

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.

Mixed Dementia: Emerging Concepts and Therapeutic Implications

Langa KM, Foster NL, Larson EB

Background: Mixed dementia is defined as the coexistence of Alzheimer's disease (AD) and vascular dementia (VaD). As the population ages, the prevalence of mixed dementia is likely to increase. The objectives of this study were to provide an overview of the diagnosis, pathophysiology, and interaction of AD and VaD in mixed dementia, and to provide a systematic literature review of the current evidence for the pharmacologic therapy of mixed dementia. **Data Sources, Study Selection, and Data Extraction:** The Cochrane Database of Systematic Reviews was searched using the keyword *dementia*. MEDLINE was searched for English-language articles published within the last 10 years using the keywords *mixed dementia*; the combination of keywords *Alzheimer's disease, cerebrovascular disorders, and drug therapy*; and the combination of keywords *vascular dementia and drug therapy*. **Data Synthesis:** Dementia is more likely to be present when AD and vascular lesions coexist, an especially common scenario with increasing age. The measured benefits in clinical trials for the treatment of mixed dementia are best described as clinician and caregiver impressions of change and statistically significant differences in cognitive test scores. The control groups' scores typically decline while the treatment groups' improve slightly or decline to a lesser degree over the study period in these trials. Nevertheless, those patients who experience benefits from treatment eventually decline. Cholinesterase inhibitor (ChI) therapy for mixed dementia has resulted in modest clinical benefits similar to those found for ChI treatment of AD. The N-methyl-D-aspartate (NMDA) antagonist memantine also shows modest clinical benefits for the treatment of moderate to severe AD and mild to moderate VaD but has not been studied in mixed dementia specifically. A more effective way to protect brain function as primary, secondary, and tertiary prevention for mixed dementia may be through treatment of cardiovascular risk factors, especially hypertension. **Conclusions:** Once a patient has developed mixed dementia, currently available medications provide only modest clinical benefits. Cardiovascular risk factor control (especially for hypertension and hyperlipidemia), as well as other interventions to prevent recurrent stroke, most likely represent important strategies for slowing or preventing progression of mixed dementia. Additional research is necessary to better define what individuals and families hope to achieve from dementia treatment and to determine the most appropriate use of medication to achieve these goals.

(*JAMA* 2004;292:2901-2908)

Effectiveness of Low Doses of Paroxetine Controlled Release in the Treatment of Major Depressive Disorder

Trivedi MH, Pigott TA, Perera P, et al.

Context: Paroxetine controlled release (CR) is approved for the treatment of major depressive disorder (MDD) in the dosage range of 25 to 62.5 mg daily. However, lower daily doses (12.5 mg and 25 mg) of this formulation have not been investigated in the treatment of MDD. If the 12.5-mg and 25-mg doses are found to be efficacious, these lower doses may well convey a superior tolerability profile for paroxetine CR in the treatment of MDD. **Objective:** To evaluate the antidepressant efficacy and tolerability profile of daily doses of paroxetine CR 12.5 mg and 25 mg versus placebo in the treatment of MDD. **Design and Setting:** Randomized, double-blind, placebo-controlled clinical trial conducted in 40 clinical investigation centers in the United States. **Participants:** 447 adult (≥ 18 years of age) outpatients who met DSM-IV criteria for MDD and with a baseline 17-item Hamilton Rating Scale for Depression (HAM-D) score of at least 20 comprised the intent-to-treat study population (mean age = 38.8 years; 58.4% female; 75.6% white). **Intervention:** Eligible patients completing a 1-week single-blind placebo run-in period were randomly assigned to receive once-a-day study medication (paroxetine CR 12.5 mg [N = 156], paroxetine CR 25 mg [N = 154], or placebo [N = 149]) in an 8-week, double-blind, parallel cell comparison. **Main Outcome Measures:** The primary efficacy measure was the change from baseline to study endpoint (week 8) as measured by the HAM-D. Secondary efficacy measures included change from baseline to study endpoint as

