Consider Three Variables in ADHD Prescribing

Take characteristics of the medication, efficacy studies, and patient into account before treatment.

BY SHARON WORCESTER
Southeast Bureau

MIAMI BEACH — Three variables—medicine characteristics, efficacy study characteristics, and patient characteristics—should be considered when prescribing for attention-deficit hyperactivity disorder, said Dr. Richard Rubin at the annual meeting of the American Society for Adolescent Psychiatry.

Medicine characteristics include effect duration, influence on comorbidities, individual safety risk, patient acceptance, cost, and access for continuous adherence, said Dr. Rubin, director of the private practice–based Clinical Study Center in Burlington, Vt.

Efficacy study characteristics—such as patient selection, rating measurements used, dosing, and treatment duration—should be considered in regard to how they might limit the findings and apply to patient care.

Patient characteristics important to consider include potential response mediators and moderators.

Compliance, for example, is a mediator that frequently causes problems in achieving desired outcomes. Data from 2004 on the three most commonly prescribed ADHD medications show that refill adherence after 2 months is only 50%. Patient/parent benefit expectations, subjective discomfort complaints, and side-effect fears appear to play an important role in compliance, and should be addressed by prescribers.

Comorbid disorders are common moderators that also require careful evaluation and consideration in ADHD prescribing, said Dr. Rubin at the meeting cosponsored by the University of Texas at Dallas.

Medications specifically approved for ADHD included amphetamine formulations, various methylphenidate products, and atomoxetine (Strattera). Useful medications not approved for ADHD include the antidepressants bupropion, imipramine, and nortriptyline, and the α_2-adrenergic agonists clonidine and guanfacine. Pemoline was withdrawn from the market, Dr. Rubin noted.

In the past year, new FDA approvals for adolescents were granted for a 72-g dose of osmotic-release oral system (OROS) methylphenidate, a methylphenidate transdermal system (Daytrana), and extended-release mixed amphetamine salts. An extended-release formulation for dexmethylphenidate (Focalin XR) was also approved for children, adolescents, and adults.

In addition, an "FDA approvable" letter was issued for an ADHD formulation of modafinil (Provigil), he noted.

Other topics Dr. Rubin addressed included:

► **Stimulant pharmacokinetics and efficacy.** One study looking at the effects of weight, age, and gender on mixed amphetamine salts (MAS) pharmacokinetics showed that the area under the curve and C_{max} decreased, and half-life increased as weight increased in children, adolescents, and adults. Age and gender had no effect on the parameters, independent of weight.

A 4-week randomized, placebo-controlled study of MAS in 318 adolescents showed those treated with 10-40 mg/day had a mean 17.8-point decrease on the ADHD Rating Scale (ADHD-RS), those treated with 50 mg/day had a mean 16.9-point decrease, and those in the 60-mg group had a mean 14-point decrease, compared with a mean 9.4-point decrease in the placebo group. An OROS methylphenidate dosing study of 177 13- to 18-year-olds with combined type ADHD showed that 38% required the 72-mg dose to achieve at least a 30% ADHD-RS improvement, with a mean change of 15.3.

► **Schedule II prescribing rules.** Federal regulations updated in November 2005 to clarify physician responsibilities state that physicians are not required to see a patient every month or whenever schedule II drugs are prescribed. Prescriptions due for a refill can be mailed to a patient, or mailed or faxed to a pharmacy, but the physician should have a contact with the patient to verify ongoing safety. Physicians cannot provide refill prescriptions dated in advance. The amount of medicine that can be prescribed (for example, a 30- or 90-day supply) is regulated by the state or a third-party payer.

► **Tricyclics for ADHD.** These drugs may still have some selected use in ADHD, for example, with comorbid tics, but the risks for overdose fatality remain. Also, case reports suggest there is a risk for tricyclic-marijuana adverse interactions.

► **α_2 Noradrenergic agonists for ADHD.** Clonidine and guanfacine have been shown to be effective when added to stimulants for aggression with ADHD, and also appear effective for tics with ADHD. While the sedative properties of clonidine are commonly used at bedtime after daytime stimulants, physicians should be conscientious about the differential diagnosis and treatment of sleep problems in ADHD adolescents, Dr. Rubin advised.

Data from 2004 on the three most commonly prescribed ADHD medications show that refill adherence after 2 months is only 50%.

