

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.

Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice

Trivedi MH, Rush AJ, Wisniewski SR, et al.

Am J Psychiatry 2006;163:28–40

Objective: To assess the efficacy of citalopram using measurement-based care in actual practice and to determine predictors of symptom remission in outpatients with major depressive disorder.

Method: Outpatients with major depressive disorder who received treatment in 23 psychiatric and 18 primary care “real world” settings were included. Flexible doses of citalopram were prescribed by clinicians for up to 14 weeks. A clinical research coordinator aided clinicians in the application of measurement-based care, which included the routine measurement of symptoms and side effects at each treatment visit and the use of a treatment manual to identify circumstances under which to modify medication doses based on these measures. The primary outcome measure was the 17-item Hamilton Rating Scale for Depression (HAM-D), and remission was defined as an exit score of ≤ 7 . The secondary outcome measure was the 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR), and remission was defined as a score of ≤ 5 . A reduction of $\geq 50\%$ in baseline QIDS-SR score indicated response.

Results: Of the 2876 outpatients in the analyzed sample, nearly 80% had chronic or recurrent major depression, and the majority also had a number of comorbid general medical and psychiatric conditions. The mean citalopram dose at study exit was 41.8 mg/day. Remission rates were 28% (HAM-D) and 33% (QIDS-SR), and response rate was 47% (QIDS-SR). Remission or response rates did not differ whether patients were treated in primary or psychiatric care settings. Among participants who achieved either response or remission at study exit, a high proportion did so at or after 8 weeks of treatment. Higher HAM-D remission rates were found in participants who were Caucasian, female, employed, or had higher levels of education or income; lower HAM-D remission rates were associated with longer index episodes, more concurrent psychiatric disorders (especially anxiety disorders or drug abuse), more general medical disorders, and lower baseline function and quality of life.

Conclusions: The response and remission rates in this study closely resemble those reported in 8-week efficacy trials. The methodical use of measurement-based care processes that are easily applied may have helped in attaining these ends.

The Health Care Crisis of Childhood-Onset Bipolar Illness: Some Recommendations for Its Amelioration

Post RM, Kowatch RA

J Clin Psychiatry 2006;67:115–125

Objective: To describe new data on the incidence and impact of childhood- and adolescent-onset bipolar illness and make recommendations to help accelerate the acquisition of knowledge in this area.

Data Sources: Two large, multicenter outpatient studies in adults with DSM-IV bipolar disorder—the Systematic Treatment Enhancement Program for Bipolar Disorder and the Bipolar Collaborative Network—were the primary sources of retrospective data on age at onset.

Study Selection: We focused on the 2 retrospective studies because they supplied more immediate data on age at onset and long-term prognosis than current prospective studies.

Data Synthesis: The 2 studies revealed that 15% to 28% of adults experienced an onset of illness prior to age 13 years. Those with childhood versus adult onset had a more severe, complicated, and adverse course of bipolar illness, assessed retrospectively and confirmed prospectively during naturalistic treatment. The time lag from onset of first symptoms to first treatment was strongly inversely related to age at onset and was a mean \pm SD of 16.8 ± 10 years in those with childhood onset. Recommendations include defining temporary consensus threshold criteria for each bipolar subtype and its prodrome; conducting studies using less onerous than traditional designs, including randomized open comparisons to acquire preliminary data in this age cohort; and forming clinical and

academic treatment outcome networks to more quickly acquire treatment outcome data in this understudied population.

Conclusions: The data reveal a substantial rate of childhood-onset bipolar illness, extraordinary delays in onset to first treatment, and an adverse long-term outcome. Several approaches to accelerating the rate of acquisition of treatment outcome data in this cohort are outlined.

Bupropion Improves Sexual Functioning in Depressed Minority Women: An Open-Label Switch Study

Dobkin RD, Menza M, Marin H, et al.

