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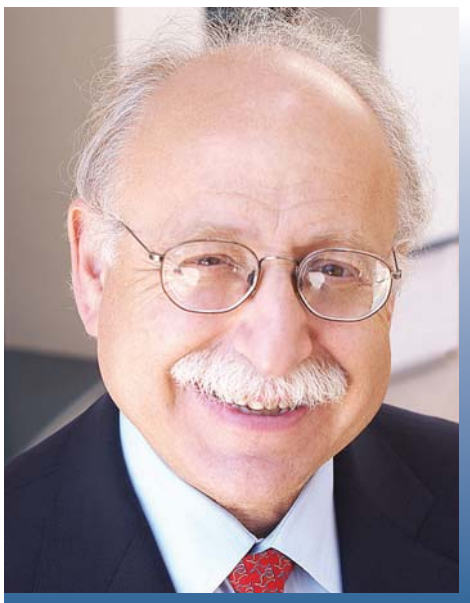
Newspaper of the
American
Psychiatric
Association

PSYCHIATRIC NEWS

Inside

PERIODICALS:
TIME-SENSITIVE MATERIALS



APA ELECTION

Carol Bernstein, M.D. (right), has been elected APA's next president-elect. She will assume that post at the end of APA's 2009 annual meeting in May, when Alan Schatzberg, M.D., will become president.

Bernstein Wins APA Presidency

APA's new president-elect has served the Association in a wide array of leadership posts, which should serve her well in her goal to reshape APA to better meet the needs of younger psychiatrists.

BY KEN HAUSMAN

Longtime psychiatric educator and APA leader Carol Bernstein, M.D., won the nod from her colleagues to become the Association's next president-elect.

Now in the final months of a two-year term as APA vice president, Bernstein will take over as president-elect at the close of APA's 2009 annual meeting in San Francisco on May 21.

The president-elect race was one of several three-way contests this year and the only one in which the victor received a majority on the first vote, thus avoiding the need to proceed through APA's preferential voting process. Bernstein won 50.5 percent of the vote, outpolling Roger Peele, M.D., who received 29.6 percent of the vote, and Michael Blumenfield, M.D., who garnered 19.9 percent of the vote.

Bernstein previously served as APA treasurer, chair of the Committee on Graduate Medical Education, and an Assembly representative from the New York County District Branch. She is an associate professor of psychiatry and associate dean for graduate medical education at New York University School of Medicine.

Bernstein said that she is "proud and thrilled to have this extraordinary opportunity to represent psychiatry at such an exciting time, especially since President Obama has made health care reform a major priority for the nation."

She noted that Obama is the first president in decades who has reached out to the mental health community for its input on how to improve the health care system. "And with the new parity law in place," she added, "mental health disorders will be considered on an equal basis with all other medical illnesses."

As for the challenges facing APA in the next several years, Bernstein said that the Association is "struggling with its relevance to the next generation of psychiatrists," who have different expectations for their work

please see ***Election Results*** *on page 30*

Psychiatrists Lobby Congress On Health Reform, Privacy Issues

APA members emphasize to Congress the need to include mental health care in the national effort to reform health care and to closely monitor regulations governing the new parity law.

BY RICH DALY

APA members lobbied members of Congress during APA's 2009 Advocacy Day events last month to ensure strong and timely regulations in the coming months that will implement the landmark federal insurance parity law enacted late last year.

The timing of the advocacy events, which took place from February 8 to 11, coincided with congressional consideration and passage of the massive American Recovery and Reinvestment Act of 2009 (ARRA, PL 111-5). The legislation, which was signed by President Obama on February 17, included federal electronic medical record (EMR) privacy protections.

This year's Advocacy Day brought 105 APA members from 43 states, the District of Columbia, and Puerto Rico to Washington, D.C., to learn about the major federal health policy challenges facing psychiatry and to urge their representatives in Congress to support APA-backed solutions. Attendees participated in several days of training and heard multiple issue updates before making 262 visits to the offices of members of Congress.

"I am pushing for strong privacy standards in electronic medical records," Leslie Secrest, M.D., of Dallas told *Psychiatric News* before his scheduled visits with his congressional representatives during Advocacy Day. "The thing that makes [EMRs] different is knowing how quickly [the information] can be transmitted."

The patient-privacy message that Secrest and other psychiatrists took to Capitol Hill may have made some impact because, despite long-held opposition in the Senate, the law contains a series of privacy protections long called for by APA and other mental health advocates. The law includes an expansion of the scope and penalties of violations of the federal privacy and security rules under the Health Insurance Portability and Accountability Act and a reduction in the amount of the information physicians must reveal to insurers (see article on page 8).

The other main issue that psychiatrists visited their congressional representatives

please see ***Lobby*** *on page 4*

Contents

Features

Volume 44
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Departments

Newspaper of the American Psychiatric Association **PSYCHIATRIC NEWS**

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Drug Companies See Big Profits In Online Social Media Advertising

As the focus of pharmaceutical marketing shifts from TV to the Internet, physicians should be prepared to respond to patients who begin a question with, "Doctor, I saw videos about this drug on YouTube …"

BY JUN YAN

Consumers may still see a barrage of ads featuring healthy, happy people and pronouncements of "Ask your doctor about" prescription so-and-so on television, but pharmaceutical marketing is quietly moving its investment out of this medium. Companies are dipping their toes into the bustling Internet, trying to gain a foothold in the rapidly expanding online social media.

In February, Sanofi-Aventis launched a YouTube channel, "Go Insulin," consisting of informational videos and patients' personal testimonials about type 2 diabetes and insulin treatment, but it does not provide direct promotional content for the insulin products the company manufactures. AstraZeneca has also launched a YouTube channel, titled "My Asthma Story," to promote its asthma drug with videos and patient testimonials. Interestingly, neither companies' names are featured prominently on these video Web sites. The AstraZeneca site was identified as only "Brought to you by the maker of Symbicort."

These YouTube-based marketing campaigns followed those of several other companies, including Johnson and Johnson and GlaxoSmithKline, which started their branded channels on YouTube in 2008.

YouTube is far from the only forum for online direct-to-consumer (DTC) advertising. Companies have long used product-specific Web sites to disseminate information about specific medications and devices to consumers and health care professionals. However, online social networks such as YouTube, FaceBook, and MySpace are drastically changing the ways people and groups connect with each other. Messages are transmitted laterally through the Web, rather than vertically, from the originator to the end user, and rely heavily on word of mouth for a successful message campaign.

In recent years television DTC advertisements have been accused of false representation and have drawn increasing criticism from lawmakers and consumer-advocacy groups (*Psychiatric News*, January 16). Even industry insiders began to question the viability of traditional DTC marketing.

The online media provide a far less expensive, more flexible, and more interactive playing field for marketers than do broadcast television and other traditional media. For example, YouTube channels can encourage patients to submit their own testimonial videos that cost nothing to produce and appear authentic. These advantages make online multimedia advertisements attractive to manufacturers at a time when DTC marketing bud-

please see ***Advertising*** *on page 29*

Important Annual Meeting Announcements

» Register Now for APA's 2009 Annual Meeting and Take Advantage of Advance Fees!
Meeting and hotel information, including rates and hotel descriptions and course information, can be accessed on APA's Web site at <www.psych.org> by clicking on the 2009 annual meeting logo and then "APA Members" under "Meeting Registration." San Francisco is a popular city for APA members, so you are advised to act quickly and save on fees. Advance registration closes April 10.

» Look for Annual Meeting Information Online
APA has gone *green!* The Association is trying to do its part in helping save the environment, while also saving money on printing and mailing costs. Thus, APA is no longer mailing an advance registraton information packet; instead, the information and registration and hotel-reservation forms it had traditionally contained have been posted on APA's Web site. Access information appears above.

More information is available by contacting Vernetta Copeland at (703) 907-7382 or vcopeland@psych.org.

APA RESOURCES

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

Our Debt to India

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


Credit: David Hathcox

It's a long way from Chicago to New Delhi: 15 hours—on a nonstop flight. I represented APA at the annual meeting of the Indian Psychiatric Society in January. I came from a country rich in resources and personnel to a country rich in tradition and family. There are 38,000 members of APA; there are 4,000 psychiatrists in India—to care for a population of over a billion. Clearly, mental health care is provided by primary care physicians, nurses, and lay therapists as well as psychiatrists, and families are crucial participants in care; some inpatient units are set up with the expectation that at least one family member will live in with the patient.

The Indian Psychiatric Society meeting was in Agra, home of the Taj Mahal. Also in Agra is the 700-bed Institute of Mental Health and Hospital, which was founded over a hundred years ago. At this institute, the late psychiatrist Professor K.C. Dube was the Indian investigator in a WHO multinational study of schizophrenia and opened the hospital's locked wards in the "Agra Experiment." At this year's meeting, his son and APA member Sanjay Dube, M.D., of Indianapolis delivered the K.C. Dube Memorial Oration, pointing out that many important medical discoveries, like penicillin, were made by someone who was alert and open-minded *and* followed up an unexpected finding.

The four-day meeting in Agra offered sessions on the same array of topics as APA's meeting: from imaging to CBT and spirituality. Many of our Indo-American colleagues come from the United States and Canada for the meeting each year. They stay connected to friends, family, and colleagues in India and contribute to clinics and schools.

One Indian couple asked my advice about a planned trip to the United States. I was about to tell them that they could visit historic sites going back more than *300 years* when I remembered that Indian history goes back *3,000 years*. American clothing styles can change drastically from year to year; women in India have worn saris for centuries. They treasure saris handed down from their mothers and grandmothers. I wish I felt comfortable in a sari. Those five yards of fabric are easy to pack and, once expertly wound and draped, attractive on women of every shape. One tradition sees the world as a constant; the other expects constant change and "progress." I wonder how those world views affect psychiatric patients and practice. Would the Indian tradition make people more likely to accept symptoms as just a part of life instead of seeking care that could relieve them? Or would it complement psychotherapy by helping patients to accept life's inevitable disappointments? Many Americans live in nuclear families, far from parents and siblings. Many Indians live with several generations of their families. No one has improved on either the sari or the family. India is also bustling with innovations in technology, educating millions of people who will have opportunities their ancestors could not have imagined—opportunities that move them away from village families and into cities. Progress has its price.

Before I left Chicago, I had seen "Slumdog Millionaire," an art-house film that has unexpectedly garnered international acclaim—and eight Academy Awards. It is a powerful and moving portrayal of the same extreme hardships and enormous resiliency that I saw in India. Despite the title, it is really a story about the pursuit of love, not the pursuit of money, in a country of many landscapes and climates, dotted with centuries-old forts and palaces, and a wealth of traditional and stunning craftsmanship.

Our debts to India are both cultural and professional. As a representative of APA and a colleague, I enjoyed solicitous hospitality from the incoming president of the Indian Psychiatric Society, Dr. Mohan Das, and the president of the Association of Private Practice Psychiatrists, Dr. Advesh Sharma—and all our Indian colleagues. American residency programs, research laboratories, medical schools, and patients enjoy the contributions of medical graduates from India. How can we repay these debts? Our Indian colleagues are eager to collaborate with us. Despite our differences, we have much in common: educating the public, combating stigma, navigating bureaucracies, and maintaining private practices. Despite current economic woes, we are still resource rich. Ask your Indo-American colleagues how we can best share our American good fortune. ■

No Need to Wander In Cyberspace!

Get connected by attending the 2009 annual meeting of the American Association for Technology in Psychiatry (AATP), which will be held in conjunction with APA's 2009 annual meeting in San Francisco. The AATP meeting is scheduled for Saturday, May 16, from 7:30 a.m. to 5 p.m. at the Marriott Courtyard Downtown at 299 Second Street.

The keynote speaker is Gary Small, M.D., a professor of psychiatry at the UCLA Semel Institute. He will discuss the concept of "digital natives" and "digital immigrants" as described in his recently published book, *iBrain*. Professional networking, electronic medical records, personal health records, and security on the Internet will be reviewed.

More information about the meeting and online registration can be accessed at <www.techpsych.org>. ■

1 Benjamin Liptzin, M.D., discusses advocacy plans in one of the APA Advocacy Day events with psychiatrist Yael Dvir, M.D. **2** Scott Keefer, J.D. (center), vice president of Policy Development at America's Health Insurance Plans, discusses the outlook for federal health care reform with panelists Eric Goplerud, Ph.D., director of Ensuring Solutions to Alcohol Problems at George Washington University Medical Center in Washington, D.C., and APA President Nada Stotland, M.D., M.P.H. **3** Rep. Joe Wilson (R-S.C.) discusses mental health care with (from left) Deborah Cross, M.D., Adrian Buckner, M.D., and Eric Williams, M.D. **4** Former Oregon Sen. Gordon Smith (left), a longtime mental health advocate, discusses federal health care policies with John Wernert III, M.D., chair of the Board of Directors of APA*PAC*. **5** Rep. Bill Foster (D-Ill., left) speaks with Louis Kraus, M.D.

Photos by Maureen Keating

Lobby

continued from page 1

to discuss was the need for careful oversight of the regulations that federal health officials promulgate to implement the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (PL 110-343). This milestone law requires health insurance plans that offer mental health benefits to provide coverage for treatment of mental illness on the same terms as for other medical and surgical care.

Some employers have indicated that substantial time will be needed to implement the parity requirements in their insurance plans. Thus, APA has been urging the departments of Health and Human Services and the Treasury—the two departments charged with implementing the law—to quickly release to the public the regulations under consideration. For most insurance plans, the law requires parity benefits to be effective by January 2010.

Kenison Roy III, M.D., of Metairie, La., told *Psychiatric News* that he planned to urge members of Congress and staff members whom he visited to consider broadening the parity mandate to encompass all of the public sector, including military health care systems, and "nurture it through any health care reform." The Federal Employees Health Benefits Program already has parity coverage for mental illness.

The enactment of mental health parity and the reduction of the Medicare copay for outpatient mental health services to 20 percent were major accomplishments this past year, and APA leaders are urging Congress and the Obama administration to ensure that psychiatric care is covered on an equal basis with other types of care under any proposals to reform health care.

The APA members who met with members of Congress disseminated APA's Principles for Health Care Reform for Psychiatry, which were approved by APA's Assembly and Board of Trustees late last year. One principle, for example, states that Americans with psychiatric symptoms have the right to comprehensive evaluation and an accurate diagnosis leading to an appropriate, individualized plan of treatment.

The need for psychiatric health care to be included as a part of basic health care was repeated often by APA members during Advocacy Day.

"We know that health care reform is a primary focus of the Obama administration, so we need to make sure parity is protected within that," APA President Nada Stotland, M.D., M.P.H., said in opening remarks to the psychiatrists participating in the Advocacy Day events. "By being here this week, you are the front line of psychiatry's advocacy effort."

The psychiatrists also were encouraged by a former Senate champion, Gordon Smith. Smith, who was defeated in a reelection bid last November as a senator from Oregon, was a staunch APA ally and sponsor of the 2004 suicide-prevention law named after his son who had taken his own life.

"Your job is to make sure that mental health is not put on the back burner" as some money-saving measure in health care reform proposals, Smith said.

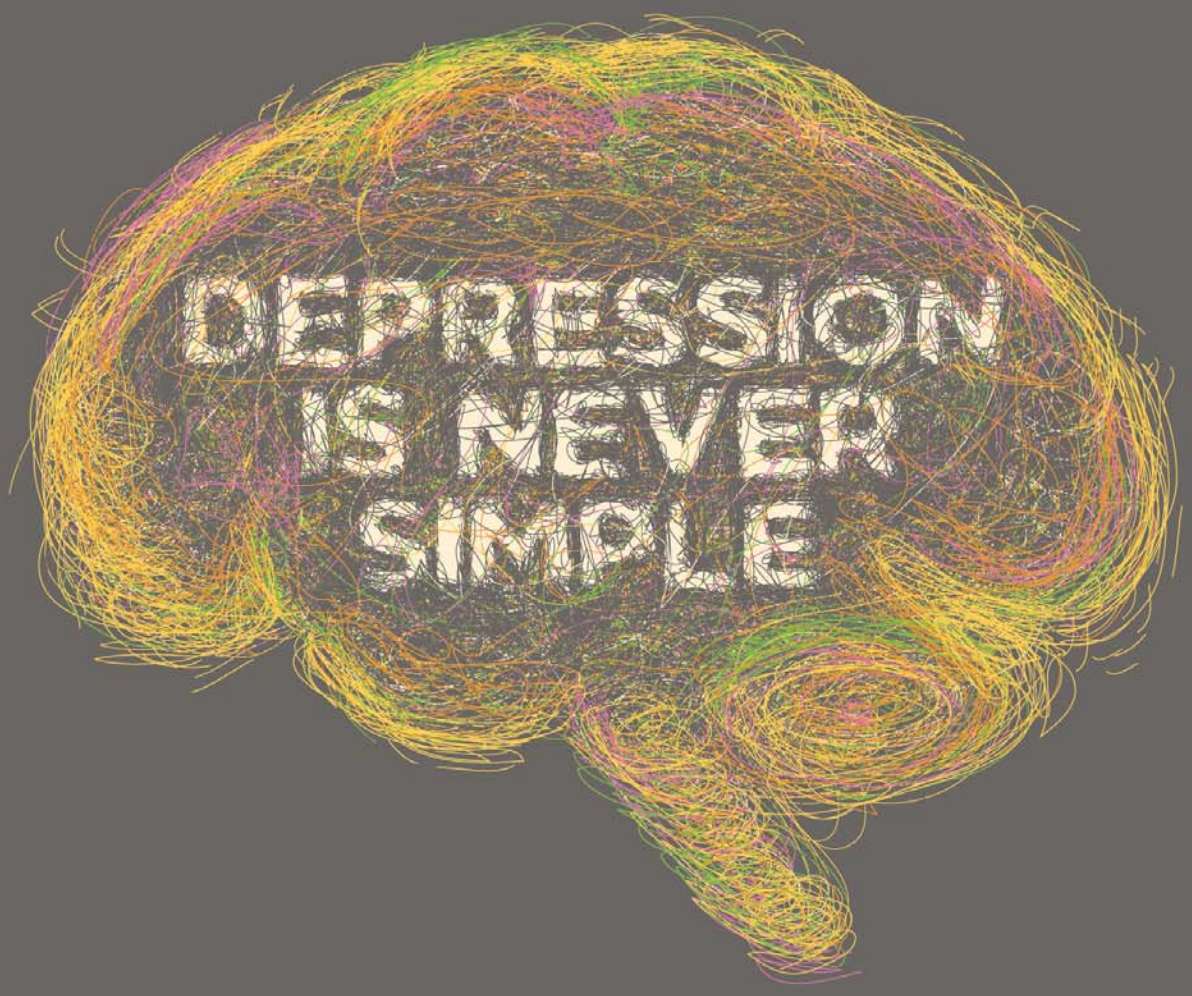
Smith urged psychiatrists to seek support from their long-time advocates, as well as from some members of Congress who may be more supportive than they suspect, including Sens. Olympia Snow (R-Maine), Susan Collins (R-Maine), and Tom Coburn (R-Okla.).

"Remember that mental health doesn't register 'R' and 'D,' " Smith said. "Your issue doesn't have to be partisan."

John Wernert III, M.D., chair of the Board of Directors of APA*PAC*, also emphasized the need to support the monetary advocacy that provides the access and relationships APA needs to build with congressional leaders.

"How important is the PAC? I think it is pretty evident," he said about the 2008 passage of parity and the Medicare copay change that APA had urged for decades.

The text of the American Recovery and Reinvestment Act can be accessed at <http://thomas.loc.gov> by searching on the law number, PL 111-5. APA's Principles for Health Care Reform for Psychiatry are posted at <www.psych.org/MainMenu/AdvocacyGovernmentRelations/GovernmentRelations/PrinciplesforHealthcareReformforPsychiatric.aspx>. ■



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*Venlafaxine Extended Release Tablets are not indicated for the treatment of generalized anxiety disorder or panic disorder.

Venlafaxine Extended Release Tablets (VENLAFAXINE HYDROCHLORIDE)

37.5 mg 75 mg 150 mg 225 mg

IMPORTANT SAFETY INFORMATION

WARNING: Suicidality and Antidepressants

See full Prescribing Information for complete boxed warning.

Increased risk of suicidal thinking and behavior has been reported in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Venlafaxine Extended Release Tablets are not approved for use in pediatric patients.

Venlafaxine Extended Release Tablets (venlafaxine hydrochloride) are indicated for the treatment of Major Depressive Disorder (MDD) and Social Anxiety Disorder (SAD). Efficacy of venlafaxine HCl was shown in both short-term trials and a longer-term trial in MDD, and in short-term SAD trials. Venlafaxine Extended Release Tablets are contraindicated in patients taking monoamine oxidase inhibitors (MAOIs).

All patients should be monitored appropriately and observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose. Such monitoring should include daily observation by families and caregivers for emergence of agitation, irritability, unusual changes in behavior, or emergence of suicidality.

Venlafaxine Extended Release Tablets 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 Extended Release Tablets before starting an MAOI. The development of a potentially life-threatening serotonin syndrome may occur with Venlafaxine Extended Release Tablets, particularly if used concomitantly with serotonergic drugs (including SSRIs, SNRIs, and triptans) or with MAO inhibitors.

Treatment with venlafaxine hydrochloride is associated with sustained hypertension in some patients. Regular blood pressure 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 should be monitored.

Dosing must be individualized according to the patient's hepatic and renal function status. Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms (generally self-limiting; serious symptoms possible). A gradual reduction in the dose rather than abrupt cessation is recommended.

After treatment with venlafaxine hydrochloride, insomnia and nervousness, activation of mania/hypomania, symptomatic hyponatremia, seizures, abnormal bleeding (most commonly ecchymosis), clinically relevant increases in serum cholesterol, interstitial lung disease and eosinophilic pneumonia have been reported. Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of seizures. Measurement of serum cholesterol should be considered during long-term treatment. Patients should be cautioned about the risk of bleeding associated with concomitant use of Venlafaxine Extended Release Tablets and NSAIDs, aspirin, or other drugs that affect coagulation.

Venlafaxine Extended Release Tablets should be used during pregnancy and nursing only if clearly needed due to the potential for serious adverse reactions.

Adverse reactions occurring in short-term studies of major depressive disorder* were abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, anorexia), CNS complaints (dizziness, somnolence, abnormal dreams) and sweating. Adverse reactions occurring in short-term studies of social anxiety disorder* were asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

*Occurring in at least 5% of patients receiving venlafaxine extended release capsules and at a rate at least twice that of placebo.

Please see brief summary of full Prescribing Information, including complete boxed warning, on adjacent pages.

Reference: 1. Venlafaxine Extended Release Tablets [package insert]. Wilmington, NC: Osmotica Pharmaceutical Corp.; 2008.

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For more information, **call 1.888.299.1053** or visit **www.VERTablets.com**

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Venlafaxine Extended Release Tablets (venlafaxine hydrochloride)

BRIEF SUMMARY. See package insert for full Prescribing Information. For further product information and current package insert, please visit www.VERTablets.com or call our medical communications department toll-free at 1-888-299-1053.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Venlafaxine Extended Release Tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 or older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Venlafaxine Extended Release Tablets are not approved for use in pediatric patients. [See *Warnings and Precautions and Patient Counseling Information* in the full Prescribing Information.]

