Peter F. Buckley, MD
Editor-in-Chief

Includes 2008 APA Annual Meeting Updates

Continued Interest in Developing Alpha-7 Nicotinic Agonist Drugs for Treating Cognitive Deficits in Patients with Schizophrenia

EnVivo Pharmaceuticals has initiated a clinical safety study of an alpha-7 nicotinic agonist (EVP-6124) in twenty patients treated with a second-generation antipsychotic medication. EVP-6124 is a potent full agonist at the alpha-7 nicotinic receptor. The objectives of this study are to evaluate the safety of multiple doses of EVP-6124 in this schizophrenia patient population and to investigate potential drug-drug interactions. Patients will receive one or two dose regimes of EVP-6124 or placebo. The study is of particular interest because it has included measurements that may be biomarkers for treatment response and sensitivity to this nicotinic agonist. The study may determine the effects of EVP-6124 on sensitive electrophysiology markers (the P50 auditory evoked response and mismatch negativity). Patients with schizophrenia are known to have abnormalities in sensory gating that have been shown in preclinical animal studies to be responsive to alpha-7 nicotinic receptor stimulation. The evoked response paradigm involves testing the extent to which normal suppression is lost. When repetitive auditory stimuli are presented to patients, the evoked electrophysiologic brain response (the P50 response measured 50 msec after each stimulus) is suppressed by up to 80% in normal subjects. Patients with schizophrenia have a failure of this suppression. This abnormality has been linked to an allele on chromosome 15, the gene locus for the alpha-7 receptor. Alpha-7 nicotinic agonists have recently been shown to improve cognition and the P50 response in patients with schizophrenia. Thus, the P50 response may turn out to be a sensitive biomarker for assessing the pro-cognitive effect of an alpha-7 nicotinic agonist in schizophrenia.

Additionally, mismatch negativity is another electrophysiological biomarker well known to be abnormal in patients with schizophrenia. Mismatch negativity is assessed by the ability of the patient to detect a unique stimulus embedded in a repetitive train of otherwise identical auditory stimuli. Thus, assessments of the effect of EVP-6124 on P50 evoked response and mismatch negativity will also help determine whether these measures could be used as sensitive biomarkers for this class of drugs.

Another nicotinic alpha-7 agonist drug, Memory Pharmaceuticals' MEM 3454, is currently under investigation for use in neurological and psychiatric disorders. In early May, Roche exercised its option to further develop and commercialize MEM 3454.

New Indications for Second-Generation Antipsychotics

Since our last issue of ***CS***, there have been additional approvals of antipsychotics for expanded clinical indications. Aripiprazole now has expanded indications in bipolar I disorder and schizophrenia. Aripiprazole also is indicated now for maintenance treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in pediatric patients (aged 10–17) and for maintenance treatment of schizophrenia in adolescents (aged 13–17). In addition, aripiprazole also now has a U.S. Food and Drug Administration (FDA) indication for adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in pediatric patients (aged 10–17). The safety and effectiveness of aripiprazole in pediatric patients with bipolar mania were established in a four-week, placebo-controlled clinical trial in 197 pediatric patients (aged 13–17). The safety and effectiveness of aripiprazole in adolescents with schizophrenia were established in a six-week, placebo-controlled clinical trial in 202 pediatric patients (aged 13–17). Both studies demonstrated efficacy of aripiprazole in these patient groups. These were short-term trials, however, and maintenance efficacy in these patient populations has not been systematically evaluated.

Additionally, the indication for adjunctive aripiprazole with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been studied directly. Nevertheless, there is no evidence of data concerning potential drug interactions, and there is no evidence of pharmacokinetic interaction between aripiprazole and lithium or valproate from available data in the adult population.

Also, the FDA has approved quetiapine fumarate tablets for the maintenance treatment of patients with bipolar I disorder as adjunct therapy to lithium or divalproex. It is approved, as well, for the treatment of both depressive episodes in bipolar disorder and acute manic episodes associated with bipolar I disorder. The FDA approval was based on two multicenter, randomized, double-blind, placebo-controlled clinical trials that evaluated quetiapine as an ad-

