Drug Monitor

Measuring Adequacy of Antidepressant Treatment

Using extended-release venlafaxine (venlafaxine XR) as a first-line antidepressant may increase the odds of an adequate course of therapy, suggest a team of researchers from Prescriptions Solutions, Costa Mesa, CA and Wyeth Research, St. Davids, PA. They conducted a retrospective analysis involving a large cohort of patients who were prescribed either venlafaxine XR or fluoxetine for the first time between January 2000 and February 2001 and whose pharmacy claims were captured by a California-based pharmacy benefit management organization, and found that patients taking venlafaxine XR were at least three times more likely to be treated adequately through the critical first months of therapy.

The original cohort of 11,298 patients had a mean age of 46.8 years and was predominantly female (73%). After excluding patients who switched therapy during the study or never refilled their antidepressant prescription, the researchers were left with 7,430 patients—5,231 taking only fluoxetine and 2,199 taking only venlafaxine XR.

During the 84-day acute phase of treatment, 72% of patients taking venlafaxine XR and 65% of patients taking fluoxetine received continuous treatment with their respective drug. This significant difference persisted during the next phase of treatment: 48% of venlafaxine XR patients received 180 days of continuous treatment, compared with 43% of fluoxetine patients.

Among continuously treated patients, the researchers determined the adequacy of treatment based on previously established adequate daily doses of 75 to 150 mg for venlafaxine XR and 20 mg for fluoxetine. They found that 79% of continuously treated venlafaxine XR patients received an adequate 84-day trial and 77% received an adequate 180-day trial, versus 57% and 52%, respectively, of fluoxetine patients. Even after adjusting for confounding variables—such as age, specialty of prescribing provider, and type of pharmacy benefit—venlafaxine XR showed a clear advantage.

The researchers looked at pharmacy claims, which they say reflect patients' actual behavior in filling prescriptions rather than physicians' intended treatment regimen. In addition, they didn't collect data on depression diagnoses or illness severity, both of which affect the definition of adequate therapy. But because more than three quarters of U.S. patients taking venlafaxine XR or fluoxetine are prescribed the drug for depression with or without anxiety, the researchers feel that not analyzing depression diagnosis probably had a minimal effect on their results.

Given the well documented negative impact of inadequate dosage and duration of antidepressant therapy, the researchers call for an approach to antidepressant selection that takes into account the real-world performance of a drug (which is reflected in patients' refilling and adherence behaviors)—as well as the traditional criteria of efficacy, safety, and tolerability.

Source: *Pharmacotherapy*. 2004;24:33–40.

Just How Tolerable is Irbesartan?

Clinical trials that led to the approval of the angiotensin II receptor blocker (ARB) irbesartan as an antihypertensive agent demonstrated impressive tolerability, with an adverse drug reaction (ADR) profile similar to placebo. But would this level of safety, determined under the highly controlled research setting, be supported by actual clinical experience? Results from the KARTAN study—an observational, uncontrolled, longitudinal, prospective, postmarketing surveillance study involving 852 primary care physicians and 4,887 adult patients from across Spain—are reassuring.

The primary objective of the study was to characterize relatively uncommon ADRs. Data gathered by the primary care physicians at one-, three-, and six-month visits revealed 21 ADRs occurring at a frequency of less than 0.05%. These included such diverse clinical manifestations as dry mouth, rash, pyrosis, vertigo, constipation, nightmares, and urinary

retention. In addition, two serious events (one allergic reaction and one episode of syncope related to hypotension) occurred in two elderly patients, both of whom required hospitalization.

Overall, though, the majority of ADRs were mild to moderate. Headache was the most common (occurring in 0.5% of patients), followed by epigastralgia (0.35%) and nausea or vomiting (0.35%). In total, 108 patients experienced 162 ADRs. Seventeen of these patients (15.7%)—who, collectively, had a total of 49 ADRs (30.2%)—stopped taking irbesartan. Most reactions (38 and 41, respectively) were classified as probably or possibly related to the drug. The incidence of cough was low (0.184%), which supports the notion that a lack of interference with bradykinin makes ARBs less likely than angiotensin converting enzyme inhibitors to cause cough.