INDICATIONS AND USAGE: Venlafaxine Extended Release Tablets (venlafaxine hydrochloride) are indicated for the treatment of major depressive disorder (MDD) and Social Anxiety Disorder (SAD), also known as Social Phobia, as defined by DSM-IV. Efficacy of venlafaxine in MDD was shown in both short-term trials and a longer-term trial. Efficacy in SAD was established in short-term trials. **CONTRAINDICATIONS:** Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) [see Warnings and Precautions, Potential for interaction with Monoamine Oxidase inhibitors]. **WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk:** Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder, or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration (2.5) and Warnings and Precautions (5.7) in the full prescribing information for a description of the risks of discontinuation of Venlafaxine Extended-Release Tablets*]. **Families and caregivers of 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 Venlafaxine Extended Release Tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Potential for Interaction With Monoamine Oxidase Inhibitors: Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine hydrochloride, or who recently discontinued venlafaxine hydrochloride 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. Venlafaxine Extended Release Tablets 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 hydrochloride before starting an MAOI.** 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. It should be noted that Venlafaxine Extended Release Tablets are not approved for use in treating bipolar depression. **Serotonin Syndrome:** The development of potentially life-threatening serotonin syndrome may occur with Venlafaxine Extended Release Tablets treatment, particularly with (1) concomitant use of serotonergic drugs and (2) drugs that impair metabolism of serotonin [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information]. If concomitant treatment of Venlafaxine Extended Release Tablets treatment, particularly with concomitant use of serotonergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (including MAOIs). The concomitant use of Venlafaxine Extended Release Tablets with MAOIs is contraindicated [*see Contraindications (4) and Warnings and Precautions (5.2)*]. If concomitant treatment of Venlafaxine Extended Release Tablets with an SSRI, an SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Venlafaxine Extended Release Tablets with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension:** Venlafaxine hydrochloride is associated with sustained dose-related increases in blood pressure (BP) in some patients. Sustained BP increases could have adverse consequences. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by BP increases. Preexisting hypertension should be controlled before Venlafaxine Extended Release Tablets therapy is initiated. It is recommended that patients receiving Venlafaxine Extended Release Tablets have regular monitoring of BP. For patients experiencing sustained increase in BP, either dose reduction or discontinuation should be considered. **Elevations in Systolic and Diastolic Blood Pressure (SBP, DBP):** In placebo-controlled premarketing studies, there were changes in mean BP. In most indications, a dose-related increase in SBP and DBP was evident. Across all trials, 1.4% of patients receiving extended-release venlaxafine hydrochloride experienced a ≥15 mm Hg increase in supine DBP with BP ≥105 mm Hg, compared to 0.9% of patients in the placebo groups. One percent of patients receiving venlaxafine hydrochloride experienced a ≥20 mm Hg increase in supine SBP with BP ≥180 mm Hg compared to 0.3% of patients in the placebo groups. **Mydriasis:** Mydriasis has been reported in association with venlafaxine hydrochloride; patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma should be monitored. **Discontinuation of Treatment with Venlafaxine Extended Release Tablets:** Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials and retrospective surveys of trials in MDD and SAD. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been associated with the appearance of new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, impaired coordination and balance, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. During marketing of venlafaxine hydrochloride extended-release capsules, other SNRIs, and SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment. 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 (2.4) in full prescribing information*]. **Insomnia and Nervousness:** Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with venlafaxine hydrochloride extended-release capsules than with placebo in pooled analyses of short-term MDD and other clinical studies, as shown in *Table 5 in the full prescribing information*. **Changes in Weight:** In some placebo-controlled trials in MDD, 4% of the patients treated with venlafaxine hydrochloride extended-release capsules and 1% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 6 months of treatment. The safety and efficacy of venlafaxine therapy in combination with weight loss agents have not been established. Co-administration of Venlafaxine Extended Release Tablets and weight loss agents is not recommended. Venlafaxine Extended Release Tablets are not indicated for weight loss alone or in combination with other products. **Changes in Height:** Pediatric Patients: In the six-month, open-label MDD study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates 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 patients treated with venlafaxine hydrochloride extended-release capsules than for placebo-treated patients in the pool of short-term, double-blind, placebo-controlled MDD (8% vs 4%) and SAD (20% vs 2%) studies. Pediatric Patients: In placebo-controlled trials in MDD and another disorder, 10% of patients aged 6-17 treated with venlafaxine hydrochloride extended-release capsules for up to eight weeks and 3% of patients treated with placebo reported treatment-emergent anorexia. **Activation of Mania/Hypomania:** Mania or hypomania occurred during MDD studies in 0.3% of patients treated with extended release venlafaxine compared with 0% of placebo patients. With immediate release venlafaxine, the rate was 0.5% compared with 0% of placebo patients. No reports of mania or hypomania were reported in trials with SAD. As with all drugs effective in the treatment of MDD, Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of mania. **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Venlafaxine Extended Release Tablets. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volumes depleted may be at greater risk [*see Use in Specific Populations (8.5) in full prescribing information*]. Discontinuation of Venlafaxine Extended Release Tablets should be considered in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted. **Seizures:** In all premarketing venlafaxine hydrochloride MDD trials, seizures were reported in 0.3% of venlafaxine hydrochloride-treated patients. Venlafaxine Extended Release Tablets should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures. **Abnormal Bleeding:** SSRIs and SNRIs, including Venlafaxine Extended Release Tablets, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Venlafaxine Extended Release Tablets and other drugs that affect coagulation. **Serum Cholesterol Elevation:** Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine hydrochloride-treated patients and 0.0% of patients receiving placebo for at least 3 months in trials. Measurement of serum cholesterol levels should be considered during long-term treatment. **Interstitial Lung Disease and Eosinophilic Pneumonia:** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine therapy have been rarely reported. The possibility of these adverse reactions should be considered in venlafaxine-treated patients who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo prompt medical evaluation, and discontinuation of venlafaxine therapy should be considered. **Use in Patients with Heart Disease:** Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering Venlafaxine Extended Release Tablets to patients with diseases or conditions that could affect hemodynamic responses. Venlafaxine 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 systematically excluded from many clinical studies during venlafaxine's premarketing testing. As increases in heart rate (mean increase of 4 beats per minute in MDD trials and 5 beats per minute in SAD trials) were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction). **ADVERSE REACTIONS: Clinical Studies Experience: Short-Term, Placebo-Controlled Trials:** ***Adverse Events Leading to Discontinuation of Treatment:*** Approximately 11% of the 357 patients who received venlafaxine hydrochloride extended-release capsules in MDD trials discontinued treatment due to an adverse reaction (vs 6% of the 285 placebo-treated patients). Adverse reactions that led to treatment discontinuation in at least 2% of drug-treated patients were nausea, dizziness and somnolence. Approximately 17% of the 277 patients in SAD trials who received venlaxafine hydrochloride extended-release capsules discontinued treatment due to an adverse reaction (vs 5% of the 274 placebo-treated patients). Adverse reactions that led to treatment discontinuation in at least 2% of drug-treated patients were nausea, insomnia, impotence, headache, dizziness and somnolence. **Adverse Events Occurring at an Incidence of 5% or More:** Major Depressive Disorder: Note in particular the following adverse reactions that occurred in at least 5% of the patients receiving venlafaxine hydrochloride extended-release capsules and at a rate at least twice that of the placebo group for all placebo-controlled trials for the MDD indication (see Table 6): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional reactions occurred in at least 5% of patients treated with venlafaxine hydrochloride extended-release capsules (n = 192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning. Social Anxiety Disorder: Note in particular the following adverse reactions that occurred in at least 5% of the patients receiving venlafaxine hydrochloride extended-release capsules and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the SAD indication (see Table 7): Asthenia, gastrointestinal complaints (anorexia, constipation, dry mouth, nausea), CNS complaints (dizziness, insomnia, libido decreased, nervousness, somnolence), abnormalities of sexual function (abnormal ejaculation, impotence, libido decreased, orgasmic dysfunction), yawn, sweating, and abnormal vision. **Adverse Events Occurring at an Incidence of 2% or More:** MDD and SAD trials included patients receiving venlafaxine hydrochloride extended-release capsules in doses ranging from 75 mg to 225 mg/day for up to 12 weeks. The prescriber should be aware that the following adverse reactions figures cannot be used to predict the incidence of adverse reactions in the course of usual medical practice. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to adverse reaction incidence rate in the population studied. [See **TABLE 6** in full Prescribing Information.] **TABLE 6: Treatment Emergent Adverse Reaction Incidence in Short-Term Placebo-Controlled Clinical Trials with Venlafaxine Hydrochloride Extended-Release Capsules in Patients with Major Depressive Disorder.** This table reports adverse events that occurred in 2% or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules (n=357) was greater than the incidence for the respective placebo-treated patients (n=285). For each adverse reaction, the incidence of reactions in the drug-treated patients is listed before the incidence in placebo-treated patients. **Body as a Whole:** Asthenia (8% and 7%). **Cardiovascular System:** Vasodilation (4% and 2%); Hypertension (4% and 1%). **Digestive System:** Nausea (31% and 7%); Constipation (8% and 5%); Anorexia (8% and 4%); Vomiting (4% and 2%); Flatulence (4% and 3%). **Metabolic/Nutritional:** Weight Loss (3% and 0%). **Nervous System:** Dizziness (20% and 9%); Somnolence (17% and 8%) Insomnia (17% and 11%); Dry mouth (12% and 6%); Nervousness (10% and 5%); Abnormal Dreams (7% and 2%); Tremor (5% and 2%); Depression (3% and <1%); Paresthesia (3% and 1%); Libido Decreased (3% and <1%); Agitation (3% and 1%). **Respiratory System:** Pharyngitis (7% and 6%); Yawn (3% and 0%). **Skin:** Sweating (14% and 3%). **Special Senses:** Abnormal vision (4% and <1%). **Urogenital System:** Abnormal ejaculation (16% and <1%); Impotence (4% and <1%); Female anorgasmia (3% and <1%). [See **TABLE 7** in full Prescribing Information]. **TABLE 7: Treatment Emergent Adverse Reaction Incidence in Short-Term Placebo-Controlled Clinical Trials with Venlafaxine Hydrochloride Extended-Release Capsules in Patients with Social Anxiety Disorder.** This table reports adverse events that occurred in 2% or more of patients treated with venlafaxine hydrochloride extended-release capsules where the incidence in patients treated with venlafaxine hydrochloride extended-release capsules (n=277) was greater than the incidence for the respective placebo-treated patients (n=274). For each adverse reaction, the incidence of reactions in the drug-treated patients is listed before the incidence in placebo-treated patients. **Body as a Whole: Headache** (34% and 33%); Asthenia (17% and 8%); Flu Syndrome (6% and 5%); Accidental Injury (5% and 3%); Abdominal Pain (4% and 3%). **Cardiovascular System:** Hypertension (5% and 4%); Vasodilation (3% and 1%); Palpitation (3% and 1%). **Digestive System:** Nausea (29% and 9%); Anorexia (20% and 1%); Constipation (8% and 4%); Diarrhea (6% and 5%); Vomiting (3% and 2%); Eructation (2% and 0%). **Metabolic/Nutritional:** Weight Loss (4% and 0%). **Nervous System:** Insomnia (23% and 7%); Dry mouth (17% and 4%); Dizziness (16% and 8%); Somnolence (16% and 8%); Nervousness (11% and 3%); Libido Decreased (9% and <1%); Anxiety (5% and 3%); Agitation (4% and 1%); Tremor (4% and <1%); Abnormal Dreams (4% and <1%); Paresthesia (3% and <1%); Twitching (2% and 0%). **Respiratory System:** Yawn (5% and <1%); Sinusitis (2% and 1%) **Skin:** Sweating (13% and 2%). **Special Senses:** Abnormal vision (6% and 3%). **Urogenital System:** Abnormal ejaculation (16% and 1%); Impotence (10% and 1%); Female Orgasmic Dysfunction (8% and 0%). **Vital Sign Changes:** Venlafaxine hydrochloride was associated with a mean increase in pulse rate of 4 beats/min in SAD trials. In premarketing trials, the mean change from baseline heart rate for patients treated with extended-release venlafaxine hydrochloride in MDD and SAD trials was 4 beats-per-minute and 5 beats-per-minute, respectively. In a flexible-dose study with doses ranging from 200 mg to 375 mg/day, patients receiving extended-release venlafaxine hydrochloride had a mean increase in heart rate of 8.5 beats-per-minute [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information for effects on heart rate and blood pressure]. **Laboratory Changes:** Clinically relevant increases in serum cholesterol were noted in venlafaxine hydrochloride clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. **ECG Changes:** In a flexible-dose MDD study with doses of venlafaxine hydrochloride immediate-release tablets in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo. [*See Warnings and Precautions (5.17)*]. **POSTMARKETING EXPERIENCE:** Voluntary reports of other adverse reactions temporally associated with the use of venlafaxine have been received since market introduction. Because these reactions have been reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports include the following reactions: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, impaired coordination and balance, 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 torsade de pointes; epidermal necrolysis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic reactions (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neuroleptic malignant syndrome-like reactions (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 syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly). **DRUG INTERACTIONS: Alcohol:** The effect of alcohol on plasma levels of Venlafaxine Extended Release Tablets is not known. **Cimetidine:** Use caution when administering venlafaxine hydrochloride with cimetidine to patients with preexisting hypertension or hepatic dysfunction, and the elderly. **Diazepam:** A single dose of diazepam did not appear to affect the PK of either venlafaxine hydrochloride (150 mg/day) or its major active metabolite, 0-desmethylvenlafaxine (ODV). Venlafaxine hydrochloride 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 hydrochloride (150 mg/day) 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 $t_{1/2}$ was unchanged. **Lithium:** A single dose of lithium (600 mg) did not appear to affect the PK of either venlafaxine hydrochloride (150 mg/day) or ODV. Venlafaxine hydrochloride had no effect on the PK of lithium. **Drugs Highly Bound to Plasma Proteins:** Venlafaxine hydrochloride is not highly bound to plasma proteins; coadministration of Venlafaxine Extended Release Tablets and a highly protein-bound drug should not cause increased free concentrations of the other drug. **Drugs That Inhibit Cytochrome P450 Isoenzymes:** CYP2D6 and CYP3A4 Inhibitors: Venlafaxine hydrochloride is metabolized to ODV by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine hydrochloride and decrease those of ODV. Because venlafaxine hydrochloride and ODV are approximately equiactive and equipotent, no dosage adjustment is required when venlafaxine hydrochloride is coadministered with a CYP2D6 inhibitor. Pharmacokinetic studies with ketoconazole in both poor and extensive metabolizers of CYP2D6 resulted in higher plasma concentrations and AUCs of both venlafaxine hydrochloride and ODV in most subjects following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors and venlafaxine hydrochloride may increase levels of both venlafaxine hydrochloride and ODV. Use caution if therapy includes venlafaxine hydrochloride and any CYP3A4 inhibitor. **Drugs Metabolized by Cytochrome P450 Isoenzymes:** Venlafaxine hydrochloride is a relatively weak inhibitor of CYP2D6 in vitro. Imipramine: Venlafaxine hydrochloride did not affect the PK of imipramine or 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine hydrochloride. The 2-OH-desipramine AUCs increased by 2.5 to 4.5 fold (with venlafaxine hydrochloride doses of up to 75 mg q 12h). The clinical significance of elevated 2-OH-desipramine is unknown. Imipramine did not affect the PK of venlafaxine hydrochloride and ODV. Metoprolol: Venlafaxine hydrochloride (50 mg q 8h for 5 days) appeared to reduce the blood-lowering effect of metoprolol (100 mg q 24h for 5 days) in one study. Caution should be exercised when these drugs are given together. Risperidone: Venlafaxine hydrochloride (150 mg/day) slightly inhibited metabolism of a single 1-mg dose of risperidone, resulting in an about 32% increase in risperidone AUC. Venlafaxine hydrochloride coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus its metabolite 9-hydroxyrisperidone). CYP3A4: Venlafaxine hydrochloride did not inhibit CYP3A4 in vitro or in vivo. Indinavir: In healthy volunteers, venlafaxine hydrochloride (150 mg/day) resulted in a 28% decrease in the AUC of a single dose of a single 800-mg dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine hydrochloride and ODV. CYP1A2: Venlafaxine hydrochloride did not inhibit CYP1A2 in vitro or in vivo. CYP2C9: Venlafaxine hydrochloride did not inhibit CYP2C9 in vitro. In vivo, venlafaxine hydrochloride 75 mg (75 mg q 12h) did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-OH-tolbutamide. CYP2C19: Venlafaxine hydrochloride did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see Diazepam above). **MAOIs:** [See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS in full Prescribing Information.] **Other CNS-Active Drugs:** Caution is advised if there is concomitant use of venlafaxine and other CNS-active drugs. Serotonergic Drugs and Triptans: Based on the mechanism of action of Venlafaxine Extended Release Tablets and the potential for serotonin syndrome, caution is advised when Venlafaxine Extended Release Tablets are coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's Wort. If concomitant treatment of Venlafaxine Extended Release Tablets with these drugs is warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of Venlafaxine Extended Release Tablets with tryptophan supplements is not recommended [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information]. There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant use of Venlafaxine Hydrochloride Extended Release tablets with a triptan is warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information]. **Drugs That Interfere With Hemostasis:** Interference with serotonin reuptake may affect platelet function and result in bleeding. Concurrent use of NSAIDs or aspirin may increase this risk. Increases in prothrombin time (PT), partial thromboplastin time (PTT), or INR have been reported when venlafaxine hydrochloride was given to patients on warfarin therapy. Patients on warfarin should be carefully monitored when Venlafaxine Extended Release Tablets are begun or discontinued. **Electroconvulsive Therapy:** There is no clinical data establishing the benefit of electroconvulsive therapy combined with Venlafaxine Hydrochloride Extended Release Tablets. **Postmarketing Spontaneous Drug Interaction Reports:** There have been reports of elevated clozapine levels temporally associated with adverse reactions, including seizures, following the addition of venlaxafine. There have been reports of increases in PT, PTT, or INR when venlafaxine was given to patients also receiving warfarin. **USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C:** There are no adequate and well-controlled studies of venlafaxine in pregnant women. Venlafaxine Extended Release Tablets should be used during pregnancy only if clearly needed. **Non-Teratogenic Effects:** Neonates exposed to venlafaxine hydrochloride 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, unstable temperature, feeding difficulty, vomiting, hypoglycemia, hypo- and hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a toxic effect of SSRIs or SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Venlafaxine Extended Release Tablets during the third trimester, carefully consider the potential risks and benefits of treatment. **Labor and Delivery:** The effect of venlafaxine hydrochloride on labor and delivery in humans is unknown. **Nursing Mothers:** Venlafaxine hydrochloride and ODV, its active metabolite, are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Venlafaxine Extended Release Tablets, 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 **BOXED WARNING** and **Warnings and Precautions: Clinical Worsening and Suicide Risk**]. Anyone considering using Venlafaxine Extended Release Tablets in a child or adolescent must balance the potential risks with the clinical need. While no studies have adequately assessed the impact of venlafaxine hydrochloride on growth, development, and maturation of children and adolescents, studies suggest it may adversely affect weight and height [see **WARNINGS AND PRECAUTIONS: General: Changes in Height** and **Changes in Weight** in full Prescribing Information]. Should the decision be made to treat a pediatric patient with Venlafaxine Extended Release Tablets, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of venlafaxine hydrochloride in pediatric patients has not been assessed for treatment beyond 6 months. In patients aged 6-17, clinically relevant blood pressure and cholesterol increases were similar to those observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use:** While no overall differences in effectiveness or safety were observed between geriatric and younger patients, greater sensitivity of some older individuals cannot be ruled out. The elderly may be at greater risk for significant hyponatremia. No dose adjustment is recommended based on age alone. **Patients With Hepatic Impairment:** Decreased clearance was noted in patients with cirrhosis. A lower dose may be necessary in these patients; extra caution should be used in these patients. **Patients With Renal Impairment:** In patients with GFR = 10 to 70 mL/min, clearance of venlafaxine hydrochloride and its metabolites were decreased. It is recommended that total daily dose of Venlafaxine Extended Release Tablets be reduced by 25% to 50% in these patients. Individualization of dosage may be desirable in some patients. In hemodialysis patients, it is recommended that total daily dose be reduced by 50%. Venlafaxine Extended Release Tablets should be used with caution in such patients. **DRUG ABUSE AND DEPENDENCE:** Venlafaxine Extended Release Tablets are not a controlled substance. Carefully evaluate patients for history of drug abuse and observe such patients closely for signs of misuse or abuse of venlafaxine hydrochloride. Discontinuation effects have been reported in patients receiving venlafaxine hydrochloride [see **WARNINGS AND PRECAUTIONS;** and **DOSAGE AND ADMINISTRATION** in full Prescribing Information]. **OVERDOSAGE:** In postmarketing experience, overdosage has occurred predominately in combination with alcohol and/or other drugs. The most commonly reported reactions include tachycardia, changes in consciousness, mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. 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 hydrochloride are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on treatment. 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 Venlafaxine Extended Release Tablets. At least 7 days should be allowed after stopping Venlafaxine Extended Release Tablets before starting an MAOI** [see **WARNINGS AND PRECAUTIONS** in full Prescribing Information].

To report SUSPECTED ADVERSE REACTIONS, contact Upstate Pharma, LLC Pharmaceutical Corp. at 1-888-299-1053 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

This brief summary is based on Venlafaxine Extended Release Tablets Prescribing Information, August 2008. Osmotica Pharmaceutical Corp.

Marketed by Upstate Pharma, LLC, Rochester, NY 14623 for Osmotica Pharmaceutical, Wilmington, NC 28405.

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Stimulus Law Directs Funds To Health Care Improvement

Temporary health insurance assistance to workers who lose their jobs and a big boost in mental illness research are included in the Obama administration's recently passed stimulus package.

BY RICH DALY

A massive spending and tax-relief stimulus law designed to cut unemployment, aid struggling families, and boost a sliding economy includes numerous provisions urged by APA and other mental health advocates.

The American Recovery and Reinvestment Act of 2009 (ARRA, PL 111-5), signed by President Barack Obama on February 17, includes a large funding increase for state Medicaid plans and further delays implementation of Medicaid regulations that are opposed by APA.

These provisions are extremely timely because "states are desperate for more money because revenues are down and their Medicaid costs are constant or rising," said Lizbet Boroughs, associate director of APA's Department of Government Relations.

The law includes a temporary $87 billion increase in the Federal Medical Assistance Percentage, which means that the federal share of Medicaid costs will rise, helping states avoid program cuts. Medicaid is dually funded by states and the federal government. The law provides a 6.2 percent across-the-board increase to each state's Medicaid program and extra funding for states with the highest unemployment rates.

The lack of a specific line item for mental health care in the new Medicaid funding concerns mental health advocates, including David Shern, president and CEO of Mental Health America. His organization—and APA—lobbied for such an addition so people with psychiatric conditions would not lose out to other programs as states tinker with Medicaid programs.

Also on the Medicaid front, a moratorium set to expire next month on regulations promulgated by the Bush administration and related to Medicaid targeted case management (TCM) was extended until the end of June. APA opposed the tightening of TCM regulations—intended as a money-saving measure—because it could sever a critical coordinating service that benefits many mentally ill people who receive Medicaid benefits (*Psychiatric News*, August 1, 2008).

Focus on Public-Health Jobs

Another measure aimed primarily at the public-health sector is the creation of the $1 billion Prevention and Wellness Fund to support evidence-based clinical and community-based prevention and wellness strategies. Among the largest provisions in the fund is $500 million designated for bolstering the general- and public-health workforces.

Mental health advocates said the funding measure could save or create 20,000 public-health jobs, including some of those of the 11,000 such workers already terminated in the recession. Retaining and rehiring public health workers is an important step to ensuring the availability of health care services for the unemployed, uninsured, and underinsured during the recession, according to mental health advocates.

Health workers also could benefit from $500 million that the law allocates to the Health Resources and Services Administration for health profession development through scholarships, loan-repayment help, and training grants. The funds can also be used to coordinate cross-state telemedicine services.

Psychiatrists are among those designated in ARRA as eligible for scholarships, loan-repayment help, and grants through the National Health Service Corps. The corps aims to boost the number of clinicians in rural and other "medically underserved" areas of the country.

Another significant aspect of ARRA for physicians is the inclusion of $19 billion to invest in health information technology, including efforts to ensure patient-privacy protections (see top article on page 8).

Medical Research Gets Boost

Additional funding is directed to the National Institutes of Health, whose Fiscal 2009 budget was increased by 34 percent over 2008, from $29 billion to $39 billion. The allocation of ARRA funds will direct about $1 billion in total to the National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, and National Institute on Mental Health.

The 34 percent boost dwarfs NIH's 1.5 percent increase in the last budget cycle.

"Hundreds of grant applications scored high enough to be funded last year, but [NIH] ran out of money before they could be funded," Boroughs said. The hope is that the additional funding will lead to more psychiatric research receiving support.

In addition, the law includes $1.1 billion for "comparative effectiveness research" through NIH and the Agency for Healthcare Research and Quality that compares two or more therapies for a given medical condition. The funds also may be used to analyze existing studies, including NIMH-sponsored trials of treatments for schizophrenia, bipolar disorder, and major depression.

Other provisions of the law aim to ensure that comparative effectiveness research is conducted and findings disseminated in a way that ensures that clinical effectiveness and quality outcomes are

please see ***Stimulus Law*** *on page 30*

Incentive Payment Will Go to M.D.s Who Adopt Electronic Records

Hard-won, physician-supported privacy protections were included in the stimulus law to protect patients from information leaks.

BY RICH DALY

The massive federal stimulus law enacted last month includes unprecedented funding to transition toward the use of electronic medical records. Privacy protection measures—especially important to psychiatric care patients—were included in the measure.

The American Recovery and Reinvestment Act of 2009 (ARRA, PL 111-5), signed by President Barack Obama on February 17, includes provisions to encourage the use of electronic health records (EHRs), health information technology (HIT, which includes both the software and hardware needed to operate EHRs), and e-prescribing.

The law, considered part of Obama's overall health reform effort (see page 7), requires the government to take a leadership role in developing standards by 2010 that will allow for the nationwide electronic exchange and use of health information that aims to improve the quality and coordination of care. The measure requires Department of Health and Human Services (HHS) officials to establish interoperability standards, implementation specifications, and certification criteria by December 31, as well as to provide financial resources to current and future physician users of HIT systems.

The measure provides $19 billion for health information technology infrastructure grants from HHS and for Medicare and Medicaid incentives to encourage physicians, hospitals, and health care providers to use HIT for the electronic exchange of patients' health information.

Community mental health centers are eligible for grants from HHS and incentive payments under Medicare and Medicaid. Specifically eligible for grants and incentive payments to upgrade their HIT systems are those community mental health centers that meet federal criteria, child mental-health programs, psychosocial rehabilitation programs, mental health peer-support programs, and mental health primary consumer-directed programs.

In terms of funding, the law includes Medicare incentive payments for physicians who adopt HIT, defined as "hardware, software, integrated technologies or related licenses, intellectual property, upgrades, or packaged solutions sold as services that are designed for or support the use by health care entities or patients for the electronic creation, maintenance, access, or exchange of health information."

The payments are up to $15,000 for the first payment year, with incentive payments in subsequent years of up to $12,000, $8,000, $4,000, and $2,000, respectively, ending in 2015. Physicians who report already using an EHR that is also capable of e-prescribing will no longer be eligible for earlier e-prescribing bonuses but will be eligible for HIT incentives.

Physicians who have already implemented HIT systems and those who adopt them by 2012 will be eligible for an initial, larger incentive payment of up to $18,000. By 2014 the maximum payment for physicians who begin using the technology at that point will drop to $12,000.

Physicians in a federally designated rural health professional shortage area will have their Medicare incentive payments for HIT increased by 10 percent.

Also included are incentives for eligible physicians, hospitals, federally qualified health centers, rural health clinics, and other providers under Medicaid.

The incentive ends and penalties begin for physicians who accept Medicare and have not adopted HIT by 2015, including a 1 percent reduction in Medicare physician payments, increasing to a 3 percent reduction in 2017 and beyond.

Federal health officials can increase penalties up to a 5 percent reduction in Medicare payments after 2018. The measure allows exceptions on a case-by-case basis for "significant hardships," such as rural areas without sufficient Internet access.

The new measure includes many features long advocated by APA that are designed to strengthen federal privacy and security law, including protections against misuse of identifiable health information. The privacy measures had long been downplayed in the Senate, where the advancing legislation last year emphasized creation of a nationwide EHR network despite privacy and interoperability concerns. So inclusion of strong privacy measures in the final stimulus measure was seen as a win for psychiatry and mental health care recipients.

Among the privacy measures is a new HIT Policy and Standards Committee that will include public and private representatives, including physicians. The committee will provide recommendations on the HIT policy framework, standards, implementation specifications, and certification criteria for electronic exchange and use of health information.

The law expands on the privacy and security provisions of the Health Insurance Portability and Accountability Act (HIPAA) to protect patient health information by defining which actions constitute a breach. Also, restrictions have been added on certain disclosures, sales, and marketing of protected health information. The law requires an accounting of disclosures to patients upon request and authorizes increased civil monetary penalties for HIPAA violations. State attorneys general also are authorized to enforce HIPAA.

The law expands HIPAA rules and penalties to "business associates" of health care entities, such as the technology firms involved in electronic records creation and data storage.

Another provision supported by APA establishes that physicians or others sharing information with insurers or other payers must limit the information to the "minimum necessary" to fulfill the request for information. Insurers will no longer be allowed to decide what information is the minimum necessary as the new law directs HHS to promulgate guidelines to define that. A 2002 APA position statement called for such a "minimum necessary" provision on information released to third parties to be a part of federal medical privacy rules.

The "minimum necessary" provision of the law does not affect the information physicians can share with other clinicians treating that patient. Instead, the law serves as a floor for privacy rights, and some state laws go beyond it to restrict information physicians can share with other physicians, if requested by patients.

A "right to request" allows patients to request that physicians not share their information with other medical providers, and if physicians agree, they cannot later change their mind and release data from the period during which they agreed to restrict such information.

Laura Fochtmann, M.D., chair of APA's Corresponding Committee on Electronic Health Records, described the privacy protection provisions of the law as "a major step forward."

"Confidentiality is at the heart of the therapeutic relationship between a patient and a psychiatrist," Fochtmann told *Psychiatric News*. "Without the means to preserve confidentiality—whether it is in the paper record or the electronic record—there will be additional impediments to developing a trusting and therapeutically beneficial alliance."

Patient privacy issues are not unique to psychiatry, Fochtmann said, but psychiatrists have been at the forefront of calling attention to these issues.

The text of the stimulus measure can be accessed at <http://thomas.loc.gov> by searching on the law number, PL 111-5. ■

Obama's First Budget Shows Commitment to Health Reform

Obama plans to work with physicians and others to expand access to health care for all Americans and reduce costs in Medicare and Medicaid.

BY RICH DALY

In his first address to a joint session of Congress, President Barack Obama pledged a "historic commitment to comprehensive health care reform" that aims to reduce costs and expand access to "quality, affordable" health care for all Americans.

"The cost of health care eats up more and more of our savings each year, yet we keep delaying reform," Obama told members of Congress on February 24.

Obama's recently submitted proposed federal budget for Fiscal 2010 shows his determination to follow through on campaign promises to expand access to health care. He described his budget as building on the enactment of legislation in the first weeks of the new Congress that expanded access to the State Children's Health Insurance Program to 4 million more children of the working poor and unprecedented funding to transition toward the use of digital medical records (see article above).

The health reform provisions of the proposed budget—which include broad goals and few health care line items—will act as a "down payment on the principle that we must have quality, affordable health care for every American," said Obama, by addressing inefficiencies in the health care system to help reduce future deficits.

The budget calls for setting aside $634 billion over the next 10 years in a "reserve fund for health care reform" to expand government-subsidized health coverage The expansion would be funded from taxes on high-income earners and from cuts in Medicare payments to insurance companies, hospitals, and insurers.

The reserve would be used to fund affordable insurance programs for individuals and employers. It also would help finance disease prevention, wellness programs, and research on cost-effective treatments that aim to cut health care costs.

One item that could particularly impact physicians is the proposed budget's assumption that Congress will refrain from cutting Medicare clinician payments scheduled to occur under current law, including a 21 percent reduction planned for 2010.

"Widespread physician shortages coupled with aging baby boomers highlight the urgent need for permanent Medicare physician payment system reform to preserve seniors' access to health care," said Nancy Nielsen, M.D., president of the AMA, in a statement regarding Obama's proposed budget.

The president's budget also would expand eligibility for Medicaid benefits while requiring drug companies to give bigger discounts, or rebates, to Medicaid and saving $37 billion over the next decade from payments to home health agencies.

The president said his plan will unfold through discussions with the public and various health care groups.

"Now, there will be many different opinions and ideas about how to achieve reform, and that is why I'm bringing together businesses and workers, doctors and health care providers, Democrats and Republicans to begin work on this issue next week," Obama said in his February address.

"The passage of health insurance parity and the elimination of the discriminatory Medicare copay for mental health care are landmarks in the evolution of American health care," APA President Nada Stotland, M.D., M.P.H., commented to *Psychiatric News* about Obama's proposal. "Efforts to reform the health care system as a whole, however, have been politically

please see ***Reform*** *on page 30*

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62-1014307R R2 03/09

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

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

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

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

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

Special Populations
Hepatic Impairment
Namenda undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Namenda should be administered with caution to patients with severe hepatic impairment.

Renal Impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in Full Prescribing Information).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	[illegible]	2
Pain	[illegible]	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, paronia, delirium, depersonalization, necrosis, 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, retina detachment.

Urinary System: *Frequent:* frequent micturition. *Infrequent:* dysuria, hematuria, urinary retention.

Events Reported Subsequent to the Marketing of Namenda, both US and Ex-US
Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: aspiration pneumonia, asthenia, atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST and hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lethargy, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged QT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, thrombocytopenia, and hallucinations (both visual and auditory).

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

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

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

OVERDOSAGE
Signs and symptoms associated with memantine overdosage in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

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U.K. Doctors Want Industry Out of Medical Education

A British physicians organization urges the end of the tradition of physicians' accepting gifts from the pharmaceutical industry and calls for pooled funding for continuing medical education.

BY JUN YAN

Medical education and practice should minimize industry influence, and a government agency should become more actively involved in medical research and education, the Royal College of Physicians (RCP) in the United Kingdom recommended in a report issued February 4.

The RCP is the oldest professional association for physicians in England, Wales, and Northern Ireland, chartered by King Henry VIII in 1518 and now boasting a membership of 22,000. In 2007 the RCP set up a working group of representatives from medicine, industry, and the National Health Service (NHS) to review the relationships among the NHS, academic medicine, and the pharmaceutical industry.

The report produced by the group, titled "Innovating for Health: Patients, Physicians, the Pharmaceutical Industry, and the NHS," contains 42 recommendations aimed at redefining the relationships among medicine, research, industry, and regulators with the goal of optimizing patient care.

The group surveyed the Patient and Carer Network, a 75-member group of patients, caregivers, and members of the public who are directly involved in the RCP discussions, to obtain patients' concerns and opinions about health care services. The survey revealed that patients and their caregivers were concerned about whether all patients in the United Kingdom have equal access to the most effective medicines. They were also troubled about the relationship between their physicians and pharmaceutical companies; many believed that gifts and information from industry to physicians may affect their independence in making decisions about what treatment is in their patients' best interests.

"Education is one of the most contentious areas between doctors, scientists, and industry," the report noted. "Students . . . need to be protected from undue pharmaceutical marketing." The report also found that "continuing professional development programmes are too dependent on industry support." The report called for reducing industry sponsorship for postgraduate medical education and increasing the role of the NHS.

The report authors stopped short, however, of calling for a ban on industry's involvement with medical education and instead recommended that companies place their educational grants into a pooled fund to decouple funding from specific products.

They also recommended that medical schools and institutions find alternative and sustainable sources for continuing medical education and that physicians should take "greater financial responsibility for their own postgraduate education."