J Clin Psychopharmacol 2006;26:21–26

Background: Beliefs and expectations about medical treatment are often unique for minority women. Few data currently address how depressed minority women respond to pharmacologic therapy targeting the sexual sequelae of depression. This study is the first to ask how switching medication from a selective serotonin reuptake inhibitor (SSRI) to bupropion SR would affect sexual functioning in depressed minority women.

Method: This prospective open-label study enrolled 18 minority women (5 Hispanic, 10 African American, 2 Asian American, and 1 Native American) who had failed to respond to and/or tolerate an adequate trial of an SSRI for depression with concomitant lowered libido. Medications were switched by cross-tapering with a target dose of 150 to 300 mg of bupropion SR. Sexual functioning and depression (Hamilton Rating Scale for Depression) were measured in an academic medical setting, and participants were followed for 10 weeks. Data were collected from July 2003 to December 2004.

Results: Overall, significant improvements in desire ($F = 34.86$, $df = 1,17$; $p < .001$), arousal ($F = 25.99$, $df = 1,17$; $p < .001$), and orgasm ($F = 20.16$, $df = 1,17$; $p < .001$), on the Changes in Sexual Functioning Questionnaire resulted from the intervention. After the medication switch, the greatest improvement in depression was found among African American women ($F = 9.55$, $df = 1,16$; $p = .006$), desire ($F = 8.62$, $df = 1,16$; $p = .01$), and arousal ($F = 8.83$, $df = 1,16$; $p = .009$).

Conclusion: On the whole, bupropion SR seemed efficacious in treating lowered libido in a varied group of depressed minority women. The trial was successfully completed by most of the women, and they planned to continue using bupropion SR after the study ended.

Topiramate Treatment for Women With Borderline Personality Disorder: A Double-Blind, Placebo-Controlled Study

Loew TH, Nickel MK, Muehlbacher M, et al.

J Clin Psychopharmacol 2006;26:61–66

Objective: To evaluate whether topiramate can improve borderline psychopathology, health-related quality of life, and interpersonal problems.

Method: Women who met the DSM-IV criteria for borderline personality disorder were randomly assigned to topiramate ($N = 28$) or placebo ($N = 28$). Study duration was 10 weeks during which time, topiramate was titrated from 25 to 200 mg/day. Changes on the Symptom Checklist, on the SF-36 Health Survey, and on the Inventory of Interpersonal Problems served as primary outcome measures. Weekly assessments of body weight and additional side effects were also conducted.

Results: In the intent-to-treat analysis, significant changes (all p values $< .001$) on the somatization, interpersonal sensitivity, anxiety, hostility, phobic anxiety, and global severity index

scales of the Symptom Checklist were seen after 10 weeks in the participants treated with topiramate, but no significant changes were seen on the obsessive-compulsive, depression, paranoid ideation, and psychoticism scales. Significant differences were seen on all 8 scales of the SF-36 Health Survey (all p values $< .01$ or $< .001$). Significant differences (all p values $< .001$) were found in the Inventory of Interpersonal Problems scales for overly autocratic, overly competitive, overly introverted, and overly expressive, but no significant differences were observed for overly cold, overly subservient/subservient, overly exploitable/compliant, and overly nurturant/friendly). Significant ($p < .001$) weight loss also occurred.

Conclusion: Topiramate may be a safe and effective treatment for women with borderline personality disorder, although weight loss should be anticipated.

Premenstrual Symptoms and Perimenopausal Depression

Richards M, Rubinow DR, Daly RC, et al.

Am J Psychiatry 2006;163:133–137

Objective: Because ovarian steroids play a role in both premenstrual dysphoria and perimenopausal depression, the possibility that these conditions represent expressions of the same underlying disorder has been raised. This study addressed premenstrual mood symptoms in women with perimenopausal depression.

Method: Seventy depressed perimenopausal women attending a menopause clinic and 35 nondepressed perimenopausal women were assessed with self-reports and daily symptom ratings during 1 menstrual cycle.

