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The Voices Go, But the Song Remains the Same: How Can We Rescue Cognition in Early-Onset Schizophrenia?

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Current treatments for psychosis in children and adolescents are sorely in need of efficacy data. In the past decade we have seen a dramatic increase in the prescription of antipsychotic medication for individuals younger than 18 years¹ and an increased awareness that subclinical and overt psychotic symptoms are more prevalent in pediatric populations than previously believed.² Despite its widespread implementation, exactly how pharmaceutical intervention affects cognitive and psychosocial functioning in youth remains unknown.

The Treatment of Early-Onset Schizophrenia Spectrum Disorders study,³ a multisite, longitudinal investigation of antipsychotic medication efficacy and potential moderators of treatment response in youth with psychotic illness, has proved a welcome platform for informing and optimizing treatment guidelines and for gaining insight into the pathophysiology of early-onset schizophrenia (EOS). Youth diagnosed with EOS (8-19 years old) were evaluated first in an acutely symptomatic state at baseline, 8 weeks later, and a 52-week follow-up. All participants were randomized to one of three medications at baseline: risperidone or olanzapine, second-generation antipsychotics, or molindone, a first-generation antipsychotic. Measurements of clinical symptomatology and cognition were administered at each time point.

This study addresses several important aspects of antipsychotic response in EOS: Does antipsychotic therapy improve cognitive functioning in this population? If yes, is this effect the indirect result of a medication-related improvement in clinical symptomatology? Do different antipsychotic medications (including “first-” and “second-generation” antipsychotic medications) have differential effects on cognitive functioning? Identifying whether cognitive functioning improves as a result of antipsychotic medication is important

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in its own right, but cognition also has been shown to predict future real-world functioning in EOS.⁴ Furthermore, because psychosocial functioning is so profoundly impaired in this population, any intervention that may improve functioning holds great promise for decreasing that burden.

Unfortunately, although these medications were effective in decreasing symptom severity, they did not induce meaningful improvement in cognitive functioning (beyond what might be expected from practice effects). Although small changes were seen in domains of fine motor, inhibitory control, social cognition, and problemsolving efficiency over the course of treatment, no improvement was observed in working memory, Full-Scale IQ, or academic achievement. In addition, there were no differences among the three medication groups in any neurocognitive domain.

Although the sample size for each medication group was somewhat limited, this lack of superiority for atypical antipsychotics over first-generation medications mirrors recent findings in adult-onset schizophrenia,⁵ suggesting that any differential cognitive benefit of second-generation antipsychotic treatment is unlikely. This outcome is particularly disappointing because adolescence may represent a time of greater brain plasticity and structural reorganization,⁶ which presumably would present an ideal time to intervene and alter the course of illness. However, as this study showed quite clearly, clinically effective antipsychotic medication regimens did not result in meaningful improvements in adolescent patients' cognitive functioning. Clinicians and researchers alike are left with the question: what can we do to achieve better treatment outcomes in patients with EOS?

In patients with adult-onset schizophrenia (with a mean age in the mid-30s), cognitive remediation techniques tend to show post-treatment improvements in the range of a medium effect size (Cohen's d) for global psychosocial functioning ($d = 0.43$) and global cognition ($d = 0.45$).⁷ To our knowledge, only two small studies of cognitive remediation in EOS have been published. One study did not find generalized improvement in cognition or psychosocial functioning but did find improved performance on measurements of executive function⁸; the other reported comparable improvement in cognitive performance for the cognitive remediation group and a psychoeducation control group.⁹ These two studies had small samples, making it difficult to draw any definitive conclusions on the efficacy of cognitive remediation in patients with EOS. Findings from clinical trials in adult patients, however, have underscored the potential utility of further examining the effects of cognitive remediation in patients with EOS.

The study by Frazier et al.³ in this issue of the *Journal* also points to the need to assess how other psychosocial therapies (e.g., cognitive-behavioral therapy) may serve as effective adjunctive treatments to antipsychotic medication in EOS. Studies examining the efficacy of psychosocial treatments, paired with antipsychotic intervention, in adults experiencing their first episode of schizophrenia have shown promising results, including improvements in symptoms and functioning.¹⁰ Rarely is neurocognition included as an outcome measurement in psychosocial treatments other than cognitive remediation. Although other approaches, such as cognitive-behavioral therapy, may seem less intuitive than cognitive remediation for targeting cognition, the common goal of improving real-world functioning may be

achievable by multiple routes. For instance, children and adolescents with a diagnosis of obsessive-compulsive disorder showed “normalization” of cognitive function after treatment with a combination of medication and psychosocial therapy.¹¹ An important next step in this approach is the modification of adult psychosocial interventions for youth with EOS by taking developmental stage into account and including neurocognition as an outcome measurement.

In developing novel treatments for EOS, we must remain mindful that physiologic mechanisms underlying treatment response (e.g., neurotransmitter changes, alterations in gene expression) may operate differently in childhood and adolescence than in adulthood,¹² meaning that critical pathophysiologic mechanisms may be moving targets. Exactly how a given intervention interacts with a patients’ physiology over time to affect neurodevelopment is an additional unknown contributing to this complexity. Neurodevelopment is a highly complex, dynamic process, and there are significant gaps in our knowledge of how medications may affect the developing brain.⁶

Standing against this tremendous uncertainty, the Treatment of Early-Onset Schizophrenia Spectrum Disorders study offers an essential first step in developing treatments to improve the course of EOS. Although the results of this study suggest that a solution may be quite challenging to find, the devastating toll the illness takes on youth¹³ demands that we continue to work toward improved outcomes for children and adolescents with psychotic disorders.

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