

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 Work Impact of Dysthymia in a Primary Care Population

Adler DA, Irish J, McLaughlin TJ, et al.

Background: Physicians perceive that patients with dysthymia have relatively normal levels of functioning. This article examines in detail the work impact of dysthymia in a population of employed primary care patients. **Method:** This study was conducted between 2001 and 2003 in clinics associated with 3 health plans in Massachusetts as part of an observational study. Comparisons were made between 69 patients diagnosed with DSM-IV dysthymia without concurrent major depressive disorder and 175 depression-free controls. Patients had no major comorbid medical conditions, were employed at least 15 hours per week, and had no immediate plans to leave the labor market. Work absences and productivity loss due to on-the-job performance limitations ("presenteeism") were assessed. **Results:** Compared with controls, patients with dysthymia had less stable work histories and a greater frequency of significant problems at work. Individuals with dysthymia experienced significantly greater on-the-job productivity loss (6.3% vs. 2.8%, $p < .0001$), however, absence rates were not significantly different (1.2 vs. 0.74 days, $p < .09$). **Conclusion:** Dysthymia is an unrecognized cause of work impairment. The disorder has long-term negative consequences for individuals and their employers. New interventions are warranted given the persistence of dysthymia and its serious impact on work functioning.

(*Gen Hosp Psychiatry* 2004;26:269–276)

A Survey of Reports of Quetiapine-Associated Hyperglycemia and Diabetes Mellitus

Koller EA, Weber J, Doraiswamy PM, et al.

Objective: To explore the clinical characteristics of hyperglycemia in patients treated with quetiapine. **Method:** A pharmacovigilance survey of spontaneously reported adverse events in quetiapine-treated patients was conducted using reports from the U.S. Food and Drug Administration MedWatch program (January 1, 1997, through July 31, 2002) and published cases using the search terms hyperglycemia, diabetes, acidosis, ketosis, and ketoacidosis. **Results:** We identified 46 reports of quetiapine-associated hyperglycemia or diabetes and 9 additional reports of acidosis that occurred in the absence of hyperglycemia and were excluded from the immediate analyses. Of the reports of quetiapine-associated hyperglycemia, 34 patients had newly diagnosed hyperglycemia, 8 had exacerbation of preexisting diabetes mellitus, and 4 could not be classified. The mean \pm SD age was 35.3 ± 16.2 years (range, 5–76 years). New-onset patients (aged 31.2 ± 14.8 years) tended to be younger than those with preexisting diabetes (43.5 ± 16.4 years, $p = .08$). The overall male:female ratio was 1.9. Most cases appeared within 6 months of quetiapine initiation. The severity of cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma. There were 21 cases of ketoacidosis or ketosis. There were 11 deaths. **Conclusion:** Atypical antipsychotic use may unmask or precipitate hyperglycemia. **Update:** An additional 23 cases were identified since August 1, 2002, the end of the first survey, by extending the search through November 30, 2003, bringing the total to 69.

(*J Clin Psychiatry* 2004;65:857–863)

The Current Understanding of Lamotrigine as a Mood Stabilizer

Hahn C-G, Gyulai L, Baldassano CF, et al.

Objective: To examine whether lamotrigine has a unique role in the treatment of bipolar disorder, we evaluated the results of recent clinical trials and molecular and cell biological studies on lamotrigine. **Data Sources:** Using keywords such as *bipolar disorder, lamotrigine, clinical trial, outcomes studies, and mechanisms*, we conducted a search for English-language articles on MEDLINE and Index Medicus and also on abstracts presented in recent research conferences. **Data Synthesis:** Several studies have strongly suggested that lamotrigine is effective for the acute treatment of bipolar depression as well as for long-term maintenance treatment of bipolar disorder. Stevens-Johnson syndrome is a con-

cern, but the incidence of this side effect may not be as high as previously believed, if dosing is slowly titrated. The action mechanisms underlying the mood-stabilizing effects of lamotrigine are unknown at present but recent studies have produced interesting leads. Lamotrigine modulates various ion channels, altering neuronal excitability. The use-dependent inhibition of neuronal firing by lamotrigine is potentially important because it could result in attenuating supranormal neuronal activities that are possibly associated with bipolar disorder. Lamotrigine inhibits the release of glutamate, similarly to lithium, and its possible association with mood-stabilizing or antidepressant effects needs to be further examined. Unlike lithium or valproic acid, however, lamotrigine does not down-regulate the expression of protein kinase C or MARCKS, suggesting that lamotrigine employs different intracellular mechanisms for long-term changes in neurobiology from those of lithium or valproic acid. **Conclusion:** The efficacy of lamotrigine for bipolar depression may provide us with new options in the treatment of bipolar disorder. Examining the effects of lamotrigine on various molecular mechanisms in correlation with its unique efficacy on bipolar depression may enhance our understanding of action mechanisms of the mood stabilizers.