Results: Premenstrual symptoms were endorsed by 26% of the depressed and 9% of the nondepressed women. Criteria for significant menses-related symptom cyclicality (at least a 30% increase in the average ratings of at least 2 of 4 measured negative mood symptoms in the premenstrual versus the postmenstrual week) were fulfilled by 31% of the depressed and 20% of the nondepressed women. Premenstrual symptoms were endorsed in self-reports submitted by 5 of these depressed women and none of the comparison subjects. Finally, criteria for premenstrual dysphoria (symptom cyclicality and at least moderate severity, with symptoms exceeding a minimum luteal symptom severity threshold of 2.5) were met by 21% of the depressed and 3% of the nondepressed women.

Conclusions: Menses-related symptom cyclicality and premenstrual dysphoria were seen in perimenopausal depressed women at a rate higher than expected. Nonetheless, neither menses-related symptom cyclicality nor premenstrual dysphoria was an invariant accompaniment of perimenopausal depression. Furthermore, initial self-reports failed to predict the rate of premenstrual dysphoria.

Combination Lithium and Divalproex Sodium in Pediatric Bipolar Symptom Restabilization

Findling RL, McNamara NK, Stansbrey R, et al.

J Am Acad Child Adolesc Psychiatry 2006;45:142–148

Objective: Treatments that have been previously effective in bipolar disorder are reported to become less so with each symptomatic relapse. This study tested the rate of restabilization with lithium plus divalproex after relapse while taking either medication alone.

Method: This prospective, 8-week, open-label outpatient lithium/divalproex combination therapy trial enrolled patients

(aged 5 to 17 years) between January 1999 and January 2003 who had bipolar disorder type I or II and had achieved symptom remission with the combined treatment but had later relapsed during treatment with lithium or divalproex alone.

Results: Thirty-four (89.5%) of 38 patients enrolled (mean age = 10.5 years) responded to treatment with combined lithium/divalproex treatment; lingering symptoms in 4 patients necessitated adjunctive antipsychotic therapy. On the whole, reinitiation of lithium/divalproex combination therapy was tolerated well; no subjects withdrew from the trial because of an adverse event related to medication.

Conclusions: The majority of children and adolescents with bipolar disorder who are stabilized on combination lithium/divalproex therapy and experience relapse afterwards during therapy with either lithium or divalproex alone can safely and effectively be restabilized when lithium/divalproex combination treatment is reinitiated.

Antidepressants in Amniotic Fluid: Another Route of Fetal Exposure

Loughhead AM, Fisher AD, Newport DJ, et al.

Am J Psychiatry 2006;163:145–147

Objective: To evaluate the concentration of antidepressants in amniotic fluid during maternal treatment of depression.

Method: Women taking antidepressants who were having amniocentesis for obstetric reasons were enrolled. High-performance liquid chromatography was used to assess antidepressant concentrations in amniotic fluid and maternal serum.

Results: Antidepressant concentrations in the amniotic fluid obtained from 27 women varied widely. Mean amniotic fluid concentrations for the parent compounds of selective serotonin reuptake inhibitors were 11.6% (SD = 9.9%) of maternal serum concentrations (N = 22). For venlafaxine, amniotic fluid to maternal serum ratios were higher (172% [SD = 91%]; N = 3). Interestingly, the patterns of amniotic fluid to maternal serum ratios for the metabolites (N = 19) were not consistent compared with the parent compound ratios. The ratio of amniotic fluid to maternal serum for the metabolites was higher than the parent compound in 10 patients and lower in the remaining 9 subjects.

Conclusions: The pattern of antidepressant concentrations in amniotic fluid is consistent with that seen in recent data for placental passage. Although the significance of amniotic fluid exposure is not yet known, these results demonstrate that antidepressants given to the mother are accessible to the fetus in a manner not understood before.

Comorbidity in Bipolar Disorder Among the Elderly: Results From an Epidemiological Community Sample

Goldstein BI, Herrmann N, Shulman KI

Am J Psychiatry 2006;163:319–321

Objective: This trial attempted to assess psychiatric comorbidity among elderly individuals with bipolar disorder.

