EDITOR'S NOTE

This column reflects our commitment to provide you, the primary care physician, with information that will prove helpful in making informed decisions about the care of your patients who suffer from psychiatric disorders. We will highlight abstracts of high interest to you from our sister publication, *The Journal of Clinical Psychiatry*, and summarize pertinent articles from the general scientific literature. We hope that this section is clinically relevant to your practice and that it will encourage you to expand your horizons.

The Course of Depressive Illness in General Practice

Limosin F, Loze JY, Zylberman-Bouhassira M, et al.

Background: In primary care settings, depression is reported to be common and to have a high likelihood of relapse during the 4- to 6-month period following initial symptomatic improvement. Most prospective studies of long-term treatment of depression have been conducted with patients selected for participation in placebo-controlled drug protocols or psychiatric clinics associated with tertiary referral centers. ***Method:*** The treatment course and outcome of outpatients with major depressive episode treated in a primary care setting were examined. General practitioners chose the treatment and its duration. Physicians were required to assess the therapeutic outcome in terms of efficacy and safety and to perform a final evaluation at the end of the 6-month observation period. If the patient was treated for a shorter period, the assessment was conducted at the end of the treatment. ***Results:*** Of the 476 patients who participated in the study, 308 (64.7%) responded to treatment and remained well, 51 (10.7%) had an early relapse after initial improvement, and 117 (24.6%) showed no response. The history of recurrent depression was the only variable with a significant effect size in predicting the course of the illness among the demographic, clinical, and therapeutic factors studied. ***Conclusion:*** Patients with recurrent depression were at higher risk of nonresponse or relapse.

(Can J Psychiatry 2004;49:119–123)

Glycogen Synthase Kinase-3: A Target for Novel Bipolar Disorder Treatments

Gould TD, Zarate CA, Manji KG

The enzyme glycogen synthase kinase-3 (GSK-3) is a direct target of lithium. While GSK-3 was originally recognized as an important molecule in a limited number of cellular processes, with unclear significance for the treatment of bipolar disorder, recent evidence suggests it has critically important cellular functions in the adult brain. GSK-3 has an essential role in a number of signaling pathways and regulates the function of a diverse number of proteins, notably transcription factors and cytoskeletal elements. The most important functions of the enzyme in regard to bipolar disorder may be critical effects on cellular resilience and neuronal plasticity. There is tremendous interest in GSK-3 inhibitors as novel therapeutic agents, and selective, small-molecule compounds are rapidly being developed for a broad range of other maladies including diabetes, Alzheimer's disease, stroke, and inflammatory conditions. In this perspectives article, we provide an overview of the molecular targets of lithium, focusing on GSK-3–regulated signaling pathways and the important functions of GSK-3 that may have relevance for the treatment of bipolar disorder. We conclude with a discussion of the GSK-3 inhibitors furthest in development and the clinical trials that may emerge.

(J Clin Psychiatry 2004;65:10–21)

Cabergoline Treatment of Risperidone-Induced Hyperprolactinemia: A Pilot Study

Cavallaro R, Cocchi F, Angelone SM, et al.

Background: D_2 blockers, including the atypical antipsychotic risperidone, induce hyperprolactinemia in a significant number of patients treated. The endocrine and sexual side effects related to hyperprolactinemia significantly impair tolerability and compliance in patients, including those with a good response to risperidone. This pilot study aimed to evaluate the efficacy and tolerability of a low dose of cabergoline, a D_2 agonist, in the treatment of risperidone-induced hyperprolactinemia. ***Method:*** Nineteen male and female DSM-IV–defined schizophrenic patients who were clinical responders to risperidone but were suffering from symptomatic hyperprolactinemia were treated with cabergoline, 0.125 to 0.250 mg/week for 8 weeks. Plasma prolactin level was assessed at baseline and at the end of the study. Data were collected from January 2002 to

April 2003. ***Results:*** After cabergoline treatment, the mean decrease in plasma prolactin levels was statistically significant ($p < .05$) for the total sample, and 11 patients showed remission of clinical signs with prolactin values within the normal range. No side effect was observed or reported, and the patients' psychopathology was unchanged. ***Conclusions:*** Results suggest that low-dose cabergoline treatment of risperidone-induced hyperprolactinemia may be safe and clinically effective in a relevant number of patients.