The authors recommended that "all gifts to doctors, including food and travel, . . . should end." Echoing a recent trend in the United States, they also called for establishment of a public database to report all honoraria or fees a physician receives from pharmaceutical companies.

They cited controversies and debates currently raging in the U.S. medical community over the relationship between medicine and the pharmaceutical industry and its effect on patient care. They acknowledged similar concerns and criticisms in the United Kingdom from the media and the public despite important differences in the two countries' health care systems and policies.

Meanwhile, the report authors emphasized that collaboration between medicine and industry, with more support and investment from the NHS, is necessary and beneficial to advancing medicine and improving the quality of patient care. Both industry and academic researchers in the United Kingdom complain about losing the vitality of clinical research to other countries because of government bureaucracy and common anti-industry suspicions.

In an editorial in the February 7 *The Lancet*, Richard Horton, M.D., chair of the RCP working group and editor in chief of *The Lancet*, insisted that "all potentially adverse influences on doctors should be eliminated from the educational environment they train and work in." ■

FDA OKs Brain-Stimulation Device For Treatment-Resistant OCD

Approval of the brain-implant device offers hope for a small group of severely disabled patients with chronic OCD, but deep brain stimulation is far from an easy, instant cure.

BY JUN YAN

A pacemaker-like brain implant has been cleared by the Food and Drug Administration (FDA) for marketing as a treatment for severe and chronic obsessive-compulsive disorder (OCD), the agency announced on February 19.

Surgically implanted deep brain stimulation (DBS) devices are already on the market for treating tremor, dystonia, and movement disorder associated with Parkinson's disease. In recent years scientists in Europe and North America have been conducting clinical research on its effectiveness in the treatment of OCD and depression by applying electrical pulses to different brain circuits (*Psychiatric News*, December 19, 2008). Some of the studies, although small, produced encouraging results for patients who are severely disabled and have failed to respond to conventional treatments.

The device, manufactured by Medtronic Inc., is the first to be approved for treating severe OCD. The FDA said that it granted the approval based on the humanitarian device exemption regulation authorized by the federal Food, Drug, and Cosmetic Act, which applies to devices "intended to treat or diagnose a disease or condition affecting fewer than 4,000 people per year in the United States."

The FDA reviewed clinical data from four centers at which 26 patients with severe, treatment-resistant OCD received the implant and at least 12 months of stimulation. The patients experienced on average a 40 percent reduction in symptoms at the end of one year. Two-thirds of the patients had "marked functional improvements" in psychological, social, and occupational" areas, according to the company's announcement about the study results. The pooled results of the multisite clinical trials were published in *Molecular Psychiatry* online on May 20, 2008.

The device consists of a four-electrode stimulator to be implanted in the brain, which is connected to a small battery that is surgically embedded under the skin near the collar bone or the abdomen. The stimulator is implanted on one side or both sides of the brain.

Adverse effects seen in the clinical trials were mostly related to the brain surgery or resolved after postsurgery adjustments to the device setting, such as altering the intensity and frequency of the electrical pulses. In the clinical trials, all patients were required to have regular checkups after the surgery, and some needed to have the device's battery replaced after a period of time.

Medtronic said in the press release that it was going to conduct clinical trials on DBS for treatment-resistant severe depression at five medical centers in the United States. ■

Canadian Vet Develops Peer-Support Program for Wars' MH Casualties

A Canadian armored corps officer takes up the cause of destigmatizing the mental health consequences of military deployment.

BY AARON LEVIN

Canadian soldiers are fighting in Afghanistan as part of the NATO force there, and for decades before that, Canadian units served on peacekeeping missions in places such as Cyprus, Haiti, Rwanda, and the former Yugoslavia. Regardless of their mission, the Canadians have faced the same stresses that affect their U.S. counterparts.

And some Canadian soldiers returned with minds disturbed by the experience. One was Lt. Col. Stéphane Grenier. Grenier is not a doctor. A self-described tough armored corps officer, Grenier found himself one morning years after his return from Rwanda sitting in his car for 45 minutes outside the base clinic wondering how he was going to describe his internal turmoil to the corporal on duty.

"I was oblivious," he recalled for listeners at a symposium at Canada's embassy in Washington, D.C., in February. "I had been injured in Rwanda and didn't know it."

Grenier has helped turn his struggle with the horrors of the Rwandan genocide into a source of refuge for fellow members of the Canadian forces similarly affected by the outcomes of their missions. He is now director of casualty support management at National Defence Headquarters in Ottawa, home of the Operational Stress Injury Social Support Program (OSISS). The program was proposed in 2000, and the first peer coordinator came on board in 2002.

Most existing support programs depended on social workers or other providers for coordination, Grenier found in the course of researching the idea of a support program, but he ultimately decided that only a veteran of military service would have the needed credibility with soldiers.

To that end, OSISS recruits and trains people who have not only served in Canada's armed forces but have also been through the same trials by fire as those they assist: all have been diagnosed with mental health problems at some point in their careers. They can tell the soldiers they're helping: "We've experienced it too, but we're in a healthier place now."

All have to be screened by doctors before they can work in the program. "No

please see ***Peer Support*** *on page 31*

Medical Marijuana Verdict Elusive Despite Study, Debate

At least one addiction psychiatrist says the question of legalizing marijuana for medical uses cannot be disentangled from the larger social context in which marijuana is widely used—addictively by many—for recreational purposes.

BY MARK MORAN

To say "that the use of [cannabis] should be prevented by a prohibitive tax loses sight of the fact that future investigation may show that there are substantial medical uses for Cannabis."

So stated William C. Woodward, M.D., J.D., legislative counsel to the AMA, in testimony in 1937 before the House Ways and Means Committee on the "Marijuana Taxation Bill," which would have taxed physicians who prescribed—and pharmacies that dispensed—cannabis.

(The bill passed, and in 1942 "cannabis" was officially removed from the U.S. Pharmacopeia.)

Seventy years after Woodward's testimony, whether research has proven "substantial medical uses" for cannabis—either smoked in the form of the marijuana plant or taken in some other form—still appears to be a matter of passionate debate.

Thirteen states have passed laws to make marijuana more accessible for medical use. Many physicians and patients cite anecdotal evidence of the efficacy of cannabis for chemotherapy-related nausea, AIDS-related wasting, neuropathic pain, and other conditions; and a body of randomized controlled trials exists—mostly with relatively small samples and short follow-up times—documenting the benefits of cannabis for discrete conditions.

The American College of Physicians, among other groups, has called for reclassification of marijuana under the Controlled Substances Act from a Schedule I drug—under which it is deemed to have high abuse potential and no proven medical uses—to another schedule that would make it more available to researchers and clinicians.

On the opposing side are many physicians, including psychiatrists and addiction specialists, who say that research on cannabis, especially its long-term effects, is not sufficient to warrant rescheduling; that legalization would lead to greater abuse—by nonpatients in the general population, if not by patients; and that the medical community should proceed with great caution before declaring marijuana "safe."

At the meeting of the AMA's House of Delegates last November, a resolution to advocate for rescheduling marijuana was the subject of unusually lengthy and passionate debate, only to be sent to the AMA's Council on Science and Public Health for a report back to the House and the AMA Board of Trustees (*Psychiatric News*, January 2).

Council chair and past APA President Carolyn Robinowitz, M.D., said she could not comment on the issue prior to the council's deliberations except that "there seem to be more opinions than data."

She said, "The council will look at the available evidence and consider it carefully, and present—to the extent that it is possible—an evidence-based report to the house."

Studies Indicate Some Acute Benefit

To Sunil Aggarwal, Ph.D., the verdict is already in.

Aggarwal is a third-year medical student at the University of Washington School of Medicine and a fellow in the Medical Scientist Training Program. His doctoral dissertation, titled "The Medical Geography of Cannabinoid Botanicals in Washington State: Access, Delivery, and Distress," discussed the successful use of medical marijuana or cannabinoid botanicals by 176 chronically and critically ill patients in Washington state.

(The term "cannabinoids" refers to any of the substances that are structurally related to tetrahydrocannabinol, or THC, the psychoactive ingredient in marijuana.)

At the AMA meeting, Aggarwal spoke to the Section Council on Psychiatry and asserted that since 2001—when the House of Delegates last voted to retain the Schedule I status of marijuana pending the outcome of research—at least 10 randomized, controlled trials had been completed on the use of cannabis for chronic neuropathic pain of multiple etiologies, appetite and weight loss in HIV/AIDS, spasticity in multiple sclerosis, and severe nausea.

In each of these studies, researchers used a federal-government supply of marijuana grown in Mississippi.

Aggarwal told psychiatrists at the meeting that the total body of literature on the subject shows "that cannabinoids, of which cannabis contains roughly 100 . . . have activity at the body's cannabinoid receptors and have many distinct pharmacologic properties, including analgesic, antiemetic, antispasmodic, antioxidative, neuroprotective, antidepressant, anxiolytic, and anti-inflammatory properties, as well as glial cell modulation and tumor growth regulation."

The 10 randomized controlled trials published since 2001 have relatively small numbers—four had sample sizes of under 20 subjects, and the largest had 62. And all were looking only at acute effects.

A meta-analysis of studies looking at longer-term effects published in the July 2003 *Journal of the International Neuropsychological Society* found that few studies on nonacute neurocognitive effects met current research standards, but the studies that do exist suggest neurocognitive risks may be minimal.

"Our results indicate that there might be decrements in the ability to learn and remember new information in chronic users, whereas other cognitive abilities are unaffected," the analysis concluded. "However, from a neurocognitive standpoint, the small magnitude of these effect sizes suggests that if cannabis compounds are found to have therapeutic value, they may have an acceptable margin of safety under the more limited conditions of exposure that would likely obtain in a medical setting."

But for addiction psychiatrists like Stuart Gitlow, M.D., M.P.H., the question is far from resolved. "Do the benefits outweigh the risks?" he asked in an interview with *Psychiatric News*. "We don't have anything in the literature to suggest that the answer is yes. None of the damage that has been shown to result from marijuana use is evident in a short-term observation."

Gitlow said he is not opposed to marijuana's being used individually in discrete situations, such as end-of-life care. But the question of legalizing marijuana for medical uses, he said, cannot be disentangled from the larger social context in which marijuana is widely used—addictively by many—for recreational purposes.

He added, "At the individual level, there may not be a problem, but when you look at it from a population basis, it's a different story. We know from experience that when opioids, stimulants, and sedatives are present in the home, they frequently find their way to people who aren't prescribed the drug."

Making Marijuana Accessible for Research

Yet the individual cases can be emotionally compelling. Said Aggarawal, "If you see someone suffering from neuropathic pain and there is no opioid that is helping, but you know that cannabinoids have a unique therapeutic effect on this type of pain, are you going to let the person suffer because his neighbor uses marijuana recreationally to enhance listening to music? Morally, I fall on the side of treating."

On the question of whether legalization of marijuana for medical uses would increase potential for drug abuse, a 1999 Institute of Medicine (IOM) report (see box) is agnostic. "[P]resent data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse," the IOM report concluded.

The report also noted, "This question is beyond the issues normally considered for medical uses of drugs and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids."

Perhaps the most enduring conclusion from the IOM report is the need for more research—the one point on which

please see ***Marijuana*** *on page 31*

IOM Report Still Sets Standard On Medical Marijuana

In an area where ideology may sometimes trump evidence, the 10-year-old Institute of Medicine report titled "Marijuana and Medicine: Assessing the Science Base" still appears to be the clearest statement of scientific understanding about the therapeutic potential of marijuana. The report came to a number of conclusions, including the following:

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory. The natural role of cannabinoids in immune systems is likely multifaceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine; withdrawal symptoms can be observed in animals but appear to be mild.
- Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.
- The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria, can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations and beneficial for others.
- Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.
- A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short-lived.

The report concluded that short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- Failure of all approved medications to provide relief has been documented.
- The symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs.
- Such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness.
- Treatment involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

"Marijuana and Medicine: Assessing the Science" is available online for purchase at <www.iom.edu/?id=12668>.

CMS Announces Delay In Use of *ICD-10* Codes

The use of new diagnostic codes for claims forms will not be required until October 2013 and could impact *DSM-V*.

BY RICH DALY

Physicians and insurers were given two additional years to familiarize themselves with the next generation of diagnostic codes following a recent decision by federal regulators, but psychiatrists did not support the delay.

The Centers for Medicare and Medicaid Services (CMS) released a final rule in January that physicians, hospitals, and payers must adopt an updated version of the *International Classification of Diseases* code sets, or *ICD-10*, by October 1, 2013. This rule, among the last issued by the Bush administration, delayed the scheduled implementation of *ICD-10* codes from October 1, 2011.

The World Health Organization (WHO) published its *ICD-10* in 1993, and most nations use it as the basis for their versions. The diagnostic categories used in *DSM-IV* and *DSM-IV-TR* are identified by both *ICD-9* and *ICD-10* codes.

The delay followed complaints to CMS by some physician organizations, including the AMA, and health insurers that the 2011 deadline left insufficient time to upgrade practice and billing systems to the new code set, which is capable of tracking many more diagnoses with greater specificity.

The extension of the *ICD-10* implementation deadline was supported by many physician groups as necessary to help physicians, coders, and others prepare for a smooth transition.

APA did not advocate for the postponement. In a letter to CMS last October, APA and other organizations called for quick implementation of *ICD-10* to replace the "outdated" *ICD-9-CM*.

The version that will be used in the United States is *ICD-10-CM*. "CM" stands for "clinical modification."

"*ICD-10-CM* will allow for greater specificity in diagnosis and thus better disease tracking than can be currently found with *ICD-9-CM*," wrote APA, the American Association for Geriatric Psychiatry, and the American Academy of Child and Adolescent Psychiatry.

Among the reasons cited in support of quick implementation is the inability of *ICD-9-CM* to accommodate new *DSM* diagnoses developed over the last two decades within the limited number of codes allotted for mental disorders, the need for clinicians and payers to keep closer track of the health of patients with chronic health conditions, and the need for "fully harmonizing" the codes with *DSM-IV*.

Darrel Regier, M.D., M.P.H., director of APA's Division of Research and of the American Psychiatric Institute for Research and Education, told *Psychiatric News* that APA has been seeking implementation of a U.S. national version of the WHO-developed *ICD-10* codes since 2000 to bring them up to date with the more specific disease codes under the international *ICD-10* system

"We're disappointed that *ICD-10* was not implemented more quickly," Regier said. "When it is finally implemented, it will be 23 years since it was approved as a diagnostic set by WHO."

The delay is likely to impact the development of *DSM-V*, for which APA was hoping to match *DSM* diagnoses with the *ICD-10* codes. The delay will likely mean APA will perform "an approximation" of *DSM-V* diagnostic codes to older *ICD-9* codes and then update them when *ICD-10* is implemented, Regier said. *DSM-V* will be published in 2012.

ICD-9, developed over 30 years ago, contains 17,000 codes. *ICD-10* contains more than 155,000 codes and can accommodate a host of new diagnoses and procedures. The limitations of *ICD-9* have led CMS to begin assigning codes to unrelated chapters because many of the *ICD-9-CM* chapters are full. For example, codes related to neurological procedures have been placed under the cardiovascular chapter because there was no room for additional codes in the neurological chapter.

Another delay was granted by CMS for clinicians to adopt the so-called 5010 electronic transaction standards, which is the latest update on the specifications of how medical data can be transmitted under the Health Insurance Portability and Accountability Act (HIPAA).

Implementation of the transmission update is considered a prerequisite for moving to *ICD-10*. Under another final rule also issued in January, that deadline was extended from April 1, 2010, to January 1, 2012.

Officials in the Obama administration are reviewing both rules—among other regulations issued in the final days of the Bush administration.

"A transition of this magnitude will require a workable implementation process and timeline for all HIPAA-covered entities and comprehensive outreach and education initiatives to support health care providers, especially small physician practices, throughout this complex move to *ICD-10*," wrote the AMA and other physician organizations in letter last October calling for delay of both *ICD-10* and the 5010 electronic transaction standards.

Information on ICD-10 is posted at <www.cdc.gov/nchs/about/otheract/icd9/abticd10.htm>. ■

Women's Psychological Traits Pave Creative Leadership Path

What does it take for a woman to be a successful leader? And can therapy help women whose leadership skills may suffer due to childhood trauma or other issues? Psychoanalysts explore these issues.

BY JOAN AREHART-TREICHEL

Women hold all sorts of positions of power these days. For example, Nancy Pelosi is speaker of the U.S. House of Representatives, Angela Merkel is chancellor of Germany, and as of January Carol Bartz is chief executive officer (CEO) of Yahoo!, a Fortune 500 company.

What makes such women tick? What psychological traits or behaviors contribute to their professional success or for others hinder their achievements?

Several psychoanalysts tackled these questions at the American Psychoanalytic Association (APsaA) meeting in New York City in January at the session "When Women Lead: Power and Authority in the Organization." They were Prudence Gourguechon, M.D., a Chicago analyst and president of APsaA; Laura Huggler, Ph.D., a West Bloomfield, Mich., analyst who consults to companies and has worked with a number of women CEOs; and Kenneth Settel, M.D., a Brookline, Mass., analyst.

Some women in leadership positions seem to naturally have what it takes to be successful, a January 16 *New York Times* article about Bartz suggested. The article described Bartz as "combative, decisive, and very much in command" and as a person who displays "a mix of candor and toughness." Whether Bartz is really a "natural" or whether she had to work on her leadership style to become so successful is not clear from this article.

What is clear, however, is that other women have to make some effort to become successful leaders, just as some men do. Gourguechon cited herself as an example. During the six months that she has been president of APsaA, Gourguechon said, she has "found an authoritative voice, but it is also strange and eerie and a way of speaking and acting that I had never used before."

To illustrate the point further, Huggler described the case of a woman who was a CEO of a nonprofit organization.

Credit: Joan Arehart-Treichel

Prudence Gourguechon, M.D.: "I have found an authoritative voice [as APsaA president], but it is also strange and eerie and a way of speaking and acting that I had never used before."

The CEO, "Sarah," had a number of positive qualities—"she was warm and engaging, she had an astute political sense, and she was great at fundraising." However, when she was absent from her office, her "staff was on the edge of mutiny," and there was a lot of in-house fighting. Moreover, there was "Beth," Sarah's second-in-command. Beth was rigid and authoritative; she thought that only she knew what was best for the operation. A "competitive struggle" ensued between the two women. Beth grew bolder and bolder; Sarah capitulated to her demands. Only after extensive psychotherapy did Sarah come to realize that she unconsciously identified her dictatorial, intimidating subordinate Beth with her own dictatorial, intimidating mother, and only then was she able to take steps to fire Beth.

please see ***Women*** *on page 31*

Credit: Joan Arehart-Treichel

Laura Huggler, Ph.D., a Michigan psychoanalyst, is a consultant to various companies and has worked with a number of female CEOs.

Lawyer With Schizophrenia Says Analysis Saved Her Life

Thanks to psychoanalysis, a law professor comes to accept that she has a serious mental illness—and that she needs to remain on antipsychotic medications indefinitely.

BY JOAN AREHART-TREICHEL

Often people hear about the horrors of schizophrenia. But rarely do they hear about persons who are prevailing against this grave illness—that is to say, the success stories.

One such person is Elyn Saks, J.D., a professor of law and psychiatry at the University of Southern California and a specialist in mental health law. Saks told her uplifting story at the American Psychoanalytic Association meeting in New York City in January.

Actually, "analysis is the star of my show," she declared. "Analysis really saved my life."

Saks grew up in a prosperous home in Miami with two younger brothers. "My parents loved us and cared for us as best they could." However, at age 15 she had a psychotic experience: colors around her became very intense, and houses sent messages to her. While studying at Vanderbilt University, she also had some psychotic episodes, but courses in philosophy seemed to stave off the episodes to some degree.

"They provided me with a structure to my mind and order to my days," she reflected.

After graduating from Vanderbilt, she won a scholarship to study at Oxford University in England. There, she became very depressed and isolated. "I believed that people were talking about me behind my back, which actually might have been true," she said. "I thought of myself as a bad person." She was hospitalized for a few months.

"I was mostly depressed then [with some psychotic features] and did not receive a diagnosis of schizophrenia until later," she recalled.

After she was released from the hospital, the hospital doctors advised her to return to the United States. However, she decided against it and continued at Oxford. But during this period, she also saw a psychoanalyst to help her manage her mental illness.

please see ***Lawyer*** *on page 31*

MH Advocacy Group Celebrates Century of Achievement

Mental Health America—which was founded by a Wall Street financier who championed the rights of people with mental illness—reaches an impressive milestone and looks to its future as well as its past.

BY EVE BENDER

Psychiatric treatment has come a long way during the past century—over the years, straitjackets and cold wraps have given way to psychotherapy and medications that address neurochemical problems in the brain and help people recover from mental illness.

At the turn of the 20th century, however, many people with mental illness suffered rather than thrived under the conditions that were then common in sanitariums.

One man's struggles to get help during this era led him to establish a committee that contributed to the enactment of important reforms in mental health treatment. That committee became what is today known as Mental Health America (MHA).

This year, MHA is celebrating its 100th anniversary and a century's worth of accomplishments.

The nonprofit advocacy organization, which is based in Alexandria, Va., has more than 300 affiliates worldwide and members who are consumers of mental health care, relatives of people with mental illness, psychiatrists, mental health professionals, policymakers, and researchers.

MHA founder and Yale graduate Clifford Beers began experiencing the symptoms of what became known as bipolar disorder after beginning work on Wall Street as a financier. One day, he attempted suicide by jumping out of a third-story window.

Beers survived but was seriously injured and spent the next three years in Connecticut psychiatric hospitals, where he was mistreated by staff. At one point during his hospitalization, according to MHA, he was placed in a straitjacket for 21 consecutive nights.

In Beers' 1908 autobiography, *A Mind That Found Itself*, he wrote about his experiences with mental illness treatment to heighten awareness of the struggles of those with similar illnesses.

please see ***Century*** *on page 29*

AJP 'Readers' Have Options For Learning the Latest

The *American Journal of Psychiatry* has spawned several online products that give practitioners and residents new ways to access cutting-edge information.

BY STEPHANIE WHYCHE

Have you noticed? The *American Journal of Psychiatry* (*AJP*) has grown beyond its hard-copy format born 166 years ago. In recent years it has been plumbing the dynamic field of electronic communications to identify ever more creative ways to reach and increase its audience.

The most visible is *AJP in Advance*, which debuted two years ago. The bimonthly advance edition of the hard-copy monthly journal gives subscribers an early look at cutting-edge research making it competitive with weekly and biweekly medical publications. But before *AJP in Advance*, there were two other innovative initiatives that debuted with little fanfare: its *AJP* Audio and *Residents' Journal*.

AJP Audio

AJP Audio was launched about three years ago as an alternative format to *AJP*'s hard-copy monthly to attract new readers, especially busy ones on the go. The audiocasts, roughly 30 minutes long, highlight the contents of each month's *AJP*. Audiocasts going back to April 2006 can be accessed online at no charge. Susan Schultz, M.D., a psychiatrist in Iowa City, Iowa, is one of five deputy editors of *AJP* and one of the two voices listeners hear on the audiocasts. The other voice belongs to Michael Roy, editorial director of *AJP*.

"I've been listening to *AJP* Audio Podcasts now for a few months and want to let you know what a great resource this is" is how APA member Charles Peters, M.D., of Towson, Md., put it about a year ago in an unpublished letter. "Journals have piled up on my desk for years, and I rarely got through them in a timely way. Now I download a Podcast, take my iPod with me when I run or walk, and enjoy getting through each month's issue."

Today, nothing has changed Peters's sentiments: "That's very much how I feel about it a year later," he said in an interview.

"Every month we publish articles that can influence how clinicians practice so we want to make our articles as accessible as possible," Schultz said. The audiocasts "help us to make our articles available in a way that is user friendly for the busy clinician."

She and Roy read the scripts in professional sound studios. Roy said professional editing helps create the flawless presentation that listeners hear. Once completed, the recordings are saved in MP3 format, an audio compression structure widely used on the Internet, and uploaded onto *AJP*'s homepage.

"Because we use 'in-house' writing and voice talent, and because of their familiarity and enthusiasm for the material, costs to produce are minimal," Roy said—"just nominal costs to book the studio and for the sound engineer's editing time."

Jane Weaver, a senior *AJP* editor and feature writer, creates the scripts. "I have written most of them, but Susan Schultz wrote the first two [scripts]." Weaver said in an interview. "It's a large task. We cover many articles and modify the writing for an audio presentation."

A cross-section of topics from each month's *AJP* is highlighted in each script. "It takes some time to boil the articles down to a few paragraphs," Weaver said. "You have to decide what is essential . . . [and] use short, simple sentences and not too many 'esses.' "

Roy said it's hard to know exactly how many listeners have been drawn to *AJP* Audio over the years. But "from usage statistics and other reports, we estimate that several thousand people listen to at least a few minutes of the program each month."

Residents' Journal

The *Residents' Journal*, which last year became a joint initiative of *AJP* and APA's Committee of Residents and Fellows, was also born three years ago, with an updated design unveiled in January. Molly McVoy, M.D., chief psychiatry resident at University Hospitals and Case School of Medicine in Cleveland, is the *Residents' Journal*'s editor in chief.

Organizationally, the journal has two aspects to it: an e-mailed portion that's sent to residents and the online portion that can be accessed online directly. The e-mail highlights two articles for discussion from the current *AJP* and includes links to the table of contents of the current *AJP* and to *AJP* Audio.

"Every article in the *Residents' Journal* is written by a resident [and] each month has a resident [issue] editor who is responsible for all of the journal's content," McVoy told *Psychiatric News*.

The online publication typically contains from five to 10 page views of content, she noted, and the topics covered are wide ranging. "Recent issues have covered everything from the psychiatric aspects of weight loss to leadership development to medical anthropology."

Angela Moore, *AJP*'s staff editor of the *Residents' Journal*, reports the circulation of the journal to be about 2,000 residents.

"The publication has evolved in both appearance and content," Moore told *Psychiatric News*. "Many of the articles are now more scholarly, and the new layout and design of the issues are more sophisticated and attractive, with graphics as well as modern navigation tools for online viewing."

Steve Hennessey, *AJP*'s graphic designer, created the updated look of the journal. He recounted that in redesigning it, he and *AJP* staff looked to improve its readability and in-document navigation and to include more direct links to out-of-document resources.

"This was accomplished," he said, "by reorganizing and reformatting elements of the newsletter to create a more professional page-based layout that incorporates more inviting aesthetics."

Each article can be accessed by clicking on it from the online cover. And there are other useful resources that are accessible from within the pages of the articles.

'Visionary' at Helm of *AJP*

Of course, *AJP* Audio and the *Residents' Journal* hardly just materialized. Ask anyone at *AJP* what or who is the impetus for these projects and they all agree. They say *AJP* Editor-in-Chief Robert Freedman, M.D., is the visionary force behind *AJP* Audio, *Residents' Journal*, and *AJP in Advance*.

"Under Dr. Freedman's editorship, the *Journal* has been enjoying a resurgence," Roy commented. "We have always been proud of our publication's long, rich history, but it's also very exciting that with Dr. Freedman's ideas and energy, this venerable publication continues to play an integral role in defining the future of the field, both in what we publish and how we disseminate it."

For his part, Freedman credits the *AJP* staff and its APA member editors for the high quality and scope of *AJP* Audio and *Residents' Journal*.

"I appreciate the way Susan Schultz and Michael Roy can make our content as easy to hear and understand as an NPR radio program," Freedman told *Psychiatric News*. "Residents helped initiate the *Residents' Journal* to direct them to the parts of the *American Journal of Psychiatry* that are of most interest to them. Under Molly McVoy's leadership, resident editors and authors have now expanded it to address issues that are important in their training."

Freedman, meanwhile, is already thinking about what's next in the evolution of the *Residents' Journal*: "We hope," he said, "that residents will attend the focus group [see box] that the Committee of Residents and Fellows cosponsors with us at the APA annual meeting to consider what should be in the *Residents' Journal* in the future." ■

Credit: Susan McClellen of Creative Media Group, University of Iowa

Susan Schultz, M.D., a deputy editor of the *American Journal of Psychiatry,* is one of the voices heard on *AJP* Audio, a monthly audiocast that presents highlights of each month's journal.

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Also,* AJP *in Advance is accessible at <http://ajp.psychiatryonline.org>, and the* Residents' Journal *at <http://ajp.psychiatryonline.org/misc/Residents_Journal.dtl>.

Got an Opinion?

The editor of the *American Journal of Psychiatry (AJP),* Robert Freedman, M.D., invites psychiatry residents to participate in the fourth annual residents' focus group at APA's 2009 annual meeting in San Francisco to share their thoughts on how *AJP*'s *Residents' Journal* can be made a more valuable resource for them. The meeting is scheduled for Tuesday, May 19; location to be announced.

More information is available by sending an e-mail to ajp@psych.org.

Medication Resistance Signals Risk for Post-ECT Relapse

Patients with depression who have failed to respond to an adequate pharmacotherapy regimen may achieve an "unstable" remission with ECT and still need aggressive continued treatment.

BY JUN YAN

Electroconvulsive therapy (ECT) is usually reserved for difficult-to-treat depression patients who are not suitable for or have failed to respond to antidepressant medications. However, patients who have failed at least one adequate course of medication have a 1 in 3 chance of relapse within a week after responding to ECT.

A study published online in the *Journal of Clinical Psychiatry* on January 13 presented new data analyses from a large multicenter clinical trial on the long-term effectiveness of ECT conducted from 1997 to 2004. The trial was conducted by the Consortium for Research on Electroconvulsive Therapy (CORE), a group of medical centers across the country that have been collaborating on clinical research to investigate ECT effectiveness and relapse prevention in the real-world patient-care setting.