assessed by both the depressed mood item on the HAM-D and the Clinical Global Impressions (CGI) Severity of Illness scale (CGI-S). The proportion of patients considered at study endpoint to be in response (CGI-Improvement score of 1 or 2) or in remission (HAM-D ≤ 7) in the 3 treatment groups was also compared. Quality of life was assessed by the change from baseline in total score of the short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Safety observations were made by assessing the proportion of patients who had adverse experiences, including laboratory and electrocardiographic abnormalities, during the treatment period. **Results:** The primary efficacy analysis revealed that both the 12.5-mg and the 25-mg paroxetine CR treatment groups were associated with significant therapeutic effects (change in HAM-D score) from baseline to study endpoint (LOCF: $p = .038$, 95% CI = -3.38 to -0.09 and $p = .005$, 95% CI = -4.06 to -0.74 , respectively). Results from the Wilcoxon rank sum test of the depressed mood item of the HAM-D ($p = .011$, 95% CI = -0.57 to -0.07) demonstrated significant efficacy in the 25-mg treatment group but not in the 12.5-mg group. However, LOCF analysis of the CGI-S revealed significant therapeutic effects for both the 12.5-mg ($p = .018$, 95% CI = -0.61 to -0.06) and 25-mg ($p < .001$, 95% CI = -0.78 to -0.22) treatment groups. Significantly more patients in the 25-mg paroxetine CR-treated group than in the placebo-treated group met criteria for response (CGI-Improvement score of 1 or 2, $p = .035$, OR = 1.68, 95% CI = 1.04 to 2.73) as well as for remission (HAM-D score ≤ 7 , $p = .013$, OR = 1.96, 95% CI = 1.15 to 3.33). Neither HAM-D remission analysis nor CGI responder analysis showed statistical separation from placebo for paroxetine CR 12.5-mg treatment. Quality of life improvements were statistically significant for the 25-mg treatment ($p = .041$, 95% CI = 0.17 to 8.03) on the Q-LES-Q total score. Post hoc LOCF analyses of HAM-D sleep disturbance, psychic anxiety, and anxiety/somatization factors revealed significant improvements from baseline in the paroxetine CR 25-mg and 12.5-mg treatment groups. The types of adverse events reported in the 12.5-mg and 25-mg groups were similar to those reported with paroxetine CR at the customary 25-mg to 62.5-mg range; however, the lower doses of paroxetine CR were associated with a relatively reduced incident rate of these adverse events and an overall improved tolerability compared with the incident rate and tolerability profile associated with the customary dose range of paroxetine CR (25 to 62.5 mg). **Conclusion:** Paroxetine CR, at 12.5 mg/day and 25 mg/day, demonstrated significant antidepressant effects.

(*J Clin Psychiatry* 2004;65:1356-1364)

Prevalence of Chronic Obstructive Pulmonary Disease Among Those With Serious Mental Illness

Himelhoch S, Lehman A, Kreyenbuhl J, et al.

Background: Smoking is a significant risk factor for chronic obstructive pulmonary disease (COPD), and individuals with serious mental illness have elevated smoking rates. The objective of this study was to determine the prevalence of COPD among those with serious mental illness. **Method:** A random sample of 200 adults with serious mental illness was surveyed with questions from the National Health and Nutrition Examination Study III that were previously used to estimate the national prevalence of COPD. The prevalence of COPD in the sample was compared to a randomly selected matched subset of national comparison subjects. **Results:** The prevalence of COPD was 22.6%. Subjects with serious mental illness were significantly more likely to

have emphysema (7.9% vs. 1.5%) and chronic bronchitis (19.5% vs. 6.1%) than the comparison subjects. **Conclusions:** Among those with serious mental illness, the prevalence of COPD is significantly higher than among comparison subjects. Improved primary and secondary prevention is justified.

(*Am J Psychiatry* 2004;161:2317-2319)

Perinatal Risks of Untreated Depression During Pregnancy

Bonari L, Pinto N, Ahn E, et al.