Method: Eighty-four elderly (aged ≥ 65 years) respondents with bipolar disorder, 1327 younger adults with bipolar disorder, and 8121 elderly respondents without bipolar disorder were found with an epidemiological community survey.

Results: Lifetime and 12-month rates of comorbid alcohol use disorders (38.1%, 38.1%, respectively), dysthymia (15.5%, 7.1%), generalized anxiety disorder (20.5%, 9.5%), and panic disorder (19.0%, 11.9%) were reported in elderly respondents with bipolar disorder. These rates were significantly higher than

among elderly respondents without bipolar disorder. Elderly respondents with bipolar disorder had lower lifetime and 12-month rates of alcohol use disorders and lower 12-month rates of dysthymia and panic disorder than younger adults with bipolar disorder. A higher incidence of alcoholism was reported by elderly men with bipolar disorder, while elderly bipolar women reported a higher frequency of panic disorder.

Conclusions: Elderly individuals with bipolar disorder commonly experience comorbid Axis I disorders, including panic disorder.

Predictors and Correlates of High Levels of Depression and Anxiety Symptoms Among Children at Age 10

Leech SL, Larkby CA, Day R, et al.

J Am Acad Child Adolesc Psychiatry 2006;45:223–230

Objective: This study sought to recognize factors that predict or are correlated with symptoms of depression and anxiety in 10-year-olds.

Method: The study followed mothers and their offspring from the fourth prenatal month through 10 years. At 10 years, 83% of the birth cohort (636 mother-child pairs) remained in the study. At each phase of the study, cognitive, psychological, sociodemographic, and environmental factors were measured. Having several symptoms that were more than 1 standard deviation above the mean for each measure was considered high depression and anxiety. High depression and/or anxiety (D/A) at 10 years of age was represented by combining these measures.

Results: More maternal depression symptoms, African American race, less social support, greater household density, and prenatal marijuana exposure were prenatal predictors of depression and/or anxiety at 10 years. Lower child IQ, child injuries at age 3, and attention problems were predictors from 18 months through 6 years of symptoms of depression and/or anxiety at age 10. Lower child IQ, household density during pregnancy, attention problems, early childhood injuries, and prenatal marijuana exposure were predictors across all study phases of D/A. Psychological and sociodemographic factors of the mother failed to be significant in the final model.

Conclusions: Details from gestation and early childhood predict high symptom levels of depression and anxiety at age 10. Maternal depression and socioeconomic status were not significantly associated with early-onset depression and/or anxiety when prenatal exposure, early environmental elements, and child characteristics were considered. In utero exposure to marijuana was only a slight predictor of D/A at age 10.

Neurocognitive Function in Unmedicated Manic and Medicated Euthymic Pediatric Bipolar Patients

Pavuluri MN, Schenkel LS, Aryal S, et al.

Am J Psychiatry 2006;163:286–293

Objective: To elucidate the types of cognitive deficits associated with acutely ill and euthymic phases of pediatric bipolar disorder and the effects of medication on these deficits through systematic evaluation of neuropsychological functioning in individuals with this disorder.

Method: Cognitive testing was completed in groups of unmedicated (N = 28) and medicated (N = 28) pediatric bipolar patients and healthy individuals (N = 28) (mean age = 11.74

years, $SD = 2.99$) matched according to age, sex, race, socioeconomic status of parents, general intelligence, and single-word reading ability. Attention, executive function, working memory, verbal memory, visual memory, visuospatial perception, and motor skills were assessed with a computerized neurocognitive battery and standardized neuropsychological tests.

Results: Irrespective of medication and illness status, participants with pediatric bipolar disorder demonstrated impairments in attention, executive functioning, working memory, and verbal learning compared with healthy participants. In addition, compared with subjects who had no comorbid disorders, bipolar participants with comorbid attention-deficit/hyperactivity disorder (ADHD) performed worse on tasks assessing attention and executive function.