(J Clin Psychiatry 2004;65:187–190)

Comparisons of Patients With Comorbid Psychiatric and Substance Use Disorders: Implications for Treatment and Service Delivery

Havassy BE, Alvidrez J, Owen KK

Background: Individuals with co-occurring substance use and psychiatric disorders are treated in substance abuse treatment and mental health systems; however, research on comorbid disorders seldom includes comparisons across systems. Knowledge about patients who are found in different treatment sectors but share the label "comorbid" should inform policy development and illuminate service issues. Similarities across systems should indicate the value of the integration of services; differences across systems should provide support for separate treatments. This study tested the hypothesis that meaningful clinical differences exist between patients with comorbid mental health disorders and patients in drug treatment. ***Method:*** As part of a larger longitudinal study, 106 patients with comorbid illness from mental health (N = 106) and drug treatment (N = 120) settings were compared regarding diagnosis, drug use, and problem severity. The Diagnostic Interview Schedule for DSM-IV and the Addiction Severity Index were used to obtain data. ***Results:*** Few differences between groups emerged. There were no diagnostic differences except that schizophrenia spectrum disorders were more common among mental health (43%) than drug treatment (31%) patients. The average number of days of drug use in this period was not different, although more drug abuse than mental health subjects reported drug use in the 30 days before treatment entry. ***Conclusions:*** These findings document the high prevalence of serious drug problems in mental health patients and of serious mental illness in drug treatment clients. Only minimal differences were found between the groups and none that indicated the need for specialized treatments in separate systems of care.

(Am J Psychiatry 2004;161:139–145)

Selective Serotonin Reuptake Inhibitors in Childhood Depression: Systematic Review of Published Versus Unpublished Data

Whittington CJ, Kendall T, Fonagy P, et al.

Background: The safety of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression in children has been questioned recently. Therefore, we compared and contrasted published and unpublished data on the risks and benefits of these drugs. ***Method:*** We conducted a meta-analysis of data from randomized controlled trials that evaluated an SSRI versus placebo in participants aged 5 to 18 years. All data were published in peer-reviewed journals or were unpublished and included in a review by the Committee on Safety of Medicines. Outcomes included remission, response to treatment, serious adverse events, depressive symptom scores, suicide-related behaviors, and discontinuation of treatment due to adverse events. ***Results:*** Data from 2 published trials suggest that fluoxetine has a favorable risk-benefit profile, and this finding is supported by unpublished data. Published data from 1 trial of paroxetine and 2 trials of sertraline suggest equivocal or weak positive risk-benefit profiles. In both cases, however, unpublished data indicate that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine present unfavorable risk-benefit profiles. ***Conclusion:*** A favorable risk-benefit profile is suggested for some SSRIs in published data. Addition of unpublished data, however, indicates that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and young people. Clinical decisions regarding treatment and clinical guideline development are largely dependent on an evidence base published in peer-reviewed journals. The omission of important data from published trials or nonpublication of trials, for whatever reason, can lead to erroneous recommendations for treatment. Greater openness and transparency with respect to all intervention studies are needed.

(Lancet 2004;363:1341–1345)

The Cost Consequences of Treatment-Resistant Depression

Russell JM, Hawkins K, Ozminkowski RJ, et al.