In the clinical trial, 531 patients with unipolar depression received ECT three times a week until they either reached remission or completed 10 ECT sessions without remission. Patients were assessed at baseline and after each ECT session.

The criterion for remission was achieving a 60 percent reduction from baseline in the 24-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{24}$) score and two consecutive assessments in which the scores were no more than 10, with no more than a three-point drop between the two assessments to ensure the response was stable. At baseline each patient was questioned about past treatment to determine whether he or she had had a previous trial of antidepressant treatment with adequate dosage and duration.

The 341 patients who achieved remission waited for one week before they were randomized to the long-term phase of the trial, which compared the effectiveness of maintenance ECT with that of pharmacotherapy. This study examined only the subsample of 146 patients who reached remission within 10 sessions, had no psychotic features, and provided treatment history at baseline.

During the one-week interim period when patients in remission had no treatment for depression, nearly a third (31.4 percent) of the 105 nonpsychotic patients with a history of medication resistance relapsed, meaning that their $HAM\text{-}D_{24}$ score rose back above 10. This relapse rate was significantly higher than the 9.8 percent rate in the 41 patients who did not have a history of medication resistance.

The study findings suggested "the fragile nature of ECT-induced remissions in previously medication-resistant patients," the researchers concluded.

At the end of the interim week, 73 patients who were still in remission were randomized to receive either pharmacotherapy or maintenance ECT for the next six months. About 48 percent of these patients relapsed during the six-month period, 40 percent did not relapse, and the remainder dropped out of the study.

By the end of the six-month maintenance period, 53 percent of patients with a history of medication resistance and 38 percent of patients without such a history relapsed despite treatment. This difference, however, was not statistically significant.

Keith Rasmussen, M.D., a psychiatrist in the Department of Psychiatry and Psychology at the Mayo Clinic and the lead author of the study, recommended that psychiatrists should not "be dissuaded from doing ECT in a patient who is medication refractory, but [should] be aggressive in planning the treatment-continuation strategies."

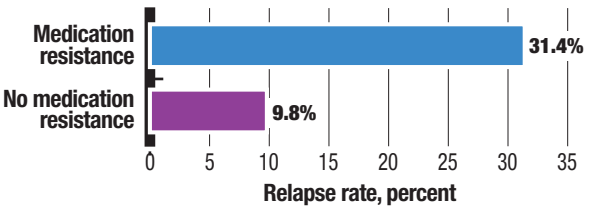
These strategies, he noted, "would include starting medications immediately after the end of ECT and possibly before it," he told *Psychiatric News*.

The study was funded by grants from the National Institute of Mental Health.

An abstract of "Is Baseline Medication Resistance Associated With Potential for Relapse After Successful Remission of a Depressive Episode With ECT? Data From the Consortium for Research on Electroconvulsive Therapy (CORE)" is posted at <www.psychiatrist.com/abstracts/abstracts.asp?abstract=oap/ej08m04092.htm>. ■

Medication Resistance Linked to Relapse After ECT

Among 146 patients with nonpsychotic depression who reached remission after thrice-weekly electroconvulsive therapy (ECT), those who had a history of medication resistance (n=105) had a significantly higher rate of relapse during one week of no treatment compared with patients without the history (n=41) at baseline.



Source: Keith Rasmussen, M.D., et al., *Journal of Clinical Psychiatry*, published online January 13, 2009

Biological Marker May Predict Postpartum Depression

Could an elevated level of a stress hormone—corticotropin-releasing hormone (CRH)—during mid-pregnancy become a routine way to identify women who will develop postpartum depression?

BY JOAN AREHART-TREICHEL

Some risk factors for postpartum depression are well documented. They include anxiety, stress, lack of social support, low self-esteem, depression before or during pregnancy, a history of premenstrual syndrome, and a history of oral contraceptive–induced mood changes.

A biological marker for postpartum depression may now have been discovered as well. The marker is an elevated level of the hypothalamic hormone corticotropin-releasing hormone (CRH) during the 25th week of pregnancy.

This study "supports [the notion] that women who suffer from postpartum depression have a biological vulnerability, and that risk may be assessed during pregnancy. . . ."

The finding was reported in the February *Archives of General Psychiatry*. The lead investigator was Ilona Yim, Ph.D., an assistant professor of psychology and social behavior at the University of California, Irvine.

CRH is known to play an important role in the origin of depression in the non-pregnant state. CRH levels are also known to soar during pregnancy. Yim and her coworkers suspected that a surge of CRH during pregnancy might help set the stage for postpartum depression in some women, so they launched a longitudinal cohort study to test the hypothesis.

One hundred pregnant women were recruited into the study. Blood samples were obtained at 15, 19, 25, 31, and 37 weeks of pregnancy from each of the women. The blood samples were screened not just for CRH, but for the pituitary hormone adrenocorticotropic hormone (ACTH), which is regulated by CRH, and for the adrenal cortex hormone cortisol, which is regulated by ACTH. Each woman was assessed for depressive symptoms four times during pregnancy and on average nine weeks after delivery. Out of the 100 women, 16 developed postpartum depression symptoms.

After taking prenatal depressive symptoms into consideration, the researchers looked to see whether there was any link between pregnancy levels of CRH, ACTH, or cortisol and the development of postpartum depression symptoms. They found only one link, and that concerned CRH. An elevated level of CRH at 25 weeks of pregnancy was a highly significant predictor of postpartum depression—that is, it predicted postpartum depression with an accuracy of 75 percent and with a misclassification rate of 24 percent.

Although Yim and her colleagues had anticipated that CRH might predict postpartum depression, she "was surprised at how robust this finding was," Yim told *Psychiatric News*. "I also did not anticipate a timing effect. I would have speculated that overall CRH exposure throughout pregnancy would play a bigger role."

Yim and her group will now attempt to replicate their findings. If they manage to do so, and if other groups manage to do so as well, "it may be considered useful to implement a CRH-postpartum depression screen into standard prenatal care," they wrote in their study report. "Because blood draws to screen for gestational diabetes are typically performed at 24 to 28 weeks of gestation, a potential postpartum depression screen could be completed at the same time."

Meanwhile, Yim and her colleagues will attempt to determine why a large surge in CRH around 25 weeks of pregnancy seems to predict postpartum depression. They do know that the placenta starts to churn out large amounts of CRH around this time, supplementing the amount of CRH that is already being made by the hypothalamus. But why many women who develop postpartum depression tend to produce even more CRH at 25 weeks of pregnancy than do women who do not develop postpartum depression is not clear.

"This work is an exciting contribution in the area of postpartum depression," Marlene Freeman, M.D., told *Psychiatric News*. "It supports [the notion] that women who suffer from postpartum depression have a biological vulnerability, and that risk may be assessed during pregnancy at a specific point. It would be important to build upon this work to determine how women at risk for postpartum major depressive episodes might be clearly identified for careful monitoring, early treatment, and even prophylaxis."

Freeman is a psychiatrist with a focus on the interface between psychiatry and obstetrics. She is affiliated with the Perinatal and Reproductive Psychiatry Clinical Research Program at Massachusetts General Hospital.

The study was funded by the National Institute of Child Health and Human Development.

An abstract of "Risk of Postpartum Depressive Symptoms With Elevated Corticotropin-Releasing Hormone in Human Pregnancy" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/66/2/162>. ■

One MH Care Racial Disparity Seems to Be Disappearing

A race-related difference in visit duration was evident among visits financed by Medicare but not other sources of payment.

BY MARK MORAN

The difference in outpatient psychiatric office visit duration for white people and African Americans—a proxy for quality of care—appears to have narrowed dramatically in recent years.

The average duration of outpatient visits by African Americans between 2001 and 2006—adjusted to account for potentially confounding patient, psychiatrist, and practice characteristics—was 3.5 minutes shorter than visits by white people, according to a report in the February *Archives of General Psychiatry*.

But that disparity is largely due to the substantial gap of 7.4 minutes that existed in the early years of the period, 2001 to 2004. Between 2004 and 2006 the gap virtually disappeared, dropping to 0.1 minute.

The analysis controlled for difference in duration of visits for psychotherapy and medication management, so that the racial difference in visit duration during the five-year period—as well as its significant narrowing in the last three years of the study period—was not mediated by psychotherapy, use of medication, or changes in these variables on the part of either racial group.

"Office visit duration can be thought of as a proxy for clinical attention and therefore serves as a measure of quality of care," said study author Marc Olfson, M.D., a professor of clinical psychiatry at Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute. "It's heartening, because it seems the differences between the races [with regard to this variable] have all but disappeared in recent years. And that change is not attributable to changes in rates of psychotherapy or medication management."

Nor can the closing of the gap in visit duration be explained by an overall decrease in visit length from the 2001-2003 period to the 2003-2006 period. In the first three years, the average adjusted length of an office visit for white people was 32.9 minutes; in the latter half of the study period, that figure dropped only slightly to 32.5 minutes.

But the average length of visits for African Americans rose from 25.5 minutes in the first three years to 32.4 minutes in the later half of the study period.

"We are left with a puzzle," said Olfson. "I can only speculate that perhaps there really have been recent changes in public attitudes with people, including psychiatrists, becoming more comfortable talking across racial groups about mental health problems."

He noted that the study analyzes a period when racial disparities in access to and quality of care became a subject of national focus. "It's also true that there has been a lot of attention devoted to this general topic and a greater public awareness of threats to the quality of health care posed by racial disparities," he said. "The narrowing of the racial gap in visit duration in recent years is a welcome development, but it's not one that we can confidently assign to any one particular cause."

Data for the study were drawn from the 2001-2006 National Ambulatory Medical Care Survey, a probability sample survey of office-based physicians in the United States conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics.

Physicians were instructed to fill out a patient record form for each sampled visit. The number of forms completed each year by respondent psychiatrists ranged from a low of 1,469 in 2003 to a high of 1,896 in 2004. A total of 7,094 office visits were made by white patients, and 504 visits were made by African-American patients.

The unadjusted mean duration of psychiatric outpatient visits by African-American patients over the entire study period was 4.4 minutes shorter than that of white patients and 3.5 minutes shorter after controlling for potential confounding variables.

Interestingly, a significant race-related difference in visit duration was evident among visits financed by Medicare but not other sources of payment. Olfson noted that African Americans are much less likely to have private supplemental insurance to cover charges above Medicare-approved amounts.

"It may be that additional reimbursement from supplemental insurance contributes to longer visits," he told *Psychiatric News*. "It's one area where there are persisting differences."

An abstract of "Racial Differences in Visit Duration of Outpatient Psychiatric Visits" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/66/2/214>. ■

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IMPORTANT SAFETY INFORMATION FOR RISPERDAL® CONSTA®

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of patients with dementia-related psychosis.

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

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including RISPERDAL® CONSTA®. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose. Elderly patients appeared to be at increased risk for TD. Prescribing should be consistent with the need to minimize the risk of TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

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® CONSTA®. Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment.

Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, RISPERDAL® CONSTA® elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Orthostatic Hypotension: RISPERDAL® CONSTA® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. RISPERDAL® CONSTA® should be used with caution in patients with known cardiovascular disease, and conditions that would predispose patients to hypotension.

Potential for Cognitive and Motor Impairment: RISPERDAL® CONSTA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that RISPERDAL® CONSTA® does not affect them adversely.

Seizures: RISPERDAL® CONSTA® should be used cautiously in patients with a history of seizures.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses. Close supervision of high-risk patients should accompany drug therapy.

Administration: Care should be taken to avoid inadvertent injection into a blood vessel.

Extrapyramidal Symptoms (EPS): The overall incidence of EPS-related adverse events in patients treated with 25 mg and 50 mg of RISPERDAL® CONSTA® and placebo, respectively, were akathisia* (4%, 11%, 6%), Parkinsonism† (8%, 15%, 9%) and tremor (0%, 3%, 0%).

* Akathisia and restlessness

† Extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia

Weight Gain: In a 12-week trial, the percentage of patients experiencing weight gain (>7% of baseline body weight) was 6% placebo versus 9% RISPERDAL® CONSTA®.

Maintenance Treatment: Patients should be periodically reassessed to determine the need for continued treatment.

Commonly Observed Adverse Reactions for RISPERDAL® CONSTA®: The most common adverse reactions in clinical trials (≥5%) were headache, Parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremities, and dry mouth.

01CS08008R1

Please see accompanying brief summary of full Prescribing Information for RISPERDAL® CONSTA®.

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January 2009 01CS1026ER1

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RISPERDAL® CONSTA®
(risperidone) LONG-ACTING INJECTION

Brief Summary

BEFORE PRESCRIBING RISPERDAL® CONSTA®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions]*

RISPERDAL® CONSTA® (risperidone) is indicated for the treatment of schizophrenia *[see Clinical Studies in full PI].*

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

WARNINGS AND PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with oral risperidone compared to patients treated with placebo. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis *[See also Boxed Warning and Warnings and Precautions]* **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. 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 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. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. 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. RISPERDAL® CONSTA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. 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 treated with RISPERDAL® CONSTA®, drug discontinuation should be considered. **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. **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. **Orthostatic Hypotension:** RISPERDAL® CONSTA® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period with oral risperidone, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499 patients) of patients treated with RISPERDAL® CONSTA® in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). RISPERDAL® CONSTA® should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral RISPERDAL® and antihypertensive medication. **Potential for Cognitive and Motor Impairment:** Somnolence was reported by 5% of patients treated with RISPERDAL® CONSTA® in multiple-dose trials. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL® CONSTA® does not affect them adversely. **Seizures:** During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with RISPERDAL® CONSTA®. Therefore, RISPERDAL® CONSTA® should be used cautiously in patients with a history of seizures. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® CONSTA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. *[See also Boxed Warning and Warnings and Precautions]* **Priapism:** Priapism has been reported during postmarketing surveillance *[see Adverse Reactions].* Severe priapism may require surgical intervention. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown. **Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® or RISPERDAL® CONSTA® use. Caution is advised when prescribing RISPERDAL® CONSTA® for patients who will be exposed to temperature extremes. **Administration:** RISPERDAL® CONSTA® should be injected into the deltoid or gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel. *[See Dosage and Administration in full PI and Adverse Reactions]* **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. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. RISPERDAL® CONSTA® is to be administered by a health care professional *[see Dosage and Administration in full PI];* therefore, suicide due to an overdose is unlikely. **Use in Patients with Concomitant Illness:** Clinical experience with RISPERDAL® CONSTA® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL® CONSTA®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome. Caution is advisable when using RISPERDAL® CONSTA® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2) treated with oral RISPERDAL®; an increase in the free fraction of risperidone is also seen in patients with severe hepatic impairment. Patients with renal or hepatic impairment should be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL® CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with renal or hepatic impairment *[see Dosage and Administration in full PI].* **Osteodystrophy and Tumors in Animals:** RISPERDAL® CONSTA® produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks. RISPERDAL® CONSTA® produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL® CONSTA® produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. **Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone.** Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study. The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail in *Nonclinical Toxicology in full PI.* The relevance of these findings to human risk is unknown. **Monitoring: Laboratory Tests:** No specific laboratory tests are recommended.

ADVERSE REACTIONS: The following are discussed in more detail in *Boxed Warning and Warnings and Precautions* sections of the labeling: • Increased mortality in elderly patients with dementia-related psychosis • Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis • Neuroleptic malignant syndrome • Tardive dyskinesia • Hyperglycemia and diabetes mellitus • Hyperprolactinemia • Orthostatic hypotension • Potential for cognitive and motor impairment • Seizures • Dysphagia • Priapism • Thrombotic Thrombocytopenic Purpura (TTP) • Disruption of body temperature regulation • Avoidance of inadvertent injection into a blood vessel • Antiemetic effect • Suicide • Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies • Diseases or conditions that could affect metabolism or hemodynamic responses • Osteodystrophy and tumors in animals The most common adverse reactions in clinical trials (≥ 5%) were: headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth. The most common adverse reactions that were associated with discontinuation from the 12-week double-blind, placebo-controlled (causing discontinuation in ≥ 1% of patients) were agitation, depression, anxiety, and akathisia *[see Adverse Reactions].* The data described in this section are derived from a clinical trial database consisting of 2392 patients exposed to one or more doses of RISPERDAL® CONSTA® for the treatment of schizophrenia. Of these 2392 patients, 332 were patients who received RISPERDAL® CONSTA® while participating in a 12-week double-blind, placebo-controlled trial. Two hundred two (202) of the 332 were schizophrenia patients who received 25 mg or 50 mg RISPERDAL® CONSTA®. The conditions and duration of treatment with RISPERDAL® CONSTA® varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 4 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs. Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology. Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of RISPERDAL® CONSTA® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for RISPERDAL® CONSTA® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The majority of all adverse reactions were mild to moderate in severity. **Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials:** Table 1 lists the adverse reactions reported in 2% or more of RISPERDAL® CONSTA®-treated patients with schizophrenia in one 12-week double-blind, placebo-controlled trial. **Table 1. Adverse Reactions in ≥ 2% of RISPERDAL® CONSTA®-Treated Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial: System Organ Class, Percentage of Patients Reporting Event RISPERDAL® CONSTA® 25mg (N=99)** first, **50 mg (N=103)** second, **Placebo (N=98)** third, **Adverse Reaction, Eye disorders:** Vision blurred 2, 3, 0; **Gastrointestinal disorders:** Constipation 5, 7, 1; Dry mouth 0, 7, 1; Dyspepsia 6, 6, 0; Nausea 3, 4, 5; Toothache 1, 3, 0: Salivary hypersecretion 4, 1, 0; **General disorders and administration site conditions:** Fatigue* 3, 9, 0; Edema peripheral 2, 3, 1; Pain 4, 1, 0; Pyrexia 2, 1, 0; **Infections and infestations:** Upper respiratory tract infection 2, 0, 1; **Investigations:** Weight increased 5, 4, 2; Weight decreased 4, 1, 1; **Musculoskeletal and connective tissue disorders:** Pain in extremity 6, 2, 1; **Nervous system disorders:** Headache 15, 21, 12; Parkinsonism* 8, 15, 9; Dizziness 7, 11, 6; Akathisia* 4, 11, 6; Sedation* 5, 6, 3; Tremor 0, 3, 0; Syncope 2, 1, 0; Hypoesthesia 2, 0, 0; **Respiratory, thoracic and mediastinal disorders:** Cough 4, 2, 3; Sinus congestion 2, 0, 0; **Skin and subcutaneous tissue disorders:** Acne 2, 2, 0; Dry skin 2, 0, 0. * Fatigue includes fatigue and asthenia. Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia. Akathisia includes akathisia and restlessness. Sedation includes sedation and somnolence. **Other Adverse Reactions Observed During the Premarketing Evaluation of RISPERDAL® CONSTA®:** The following adverse reactions occurred in < 2% of the patients in the above 12-week double-blind, placebo-controlled trial. In addition, the following also includes adverse reactions reported in RISPERDAL® CONSTA®-treated patients who participated in other studies, including double-blind, active-controlled and open-label studies in schizophrenia. **Blood and lymphatic system disorders:** anemia, neutropenia **Cardiac disorders:** tachycardia, atrioventricular block first degree, palpitations, sinus bradycardia, bundle branch block left, bradycardia, sinus tachycardia, bundle branch block right **Ear and labyrinth disorders:** ear pain, vertigo **Endocrine disorders:** hyperprolactinemia **Eye disorders:** conjunctivitis **Gastrointestinal disorders:** diarrhea, vomiting, abdominal pain, stomach discomfort, gastritis **General disorders and administration site conditions:** injection site pain, chest discomfort, chest pain, influenza like illness, sluggishness, malaise, induration, injection site induration, injection site reaction **Immune system disorders:** hypersensitivity **Infections and infestations:** nasopharyngitis, influenza, bronchitis, urinary tract infection, rhinitis, ear infection, pneumonia, lower respiratory tract infection, pharyngitis, sinusitis, viral infection, infection, localized infection, cystitis, gastroenteritis, subcutaneous abscess **Injury and poisoning:** fall, procedural pain **Investigations:** blood prolactin increased, alanine aminotransferase increased, electrocardiogram abnormal, gamma-glutamyl transferase increased, blood glucose increased, hepatic enzyme increased, aspartate aminotransferase increased **Metabolism and nutritional disorders:** increased appetite, decreased appetite **Musculoskeletal, connective tissue and bone disorders:** myalgia, back pain, arthralgia, buttock pain, muscular weakness, neck pain, musculoskeletal chest pain **Nervous system disorders:** dyskinesia, dystonia, tardive dyskinesia, drooling, paresthesia, dizziness postural, convulsion **Psychiatric disorders:** insomnia, agitation, anxiety, sleep disorder, depression, libido decreased, nervousness **Renal and urinary disorders:** urinary incontinence **Reproductive system and breast disorders:** amenorrhea, erectile dysfunction, galactorrhea, sexual dysfunction, gynecomastia **Respiratory, thoracic and mediastinal disorders:** nasal congestion, pharyngolaryngeal pain, dyspnea, rhinorrhea **Skin and subcutaneous tissue disorders:** rash, eczema, pruritus **Vascular disorders:** hypertension, hypotension, orthostatic hypotension **Discontinuations Due to Adverse Reactions:** Approximately 11% (22/202) of RISPERDAL® CONSTA®-treated patients in the 12-week double-blind, placebo-controlled trial discontinued treatment due to an adverse event, compared with 13% (13/98) who received placebo. The adverse reactions associated with discontinuation in two or more RISPERDAL® CONSTA®-treated patients were: agitation (3%), depression (2%), anxiety (1%), and akathisia

(1%). **Dose Dependency of Adverse Reactions in Clinical Trials:** Extrapyramidal Symptoms: Two methods were used to measure extrapyramidal symptoms (EPS) in the 12-week double-blind, placebo-controlled trial comparing three doses of RISPERDAL® CONSTA® (25 mg, 50 mg, and 75 mg) with placebo, including: (1) the incidence of spontaneous reports of EPS symptoms; and (2) the change from baseline to endpoint on the total score (sum of the subscale scores for Parkinsonism, dystonia, and dyskinesia) of the Extrapyramidal Symptom Rating Scale (ESRS). As shown in Table 1, the overall incidence of EPS-related adverse reactions (akathisia, dystonia, Parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL® CONSTA® was comparable to that of patients treated with placebo; the incidence of EPS-related adverse reactions was higher in patients treated with 50 mg RISPERDAL® CONSTA®. The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with RISPERDAL® CONSTA® compared with patients treated with placebo: 0 (placebo group); -1 (25-mg group, significantly less than the placebo group); and 0 (50-mg group). *Dystonia: Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. **Changes in Body Weight:** In the 12-week double-blind, placebo-controlled trial, 9% of patients treated with RISPERDAL® CONSTA®, compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint. **Changes in ECG:** The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® and 98 schizophrenic patients treated with placebo in the 12-week double-blind, placebo-controlled trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL® CONSTA®. **Pain Assessment and Local Injection Site Reactions:** The mean intensity of injection pain reported by patients using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® experienced redness, swelling, or induration at the injection site. In a separate study to observe local-site tolerability in which RISPERDAL® CONSTA® was administered into the deltoid muscle every 2 weeks over a period of 8 weeks, no patient discontinued treatment due to local injection site pain or reaction. Clinician ratings indicated that only mild redness, swelling, or induration at the injection site was observed in subjects treated with 37.5 mg or 50 mg RISPERDAL® CONSTA® at 2 hours after deltoid injection. All ratings returned to baseline at the predose assessment of the next injection 2 weeks later. No moderate or severe reactions were observed in any subject. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of risperidone; because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: agranulocytosis, alopecia, anaphylactic reaction, angioedema, atrial fibrillation, diabetic ketoacidosis in patients with impaired glucose metabolism, inappropriate antidiuretic hormone secretion, hypothermia, intestinal obstruction, jaundice, mania, pancreatitis, priapism, QT prolongation, sleep apnea syndrome, thrombocytopenia, and water intoxication. In addition, the following adverse reactions have been observed during postapproval use of RISPERDAL® CONSTA®: cerebrovascular disorders, including cerebrovascular accidents, and diabetes mellitus aggravated. Retinal artery occlusion after injection of RISPERDAL® CONSTA® has been reported during postmarketing surveillance. This has been reported in the presence of abnormal arteriovenous anastomosis. Serious injection site reactions including abscess, cellulitis, cyst, hematoma, necrosis, nodule, and ulcer have been reported with RISPERDAL® CONSTA® during postmarketing surveillance. Isolated cases required surgical intervention.

DRUG INTERACTIONS: The interactions of RISPERDAL® CONSTA® with coadministration of other drugs have not been systematically evaluated. The drug interaction data provided in this section is based on studies with oral RISPERDAL®. **Centrally-Acting Drugs and Alcohol:** Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® CONSTA® is administered in combination with other centrally-acting drugs or alcohol. **Drugs with Hypotensive Effects:** Because of its potential for inducing hypotension, RISPERDAL® CONSTA® may enhance the hypotensive effects of other therapeutic agents with this potential. **Levodopa and Dopamine Agonists:** RISPERDAL® CONSTA® may antagonize the effects of levodopa and dopamine agonists. **Amitriptyline:** Amitriptyline did not affect the pharmacokinetics of risperidone or of risperidone and 9-hydroxyrisperidone combined following concomitant administration with oral RISPERDAL®. **Cimetidine and Ranitidine:** Cimetidine and ranitidine increased the bioavailability of oral risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of risperidone and 9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%. **Clozapine:** Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Lithium:** Repeated doses of oral RISPERDAL® (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated doses of oral RISPERDAL® (4 mg once daily) 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 oral RISPERDAL®. **Digoxin:** Oral RISPERDAL® (0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Topiramate:** Oral RISPERDAL® administered at doses from 1-6 mg/day concomitantly with topiramate 400 mg/day resulted in a 23% decrease in risperidone Cmax and a 33% decrease in risperidone $AUC_{0\text{-}12\ hour}$ at steady state. Minimal reductions in the exposure to risperidone and 9-hydroxyrisperidone combined, and no change for 9-hydroxyrisperidone were observed. This interaction is unlikely to be of clinical significance. There was no clinically relevant effect of oral RISPERDAL® on the pharmacokinetics of topiramate. **Drugs That Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs *[see Clinical Pharmacology in full PI]*. Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≅70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. *In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. Fluoxetine and Paroxetine: Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily), CYP 2D6 inhibitors, 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 dose of RISPERDAL® CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 25 mg RISPERDAL® CONSTA®, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. When RISPERDAL® CONSTA® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[See also Dosage and Administration in full PI]*. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied. Erythromycin: There were no significant interactions between oral RISPERDAL® and erythromycin. **Carbamazepine and Other CYP 3A4 Enzyme Inducers:** Carbamazepine co-administration with oral RISPERDAL® decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known CYP 3A4 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 RISPERDAL® CONSTA® treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4–8 weeks, since the dose of RISPERDAL® CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of RISPERDAL® CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 enzyme inducers to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose of 25 mg RISPERDAL® CONSTA® and discontinuing from carbamazepine or other CYP 3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL® CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL® CONSTA® treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[See also Dosage and Administration in full PI]* **Drugs Metabolized by CYP 2D6:** *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® CONSTA® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral RISPERDAL® did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C.: The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the oral MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m^2 basis. No studies were conducted with RISPERDAL® CONSTA®. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to oral RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® CONSTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® CONSTA® on labor and delivery in humans is unknown. **Nursing Mothers:** Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women should not breast-feed during treatment with RISPERDAL® CONSTA® and for at least 12 weeks after the last injection. **Pediatric Use:** RISPERDAL® CONSTA® has not been studied in children younger than 18 years old. **Geriatric Use:** In an open-label study, 57 clinically stable, elderly patients (≥ 65 years old) with schizophrenia or schizoaffective disorder received RISPERDAL® CONSTA® every 2 weeks for up to 12 months. In general, no differences in the tolerability of RISPERDAL® CONSTA® were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern *[see Warnings and Precautions]*. Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis: In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with oral placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of oral risperidone regardless of concomitant use with furosemide. RISPERDAL® CONSTA® is not approved for the treatment of patients with dementia-related psychosis. *[See Boxed Warning and Warnings and Precautions]*

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL® CONSTA®. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension and instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position) *[see Warnings and Precautions]*. **Interference with Cognitive and Motor Performance:** Because RISPERDAL® CONSTA® has 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 treatment with RISPERDAL® CONSTA® does not affect them adversely *[see Warnings and Precautions]*. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy and for at least 12 weeks after the last injection of RISPERDAL® CONSTA® *[see Use in Specific Populations]*. **Nursing:** Patients should be advised not to breast-feed an infant during treatment and for at least 12 weeks after the last injection of RISPERDAL® CONSTA® *[see Use in Specific Populations]*. **Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see Drug Interactions]*. **Alcohol:** Patients should be advised to avoid alcohol during treatment with RISPERDAL® CONSTA® *[see Drug Interactions]*.

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Janssen
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Risperidone is manufactured by:
Janssen Pharmaceutical Ltd.
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What Does Left Hand Know That Right Hand Doesn't?

Many accomplished people have been, or are, left-handed. But left-handedness also has another side, psychiatric research suggests.

BY JOAN AREHART-TREICHEL

On January 20, Barack Obama was sworn in as president of the United States. It was a triumphant day not just for Democrats, African Americans, and Americans who wanted a leadership change, but for left-handed Americans. The reason? Only 10 percent of the American population is left-handed, and Obama is one of this minority group.

In fact, four of the past six presidents—Gerald Ford, Ronald Reagan, George H.W. Bush, and Bill Clinton—were also left-handed, demonstrating that in spite of the age-old prejudice and discrimination against left-handed individuals, "lefties may have the right cerebral stuff." Moreover, many other famous people have been, or are, left-handed—the Roman general Julius Caesar, the Renaissance painter Michelangelo, American novelist Mark Twain, Beatle Paul McCartney, television mogul Oprah Winfrey, and Supreme Court Justice Ruth Bader Ginsberg.