The KARTAN study also confirmed the antihypertensive efficacy established for irbesartan by the earlier clinical trials. By one month, irbesartan reduced blood pressure to statistically significant levels—and kept them there for the remainder of the study. In addition, 40% of the patients achieved both their systolic and diastolic blood pressure goals.

The value of postmarketing studies such as this, the researchers say, isn't in their design, since they seldom are double-blinded or controlled. Instead, their power lies in their ability to enroll larger numbers and more diverse groups of patients. In this study, the number of patients enrolled was 11.8% greater than that calculated as necessary to detect low incidence ADRs.

Source: *Clin Therapeutics*. 2004;26:232–244.

Peginterferon Alfa-2a Plus Ribavirin for HCV: How Long and How Much?

The use of interferon alfa and ribavirin has revolutionized the treatment of hepatitis C virus (HCV) infection, but both drugs are associated with serious adverse effects. For this reason, researchers have sought opportunities to limit patients' exposure to the drugs—through lower dosages and shorter durations of therapy. Studies have established that, in patients infected with HCV genotype 2 or 3, combination therapy with conventional interferon alfa and ribavirin generally works just as well when it's given for 24 weeks instead of 48 weeks and when the ribavirin dosage is reduced from the standard 1,000 or 1,200 mg/day to 800 mg/day.

Less is known, however, about combination therapy with the newer pegylated interferons and ribavirin. Given that pegylated interferons are becoming the standard of HCV care, the PEGASYS International Study Group conducted a phase III, randomized, double-blind trial—involving 1,311 patients with chronic HCV infection from 99 international medical centers—in order to compare 24 and 48 weeks of therapy with peginterferon alfa-2a plus either low dose or standard dose ribavirin.

They found that, overall, patients treated for 48 weeks were about one and a half times more likely than those treated for 24 weeks to have a sustained virologic response. Similarly, standard doses of ribavirin were more effective than low doses when all patients were analyzed together.

When the researchers stratified the results according to various characteristics, however, they found statistically significant differences between the two treatment durations and the two ribavirin dosages in patients with HCV genotype 1. For these patients, a sustained virologic response was significantly more likely with 48 weeks of treatment and with a standard dose of ribavirin (odds ratios, 2.19 and 1.55, respectively). On the other hand, patients with HCV genotypes 2 or 3 could be treated satisfactorily with the 24-week regimen of peginterferon alfa-2a plus low dose ribavirin.

These results, the researchers say, should help refine treatment regimens in patients with chronic HCV infection who have elevated liver enzyme levels and compensated liver disease—both enrollment criteria for this study. They caution, however, that the results don't apply to the large group of patients with persistently normal alanine aminotransferase levels or to the growing number of patients with HIV-HCV coinfection.

Source: *Ann Intern Med*. 2004; 140:346–355.

Keeping Breast Cancer at Bay

Five years of tamoxifen is the standard adjuvant treatment for primary estrogen receptor-positive breast cancer in postmenopausal women. Even with this treatment, though, some patients relapse. Interim results from the international, double-blind, randomized Intergroup Exemestane Study (IES) indicate that, after two to three years of tamoxifen, a woman might be better off switching to the aromatase inhibitor exemestane.

The researchers assigned 2,362 postmenopausal women with histologically confirmed, completely resected, unilateral, invasive breast car-

cinoma to switch from tamoxifen—which they'd been taking for two to three years—to exemestane. The other 2,380 patients continued taking tamoxifen.

After a median of 30.6 months of follow-up, the exemestane group had experienced 183 events (local or metastatic recurrence, contralateral breast cancer, or death), compared with 266 in the tamoxifen group. That translates to a 32% reduction in risk. At three years into the study, disease free survival rates were 91.5% in the exemestane group and 86.8% in the tamoxifen group. Furthermore, only nine women taking exemestane developed cancer in the opposite breast, compared with 20 in the tamoxifen group. Overall survival, however, wasn't significantly different in the two groups: 93 women taking exemestane and 106 taking tamoxifen died.

Arthralgia and diarrhea were more common with exemestane, but tamoxifen was associated more often with gynecologic symptoms, vaginal bleeding, and muscle cramps. Tamoxifen patients also were more likely to have thromboembolic events (55 versus 30 in the exemestane group). There was a slight, nonsignificant rise in the rate of osteoporosis and reported fractures in the exemestane group. This finding isn't surprising, say the researchers, given evidence that third generation aromatase inhibitors or inactivators increase bone resorption.