(*J Clin Psychiatry* 2004;65:791–804)

Does a Depression Intervention Result in Improved Outcomes for Patients Presenting With Physical Symptoms?

Keeley RD, Smith JL, Nutting PA, et al.

Background: The objective of this study was to investigate the effects of exclusively physical presentation of depression on (1) the impact of an intervention to improve management and outcomes and (2) depression management and outcomes under usual care conditions. **Method:** Two hundred adults from 12 community-based primary care practices were included in this secondary analysis of a depression intervention trial. All participants were starting a new treatment episode for depression. Measurements included the following: presenting complaint and physician depression query at index visit, antidepressant use, completion of adequate antidepressant trial, change in depressive symptoms, and physical and emotional role functioning at 6 months. **Results:** 66% presented exclusively with physical symptoms. Under usual care conditions, physical presenters were less likely than psychological presenters to complete an adequate trial of antidepressant treatment but experienced equivalent improvements in depressive severity and role functioning. In patients presenting with psychological symptoms, the intervention significantly improved receipt of any antidepressant (79.9% vs. 38.0%; $p = .01$) and an adequate antidepressant trial (46.0% vs. 23.8%; $p = .004$). The intervention also improved depression severity and physical and emotional role functioning in those patients. In patients presenting exclusively with physical symptoms, the intervention did not significantly improve depression severity or role functioning, but did significantly improve physician query (40.8% vs. 18.0%; $p = .06$), receipt of any antidepressant (63.0% vs. 20.1%; $p = .001$), and an adequate antidepressant trial (34.9% vs. 5.9%; $p = .004$). **Conclusions:** Results indicate that there is a differential intervention effect by presentation style at the index visit. Current interventions therefore should be targeted at psychological presenters and new approaches should be developed for physical presenters.

(*J Gen Intern Med* 2004;19:615–623)

A Longitudinal Population-Based Study of Treated and Untreated Major Depression

Wang J

Background: In relation to mental health service utilization, few studies have investigated the factors associated with different outcomes in individuals with major depressive episode (MDE). **Method:** Depressed individuals who used and did not use mental health services were included in a population-based longitudinal analysis. The objectives of the study were to compare demographic, psychosocial, and clinical characteristics; estimate risk of MDE in a 6-year follow-up period; and identify factors associated with the persistence/recurrence of MDE. Participants included the longitudinal cohort of the Canadian National Population Health Survey who reported MDE at the baseline survey ($N = 609$). The Composite International Diagnostic Interview-Short Form for Major Depression was used to measure MDE. **Results:** In the 6-year follow-up period, 49.8% of participants with treated depression developed subsequent MDE, and 28.7% of those patients with untreated depression reported MDE. Among those subjects who reported the use of mental health services, multivariate analysis showed that childhood and adulthood traumatic events and functional impairment were related to the recurrence of MDE. Among those subjects who did not use mental health services, reported negative life events and the severity of depressive symptoms were predictive of recurrent MDE. **Conclusions:** Risk of the recurrence of MDE and associated factors differ in users and nonusers of mental health services. Future studies must confirm these results and identify service barriers for those individuals who do not use the services and who are at a high risk of MDE.

(*Med Care* 2004;42:543–550)

Renal Insufficiency in Long-Term Lithium Treatment

Lepkifker E, Sverdluk A, Iancu I, et al.

