Time Pressures Raise Stakes When First Antidepressant Fails

BY CARL SHERMAN
Contributing Writer

NEW YORK — Time is a crucial factor in depression treatment, as repeated failed trials and delay in achieving an adequate response take a cumulative toll on patient morale, ability to function, and finances, Jeffrey E. Kelsey, M.D., Ph.D., said at a meeting on psychopharmacology sponsored by New York University.

Good practice often requires the application of both evidence and clinical experience. "Proven therapies are a good place to start, but we can't get by solely on what evidence tells us," said Dr. Kelsey, medical director of the Georgia Institute of Mood and Anxiety Disorders, Atlanta.

The choice of an initial antidepressant is "little more than an educated guess" for the most part, he said. If an adequate trial fails to achieve a response, the choice is between switching to a different agent and augmentation with polypharmacy.

"If the first drug isn't working at all, I would stop it before adding something else," Dr. Kelsey said. An agent with a different mechanism of action would seem a better choice than one of the same class.

The switch, however, should not be too abrupt: A schedule that phases in the second drug while slowly tapering the first will minimize the possibility of the discontinuation syndrome that can occur when serotonergic drugs are withdrawn. The patient should be counseled about the possibility of such symptoms as malaise, gastrointestinal upset, anxiety, irritability, insomnia, and paresthesias so these symptoms are not ascribed to the new drug, he said.

Augmentation, when the first drug is well tolerated and has achieved some degree of response, is likely to achieve quicker results than switching, Dr. Kelsey said.

Lithium and thyroid hormone augmentation are "classic" strategies that have been shown to be more effective than placebo, he said.

Lithium, in particular, is underutilized. Dr. Kelsey advised a modest target blood level of 0.4-0.5 mEq/L, which is generally adequate and less likely to cause tolerability problems than higher blood levels.

Thyroid augmentation should be based on thyroid hormone assay. If only T_3 is low, just T_3 should be added; if both T_3 and T_4 are low, just T_4. "Sometimes the improvement is amazing," he said.

With long-standing or treatment-resistant depression, the chances for a good response are substantially increased if psychotherapy is added.

When an atypical antipsychotic is used for augmentation, the possible effect of drug-drug interactions must be kept in mind. Risperidone (Risperdal), for example, should be started at 0.5 mg/day and increased to 1 mg/day, but when it is used to augment an SSRI that may inhibit cytochrome P450 2D6, those dosages should be halved.

Dopaminergic agents are particularly apt for augmentation when apathy and low energy are prominent. With use of a dopamine agonist like pramipexole (Mirapex), a gradual escalation from a low dose will minimize nausea and improve tolerability.

Reducing, rather than increasing, the SSRI should be considered in this situation since anergic, amotivational symptoms may be related to dopaminergic downregulation in the frontal lobe, Dr. Kelsey explained.

With any long-standing or treatment-resistant depression, the chances for a good response are substantially increased if psychotherapy is added to whatever medication regimen is used.

As patients become more refractory, a longer trial is necessary before concluding that a treatment approach isn't working. "You won't get an immediate response, as in early illness," Dr. Kelsey said. "Remember, the clock is ticking." ■

Study Examines Local Effect Of Antidepressant Warnings

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — A specific warning issued in June 2003 by the United Kingdom Committee on Safety of Medicines that advised physicians not to use paroxetine in patients younger than 18 years of age significantly influenced how the drug was prescribed in young patients in Ontario.

Yet subsequent, more generalized warnings about selective serotonin reuptake inhibitors (SSRIs) issued in the United States and Canada did not influence antidepressant prescription trends in any age group of Ontario residents, Paul A. Kurdyak, M.D., reported during a poster session at the American Psychiatric Association's Institute on Psychiatric Services.

"From a policy perspective, vague warnings don't do anything in Ontario," Dr. Kurdyak, a research fellow in the department of psychiatry at the University of Toronto, said in an interview. "I don't know about the United States. It might be different there because you're more litigious here than we [in Canada] are."

In a study supported by AstraZeneca Pharmaceuticals and the Canadian Institute of Health Research, Dr. Kurdyak and his associates analyzed new antidepressant prescriptions dispensed by the Ontario Drug Benefits Program between April 1998 and March 2005. Three age groups were studied: younger than 20 years, 20-65 years, and 66 years and older.