Context: Treatment-resistant depression is a significant public health problem with profound effects on general medical and mental health–related health care costs. ***Objective:*** To describe health care costs of patients with treatment-resistant depression as their illness progresses, in terms of pharmaceutical and medical expenditures, and to identify factors associated with increasing degrees of treatment resistance. ***Data Sources:*** The MEDSTAT MarketScan Private Pay Fee for Service (FFS) Database, a medical and prescription claims database covering over 3.5 million enrollees, from 1995–2000. ***Design and Study Subjects:*** 7737 patients with depression (ICD-9) who had 2 or more unsuccessful trials of antidepressant medication at an adequate dose for at least 4 weeks from 1995–2000 were defined as treatment-resistant in this study. Demographic and clinical characteristics were assessed for these patients with treatment-resistant depression. The number of changes in depression medication treatment regimens was used as a proxy for increasing degrees of treatment resistance and its severity. ***Major Outcome Measure:*** Differences in health care expenditures associated with increasing degrees of treatment-resistant depression. ***Results:*** Total depression-related and general medical health care expenditures increased significantly as treatment-resistant depression increased in severity. Multivariate analyses of patient demographic characteristics were not associated with ongoing treatment resistance. Disease severity, type of antidepressant at index, comorbid mental health disorders, and membership in a managed health care plan were associated with increasing degrees of treatment resistance. ***Conclusions:*** Depression and general medical health care expenditures increase with the degree of treatment-resistant depression. Disease management interventions for treatment-resistant depression that result in sustained remission early in the course of illness are most likely to be cost effective.

(J Clin Psychiatry 2004;65:341–347)

Limbic Paroxysmal Magnetoencephalographic Activity in 12 Obsessive-Compulsive Disorder Patients: A New Diagnostic Finding

Amo C, Quesney LF, Ortiz T, et al.

Background: We describe frontotemporal paroxysmal rhythmic activity recorded by magnetoencephalography (MEG) in patients with obsessive-compulsive disorder (OCD). ***Method:*** Twelve patients with OCD (per ICD-10 and DSM-IV criteria), aged 18 to 65 years, were assessed using MEG. Patients' classification according to the Yale Brown OCD Scale was as follows: severe = 8, moderate = 3, and mild = 1. MEG findings were compared with those of 12 age- and sex-matched healthy subjects (control group) with no previous history of psychiatric or neurologic disorders. All study participants underwent neurologic and basic medical examinations, including magnetic resonance imaging, electrocardiograms (EEGs), and electrooculograms. The study was conducted between January 2001 and January 2002. ***Results:*** Two types of MEG activity were observed in patients with OCD: (1) frontotemporal paroxysmal rhythmic activity with low-amplitude spikes (< 1 picoTesla) in 92% (11/12) of patients and (2) intermittent isolated spikes and sharp waves in all patients (12/12). The OCD group had paroxysmal rhythmic MEG activity in the cingulate cortex (12/12), insula (10/12), hippocampus (9/12), temporal superior gyrus and angular and supramarginal gyri (9/12), precentral and postcentral gyri (8/12), orbitofrontal cortex (5/12), and parietal lobes (5/12). MEG recordings were normal in the control group, and EEG findings were normal in both the OCD and control groups. ***Conclusions:*** Frontotemporal paroxysmal rhythmic activity with a preferential limbic distribution is a sensitive MEG finding in patients with OCD. Although the pathophysiology of this abnormality remains unknown, a corticostriatal network dysfunction was hypothesized.

(J Clin Psychiatry 2004;65:156–162)

Clinical and Legal Correlates of Inmates With Bipolar Disorder at Time of Criminal Arrest

Quanbeck CD, Stone DC, Scott CL, et al.

Background: In an effort to determine illness factors associated with criminality among bipolar patients, we identified bipolar arrestees housed in the psychiatric division of the Los Angeles County Jail who had a history of psychiatric treatment in the Los Angeles County community mental health system. ***Method:*** Los Angeles County's computerized management information system was utilized to retrospectively identify all inmates evaluated over a 7-month period from July 1999 to Jan. 2000 with a DSM-IV diagnosis of bipolar I disorder, their symptoms at time of arrest, and the nature of community treatment preceding arrest. Criminal history was assessed using Sheriff's Department legal records. Demographic and clinical characteristics of these inmates were compared with characteristics present in a group of hospitalized bipolar patients without a history of arrest in Los Angeles County. ***Results:*** Of the 66 inmates identified as having a clear diagnosis of bipolar disorder with previous community treatment in the Los Angeles County Mental Health system, the majority were manic (49/66, 74.2%) and psychotic (39/66, 59%) at time of arrest. Manic arrestees were recently released from community inpatient treatment and most were not involved in outpatient treatment postdischarge. The bipolar inmates had significantly higher rates of comorbid substance abuse than did the hospitalized bipolar patients without an arrest history (75.8% [50/66]) vs. 18.5% [10/54]). ***Conclusions:*** The results of this study suggest that manic symptoms place bipolar patients at significant risk for criminal offending and arrest. Intensive treatment intervention by the community mental health and criminal justice system may be needed, particularly in the immediate postmanic hospitalization period, in order to prevent incarceration of patients with bipolar disorder.

