

Noteworthy Briefs From the Field

FDA Approves Dexmethylphenidate HCl Extended Release for ADHD

In June, the United States Food and Drug Administration approved dexmethylphenidate hydrochloride extended release (Focalin XR, Novartis) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. The prescribing information indicates that the recommended starting dosage is 5 mg/day for the pediatric population and 10 mg/day for the adult population, with a maximum daily dose of 20 mg/day in both the pediatric and adult populations. The drug should be titrated in 5-mg increments in pediatric patients, and 10-mg increments for adult patients. The dosage should be adjusted according to individual tolerability and response to the medication.

The FDA approval was based on two clinical trials of approximately 325 children and adults. Two hundred and twenty-one adults between 18 and 61 years of age took part in a 5-week, double-blind, placebo-controlled trial of dexmethylphenidate HCl. After completing this trial, 170 patients continued on to a 6-month, open-label extension phase, where the medication continued showing improvements on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition ADHD Rating Scale assessments.

The pediatric trial consisted of 103 children between 6 and 17 years of age administered dexmethylphenidate HCl or placebo once per day for 7 weeks. This trial found dexmethylphenidate HCl to be superior to placebo via the Conners ADHD/DSM-IV Scales for Teachers.

The most commonly reported adverse events in adults were headache, insomnia, and decreased appetite and in children and adolescents were decreased appetite, headache, dyspepsia, upset stomach, and anxiety. —CN

Efficacy of Pregabalin for Somatic Symptoms of GAD

Generalized anxiety disorder (GAD) is the most prevalent anxiety disorder diagnosed in primary care settings, partly because many of the symptoms

of GAD, such as somatic symptoms, pain, and insomnia, interfere with the patient's daily life and compel them to seek care. Previous studies have demonstrated the efficacy of pregabalin in the treatment of somatic symptoms associated with GAD, as early as week 1 of treatment

In the present study, Karl Rickels, MD, and colleagues at the University of Pennsylvania determined that clinically meaningful improvement of somatic symptoms observed early on in GAD patients taking pregabalin, is maintained over 4–6 weeks. Utilizing the Hamilton Rating Scale for Anxiety (HAM-A), Rickels and colleagues combined data from 6 placebo-controlled, short-term trials (4–6 weeks) in the treatment of GAD. Three clinically relevant dosage treatment groups were identified: 150 mg/day, 200–450 mg/day, and 600 mg/day. All subjects were adult outpatients diagnosed with GAD using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision. They had minimum of ≥ 20 HAM-A total score, ≥ 9 Covi-anxiety score, and ≤ 7 Raskin depression score at baseline. Subjects were considered persistent responders if they maintained $>30\%$ improvement on the HAM-A Somatic Factor score at week 1, that persisted through endpoint at all or all but one visit.

Rickels and colleagues found that pregabalin at dosages of 200–450 mg/day and 600 mg/day reduced the somatic symptoms of GAD as early as week 1 and persisted throughout the 4-week trial (Figure). At least 40% of the outpatients were shown to be persistent responders beginning in the first week compared to approximately 25% in the placebo group. A subgroup analysis of patients with severe GAD (HAM-A >26) also showed significantly more rapid, persistent responders by week 1 through endpoint compared to placebo. The most common adverse effects—sedation, somnolence, and dizziness—were mild to moderate in severity and were transient in most patients. Further, discontinuations on pregabalin due to adverse events showed a dose-related trend: 6.2% with

150 mg/day, 8.3% with 200–450 mg/day, and 18.0% with 600 mg/day. According to the authors, the results indicate that pregabalin is a well-tolerated treatment that provides rapid, robust efficacy for the improvement of physical-somatic symptoms of GAD.

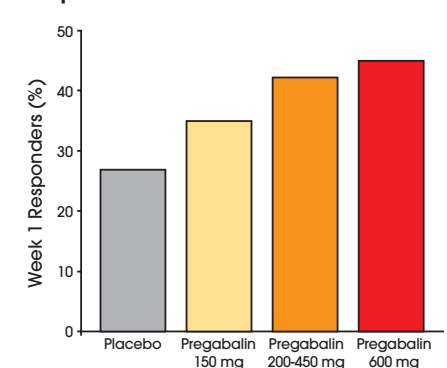
(Poster NR429, APA 2005) —JKH

Effects of Weight Gain on Quality of Life and Overall Health in Bipolar Patients

Patients with bipolar disorder have a greater risk for obesity than the general population and this risk can be exacerbated by treatment with antipsychotics and mood stabilizers. Although weight gain can be distressing to patients, no prior studies have examined its impact on quality of life in those with bipolar disorder.

