriatric patients.

Very Competitive Salary and Benefits Package. Located a few miles North of Boston. A Financially Strong and Progressive Healthcare System with two hospital campuses. Expanding Behavioral Health Service Line.

Send CV to:

Janet Lensing, System Director of Behavioral Health Services
Hallmark Health System, Inc.
585 Lebanon St
Melrose, MA 02176
Fax: 781-979-3326

North Shore Medical Center Department of Psychiatry

Child Psychiatrist

Position available for BE/BC Psychiatrist 20-40 hours per week. Responsibilities include Child Inpatient Psychiatry or Partial Hospital Program, and Child Outpatient Mental Health.

Adult Psychiatrist

Positions available for BE/BC Psychiatrist 20-40 hrs per week. Responsibilities include Adult Psychiatry and/or Partial Hospital Program.

NSMC provides an excellent collegial work environment, opportunities for participation in clinical research and academic appointment. Salary and benefit packages are highly competitive. Member of Partners HealthCare, founded by Massachusetts General Hospital and Brigham and Women's Hospital. NSMC is an equal opportunity employer. For more information, visit http://www.nsmc.partners.org

Please send cover letter and CV to: Mark Schechter, MD, Chairman, Department of Psychiatry, 81 Highland Avenue, Salem, MA 01970, Email (preferred): mschechter@partners.org, or telephone: (978) 354-4010, FAX: (978) 825-6101.

ON call psychiatrist - Southbridge, MA. Harrington memorial Hospital has on call opportunities. Salaried position, 1 in 7 rotation, weekend rounds, very flexible. Excellent working conditions. For more information, write/call: Zamir Nestelbaum, M.D., @ G.B. Wells Center, 29 Pine St., Southbridge, MA, 01550. 508-765-9167. An AA/EOE/ADA Employer.

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.

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Don Ceniza
800-583-2256

Psychiatrist - Southbridge/Sturbridge area. Part time adult psychiatrist needed for G.B. Wells Center, a large, friendly community mental health center and part of Harrington Memorial Hospital. Excellent working conditions, very flexible. For more information, write/call: Zamir Nestelbaum, M.D., @ G.B. Wells Center, 29 Pine St., Southbridge, MA, 01550. 508-765-9167. An AA/EOE/ADA Employer.

BOSTON MEDICAL CENTER
Boston University School of Medicine

Boston University School of Medicine / Boston Medical Center, Department of Psychiatry, is seeking board-certified psychiatrists for the following positions:

Adult Psychiatrist to provide direct patient care our consultation/ liaison and outpatient adult psychiatry services Position includes teaching and supervision of medical students and residents.

Child/Adolescent Psychiatrist to provide direct patient care in our outpatient/urgent care and consultation/liaison child/adolescent psychiatry services. Special interest and experience in neuropsychological conditions preferred. This position involves program leadership, direct patient care and supervision of medical students and residents.

Academic/Clinical specialties of the Department of Psychiatry include psychological trauma, medical psychiatry, consultation-liaison, emergency psychiatry and community mental health.

Boston Medical Center, a teaching hospital for the Boston University School of Medicine, is a busy community hospital in Boston which serves a diverse, multicultural patient population.

Academic appointment commensurate with experience. Competitive salary base with incentive and full benefits. All interested applicants should send CV and cover letter to Marice Nichols, 85 East Newton Street, Suite 802, Boston, MA 02118 or fax to (617) 414-1975. Boston University School of Medicine/ Boston Medical Center is an equal opportunity/affirmative action employer.

MISSISSIPPI

Memorial Hospital at Gulfport is currently seeking a board certified Psychiatrist to provide medical services for adults/adolescents/children in its Behavioral Health Center. Competitive salary plus benefits and full relocation package. Memorial is a county/city owned nonprofit hospital located in Gulfport, MS along the Gulf of Mexico. Please send CV attention: Michael Zieman, Administrator for Behavioral Health, Memorial Hospital, Fax (228) 575-1875 or e-mail **mzieman@mhg.com**. EOE. M/F/D/V.

MISSOURI

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

ST. LOUIS, MISSOURI - CHRISTIAN HOSPITAL: Seeking a BC/BE Psychiatrist for Inpatient adult and geriatric practice at Christian Hospital in St. Louis County. Collegial work environment. Shared call. No commuting with both inpatient units located side by side. Be your own boss in this contract position! St. Louis is a large city with a small town feel. **To learn more, contact Michelle Kraft at 800-678-7858, x63705; fax 314-726-0026; e-mail mkraft@cejkasearch.com.** ID#26770PY. *For more opportunities, visit www.cejkasearch.com.*

PSYCHIATRIST POSITIONS

The Department of Mental Health's Central Region is seeking qualified BC/BE PSYCHIATRISTS for Fulton State Hospital and Mid Missouri Mental Health Center. These facilities are located in the heartland of Missouri. Both facilities are very progressive and stay up-to-date with advances in Psychiatry. Residency and Fellowship programs permit out staff continuous professional growth and development in Neurosciences. Candidates must obtain a full and unrestricted license to practice medicine in Missouri. Excellent compensation, plus extensive benefits for health care, retirement, and deferred compensation investment plans.

FULTON STATE HOSPITAL

Fulton State Hospital is a large JCAHO accredited facility located in Fulton Missouri. The campus is located 30 minutes from the University of Missouri in Columbia (UMC). Programming at Fulton State Hospital includes Psychosocial Rehab, Cognitive Behavior, and Social Learning programs at different levels, and a strong biological program. Please send CV to: Judith Fisher, D.O., Clinical Director, Fulton State Hospital, 600 East Fifth Street, Fulton, MO 65251. **Telephone 573-592-3409; FAX to 573-592-3023, judith.fisher@dmh.mo.gov.**

MID-MISSOURI MENTAL HEALTH CENTER

Mid Missouri Mental Health Center is a 69 bed JCAHO accredited facility located on the University of Missouri Campus in Columbia Missouri. We have a close relationship with the Department of Psychiatry and Neurology at the University of Missouri-Columbia, which makes our research and academic opportunities unique. Please send CV to: Ron Lacey, M.D., Clinical Director, Mid-Missouri Mental Health Center, #3 Hospital Drive, Columbia, MO 65201. **Telephone 573-884-1088. Fax to 573-884-1090, Ron.LaceyMD@dmh.mo.gov.**

An Equal Opportunity/Affirmative Action Employer.

MONTANA

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

The University of Nevada School of Medicine, Department of Family Medicine, is seeking candidates for two full-time, administrative faculty positions as physicians/psychiatrists at the Mojave Adult, Child and Family Services (MACFS) mental health clinic in Las Vegas. Excellent benefits package available. For complete position description and requirements, contact: Search Chair/Coordinator, (Jim Parcells, C.O.O., 702-968-5000/Pam Soucy, PHR, 702-968-5071) or view at http://jobs.unr.edu (reference posting #60025).

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

NEW HAMPSHIRE

EMPLOYMENT OPPORTUNITIES IN PSYCHIATRY

Riverbend Community Mental Health, Inc. is a mission driven, comprehensive provider of community-based behavioral health services. Affiliated with Capital Region Health Care, in Concord, New Hampshire, Riverbend serves a broad range of individuals and families with behavioral health and related needs. We have a staff of over 200, including six full-time psychiatrists. The following employment opportunities are currently available:

GEROPSYCHIATRIST

Riverbend 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.