For example, the ADHD itself, or comorbidities such as anxiety, oppositional defiant disorder, and substance abuse might play a role in sleep problems. Stimulant side effects, a primary sleep disorder such as obstructive apnea, restless legs, or poor sleep-hygiene practices may also be to blame.

► **Bupropion.** This drug is still a useful off-label treatment option for ADHD, particularly in those with substance use disorder, mood disorder, and/or conduct disorder, recent studies suggest. The dose needs to be high enough (450 mg/day for the XL form and 400 mg/day for SR form), and with duration of at least 4 weeks to achieve a 50% reduction in symptoms. The XL once-daily dose is associated with better adherence than the twice-daily SR dose, he noted.

► **Atomoxetine initiation.** The use of atomoxetine can be simplified and compliance might be improved with small deviations from the original package insert instructions.

Dr. Rubin recommended a titration schedule of 0.5 mg/kg per day the first week, 1.0 mg/kg per day the second week, and 1.5 mg/kg per day the third week. He said this allows only one pill size, but noted that the titration can be done as 40, then 80, then 120 mg in larger patients.

The basic visit schedule should include a visit at week 2 to evaluate tolerability and compliance, a visit at week 4 to look for response signals. Early tolerability problems can often be ameliorated with slower titrations, dose time change, or dose splitting to b.i.d., and a visit at week 6 to evaluate for extent of response and treatment moderators. Stimulant augmentation is useful for partial responders.

An alternate treatment should be considered in nonresponders. Initial evening postdinner dosing has the best tolerability, but a later switch to morning or twice-daily dosing may provide better efficacy. Some late adolescents, particularly college students, may adhere best with noon dosing along with lunch. While rare in adolescents, noradrenergic side effects are relieved by a 50% slower titration.

► **Long-term stimulant side effects.** There is no evidence of major adverse events with long-term stimulant use. Side effects that tend to persist include insomnia, decreased appetite and/or weight loss, and headache. Growth rate may be affected, but no evidence exists of an ultimate adult height reduction. However, if weight or height drops 10 or more percentile points after 1 year of treatment, a medication change should be considered.

► **Sudden cardiac death and ADHD treatment.** After Canada's withdrawal of MAS because of sudden cardiac death concerns and the drug's subsequent reinstatement, a Canadian physician advisory report advised strenuous exercise, use of other stimulants, and family history should be considered in risk-benefit assessment for individual patients.

► **Atomoxetine and liver injury.** Although a package insert warning was announced in December 2004, no Food and Drug Administration or psychiatric guideline for screening in healthy individuals has been issued.

If liver enzymes are measured, it is important to recognize that other factors, such as alcohol intake, acetaminophen, viral syndromes, and obesity can cause temporary changes.

An increase in liver enzymes to more than two times the baseline is a guide used in clinical trials for determining clinical significance. Any increase in bilirubin level is a red flag needing further evaluation. ■

Metaanalysis Shows Stimulant Therapy Inhibits Growth

SAN FRANCISCO — The question of whether stimulant therapy for attention-deficit hyperactivity disorder inhibits a child's growth has long been controversial, with well-designed studies providing conflicting results.

Now, a metaanalysis has indicated that stimulant therapy inhibits both weight gain and expected height gain. Dr. Omar Khwaja reported the results of this metaanalysis in a poster presentation at the annual meeting of the Pediatric Academic Societies.

Twenty-two studies including 2,383 patients were selected for the metaanalysis. The children, aged 0-18 years, were treated with either dextroamphetamine or methylphenidate for a mean duration of 1.5 years.

The metaanalysis included clinical trials, observational cohort studies, and case-control studies.

The effect sizes, as measured by a statistic called Cohen's d, were statistically significant for both weight and height, but greater for weight. However, the meta-analysis found that the effect size favoring weight gain restriction was –0.63, and the effect size favoring restriction in expected height gain was –0.41.

Standard interpretations of the Cohen's d statistic describe an effect size of –0.41 as small to medium, and an effect size of –0.63 as medium to large.

The effect was more pronounced for dextroamphetamine than for methylphenidate, wrote Dr. Khwaja, of Children's Hospital, Boston, and his colleagues.

Their meta–regression analysis evaluated the relative effects of the study's duration, medication type, the study's outcome metric, and the child's age at treatment.

The authors found that medication type proved to be the only statistically significant variable.

"Physicians should continue to be vigilant in monitoring growth parameters in stimulant-treated children," the authors wrote.

—Robert Finn