(J Clin Psychiatry 2004;65:198–203)

Depression in Primary Care: Effectiveness of Venlafaxine Extended-Release in Elderly Patients— Observational Study

Cervera-Enguix S, Baca-Baldomero E, Garcia-Calvo C, et al.

Background: Depression is common in the elderly but often is not recognized or treated as such. The effectiveness and tolerability of venlafaxine extended-release in patients over age 60 years have been assessed in only a few studies in the primary care setting. The aim of this study was to demonstrate the safety and effectiveness of venlafaxine extended-release in depressive disorders in an elderly population. ***Method:*** This observational, multicenter, prospective study included an outpatient population over age 60 years in need of pharmacologic treatment for depressive symptoms and with a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17). Effectiveness of venlafaxine extended-release was assessed by the HAM-D-17. All possible adverse effects were recorded, and the physician's assessment of the patient's global status was utilized. Venlafaxine extended-release was administered for 6 months at 75 mg/day and thereafter up to 150 mg/day according to clinical criterion. ***Results:*** Data from 1214 patients were obtained, with remission rates in 70.2% of patients and response rates (50% decrease in HAM-D-17 score) of 83.2%. Global assessment of the patient's status significantly improved at each visit. After 6 months of treatment, 87.6% of patients continued taking 75 mg/day of venlafaxine extended-release. Adverse events were reported by 4.6% of patients during the study. ***Conclusion:*** In elderly patients managed by primary care physicians, venlafaxine extended-release is safe and effective for the treatment of depression.

(Arch Gerontol Geriatr 2004;38:271–280)

Citalopram and Bupropion-SR: Combining Versus Switching in Patients With Treatment-Resistant Depression

Lam RW, Hossie H, Solomons K, et al.

Objective: There are limited data comparing medication strategies in patients with treatment-resistant depression. In this study, we compared the effects of combining citalopram and bupropion-SR versus switching to the other monotherapy in treatment-resistant depression. ***Method:*** This was a naturalistic, open-label cohort study. Patients with DSM-IV major depressive disorder who had not responded to at least 1 previous antidepressant and at least 6 weeks of treatment with citalopram or bupropion-SR were treated in a standard clinical protocol. In alternate months, eligible consecutive patients were treated by adding citalopram or bupropion-SR, or by switching to the other medication. Patients were assessed at baseline and after 6 weeks of treatment with the 29-item version of the Structured Inter-

view Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD). ***Results:*** A total of 61 patients completed the study: 32 in the combination condition and 29 in the monotherapy switch condition. The combination condition was superior to the monotherapy switch in the SIGH-SAD change score (–14.8 vs. –10.1, respectively, $p < .04$) and the proportion of patients in clinical remission (28% vs. 7%, $p < .05$). There were no differences in the proportion of patients who had side effects or in the severity of the side effects experienced. ***Conclusion:*** The results of this cohort study suggest that combining citalopram and bupropion-SR is more effective than switching to a monotherapy. Combination treatment was well tolerated with no greater side effect burden than monotherapy. Limitations of this study include the nonrandomized design, open-label treatment, and small sample size.

(J Clin Psychiatry 2004;65:337–340)

First Episode of Depression in Children at Low and High Familial Risk for Depression

Williamson DE, Birmaher B, Axelson DA, et al.