CHILD PSYCHIATRIST

Riverbend seeks a **BC/BE Child and Adolescent Psychiatrist.** This position includes providing comprehensive psychiatric evaluations and psychopharmacological management as part of a multidisciplinary child and adolescent team. Willingness to do general adult psychiatry in addition to child and adolescent psychiatry is a plus.

Both positions include responsibility for participation in a shared on-call rotation covering a 15-bed in-patient psychiatric unit in a general hospital and providing in-patient consultations.

These positions are full-time, salaried with excellent benefits including generous paid leave benefits, medical, dental, life, disability, retirement plan, paid malpractice insurance, continuing medical education, and reimbursement for professional expenses. To apply, please forward a cover letter and CV to: Riverbend CMHC, Attn: Human Resources, PO Box 2032, Concord, NH, 03302 ore-mail to hr@riverbend-cmhc.org. Electronic applications preferred in Microsoft Word format. EOE

If you have questions or would like more information, please call Robert Murray, MD, at (603) 226-7567 x 2262 or Jaime Corwin, HR Manager, at (603) 226-7505 x 3993.

NEW JERSEY

Psychiatrist - well established, for profit outpatient mental health practice located in south jersey, has immediate opening for experienced adult, adolescent and/or child psychiatrist. Fee for service cliental, private practice model within comprehensive multi-disciplinary group of highly qualified clinicians. Fax CV to (856) 985-8148 or call (856) 983-3866 ext. 3018.

If you are a child or adult board certified psychiatrist looking to grow in a private practice that is not dependent on managed care, call us at 908.273.0800 and fax CV to 908.273.0815. We have a growing private practice in Summit, NJ, an affluent suburban community.

NEW MEXICO

Presbyterian Medical Services is a non-profit integrated healthcare network with JCHO accreditation providing medical, dental, behavioral health, children's services and supportive living services to the multi-cultural people of New Mexico. We are seeking a **Psychiatrist** who will see clients of all ages to work in our Farmington clinic. Excellent benefits. Sign-on bonus offered. For more information contact Diane Kramer at (800) 477-7633; fax (505) 954-4414; diane_kramer@pmsnet.org; P.O. Box 2267, Santa Fe, NM 87504. EOE.

Medical Director of Child & Adolescent Division

The Department of Psychiatry at the University of New Mexico, School of Medicine is seeking an outstanding Child & Adolescent Psychiatrist for the position of Director of Child & Adolescent Psychiatry. This person also serves as Medical Director of Child and Adolescent Inpatient and Outpatient services. This Division encompasses a variety of activities including a fellowship in Child & Adolescent Psychiatry; an internship in Clinical Psychology; Telemedicine/Rural Psychiatry, juvenile corrections, and inpatient and outpatient services. The Director collaborates and participates in strategic planning and program development with University Hospital as well as multiple local, state and national agencies. Teaching duties include supervision of medical students, residents, psychology interns and trainees of multiple disciplines. We are eager to put together the right package to assure that we recruit the best person for this position. Minimum qualifications include Doctorate Degree, licensable in New Mexico, board certified in Child & Adolescent Psychiatry, proven clinical experience, and United States citizenship or permanent residence. Desirable qualifications: leadership experience in academic administration, research experience, teaching and curriculum development experience. This position may be subject to criminal records screening in accordance with New Mexico law. For best consideration, interested parties should send Curriculum Vitae, a brief signed letter indicating interests, and the names of three current references to the attention of Renu Prinja, Medical Department Personnel Representative, University of New Mexico, School of Medicine, Department of Psychiatry, 2400 Tucker NE MSC 09 5030, Albuquerque, NM 87131. The position will remain open until filled. For preliminary inquiries contact, Samuel J. Keith M.D. Milton Rosenbaum Professor, Chairman, Department of Psychiatry, University of New Mexico, 2400 Tucker NE, MSC 095030 Albuquerque, NM 87131. The University of New Mexico is an Affirmative Action / Equal Opportunity employer and educator.

NEW YORK CITY & AREA

Psychiatrists

Full Time/Part Time/Inpatient Positions for NYS licensed, board eligible/board certified psychiatrists are available at Manhattan Psychiatric Center, an OMH facility specializing in the treatment of the refractory patient with innovative pharmacological and manualized cognitive behavioral interventions. The psychiatrist leads a multidisciplinary team, with opportunities to utilize clinical, administrative, and teaching skills on specialty units. MPC is a residency training affiliate of NYU with rotations in the STAIR program, research and outpatient clinic as well as opportunities for teaching medical students. We are conveniently located near the Triboro Bridge.

Please fax resume to:
Manhattan Psychiatric Center
Ward's Island Complex
Ward's Island, NY 10035
Samuel J. Langer, M.D., Chief of Psychiatry
646 672 6386
MPC is an equal opportunity employer
A Bridge to Recovery

Psychiatrist
Part-time, 21 hours (Tues., Thurs, Fri, 9:00am-3:00pm)

NY Physician licensed required. Board Certified in general psychiatry, and Board Eligible in child and adolescent psychiatry required. Must be computer literate. Ability to travel within 5 boroughs expected. Knowledge or interest in caring for the child welfare population highly preferred.

Interested applicants should email confidential resume to: resumes@jordananderson.com, indicating JAA Box 92 in subject line, or mail to JAA Box 92, 180 Varick Street, 12th Floor, New York, NY 10014.

AA/EOE

ALBERT EINSTEIN
COLLEGE OF MEDICINE
Of Yeshiva University
Department of Psychiatry and Behavioral Science

The Sound View Throgs Neck Community Mental Health Center

PSYCHIATRIST - Full-time. Continuing Day Treatment and MICA Program. PSYCHIATRISTS - Part-Time Child/Adolescent and Adult Outpatient Programs. These Programs seek psychiatrists experienced in diagnostic evaluation and psychopharmacology, to provide clinical care, supervise a team and teach medical students, psychiatry residents and clinical fellows. New York State License, Board Certified/Board Eligible in Psychiatry. DEA Registration. These positions carry a faculty appointment. Knowledge of Spanish a plus.

In return for your expertise, we offer a competitive salary, outstanding benefits package and a professional work environment offering career growth potential. For consideration, please submit your CV with salary history to: **Thomas F. Betzler, MD., Executive Director, Sound View Throgs Neck Community Mental Health Center, 2527 Glebe Avenue, Room 304, Bronx, NY 10461; Fax: (718) 931-7307; Email: tbetzler@aecom.yu.edu . Equal Opportunity Employer.**

Coastal suburbs of New York City! Facility is looking to add a C&A psychiatrist willing to work with mostly children in both an inpatient & outpatient setting. This is a highly lucrative opportunity & current psychiatrists are making at least **$200,000 with full benefits! NO CALL!** The facility is located on a beautiful campus close to Manhattan. **All applicants must be board certified**. For more info, contact Ariana Sanjabi @ 800-735-8261 x 214, fax your CV to 703-995-0647 or email: asanjabi@medsourceconsultants.com

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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!

NYC-Highly sought after Academic Opp't! Supervise $ teach residents and medical students. Academic experience preferred. Job entails oversight and teaching of psych Residents + some research. Clinical duties are for inpatient work. Salary + bene. Call Dave Featherston @ 800-575-2880 x 314.

Psychiatrists

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 part time and Fee for Service psychiatrists.

