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Clinical & Research News

Research on Children Yielding Valuable Clinical Information

Jun Yan

A wealth of knowledge that's been generated from pragmatically designed, NIMH-funded clinical trials can help clinicians provide evidence-based care for children and adolescents.

Selective serotonin reuptake inhibitors (SSRIs) work faster than cognitive-behavioral therapy (CBT) in treating adolescents with depression, but CBT beats SSRIs in effectiveness and safety in treating children with obsessive-compulsive disorder.

Preschoolers metabolize methylphenidate less efficiently than older children, and feedback from both parents and teachers is necessary to determine the best dosage of methylphenidate for children with attention-deficit/hyperactivity disorder (ADHD).

These are some of the practical lessons being gleaned from several large clinical trials funded by the National Institute of Mental Health (NIMH).

Researchers who had led these studies summarized these lessons and other practice implications at the American Academy of Child and Adolescent Psychiatry annual meeting in Boston in October.

Unlike most industry-sponsored clinical trials, which seek to find out a drug's safety, efficacy, and mechanism of action and are conducted in tightly controlled, ideal conditions, these clinical trials enrolled subjects from the community who often have comorbidities. The trials were designed to reflect real-world clinical practice and tried to answer complex questions, explained John March, M.D., a professor of psychiatry and chief of Child and Adolescent Psychiatry at Duke University Medical Center.

Furthermore, most of these studies made head-to-head comparisons among medications, CBT, and a combination of both to clarify their relative safety and efficacy in this vulnerable population. "These kind of studies have to be supported by public money," Benedetto Vitiello, M.D., chief of the Child and Adolescent Treatment and Preventive Intervention Research Branch at NIMH, pointed out. "There is no interest from the industry to look at such comparisons."

One of the lessons from the Multi-modal Treatment Study of Children with ADHD (MTA) described at the meeting was the importance of obtaining both parents' and teachers' feedback on a child's ADHD symptoms, as parents may not observe some aspects of children's difficulties that are more apparent in school, explained Peter Jensen, M.D., director and CEO of the REACH (Resource for Advancing Children's Health) Institute. During the study, the researchers found that teachers' assessment of ADHD symptoms was critical for methylphenidate dose adjustment, while parents provided important feedback about the side effects. The MTA study compared the effectiveness and safety of methylphenidate, CBT, a combination of both, and usual community care in children aged 7 to 10 with ADHD. It demonstrated the important role of medication in the overall treatment plan for most patients (*Psychiatric News*, August 17).

Combination Treatment Most Effective

The greater effectiveness seen in the medication and combination treatments compared with community care, Jensen suggested, could be attributed partially to the frequent interaction of patients and their parents with study practitioners.

"Families don't particularly like medicine," he said. The dose increase in the medication and combination group was more aggressive than in the community-care group, a process facilitated by the families' trust and relationship with care-givers that grew out of the frequent and in-depth visits by the intervention groups.

Another message gleaned from the study was the differential effectiveness of methylphenidate in subgroups of ADHD patients with comorbidities. Children with ADHD and anxiety, for example, responded far better to CBT with medication than did those without anxiety. Nonetheless, "medicine did the same with or without [CBT] for the 'clean' ADHD type," said Jensen. "Kids with ODD

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[oppositional defiance disorder] or CD [conduct disorder] did not respond [generally] to behavioral therapy."

Preschoolers Evaluated

Despite the Food and Drug Administration (FDA) warnings against giving children younger than 6 years old methylphenidate, many preschoolers are diagnosed with ADHD and treated with the drug, said Laurence Greenhill, M.D., a professor of clinical psychiatry and director of the Research Unit of Pediatric Psychopharmacology at Columbia University and the New York State Psychiatric Institute. This was the impetus for conducting the Preschool ADHD Treatment Study (PATS) in children aged 3 to 5-and-a-half years who were diagnosed with ADHD that caused moderate to severe impairment and who had failed a course of intervention based on parent training (*Psychiatric News*, December 15, 2006).