junct therapy to lithium or divalproex in the maintenance treatment of adult patients with bipolar I disorder (n=703, n=623, respectively). The study was designed as a 12- to 36-week stabilization phase followed by a longer term, randomized, double-blind treatment phase that had a mean duration of exposure of 213.2 days for quetiapine and 152.4 days for placebo. Patients with bipolar I disorder whose most recent episode was manic, depressed or mixed were treated with either quetiapine (flexible dosing between 400 and 800 mg per day in divided doses) plus lithium or divalproex or placebo plus lithium or divalproex. Patients treated with quetiapine plus lithium or divalproex (n=646) had a risk reduction of 70% relative to those treated with placebo plus lithium or divalproex (n=680) for time to recurrence of a mood event recurrence of a depressive, manic or mixed mood event. This reduction in risk was significant for both recurrences of manic and depressive episodes. The proportion of patients who relapsed when treated with quetiapine was 19.3% versus 50.4% of patients on placebo. Adverse events in these trials were generally consistent with those reported in short-term, placebo-controlled trials for quetiapine. A greater incidence of blood glucose increases was observed in patients receiving quetiapine plus lithium or divalproex.

New Data on Loxitane

Loxitane, a long standing first-generation antipsychotic, is an interesting antipsychotic because of its high extent of serotonin (5HTTza) antagonism that is also a characteristic of several second-generation antipsychotics (SGAs). A Phase 2a clinical trial of inhaled loxitane (AZ-004) for the treatment of acute agitation in schizophrenia patients was presented at the May 2008 American Psychiatric Association (APA) Annual Meeting in Washington, DC. This study delivered loxitane in an aerosol formulation, an approach which allows rapid absorption. In this twenty-four hour, inpatient study of 129 acutely agitated patients, low doses of inhaled loxitane (5 mg or 10 mg) were compared to placebo (inhalation or inert product). The study methodology was similar to other recent studies of acute intramuscular formulations of SGAs. Under these conditions, the inhaled version of loxitane demonstrated clinical efficacy, was an acceptable approach for patients and was well tolerated. This is an interesting approach to drug delivery.

New Data on Long-Acting Injectable Antipsychotics

Two new studies presented at the 2008 APA Annual Meeting provided long-term data on risperidone microspheres:

An international study of 710 patients (355 randomized to received risperidone long-acting injectable [mean dose 32.75 mg] and 355 to receive quetiapine [mean dose 397 mg]) compared, over a twenty-four month period, treatment with risperidone long-acting injectable (RLAI) versus oral quetiapine in a routine psychiatric care setting.

Results demonstrated that the average relapse-free time was significantly longer in patients treated with RLAI (607 days) compared with quetiapine (533 days). Relapse occurred in 16.5% of patients treated with RLAI versus 31.3% in the quetiapine treatment arm. Reasons for withdrawing from the study, other than relapse, were equivalent in both treatment groups, except that more withdrawals due to noncompliance/refusing injection were reported for RLAI (3%) than quetiapine (1%).

Both RLAI and quetiapine had generally comparable safety profiles. Extrapyramidal symptoms (EPS) attributed to medication were observed in 10% of the patients receiving RLAI and in 6% of the patients in the quetiapine group. Weight gain was observed in both treatment arms, with no statistically significant differences in changes in body mass index (BMI) versus baseline (7% weight gain for RLAI versus 6.2% for quetiapine). Potentially prolactin-related adverse events were observed in 16.7% of the patients in the RLAI arm and in 3% of patients in the quetiapine arm.

The most common serious adverse events were psychiatric symptoms (15% with RLAI and 18% with quetiapine). Death occurred in three patients treated with RLAI and in two patients treated with quetiapine. None of the deaths were considered to be possibly or probably related to study drug.

Separately, an interim analysis from a two-year U.S. observational study from sixty-six community health centers and Veterans Affairs centers reports patients taking RLAI had significantly improved functioning within three months after starting treatment. That study enrolled 532 patients in the United States. At the time of this interim analysis, 107 patients had completed the full two-year period. The interim analysis showed an overall significant improvement in patient functioning from "serious" to "occasional" impairments following initiation of RLAI; 11% more patients reported they were "very" or "extremely" satisfied with their current antipsychotic therapy at the first visit after the initiation of treatment with RLAI compared to their first visit prior to the initiation of RLAI.

Data on an investigational, long-acting injectable form of paliperidone—paliperidone palmitated—were also presented at the 2008 APA Annual Meeting. In a thirteen-week, placebo-controlled, double-blind study comparing three doses of paliperidone palmitate (25 mg, 50 mg, 100 mg equivalent, given at four-week intervals), paliperidone was efficacious and had a lower discontinuation rate than the placebo-injection group. Paliperidone was well tolerated. Weight gain was seen, particularly at the 100 mg dose (1.3 kg over the study duration).