Patricia Corey-Lisle, PhD, and a multi-centered team of colleagues, examined 100 outpatients (66% female, mean age=42.8 years) with bipolar disorder. In addition to height and weight measures, participants were assessed using the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) measure—a validated self-report assessment of weight-related quality of life that provides overall total score and domain scores on physical function, self-esteem, sexual life, public distress,

Figure
Week-1 Persistent Physical-Somatic Responders



*P<.0001 versus placebo.

Responders defined with $\geq 30\%$ improvement on the HAM-A somatic factor score at week 1 and at all or all except one visits through endpoint.

HAM-A=Hamilton Rating Scale for Anxiety.

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and work. Items are rated on a 5-point scale ranging from 1 (never true) to 5 (always true), and higher scores are indicative of better quality of life. Total and domain scores of participants were compared according to body mass index (BMI) classification.

The researchers found that 86% of all participants were categorized as overweight/obese. BMI significantly ($P < .001$) correlated with IWQOL-Lite total score ($r = -.691$) and all domain scores. Decreases in IWQOL-Lite scores corresponded to increases in BMI. Eta-square for BMI on the total score was .329, indicating that 32.9% of the variance was due to BMI classification.

The results indicate that obesity has a substantial negative impact on quality of life for patients with bipolar disorder and that better preventative measures are needed. Because obesity can also lead to morbidity and mortality as a result of weight-related illnesses, it is critical that clinicians assess metabolic health risks when selecting an agent for long-term treatment.

Funding for this research was provided by Bristol-Myers Squibb and Otsuka Pharmaceuticals.

(Poster NR321, APA 2005) —SW

Acamprosate Found to be Safe and Well-Tolerated for the Maintenance of Abstinence in Patients with Alcohol Dependence

An estimated 8 million individuals in the United States meet standard diagnostic criteria for alcohol dependence annually. Pharmacotherapy, in combination with psychosocial support, has been shown to be effective in the treatment of alcoholism.

In a post-hoc analysis of 13 randomized, double-blind, placebo-controlled trials, Richard N. Rosenthal, MD, at Columbia University College

of Physicians and Surgeons, and colleagues, found acamprosate to be a safe and well-tolerated treatment for alcohol dependence. The trials included 4,234 alcohol-dependant patients from both the US and Europe, ranging between 16 and 72 years of age (*Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised [*DSM-III-R*] or *DSM-IV* criteria). Eight trials were short term (<26 weeks; $n = 2,564$) and 5 were long term (>48 weeks; $n = 1,670$). Patients were detoxified and abstinent at baseline and were then administered acamprosate 1,332 mg/day ($n = 440$); 1,998 mg/day ($n = 1,749$); 3,000 mg/day ($n = 1,962$); or placebo ($n = 1,962$).

Overall, approximately 50% of randomized patients completed the treatment phase; 49% of short-term and 45% of long-term patients failed to complete the study due to adverse events, protocol violations, treatment failure, or personal decisions. There were no meaningful differences between treatment groups in discontinuation due to adverse events. Adverse events occurring significantly more frequently in acamprosate-treated patients included diarrhea (16% versus 10%), asthenia (6% versus 5%), nausea (4% versus 3%), pruritus (4% versus 3%), and flatulence (3% versus 2%). Most adverse events, including diarrhea, occurred with mild-to-moderate severity and decreased in incidence after 4 weeks of treatment. While suicidal nature among patients was rare overall, it was also more common in the acamprosate groups at 1.4% versus 0.5% in the short-term trials and 2.4% versus 0.8% in the long-term trials. Further, adverse events were higher in patients taking concomitant medications, such as antidepressants and anxiolytics, but were comparable across all treatment groups (Table).

"The safety profile of acamprosate should help make it more of a first-

tier medication for psychiatrists and a reasonable strategy for primary care physicians who wish to undertake the pharmacologic component of the treatment of alcohol dependence," Dr. Rosenthal said.

While acamprosate appears to be a viable treatment option for the maintenance of abstinence in alcohol-dependant patients, the researchers noted that it should be used in conjunction with psychosocial support.

Dr. Rosenthal also noted that while major findings of efficacy studies have shown that acamprosate increases rates of complete abstinence over a year's time, the drug may also reduce heavy drinking. "This may potentially make it useful in alcohol diagnoses other than dependence," he said.

Further research in the US may also be warranted, since most of the clinical trials were performed in Europe.

Funding for this research was provided by Forest Pharmaceuticals.

(Poster NR218, APA 2005) —JKH

Long-Term Study Reports Effect of Remission on Overall Health Outcomes

Few studies have examined the long-term course of depression and whether remission is associated with an overall normalization of health, use of health services, and work productivity.