Background: The purpose of this prospective study was to examine the development of first-onset major depressive disorder (MDD) in children at high and low familial risk for depression. ***Method:*** The study included high-risk children (N = 76) who were free of any lifetime affective disorder and had at least 1 first-degree and 1 second-degree relative with a lifetime history of childhood-onset, recurrent, bipolar, or psychotic depression. Low-risk children (N = 63) were included if they were free of any lifetime psychiatric disorder and had no first-degree relatives and fewer than 20% of their second-degree relatives with a lifetime affective disorder. The Schedule for Affective Disorders and Schizophrenia for School Age Children-Epidemiologic version was used to assess children and their parents. The mean follow-up period was 6 years, and the mean interval between follow-up interviews was 18 months. ***Results:*** Compared with low-risk children, high-risk children had approximately a 3-fold increased risk of developing first-onset MDD (odds ratio [OR] =3.21). The mean ± age of new-onset MDD was 14.0 ± 2.9 years (range, 9.5–19.5 years). Above and beyond the familial loading for MDD, mother's lifetime anxiety disorder (OR = 2.84) and lifetime behavioral disorder (OR = 3.25) in the child significantly added to the risk of developing a first-onset MDD. ***Conclusions:*** Having a mother with an anxiety disorder, a behavioral disorder in the child, and a high familial loading for affective disorders all significantly contributed to the risk of developing depression.

(J Am Acad Child Adolesc Psychiatry 2004;43:291–297)

Depressive Disorders Are Related to Nicotine Dependence in the Population but Do Not Necessarily Hamper Smoking Cessation

John U, Meyer C, Rumpf HJ, et al.

Background: Evidence shows considerable comorbidity between nicotine dependence and depression. However, little is known from the population about specific factors involved. The goal was to analyze smoking, nicotine dependence, and depression cross-sectionally and to analyze whether or not depression predicts the sustenance of smoking after 3 years. ***Method:*** A population-based random sample, representative for the adult population aged 18 to 64 years in a German region, was interviewed face to face (N = 4075). Among these were 2458 daily smokers, of whom 320 (13.0%) had a lifetime diagnosis of depression. Current smokers at baseline were followed up 36 months later. Measurements included DSM-IV diagnoses of depression and nicotine dependence by the Composite International Diagnostic Interview. Smoking cessation was defined as the abstinence from smoking for at least 4 consecutive weeks. ***Results:*** The rate of subjects with a depressive disorder among female never nicotine dependents was 13.7% and among female current nicotine dependents 31.6% ($c^2 = 49.9$, $df = 2$, $p < .001$); the respective rate among male never nicotine dependents was 5.6% and among male current nicotine dependents 13.4% ($c^2 = 20.2$, $df = 2$, $p < .001$). Subjects with a lifetime history of depressive disorder revealed the same rate of smoking cessation after 3 years as those without a depressive disorder ($c^2 = 0.7$, $df = 1$, not significant). The use of nicotine replacement therapy was equally distributed among subjects with a depressive disorder and those without a depressive disorder ($c^2 = 0.03$, $df = 1$, not significant). ***Conclusion:*** The risk for depression increases as the number of nicotine dependence symptoms increases or dependence criteria are fulfilled. Despite this association, depressed subjects may show the same prospect for smoking cessation as nondepressed subjects.

(J Clin Psychiatry 2004;65:169–176)

Identifying Depression in the First Postpartum Year: Guidelines for Office-Based Screening and Referral

Peindl KS, Wisner KL, Hanusa BH

Background: Postpartum-onset major depression (PPMD) affects approximately 10% to 15% of women. In this study, the objective was to determine if the Edinburgh Postnatal Depression Scale (EPDS) is an effective method to prospectively screen for major depression (MD). The study outcome was identification of a recurrence of MD in the first year postpartum by clinical interview and the EPDS. The relationship between EPDS scores and PPMD was examined. ***Method:*** Study participants were pregnant women who were well during their index pregnancy but who had experienced an episode of previous PPMD. The study was part of a double-blind, randomized clinical trial in which new mothers received placebo or nortriptyline within 24 hours after delivery for prevention of PPMD. Research Diagnostic Criteria were used to establish recurrence of depression. The EPDS was completed by participants weekly through 20 weeks postpartum and into a 1-year follow-up phase. ***Results:*** Of 50 women, 13 experienced recurrence of MD within the first 20 weeks postpartum. A total of 20 of 50 experienced recurring MD within the first year. The EPDS score of > 9 at week 4 postpartum identified 60% of women who nurtured in the first 20 weeks and 80% who recurred in the first postpartum year. A limitation that restricts generalizability was that only women who had a previous episode of PPMD were included in the study population. ***Conclusions:*** The EPDS is an effective depression screening tool for women who had a previous episode of PPMD. Clinical guidelines for use of the EPDS to identify MD in the first postpartum year in primary care settings are provided.