The investigators conducted a time-series analysis to assess the impact of five advisory dates on the prescription of antidepressants. Those dates were:

► **June 10, 2003.** The UK Committee on the Safety of Medicine advises against the use of paroxetine in patients with depression younger than 18 years of age.

► **Oct. 27, 2003.** The U.S. Food and Drug Administration issues a more general public health advisory emphasizing that newer antidepressants should be used with caution in pediatric patients.

► **March 22, 2004.** The FDA issues a public health advisory about the need to closely monitor patients of all ages for worsening depression or suicidality after initiation of antidepressant therapy.

► **June 3, 2004.** Health Care Canada follows suit with a similar warning.

► **Oct. 15, 2004.** The FDA issues a black box warning for the use of antidepressants in pediatric patients.

Analysis revealed that the mean number of monthly new prescriptions for any SSRI per 10,000 individuals was 5.5 for patients younger than 20 years; 29.7 for patients aged 20-65 years, and 16.4 for patients aged 66 years and older.

"The number of new prescriptions for SSRIs as a group did not change after any antidepressant warning in any age group," the investigators wrote in the text of their poster.

"However, the rate of new paroxetine prescriptions in patients younger than 20 years of age declined by 54% immediately following the first UK warning for paroxetine in June 2003."

That particular warning "had no effect on new paroxetine prescriptions in the other age categories, [and] no warnings influenced new prescription rates for any other antidepressants in any other age group," they added. ■

Early Worsening Is a Harbinger of Poor Outcome With Fluoxetine

BOCA RATON, FLA. — Early worsening of symptoms after initiation of fluoxetine for major depressive disorder occurs in approximately 30% of patients and is associated with poorer outcomes and an increased likelihood of discontinuation, Cristina Cusin, M.D., said in a poster presentation at a meeting of the New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health.

Patients should be monitored very carefully in the weeks after new treatment with fluoxetine, she said.

Dr. Cusin and her associates studied 694 outpatients (mean age 39 years) with major depressive disorder. Participants received 20 mg of fluoxetine per day for up to 12 weeks. The investigators assessed participants at regular intervals with a modified Hamilton Depression Rating Scale (mHAM-D) and defined worsening as a 5-point increase in score since the previous visit, occurring at least 1 week after starting treatment. Eli Lilly funded the study.

"Not all patients respond the same way. Some get worse before they get better," said Dr. Cusin of Massachusetts General Hospital, Boston. Dr. Cusin has no affiliation with Eli Lilly.

A total of 211 patients (30%) had worsening of their depression between weeks 2 and 6. Researchers looked for clinical correlates to predict who might fall into this group. They found no significant differences—based on age, duration of illness, number of previous depressive episodes, baseline mHAM-D scores, or fluoxetine/norfluoxetine plasma levels—between this group and the 483 who reported no worsening.

But an increase in the mHAM-D scores at weeks 2, 3, 4, and 6 was significantly associated with a lower probability of improvement at weeks 8 and 12.

—Damian McNamara

Depression Screening for Parents Accepted in Well-Child Visits

WASHINGTON — Screening for parental depression at well-child visits is feasible and parents are receptive to the idea, Ardis L. Olson, M.D., reported at the annual meeting of the Pediatric Academic Societies.

A brief, validated questionnaire, the two-question version of the Patient Health Questionnaire depression module (PHQ-2), was completed by almost 8,000 parents in about half of the well-child visits conducted in six small- to medium-sized practices during a 6-month period.

The practices had been prepared for screening with provider and parent education, said Dr. Olson of Dartmouth-Hitchcock Medical Center in Lebanon, N.H.

Rates of positive PHQ-2 screens were similar for both mothers and fathers (about 5% for each). Pediatricians were more likely to refer mothers who screened positively (39%) than fathers who screened positively (21%), however, to primary care or mental health providers. They were equally as likely to refer mothers and fathers (26%) to a telephone support referral service called the Parent Support Line.

One-quarter of the parents accepted the services of the Parent Support Line when they were offered a call from the service, while fewer than 1% accessed the service when given a Web site or 800 number—a finding that indicates that follow-up must be proactive, Dr. Olson said.

—Christine Kilgore