To examine long-term remission status and health outcomes, Ruth Cronkite, PhD, at Stanford University Medical Center, and colleagues, followed up on a 1980 survey of 424 patients treated for unipolar depression and 424 controls who were recruited at six San Francisco Bay Area treatment centers. Over time, 81.6% of the depressed patients and 79.1% of controls were followed four times over 23 years (at 1, 4, 10, and 23 years). Data were collected by mailed survey, personal visit, and/or telephone interview. Assessments included the Health and Daily Living Inventory, the Patient Health Questionnaire, and the Brief Pain Inventory. Patients were compared on health outcomes, use of health services, and work productivity. Analysis of covariance was conducted on outcomes adjusting for age, gender, education, and medical conditions.

Patient subgroups were identified as having a course of remission ($n = 72$, 30%), partial remission ($n = 74$, 31%), or

Table

Adverse Events Reported by Patients Taking Acamprosate and Concomitant Medications

Concomitant Medication	N	Placebo	Acamprosate
Antidepressants	291	84%	78%
Anxiolytics	739	68%	75%
Sedatives/hypnotics	261	77%	79%
Analgesics	518	91%	94%

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nonremission (n=93, 39%). After adjusting for covariates, remitted patients (30% of patient cohort) were similar ($P>.11$) to controls on mean number of Patient Health Questionnaire physical symptoms (4.3 versus 3.8) and anxiety symptoms (0.6 versus 0.8), current medications (2.4 versus 2.4), doctor visits (3.7 versus 3.4), and family activities (4.6 versus 5.0). Partially remitted and nonremitted cohorts were significantly ($P<.05$) worse on these outcomes. Full and partially remitted cohorts were similar to controls on hospitalizations over the past 12 years (admissions 1.0 versus 1.1 versus 0.9), days hospitalized in the past 12 years (4.5 versus 7.5 versus 4.8), and inability to work due to emotional problems (2% versus 1% versus 1%); the nonremitted cohort used significantly more services (1.5 hospitalizations and 27.4 days hospitalized) and were more unable to work due to emotional problems (12%). Patients with a course of nonremission consistently had the lowest levels on outcomes. Pain severity and interference were comparable among remitted patients and controls, and highest among patients with a course of nonremission.

Outcomes of remitted patients appear to resolve to rates comparable to controls at 23 years, indicating the benefits of maintaining remission. However, this study did not address intermittent depressive status across the wide ranges of years between study waves. It was observed that patients with a course of remission seek help from mental health sources at the same level as controls, but tend to seek somewhat more help from non-mental health sources. Patients with a course of nonremission tend to have the highest levels of help-seeking behaviors. Continued remission for unipolar depression has a significant impact

on quality of life and healthcare costs and continuing to seek help from non-mental health sources may be particularly important for helping patients to maintain remission.

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(Poster NR361, APA 2005) —SW

Effects of Lithium on Breastfed Infants

Due to the dearth of clinical data documenting potential risks of lithium to neonates, use of the agent in breastfeeding mothers has been limited. Current American Academy of Pediatrics guidelines advise using lithium with caution during breastfeeding and recommend monitoring infants' serum lithium concentration.

In the largest systematic study to date, Adele C. Viguera, MD, and colleagues, from Massachusetts General Hospital, gathered samples of maternal serum, breast milk, and infant serum from 10 mother-infant pairs. In addition to evaluating the concentrations of each, the researchers also sought to examine potential renal and thyroid dysfunction in infants exposed to lithium. Baseline samples were taken 4–12 weeks postpartum and within 12 hours after a dose of lithium, and repeat samples were obtained from five test subjects. The data were then averaged.

Out of the 10 infants studied, only one showed adverse effects. The infant had an elevated thyroid stimulating hormone (TSH, 7.31), but within 2 weeks of discontinuing lithium these levels were normalized. TSH levels remained within normal limits (mean=2.07±1.33) for all other infants in the study. Infant

renal function (mean=5.82±1.56; range: 3–9 µg/dL) and creatinine (mean=0.28±0.07; range: 0.20–0.40 µg/dL) remained within normal limits for blood urea nitrogen (BUN) levels. There were no other acute adverse effects or later developmental abnormalities observed or reported.

Although previous study estimated infant serum lithium concentration to be 43% that of the maternal levels, this study found it to average only 25% of maternal levels. According to the authors, a tentative “rule of halves” is suggested by these findings—there is half the maternal serum concentration of lithium in breast milk, and infant serum contains approximately half that in maternal milk; therefore, infant serum is approximately one-quarter of maternal serum.

Viguera and colleagues found that exposure to lithium through breast milk produced only rare and clinically nonsignificant adverse clinical effects. Still, they recommend close clinical monitoring of infants exposed to lithium via breast milk, with serum assays of infant lithium, BUN, and creatinine drawn every 6–8 weeks for the duration of breastfeeding.

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