Finally, Chiliza and colleagues from South Africa presented at the 2008 APA Annual Meeting an interim analysis from an interesting study of long-acting injectable flupenthixol decanoate in first-episode schizophrenia patients. In an analysis of the first three months of treatment among twenty patients, they reported just over a 40% reduction in Positive and Negative Syndrome Scale (PANSS) total scores. Extrapyramidal side effects peaked at the fourth week; the average increase in BMI at three months was 1:45 units.

Genetic Variation Associated with Treatment Response for New Antipsychotic

Iloperidone is a new antipsychotic with a predominantly serotonin-dopamine (5HT2A/D2)—and norepinephrine—antagonism profile. Results of clinical trial programs have recently been published in a journal supplement (see below). Vanda Pharmaceuticals has recently submitted a new drug application (NDA) to the FDA for consideration of iloperidone (Fanapta™) in the treatment of schizophrenia. As part of the clinical data, a recently reported study by Lavedam and colleagues found that a genetic variation (rs1800169 genotype G/G versus nonGG) in the Ciliary Neurotrophic Factor gene (CNTF) may affect treatment response. Patients were evaluated for a genetic variation in the CNTF gene, CNTF being a neurotrophic factor that regulates neuronal integrity. There is a great interest currently in the role of neurotrophins in schizophrenia and mood disorders. There is some evidence that another neurotrophin, Brain-Derived Neurotrophic Factor (BDNF), is altered during relapse in mood disorders. It also has been shown to increase with treatment with antidepressants. Decrements in BDNF have also been shown in schizophrenia, and there are also genetic studies of BDNF in both schizophrenia and mood disorders.

In this interesting study, treatment with iloperidone was significantly better than placebo in symptom improvement among patients with both intact copies of CNTF. In patients carrying at least one truncated copy of the CNTF protein (25% of patients), both placebo- and iloperidone-treated patients had a significant improvement from baseline, indicating an enhanced placebo response among this group of patients. Thus, the impact of iloperidone was more pronounced in patients who were homozygous (G/G) for the polymorphism on this gene. These are exciting new data. They also give an appreciation of the potential of pharmacogenetics to better predict treatment response for schizophrenia.

The articles in the journal supplement provide a good overview of early studies in the clinical trials program for iloperidone. In brief, six-week, double-blind, placebo-controlled trials (with haloperidol or risperidone as an active comparator), studies demonstrated the short-term efficacy of iloperidone (Potkin et al., 2008). Another four-week, double-blind, placebo-controlled trial (with ziprasidone as an active comparator) described the short-term efficacy of iloperidone (Cutler et al., 2008). A 52-week maintenance study found iloperidone (4–16 mg/day) superior to haloperidol (5–20 mg/day) in maintaining clinical stability and with a favorable metabolic profile (Kane et al., 2008). The short-term studies also demonstrated mild weight gain (similar to risperidone), minimal metabolic effects, propensity for low extrapyramidal side effects, and a prolactin-spanning effect.

Lavedan C, Volpi S, Polymeropoulos MH, Wolfgang CD. Effect of a ciliary neurotrophic factor polymorphism on schizophrenia symptom improvement in an iloperidone clinical trial. Pharmacogenomics 2008;9(3):289-301.

Potkin SG, Litman RE, Torres R, Wolfgang CD. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. J Clin Psychopharmacol 2008;28(2 Suppl 1):S4-11.

Cutler AJ, Kalali AH, Weiden PJ, Hamilton J, Wolfgang CD. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with exacerbations of schizophrenia. J Clin Psychopharmacol 2008;28(2 Suppl 1):S20-28.

Kane JM, Lauriello J, Laska E, Di Marion M, Wolfgang CD. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. J Clin Psychopharmacol 2008;28(2 Suppl 1):S29-35.

Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. J Clin Psychopharmacol 2008;28(2 Suppl 1):S12-19.

Update on Asenapine Data from Olympia Trial Program

An overview of asenapine clinical trials from the Olympia Trial Program was presented at the 2008 APA Annual Meeting. Data from the studies, involving patients with bipolar I disorder and schizophrenia, were presented along with long-term safety and efficacy data from a clinical trial involving patients with schizophrenia and schizoaffective disorders.

