SSRI Benefit in Autism May be Overstated

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The reported benefits of selective serotonin reuptake inhibitors (SSRIs) for treating the repetitive behaviors of autism spectrum disorders (ASDs) may be exaggerated by the selective publication of positive results, researchers found.

In a meta-analysis, the use of SSRIs and the tricyclic antidepressant clomipramine (Anafranil) was associated with a modest but significant improvement in repetitive behaviors (P<0.005), according to Melisa Carrasco, PhD, of the University of Michigan in Ann Arbor, and colleagues.

After accounting for publication bias, however, the improvement lost statistical significance, the researchers reported online ahead of the May issue of *Pediatrics*.

"Without timely, transparent, and complete disclosure of trial results, it remains difficult to determine the efficacy of available medications," they concluded, noting that there is some evidence that SSRIs may be effective for managing comorbid anxiety in patients with ASDs.

Action Points

A meta-analysis found substantial selection bias, which led to the conclusion that the small observed benefit of selective serotonin inhibitors (SSRIs) on repetitive behavior in children with autism spectrum disorder was not significant.

Note that a second study found that only about one-half of NIH-sponsored clinical trials in children were published and less than one-third of other completed trials.

Although several randomized trials have examined the efficacy of SSRIs in patients with ASDs, uncertainty about their usefulness remains.

To address that uncertainty, Carrasco and colleagues searched for completed randomized, double-blind, placebo-controlled trials, and found five that were published and five that were not.

The meta-analysis included the five published studies and one of the unpublished studies for which data were obtained; data for the other four were requested but not supplied.

The six trials included 365 patients and evaluated clomipramine, fluvoxamine (Luvox), fluoxetine (Prozac), and citalopram (Celexa).

In the initial analysis, there was a significant improvement in repetitive behaviors, including obsessions and compulsions (standardized mean difference 0.22). But after accounting for publication bias, the benefit was attenuated and became nonsignificant (standardized mean difference 0.12).

"This lack of timely and complete disclosure of trial findings results in physicians being unable to make rational informed decisions about the efficacy and risks of serotonin receptor inhibitor treatment of children with autism spectrum disorders," wrote Scott Denne, MD, of Indiana University School of Medicine in Indianapolis, in an accompanying editorial.

"It is especially ironic that problems in making research data available about the use of this class of drugs in children created a firestorm almost 10 years ago," he noted. "Unfortunately, this problem has not been resolved."

An additional study in *Pediatrics*, reported by Tatyana Shamliyan, MD, and Robert Kane, MD, of the University of Minnesota School of Public Health in Minneapolis, underscored that the problem of pediatric publication bias is not confined to studies of SSRIs.

Shamliyan and Kane evaluated 160 randomly selected, NIH-funded studies and 758 randomly selected completed studies involving children. They found that only 53% of the former, and 29% of the latter, were published, which they cited as evidence of "substantial publication bias."

In his editorial, Denne noted that the American Academy of Pediatrics has a policy that all clinical trials should be registered and any results should either be published or made available to researchers and the public.

"At present, the results of most clinical studies of children are unavailable to the pediatric research community and the public," Denne wrote. "As a consequence, trials may be unnecessarily repeated, and the information cannot be used to guide therapy."

But beyond the clinical need, Denne noted that there is an obligation to the children and families who have enrolled in clinical trials to make sure that their contributions can help all children.

"Only timely, complete, and readily available clinical trial results can meet this obligation. We have a viable mechanism (ClinicalTrials.gov) to post trial results, but have fallen far short of the goal," he wrote. "Addressing this deficiency will require a renewed commitment by clinical investigators, the NIH, the pharmaceutical industry, and the FDA. It is time for urgent action."

The study by Carrasco and colleagues was supported by the National Institute of Mental Health, the NIH, the National Center for Research Resources, and the NIH Roadmap for Medical Research. The researchers reported that they had no conflicts of interest.

The study by Shamliyan and Kane was supported by the University of Minnesota Evidence-based Practice Center. They reported that they had no conflicts of interest.

Denne reported that he had no conflicts of interest.

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