Some scientific studies also attest to the positive mental aspects of being left-handed or ambidextrous.

Two Pakistani researchers explored the effect of handedness on the intelligence level of students. The sample included an equal number of left-handed and right-handed students drawn from various universities in Pakistan, altogether 150 subjects. Subjects were assessed for both handedness and intelligence. The researchers found no significant difference in intelligence between subjects from various educational levels, but they did find that left-handed subjects were significantly more intelligent than right-handed subjects. Results were published in the January 2007 *Journal of the Indian Academy of Applied Psychology*.

In a study of 250 healthy undergraduate students, ambidextrous individuals were found to engage in more magical ideation than either left-handed or right-handed persons were. Such ideation, the researchers proposed, may reflect heightened creativity. Study results appeared in the January 2002 *Laterality: Asymmetries of Body, Brain, and Cognition*.

Then Johns Hopkins economists determined, in a nationally representative sample of 5,000 men and women, that left-handed college-educated men earned 15 percent more than right-handed college-educated men did, even after possibly confounding factors such as age, race, IQ, level of education, and marital status were considered.

"Our findings are quite contrary to expectations," they acknowledged in their study report, which was published by the National Bureau of Economic Research in 2006. However, they did not find the same wage differential for women in the sample.

Nonetheless, some studies reported in the psychiatric research literature suggest that being left-handed or ambidextrous has another side—that left-handed or ambidextrous persons are more likely to have certain mental disorders than right-handed persons are. Moreover, the number of these studies, as well as their quality, intimate that the links they have made between left-handedness or ambidexterity and mental disorders are not simply related to chance.

During the 1970s and 1980s, for instance, some studies noted what appeared to be an unusually large percentage of left-handed or ambidextrous people among those with autism, dyslexia, stuttering, or neurodevelopmental disorders. Much more recently, *DSM-IV* developmental coordinational disorder (DCD), which can impair both large and fine motor skills and make everyday activities such as getting dressed, writing by hand, and participating in sports difficult, has also been coupled with left-handedness. In the February 2008 *Journal of Child Neurology*, two Israeli scientists reported that out of 98 children with DCD, 31 percent were left-handed, and 13 percent were ambidextrous. In the October 2008 *Canadian Journal of Psychiatry*, Canadian researchers reported that out of 19 children with DCD, 37 percent were left-handed.

An unusually large number of persons with schizophrenia also appear to be left-handed. In one study, some 400 subjects with schizophrenia, major depression with psychosis, bipolar psychosis, or no psychiatric illness were evaluated on handedness. The schizophrenia subjects were left-handed significantly more often than the other groups were, the researchers reported in the May 1994 *Journal of Abnormal Psychology*.

Tyrone Cannon, Ph.D., a professor of psychiatry at the University of California at Los Angeles, and coworkers have since discovered, while comparing the childhood neurocognitive test results of individuals with schizophrenia with those of their siblings or controls—altogether 258 subjects—that 32 percent of those with schizophrenia were left-handed, compared with only 12 percent of their siblings and only 9 percent of the controls. These results were published in the November 2003 *American Journal of Psychiatry*.

Further, Clyde Francks, Ph.D., of the University of Oxford in England, and his team reported something intriguing in the July 31, 2007, *Molecular Psychiatry*—that they had found a gene that increases the odds of being left-handed. The gene, dubbed LRRTMI, appears to be the first gene discovered that has an effect on handedness. They also found that the gene might slightly increase the risk of developing schizophrenia.

Credit: AP Photo

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Some famous left-handed people (clockwise from upper left): Gerald Ford, Paul McCartney, Bill Gates, and Babe Ruth.

PTSD: A View From the Left

Posttraumatic stress disorder (PTSD), too, has been coupled with left-handedness. Two Scottish researchers—Carolyn Choudhary, Ph.D., and Ronan O'Carroll, Ph.D., of the University of Stirling—screened a general population sample of some 600 people for handedness and PTSD. They found that 11 percent of the sample was left-handed, that 9 percent of the sample met all *DSM-IV* criteria for PTSD, and that significantly more left-handers than right-handers comprised the PTSD group. Results were reported in the June 2007 *Journal of Traumatic Stress*.

PTSD has likewise been associated with ambidexterity. A study of some 2,500 U.S. Army veterans found that veterans who were extremely ambidextrous (about 3 percent of the study sample) were twice as likely to have developed PTSD after combat as were veterans who were not extremely ambidextrous. Veterans who were extremely ambidextrous and who experienced especially high combat exposure were nearly five times as likely to have developed PTSD after combat as were those who were not extremely ambidextrous and who experienced especially high combat exposure. Study results, published in the May 17, 2007, *Psychosomatic Medicine*, held firm even when some possibly confounding factors such as age, race, intelligence, and age at entry into the Army were considered.

But perhaps the greatest surprise is that left-handedness has been linked with a mental disorder considered more psychosocial than biological in origin—pedophilia. James Cantor, Ph.D., an assistant professor of psychology at the University of Toronto in Canada, and colleagues found, in a study of some 400 sexual offenders, that the odds of being left-handed were about two times greater among pedophiles than among sexual offenders targeting adults as their victims. In fact, more than 30 percent of the pedophiles were left-handed, that is, three times the rate in the general population. Results were published in the August 2005 *Archives of Sexual Behavior*.

Researchers Offer Theories

So, since left-handedness and ambidexterity have been linked with certain neurodevelopmental disorders, schizophrenia, PTSD, and pedophilia, what might that link be?

Left-handedness and ambidexterity may share some underlying biological origins with them, some researchers contend.

For example, Choudhary and O'Carroll do not believe that the reason why left-handed persons are more likely to develop PTSD is because they are more at risk of trauma in a right-handed world than are right-handed people. The reason why is because they found no significant difference between the number of traumas experienced by left-handed subjects and by right-handed ones. However, the researchers do suspect that the reason that left-handed

please see ***Left-Handed*** *on facing page*

Joan Arehart-Treichel is left-handed.

COMPILED BY JUN YAN

Regulatory Briefs

• The maker of ***risperidone long-acting injection***, Johnson and Johnson Pharmaceutical Research and Development (J&JPRD), announced on February 10 that it had received a "complete response letter" from the Food and Drug Administration (FDA) requesting additional information about the medication. The agency's letter was in response to the company's supplemental application, which sought approval for the new indication of adjunctive maintenance treatment for patients with bipolar disorder who relapse frequently. According to the company's announcement, the agency outlined questions that must be answered before the application can be approved, but did not require that more clinical trials be conducted.

Risperidone long-acting injection is currently approved for the treatment of schizophrenia.

• The FDA sent a complete response letter to Eli Lilly regarding its application for marketing ***olanzapine pamoate long-acting injection*** for treatment of schizophrenia. Lilly said the FDA requested the company to provide a detailed plan on postmarketing strategies for safety surveillance. The agency has been concerned about uncommon but potentially severe adverse events associated with the drug in clinical trials. These adverse events included heavy sedation, confusion, and loss of consciousness in some cases. The FDA convened an advisory-committee meeting about the medication a year ago and has not approved the product since then (*Psychiatric News*, March 21, 2008). Lilly said it was preparing a Risk Evaluation and Mitigation Strategy as requested and would submit it to the agency soon.

• Schering-Plough, the company seeking regulatory approval for the investigational antipsychotic drug ***asenapine sublingual tablets***, announced on January 14 that it received the FDA's complete response letter for the new drug application. The agency asked for additional data and proposed labeling language, but did not request that the company conduct additional clinical trials. The company is seeking approval for its indications as a treatment for schizophrenia and manic or mixed bipolar disorder episodes.

• The FDA sent a warning letter to Abbott Laboratories regarding "misbranding" information in promotional material about its products ***divalproex sodium delayed-release tablets*** (Depakote and Depakote ER). The letter noted that a pharmacy formulary flashcard omits certain risk and other important information and broadens indications in the drug information printed on the flashcard. The agency asked the company to stop distributing the materials immediately.

• The FDA issued a follow-up announcement on January 13 about the agency's safety review of potential neuropsychiatric risks associated with ***montelukast***. In March 2008 the FDA told the public that it was closely examining clinical trial evidence for a suspected link between the asthma/allergy drug and reports of mood changes, suicidal thoughts and behaviors, and suicides. About nine months later, the agency said it had not reached a definitive conclusion about the matter, and its review would continue.

• A new drug treatment for fibromyalgia, ***milnacipran hydrochloride***, has been approved by the FDA, the makers Forest Laboratories and Cypress Bioscience announced on January 14. Milnacipran is a selective serotonin and norepinephrine reuptake inhibitor and has been tested in two large, phase 3 clinical trials involving more than 2,000 patients. Two other drugs, pregabalin and duloxetine, have already been approved for treating fibromyalgia.

Legal Briefs

• U.S. Sens. Herb Kohl (D-Wis.) and Charles Grassley (R-Iowa) have proposed new legislation to outlaw pharmaceutical companies' deals intended to keep generic drugs off the market, according to an announcement by Kohl's office on February 3. In recent years large pharmaceutical companies that market brand-name "blockbuster" drugs have entered settlements with generic drug makers over patent disputes. The results were that the generic manufacturers would delay the marketing of generic versions of these drugs while receiving multimillion-dollar payments or other types of business compensation from the brand-name makers. The Federal Trade Commission has been investigating and opposing these deals, but they have been approved by courts.

The proposed legislation, known as the Preserve Access to Affordable Generics Act, will prohibit such pay-off agreements between brand-name and generic drug makers. The bill is cosponsored by Sens. Russ Feingold (D-Wis.), Richard Durbin (D-Ill.), and Sherrod Brown (D-Ohio).

• In January Sens. Grassley and Kohl introduced a revised version of legislation they had proposed two years before that had sought to require public disclosure of industry gifts and payments to physicians. This Physician Payments Sunshine Act of 2009 has lowered the threshold of gift value for disclosure from $500 in the previous draft to $100. If passed, the bill will require all drug, device, and biologic manufacturers to report their gifts and payments to physicians, including travel and consulting fees, valued above $100. A searchable database would be established by the Department of Health and Human Services to post this information for public access.

The previous bill received support from several major pharmaceutical companies, such as Eli Lilly, which have begun or announced plans to begin posting payments and gifts to physicians on their company Web sites. The latest company to get on the bandwagon was Pfizer, which said in a February 9 announcement that it would publicly disclose all gifts and payments above $500 to physicians starting in 2010.

• On January 28 a U.S. district court judge in Florida dismissed two multimillion-dollar lawsuits against AstraZeneca alleging that its antipsychotic drug ***quetiapine fumarate*** caused harm, including diabetes and weight gain. These suits were brought by the first two of 15,000 plaintiffs who have filed lawsuits in the United States for similar claims regarding the drug. The judge ruled that the lawsuits did not meet the standards required for a case to proceed to trial.

• Eli Lilly has settled civil lawsuits and a criminal charge with the federal government and about 30 state governments over its antipsychotic drug ***olanzapine*** for a massive $1.42 billion, according to a January 15 Associated Press report. The company pleaded guilty to a misdemeanor violation for promoting the drug for off-label use in patients with dementia from September 1999 to March 2001. The civil lawsuits were related to overcharging state Medicaid programs.

Industry Briefs

• J&JPRD announced on February 6 that it filed a new drug application with the FDA for expanding the indication of ***paliperidone tablets*** to schizoaffective disorder. Paliperidone is currently approved for treating schizophrenia. The company is also seeking FDA approval for ***paliperidone palmitate***, the long-acting injection formulation of paliperidone, for the treatment of schizophrenia.

• AstraZeneca has licensed a number of triple reuptake inhibitor molecules, discovered by Mayo Clinic and Virginia Tech Intellectual Properties Inc. scientists, that it hopes will lead to development of a new class of medication for depression treatment. According to a February 9 company announcement, these triple reuptake inhibitors are expected to interact with serotonin, norepinephrine, and dopamine receptors.

Currently available antidepressants affect the reuptake receptors of either serotonin or both serotonin and norepinephrine. The novel molecules will have to go through preclinical animal experiments before they can be tested in clinical trials.

• Supernus Pharmaceuticals announced on January 30 that it had begun a phase 2a clinical trial of ***SPN810***, an investigational drug for the treatment of conduct disorder in pediatric patients with attention-deficit/hyperactivity disorder. It would be a randomized, open-label trial lasting six weeks.

• ***NPL-2008***, a formulation of fluoxetine being tested for autistic disorder, disappointed in a phase 3 clinical trial, the company developing the drug, Neuropharm, announced on February 18. In this trial, 158 patients with autistic disorder aged 5 to 17 were treated with either NPL-2008 or placebo for 14 weeks, but the drug did not differ significantly from placebo in improving the symptom of repetitive behaviors. ■

Left-Handed

continued from facing page

individuals may be more likely to develop PTSD is because their brains are responding to, or processing, emotional events differently from the brains of right-handers.

Francks suspects that the gene LRRTMI might set the stage for both left-handedness and schizophrenia by influencing the development of brain asymmetry. Asymmetry is an important feature of the human brain, with the left side usually controlling speech and the right side controlling emotion. In left-handers, this pattern is usually reversed. Iris Sommer, M.D., Ph.D., of the University of Utrecht in the Netherlands, agreed with Francks. In fact, she has found that, just as speech often originates in the right side of the brain in left-handed persons, it is also the case for persons with schizophrenia.

And as for why left-handed persons may be disproportionately represented among known pedophiles, Cantor believes that the answer may lie in brain characteristics common to both conditions.

In any event, even if left-handedness and ambidexterity share common biological pathways with some mental disorders, left-handed individuals should not conclude that they will necessarily develop these mental disorders, authorities on the subject stress.

For example, regarding the finding that Francks and his colleagues have made—that the gene that predisposes to left-handedness may also increase the risk of schizophrenia—"People really should not be concerned by this result," he said. "There are many factors which make individuals more likely to develop schizophrenia, and the vast majority of left-handers will never develop the problem."

As for Choudary and O'Carroll's finding that left-handers are significantly more at risk of PTSD, Choudhary said, "The development of PTSD is multifactorially determined and incompletely understood. In this context, left-handedness seems to be an important part of the jigsaw and one previously neglected, but though apparently important, is only one determinant of who might develop PTSD following trauma."

All in all, Choudhary stressed, "The majority of left-handers are not going to develop mental health problems because of their left-handedness."

Cantor agreed: "The association between left-handedness and disease is very complex . . . Being left-handed does not make a person appreciably more likely to have any given disease."

So being left-handed or ambidextrous, like virtually everything in life, has both its pluses and minuses. And if you are left-handed or ambidextrous, why not try to capitalize on your mental strengths—say, exceptional intelligence, economic shrewdness, or creativity? Who knows, you might even become president! ■

No Matter Your Passion, There's a Session to Pique It

The theme of APA's 2009 annual meeting is "Shaping Our Future: Science and Service." Among the meeting's new features is the "Clinical Knowledge and Skills Series" of courses.

BY STEPHANIE WHYCHE

Credit: SFCVB photo by Phil Coblentz

Thinking about attending APA's May 16-21 annual meeting in San Francisco? As returning members already know (and newcomers will soon discover), the things to do and places to go are as captivating as the "City by the Bay's" skyline.

APA members the world over will gather May 16 to 21 for the annual meeting in San Francisco, the City by the Bay known for its Mediterranean-like temperatures, ubiquity in song, and multicultural offerings.

Exactly what is so attractive about San Francisco that it draws tens of thousands of tourists each year and is one of the country's most popular convention sites?

"What's not to like about San Francisco?" asked Josepha Cheong, M.D., of Gainesville, Fla., chair of APA's Scientific Program Committee for the annual meeting and a former resident of San Francisco for 20 years.

Among the city's many plusses, Cheong noted, are "the weather, the great vistas, the history, the shopping, the vibrant arts and performance culture, and all of the different walking neighborhoods and parks."

Indeed, there are Golden Gate Park, Union Square, Nob Hill, Telegraph Hill, Russian Hill, Castro District, Haight-Ashbury, Chinatown, the Italian enclave of North Beach, Fisherman's Wharf, and Pier 39, to name a few.

"Best of all [is] the variety of restaurants and culinary options," said Cheong.

Yes, the city will offer exciting attractions, but the real star of the show is APA's scientific program.

The theme of this year's meeting is "Shaping Our Future: Science and Service." It was chosen by APA President Nada Stotland, M.D., M.P.H., who has dedicated her professional life to applying the scientific principles of psychiatry in service to individuals, communities, and the public's health overall.

In keeping with this theme, both science and service will be reflected throughout the meeting's six days through interactive forums, lectures, courses, workshops, and symposia. Most are focused on the latest basic and applied research in psychiatry, while others explore topics that relate to the practice of psychiatry such as practice-management issues, health care economics, health information technology, psychiatry and the law, industry relationships, and ethics.

A featured attraction that's new to the meeting is the "Clinical Knowledge and Skills Series." It consists of three day-long courses chaired by master educators; the topics are cognitive-behavioral therapy, psychodynamic psychotherapy, and neuropsychiatry *(Psychiatric News*, February 20).

Meanwhile, psychiatrists preparing to take Part 1 of the ABPN board certification exam might be interested in registering for the May 16 ABPN board review course. That includes PGY-4 residents, who for the first time this year can sit for the test before their training has been completed. James Bourgeois, M.D., co-editor of the *APPI Board Prep and Review Guide for Psychiatry*, will lead the course. This course will be held Saturday, May 16, from 8 a.m. to 5 p.m.; course registration is required.

Check out the lecture by Dean Ornish, M.D., best-selling author of *Eat More, Weigh Less*, and other books, and founder and president of the nonprofit Preventive Medicine Research Institute in Sausalito, Calif. Ornish, a clinical professor of medicine at the University of California, San Francisco, will explore the impact of depression on cardiac health and vice versa.

The same day, past APA President Carolyn Robinowitz, M.D., will chair a symposium on depression and heart disease titled "Matters of the Heart."

Meanwhile, San Francisco—or at least two aspects of it—will be the topics of two of the seven Presidential Symposia. Addictions specialists Mark Gold, M.D., and David Smith, M.D., will present "Grandkids of the 1967 Flower Children: Lessons From Haight-Ashbury." Mel Blaustein, M.D., will lead the session "Suicide and the Golden Gate Bridge."

Blaustein also will introduce the showing of the documentary film "The Bridge." Eric Steel, the film's director, relates the stories of six individuals who during one recent year made use of the bridge to end their lives.

"The public is ambivalent about suicide, but suicide is very impulsive, and because it's impulsive, it's preventable and treatable," Steel said in a *San Francisco Chronicle* article that ran shortly before the film's April 30, 2006, West Coast premiere.

Here are other meeting highlights:

• The Northern California Psychiatric Society is sponsoring a panel discussion featuring APA leaders who were at the forefront of social change in the period 1970 to 1992. They include Alfred Freedman, M.D., who was APA president when APA's Trustees voted in 1973 to remove homosexuality as a mental disorder from *DSM*; Carol Nadelson, M.D., APA's first woman president; Lawrence Hartmann, M.D., APA's first openly gay president; and Melvin Sabshin, who was APA's medical director from 1974 to 1997. The session will also include a discussion of Harvey Milk, San Francisco's first openly gay supervisor, by his campaign manager and aide, Anne Kronenberg. She will show film clips of the film "Milk." The session, titled "Breaking the Barriers," will be held Monday, May 18, at 2 p.m. in Room 304 on the Esplanade Level of the Moscone Center.

• The American Psychiatric Foundation is holding its annual fundraising gala on Saturday, May 16, at 7 p.m. at the picturesque Ferry Building overlooking San Francisco Bay. In addition to dinner, the evening's program includes a silent auction and the presentation of the Awards for Advancing Minority Mental Health. Event proceeds support the foundation's grants, programs, research funding, and awards that advance public understanding that mental illnesses are real and treatable. The ticket price is $225. Tickets may be purchased online at <www.psychfoundation.org> or by phone at (703) 907-8503.

please see ***Session*** *on page 30*

REGISTER NOW FOR THE MEETING!

There are three easy ways to register for APA's 2009 annual meeting and courses, and you can save on fees by registering before **April 10.** Forms to register by mail or fax can be printed out from the annual meeting booklet posted at <www.psych.org/MainMenu/EducationCareerDevelopment/Meetings/AdvanceRegistrationInformation.aspx>.

REGISTER ONLINE

Click on the 2009 annual meeting logo on APA's homepage at <www.psych.org> or go directly to <www.psych.org/MainMenu/EducationCareerDevelopment/Meetings.aspx> and then look for "Meeting Registration." "Housing Registration" can also be found here.

FAX REGISTRATION FORM

Fax your completed registration form with credit card information to (703) 907-1097.

MAIL REGISTRATION FORM

Mail your completed registration form and payment by credit card or check made payable to APA to Registration, APA, Suite 1825, Arlington, Va. 22209-3901.

After April 10, you may register online only (on-site fees apply), not by mail or fax.

APA Minority Fellows In the Spotlight

The work of APA's minority fellows will be celebrated at the Evening of Excellence Poster Session at APA's 2009 annual meeting in San Francisco on **Tuesday, May 19, from 5:30 p.m. to 7 p.m.** at the Marriott San Francisco Hotel. The event is open to all attendees and is one of the highlights of the fellows' activities at the annual meeting. Come see what these fine young minds are accomplishing in the field of psychiatry. Below are their names and poster titles:

Farah Abbasi, M.D.: "Accept: Redefining Cultural Competence, Learning to Coexist"

Shirin Ali, M.D.: "Management of Prolactinoma in a Patient With Schizophrenia"

Icelini Garcia-Sosa, M.D.:"Conviction and Doubt in Delusions"

Helena Hansen, M.D., Ph.D.: "Ethnicity and Social Class in Distribution of Buprenorphine Versus Methadone for Opiate Dependence in New York City: A Tale of Two Tiers?"

Lorraine Lothringer, M.D.: "A Brazilian HIV Prevention Intervention for Adults With Severe Mental Illness: A Randomized Clinical Trial Feasibility Study"

Shirley Liu, M.D.: "Cultural Factors in Use of the CBCL and Conners' Scale in Asian and Caucasian Children in a Clinical Setting"

Kristen Ochoa, M.D.: "Mentally Ill Immigration Detainees: Evaluation, Treatment, and Advocacy for a Hidden Population in Need"

Suzan Song, M.D.: "When the War Isn't Over for the Children: Mental Health Policy for Former Child Combatants and War-Affected Youth"

Wendy Woods, M.D.: "Resident-Facilitated Exploration of the Attitudes and Perceptions Regarding Mental Illness and Mental Health Professionals Observed in a Sample African-American Population"

Come to the Mentor Orientation Breakfast as Well!

You can be a part of APA's important work in fostering the careers and development of your younger minority colleagues by joining APA's National Minority Mentors Network.

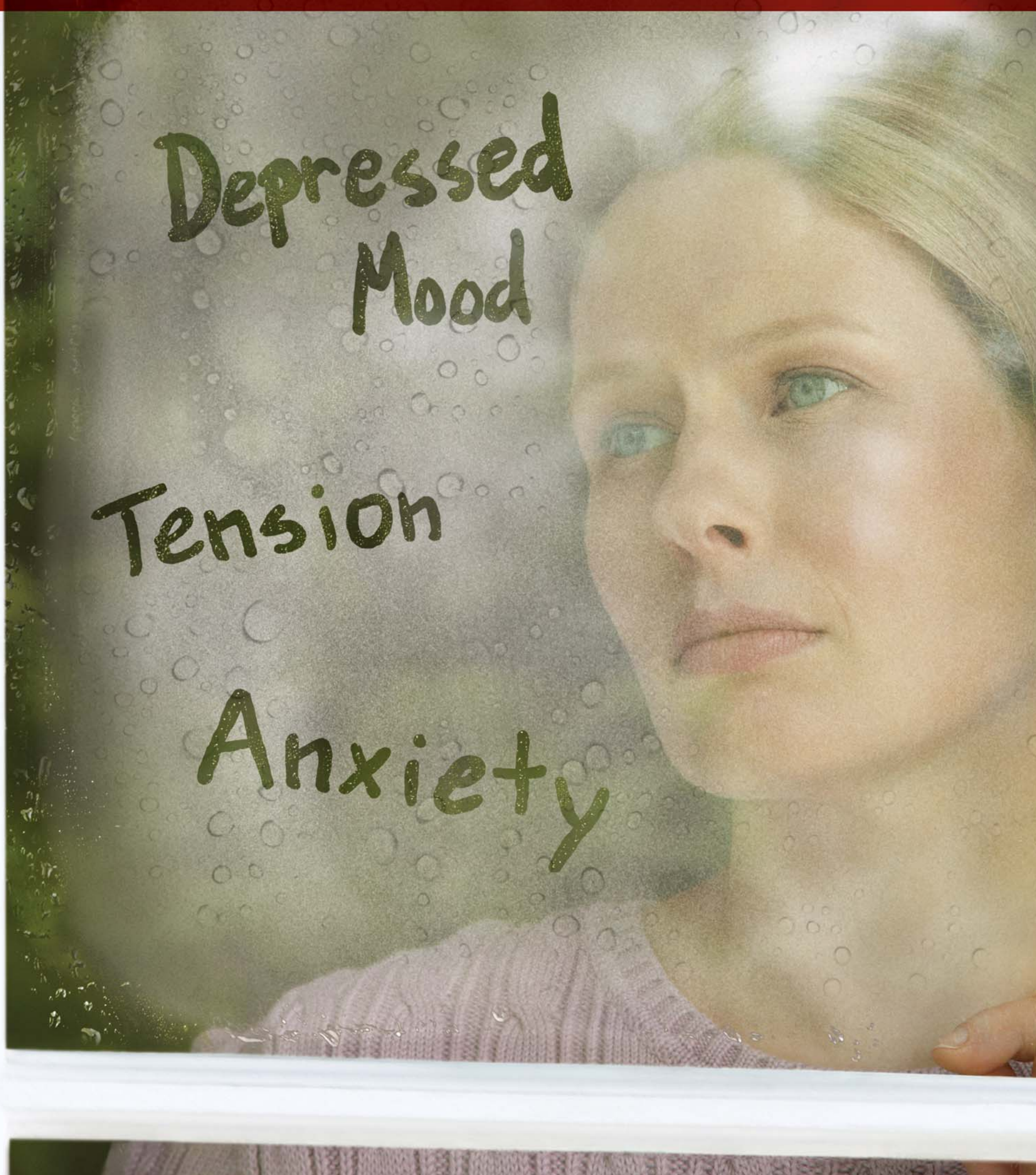
APA members interested in joining the National Minority Mentors Network and are coming to APA's 2009 annual meeting in San Francisco are invited to attend the mentor orientation breakfast for current fellows and medical students on **Sunday, May 17, 7:30 a.m. to 10 a.m.** Mentors play an important role in the professional growth and development of beginning psychiatrists and are critical to fostering successful careers in psychiatry and ensuring the field's future success.

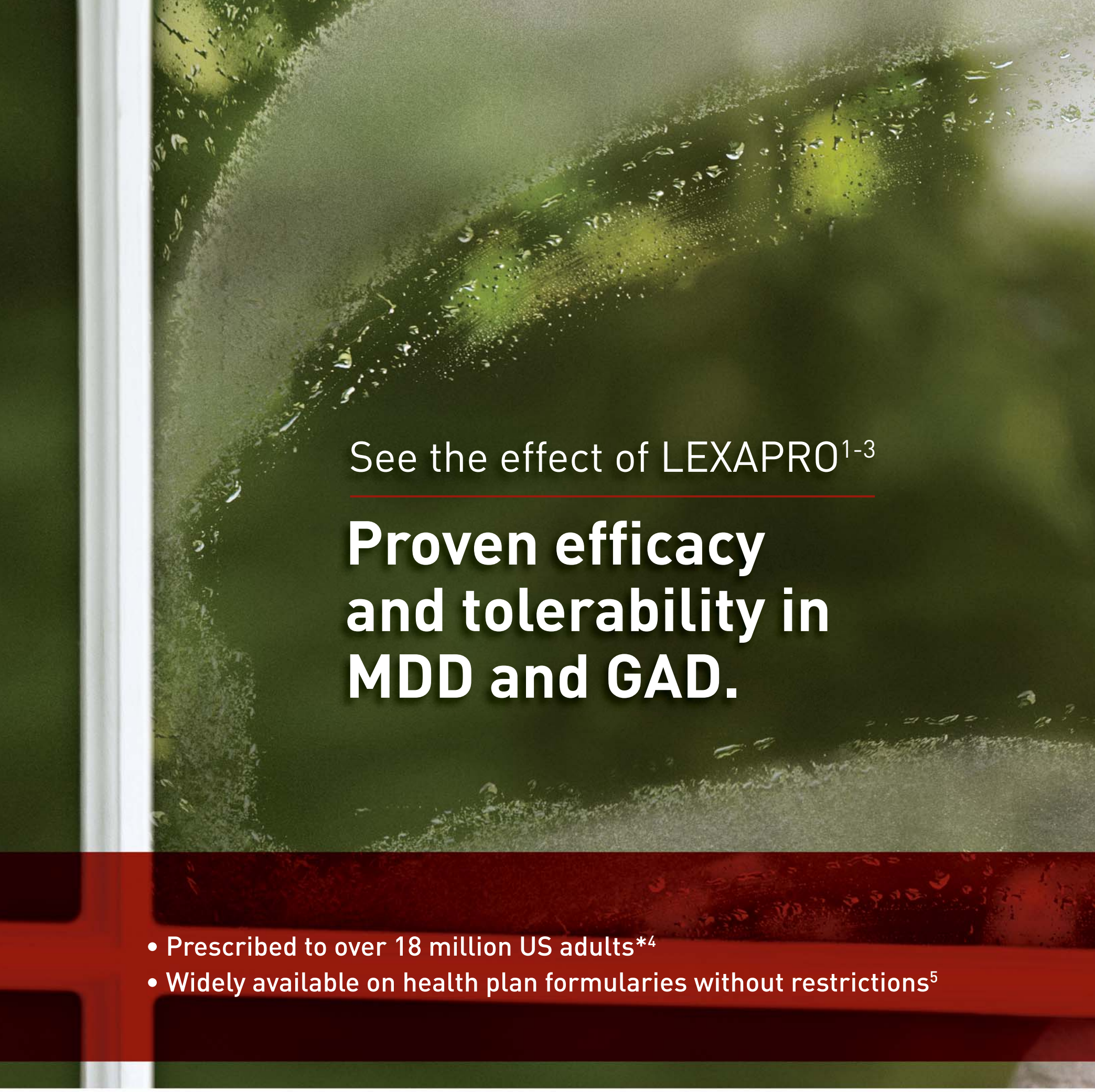
There are a large number of residents and medical students attending the mentor breakfast again this year. To make this a worthwhile and enjoyable activity, the commitment and support of APA members are urgently needed.