- Bronx Adult Group Homes - FFS
- Brooklyn - Child & Adult - PT
- Bronx - 3 month - TEMP - Child - 1 day per week

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

NEW YORK STATE

GREATER BINGHAMTON HEALTH CENTER
ADULT PSYCHIATRIST
And
CHILD/ADOLESCENT PSYCHIATRISTS

GBHC, (JCAHO-Accredited New York State Office of Mental Health facility) is seeking full time, board certified/board eligible **ADULT PSYCHIATRISTS** for its 140 bed adult inpatient facility and **CHILD/ADOLESCENT PSYCHIATRISTS** for its Child/Adolescent unit. Abundant on-site CME. Salaried, permanent positions with excellent New York State benefits.

Submit CV to: Personnel Office, Greater Binghamton Health Center, 425 Robinson St., Binghamton, NY 13904. Fax: (607) 773-4117. EOE/AAE.

P/T CHILD/ADOLESCENT PSYCHIATRIST WANTED. Outpatient position with leading LI Children and Family Mental Health Agency. Fax Resume: HR-(516)626-8403.

PSYCHIATRISTS NEEDED

The Mid-Hudson Forensic Psychiatric Center is a secure facility operated by the NYS Office of Mental Health and is accredited by both CMS and JCAHO. Located in the lower Hudson Valley near Middletown, NY, the facility provides an excellent opportunity for both general and forensic psychiatry for both licensed and Board certified psychiatrists. Starting base salary for licensed psychiatrist is $128,922.00. Board certified psychiatrists are guaranteed $133,978.00 and an anticipated increase, with salary differentials and excellent fringe benefits. Affirmative Action/Equal Opportunity Employer.

Contact: Salil Kathpalia, M.D.
Clinical Director
MHFPC
Box 158, Route 17M
New Hampton, NY 10958
Phone: (845) 374-3171, ext, 3155
Email: MHMDSKK@omh.state.ny.us
Fax# - (845) 374-3961

Inpatient/ Outpatient Psychiatrists
Ellis Hospital
Schenectady, NY 12308

The Ellis Hospital Department of Psychiatry, a respected leader in mental health in the Capital Region of New York State, has openings for full-time NYS licensed, BC/BE inpatient and outpatient psychiatrists. The hospital offers a generous salary and benefit package, opportunities for continuing education, and a stimulating work environment.

Ellis Hospital is located in Schenectady, NY, in the Mohawk Valley at the foothills of the Adirondack Mountains. The area is well-known for its beautiful lakes, including scenic Lake George, numerous parks, ski resorts, golf courses, and the famous Saratoga Raceway, all within an hour's drive. Major cities within a three-hour drive include New York and Boston.

For further information, contact Anthony Yacona, M.D., Chairman, Department of Psychiatry, Ellis Hospital, 1101 Nott St., Schenectady, NY 12308 at (518)-243-4154 or e-mail yaconaa@ellishospital.org.

TLC Health Network seeking full time psychiatrist with interest in a progressive health network providing a variety of behavioral and chemical dependency services. Competitive compensation and benefits. Send CV to Gary Baltz, VP for Behavioral Health, TLC Health Network, 100 Memorial Drive, Gowanda, NY 14070 or call (716) 532-8940.

NORTH CAROLINA

FORENSIC PSYCHIATRISTS
The Federal Medical Center located in Butner, North Carolina, is seeking BC/BE staff psychiatrists. Board certification or an interest in Forensic Psychiatry is ideal. The 310 bed all male Mental Health Component is part of a 989 bed JCAHO accredited facility located north of Raleigh and the Research Triangle Park. Applicants are required to possess a license to practice medicine in any of the 50 states and full U.S. citizenship. Staff psychiatrists are part of a multidisciplinary team with a primary focus in performing court ordered forensic evaluations. Care of the chronically mentally ill is a part of the job responsibilities. FMC Butner is a site for community rotations for psychiatry residents from the nearby Duke University Medical Center and a site for the Forensic Psychiatry Fellowship sponsored by the University of North Carolina at Chapel Hill. Interested candidates should contact Mona Hill, Medical Recruiter, at (919) 575-3900, ext. 6040, or J. Zula, M.D., Chief of Psychiatry, at ext. 5475. **FMC Butner is an Equal Opportunity Employer committed to a policy of nondiscrimination on the basis of race, gender, religion, color, national origin, disability, marital status, and status as a covered veteran.** EEO/AA Employer

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100% Outpatient work in NC's most scenic and affordable area. Established Mental Health Organization seeks 2 Psychiatrists. Call is by telephone only, and is extremely light. Client can provide Loan Repayment, and sponsor candidates on a J1 Visa. Call Ken Pruchnicki @ 800-575-2880 ext. 319.

Big city excitement with Carolina style! Exceptional opportunities in 3 metropolitan cities in NC. Adult & C/A Psychiatry need. **100% OUTPATIENT!** Possible teaching and /or research opportunities. **Rewarding opportunities** with competitive base salaries & full benefits package! Possibility to **make over $200,000!** For more info, contact Carrley Ward at 800-735-8261 x 219, fax your CV to 703-995-0647 or email: cward@medsourceconsultants.com

NORTH DAKOTA

PRAIRIE ST. JOHN'S

We have an exciting opportunity for a talented and dynamic **Child and Adolescent Psychiatrist** to join a growing, well-respected, mission-focused organization that Offers Hope and Healing to Those Suffering From Psychiatric Conditions and Addictions.

Prairie St. John's, a Catholic Psychiatric and Addictions Health Care Organization, based in Fargo, ND is seeking a Child & Adolescent Psychiatrist to join our group of 10 Psychiatrists (including eight C&A trained). Prairie provides mental health, chemical dependency and dual diagnosis treatment programs in a continuum of care that includes inpatient, partial hospital, residential, intensive outpatient and clinic services to children, adolescents, and adults. Starting salary up to $210,000 dependent on site of practice and qualifications, plus productivity compensation. Excellent benefits. Fargo is a great place to live, raise a family, work and do business. Prairie is a great place to practice Psychiatry. View us on-line at www.prairie-stjohns.com.

Send CV and letter of interest to: Karen Frigen, Development Specialist, Prairie St. John's, 510 4th St. S., Fargo, ND 58103 or via e-mail to kfrigen@prairie-stjohns.com.

PRAIRIE ST. JOHN'S

Medical Director Opportunity

Prairie St. John's, located in Fargo, ND is seeking a talented and experienced Medical Director. This position actively directs and coordinates the activities of both Child_Adolescent and Adult Services, along with providing clinical care for an Adult inpatient caseload; primarily chemically dependent patients. The Medical Director's duties include Psychiatric personnel selection, orientation, and evaluation, overall clinical program refinement and oversight, and policy development and review. Approximately 1/3 administrative, 2/3 clinical practice. Reports to Chief Executive Officer. Requires BC in General Psychiatry and previous supervisory experience. Salary $210k - $240k depending on qualifications.

The Fargo, ND-Moorhead MN metro area has a population of 180,000 and has been named one of the best places to live, raise a family, work and do business by Forbes magazine (May 2005). We are a college community located near the beautiful Minnesota lakes country offering excellent educational systems, recreation and sporting activities as well as a variety of entertainment and cultural events.

Prairie St. John's provides an excellent compensation and benefits package. View us on-line at www.prairie-stjohns.com.