Asenapine, a fast-dissolving, new antipsychotic is currently under review by the FDA. In the Olympia Trial Program, asenapine was shown to be effective in two short-term bipolar mania studies with a nine-week extension, and in two out of four short-term schizophrenia studies. In the third short-term schizophrenia study, neither asenapine nor the active control differentiated from placebo; in the fourth study, asenapine did not differentiate from placebo, while the active control did. Overall, asenapine was well tolerated in the Olympia Trial Program.

The bipolar I disorder program included two placebo- and active-controlled, three-week trials as well as a one-year extension study. Almost 1,000 patients with bipolar I dis-

order were involved in this program. In both trials, asenapine had a significant reduction in Young Mania Rating Scale (MRS) total scores (of 13 and 14 points) compared to placebo after three weeks of treatment. Olanzapine was also effective and was included as an active control drug, although there was no direct comparison between asenapine and olanzapine. In a nine-week extension of the three-week trials, asenapine was comparable to olanzapine in efficacy. Treatment-related adverse events (AEs) were recorded in 60.8% of the asenapine-treated patient group, in 52.9% of the olanzapine group, and in 36.2% of the placebo group. The most commonly reported adverse events (AEs) with asenapine included sedation, dizziness, somnolence and weight increase.

The schizophrenia program included four placebo- and active-controlled, six-week trials. Over 1,300 patients with schizophrenia were included in these studies. In two of the trials (involving almost 700 patients), asenapine was effective and significantly superior to placebo and was associated with 19- to 20-point reductions in PANSS total score. In the third study (approximately 260 patients), asenapine did not (nor did the active control, olanzapine) differentiate from placebo. The fourth trial (approximately 400 patients) was considered a negative trial, as olanzapine (the active control) differentiated from placebo whereas asenapine did not. The most commonly reported AEs with asenapine were somnolence and akathisia.

In a year-long, double-blind, randomized study of 1,200 patients with schizophrenia or schizoaffective disorder treated with asenapine or olanzapine, the overall rates of AEs were similar between asenapine (5–10 mg BID) and olanzapine (10–20 mg QD). Improvements in PANSS total score were seen for both drugs within the first six-to-eight weeks of treatment and were maintained throughout the fifty-two week study period. In an exploratory secondary analysis, the between-group difference at fifty-two weeks favored olanzapine. Overall, these studies show that asenapine has antipsychotic efficacy and is tolerated during both short-term and long-term treatment.

From the viewpoint of clinical trials methodology, these studies illustrate the importance of including both placebo and active-comparator conditions when evaluating a new drug. The placebo arm helps differentiate when a drug works by comparison to placebo condition. The active comparator is actually a "reference drug," included to confirm trial validity. Thus, the active comparator provides a way to test whether the placebo arm is valid in that the comparator drug is a well "tried and trusted" agent (in this case, olanzapine) that one would expect to be superior to placebo. That way, the comparator arm provides "an internal check" on the study, and when it does not differentiate from placebo, it raises questions about the study sample/design. The Olympia Trial Program is of interest in both demonstrating the efficacy of asenapine and also from a clinical trials methodology perspective. Asenapine is currently under review by the FDA.

New Data on Expanded Use of Antipsychotics

During the 2008 APA Annual Meeting, Dr. Michael Liebowitz and colleagues from New York presented an interesting clinical trial on ziprasidone monotherapy for bipolar II depression. Twenty patients had been enrolled in this ongoing, eight-week, open-labeled, monotherapy trial in patients with bipolar II disorder with a major depressive episode. Sixty percent of patients were responders and 45% of patients met remission criteria by the end of the study. Ziprasidone was well tolerated, and no patient became manic. Interestingly, the mean dose of ziprasidone was rather low at 53 mg/day.

In another study of ziprasidone presented at the 2008 APA, this one involving obese/overweight patients with bipolar disorder, Wang and colleagues from Stanford reported that when ziprasidone was added the average weight dropped by 0.85 pounds per week. Additionally, nineteen of twenty patients had either a decrease or cessation of other psychotropic drugs being used to treat their mood symptoms, and 60% of patients opted to continue on ziprasidone after the study was finished. The average dose of ziprasidone here was 108 mg/day.

New study data on quetiapine fumarate extended-release tablets (quetiapine XR) for the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD) in adult patients were also presented at the 2008 APA. The quetiapine XR clinical development programs for MDD and GAD included seven Phase III, placebo-controlled studies in MDD, as well as four Phase III, placebo-controlled studies in GAD.