The researchers cite several reasons to consider switching patients to exemestane midway through tamoxifen treatment. For one, they say, tamoxifen resistance occurs after as few as 12 to 18 months of treatment. For another, the researchers suggest that tamoxifen can act as an agonist, potentially stimulating the division of breast cancer cells. Third, they say, tamoxifen can have serious adverse effects, such as thromboembolism and uterine cancer, after prolonged use. Finally, they point out that in their study, switching to exemestane not only reduced the risk of contralateral breast and endometrial cancers but also reduced risk of other primary cancers. They acknowledge, however, that some issues still need to be clarified, such as the correct sequence of therapy and the precise effects of aromatase inhibitors on bone metabolism.

Source: *N Engl J Med.* 2004; 350:1081–1092.

TB Treatment and Electrolyte Disturbance

Results from a retrospective case series revealed that, of 115 patients screened while receiving treatment for multidrug-resistant tuberculosis (TB) at a health center in Lima, Peru, one third had abnormally low levels of potassium. Conducted by researchers from Brigham and Women's Hospital and Partners In Health, both in Boston, MA; and Socios En Salud and the Peruvian National Tuberculosis Program, both in Lima, Peru, the analysis suggests that while such hypokalemia—defined as serum potassium levels below 3.3 mEq/L—is associated with high morbidity rates, effective management of this adverse effect is possible without sacrificing treatment efficacy.

Many factors—including TB itself, malnutrition, and treatment-induced diarrhea and vomiting—can contribute to the development of electrolyte disturbances during pharmacotherapy for multidrug-resistant TB. Through their analysis, the researchers found that the use of capreomycin and low initial body weight were both additional risk factors for hypokalemia. Several of the patients with hypokalemia also had hypomagnesemia (serum magnesium levels below 1.5 mEq/L), say the researchers, which likely was induced by the same mechanism of electrolyte wasting. Hypokalemia was diagnosed, on average, five months after treatment started.

For 86% of the patients, potassium levels normalized after intervention (usually oral or intravenous supplementation of potassium and magnesium, with some patients also receiving amiloride). Failure of hypokalemia to resolve, however, was associated significantly with higher mortality. Given the subtle symptoms and significant morbidity associated with unresolved electrolyte disturbance, the researchers recommend close monitoring for and aggressive management of these conditions in all patients receiving TB treatment.

Source: *Chest*. 2004;125: 974–980.

Rasagiline: The Sooner, the Better

Starting rasagiline mesylate treatment earlier rather than later may help slow the functional decline associated with Parkinson's disease (PD). In a double-blind, parallel-group, delayed-start, multicenter trial conducted in the United States and Canada, 404 patients with early PD who didn't require dopaminergic treatment were randomly assigned to receive 1 or 2 mg/day of rasagiline (an irreversible monoamine oxidase type B inhibitor) for one year or placebo for six months followed by rasagiline 2 mg/day for six months.

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Of those patients, 371 were included in the one-year analysis. The patients who were treated with rasagiline 2 mg/day for one year had significantly less disease progression. Increases in their mean adjusted total score on the Unified Parkinson's Disease Rating Scale was 2.29 units smaller than that of patients who received the rasagiline after six months of placebo. The effects, the researchers say, were seen over a relatively short period of observation. They add that the immediate effects of rasagiline on PD symptoms couldn't fully explain the differences in performance seen at the final examination, because all the patients had been receiving rasagiline for at least six months by that point.

The researchers suggest several possible mechanisms for rasagiline's ability to slow PD progression. For example, rasagiline has been shown to protect neurons against damage from hypoxic injury, oxidative stress, and cerebral trauma. It also may promote better function of surviving dopaminergic neurons.

Rasagiline was well tolerated throughout the study, with few adverse events during either the placebo or the active treatment phases. In fact, the researchers say, adverse events that are relatively frequent with other antiparkinsonian medications (such as hallucination, nausea, and somnolence) were uncommon in their study. ●

Source: *Arch Neurol*. 2004;61: 561–566.