Send CV and letter of interest to: Karen Frigen, Development Specialist, Prairie St. John's, 510 4th St. S., Fargo, ND 58103 or via e-mail to kfrigen@prairie-stjohns.com.

MeritCare Health System of Fargo, ND is seeking an Adult Psychiatrist to join its 32-member multi-disciplinary Psychiatry Department. Faculty appointment and teaching of psychiatry residents is available through University of North Dakota School of Medicine. MeritCare is an integrated 384-physician multi-specialty group practice, 583-bed Level II tertiary/trauma hospital with 26 primary care clinic sites in two states. Sister cities, Fargo, ND and Moorhead, MN are a tri-college community of 200,000 located near the heart of Minnesota's lake country. Fargo-Moorhead offers excellent educational systems, recreation and sporting activities as well as a variety of entertainment and cultural events. This is an excellent opportunity with a competitive compensation and benefits package being offered. Drug-free workplace. AA/EOE. This is not a designated HPSA site.

To apply send CV to:

Jill Gilleshammer, Physician Recruiter
MeritCare Health System
P O Box MC
Fargo, North Dakota 58122
Phone: (800) 437-4010, ext. 280-4851
Email: Jill.Gilleshammer@meritcare.com

OHIO

SEEKING Executive Director for Summit County, Ohio Alcohol, Drug Addiction and Mental Health Services Board. Professional with extensive administrative experience in operating large governmental agency or nonprofit with understanding of mental health and addiction recovery and prevention services. Leadership, communication skills, fiscal, government funding and managed care knowledge required. Successful experience with voted local levy support preferred. Equal employment opportunity. Respond in writing with resume, references and salary requirements by August 31, 2006 to ADM Search Committee, c/o Greg Kavinsky, Co-Chair, 2558 Arbor Court, Uniontown, OH 44685-7814.

PSYCHIATRIST NEEDED

A leading behavioral health agency is seeking a psychiatrist in the central Ohio area. This position will be responsible for all psychiatric/medical services provided to a broad range of patients, formulating and implementing clinical and organizational policies. Successful candidate will be Board eligible/Board certified in psychiatry and willing to obtain a current Ohio medical license. Salary commensurate with experience and qualifications with excellent comprehensive benefit package.

Interested applicants may submit résumés' to:

Human Resources
North Central Mental Health Services
1301 N. High Street
Columbus, OH 43201 or
Fax to 614-298-2227,
Email astuart2002@yahoo.com

OREGON

Oregon State Hospital

Oregon State Hospital is currently recruiting for Psychiatrists with interest and/or experience in adult and forensic programs. A strong benefits package complements salary. Opportunities for additional on-call work can increase your income substantially.

Oregon State Hospital provides specialized mental health services, including general adult, geriatric, and forensic treatment programs with campuses in Salem and Portland. Oregon State Hospital currently employs approximately 1,200 staff, including 30 Psychiatrists.

Located in the beautiful Willamette Valley, the area offers a great diversity of recreational activities. Within an hour's drive one finds the Cascades, the Coastal Range, and the Pacific Ocean. Oregon is justifiably famous for its world-class fishing, hunting, skiing, golfing, windsurfing, white water rafting, camping, and mountaineering opportunities.

Contact:
Becky Hawkins, Office of Human Resources
Oregon State Hospital
2600 Center Street NE
Salem, OR 97301-2682

Phone: (503) 945-2822
Fax: (503) 945-9910
E-Mail: Becky.Hawkins@state.or.us

PENNSYLVANIA

NORTHWEST PENNSYLVANIA - BC/BE Adult Psychiatrist with interest in Geriatric Psychiatry desired for Saint Vincent Health Center in Erie, Pennsylvania. Join our team of 4 Adult Psychiatrists and 2 Child Psychiatrists in a 413-bed tertiary care hospital setting including IP and OP services as well as a new 10-bed geropsychiatric unit. Our 32-bed unit is staffed with professionals who are willing to go "the extra mile" to meet the patient's needs. Patient services include acute care, consultation liaison services as well as psychiatric evaluations and medication management, crisis services, treatment of chemical dependency, and contracted services to several community programs. Located on the shores of Lake Erie with 7 miles of beaches, Erie is the fourth largest city in Pennsylvania with a metropolitan population of 280,000 and a referral base of 750,000. Competitive salary and benefits. For more information contact **Sue McCreary, Physician Recruiter, Saint Vincent Health Center 232 W. 25th Street, Erie, PA 16544. Phone 814-452-7822, FAX 814-455-1524 or email smccrear@svhs.org Visit our website at www.saintvincenthealth.com**

PSYCHIATRISTS
In the Quaker tradition, Friends Hospital has improved the lives of individuals suffering from mental illness for the last 190 years. Friends Hospital, the nation's first private psychiatric hospital located in Philadelphia, is recruiting board eligible/certified psychiatrists.

Dual Diagnosis Medical Director: The hospital is seeking a psychiatrist with addiction fellowship training/ exp to serve as the Medical Director of the Dual Diagnosis Unit. The position is supported by an addiction psychologist & a strong clinical staff.

Intensive Adult Medical Director: The IA Unit is dedicated to individuals who suffer from chronic & persistent mental disorders. The Medical Director has the responsibility of interacting with the Public Sector providers to promote appropriate linkage to community resources.

Psychiatric Crisis Physician: Part-time coverage opportunities are available in the evening & weekends in the Admissions Department. Friends offers a generous salary, benefits, life insurance, paid medical malpractice, one week CME with allowance, and a 401(k) plan.

Friends Hospital is the training site of Drexel University Department of psychiatry. Qualified applicants will be reviewed for faculty appointments.

If you are interested in an exciting practice opportunity, please submit your CV by fax or email.
Rodgers Wilson, M.D.
Chief Medical Officer
C/o Ms. V. Combs
Ph: 215-831-7935
Fax: 215-831-4686
viviancombs@fbhs.org
4641 Roosevelt Blvd.
Philadelphia, Pa. 19124-2399

Pennhurst Medical Group, P.C. Various Pennsylvania locations BC/BE, Excellent Salary, Benefits, Full Time, No Billing, Part Time and Locums Positions. Send CV to bp@pennhurstmedical.com or by fax 610-524-0952. Feel free to call Bob Plunkett at 610-524-2400 x 160 with any questions or for more information.

UNIQUE CAREER OPPORTUNITY FOR ADULT PSYCHIATRIST

This is a superb opportunity for a BC/BE psychiatrist interested in a combination of emergency psychiatry and inpatient care. Establish a close working relationship with our psychiatric emergency service and our inpatient behavioral science unit. You will work with a large salaried hospital-based group who practice at LVH, an 800-bed academic community hospital where opportunities exist to teach medical students and residents and pursue career advancement. The successful candidate will also be eligible for faculty appointment at Penn State/Hershey. We are offering an excellent call schedule and a favorable lifestyle so that you can enjoy the beautiful Lehigh Valley where more than 700,000 people appreciate safe neighborhoods, good schools and easy access to major metropolitan areas. Philadelphia is 1 hour south and NYC is 1.5 hours east. For more information, call 610-969-0213. Email CV to Pamela.Adams@LVH.com or fax to (610) 969-0214.