Background: The purpose of this study was to review the literature on the perinatal risks involved in untreated depression during pregnancy. **Method:** The authors searched MEDLINE and medical texts up to the end of April 2003 for all studies pertaining to this area. Key phrases included *depression and pregnancy*, *depression and pregnancy outcome*, and *depression and untreated pregnancy*. Bipolar depression was not included. **Results:** Untreated depression during pregnancy appears to carry substantial perinatal risks, although there is wide variability in reported effects. These risks may be secondary to unhealthy maternal behaviors arising from the depression or direct risks to the fetus and infant. Recent human data suggest that untreated postpartum depression, not treatment with antidepressants in pregnancy, results in adverse perinatal outcome. **Conclusion:** The biological dysregulation caused by gestational depression has not received appropriate attention. Most studies focus on the potential but unproven risks of psychotropic medication. In-depth discussion of the role of psychotherapy is unavailable. This imbalance may lead women suffering from depression to fear teratogenic effects and refuse treatment, because they are unaware of the potentially catastrophic outcome of untreated maternal depression.

(*Can J Psychiatry* 2004;49:726-735)

Treatment of Posttraumatic Stress Disorder With Phenytoin: An Open-Label Pilot Study

Bremner JD, Mletzko T, Welter S, et al.

Background: Phenytoin is an anticonvulsant used in the treatment of epilepsy. Its mechanism of action is incompletely understood but most likely involves modulation of glutamatergic transmission. The neurobiology of posttraumatic stress disorder (PTSD) has been hypothesized to involve, at least in part, alterations in glutamatergic transmission in the hippocampus and possibly other brain regions. The purpose of this study was to assess the effects of phenytoin on symptoms of PTSD. **Method:** Phenytoin was administered in an open-label fashion for 3 months to 9 adult male and female patients with DSM-IV PTSD related to a variety of traumas including childhood abuse, combat, and car accidents. Dosage was adjusted to maintain the therapeutic blood levels used in the treatment of epilepsy. Subjects were assessed before, during, and after treatment for PTSD with standardized dimensional measures of disease severity including the Clinician Administered PTSD Scale (CAPS), the Hamilton Rating Scale for Depression (HAM-D), and the Hamilton Rating Scale for Anxiety (HAM-A). Data were collected from November 2001 through June 2003. **Results:** Phenytoin treatment resulted in a significant decrease in PTSD symptoms as measured with the CAPS (mean score = 65 pretreatment vs. 38 posttreatment) with reductions in each of the symptom clusters of intrusions, avoidance, and hyperarousal ($p < .05$). There

were no significant decreases in symptoms of depression severity as measured with the HAM-D or anxiety severity as measured with the HAM-A. **Conclusions:** These findings suggest that phenytoin may be efficacious in the treatment of PTSD, possibly mediated through its ant glutamatergic effects. Randomized, controlled, double-blind clinical trials are indicated to further evaluate this medication in the treatment of PTSD.

(*J Clin Psychiatry* 2004;65:1559–1564)

Clinician Screening and Treatment of Alcohol, Drug, and Mental Problems in Primary Care: Results From Healthcare for Communities

Edlund MJ, Unutzer J, Wells KB

Background: The purpose of this study was to estimate national rates of screening and treatment of alcohol, drug, and mental health problems (ADMs) in primary care. **Method:** A cross-sectional survey was administered from 1997 to 1998. Participants included a nationally representative household probability sample of 7301 primary care patients. Patient self-reports from a telephone survey were used to estimate rates of screening and treatment of common ADM problems. The survey also examined the types of screening and treatment received and investigated adherence with treatment recommendations. Covariates included measures of ADM health conditions, physical health, and sociodemographic indicators. **Results:** Among adult primary care patients, 38.6% (95% CI = 37.2 to 40.0) reported clinician screening for an ADM problem. Alcohol or drug screening was more frequent (28.3%; 95% CI = 27.0 to 29.6) than screening for depression and anxiety (21.2%; 95% CI = 20.1 to 22.2). ADM treatment in primary care was reported by 30.1% (95% CI = 27.8 to 32.4) of those screened. The most common treatments were medications (16.4%; 95% CI = 14.3 to 18.5) and counseling (18.2%; 95% CI = 16.1 to 20.3). Screening rates were higher among individuals with ADM disorders, the young and middle aged, and the college educated. Treatment rates were higher among individuals with ADM disorders. **Conclusion:** Considerable effort is used to screen and treat common ADM problems in primary care. These efforts are targeted toward those with ADM disorders; however, only approximately half of individuals with an ADM disorder report being screened. Among this group, about 60% report receiving any treatment.

