To Reveal Root of Incomplete SSRI Response, Ask

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — The goal of antidepressant treatment should be remission, but most clinical trials use a 50% response in 50% of patients as the criterion for effectiveness. Only about 20%-30% of patients achieve complete remission, and this suggests that additional treatment will be necessary, Jeffrey M. Levine, M.D., said at the annual meeting of the American College of Physicians.

But before changing a patient's selective serotonin reuptake inhibitor (SSRI) prescription because of an incomplete response, physicians should consider a series of questions, said Dr. Levine of the Albert Einstein College of Medicine, New York. First, determine whether the patient is taking the medication. Studies indicate that about 50% of SSRI prescriptions are filled only once. In addition, find out whether the patient is using alcohol or illicit drugs.

Next, use this as an opportunity to review relevant medical issues. Has the patient had recent thyroid function and HIV tests? Is he or she taking any other medications, such as glucocorticoids, β-blockers, or fluoroquinolones that could affect depression treatment? Has the patient been evaluated for sleep apnea?

It may be productive to employ the systematic approach suggested by the mnemonic CITTENNS for possible causes of altered mental status. CITTENNS stands for cardiorespiratory, infectious, toxic, traumatic, endocrine/metabolic, neurologic, neoplastic, and systemic/autoimmune.

Consider whether the patient may have something to gain from depression. 'It may just not be the time they're going to get better.'

Ask about domestic violence, ongoing safety issues, or threats to the patient. "If a patient is being abused or threatened by a partner, your antidepressants are not going to make [him or her] better," Dr. Levine said.

Consider whether the patient may have something to gain from depression. "If a patient has a comp case or a disability case going at this moment, it may be irrelevant or it may be very relevant." Dr. Levine said. "It may just not be the time they're going to get better."

Consider the possibility that the patient has bipolar disorder. Although it may seem as if it would be difficult to confuse mania with depression, recent studies have shown that about a third of patients with bipolar disorder are depressed at the time they're manic. In this mixed state, the patient may complain about depression but have features of mania, such as agitation, pressured speech, racing thoughts, and an inability to sleep.

If the physician answers all of those questions to his or her satisfaction, and the patient still has an incomplete SSRI response, the patient should be given a trial at the maximal dose: 40-60 mg of fluoxetine, 150-200 mg of sertraline, 40-50 mg of paroxetine, or 20 mg of escitalopram, for example.

If that doesn't work, there's little point in trying a different SSRI. Instead, one should either switch to a combined serotonin norepinephrine reuptake inhibitor such as venlafaxine or duloxetine, or add bupropion or mirtazapine.

Bupropion is contraindicated in patients with eating disorders or a history of seizures, but may be especially useful in the patient who reports a lack of energy.

Mirtazapine can increase appetite and cause weight gain, which may or may not be desirable, and has a strong sleep-enhancing effect.

If the addition of a norepinephrine agent doesn't work, the next step would be a low dose of a second-generation antipsychotic such as 0.5-2 mg of risperidone or 5-15 mg of olanzapine. This step is problematic for patients who have type 2 diabetes or are at risk for this condition.

In patients with possible bipolar disorder, lithium or lamotrigine can be useful.

Finally, electroconvulsive therapy might be considered in patients with persistent psychosis, continued suicidality, profound psychomotor retardation, or profound anhedonia.

Dr. Levine disclosed serving on the speakers' bureau for Pfizer Inc. ■

Prior Antidepressant Use Predicts Treatment Adherence

BY MARY ELLEN SCHNEIDER
Senior Writer

ATLANTA — Patients who are taking antidepressants for the first time are at greatest risk for discontinuing the therapy, Mark Vanelli, M.D., said in a poster presentation at the annual meeting of the American Psychiatric Association.

The research shows that patients are most likely to stop drug treatment at the time of their first refill, typically 30-45 days after the initiation of therapy, wrote Dr. Vanelli, chief medical officer of Adheris Inc., a Burlington, Mass., company that provides patient adherence intervention programs.

He and his associates analyzed blinded pharmacy records from 1,157 pharmacies across the country to find patients who filled prescriptions for fluoxetine, sertraline (Zoloft), paroxetine (Paxil CR), venlafaxine (Effexor XR), citalopram (Celexa), or escitalopram (Lexapro). A total of 211,565 patients filled prescriptions for the six antidepressants between Oct. 1, 2003, and March 31, 2004.