LEHIGH VALLEY HOSPITAL (LVH) in Allentown, PA seeks 7th Consultation/Liaison psychiatrist to join salaried group. Focus on med/surg, ob/gyn, oncology, cardiology, trauma and burn. Job is 50% C/L and 50% outpatient. LVH is an 800-bed hospital with a Level 1 trauma center, regional burn center, 3,300 births, transplant program and 10 residency programs (no psychiatry). Competitive salary and excellent benefits, including paid medical malpractice insurance. Teaching (medical student rotation) and clinical research available. Faculty appointment at Penn State/Hershey. Allentown is in the Lehigh Valley, 60 miles north of Philadelphia and 90 miles west of NYC. Email CV to Ralph A. Primelo, Chief, Section of C/L Psychiatry, c/o Pamela.Adams@lvh.com. Fax 610-969-0214. Phone (610) 969-0208.

TEXAS

Psychiatrists needed in Houston, Texas. Full-time employee, very competitive salary and benefits package. Seeking two (2) psychiatrists: Position 1 is for provision of physician services to psychiatric patients in an inpatient setting. Position 2 is for provision of physician services to psychiatric patients primarily in an outpatient setting, with some inpatient and possible psychiatric research services. Must have current Texas Medical License. Current Medicare number preferred. **Please email resume and references to: dgafford@dapaprograms.com**

HOUSTON - Baylor College of Medicine is seeking board-certified or board-eligible psychiatrists to fill clinical openings at Ben Taub General Hospital, a major teaching, service, and research hospital of the College. Positions are available in emergency psychiatry and outpatient psychiatry, including work in community clinic settings. Bilingual English/Spanish providers are encouraged to apply. Please send a confidential CV and any additional information which might be of use to the search committee to Britta Ostermeyer, MD, Baylor College of Medicine, Department of Psychiatry, One Baylor Plaza, BCM350, Houston, TX 77030 or email brittao@bcm.edu Baylor College of Medicine is an Equal Opportunity, Affirmative Action and Equal Access employer.

The Department of Psychiatry at The University of Texas Health Science Center at San Antonio is seeking three board-certified or board-eligible academic psychiatrists or psychologists to join one of the premier programs in the country. There are part-time or full-time positions on either the tenure or non-tenure track. Salary and academic rank are commensurate with qualifications. The department has strong educational, research and clinical programs in an attractive, culturally rich city situated on the edge of the Texas Hill Country, with a pleasant climate, an excellent public school system and abundant recreational activities. Interested individuals should forward their curriculum vitae to Pedro L. Delgado, M.D., Professor and Chairman, Department of Psychiatry, Mail Code 7792, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio TX 78229-3900, phone 210-567-5391, FAX 210-567-6941. The University of Texas Health Science Center at San Antonio is an Equal Employment Opportunity/Affirmative Action Employer. All faculty appointments are designated as security sensitive positions.

Dallas Suburbs! 100% OUTPATIENT with no call! Be set up in private practice and provide services to a child/adolescent program through the O/P clinic. Flexible work week and daily hours. Call **Karen Brennan at 800-575-2880 x307**. E-mail to kbrennan@medsourceconsultants.com.

Texas Forest Country - The Burke Center, a multi-site, JCAHO accredited community mental health center, has an immediate opening for either a **general psychiatrist or child psychiatrist** willing to treat some adults. The position is outpatient only, primarily located in Livingston, although there may be some work in other locations or by telemedicine. Enjoy an excellent lifestyle with a 40-hour work week, no call, competitive salary, and fantastic benefits. Physician Assistants and Advanced Nurse Practitioners will be considered as well. Recreational opportunities abound in national forests nearby. Houston is less than 2 hours away; Dallas 3 hours; major state university nearby. Please send CV to Mark Janes, M.D., Medical Director, Burke Center, 4101 S. Medford Drive, Lufkin, TX 75901. Fax: (936)634-8601. Email: markj@burke-center.org. Check out the details on our website: *www.burke-center.org*.

North Texas State Hospital

North Texas State Hospital is a preeminent psychiatric facility located in North Central Texas with campuses in Vernon and Wichita Falls. Psychiatrist in our organization have the opportunity for a professionally stimulating practice that genuinely makes a difference in these patients' lives, while at the same time affording themselves a rich quality of life in an area with a comparatively low cost of living. The Vernon Campus serves as the only adult Maximum Security facility and adolescent forensic program in the Texas Department of State Health Services and the Wichita Falls campus is a multi-faceted general psychiatric facility serving north central and west Texas. Populations served include: forensic, substance abuse, adult, child, adolescent, geriatric, and developmentally disabled. If you are looking for a challenging and rewarding position with an excellent salary, employment security, outstanding benefits* and opportunities for professional growth, we invite you to visit our progressive, modern facility at North Texas State Hospital. **No state income tax, paid sick leave, paid vacation, paid time off for CME, 12-14 paid holidays per year, retirement plan, additional pay available if on call is provided, and much more.*

Contact **Thomas R. Mareth, M.D.**
for more information.
Phone: (940) 552-4150
Fax: (940) 553-2530
thomas.mareth@dshs.state.tx.us
North Texas State Hospital-P.O. Box 2231-Vernon, Texas 76385
North Texas State Hospital is an Equal Opportunity/Drug Free Workplace
Not a Healthcare Shortage Opportunity

Lubbock Regional Mental Health Mental Retardation Center (LRMHMRC) is recruiting for a board certified or board eligible inpatient psychiatrist for Sunrise Canyon Hospital, a JCAHO accredited, 30 bed adult psychiatric community hospital. Primary responsibilities will include direct patient care and supervision of mid-level professionals.

LRMHMRC offers a competitive salary and compensation package, including 96 hours of paid vacation, 12 paid sick days and eleven paid holidays the first year. Other benefits include a company-sponsored retirement plan, fully paid professional liability insurance and one week of CME with up to $1,000 allowance annually.

LRMHMRC is one of the largest comprehensive behavioral healthcare providers in West Texas. LRMHMRC has been in operation for over 40 years, has a budget of over $24 million and serves over 6,000 people per year. The Sunrise Canyon Hospital's milieu includes a multidisciplinary treatment team approach, including collaboration among psychologists, social workers, an occupational therapist, chemical dependency counselors and crisis intervention staff.

Sunrise Canyon Hospital is located in Lubbock, Texas (population 200,000) which is home to Texas Tech University, a top-tier research institute. Lubbock offers citizens a home-town feel, with big city luxuries. The largest medical community from Dallas to Los Angeles, the city boasts more physicians per capital than Dallas, Phoenix or Denver, but has an average commute of only 17 minutes and a comparatively low cost of living. On average, Lubbock enjoys 227 days of sunshine per year. Visit www.lubbocktexas.com

For more information contact Mary Gerlach, Hospital Administrator at 806-790-5330 or by email: mgerlach@lubbockmhmr.org

LRMHMRC is an equal opportunity and Affirmative Action Employer.

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.

UTAH

Utah State Hospital, 340 Bed JCAHO / MEDICAID / HCFA accredited. Medical model/team approach with Geriatric, Forensic, Adult, Child, Adolescent, Rehab Programs. Needed: Full-time, flex shifts available, PSYCHIATRIST. Competitive pay, outstanding benefit package equal to 30% of salary, relocation allowance. Located in Provo - 45 miles south of Salt Lake City. We are relatively insulated from managed care pressures and offer a length of stay, which allows meaningful treatment. Recognized cultural center, three well-known universities, unmatched outdoor recreation. Very stable, low crime rate, economically sound. Send CV to: Richard Spencer, Clinical Director, PO Box 270, Provo, UT 84603, or phone: (801) 344-4201. EOE

CHAIR, DEPARTMENT OF PSYCHIATRY UNIVERSITY OF UTAH SCHOOL OF MEDICINE

The University of Utah School of Medicine is embarking on a national search for the position of Chair of the Department of Psychiatry. Visionary candidates with a distinguished record of clinical, educational, and investigative accomplishments are invited to apply. Past administrative experience of substance is expected. The Department of Psychiatry at the University of Utah School of Medicine is comprised of 55 full-time physicians, and 129 adjunct faculty members, as well as a very successful training program in adult, pediatric, and triple board programs.