Those interested in joining or obtaining additional information about the network should contact Marilyn King at (703) 907-8653 or mking@psych.org. Reservations for the breakfast may also be made by contacting her.

Treat core symptoms[1,2]

of Major Depressive Disorder (MDD) & Generalized Anxiety Disorder (GAD)





*Lexapro Market Overview. Patient level report based on longitudinal analysis of US electronic pharmacy claims submitted for third-party reimbursement. Patients projected based on their activity in retail pharmacies.

IMPORTANT SAFETY INFORMATION – Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Antidepressants increased the risk of suicidality (suicidal thinking and behavior) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of antidepressants in children, adolescents or young adults must balance the risk to clinical need. Patients of all ages started on antidepressant therapy should be closely monitored and observed for clinical worsening, suicidality or unusual changes in behavior, especially at the beginning of therapy or at the time of dose changes. This risk may persist until significant remission occurs. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients.

Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), pimozide (see DRUG INTERACTIONS – Pimozide and Celexa), or in patients with hypersensitivity to escitalopram oxalate. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Lexapro. SSRIs and SNRIs (including Lexapro) and other psychotropic drugs that interfere with serotonin reuptake may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to the risk. Patients should be cautioned about these risks. SSRIs and SNRIs have been associated with clinically significant hyponatremia. Elderly patients or patients taking diuretics or who are otherwise volume-depleted appear to be at a greater risk. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia, and appropriate medical intervention should be instituted. The most common adverse events with Lexapro versus placebo (approximately 5% or greater and approximately 2x placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia.

Please see the accompanying brief summary of prescribing information for LEXAPRO.

References: 1. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry.* 2002;63: 331-336. **2.** Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety.* 2004;19:234-240. **3.** LEXAPRO [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2008. **4.** Surveillance Data, Inc. (SDI), April 2008. **5.** Data on file, Forest Laboratories, Inc.

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

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

INDICATIONS AND USAGE Major Depressive Disorder Lexapro (escitalopram) is indicated for the treatment of major depressive disorder. The efficacy of Lexapro in the treatment of major depressive disorder was established in three, 8-week, placebo-controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-IV category of major depressive disorder (see **CLINICAL PHARMACOLOGY**). 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, a suicide attempt or suicidal ideation. The efficacy of Lexapro in hospitalized patients with major depressive disorders has not been adequately studied. The efficacy of Lexapro in maintaining a response, in patients with major depressive disorder who responded during an 8-week, acute-treatment phase while taking Lexapro and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). Nevertheless, the physician who elects to use Lexapro for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**). **Generalized Anxiety Disorder** Lexapro is indicated for the treatment of Generalized Anxiety Disorder (GAD). The efficacy of Lexapro was established in three, 8-week, placebo-controlled trials in patients with GAD (see **CLINICAL PHARMACOLOGY**). Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. The efficacy of Lexapro in the long-term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Lexapro for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. **CONTRAINDICATIONS** Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**). Concomitant use in patients taking pimozide is contraindicated (see **Drug Interactions – Pimozide and Celexa**). Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro. **WARNINGS WARNINGS-Clinical Worsening and Suicide Risk Clinical Worsening and Suicide Risk** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1. TABLE 1: Age Range and Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated:** Increases Compared to Placebo; <18 (14 additional cases); 18-24 (5 additional cases); Decreases Compared to Placebo; 25-64 (1 fewer case); ≥65 (6 fewer cases). No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with Lexapro**, for a description of the risks of discontinuation of Lexapro). **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.** ***Serotonin Syndrome:*** The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Lexapro treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS - Potential for Interaction with Monoamine Oxidase Inhibitors**.) If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS - Drug Interactions**). The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS - Drug Interactions**). **PRECAUTIONS General** Discontinuation of Treatment with Lexapro During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION**). Abnormal Bleeding SSRIs and SNRIs, including Lexapro, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation. Hyponatremia Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Lexapro was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk (see **Geriatric Use**). Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Activation of Mania/Hypomania In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. Interference with Cognitive and Motor Performance In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. Use in Patients with Concomitant Illness Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION**). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION**). **Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe Lexapro. Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Lexapro and triptans, tramadol or other serotonergic agents. In a study in normal volunteers, Lexapro 10 mg/day did not impair psychomotor performance. The effect of Lexapro on psychomotor coordination, judgment, or thinking has not been systematically examined in controlled studies. Because psychoactive drugs may impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. Patients should be told that, although Lexapro has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Lexapro and alcohol in depressed patients is not advised. Patients should be made aware that escitalopram is the active isomer of Celexa (citalopram hydrobromide) and that the two medications should not be taken concomitantly. Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions. Patients should be cautioned about the concomitant use of Lexapro and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breastfeeding an infant. While patients may notice improvement with Lexapro therapy in 1 to 4 weeks, they should be advised to continue therapy as directed. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Lexapro and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for Lexapro. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Lexapro. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. **Laboratory Tests** There are no specific laboratory tests recommended. **Concomitant Administration with Racemic Citalopram** Citalopram - Since escitalopram is the active isomer of racemic citalopram (Celexa), the two agents should not be coadministered. **Drug Interactions Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS-Serotonin Syndrome**). The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended (see **PRECAUTIONS - Drug Interactions**). **Triptans:** There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - Serotonin Syndrome**). CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol - Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS**. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued. Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium - Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. Pimozide and Celexa - In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. Theophylline - Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Warfarin - Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine - Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. Triazolam - Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole - Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. Ritonavir - Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. CYP3A4 and -2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. Drugs Metabolized by Cytochrome 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** Pregnancy Category C In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Pregnancy-Nonteratogenic Effects** Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**). Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery** The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers** Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or Lexapro therapy should take into account the risks of citalopram exposure for the infant and the benefits of Lexapro treatment for the mother. **Pediatric Use** Safety and effectiveness in the pediatric population have not been established (see **BOXED WARNING** and **WARNINGS—Clinical Worsening and Suicide Risk**). One placebo-controlled trial in 264 pediatric patients with MDD has been conducted with Lexapro, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Lexapro in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use** Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS**, Hyponatremia). In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see **CLINICAL PHARMACOLOGY**). 10 mg/day is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION**). Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse event information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder** Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder** Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder Table 2** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 2**). **TABLE 2: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event [Lexapro (N=715) and Placebo (N=592)]: Autonomic Nervous System Disorders:** Dry Mouth (6% and 5%); Sweating Increased (5% and 2%). **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%). **Gastrointestinal Disorders:** Nausea (15% and 7%); Diarrhea (8% and 5%); Constipation (3% and 1%); Indigestion (3% and 1%); Abdominal Pain (2% and 1%). **General:** Influenza-like Symptoms (5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1%); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder[1,2] (9% and <1%); Impotence[2] (3% and <1%); Anorgasmia[3] (2% and <1%).*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=225 Lexapro; N=188 placebo). [3]Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see **TABLE 3**). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event [Lexapro (N=429) and Placebo (N=427)]: Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder[1,2] (14% and 2%); Anorgasmia[3] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=182 Lexapro; N=195 placebo). [3]Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125): Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%).*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials** [In Males Only: **Adverse Event: Lexapro** (N=407) **and Placebo** (N=383)]: Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). [In Females Only**: Lexapro** (N=737) **and Placebo** (N=636)]: Libido Decreased (3% and 1%); Anorgasmia (3% and <1%). There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only: N=905 Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during postmarketing spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

Canadian System Works

It was good to see the letter from Nancy Porter-Steele, Ph.D., in the January 2 issue recommending the Canadian health system. I was a colleague and friend of her husband, Curtis Steele, M.D., when we were both practicing in Baton Rouge, La., in the 1960s and 1970s. I always wondered where he'd gone after I left town and we "lost touch."

For many reasons, I have been concerned about the future of private practice for many years and am now a supporter of a single-payer health system by gradually bringing everyone under Medicare (which has cared for me so well since I developed cancer and have had other problems). I finally solved most of my problems with private practice by going into public psychiatry. Dr. Steele went to Canada.

Furthermore, I frequently share meals with Canadian physicians at a bed-and-breakfast during annual trips to the Shaw Festival at Niagara-on-the-Lake in Ontario. Although I have not talked to any orthopedic surgeons (waiting lists for hip replacements?), I find that the primary care physicians who stay at the same place are quite satisfied with their practice arrangements and compensation, and as Nancy Steele describes in detail, they particularly like the low overhead and lack of "hassle." It would be interesting and useful to see letters from others with similar or different experiences in foreign practice in *Psychiatric News*.

JOHN L. KUEHN, M.D.
Medina, Ohio

Ethics Lesson

Thanks to Dr. Stotland for her January 16 column, which was both about, and not about, the man who is no longer governor of Illinois. Her column was a "lemons-to-lemonade" accomplishment on her part. She managed to turn a major embarrassment for our state into an opportunity to educate the public, and our membership, about a not-too-well-known section of our ethics code.

As chair of the Illinois Psychiatric Society's Ethics Committee, I'm aware that the so-called "Goldwater Rule"—the prohibition on APA members making public diagnoses of public figures—is not widely known. One only has to watch major news outlets to see members of various mental health professions violating this ethical canon. The resignation of Gov. Spitzer of New York and recent events in Illinois both provoked such comments.

If we impressionistically feel a public figure is harming the public, it's tempting but still wrong to publicly diagnose that individual. This would lead us down a path fraught with risk to people in public life, to our profession, and to society at large. Were we to ignore this ethics rule, public figures could be stigmatized, psychiatrists would hurt the reputation of our profession by acting outside the bounds of our expertise (diagnosing people we've never met, without their consent), and society might miss the chance to hold politicians and others accountable for their behavior through the psychiatrist's perceived grant of a pathological "excuse."

By the same token, our knowledge and experience may make us think it likely a public figure suffers from a mental disorder, but we must remember that true psychiatric diagnosis is based on a careful and objective weighing of information, and that information should be obtained directly from the person being diagnosed, at their request or at least with their consent.

As professionals with a responsibility to society as well as to our patients, we must resist the urge to assign a diagnosis to those in public life because of the harm it could do both to public discourse and to our own profession. Thanks, Dr. Stotland, for reminding us, and the public, of this important principle.

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Hinsdale, Ill.

Readers are invited to submit letters not more than 500 words long for possible publication. *Psychiatric News* reserves the right to edit letters and to publish them in all editions, print, electronic, or other media. Receipt of letters is not acknowledged. Letters should be sent by mail to *Psychiatric News*, APA, Suite 1825, 1000 Wilson Boulevard, Arlington, Va. 22209 or by e-mail to pnews@psych.org. Clinical opinions are not peer reviewed and thus should be independently verified.

Advertising

continued from page 2

gets remain flat or decline in the current economic climate.

However, the return on investment can be much more unpredictable. In the vast and rapidly morphing online world, how to grab and hold the attention of fickle users is still the biggest challenge and one that still leaves marketers scratching their heads.

Regulating promotions of medications in the new media poses new challenges. The Food and Drug Administration (FDA) Division of Drug Marketing, Advertising, and Communications (DDMAC) is in charge of regulating all marketing and promotional activities of pharmaceutical and medical-device companies. In 2008, for example, the DDMAC sent a warning letter to Shire regarding a YouTube video for Adderall XR featuring celebrity Ty Pennington that "overstate[d] the efficacy of Adderall XR" and "omit[ted] important information regarding the risks associated with" the drug. Shire withdrew the video.

"DDMAC has been and continues to monitor the many vehicles that companies use to promote their prescription drug products . . . including magazine ads, TV ads, promotional exhibits at medical conferences, Internet. . . ," Karen Mahoney, an FDA spokesperson told *Psychiatric News*. "Internet monitoring includes promotion done by or on behalf of drug companies such as on companies' own product Web sites and their placement of promotion on others' Web sites." She pointed to the FDA's actions on the Shire YouTube video as an example of the agency's effort to monitor such promotions. ■

community news

Century

continued from page 14

A year later, he created the National Committee for Mental Hygiene, which was renamed the Mental Health Association in 1976, the National Mental Health Association in 1980, and Mental Health America in 2006.

In 1917 the committee drafted a mental hygiene program at the behest of the U.S. Surgeon General, and in the 1920s it developed a set of model commitment laws, which was adopted by several states.

In the 1930s the committee convened the First International Congress on Mental Hygiene in Washington, D.C. More than 3,000 people from all over the world attended.

In the decades that followed, the committee continued to play an active role in mental health advocacy. In 1946 it was one of the leading advocate organizations working for passage of the National Mental Health Act, which established the National Institute of Mental Health.

In 1953 it commissioned the casting of the Mental Health Bell, which was forged from melted chains and shackles used to restrain people with mental illness. The bell has served as the organization's symbol ever since.

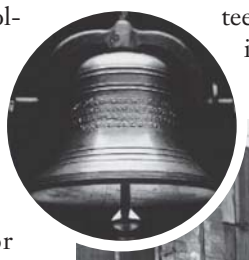
MHA President and CEO David Shern, Ph.D., told *Psychiatric News* that the Mental Health Bell has long served as a "reminder that the invisible chains of misunderstanding and discrimination still bind people."

He added that over the years, leaders in the mental health field have rung the bell to mark important achievements such as the passage of legislation to mandate insurance parity.

"It will continue to ring out in the future—for progress in improving mental health and achieving victory over mental illnesses and addiction disorders," he stated.

Members of the National Committee for Mental Hygiene worked to enact various pieces of legislation, including the Community Mental Health Centers Act, which authorized construction grants for community mental health centers and pushed for deinstitutionalization.

In the ensuing decade, the committee forced the release of $52 million in impounded government funds meant to establish community mental health centers and demanded, successfully, that the question "Have you ever been mentally ill?" be removed from federal employment applications.



Photos courtesy of Mental Health America

Maryland Gov. Theodore McKeldin and Mrs. A. Felix DuPont in 1953 pour the metal made from melted chains used to restrain people with mental illnesses to create the Mental Health Bell, which has since served as the symbol for Mental Health America.

In the 1980s and 1990s under its new name, the National Mental Health Association, the organization continued to add to its list of achievements. Among these are

- working to pass the Protection and Advocacy for Mentally Ill Individuals Act (1986),
- organizing the National Action Commission on the Mental Health of Rural Americans (1987), and
- helping to secure passage of the 1996 Mental Health Parity Act, the first federal legislation to implement some aspects of parity in health coverage for 9 million federal workers and their families.

In 2008 further progress was made on the parity front when MHA participated with a number of other advocacy and professional organizations—including APA—to ensure that the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 became law.

"As we celebrate our centennial year," Shern said, "Mental Health America is determined to continue our work to make mental health integral to overall health and promote wellness, prevention, early intervention, education, and access to care for everyone who has a mental or substance use condition."

More information about Mental Health America is posted at <www.nmha.org>. ■

Election Results

continued from page 1

life and their professional association than did the psychiatrists who preceded them and built the current APA. Bernstein, a longtime educator, said, "I have devoted my career to preparing the next generation of psychiatrists, and this is the time for APA to reshape itself so it can better meet the needs of patients, future psychiatrists, and those now beginning their careers."

Jeffrey Geller, M.D., of Massachusetts won the three-way race to succeed Bernstein as vice president. He received 55.7 percent of the vote after the preferential ballot plan was applied. Coming in second was Area 4 Trustee Sidney Weissman, M.D., of Chicago, followed by former Assembly Speaker Jeffrey Akaka, M.D., of Honolulu.

Under the preferential voting system, which is used in races with more than two candidates, voters are asked to rank the candidates in the order in which they would like to see them win. If no candidate garners a majority in the first round of counting, the candidate with the lowest number of votes is eliminated—in this case that was Akaka—and the second-choice votes on the ballots cast for him or her are redistributed to the remaining candidates. Geller received a majority after the redistributed votes were apportioned between him and Weissman.

Each year one of APA's three trustee-at-large positions is open for election, and this year it was the one reserved for an early career psychiatrist. The winner was Joyce Spurgeon, M.D., of Louisville, Ky., who outpolled Harsh Trivedi, M.D., of Providence, R.I. Spurgeon received 57.2 percent of the vote.

Three of APA's Areas also elected trustees this year, and two of the three victors will be joining the Board for the first time.

In Area 1 the new trustee will be Frederick Stoddard Jr., M.D., of Boston, who won 55.2 percent of the vote to defeat Robert Feder, M.D., of Manchester, N.H. Area 1 includes the New England states plus the Canadian district branches for Ontario and for Quebec and Eastern Canada.

The new Area 4 trustee will be John Wernert, M.D., of Indianapolis. He received 64.4 percent of the vote against his opponent, Sul Ross Thorward, M.D., of Columbus, Ohio. Area 4 is composed of the Midwestern states.

In Area 7, which includes the Rocky Mountain states, Alaska, Hawaii, the West Coast except for California, and Western Canada, William Womack, M.D., of Seattle won a second term on the Board. He garnered 51.3 percent of the vote in defeating Constance Powell, M.D., of Portland, Ore.

A trio of candidates also competed for the Board's member-in-training trustee-elect (MITTE) position. Kayla Pope, M.D., a Children's National Medical Center/National Institute of Mental Health child psychiatry fellow, emerged the winner. She received 53.2 percent of the votes after those of the third-place finisher, Erick Cheung, M.D., were redistributed between her and Laura Kent, M.D., who came in second. Cheung is a resident at the University of California at Los Angeles, and Kent is a resident at New York State Psychiatric Institute/Columbia Presbyterian Medical Center.

All of the newly elected officers and trustees take office at the close of the 2009 annual meeting in May. Also at that time President-elect Alan Schatzberg, M.D., will become president, and Melinda Fierros, M.D., currently the MITTE, will become the member-in-training trustee.

A total of 9,403 members voted this year, 31.5 percent of those eligible to vote. This percentage was about the same as in last year's election. There was, however, a substantial jump in members who chose to vote online rather than through a mailed, paper ballot. While each of the last two elections has seen about one-third of members voting online, this year 42 percent did so. ■

President-Elect

- Carol A. Bernstein, M.D. 4,685 50.5%
- Roger Peele, M.D. 2,745 29.6%
- Michael Blumenfield, M.D. 1,846 19.9%

Total votes: 9,276

Vice President

FIRST ROUND

- Jeffrey Geller, M.D., M.P.H. 3,451 38.3%
- Sidney H. Weissman, M.D. 2,925 32.5%
- Jeffrey Akaka, M.D. 2,635 29.2%

Total votes: 9,011

SECOND ROUND

- Jeffrey Geller, M.D., M.P.H. 4,576 55.7%
- Sidney H. Weissman, M.D. 3,633 44.3%

Total votes: 8,209

ECP Trustee-at-Large

- Joyce Spurgeon, M.D. 4,871 57.2%
- Harsh K. Trivedi, M.D. 3,642 42.8%

Total votes: 8,513

MIT Trustee-Elect

FIRST ROUND

- Kayla Pope, M.D., J.D. 310 37.5%
- Laura K. Kent, M.D. 263 31.8%
- Erick H. Cheung, M.D. 254 30.7%

Total votes: 827

SECOND ROUND

- Kayla Pope, M.D., J.D. 402 53.2%
- Laura K. Kent, M.D. 353 46.8%

Total votes: 755

Area 1 Trustee

- Frederick J. Stoddard Jr., M.D. 645 55.2%
- Robert Feder, M.D. 523 44.8%

Total votes: 1,168

Area 4 Trustee

- John J. Wernert, M.D. 912 64.4%
- Sul Ross Thorward, M.D. 504 35.6%

Total votes: 1,416

Area 7 Trustee

- William Womack, M.D. 399 51.3%
- Constance Powell, M.D. 378 48.7%

Total votes: 777

government news

Reform

continued from page 8

challenging. That makes it especially exciting to see the commitment of the Obama administration both to reform and to the full inclusion of psychiatric care. I hope that we will see incentives for the integration of psychiatric care with all the other medical care our patients need, and that we will see real incentives—not just rhetoric—to attract medical students into relatively low-income medical specialties like family medicine, general internal medicine, geriatrics, and psychiatry. APA is ready, willing, and able to work with the new administration to bring these good intentions to fruition."

The president's plan comes as a growing number of congressional leaders and health care advocates have begun pushing for action to overhaul the health care system and expand access sooner than the 2010 timeframe congressional leaders had previously planned.

Sen. Max Baucus (D-Mont.), chair of the Senate Finance Committee and a leader of health reform efforts, said several elements in the president's budget are consistent with his health care reform goals released late last year. They include provisions to base hospital and clinician payments on high-quality outcomes and to eliminate waste, fraud, and abuse in the system.

"We can and must achieve comprehensive health care reform this year, and this budget gives us a launching pad to move forward," Baucus said in a written statement.

The president's address at the joint session of Congress is posted at <www.whitehouse.gov/the_press_office/Remarks-of-President-Barack-Obama-Address-to-Joint-Session-of-Congress/>. ■

annual meeting

Session

continued from page 24

• The National Institute on Alcohol Abuse and Alcoholism is offering a special track of sessions on alcohol abuse. Topics include basic screening, the comorbid management of heavy drinking with such ills as post-traumatic stress or sleep disorders, and the impact of neuroscience and genetic research on pharmacological treatment.

• The International Medical Graduates Institute for foreign-born psychiatry residents will offer these physicians guidance on the practice of psychiatry in the United States. Special focus is given to the importance of developing language and communication skills and cultural perspective to foster optimum interaction with patients, fellow residents, and residency faculty. ■

Stimulus Law

continued from page 7

promoted. This approach aims to counter the use of research designed only to promote least-expensive treatment options. Mental health advocates, including the National Alliance on Mental Illness, opposed language in early versions of the measure that emphasized cost savings over clinical effectiveness and federal government restrictions on funding for treatments based on studies with limited efficacy comparisons.

Privately insured people also could benefit from a 65 percent premium subsidy for nine months of coverage under the COBRA law—the federal law that allows many workers to continue in their employer's group health insurance plan for a defined period after they leave a job. The measure, aimed at people terminated between September 1, 2008, and December 31, 2009, will help provide continuity of health care, especially for psychiatric conditions that are sensitive to disruptions in prescribed medications.

The impact of the COBRA change could be significant because fewer than 1 in 10 eligible workers opted for continuing insurance coverage under the law in 2007, due to high cost. COBRA requires workers to pay the entire premium—including the share typically paid for by employers—plus a 2 percent administrative fee. The average cost of COBRA coverage for a family of four is $13,000 a year, according to government statistics.

Numerous aspects of ARRA remain unclear, including how many of the provisions will be implemented. While, for example, the Prevention and Wellness Fund will invest in evidence-backed, community-based prevention programs that directly improve the health of Americans, the law tasks officials at the Department of Health and Human Services (HHS) with determining which programs meet the goals of this huge investment, and many senior positions at HHS have yet to be filled.

Even when the HHS positions are fully staffed, the wide latitude given to administrators to implement the law's provisions will require careful scrutiny and feedback by mental health and other advocates.

"You can bet we are going to be in there every day trying to influence how these provisions are being implemented," Boroughs said.

Information on the mental health–related provisions of ARRA is posted at <www.nami.org/Template.cfm?Section=February14&Template=/ContentManagement/ContentDisplay.cfm&ContentID=73996>. ■

Peer Support

continued from page 9

one wants to see them fail," said Grenier.

Once accepted, the peer-support coordinators take a two-week training course, not to become therapists, but rather to "listen, assess, and refer." They learn to recognize the boundaries between peer support and counseling. This part of the training is extremely complex and emotionally charged because it brings up issues the new coordinators have faced themselves, said Grenier. Additional training covers the nuts and bolts of services and programs available from the Canadian Forces or Veterans Affairs Canada.

The program has about 20 ex-military coordinators, an equal number of family coordinators, and about a dozen bereavement-support members (all of whom have lost a family member in the line of duty). They have served about 4,000 service or family members, mostly on or near half a dozen main military bases. Most cases so far have been soldiers who served in Bosnia or Croatia.

"We want employees to quickly grasp the issue the soldier has and know where to get help," Grenier said. "They know how to build trust to overcome barriers."

One barrier, he believes, is the language of therapy.

"The doctors use words to heal us, and I didn't know what the words meant," he said of his own experience. His situation was difficult enough, but he realized it had to be even harder for a combat arms corporal.

So when he began planning what has become OSISS, the place of language was critical.

Start with "operational stress injury." What happens in soldiers' minds after warfare is an injury caused by the stress of military operations—being under fire, seeing friends killed or wounded, facing the added horrors of civilian casualties. The U.S. Marine Corps and the Navy medical service that serves the corps have adopted similar language, and Grenier has consulted with Marine Corps psychiatrists in developing OSISS. Along with others, he would like to demedicalize operational stress injury.

"We're not trying to challenge the *DSM-IV* but to bridge the gap between the mental health providers and the people they care for," he said.

The entire organization meets every six months for training. The next session will concentrate on self-care and time-management skills for the coordinators. All coordinators must maintain contact with a mental health provider and run through an annual checklist to minimize burnout.

OSISS also offers services to the families of military personnel. Peer coordinators who help families must live with a person who has had a stress injury, said Melissa Bryden, an OSISS family-support peer coordinator from Winnipeg.

Bryden is not a war veteran, but she has worked for 13 years, half of them full time, as a reservist medical technician in Saskatchewan and Alberta. Her husband, also a medical technician, has served a stint in Afghanistan. Bryden is part of the second half of OSISS, the family-support side. All the family peer-support coordinators must have a family member who served in the Canadian forces.

There is other existing support for the families of deploying soldiers. They are briefed in advance about what they and their service member can expect while in the war zone. Staff at Military Family Resource Centers located on 32 bases across the country brief them again before the soldier returns home and once more six months later. The centers also offer help with child development, parenting support, crisis intervention, and other services. Family coordinators like Bryden attend those meetings. Their contact information is available from the Canadian Forces or Veterans Affairs Canada, but they do not seek out potential families in need. The families that decide they need some kind of help must take the first steps in contacting OSISS, either through using contacts on the base such as the chaplains or via an 800 phone number.

An initial interview with the family often brings a moment of recognition as the family members realize for the first time that they are not the only ones experiencing the problems they have just shared, said Bryden. The peer-support coordinator's job is to try to figure out what the service member or family members need, show them where to get it, and often help them through the inevitable paperwork and bureaucratic maze that veterans and military families in every country seem to face. They function partly as coaches, partly as case managers.

"People with mental health problems just can't navigate the system," said Bryden, so she will go to the family home and help with the paperwork or make sure someone sees a counselor.

The program also launched a speaker's bureau in January 2008 to increase awareness of operational stress injury, address the stigma surrounding mental illness, and urge early intervention.

More information on the Canadian Forces' Operational Stress Injury and Social Support Program is posted at <www.osiss.ca>. ■

Marijuana

continued from page 10

everyone agrees. Gitlow said he looks for some provision to make marijuana accessible to researchers without changing the schedule status for the general population.

"We need controlled trials for an extended period of time, because many of the effects are not going to show up in an eight-week trial," Gitlow said. "Ideally, this would be research in a controlled setting without making the drug accessible to the public at large. The first step is therefore to figure out the marijuana ingredient providing benefit and then determine a safe method of dosing that ingredient. We can't jump to the end of the process without first going through the necessary intermediate steps."

An abstract of "Nonacute (Residual) Side Effects of Cannabis Use: A Meta-Analytic Study" is posted at <www.ncbi.nlm.nih.gov/pubmed/12901774>. ■

Lawyer

continued from page 13

"I was floridly psychotic in the consulting room for much of the three years I saw her," Saks recalled. "However, I don't think she knew the extent of my psychosis as I was hiding a lot. In any event, she did not recommend medication, and I think she believed that my illness could be worked with psychoanalytically.

"My analyst's presence was comforting, and my thoughts were neither good nor bad in her view. Furthermore, she helped me become more psychologically minded and to develop an observing ego."

Saks obtained a master's degree in letters from Oxford. She then returned to the United States and attended Yale Law School. During this period, she was still not taking any antipsychotic medications, and her positive symptoms increased. She was diagnosed with schizophrenia, hospitalized for five months, and forcibly medicated with antipsychotic medications.

Upon being discharged from inpatient care, she remained on antipsychotic medications, but also saw an analyst. He, like the analyst in England, strengthened her observing ego and "was very soothing," she said.

Saks graduated from Yale Law School and started working as a lawyer. During this period, she attempted to reduce the amount of antipsychotic medications she was taking because of concerns about developing tardive dyskinesia. Her psychotic episodes returned.

Subsequently, an analyst helped her come to accept that she had a serious mental illness and that she needed to remain on antipsychotic medications indefinitely.

"Simply being on antipsychotic medications could not have brought about such acceptance," she stressed. "And this acceptance set me free psychologically. My good fortune is not having recovered from schizophrenia, which I have not, but to have found my life."