Objective: To compare long-term lithium patients who developed renal insufficiency (RI) with those who did not, and to examine what characterized these groups. **Method:** One hundred fourteen subjects with DSM-IV bipolar, major depressive, or schizoaffective disorder who had been taking lithium for 4 to 30 years from 1968 to 2000 were studied retrospectively. Subjects with blood creatinine levels ≥ 1.5 mg/dL were defined as RI patients, and creatinine levels < 1.5 mg/dL indicated no renal insufficiency (NRI). Ninety-four unmedicated subjects, matched for sex and age, served as a comparison group and had 2 measures of creatinine with a mean interval of 11.88 years. **Results:** Twenty-four (21%) of the lithium-treated patients were defined as RI patients. These subjects exhibited the “creeping creatinine” phenomenon as their creatinine levels increased progressively. The NRI subjects showed no increase of creatinine levels in up to 30 years and remained comparable to the comparison group. RI was associated with episodes of lithium intoxication and diseases or medicines that could affect glomerular function, but not with sex, psychiatric diagnosis, age at onset of diagnosed disorder, duration of lithium therapy, serum lithium concentration, and cumulative lithium dose. **Conclusions:** Long-term lithium therapy did not influence glomerular function in an overwhelming majority of patients. However, about 20% of long-term lithium patients exhibited “creeping creatinine” and developed renal insufficiency.

(*J Clin Psychiatry* 2004;65:850–856)

Atypical Antipsychotics and Weight Gain in Chinese Patients: A Comparison of Olanzapine and Risperidone

Lee E, Leung C-M, Wong E

Objective: To compare the effect of olanzapine with that of risperidone on weight change among Chinese patients in Hong Kong. **Method:** The body weight of subjects maintained on olanzapine or risperidone treatment was recorded at the outpatient clinic of a teaching hospital. Pretreatment weight of the subjects was retrieved from case records. Subjects on olanzapine treatment were matched in sex, age, and diagnosis with those on risperidone treatment, and demographic and clinical data were analyzed. The study was conducted in May and June 2002. **Results:** Twenty-eight olanzapine-risperidone matched pairs were studied. All were diagnosed with DSM-IV schizophrenia. In patients treated with olanzapine and risperidone, respectively, mean \pm SD duration of treatment with atypical neuroleptics was 103.5 ± 47.4 weeks and 93.2 ± 50.6 weeks (range, 21–255 weeks), and mean doses were 12.4 ± 6.7 mg/day and 4.5 ± 2.8 mg/day. The mean \pm SD weight gain of subjects on treatment with olanzapine and risperidone, respectively, was 8.34 ± 5.97 kg (18.53 ± 13.27 lb) and 2.74 ± 8.09 kg (6.09 ± 17.98 lb) with a statistically significant difference at $p < .005$. Lower baseline body weight and body mass index were associated with greater weight gain in both olanzapine- and risperidone-treated subjects. Gender, age, mean daily dose, and duration of treatment had no effect on weight change. **Conclusion:** Treatment with olanzapine was associated with significantly greater weight gain than treatment with risperidone in Chinese schizophrenia patients in Hong Kong. The effect of adjunctive anticonvulsant treatment on weight gain requires further study.

(*J Clin Psychiatry* 2004;65:864–866)

Treatment of Depression in Patients With Alcohol or Other Drug Dependence: A Meta-Analysis

Nunes EV, Levin FR

Background: Depression and substance abuse are common and costly disorders that frequently co-occur. Controversy exists, however, regarding effective treatment for patients with both disorders. The objective of this study was to conduct a systematic review and meta-analysis to quantify the efficacy of antidepressant medications for treatment of combined depression and substance use disorders. **Method:** PubMed, MEDLINE, and the Cochrane database were searched for the period 1970 to 2003 using the terms *antidepressant treatment* or *treatment depressed* in conjunction with each of the following *alcohol dependence*, *benzodiazepine dependence*, *opiate dependence*, *cocaine dependence*, *marijuana dependence*, and *methadone*. A search of bibliographies was also conducted, and experts in the field were consulted. Inclusion criteria used for study selection were prospective, parallel group, double-blind, controlled clinical trials with random assignment to an antidepressant medication or placebo for which trial patients met standard diagnostic criteria for a current unipolar depressive disorder and current alcohol or other drug use. More than 300 citations were extracted; 44 were placebo-controlled trials. Fourteen of those trials were selected for this analysis and included 848 patients: 5 studies of tricyclic antidepressants, 7 of selective serotonin reuptake inhibitors, and 2 from other classes. Titles and abstracts of each citation were independently screened, placebo-controlled trials of pa-