The Department of Psychiatry has exceptional opportunities, including its own inpatient hospital, the newly created University Brain Institute, and a Vanguard site for the National Children's Study.

Interested applicants should submit an electronic curriculum vitae, list of references, and a brief statement describing academic interests and professional goals to:

Jennifer L. Allie
Director, Faculty Administration
University of Utah School of Medicine
30 North 1900 East Room 1C047 SOM
Salt Lake City, UT 84132
PH: (801) 581-5705
FAX: (801) 581-3338
Email: jennifer.allie@hsc.utah.edu

UNIVERSITY OF UTAH IS AN EEO/AA EMPLOYER AND ENCOURAGES APPLICATIONS FROM WOMEN AND MINORITIES

Chief, Psychiatry - VA Salt Lake City Health Care System, Salt Lake City, Utah. VASLCHCS is affiliated with the Univ. of Utah School of Medicine, and seeks a full-time, tenured or tenure track assoc. or full professor to head Psychiatry Service. VISN 19 is a recent recipient of a Mental Illness Research, Education, and Clinical Center (MIRECC) award centered on suicide prevention, with a portion of the program at the VASLCHCS, under the direction of, Chief Psychiatry. An affiliation is available to the VASLCHCS GRECC and the newly formed Brain Institute at the School of Medicine. The VASLCHCS has 8 psychiatry residents and is a major medical student training site. You must be U.S. Citizen. Relocation expenses are authorized. Closes August 31, 2006. Send CV and three references to VASLCHCS (05C), 500 Foothill Dr., SLC, Utah 84148, announcement #C06-137. For additional information contact Tonya Mackintosh at 801-584-1284, x 2267 or Kellie Roe, x2205. Equal Opportunity Employer.

VERMONT

PSYCHIATRISTS - Northeast Kingdom Human Services, Inc. a CMHS located in St. Johnsbury, is seeking two Full-Time Psychiatrists. Opportunities exist for outpatient work with adult patients suffering from a wide range of serious mental illnesses, and for consultation to primary care practices at the primary care office. This position is perfect for someone who enjoys outdoor activities in a rural environment. You will find mountains and lakes as well as the urban lifestyle less than an hour away. NKHS provides community-based, consumer-sensitive mental health, substance abuse and developmental services for residents of Caledonia, Essex & Orleans counties of Vermont. Our agency offers an outstanding benefits package. Please apply with cover letter and resume to bbrenk@nkhs.net or Bianca Brenk, NKHS, POB 724, Newport, VT 05855. For further information please visit our web site at www.jobsinvt.com or www.nkhs.net.

Central Vermont

Washington County Mental Health Services, a CMHC located in Montpelier, is seeking a full time psychiatrist to join its high quality, dedicated psychiatric staff. Opportunities exist for outpatient work with geriatic and adult patients suffering from a wide range of mental illnesses, developmental disorders, and mental retardation. Particularly needed is a psychiatrist for a newly developing, innovative, recovery oriented and trauma informed, highly staffed, ten bed, residential program providing a level of services not previously available outside of a hospital setting in Vermont. Competitive salary and benefits; EOE. Applicant must be BE/BC. Please send cover letter and CV to: Stuart Graves, MD, 9 Heaton Street, Montpelier, VT, 05602, or e-mail to Stuartg@wcmhs.org.

The VA Medical Center, White River Jct., VT is currently seeking an Addiction Psychiatrist to join our facility. The VAMC, White River Jct., VT is closely affiliated with Dartmouth Medical School. The successful candidate will serve as Director of Addiction Treatment Services at the White River Junction VA. Duties will include direct clinical care of patients with substance use disorders and co-occurring psychiatric and substance use disorders, administration of the Addiction Services and clinical supervision of the addiction clinical team including addiction therapists, addiction fellows, psychiatry residents, and medical students. The candidate will also direct the Dartmouth Medical School Addiction Psychiatry Fellowship. Research opportunities are available and encouraged. Candidates should be Board Certified or eligible in Psychiatry. Experience and APA Added Qualifications in Addiction Psychi-

atry and/or ASAM certification are highly desired. Salary will be commensurate with experience. Successful incumbent must qualify for academic appointment at Dartmouth Medical School. Send letter of interest, CV and references to Human Resources Management Service/05, VA Medical Center, 215 N. Main St., White River Jct., VT 05009, fax (802) 296-6350. Inquiries may be directed to Vince Watts, MD, Chair Committee.
Bradley.V.Watts@Dartmouth.edu. EOE.

VIRGINIA

GEROPSYCHIATRIST: Virginia Commonwealth University, Department of Psychiatry recruiting Virginia licensable BE/BC psychiatrist in to provide clinical care, training of fellows, residents and medical students, and research activities at Piedmont Geriatric Hospital (80%) and the University campus (20%). Teaching, research experience and geropsychiatry fellowship preferred. J-1 AVAILABLE. PGH is specialty geriatric state hospital located in Burkeville, VA, 35 minutes from Richmond. VCU is a large urban university with robust health science campus and 750-bed university hospital. The Department of Psychiatry employs over 80 fulltime faculty and has well-funded research in women's mental health, genetics, addictions, child mental health and psychopharmacology. Richmond, the State Capital, has moderate climate and rich mix of history with modern facilities, excellent suburban housing, public/private schools. Internet provides comparative cost of living. Send CV to Search Committee, c/o Mary Swartz, VCU, Box 980710, Richmond VA 23298. Virginia Commonwealth University is an Equal Opportunity/Affirmative Action employer. Women, minorities, and persons with disabilities are encouraged to apply.

Christiansburg, VA - General Adult Psychiatrist needed in Virginia's New River Valley region for state-of-the-art inpatient facility with office suite contiguous to the inpatient unit. Position provides for a combination of inpatient/outpatient psychiatry, including administering ECT; on-call an average of 6-7 days/month, including 1-2 weekend days. Virginia's New River Valley region comprises the localities of Blacksburg, home of Virginia Tech, and Radford, home of Radford University, plus the town of Christiansburg and surrounding communities, a population of 175k. Carilion Health System is a nonprofit regional healthcare system comprised of several acute-care hospitals including teaching/tertiary referral center nearby, medical education programs, and 70+ multispecialty clinics. Base salary with bonus incentive plan based on quality outcome and scorecard measures. Requirements: Minimum of 3 years experience post-residency, and/or other professional experience prior to completing residency; ABMS-BC ideal, or BE acceptable with plan in place to receive certification in 2 years; excellent interpersonal and communication skills. Positions available immediately. To apply, submit CV with references and cover letter to:

Rhonda B. Creger, Physician Recruiter
Carilion Health System
POB 40032
Roanoke, VA 24022-0032
Office 540-224-5189
FAX 540-985-5329
Email: rhondac@carilion.com
Website: www.carilion.com

Norfolk Community Services Board seeks a part-time Child and Adolescent Psychiatrist for newly developed Family Development Center. Must be licensed to practice Medicine in Virginia. Board Certification in General Psychiatry with additional sub-specialty certification in Child and Adolescent Psychiatry preferred. Ideal candidate will have relevant experience working with the seriously emotionally disturbed. Excellent benefits package; salary commensurate with experience. Apply to Norfolk Community Services Board, 248 W. Bute Street, Norfolk VA 23510 or call (757) 441-5300 if you require special assistance. On-line application at www.norfolkcsb.org. EOE M/F/D/V. Background check required.