And finding her life meant setting out, in her 40s, to look for romance and a partner who would accept her as she was. She was successful. In fact, her husband, Will, was at the ApsaA meeting, providing a colorful and humorous PowerPoint presentation to illustrate her talk.

Saks also discussed some of the other ways that analysis has helped her cope with her illness:

- It has helped her understand her childhood better, and such understanding in turn has helped her cope better with her schizophrenia.
- It has helped her to become more psychologically minded and to manage her feelings better.
- As she developed an observing ego, it helped her recognize when she was having psychotic symptoms.
- Any stress or sudden change in her life at one time would send Saks into a tailspin psychologically. Analysis helped her identify and better manage stresses in her life.
- Analysis gave her an outlet to discuss her problems with schizophrenia. It also helped her "find meaning in [her] struggles with schizophrenia."

Saks is so impressed with analysis, in fact, that she is training to become a research psychoanalyst.

Saks has written a memoir about her struggles and successes with schizophrenia*, The Center Cannot Hold: My Journey Through Madness.** ***It was published by Hyperion in 2007. She will lecture at APA's 2009 annual meeting on Monday, May 18, at 11 a.m. ■

Women

continued from page 12

But how aggressive must women be to lead effectively? There doesn't seem to be an easy answer to this question, Settel noted. Women leaders need to be tough enough to confront people and to make hard decisions, yet when they exhibit such stalwartness, they may be criticized for being brash or showboating. Gourguechon agreed: as a woman in power, it may be hard to "strike the right note" as far as aggression is concerned.

But are women in leadership positions at a disadvantage because, according to popular belief, they are innately less forceful than men are? Gourguechon doesn't think so. She believes that women are at least as combative as men are. However, the way that women express their combativeness tends to differ from the way men express theirs, she observed. Men tend to display theirs through fighting, whereas women are apt to display theirs through envy or hostility.

How about maternal instincts? Do they have any place in female leadership? Sometimes, Gourguechon contended. For example, when women leaders take a less authoritative and more nurturing approach with their staff, it can be a positive move. Also, Gourguechon said she views her presidency of APsaA "as if I have a big household to run" and believes that such a stance is an attribute for the job.

However, a maternal instinct that women in power need to subdue, Gourguechon cautioned, is the impulse to always respond to the needs of others. In other words, they need to grow out of the Girl Friday role, where they are everybody's favorite person for getting the work done, and to learn how to delegate responsibility. ■

HAPA to Meet

The Hellenic American Psychiatric Association (HAPA) will hold its 10th annual meeting in May in San Francisco in conjunction with APA's 2009 annual meeting. While the meeting date has not been confirmed yet, it will most likely be Tuesday, May 19, from 7 p.m. to 10 p.m.

The meeting will feature Charles B. Nemeroff, M.D., Ph.D., whose lecture is titled "Psychopharmacology in the 21st Century: Toward Personalized Medicine in Psychiatry," and Ioannis Zervas, M.D., whose lecture is titled "On Women's Mental Health at the Athens University: A Person-Centered Approach."

Register now. More information is available by e-mail to anpapas@comcast.net. ■

UCLA
Geriatric Psychiatrist

The Division of Geriatric Psychiatry of UCLA's Department of Psychiatry and Biobehavioral Sciences in conjunction with the Jane & Terry Semel Institute for Neuroscience and Human Behavior (a multidisciplinary research institute) is seeking an academic psychiatrist at the rank of Assistant or Associate Professor, depending on qualifications.

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Phone: 774-826-2473
Email: Gary.Kaplan@va.gov

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AMERICAN PSYCHIATRIC ASSOCIATION 1844

Isaac Ray Award

The American Psychiatric Association and the American Academy of Psychiatry and the Law invites nominations for the Isaac Ray Award for 2010. This Award honors Dr. Isaac Ray, one of the original founders and the fourth President of the American Psychiatric Association, and is presented to a person who has made outstanding contributions to forensic psychiatry or to the psychiatric aspects of jurisprudence. The Award, which will be presented at the Convocation of Fellows at the Annual Meeting of the American Psychiatric Association in New Orleans, LA, in May 2010, includes an honorarium of $l,500. The recipient obligates him or herself to deliver a lecture or series of lectures on these subjects and to present the manuscript for publication.

Nominations are requested as follows:

- a primary nominating letter (sent with the consent of the candidate), which includes a curriculum vitae and specific details regarding the candidate's qualifications for the Award; and
- a supplemental letter from a second nominator in support of the candidate.

Additional letters related to any particular candidate will not be accepted or reviewed by the Award Committee. Nominators should not submit letters on behalf of more than one candidate. Nominations will be kept in the pool of applicants for two years.

The deadline for receipt of nominations is July 1, 2009.

Nominations, as outlined above, should be submitted to:

J. Richard Ciccone, M.D.
Chairperson
Isaac Ray Award Committee
American Psychiatric Association
1000 Wilson Boulevard, Suite 1825
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PLUS new hire incentives, excellent benefits, and cash allowances. For detailed information, visit **www.sbcountyjobs.com**

Job location is Santa Maria

Call Ratio:
Only one weekend every three months!

For immediate consideration, contact Dr. Edwin Feliciano, Medical Director, at 805-681-5235, or apply online at **www.sbcountyjobs.com**

The County of Santa Barbara strongly promotes diversity and equality in the workplace.

Mental Health

CALIFORNIA
BC/BE STAFF PSYCHIATRIST

Patton State Hospital is recruiting board certified/eligible psychiatrists. Patton is a Joint Commission accredited, 1500 bed, adult forensic psychiatric hospital, with an extremely interesting and challenging patient population. The hospital is nestled below Arrowhead and the San Bernardino Mountains, 65 miles east of Los Angeles; an hour's drive to beaches, Palm Springs, or mountain lakes and skiing. Salary with Board Certification starts at **$18,622 and goes to $21,311 monthly.** Salary for Board Eligible starts at **$18,146 and goes to $20,711 monthly.** In addition, Patton offers excellent benefits (health, dental, and vision; license renewal; malpractice insurance; tax-deferred compensation; paid annual leave and 12 holidays (plus one personal holiday), as well as seven days per fiscal year of Continuing Medical Education leave). Voluntary on call duty is compensated on an hourly basis over and above base salary. We provide civil service security and retirement plans (including safety retirement). For confidential consideration, send CV to Wadsworth Murad, D.O., (A) Medical Director, 3102 East Highland Avenue, Patton, California 92369, (909) 425-7326 or Fax (909) 425-6635.

COLORADO

Denver Health Medical Center is actively seeking a BE/BC general or forensic psychiatrist to join our correctional psychiatry team at the Denver County Jail. The position also includes a faculty position in the Department of Psychiatry, University of Colorado and in the Forensic Psychiatry Fellowship Program. Opportunities exist for teaching medical students, psychiatry residents, and forensic psychiatry fellows. Our team is a multidisciplinary group that provides comprehensive care to psychiatric patients in a correctional setting. We offer a competitive salary, excellent benefits, and reasonable call. Denver Health is a comprehensive, integrated health care organization that is Colorado's primary "safety net" hospital. The lifestyle in Denver and Colorado is not to be missed. Interested applicants should submit a CV and cover letter to: Gregory Kellermeyer, MD, Director of Correctional Psychiatry, Denver Health Medical Center, 1155 Cherokee Street, MC 3440, Denver, CO 80204. Office: (303)-436-3808, gregory.kellermeyer@dhha.org

CONNECTICUT

St.Vincent's Behavioral Health Services · Hall-Brooke · Ascension Health

St. Vincent's Medical Center, Behavioral Health Service, Fairfield County, CT

Inpatient and Outpatient Opportunities

St. Vincent's Medical Center, Behavioral Health Services is recruiting Psychiatrists to join its expanding clinical service at their Westport and Norwalk campuses.

A Full Time Inpatient Staff Psychiatrist is needed in the Westport, CT campus. Responsibilities include inpatient care of adults with a small percentage of adolescents. Minimal weekend and call requirements. Our 76-bed hospital has adult, geriatric, women's, addiction, and child/adolescent services, and affiliations with St. Vincent's Medical Center in Bridgeport, CT and the University of Connecticut. In addition to the inpatient services in Westport, the St. Vincent's behavioral health service line includes a 16-bed psychiatric unit at the Medical Center in Bridgeport. The combined service offers 92 behavioral health inpatient beds for treating children, adolescent and adults with mental health and substance abuse issues. This makes the inpatient behavioral health service line of St. Vincent's one of the largest in Connecticut serving approximately 2,350 individuals annually. Job responsibilities may be tailored to suit specific skill areas or interests.

A Part Time Outpatient Staff Psychiatrist is needed in our Norwalk, CT campus. This is primarily an IOP based afternoon program with some flexibility of hours. Responsibilities include outpatient care of adolescents. This position is part of a large multidisciplinary treatment team. The outpatient site at Norwalk is also part of this large continuum of Psychiatric care based in Fairfield County. For more information, please contact: Clayton Tebbetts; Physician Recruiter, St. Vincent's Medical Center - 203.576.6204 - ctebbetts@stvincents.org

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BEAUTIFUL SUBURBAN CT/ 1 ¼ HRS FROM NYC

CT licensed BC/BE Psychiatrist to join a 30 year well established multi-disciplinary practice providing adult psychiatric services. Excellent Compensation. Send CV/cover letter by fax 203-797-0877 or Email: afrymd@yahoo.com. For more information, please contact Sam at 203-792-6060 x15.

DELAWARE

Psychiatrist! An excellent opportunity awaits you! Our busy and growing practice is searching for a qualified and experienced full time general psychiatrist. We are located conveniently in Dover, DE and offer an excellent compensation and benefit package. For consideration please submit your C.V. to Elena Hall: Elena@umusa.net or fax to: (866) 230-8848.

FLORIDA

DAYTONA - MELBOURNE - ORLANDO - MIAMI - FORT LAUDERDALE - PALM BEACH - OCALA - GAINESVILLE - FORT MYERS - SARASOTA - PENSECOLA - JACKSONVILLE - Psychiatrists needed for rapidly expanding Nursing Home Service. Great support. No call. Average Salary 210K + benefits. Part-time available. Some travel required. Must have FL Medicare & FL Medicaid individual provider #s. No Restrictions (H1B Candidates Considered). Call our administrator, Christy, at 866-936-5250.

Lee Mental Health Center, Inc. (LMH) is the primary provider of mental health services in Lee County, in Southwest Florida. A private non-profit company, the Center provides a continuum of mental health and substance abuse services for adults and children, including crisis stabilization, outpatient and community based services. We are committed to the recovery model of service delivery. Visit us online at www.leementalhealth.org . We are currently seeking dynamic candidates for the following positions:

Chief Medical Officer - This position reports directly to the C.E.O. The successful candidate will provide leadership to all staff as Clinical Director for the agency; manage medical staff as a group practice and set up and provide psychiatric services that reflect the clinical standards of this company in the assessment and treatment of patients. Must be Board certified in General Psychiatry by the ABPN (Board certified in Child & Adolescent Psychiatry preferred). Must possess an active/clear FL medical license and valid DEA. Must be eligible to serve as a provider in Medicaid and Medicare programs. Two years of management experience in a medical setting required. Previous community mental health care experience is a plus!

Child & Adolescent Psychiatrists - PT or FT positions in our Crisis Stabilization and Outpatient departments available. Will be responsible for diagnostic interviews, medication management, consults, second opinions, rotating on-call duty and rounds. Will interface/collaborate with other treatment professionals, as appropriate. Successful candidates will possess an active/clear Florida medical license and a valid DEA. Must be Board certified or eligible in General/Adult or Child psychiatry. Must be eligible to serve as a provider in Medicaid and Medicare programs. Experience in community mental health and substance use disorders a plus.

Compensation/Benefits: Our commitment to you is not only a generous salary but a benefits package for FT employees that includes: Malpractice Insurance, Generous paid time off plan (includes sick, personal leave, and vacation); 10 paid holidays per year, Health, dental and life insurance, Flexible Spending Account (health care), Short Term & Long Term Disability (and other supplemental insurance options) and 403b retirement plan.
Nearby: LMH is located on the vibrant Gulf Coast of southern Florida. Lee and its neighboring counties offer a variety of residential communities with excellent public/private schools, colleges and universities. Residents enjoy easy access to year round recreational and cultural activities and unlimited sunshine. You are encouraged to come and enjoy the diversity and beauty of SW Florida!
Submit both an employment application and CV to: Lee Mental Health Center, Inc. (Attention: HUMAN RESOURCES), 2789 Ortiz Avenue, Fort Myers, FL 33905; or fax: 239-418-0094; or email: resume@leementalhealth.org Please visit www.leementalhealth.org to download an employment application and/or for additional information.
EOE/DFWP

GEORGIA

ATLANTA: General Psychiatrist - Inpatient & partial programs. Fulltime or part-time positions - salary & benefits. Also weekend coverage needs - no call required. **MOULTRIE:** General Psychiatrist for residential & partial programs - psychiatric & addiction. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

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Quiet Country Setting close to large metro area in Beautiful NW GA. Community Mental Health Opportunity for BC/BE Psychiatrist, excellent benefits and competitive salary. Send CV to jobs@highlandrivers.org or fax 706-270-5129.

Psychiatrist - Metro-Atlanta

Cobb-Douglas Community Services Board, a behavioral healthcare organization in metro Atlanta seeks a part-time BC/BE Adult Psychiatrist for Community Outpatient Behavioral Health clinic. Please send CV to cholt@cobbcsb.com or fax to Cheryl Holt at 770-948-6147.

PSYCHIATRISTS

New Horizons Community Service Board in Columbus, Georgia is seeking an Adult psychiatrist for its outpatient and residential programs. This growing community offers a pleasing climate and is situated within a short distance to Atlanta and the Gulf Coast. The qualified applicant will possess or be eligible for a valid physician's license from the State of Georgia and have completed a three-year residency in an accredited facility. Excellent salary with a comprehensive benefits package. Interested parties should fax their curriculum vitae to the attention of Shannon Robertson at 706/317-5004.
No phone calls, please.

ILLINOIS

PROGRAM DIRECTORS OF CLINICAL RESEARCH
DEPARTMENT OF PSYCHIATRY & BEHAVIORAL NEUROSCIENCE
THE UNIVERSITY OF CHICAGO

The Department of Psychiatry & Behavioral Neuroscience at The University of Chicago is seeking academically-oriented adult psychiatrists to serve as director of new clinical and translational research programs in the department. Such individuals are also expected to be involved in the clinical/didactic training of medical students, psychiatric residents/fellows, and in the clinical management of psychiatric patients. M.D. required & licensure as a Physician & Surgeon in IL will be required. Must be eligible for required board certifications. and have a record of peer-review publications. Academic rank and salary will be commensurate with background and experience. Interested candidates should send their CV and contact information to Emil F. Coccaro, M.D., Chairman, Department of Psychiatry & Behavioral Neuroscience, The University of Chicago; 5841 S. Maryland Avenue, MC 3077; Chicago, IL 60637 (e-mail for electronic copies: ecoccaro@yoda.bsd.uchicago.edu).

LOUISIANA

DEPARTMENT OF PSYCHIATRY AND NEUROLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for several general and forensic psychiatrists (clinical track) for our growing department, at the Assistant/Associate Professor level. Candidates must have completed an approved general psychiatry residency and be board certified/eligible in general psychiatry and forensic psychiatry, respectively. Responsibilities will include direct patient care, teaching of medical students and house officers (including those in our accredited forensic psychiatry fellowship program), and research (clinical and basic science) at various state hospitals, state correctional institutions, and at Tulane University Health Sciences Center. Time allocations will be based upon individual situations. Applicants must be eligible to obtain a Louisiana medical license. Applications will be accepted until suitable qualified candidates are found. Send CV and list of references to John W. Thompson, Jr., M.D., Vice Chair, Adult Psychiatry and Director, Division of Forensic Neuropsychiatry, Tulane University School of Medicine, Department of Psychiatry and Neurology, 1440 Canal Street TB53, New Orleans, LA 70112. For further information onsite, please contact Dan Winstead, MD, Chair of Psychiatry and Neurology, at 504-473-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

CHILD PSYCHIATRI STS - DEPARTMENT OF PSYCHIATRY AND NEUROLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for BE/BC child psychiatrists at the assistant professor level, salary commensurate with experience. Clinical responsibilities available in the areas of consultation/liaison psychiatry, school based mental health, community based child and adolescent psychiatry and early childhood development. Teaching responsibilities include the supervision of residents, clinical psychology fellows and interns, and medical students rotating through the clinical facilities serviced by this position as well as the presentation of grand rounds and participation in the didactic series in child psychiatry. Clinical research is strongly encouraged. The persons selected must be professionally competent and be board eligible/certified in general psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Applications will be accepted until a suitable qualified candidate is found. Send CV and list of professional/academic references to Charley Zeanah, Jr, MD, Professor and Vice Chair, Child and Adolescent Psychiatry, Tulane University School of Medicine, Department of Psychiatry and Neurology, 1440 Canal Street TB52, New Orleans, LA 70112 (czeanah@tulane.edu). Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

SEEKING PSYCHIATRIST

Community-based agency in Southeast Louisiana seeks both general and child psychiatrists to serve in the community mental health centers north of New Orleans (with easy access to Gulf Coast). In addition to competitive salary, benefits include health/life/dental insurance, retirement plans, and annual and sick leave. Medical malpractice covered.

For details contact:

FPHSA Administration
11236 Hwy 16 West
Amite, LA 70422
(985) 748-2220
www.fphsa.org

The Department of Psychiatry and Neurology at Tulane University School of Medicine is recruiting a geriatric psychiatrist for a full-time faculty position. The candidate will spend part of their time at the Southeast Louisiana Veterans Health Care System (SLVHCS) and will also be involved in the new initiatives in both clinical geriatric care and special geriatric education programs at Tulane. Responsibilities include patient care as well as contributing to the various teaching and training programs of Tulane University's Department of Psychiatry and Neurology at the SLVHCS. He/she will be provided the opportunity to pursue their research interests. The person selected for this position must be professionally competent and be board eligible/certified in general psychiatry and in geriatric psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Salary will be competitive and commensurate with the level of the candidate's academic appointment. Applications will be accepted until a suitable qualified candidate is found. Applicants should send letter of interest, updated CV and list of references to Daniel K. Winstead, MD, Heath Professor and Chair, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1440 Canal Street TB48, New Orleans, LA 70112. Interested and eligible candidates may obtain further information by contacting Daniel K. Winstead, MD at 504-988-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admissions and in employment.

The Department of Psychiatry and Neurology at Tulane University School of Medicine is recruiting for a Director of Residency Training in Psychiatry. This is a full-time faculty position with half-time devoted to the residency training program and half-time to other academic pursuits. An associate director is available to assist with program leadership and administration. The person selected for this position must be professionally competent and be board eligible/certified in general psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. This is a fully accredited psychiatry program for up to 39 general residents, 10 triple board trainees, 6 child fellows and 3 forensic fellows. We also offer combined programs in med-psych and in psych-neuro. Salary will be competitive and commensurate with the level of the candidate's academic appointment. We will continue to accept applications for this position until a suitable qualified candidate is identified. Qualified applicants should send email of interest, updated CV and list of references to Daniel K. Winstead, MD, Heath Professor and Chair, at winstead@tulane.edu or letter to Department of Psychiatry and Neurology, Tulane University School of Medicine TB48, 1440 Canal Street, Suite 1000, New Orleans, LA 70112. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admissions and in employment.

MARYLAND

"THE MARYLAND PLAN" is a nationally acclaimed program in public psychiatry. Positions are available for child and adult psychiatrists. Academic involvement with med. schools in your area of interest is encouraged. Please e-mail CV with area of interest and geographic preference to: GJordanRandolph@dhmh.state.md.us or mail to: Gayle Jordan-Randolph, M.D., Mental Hygiene Administration, Spring Grove Hospital, Dix Building, 55 Wade Avenue, Catonsville, MD 21228.

EHP® BEHAVIORAL SERVICES, LLC

Union Memorial Hospital
Department of Psychiatry
Associate Chief

We are seeking a board-certified psychiatrist that has the ambition and skills to assume a leadership role within our group and advance to the chief position within a 5-year period. Qualified candidates must be able to demonstrate the following:

- Comprehensive, efficient and quality clinical care
- Excellent interpersonal skills with:
  - Executive hospital management
  - Behavioral health professionals in our group
  - Community and hospital-based physicians
  - Hospital administrative and clinical support staff
  - Group administrative and management staff
- Practice management knowledge
- Leadership ability
- Medical administrative management knowledge
- Professional staff recruitment and retention skills

EHP is a multi-discipline, multi-location behavioral health group that provides consultation, crisis intervention services, inpatient, PHP and outpatient services at Union Memorial Hospital in Baltimore, Maryland. The selected individual will be expected to gain experience in all phases of our operation. Primary initial focus will be on consultation service management and inpatient support.

For consideration, please forward your cover letter and CV to: EHP at 3333 N. Calvert Street, Suite 670, Baltimore, MD 21218 via mail, 410-933-9085 via fax or sar@psychbillinc.com via e-mail. Should you have any questions, please feel free to contact Steven A. Rose, RN at 410-933-9000, extension 210.

MASSACHUSETTS

UMass Department of Psychiatry is looking for moonlighting BE/BC psychiatrists to assist with our coverage needs at local hospitals. This may involve either overnight or weekend coverage. Excellent reimbursement. Please email psychiatryrecruitment@umassmemorial.org or fax to 508-856-5990. AA/EOE

Starr Psychiatric Center seeks a 20-30 hr psychiatrist for dynamic established psychiatric practice On Boston's South Shore. Medical model, multi-disciplinary staff. Stimulating environment, good pay. Clinic has a reputation for successful care, where others have failed. Email davidzstarr@juno.com or call 508.580.2211.

CAMBRIDGE: Adult Psychiatry

Weekend Moonlighting Psychiatrist Positions available at Cambridge Health Alliance: Lucrative and flexible opportunities available for attending psychiatrists to provide weekend/holiday coverage of inpatient units at our Whidden Memorial Hospital campus.

Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply. CV & letter to Derri Shtasel, MD, Dept. of Psychiatry, 1493 Cambridge Street, Cambridge, MA 02139. Fax 617-665-2521. **Email preferred: DShtasel@challiance.org.**

Inpatient psychiatrist position with unique group practiceBC/BE inpatient psychiatrist wanted to join an 11 psychiatrist group in Southeastern MA. Southern New England Physicians Associates (SNEPA) provides a collegial work atmosphere in an all physician/physician run group practice environment. Our group prides itself on facilitating members individual interest while providing high quality clinical services. This position will be well compensated and with partnership tract available.
CONTACT: CV to Russell Pet, M.D or Duane Bishop, M.D.101 Page St., New Bedford, MA 02740 Fax (508) 961-5931
Call (508) 961-5930 or email c/o pepina@southcoast.org

BOSTON & SUBURBS - Brookline, Jamaica Plain, & Pembroke (Cape Cod area)! Full time & part-time positions for **Child & General Psychiatrists.** Inpatient/partial programs - **NO CALL.** Administrative/clinical positions for qualified candidates. Salary, benefits & incentive plans offered. Week night & weekend call coverage/moonlighting shifts also available. Contact Courtney Williams @ 866-227-5415 or email courtney.williams@uhsinc.com

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High Point Treatment Center is seeking a 40 hr week psychiatrist for a 16-bed Inpatient Psychiatric Unit located in Plymouth, MA. Salary ranging from $170,000 - $190,000. No weekends, paid holidays and leave time. Health benefits available. If willing to work an additional 1 hr per day salary range would be $200,000 - $215,000. If interested, please contact Jim Horvath at 508-503-2455 or email to jim.horvath@hptc.org.

The Department of Psychiatry at Mount Auburn Hospital, affiliated with Harvard Medical School, is recruiting for two positions in our Outpatient Psychiatry Service:

1) A full-time psychiatrist to serve as Medical Director of Outpatient Services. This position involves direct patient care and clinical administration, working closely with other departments in the general hospital, and contributing to the development of the psychiatry program.
2) A half-time clinical position involving evaluation and treatment of adult patients with a variety of psychiatric disorders, including dual diagnosis patients, and coordination of care with other psychiatric clinicians and with primary care and specialty physicians. There are opportunities to work with the women's mental health program and the Dept. of OB/GYN.

For both positions, academic appointment to the clinical faculty at Harvard Medical School is anticipated.

Please send letter of interest and cv to: Joseph D'Afflitti, M.D., Chair, Department of Psychiatry, Mount Auburn Hospital, 330 Mount Auburn Street, Cambridge, MA 02138; Tel: 617 499-5008; email: jdafflit@mah.harvard.edu

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Greater Boston—Northeast Hospital Corp is a local nonprofit medical and psychiatric system on Boston's North Shore, named one of the nation's top 100 integrated healthcare systems by Solucient. The Inpatient Behavioral Health division includes BayRidge Hospital, a 62 bed freestanding psychiatric facility in Lynn, an 18 bed inpatient unit at Beverly Hospital, and a 12 bed Senior Adult inpatient unit at Addison Gilbert Hospital in Gloucester, as well as Partial Hospital Programs at each site. Both BayRidge and Beverly Hospitals serve as teaching sites in psychiatry for Boston University School of Medicine. Upcoming opportunities at both the inpatient and partial hospital levels of care are anticipated. No required night call, but participation in a lucrative call system is optional. Competitive salary, and full benefit package includes generous time off as well as reimbursement for malpractice insurance and CME expenses. Contact Barry Ginsberg, M.D., Chief and Administrative Director, NHC Dept. of Psychiatry, 60 Granite Street, Lynn MA 01904. Phone (781) 477-6964, Fax (781) 477-6967, email bginsber@nhs-healthlink.org.

DIRECTOR OF INPATIENT PSYCHIATRY. Beth Israel Deaconess Medical Center in Boston, a 500+ bed tertiary care teaching hospital of Harvard Medical School, is seeking a Director of Inpatient Psychiatry, to start July 1, 2009. This is a key full-time leadership position within the Department of Psychiatry and includes oversight of clinical care and teaching on a 25 bed unit. The service is a major teaching site for Harvard Medical School and the Harvard Longwood Psychiatry Residency Training Program. Interest and experience in research is desirable. Underrepresented minorities are encouraged to apply. A Harvard Medical School appointment at an appropriate rank is available. Please send a letter of interest and a CV to Rohn Friedman, M.D., Vice-Chairman of Psychiatry, 185 Pilgrim Road, Boston, MA 02215, Tel 617-632-0907, Fax 617-632-7990 or email rfriedma@bidmc.harvard.edu.

Central Massachusetts - The University of Massachusetts Department of Psychiatry is seeking BC/BE psychiatrists for part-time to full-time positions in our community mental health centers in Worcester and Leominster. Community HealthLink (CHL) is a dynamic organization providing services to those with mental illness, developmental disabilities and substance abuse (see www.communityhealthlink.org). Work with a dedicated multidisciplinary staff. CHL psychiatrists are part of our UMass faculty with opportunities for teaching and research. Please email psychiatryrecruitment@umassmemorial.org or fax to 508-856-5990. AA/EOE

MICHIGAN

Associate Medical Director
Alpena, MI

Horizon Health, in partnership with **Alpena Regional Medical Center** in **Alpena, MI,** seeks an **Associate Medical Director** for a 15-bed Adult Inpatient Psychiatric Program.

Alpena Regional Medical Center (ARMC) is a 146-bed acute care facility with nearly 100 physicians, over 900 employees and approximately 300 volunteers. Federally-designated as a rural Regional Referral Center for all of Northeastern Michigan.

Alpena overlooks Lake Huron's picturesque Thunder Bay in northern Michigan, and is located on the Sunrise Side Coastal Highway, a 200-mile stretch of US 23 graced with scenic views, undeveloped wild areas, roomy beaches and recreational areas for hiking, biking, cross-country skiing and snowmobiling. Excellent practice and income opportunity.

Contact: Mark Blakeney, Horizon Health, 972-420-7473, fax CV: 972-420-8233, or email mark.blakeney@horizonhealth.com. EOE.

7:30 a.m. to 4:30 p.m. Position - Seeking Psychiatrist to work on adult psychiatric unit in a medical facility that houses behavioral health, extended care, and medical rehabilitation in Saginaw, MI. No E.R. Medical Director position may be available for the right candidate. Very close to Bay City on Lake Huron and Flint. Only an hour and a half to Detroit. Very attractive compensation pkg. Please call **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

MISSISSIPPI

Gulf Coast, Mississippi
Salary in excess of $200K. Sign-on bonus. Exceptional benefits including six weeks paid time off, all insurances, relocation expenses. Hospital seeks an Adult or Child Psychiatrist to become part of the behavioral health team at a free-standing Psychiatric Center treating children, adolescents, and adults with behavioral, emotional and addictive disorders. Mix of inpatient and outpatient with a Monday-Friday schedule. Stunning location on the Gulf of Mexico offers a high quality of life, strong economic growth, excellent schools, and a tremendous number of recreational and cultural activities. Contact Chris Gluz, Alpha Physician Search at 800.504-3411, cgluz@alphamg.org. View available opportunities at www.alphaps.org.

MONTANA

Medical Director
&
Associate Medical Directors
Helena, MT

Horizon Health, in partnership with **St. Peter's Hospital** in **Helena, MT,** seeks a **Medical Director** and **Associate Medical Directors** for new distinct **Adult** and **Geriatric** Inpatient Psychiatric Units, comprised of **26** total beds.

Nestled beneath the foothills of the Montana Rockies, **Helena,** the Capital of Montana, is a thriving city of 70,000 people known as the "Queen City of the Rockies". Alive with history and culture, this charming, sophisticated, and beautiful Victorian city provides a diverse attraction with many street festivals, theater, museums, symphonies, fairs and rodeos. There is truly something for everyone here!