(*Med Care* 2004;42:1158–1166)

The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline

Yaffe K, Kanaya A, Lindquist K, et al.

Background: An association between the metabolic syndrome and cardiovascular disease has been reported in several studies. There are few data on the metabolic syndrome and cognition, despite an increasing awareness that cardiovascular risk factors increase risk of cognitive decline and dementia. The objective of this study was to determine if the metabolic syndrome is a risk factor for cognitive decline and if this association is modified by inflammation. **Method:** This 5-year prospective observational study was conducted from 1997 to 2002 at community clinics at 2 sites. Participants included 2632 black and white elders (mean age of 74 years). Main outcome measures included association of the metabolic syndrome (measured using Na-

tional Cholesterol Education Program guidelines) and high inflammation (defined as above median serum level of interleukin 6 and C-reactive protein) with change in cognition (Modified Mini-Mental State Examination [3MS]) at 3 and 5 years. Cognitive impairment was defined as at least a 5-point decline.

Results: Elders with the metabolic syndrome (N = 1016) were more likely to have cognitive impairment compared with those without the metabolic syndrome (N = 1616) (26% vs. 21%, multivariate adjusted relative risk [RR] = 1.20; 95% confidence interval [CI] = 1.02 to 1.41). There was a statistically significant interaction with the metabolic syndrome and inflammation (p = .03) on cognitive impairment. Those with the metabolic syndrome and high inflammation (N = 348) had an increased likelihood of cognitive impairment compared with those without the metabolic syndrome (multivariate adjusted RR=1.66; 95% CI = 1.19 to 2.32), after stratifying for inflammation. Those with the metabolic syndrome and low inflammation (N=668) did not exhibit an increased likelihood of impairment (multivariate adjusted RR=1.08; 95% CI = 0.89 to 1.30). Stratified multivariate random-effects models demonstrated that, compared with those without the metabolic syndrome, participants with the metabolic syndrome and high inflammation had greater 4-year decline on the 3MS (p = .04), whereas those with the metabolic syndrome and low inflammation did not (p = .44). **Conclusion:** These findings support the hypothesis that the metabolic syndrome contributes to cognitive impairment in elders, but primarily in those with high levels of inflammation.

(*JAMA* 2004;292:2237–2242)

Medical Comorbidity in Late-Life Depression

Taylor WD, McQuoid DR, Krishnan KR

Background: Elderly depressed patients often have medical comorbidities, but the difference between depressed and non-depressed elderly populations is not well established. Differences between subgroups of depressed populations, such as those with magnetic resonance imaging (MRI)-defined vascular depression and those with early-onset compared with late-onset depression, are not well described. **Method:** Self-reports of medical disorders were compared between 370 depressed elderly subjects and 157 nondepressed control subjects. Subjects were additionally dichotomized on the basis of the absence or presence of subcortical MRI lesions and age at onset. Medical comorbidity was assessed by self-report only, and the clinician-rated Cumulative Illness Rating scale was also used to assess depressed subjects. **Results:** Depressed subjects were significantly more likely to report the presence of hypertension, heart disease, gastrointestinal ulcers, and hardening of the arteries when compared with nondepressed subjects. Subjects with subcortical disease were significantly older, more likely to have depression, and more likely to report the presence of hypertension. The depressed cohort with late-onset depression (occurring after age 50 years) had more male subjects, exhibited greater Cumulative Illness Rating scale scores, and greater prevalence of hypertension, but none of these findings were statistically significant using a Bonferroni correction. **Conclusions:** Vascular comorbidities are common in the depressed elderly. The finding of differences in hypertension reporting supports past work that investigated a vascular contribution to late-life depression. This population of depressed elderly deserves clinical scrutiny and research given the association between depression and poor medical outcomes of cardiac disease.

(*Int J Geriatr Psychiatry* 2004;19:935–943)