WASHINGTON

Opening for one Board Certified/Board Eligible Staff Psychiatrist and one Board Certified/Board Chief Psychiatrist with the Department of Veterans Affairs Medical Center in Walla Walla, Washington. Requires patient-oriented physician for inpatient/outpatient care which includes working with Post Traumatic Stress conditions and chemical dependency. Opening available now. Must be a US citizen. (VA physicians are covered by Federal Tort Acts and do not need malpractice insurance). Benefits includes health/life insurance, 25 days of vacation leave, plus sick leave, and a generous retirement system. Walla Walla is a pleasant town of 30,000 at the base of the beautiful Blue Mountain range of SE Washington State. Excellent schools and two fine 4-year colleges are an asset. Enjoy skiing, fishing, wind surfing, and hiking in a moderate climate. Applicants are subject to a drug screening test. Contact Jean Hulce, HR Specialist at 509-527-3453. Equal Opportunity Employer. This agency provides reasonable accommodation to applicants with disabilities. If you need a reasonable accommodation for any part of the hiring process, please notify Human Resources. The decision on granting reasonable accommodation will be on a case-by-case basis.

BC/BE PSYCHIATRIST
Seeking a BC/BE Psychiatrist with an interest in geriatrics (*fellowship training a plus*), to join a *colloborative* 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

The University of Washington and Harborview Medical Center (HMC) in Seattle, WA is accepting applications for a psychiatrist at the rank of Assistant or Associate Professor. This position is 1.0 FTE and will work on the inpatient and outpatient services. The position will also be responsible for teaching residents and medical students. University of Washington faculty engage in teaching, research and service. Please send application and CV to Peter Roy-Byrne MD, Chief Psychiatry, Harborview Medical Center 325 9th Ave. Box 359911, Seattle, WA 98104. The UW is building a culturally diverse faculty and strongly encourages applications from females and minority candidates. The UW is and EOE/AA employer.

Emergency Psychiatry Clinical Faculty Position
University of Washington, Seattle, WA

Harborview Medical Center, Department of Psychiatry and Behavioral Sciences is seeking a psychiatrist in the Psychiatric Emergency Services (PES). The coverage is shared among several psychiatrists who work under the supervision of the PES Medical Director. The position will receive a UW clinical faculty appointment. The PES attending psychiatrists provide direct evaluation, triage and acute treatment to patients, and overall supervision of the clinical team, including residents. Pay scale is highly competitive due to shift work and off-hours schedule. University of Washington faculty engage in teaching, research and service. HMC has a nationally recognized psychiatric emergency service and strives to deliver state of the art care in an academic medical setting. Please forward your letter and CV to: Peter Roy-Byrne, MD, Box 359911 Psychiatry HMC 325 9th Avenue, Seattle 98104. The UW is building a culturally diverse faculty and strongly encourages applications from females and minority candidates. The UW is and EOE/AA employer.

WEST VIRGINIA

PSYCHIATRISTS - William R. Sharpe, Jr. Hospital, a 150-bed, JCAHO-accredited, state psychiatric hospital and winner of APA Award for state/university collaboration, is searching for BE/BC psychiatrists. The facility is unique in the region for the range of psychiatric services offered and quality of care provided. The hospital is one of the largest training sites for various clinical disciplines including psychiatric residents, medical students as well as psychology, social work and nursing trainees. These are full time faculty positions with regionally competitive salaries and excellent benefits. There is no call duty. The area has an abundance of outdoor activities, four-season climate, and one of the lowest crime rates in the country. There are several metropolitan areas within easy driving distance. West Virginia University is an affirmative action/equal opportunity employer. Women and minority candidates are encouraged to apply. Positions will be open until filled. Contact Abe Adel, MD, Clinical Director, William R. Sharpe, Jr. Hospital, WVU Department of Behavioral Medicine & Psychiatry 936 William Sharpe Road, Weston, WV 26452. 304-269-1210. bettygufoster @wvdhhr.org

WISCONSIN

Outstanding private practice opportunity. One of our 3 psychiatrists is retiring. Walk in and take over his 26-year practice. No investment required. Furniture, office staff, billing system all in place. Hospital affiliation available but not required. Lakefront community of 90,000 midway between Chicago & Milwaukee. Kenosha Psychiatric Associates. Fax (262) 652-4450. Email kenoshapsych@sbcglobal.net

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Madison, WI - noted as "U.S. Best City", two years, seeks a BC/BE child psychiatrist. *Capitol Associates*, well-recognized for more than 20 years, is Madison's largest, independent, licensed mental health clinic and is dedicated to comprehensive inpatient/outpatient care. CA boasts 14 mental health professionals, including 2 psychiatrists. A university town surrounded by many lakes, Madison has abundant recreational activities, high educational standards and support for the arts. Please consider joining our caring, energetic team. Capitol Associates, LLC, Attention: Johna Gerasch, PhD (Managing Partner), 440 Science Dr., Suite 200, Madison, WI 53711. (608) 238-5176, ext. 314.

Win the Trifecta-stimulating job opp't, waterfront living, and high $$$. Adult and Child psychiatrists needed to join a conscientious staff in a collegial setting. Enjoy mostly Outpatient duties and keep 100% of the billings over guarantee. Contact Susan Springer @ 800.575.2880 ext 315

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

The Allure of the West!

- Ranked #1 in the U.S. by "Kiplinger's" for the lowest taxes paid per household
- Ideal to raise a family, possesses great schools, and retains its western charm although only 90 minutes from Denver
- United Medical Center is a 206-bed hospital that serves Wyoming, Northern Colorado, and Western Nebraska
- 16-bed Behavioral Health Unit (12 adult and 4 adolescent) and active outpatient clinic

Adult Psychiatrists
Opportunities for both inpatient and outpatient treatment of adults. Skills and experience in treating geriatrics a plus.

Addiction Specialist
Unique opportunity to spearhead and champion the expansion of a hospital-based, outpatient addiction treatment program. Specialization in addiction treatment is required.

Both candidates must be team players with excellent communication skills. Program development a plus. Board-Certified (or-eligible). Wyoming license (or-eligible).

Contact: Lauren Maines, Physician Recruiter, 214 E. 23rd St. Cheyenne, Wyoming 82001, Office: (307) 432-2649, Fax: (307) 432-3181, LMaines@umcwy.org.