tients with both substance dependence and depression were identified, the inclusion criteria were applied, and a consensus was reached. Data on study methodology, sample characteristics, and depression and substance use outcomes were extracted. The principal measure of effect size was the standardized difference between means on the Hamilton Rating Scale for Depression (HAM-D). **Results:** For the HAM-D score, the pooled effect size from the random-effects model was 0.38 (95% CI, 0.18 to 0.58). Studies with low placebo response showed larger effects, and, heterogeneity of effect on HAM-D across studies was significant ($p < .02$). Moderator analysis suggested that diagnostic methods and concurrent psychosocial interventions influenced outcome. In studies with larger depression effect sizes (> 0.5), favorable effects of medication on measures of quantity of substance use were demonstrated, although rates of sustained abstinence were low. **Conclusions:** Antidepressant medication exerts a modest beneficial effect for patients with combined depressive- and substance-use disorders, but it is not a stand-alone treatment. Concurrent therapy directly targeting the addiction is indicated, and more research is needed to understand variations in the strength of the effect. The data suggest that care be exercised in the diagnosis of depression—either by observing depression to persist during at least a brief period of abstinence or through efforts by clinical history to screen out substance-related depressive symptoms.

(*JAMA* 2004;291:1887–1896)

Impact of Gastrointestinal Symptom Severity on Response to Venlafaxine Extended-Release in Patients With Generalized Anxiety Disorder

Lydiard RB, Pitrosky B, Hackett D, et al.

Background: This retrospective analysis evaluated the prevalence and severity of pretreatment gastrointestinal (GI) symptoms in patients with generalized anxiety disorder (GAD), the impact of these GI symptoms on the efficacy and tolerability of venlafaxine extended-release (XR), and the effect of treatment on prestudy GI symptoms. **Method:** Data from 1932 nondepressed GAD patients were pooled from 5 randomized, double-blind, placebo-controlled studies of venlafaxine XR clinically conducted between May 1995 and December 1997. The GI symptom severity at baseline was estimated from item 11 on the Hamilton Rating Scale for Anxiety (HAM-A). Patients with a GI symptom severity score ≤ 2 (moderate or less) and those with a GI symptom severity score > 2 (severe/very severe) were compared for baseline characteristics and short-term (8-week) and long-term (24-week) outcomes. **Results:** At baseline, for all randomized patients with a HAM-A item 11 score, GI symptoms were rated moderate or lower in 82.8% of patients (GI-low) and severe/very severe in 17.2% (GI-high). The GI-high subgroup was statistically significantly ($p < .05$) younger, had a longer duration of GAD, and had higher mean HAM-A total scores than the GI-low subgroup. Compared with placebo, venlafaxine XR significantly reduced HAM-A total and psychic anxiety factor scores, regardless of baseline GI symptom severity. The incidence of adverse events, particularly nausea, was higher for the GI-high versus GI-low subgroup. **Conclusion:** Baseline severity of GI symptoms correlated with overall severity of GAD but had no impact on treatment outcome with venlafaxine XR. These data do not support the hypothesis that high baseline GI symptom severity has a negative effect on treatment with venlafaxine XR in GAD patients.

(*J Clin Psychiatry* 2004;65:838–844)

**The Preschool Feelings Checklist:
A Brief and Sensitive Screening Measure
for Depression in Young Children**

Luby JL, Heffelfinger A, Koenig-McNaught AL, et al.

Background: Childhood depression is widely underrecognized in primary health care settings. This phenomenon appears to increase with younger age. There is evidence for a valid depressive syndrome among preschool children. Based on the need for the earliest possible identification of depression, the development of a brief screening measure to capture young children with markers of depression from these community settings was developed and tested. **Method:** The study group included 174 preschool children who underwent a comprehensive psychiatric assessment. The majority of these children were identified in primary care settings using a 20-item checklist designed to capture depressive symptoms in young children. Also included in

the assessment were the Child Behavior Checklist and the Diagnostic Interview Schedule for Children Version modified for young children. Ratings on the 20-item checklist were subsequently compared with the independent measures of psychopathology using several analytic strategies. **Results:** The Preschool Feelings Checklist demonstrated high internal consistency; 16 items showed strong associations with independent diagnostic measures of internalizing symptoms and major depressive disorder. At a cutoff score of ≥ 3 , The Preschool Feelings Checklist demonstrated high specificity and sensitivity for the identification of major depressive disorder. **Conclusions:** The Preschool Feelings Checklist demonstrated utility for the identification of preschoolers in need of formal mental health evaluation for depression. The checklist is a brief and valid screening measure that is highly feasible for use in primary care settings.

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