Three of the seven MDD studies investigated quetiapine XR in the treatment of adult patients diagnosed with MDD as monotherapy in both short-term and maintenance treatment and as short-term adjunct treatment versus placebo (doses of 50 mg, 150 mg and 300 mg of quetiapine XR were studied in the MDD program):

- a six-week, multicenter, double-blind study (among 723 patients) compared quetiapine XR 50 mg/day, quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo. At week six, all quetiapine XR groups had significantly reduced mean Montgomery-Asberg Depression Rating Scale (MADRS) scores versus placebo. The most common adverse events (AEs) (greater than or equal to 5% and double the rate of placebo in any quetiapine XR dose group) were dry mouth, sedation, somnolence, dizziness, constipation, back pain, irritability and myalgia.

- in another six-week, multicenter, double-blind study (among 446 patients), antidepressant therapy (AD) plus quetiapine XR 150 mg/day was compared with quetiapine XR 300 mg/day plus AD, or placebo plus AD. Quetiapine XR 300 mg/day plus AD showed statistically significant improvements over placebo plus an AD for change in MADRS total score at week six, in overall treatment response (58.9% versus 46.2%; $p<0.05$), and in remission (42.5% versus 24.5%). For quetiapine XR 150 mg/day plus AD, improvements were similar to antidepressant monotherapy. The most common AEs were dry mouth, somnolence, sedation, dizziness, constipation, fatigue and weight increase.

- in a double-blind, randomized-withdrawal, parallel-group, maintenance study, 787 patients were randomized to quetiapine XR or placebo and dose-adjusted as clinically indicated. The mean daily dose of study drug at randomization (last open-label dose) was similar for the quetiapine XR group (176.6 mg/day) and the placebo group (177.9 mg/day). The risk of a depressed event was significantly reduced for quetiapine XR compared with placebo. In total, 55 (14.2%) quetiapine XR-treated patients and 132 (34.4%) placebo-treated patients experienced a depressed event.

Two GAD studies presented at the 2008 APA Annual Meeting investigated treatment with quetiapine XR in adult patients diagnosed with GAD as monotherapy in both short-term and maintenance treatment versus placebo:

- a ten-week (eight weeks active; two weeks tapering discontinuation), multicenter, double-blind, parallel-group study (951 patients) compared quetiapine XR 50 mg/day, 150 mg/day, 300 mg/day, or placebo. The mean change from baseline to week eight in the Hamilton Anxiety Scale (HAM-A) total score was significantly greater than placebo for quetiapine XR 50 mg/day and for 150 mg/day, but not for 300 mg/day. The response rates at week eight were significantly more for patients receiving quetiapine at either quetiapine 50 mg/day (60.3%) or 150 mg/day (61.5%) than among patients in the placebo group (50.7%). Remission at week eight was also significantly higher for quetiapine 150 mg/day versus placebo (37.2% versus 27.6%) and was 36.1% and 28.6% for 50 mg/day and 300 mg/day doses, respectively. The most common AEs were dry mouth, somnolence, sedation and constipation.

- a double-blind, randomized-withdrawal, parallel-group, placebo-controlled study of 433 patients compared quetiapine XR or placebo following open-label stabilization for a minimum of twelve weeks. The quetiapine XR dose was flexible: 50 mg, 150 mg or 300 mg once daily, based on clinical judgment. The risk of an anxiety event was significantly reduced for quetiapine XR compared with placebo, suggesting increased time to the event. Twenty-two (10.2%) quetiapine XR-treated patients and eighty-four (38.9%) placebo-treated patients experienced an anxiety event.

AstraZeneca has filed a new drug application (NDA) with the FDA for consideration of quetiapine XR as a treatment for generalized anxiety disorder. This is the first time any FDA approval has been sought for an antipsychotic in this treatment indication. This represents an important issue, both with respect to understanding the breadth and use of antipsychotics, as well as their therapeutic indications. If the FDA approves this indication for an antipsychotic, comparative data against other current treatments for GAD will be critical in assessing the risk-benefit profile of all agents in the pharmacotherapy of anxiety disorders.