Fellowships

The University of Iowa
Department of Psychiatry
Mental Health Clinical Research Center

POSITION: Postdoctoral Fellowships In Clinical Neuroscience

SPONSOR: Schizophrenia Research Center - University of Iowa - (NIMH/NIDA Research Training Award)

DESCRIPTION: Applications are being accepted for a 1- to 3-year NIMH-funded fellowship program funded jointly by NIMH and NIDA for training in the neurobiology of major psychotic disorders and clinical neuroscience. The fellowship is designed for either: 1) psychiatrists who have recently completed residency or are beginning their fourth year of residency and/or; 2) People who have recently completed Ph.D.s in psychology (clinical or experimental), neuroscience, biostatistics, biomedical engineering, or related fields. Major areas of activity include brain imaging (MRI, fMRI, & PET), biostatistics, cognitive neuroscience, neuroanatomy & neuropathology, neuropharmacology, & molecular genetics. The primary focus of the Schizophrenia Research Center is on schizophrenia and related psychotic disorders, and addiction, but candidates with a primary interest in addiction research are particularly encouraged to apply.

U.S. citizenship or permanent visa status required. Applicants from under-represented groups and from all ethnic backgrounds are encouraged to apply. For more information about the Mental Health Clinical Research Center, visit our website at http://iowa-mhcrc.psychiatry.uiowa.edu/.

DEADLINE: Applications are now being accepted. Immediate openings available.

CONTACT: For application write to Nancy C. Andreasen, M.D., Ph.D., Director, MHCRC, 2911 JPP,200 Hawkins Drive, Iowa City, IA, 52242-1057, (319) 356-1545 or email Vicki Foubert at vicki-foubert@uiowa.edu. The University of Iowa is an Equal Opportunity/Affirmative Action Employer.

Geropsychiatry Fellowship, Portland, Oregon. Recruiting for 07/01/07 ACGME-accredited PGY5 level, at Oregon Health & Science Univ and Portland VA Med Center. Flexible program with either research or clinical emphasis. Training sites include inpatient, outpatient, nursing home and community. Research and clinical strengths in end-of-life/palliative care, ethics, mood disorders, dementias, Parkinson's disease, and substance abuse. Contact Dr. Linda Ganzini, Dir, Geriatric Psychiatry Training, Mental Health Div, P3MHDC, PO Box 1034, Portland, OR 97207; (503) 220-8262, Ext. 56492; or at Linda.Ganzini@va.gov. EOE.

Practice for Sale

Assume well established solo practice in Nassau County-North Shore, New York, after a phase in period. About thirty hours per week currently, with good referral base for expansion. Reasonable terms. Fax inquiries to: 516-997-8402 or call 516-997-4610.

Lucrative solo practice for sale. Psychopharmacology and psychotherapy. Expected gross this year; $400,000 based on 40 hr. per week. No managed care. Located in beautiful Sun Valley. Contact Dr. Brooks at (208) 726-0055 (office) or (208) 788-4782 (home).

Furniture

PSYCHOANALYTIC COUCHES

Prestige Furniture and Design is the leading manufacturer of psychoanalytic couches. For a brochure and price list, call (800) 283-9958.

BRIEF SUMMARY. See package insert for full prescribing information.

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

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS — ***QT Prolongation:*** Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).** ***QT Prolongation and Risk of Sudden Death:*** **GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see** ***Drug Interactions*** **under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec.** ***Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS —** ***General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis)**. Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine,* 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole,* a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine,* 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS —** ***Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients.There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System — *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses — *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System — *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE—** ***Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/75).

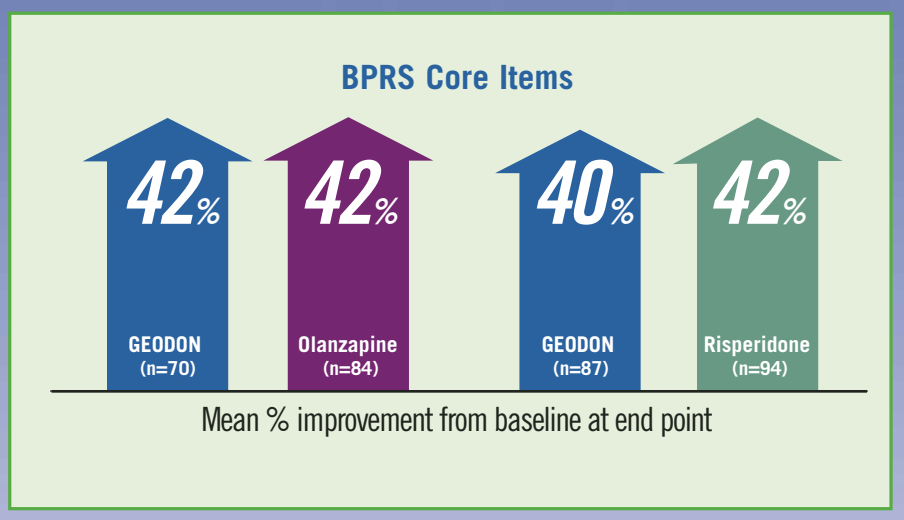
References: 1. Data on file. Pfizer Inc., New York, NY. **2.** Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161:1837-1847. **3.** Addington DEN, Pantelis C, Dineen M, Benattia I, Romano SJ. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry*. 2004;65:1624-1633. **4.** Simpson GM, Weiden P, Pigott T, Murray S, Siu CO, Romano SJ. Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. *Am J Psychiatry*. 2005;162:1535-1538. **5.** Weiden PJ, Loebel A, Yang R, Lebovitz H. Course of weight & metabolic benefits 1 year after switching to ziprasidone. Presented at: American Psychiatric Association Annual Meeting; May 1-6, 2004; New York, NY.

Revised May 2005

Treat schizophrenia with the body in mind

COMPARABLE EFFICACY

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

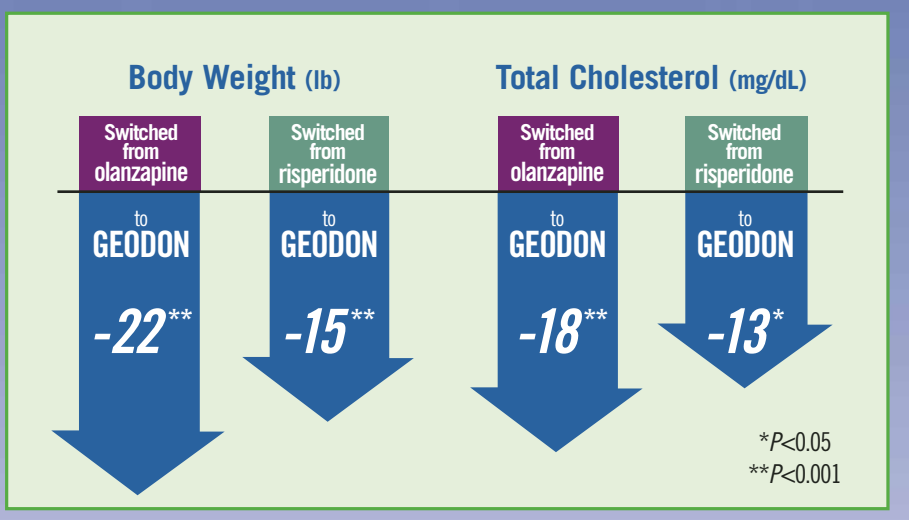


A 6-week, double-blind, randomized study of GEODON vs olanzapine and an 8-week, double-blind, randomized study of GEODON vs risperidone.

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

WITHOUT COMPROMISING METABOLIC PARAMETERS

Significant results in switch studies[1,5]



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

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

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

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

GEODON®
(ziprasidone HCl) Oral Capsules

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

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

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

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

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

Please see brief summary of prescribing information on adjacent page.

Pfizer NEUROSCIENCE