Greenhill pointed out that the effect size of methylphenidate treatment in the PATS was smaller than that in the MTA study, and the therapeutic dose after titration was an average of 14 mg/day for the preschoolers, far lower than the therapeutic dose for school-aged children in the MTA study. In addition to higher severity of ADHD among children in PATS, Greenhill cited a pharmacokinetic study based on their data, which "suggested that the clearance of methylphenidate in preschoolers was half the rate of school-aged kids. The same dose of methylphenidate may lead to higher exposure [in younger children] because of slower metabolism." Moreover, psychiatric comorbidities such as conduct disorder or anxiety hampered the effectiveness of methylphenidate, and patients with three or more comorbidities had essentially no response to the medication.

Greenhill emphasized the side effects seen in subjects in the PATS were generally similar to those seen in school-aged children (for example, irritability, difficulty falling asleep, decreased appetite) in the MTA study, with one exception: younger patients seemed to have more intense outbursts. "It was more of a brittle, tantrum-throwing kind of reaction, even though they were on average less hyperactive," said Greenhill. Meanwhile, long-term, cumulative exposure to methylphenidate was shown to slow children's expected height and weight growth. The clinician should start with the lowest dose, he recommended.

Youth With OCD Studied

The Pediatric OCD Treatment Study (POTS) was conducted by NIMH and collaborating researchers from 2000 to 2003 (*Psychiatric News*, December 3, 2004) and compared the effectiveness of CBT alone, sertraline alone, combined CBT and sertraline, and placebo over 12 weeks for treating children and adolescents with OCD.

CBT showed a clear overall advantage over medication in these patients. While the effect size was greater in the sertraline-CBT combination group, CBT alone worked better than sertraline alone, said March. The remission rate was similar between combination treatment and CBT alone, which was significantly higher than for sertraline alone.

"One of the implications of this study," said March, "is that it is no longer adequate to not offer CBT to parents and patients, even if CBT is not available at your practice." He urged psychiatrists to offer standardize CBT to treat OCD or partner with practitioners who can provide the therapy.

He also noted that in the study, the quality of CBT varied from site to site, and the combination of medication and CBT seemed to provide favorable outcomes more reliably than CBT alone.

Adolescent Depression Study

The Treatment for Adolescents With Depression Study (TADS) compared fluoxetine, CBT, a combination of both, and placebo to provide real-world data relevant to clinicians. Fluoxetine- and combination-treatment groups improved significantly more than CBT and placebo groups at three months, but the effectiveness of CBT alone caught up with medication over time, and by the end of week 36, all three groups had similar rates of improvement (*Psychiatric News*, November 2).

Vitiello emphasized that the combination treatment was superior to either medication or CBT alone in terms of remission rate, functioning, and quality of life. "If remission is the most relevant outcome for your patient, combination therapy is more powerful," he said.

In addition, the combination therapy seemed to have a protective effect against the increased suicidality associated with fluoxetine use, as the combination-therapy group saw a similar rate of suicidal events as the CBT-alone group, and both were significantly less than the fluoxetine-alone group. The reason for this potential effect of CBT is unknown. March suggested that CBT might have modified the risks of suicide in part because "it teaches kids the skills to manage emotional dysregulation and stress and reduces family conflicts."

Translating Findings a Challenge

Audience members commented that while the studies were of high quality and directly relevant to clinical practice, the dissemination and application of this wealth of knowledge seemed slow.

Given the benefits of CBT demonstrated in these large trials, the implementation is sometimes hindered by practice variability and inadequate insurance coverage for the service, as March and other presenters pointed out. The panel concurred that there is a lag from the publication of the trial results to improved quality of care despite important public implications. Practice guidelines can be slow to incorporate scientific evidence, while continuing medical education programs supported by industry funding and provided by private vendors often lack credibility and objectivity among practitioners, as several panelists pointed out. March urged clinicians to participate in the Child and Adolescent Psychiatry Trials Network (www.captn.org) to help improve the research and practice of evidence-based medicine. ■

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