Prescribing Practices, Information Sharing, and Physician Relationships with Pharmaceutical Companies All Come Under Scrutiny

Several changes are underway on how physicians might relate to pharmaceutical companies. While interactions between the pharmaceutical industry and Departments of Psychiatry around the country have contributed to the academic mission in research, education and patient services, the healthcare environment has changed such that now the public is keenly concerned that the unique relationship between patients and their healthcare providers not be compromised by the presence or even the appearance of conflicts with any commercial interests. The change in public and regulatory opinion is reflected nationally at other academic institutions, as well as in our professional organizations and accreditation bodies. Recently, new federal legislation has been proposed—the "Physician Payments Sunshine Act"—which would require drug and medical device manufacturers to disclose anything of value given to physicians, including payments, gifts, honoraria or travel. This proposal is an effort to provide greater transparency of interactions between industry and academic medicine. This proposed legislation would also create a national database. Additionally, the FDA is considering whether TV drug advertisements should carry a toll-free telephone number so that patients can report serious problems with their medications. This consideration is in response to concern that consumers may not understand adequately potential benefits and risks of the drugs being promoted by pharmaceutical companies. Direct-to-consumer advertisements have appeared with several antipsychotic agents. Moreover, the use of these agents has expanded, and as illustrated above, there are now new

indications (in mood disorder in adolescents, in autism) for some drugs for use beyond psychosis. The off-label use of drugs, in these instances antipsychotic medications, has become a hot topic.

This all comes at a time when the treatment of even schizophrenia and bipolar disorder has (paradoxically) become increasingly complex, with greater availability and choice among antipsychotic medications. For patients and clinicians, the question of "which of these medications do I use?" is now very challenging. Evidence suggests that the use of antipsychotics beyond their FDA indication is common in clinical practice. Additionally, it is a topic of enduring interest among clinicians who are always eager to understand the information contributing to key therapeutic strategies. At the present time, we are lacking a robust research literature to guide this decision making process that is the clinician's dilemma. Several pharmaceutical companies have faced federal censure for alleged "off label" promotional activities. This is also very relevant to our training of residents in how best to prescribe these antipsychotic medications. The FDA is also considering how best to oversee the content and quality of information that pharmaceutical representatives share with clinicians. Now, more than ever, it is crucial for us to stay current with FDA indications for all antipsychotic medications and to be "ever-vigilant" about off-label prescribing practices. Mossman provides an excellent account of the medicolegal aspects of this complex topic.

Finally, the Department of Human Services has launched the Sentinel Initiative, a program to allow the FDA to evaluate Medicare claims data in relation to the risks of drugs. This is complementary to other insurance directives to cease to pay for medical services that are due to (physician-induced/iatrogenic) drug side effects.

Campbell EG, Weissman JS, Ehringhaus S, Rao SR, Moy B, Feibelmann S, et al. Institutional academic industry relationships. JAMA 2007;298(15):1779-1786.

Ehringhaus SH, Weissman JS, Sears JL, Goold SD, Feibelmann S, Campbell EG. Responses of medical schools to institutional conflicts of interest. JAMA 2008;299(6): 665-671.

Guidance for industry: good reprint practices for the distribution of medical journal articles and medical or scientific reference publications on unapproved new uses of approved drugs and approved or cleared medical devices. Draft guidance. U.S. Department of Health and Human Services, Food and Drug Administration; 2008 Feb. Federal Register Docket No. FDA-2008-D-0053, OC 2007268. http://www.fda.gov/oc/op/goodreprint.html

Geppert CM. Medical education and the pharmaceutical industry: a review of ethical guidelines and their implications for psychiatric training. Acad Psychiatry 2007;31(1):32-39.

Mossman D. Evaluate liability risks in prescribing. Current Psychiatry 2008;7(4):91-95.

Rothman DJ. Academic medical centers and financial conflicts of interest. JAMA 2008;299(6):695-697.

Mental Health Parity is "Inching" Nearer

For all clinicians who treat patients with serious mental illness, the progress toward mental health insurance parity has been slow and painful. However, now after more than a decade of "stops and starts," the U.S. House of Representatives has passed a bill requiring most group health plans to provide better coverage for treatment of mental illnesses, comparable to what they provide for physical illnesses. The U.S. Senate has also passed a similar bill requiring parity in coverage of mental and physical ailments. The House bill does not apply to health plans sponsored by an employer with fifty or fewer employees. Nor does it apply to coverage in the individual insurance market. Nevertheless, this is potentially a major step forward and is consistent with greater awareness that there are now biological causes and effective treatments for mental illnesses and that stigma may now be less prominent. The House bill is named after Senator Paul Wellstone, the former Minnesota Democrat who had a brother with severe mental illness. The primary sponsor of the Senate bill, Pete V. Domenici, Republican from New Mexico, has a daughter with schizophrenia. Although, if enacted, this could transform mental health insurance, there are likely still to be many challenges and obstacles along the way.