(J Affect Disord 2004;80:37–44)

© COPYRIGHT 2004 PHYSICIANS POSTGRADUATE PRESS, INC.

Adherence to Conventional and Atypical Antipsychotics After Hospital Discharge

Diaz E, Neuse E, Sullivan MC, et al.

Background: This prospective study measured adherence to conventional and atypical antipsychotics after hospital discharge in patients with a diagnosis of schizophrenia and schizoaffective disorder. We examined the interaction of several predictors such as gender, severity of illness, attitudes toward medications, side effects, and dose frequency. ***Method:*** The sample consisted of consecutive randomized and nonrandomized patients who were discharged from an inpatient unit with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder between December 1995 and July 1999. All patients were taking oral antipsychotics and consented to the use of an electronic adherence monitor at discharge. Medications were prescribed by usual care providers, and medication adherence was followed weekly for 3 months. The outcome measure was the medication adherence rate registered in the electronic monitors. ***Results:*** We found no significant difference in adherence between the combined groups of atypical and conventional antipsychotics. Individual medication analysis found better medication adherence with olanzapine in comparison with risperidone and conventional antipsychotics, but the difference disappeared in the final model controlling for dose frequency. Dose frequency, gender, and akathisia predicted adherence. ***Conclusions:*** Olanzapine initially appeared to be associated with an adherence advantage over risperidone and conventional antipsychotics, but the apparent advantage may have been due to a usual care dose frequency practice that associated olanzapine more often with once-daily dosing. This study suggests that dose frequency is an important predictor of medication adherence. An important caveat is that these results apply only to short-term adherence.

(J Clin Psychiatry 2004;65:354–360)

Tiagabine for Posttraumatic Stress Disorder: A Case Series of 7 Women

Taylor FB

Background: Posttraumatic stress disorder (PTSD) is often a chronic disorder, and, though 2 antidepressants are now approved by the U.S. Food and Drug Administration for its treatment, it often remains refractory to pharmacotherapy. The memory of traumatic events, by repeatedly stimulating the hippocampus and amygdala (kindling phenomenon) may alter multiple biological systems, including γ-aminobutyric acid (GABA) pathways, and eventually lead to the disorder. Tiagabine, a selective GABA reuptake inhibitor, was evaluated as a treatment for PTSD. ***Method:*** Patients with DSM-IV PTSD who were stable on current medications and still symptomatic were eligible for inclusion in this open-label case series. Tiagabine was initiated at 2 mg nightly and increased by 2-mg increments every 2 to 3 days until an optimal response was achieved. The Clinical Global Impressions-Improvement scale and PTSD Checklist-Civilian Version (PCL-C) were used to evaluate changes in PTSD symptoms. ***Results:*** Seven consecutive female patients were identified as eligible. Tiagabine markedly improved PTSD symptoms within 2 weeks for 6 of the 7 patients, and 6 patients were rated as "much improved" or "very much improved." The mean PCL-C score was significantly reduced at weeks 2 and 8 ($p < .05$) as were the 3 PCL-C subscales and 1 of 2 items related to sleep disturbance. The mean effective daily dosage was approximately 8 mg (range, 4–12 mg/day). Treatment with tiagabine was generally well tolerated. ***Conclusions:*** These preliminary open-label findings suggest that the selective GABA reuptake inhibitor tiagabine may be a promising therapeutic option in the treatment of PTSD. Further study into the efficacy and safety of tiagabine for the treatment of PTSD is warranted.

(J Clin Psychiatry 2003;64:1421–1425)