St. Peter's Hospital in **Helena, MT** is an independent, community-based, 99-bed facility that partners with its patients, community, and medical staff to provide exceptional and compassionate healthcare. **St. Peter's** is accredited by the Joint Commission and is the recipient of numerous national, regional, and state awards.

Excellent practice opportunity with great income ($200K+)! For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

NEW HAMPSHIRE

Medical Director For Established, Diverse, Cutting Edge Program In Concord, New Hampshire. Competitive compensation package which includes signing bonus and performance bonuses twice a year. Call to obtain complete job description for your clinical and administrative responsibilities. Opportunity for ECT and TMS, if desired. Participate in teaching of NH Dartmouth Family Medicine Residents. EMR. One hour to Boston, the White Mountains, or the Atlantic Coast! No state income tax or sales tax. **Contact Germaine Lorbert at 800-678-7858, x63704 or glorbert@cejkasearch.com ; www.cejkasearch.com .** ID#31624PY.

NEW JERSEY

Southern NJ near Cherry Hill - Geriatric Psychiatrist. Fulltime position - inpatient & partial programs. **No weekend call.** Salary & benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

Child/Adol. or Adult Psychiatrists

Child/Adol. or Adult Psychiatrists - needed for multi-disciplinary group in affluent communities in North/Central N.J. NO Managed Care! Call Dr. S. Reiter at 908-598-2400 x1 and fax CV to 908-598-2408.

View your ad online for free!
All line classified ads are posted on the *Psychiatric News* web-site:
pn.psychiatryonline.org

NEW YORK CITY & AREA

PSYCHIATRISTS
PER DIEM/MOONLIGHTING

Moonlighting opportunities available (Weeknights, Weekends, and Holidays) for NYS licensed Psychiatrists to cover hospital ED/CL/Detox Services and/or Adult Psych Unit. Ideal for PGY4's and Fellows starting July 09! Includes payment of part-time malpractice policy premiums if contracting for blocks of shifts. Send resume/CV by FAX to Bradford M. Goff, MD at 718-630-8594 or email: bgoff@lmcmc.com. EOE/AA M/F/D/V

LUTHERAN MEDICAL CENTER
www.lutheranMedicalCenter.com

Columbia University
College of Physicians and Surgeons
Department of Psychiatry

Position available as Postdoctoral Clinical Fellow in the Department of Psychiatry of Columbia University and part time Attending Psychiatrist, as part of a Psychiatric Emergency Room Fellowship at the New York Presbyterian Hospital. Candidate must be Board Eligible in Psychiatry. Opportunities for professional development in an academic medical center. Direct patient care, team leader, teaching Columbia Medical Residents and Students. Must have NYS license and DEA certificate. Equal Opportunity, Affirmative Action Employer.

Please forward resumes to:
New York Presbyterian Hospital
Attn: Diane Looney
622 West 168th Street, HP254
New York, NY 10032
Fax #212-305-4724

MANHATTAN
Child/Adolescent Assoc Medical Director
Inpt academic clinical care with leadership, admin and teaching duties. Daytime hrs- no call, wkends or evenings. 25 day LOS, little mg'd care, great staff. Unique new opportunity/attractive salary. AdolMD@gmail.com or 917-710-2456

FULL-TIME PSYCHIATRIST: EXCELLENT OPPORTUNITY for general & geriatric psychiatrist available at The Long Island College Hospital in brownstone Brooklyn, one step from Manhattan over the Brooklyn Bridge. These BC/BE psychiatrist will be a member of a very active inpatient 39 bed unit. We offer a highly competitive salary/benefit package. We're looking for highly motivated and committed physician. Please fax resume to: THE LONG ISLAND COLLEGE HOSPITAL, DEPARTMENT OF PSYCHIATRY, 339 Hicks Street, FAX: (718) 780-1236.

Child and Adolescent Psychiatrist
P/T - 10-15 hours per week (evenings and/or weekends) in a Child and Family Mental Health Center in Brooklyn. Excellent compensation. No call. Fax resume to (718) 553-6769, or email to clinicaldirector@nypcc.org

Consulting Psychiatrists & Psychologists

BC/BE **Psychiatrists** to provide Consultation-Liaison services and **Psychologists** to provide Psychotherapy and Behavioral Management in Long Term Care settings (NH, SNF).
Facilities Located in NYC Metro area and Westchester, Putnam, Dutchess, Rockland, Orange and Ulster Counties. PT/FT Well above average salaries/benefits, flexible hours.
Recent graduates encouraged to apply.

Please contact: Carlos Rueda, M.D. at Tel: 718-239-0030 or via fax: 718-239-0032
E-mail: crueda@neuropsych-services.com

NEW YORK STATE

PSYCHIATRIST

An established and progressive private practice located in Albany, NY is seeking a N.Y.S. Certified Psychiatrist for an adolescent and adult outpatient program with flexible hours available. Excellent weekly salary and full administrative services included, in a warm and pleasant ambience. Insurance panel a plus. Please forward your C.V. to: pinbill@nycap.rr.com

GLENS FALLS - SARATOGA SPRINGS, NY - Glens Falls Hospital seeks a BC/BE Psychiatrist to join an integrated outpatient psychiatry team consisting of 8 Psychiatrists, and a team of nurses, and social workers. Primary duty is outpatient psychiatry; also provide consults to general medical units and back up to inpatient Behavioral Health Unit. Call is 1:6 with primary ED response by dedicated adjunct staff. Competitive salary and full benefits package. Situated near the Adirondacks, Lake George, and Saratoga, you have access to hiking, boating, skiing, and numerous cultural opportunities year-round. Only 3 hours to NYC, Boston, and Montreal. Send CV to Jennifer Metivier, Physician Recruiter at 518-926-1946 or jmetivier@glensfallshosp.org.

NORTH CAROLINA

Private Practice, well est. in small southern town located near Blue Ridge Mtn. and minutes from Charlotte. Need full/part-time psychiatrist out-patient, Competitive salary. Required board certification or eligibility. Please fax or mail resume to Foothills Consulting Assoc. P.O. Box 1418 Shelby, North Carolina 28150.

9 to 5 POSITION RIGHT NEAR RALEIGH - Live in Rocky Mount or Raleigh and work in a very impressive general hospital with adult and chemical dependency inpatient/outpatient services. Offering opportunity to join our Medical Director's very successful practice; or salary with benefits if preferred. Contact **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; terry.good@horizonhealth.com

Private Practice Opportunities in North Carolina

Carolina Partners in Mental HealthCare, PLLC is seeking BE/BC psychiatrists for our practices in Raleigh, Cary, and Wake Forest, NC. Child/adolescent and/or adult psychiatrists welcome. Private outpatient practices, full partnership from day one - no investment required. FT, PT flexible. Carolina Partners has ten offices in Raleigh, Durham, Cary, Chapel Hill, Pittsboro and Wake Forest, North Carolina. Good opportunity to control your life and clinical practice, while making a good income! Contact Executive Director or send CV to: Carolina Partners in Mental HealthCare, 1502 W. Hwy 54, Suite 103, Durham, NC 27707. Phone 919-967-9567; Fax 919-882-9531; Email carolinapartners@bellsouth.net. Please visit our website located at carolinapartners.com

Close to Greensboro and Winston-Salem - Due to expansion of psychiatric services in the Thomasville Medical Center, we are seeking another psychiatrist already in practice who wants to add on some inpatient work, or we can offer an income guarantee to help a psychiatrist get their practice going. Great quality of life; great location; and great income potential. Please **call Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

NORTH DAKOTA

Join Prestigious Upper Midwest Medical Group

MeritCare Health System of Fargo, ND is seeking an Adult Psychiatrist to join its multidisciplinary Psychiatry Department. Faculty appointment and teaching of psychiatry residents is available through University of North Dakota School of Medicine. MeritCare is an integrated 450-physician, multi-specialty group practice, 583-bed, Level II tertiary/trauma hospital with 27-primary care clinics in two states. Sister cities, Fargo, ND and Moorhead, MN, are a tri-college community of 190,000 located near the heart of Minnesota's lake country. Fargo-Moorhead offers excellent educational systems, recreation and sports activity as well as a variety of entertainment and cultural events. This is an excellent opportunity with a competitive compensation and benefits package being offered. This is not a designated HPSA site. To learn more about this practice opportunity visit our website at www.meritcare.com or contact:

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OREGON

Oregon Department of Human Services

The Oregon Department of Human Services (DHS) is looking for Board Certified or Board eligible Psychiatrists with interest and/or experience in adult and forensic programs. You must also be eligible for licensure to practice medicine in Oregon. Salary is very competitive and includes psychiatric differential, certification pay, and opportunities for additional on-call work can increase your income substantially. A generous benefit package includes health and dental insurance and one of the best public employee retirement programs in the country. DHS operates three Psychiatric Hospitals in Salem, Portland, and Pendleton. Please call (503) 945-2817, Fax#: (503) 945-9910; Email: osh.recruitment@state.or.us. Or mail CV to: Human Resources, 2600 Center Street NE, Salem, OR 97301-2682. The Oregon Department of Human Services is committed to affirmative action, equal employment opportunity and workplace diversity.

PENNSYLVANIA

LIFESPAN PSYCHIATRY
Rhode Island Hospital
Affiliated Hospital of the Warren Alpert Medical School of Brown University

This full-time clinical position is part of an academic medical center program, and eligible through teaching opportunities to be considered for a Clinical Faculty appointment at Brown University. There are possibilities for research participation for applicants with appropriate background and interests, although the position is primarily clinical.

The position consists of half-time inpatient unit attending role along with half-time general outpatient psychiatry.

Applicant must be Board Certified in Psychiatry or Board eligible (within three years of training completion). Salary and benefits commensurate with level of training and experience.

Please send CV's along with a letter of interest to Richard J. Goldberg, M.D., Psychiatrist-in-Chief, APC-9, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903 and/or email: rjgoldberg@lifespan.org.

(1-2-09/eh/hr/ads)

Psychiatrists:

Currently we have exciting full- and part-time positions in a rapidly expanding department. Opportunities include responsibilities in and outside our five-hospital health system. There are immediate openings for child/adolescent, adult and addictions psychiatrists.

In addition, there are private practice options in a traditional psychotherapy model. Evening and weekend positions available. Excellent salaries, no on-call nor rounding responsibilities ever and exceptional benefits package offered. Send CV to Kevin Caputo, M.D., Vice President and Chairman, Department of Psychiatry, Crozer-Keystone Health System, One Medical Center Blvd., Upland, PA 19013 or contact the department manager, Kathy Waring at 610-619-7413

Horizon Health and St. Vincent Health System
Medical Director
Erie, PA

Horizon Health, in partnership with **St. Vincent Health Center (Voted 5th Best Place to work in Pennsylvania!),** a 436-bed tertiary care hospital in **Erie, PA,** has an exciting opportunity for a **Medical Director** for a **32-bed** Adult and Geriatric Inpatient Psychiatric Program.

Opportunities for input and growth, tertiary care, teaching opportunities in FP residency program and LECOM medical school. Excellent compensation package with full benefits.

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. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

Medical Director
Ashland, PA

Horizon Health, in partnership with **St. Catherine Medical Center** in Ashland, PA is seeking a **Medical Director** for a brand new, 14-bed Adult inpatient psychiatric unit.

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Become a pioneer and get in on this truly unique ground floor opportunity! For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

PHILADELPHIA - Child Psychiatrists for Residential & Inpatient Treatment Center OR Partial Day Program only in Bucks County. **CLARION & SHIPPENSBURG** - General Psychiatrist for Adult services. Positions can be fulltime or part-time (Mon-Fri schedule) - salary & benefits. Contact Joy Lankswert @ 866-227-5415; OR email joy.lankswert@uhsinc.com

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RHODE ISLAND

Fulltime position available for board eligible/certified inpatient psychiatrist interested in clinical faculty position at Butler Hospital. This outstanding opportunity offers a collegial academic environment in the major psychiatric teaching facility of the Warren Albert School of Medicine at Brown University, located in Providence, RI. Salary and clinical faculty appointment commensurate with experience. Apply by sending CV to Steven_Rasmussen@brown.edu.

SOUTH CAROLINA

AIKEN - minutes from Augusta GA & Columbia, SC. General Psychiatrist - inpatient & partial programs. Fulltime position - salary & benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

MEDICAL DIRECTOR FOR THE DIVISION OF INPATIENT SERVICES
SOUTH CAROLINA DEPARTMENT OF MENTAL HEALTH (SCDMH)
COLUMBIA, SOUTH CAROLINA

Position is responsible for the planning, direction and policy development of the clinical programs; assists with the planning and coordination of the overall strategic plan; supervision of the medical staff in the diagnosis and treatment of mentally ill patients; establishing effective liaison relationships with principal referral sources around the state, and with other programs within the SCDMH Division of Inpatient Services in a comprehensive system of care. Services are provided at Bryan Psychiatric Hospital, Harris Psychiatric Hospital, Morris Village Alcohol and Drug Treatment Center, William S. Hall Psychiatric Hospital for Children and Adolescents, Forensic Services, the Sexually Violent Predator Treatment Program, and The C.M. Tucker Nursing Care Center. The hospital system focuses on stabilization and community re-entry. Specialty services include acute care, long-term care, children and adolescents, substance abuse treatment services, forensics, Long-Term Care, and a sexually violent predator treatment program. The mental health system is moving toward an evidence-based system of care. We promote strong academic alliances.
Preferred Qualifications: A board certified psychiatrist with eligibility for licensure to practice medicine in South Carolina, at least five years of proven experience as a mental health executive, including progressively responsible administrative experience in the management of a complex hospital care delivery system. An in-depth knowledge of health care reform, a science to services approach, a keen sense of issues related to service delivery and strong leadership ability are highly desirable.
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PACT PSYCHIATRIST - #682
STAFF PSYCHIATRIST - #694

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For more information, contact Bill Semones, Vice President, Mental Health Services, at 434-200-4514 or bill.semones@centrahealth.com

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WASHINGTON

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The University of Washington and Harborview Medical Center (HMC) in Seattle, WA is accepting applications for a psychiatrist at the rank of Instructor or Assistant Professor (without tenure). This position is 1.0 FTE and will do a mix of consultation and inpatient psychiatry. Two half days a week will be spent working in psychiatry outpatient service settings. The position requires an MD and includes responsibility for teaching residents and medical students. Please send CV and cover letter to Peter Roy-Byrne, MD, Chief of Psychiatry, HMC 325 9th Ave. Box 359911, Seattle, WA 98104. University of Washington faculty engage in teaching, research, and service. The UW is building a culturally diverse faculty and strongly encourages applications from females and minority candidates. The UW is an EOE/AA employer.

Western Washington State: Adult/Geriatric/Forensic Psychiatrist (BE/BC with a WA state license) applications considered. Western State Hospital is a fully accredited (JCAHO) and certified (CMS) 997 bed hospital serving adult, geriatric and forensic populations. Annual salary up to $158,304 DOQ. Excellent benefits, including hospitalization/medical insurance, retirement and vacation leave, plus optional deferred income plan. Send CV to Leah Muasau, Medical Staff Coordinator; Western State Hospital; 9601 Steilacoom Blvd. SW; Lakewood, WA 98498-7213. E-Mail: MUASALL@DSHS.WA.GOV.

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INFANT PSYCHIATRY FELLOWSHIP. The Section of Child and Adolescent Psychiatry at Tulane University School of Medicine is seeking a full-time Fellow in Infant Psychiatry. This one or two year fellowship includes clinical and research experiences with the multidisciplinary Infant Mental Health group at Tulane. MD/DO required. Completion of a fellowship in Child and Adolescent Psychiatry preferred. Faculty appointment at the Instructor level with very competitive salary is possible. Applications will be accepted until a suitable qualified candidate is found. Applicants should send letter of interest, updated CV and list of references to Charles Zeanah MD, Vice Chair and Director of Child and Adolescent Psychiatry, 1440 Canal Street TB52, New Orleans, LA 70112. Interested eligible applicants may obtain further information regarding this position by contacting Dr. Zeanah at 504-988-5402 or czeanah@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

Fellowship in Addiction Psychiatry
University of Massachusetts Medical School

NEWLY ACCREDITED Fellowship in Addiction Psychiatry in a department with a major focus on addictions, including psychopharmacology, multiculturalism, basic neuroscience, psychosomatic medicine (working with primary care medicine's addiction faculty), and state-of-the-art psychosocial interventions. Major public and private sector affiliations including 120-bed private sector addiction hospital, a first-of-its-kind 16-bed public sector adolescent detoxification & rehabilitation unit, a new general hospital buprenorphine clinic with an intensive outpatient program for co-occurring disorders, organizational-wide tobacco cessation program, and a continuum of care for opioid dependent patients from detoxification through substitution therapy to community rehabilitation. We are in the midst of a major expansion of clinical and research services in the addictions, and the establishment of an academic Center of Excellence in Addiction Psychiatry. There are many clinical and translational research opportunities for trainees. This is an exciting time to join the UMass Addiction Psychiatry Program. Interested persons should contact: Gerardo Gonzalez, MD, Director of Addiction Psychiatry Fellowship Program, Department of Psychiatry, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655. Call Diana Langford (508) 334-0577 or email gerardo.gonzalez@umassmed.edu AA/EOE

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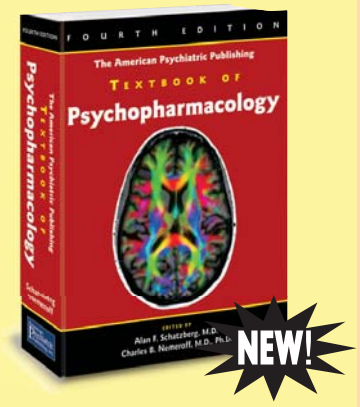

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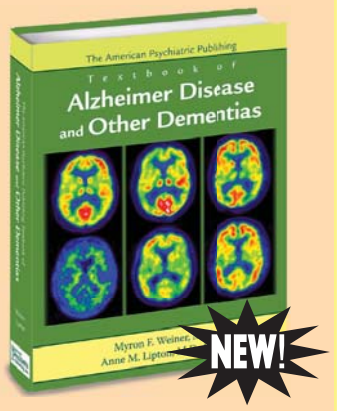

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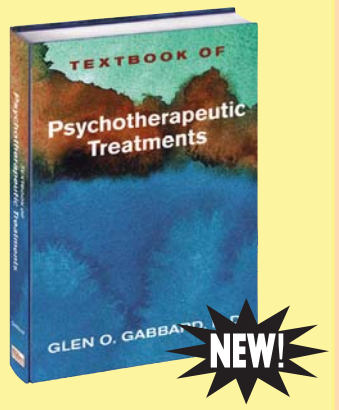

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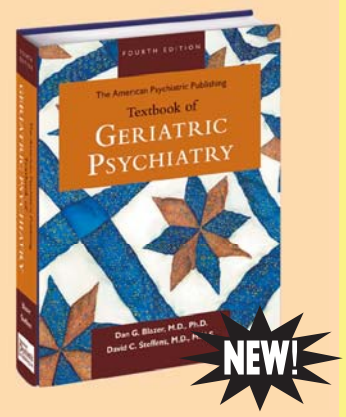

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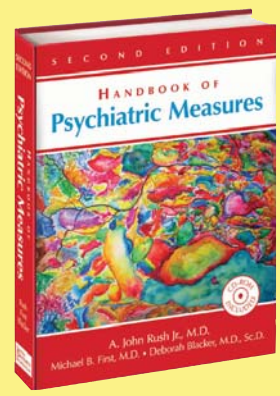

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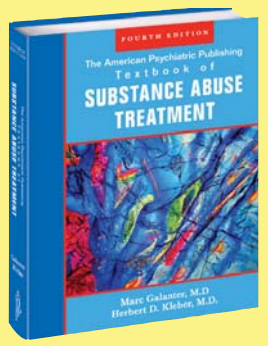

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Brief Summary: Consult the package insert for complete prescribing information.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. *[See Warnings and Precautions and Use in Specific Populations.]*

INDICATIONS AND USAGE: Major Depressive Disorder—Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD).

Generalized Anxiety Disorder—Cymbalta is indicated for the acute treatment of generalized anxiety disorder (GAD).

Diabetic Peripheral Neuropathic Pain—Cymbalta is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.

Fibromyalgia—Cymbalta is indicated for the management of fibromyalgia (FM).

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors—Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome *[see Warnings and Precautions]*.

Uncontrolled Narrow-Angle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

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

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

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms *[see Warnings and Precautions, Discontinuation of Treatment with Cymbalta]*.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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

Hepatotoxicity—There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (85/7,632) of Cymbalta-treated patients compared to 0.2% (13/5,578) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Warnings and Precautions and Drug Interactions]* and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

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

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated *[see Contraindications]*.

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*.

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*.

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2,489) of duloxetine-treated patients and 0.1% (1/1,625) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP, GAD, or fibromyalgia placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/9445) of patients treated with duloxetine and 0.01% (1/6770) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions, Vital Sign Changes]*.

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta—*CYP1A2 Inhibitors*—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions]*.

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions]*.

Potential for Cymbalta to Affect Other Drugs—*Drugs Metabolized by CYP2D6*—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered *[see Drug Interactions]*.

Other Clinically Important Drug Interactions—*Alcohol*—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions and Drug Interactions]*.

CNS Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action *[see Warnings and Precautions and Drug Interactions]*.

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations]*. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency *[see Warnings and Precautions and Use in Specific Populations]*.

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations]*.

Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma *[see Contraindications]*.

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related. In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327), GAD (N=668), DPNP (N=568) and FM (N=876). The population studied was 17 to 89 years of age; 64.8%, 64.7%, 38.7%, and 94.6% female; and 85.5%, 84.6%, 77.6%, and 88% Caucasian for MDD, GAD, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

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

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder—Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain—Approximately 14.3% (81/568) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) were nausea (duloxetine 3.5%, placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%), and fatigue (duloxetine 1.1%, placebo 0.0%).

Fibromyalgia—Approximately 19.5% (171/876) of the patients who received duloxetine in 3 to 6 month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 11.8% (63/535) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 1.9%, placebo 0.7%), somnolence (duloxetine 1.5%, placebo 0.0%), and fatigue (duloxetine 1.3%, placebo 0.2%).

Adverse Reactions Occurring at an Incidence of 5% or More and at least Twice Placebo Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled Trials for all Approved Indications—The most commonly observed adverse reactions in Cymbalta-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, hyperhidrosis, and decreased appetite.

In addition to the adverse reactions listed above, DPNP trials also included dizziness and asthenia.

Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—The incidence of treatment-emergent adverse reactions in placebo-controlled trials (N=4843 Cymbalta; N=3048 placebo) for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo were: nausea, headache, dry mouth, fatigue (includes asthenia), insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), dizziness, somnolence* (includes hypersomnia and sedation), constipation*, diarrhea, decreased appetite* (includes anorexia), and hyperhidrosis. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled MDD and GAD Trials—Table 3 in full PI gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-

Cymbalta® (duloxetine hydrochloride) PV 6860 AMP
Cymbalta® (duloxetine hydrochloride) PV 6860 AMP

controlled trials (N=2995 Cymbalta; N=1955 placebo) for approved indications that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Investigations—weight decreased*; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Nervous System Disorders—dizziness, somnolence (includes hypersomnia and sedation), tremor; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, decreased libido (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); Reproductive System and Breast Disorders—erectile dysfunction, ejaculation delayed, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); Respiratory, Thoracic, and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot flush. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Diabetic Peripheral Neuropathic Pain—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPNP placebo-controlled trials (N=115 Cymbalta 20 mg once daily; N=228 Cymbalta 60 mg once daily; N=225 Cymbalta 60 mg twice daily; N=223 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; General Disorders and Administration Site Conditions—fatigue, asthenia, pyrexia; Infections and Infestations—nasopharyngitis; Metabolism and Nutrition Disorders—decreased appetite, anorexia; Musculoskeletal and Connective Tissue Disorders—muscle cramp, myalgia; Nervous System Disorders—somnolence, headache, dizziness, tremor; Psychiatric Disorders—insomnia; Renal and Urinary Disorders—pollakiuria; Reproductive System and Breast Disorders—erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis.

Fibromyalgia—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of FM placebo-controlled trials (N=876 Cymbalta; N=535 placebo) and with an incidence greater than placebo were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, dyspepsia; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Immune System Disorders—seasonal allergy; Infections and Infestations—upper respiratory tract infection, urinary tract infection, influenza, gastroenteritis viral; Investigations—weight increased; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Musculoskeletal and Connective Tissue Disorders—musculoskeletal pain, muscle spasm; Nervous System Disorders—headache, dizziness, somnolence (includes hypersomnia and sedation), tremor, paraesthesia, migraine, dysgeusia; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), sleep disorder, abnormal dreams (includes nightmare), orgasm abnormal (includes anorgasmia), libido decreased (includes loss of libido); Reproductive System and Breast Disorders—ejaculation disorder (includes ejaculation failure and ejaculation dysfunction), penis disorder; Respiratory, Thoracic, and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis, rash, pruritus; Vascular Disorders—hot flush.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Physicians should routinely inquire about possible sexual side effects. See Table 6 in full PI for specific ASEX results.

Vital Sign Changes—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions]*. Duloxetine treatment, for up to 26-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3-4 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In fibromyalgia studies, patients treated with Cymbalta for up to 26 weeks experienced a mean weight loss of approximately 0.4 kg compared with a mean weight gain of approximately 0.3 kg in placebo-treated patients. In one long-term fibromyalgia 60-week uncontrolled study, duloxetine patients had a mean weight increase of 0.7 kg.

Laboratory Changes—Cymbalta treatment in placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients *[see Warnings and Precautions]*.

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 27,229 patients were treated with duloxetine. Of these, 29% (7,886) took duloxetine for at least 6 months, and 13.3% (3,614) for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. Cardiac Disorders—*Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia; Ear and Labyrinth Disorders—*Frequent:* vertigo; *Infrequent:* ear pain and tinnitus; Endocrine Disorders—*Infrequent:* hypothyroidism; Eye Disorders—*Frequent:* vision blurred; *Infrequent:* diplopia and visual disturbance; Gastrointestinal Disorders—*Frequent:* flatulence; *Infrequent:* eructation, gastritis, halitosis, and stomatitis; *Rare:* gastric ulcer, hematochezia, and melena; General Disorders and Administration Site Conditions—*Frequent:* chills/rigors; *Infrequent:* feeling abnormal, feeling hot and/or cold, malaise, and thirst; *Rare:* gait disturbance; Infections and Infestations—*Infrequent:* gastroenteritis and laryngitis; Investigations—*Frequent:* weight increased; *Infrequent:* blood cholesterol increased; Metabolism and Nutrition Disorders—*Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia; Musculoskeletal and Connective Tissue Disorders—*Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching; Nervous System Disorders—*Frequent:* dysgeusia, lethargy, and parasthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; *Rare:* dysarthria; Psychiatric Disorders—*Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide; Renal and Urinary Disorders—*Infrequent:* dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal.; Reproductive System and Breast Disorders—*Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms, and sexual dysfunction; Respiratory, Thoracic and Mediastinal Disorders—*Frequent:* yawning; *Infrequent:* throat tightness; Skin and Subcutaneous Tissue Disorders—*Infrequent:* cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis; Vascular Disorders—*Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

Postmarketing Spontaneous Reports—The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, gynecological bleeding, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, restless legs syndrome, seizures upon treatment discontinuation, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

DRUG INTERACTIONS: Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine t1/2 was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin *[see Warnings and Precautions]*.

Inhibitors of CYP2D6—Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) *[see Warnings and Precautions]*.

Dual Inhibition of CYP1A2 and CYP2D6—Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued *[see Warnings and Precautions]*.

Lorazepam—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption *[see Warnings and Precautions]*.

Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold *[see Warnings and Precautions]*.

Drugs Metabolized by CYP2C9—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors—Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI *[see Contraindications and Warnings and Precautions]*.

Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended *[see Warnings and Precautions]*.

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions]*.

Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol.

In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen *[see Warnings and Precautions]*.

CNS Drugs—*[see Warnings and Precautions]*.

Drugs Highly Bound to Plasma Protein—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

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

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions]*.

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions]*. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2,418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1,074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1,761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPNP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*.

Gender—The half-life of duloxetine is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—*[see Warnings and Precautions]*.

Severe Renal Impairment—*[see Warnings and Precautions]*.

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

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Sometimes the face of depression isn't a face at all*

Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD).

* Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for MDD on mean change in HAM-D_{17} Total Score,[1] Maier Subscale,[1] Psychic Anxiety,[1] and Visual Analog Pain Scales.[2] Full antidepressant response may take 4-6 weeks. MMRM=Mixed-effects Models Repeated Measures analysis

References: 1. Data on file, Lilly Research Laboratories: CYM20070220C.
2. Fava M, et al. *J Clin Psychiatry*. 2004;65(4):521-530.

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Cymbalta® DELAYED RELEASE
duloxetine HCl CAPSULES

Important Safety Information

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients of all ages started on therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.**
- **Cymbalta is not approved for use in pediatric patients.**

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or in patients with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All patients being treated with an antidepressant for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients**.

Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Cases of orthostatic hypotension and/or syncope as well as cases of hyponatremia have been reported.

Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs, including triptans. Concomitant use is not recommended.

SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.

On discontinuation, adverse events, some of which may be serious, have been reported with SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.

Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.

Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics).

Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min).

As observed in DPNP clinical trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases up to 52 weeks, an increase in HbA_{1c} in both the Cymbalta (0.5%) and routine care groups (0.2%) was noted.

If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=4843 vs 3048) were: nausea, dry mouth, somnolence,* constipation,* decreased appetite,* and increased sweating.

*Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

See Brief Summary of full Prescribing Information, including Boxed Warning, on following spread.

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