Conclusions: The lack of differences in neurocognitive profile deficits between unmedicated patients who are acutely ill and medicated patients who are euthymic suggests that these impairments may be trait-like characteristics of pediatric bipolar disorder. Significant involvement of frontal lobe systems supporting working memory and mesial temporal lobe systems supporting verbal memory, regardless of ADHD comorbidity, are suggested by the cognitive deficits of individuals with pediatric bipolar disorder.

Multisite Controlled Study of OROS Methylphenidate in the Treatment of Adolescents With Attention-Deficit/Hyperactivity Disorder

Wilens TE, McBurnett K, Bukstein O, et al.

Arch Pediatr Adolesc Med 2006;160:82-90

Objective: Efficacy and tolerability of stimulant medications in adolescent attention-deficit/hyperactivity disorder (ADHD) are poorly understood. This study assessed the efficacy and tolerability of osmotic-release oral system (OROS) methylphenidate among adolescents.

Method: Participants in this multisite controlled study were adolescents ($N = 220$) with a verified DSM-IV diagnosis of ADHD. Dose titration was used to evaluate which dosages of OROS methylphenidate ameliorated symptoms according to previously established criteria. Those participants who successfully tolerated and responded to treatment and followed the study protocol during the dose titration phase ($N = 177$) were randomly assigned to either 2 weeks' treatment with their individualized dosage of OROS methylphenidate (18, 36, 54, or 72 mg once daily) or placebo. Investigator, parent, and adolescent evaluations of ADHD were used to measure treatment efficacy.

Results: Participants treated with OROS methylphenidate showed a significant reduction from baseline in the investigator-

rated ADHD Rating Scale, the primary efficacy measure, compared with placebo. Parent- and adolescent-report measures revealed similar results. Fifty-two percent of subjects in the OROS methylphenidate group achieved a Clinical Global Impressions-Improvement subscale score of much or very much improved, compared with 31% receiving placebo. The maximum dosage of 72 mg/day was needed by 37% of the participants. Drug-related adverse events occurred at a similar rate in the 2 study groups.

Conclusion: Adolescents taking once-daily OROS methylphenidate experienced significantly reduced ADHD symptoms, and dosages up to 72 mg/day were well tolerated in this group.

Retrospective Analysis of Diabetes Risk in Elderly Patients With Dementia in Olanzapine Clinical Trials

Micca JL, Hoffmann VP, Lipkovich I, et al.

Am J Geriatr Psychiatry 2006;14:62-70

Objective: To assess the association of established risk factors for treatment-emergent diabetes among elderly patients with dementia who received treatment with olanzapine.

Methods: Data from 7 olanzapine clinical trials were pooled for a post hoc analysis. Elderly patients (aged > 65 years) with dementia were included. Categorical and time-to-event analyses were used to assess the association of established risk factors for treatment-emergent diabetes, which was defined as 2 casual (fasting or nonfasting) glucose values ≥ 200 mg/dL at any time after baseline or 1 casual glucose value ≥ 200 mg/dL at the final visit, initiation of antidiabetic medication, or new clinical diagnosis of diabetes.

Results: Elderly patients later identified with treatment-emergent diabetes ($N = 29$, 2.1%) had baseline body mass indices (24 kg/m^2) and ages (82 versus 80 years) similar to those without treatment-emergent diabetes. Only elevated casual glucose level (≥ 140 mg/dL) at baseline was significantly associated with the development of treatment-emergent diabetes (hazard ratio [HR] = 11.2, $p < .0001$) in this elderly cohort, based on a Cox proportional hazards model. Other clinical risk factors, such as body mass index $\geq 25 \text{ kg/m}^2$ (HR = 0.86), 7% weight gain (HR = 2.26), and antipsychotic treatment (HR = 1.36), were not significant.

Conclusion: An elevated casual glucose level (≥ 140 mg/dL) at baseline proved to be the only risk factor significantly associated with subsequent development of treatment-emergent diabetes in elderly patients with dementia enrolled in olanzapine clinical trials. The association of antipsychotic treatment group assignment with risk of diabetes in these studies was nonsignificant.