Patients were divided into two groups: rookies and veterans. Rookies (37% of the sample) were patients with no prior use of any antidepressant in the 180 days prior to the index fill; veterans (63% of the sample) were defined as patients with a history of antidepressant use in the last 180 days.

Researchers followed the patients for 360 days to calculate the number of days to therapy discontinuation. They also analyzed other factors that might contribute to discontinuation, including age, gender, index refills prescribed, copayments, and estimated income.

The median number of days to discontinuation was 67 for the rookies and 184 days for veterans. The likelihood of discontinuing therapy after the initial fill of the prescription was 39.6% for rookies and 19.9% for veterans, Dr. Vanelli reported.

Patients were considered to have discontinued therapy once they were 30 days late for a scheduled refill. Those who switched from one antidepressant to another were considered to have continued with the therapy.

Patient experience was the variable that best predicted medication discontinuation, Dr. Vanelli noted. However, older men with higher incomes and higher index refills prescribed were less likely to discontinue therapy. Higher copays also increased the risk of discontinuing therapy.

The basic trends of drug discontinuation were similar across the six antidepressants included in the study, he said.

However, one of the limitations of the study is that diagnostic information was not available so the intended duration of therapy could not be determined.

The research shows that interventions are needed to help first-time users of antidepressants with medication adherence. Some strategies to improve antidepressant compliance could include following up with rookie patients at the time of the first refill to check on medication response, insight into the illness, and refill status, Dr. Vanelli suggested. ■

Pilot Study: Drug Combo Spurred Speedier Antidepressant Effects

BY DAMIAN McNAMARA
Miami Bureau

BOCA RATON, FLA. — A combination of escitalopram and bupropion might produce early remission in as many as one-third of patients with unipolar depression, according to a pilot study presented at a meeting of the New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health.

However, the faster onset of action and increased remission rate observed with this combination compared with monotherapy come at a cost of increased adverse events. "In my mind, the adverse events were manageable in most patients," said Jonathan W. Stewart, M.D., a researcher with the depression evaluation service at Columbia University, New York.

Delays are inherent in a sequential monotherapy approach to antidepressant treatment. Mechanistic delays include the time it takes for biochemical effects to occur. Dosing delays occur as physicians wait for a patient to get better before increasing the dose. In addition, there are programmatic delays because "we wait to see if the first one does not work before we start the second drug," he said.

Dr. Stewart assessed 29 outpatients with major depressive disorder. The mean age was 38 years, and the patients were moderately depressed at study entry. Exclusion criteria included a history of seizures, substance abuse/dependence, bipolar disorder, or current use of other psychoactive drugs.

"We decided to mix escitalopram [Lexapro] with bupropion [Wellbutrin]. This combination may address a mechanistic delay inherent in" treatment with selective serotonin reuptake inhibitors, Dr. Stewart said. He added that the use of two effective antidepressants might overcome programmatic delays.

There was a rapid dose escalation during the first 15 days, after which dosages were stabilized to day 56. Almost half of the patients, 49%, followed the protocol dosing, and 54% were on the maximum dosages at study completion at 8 weeks.

At 2 weeks, 10 of 29 patients (34%) met remission criteria—defined as a Hamilton Rating Scale for Depression (HAMD-17) score of less than 8. "So we're getting a third of the patients better at 2 weeks," he noted. The mean score at 2 weeks was 11.

By comparison, there is a 6% remission rate with monotherapy at 2 weeks, according to Dr. Stewart's own unpublished data for more than 500 patients.

At 8 weeks, 18 patients (62%) met remission criteria, and the mean HAMD-17 score was 6. Dr. Stewart said that the remission rate with monotherapy in his own unpublished data is 38%.

A total of six patients withdrew from the study, four because of adverse events. The most common adverse events were sleep related (reported by 55% of participants), including daytime sedation and insomnia. A total of 38% reported gastrointestinal effects, including abdominal pain and constipation, and 24% reported sexual effects, including decreased libido and anorgasmia. Patients also reported word-finding difficulty, headaches, dizziness, hives, sweating, increased blood pressure, and dizziness.

Despite the early onset of action of an escitalopram (Lexapro) and bupropion combination, efficacy beyond 2 weeks looks similar to other combinations, Dr. Stewart said. ■