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**Objective:** To assess neurocognitive outcomes following antipsychotic intervention in youth enrolled in the National Institute of Mental Health (NIMH)–funded Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS). **Method:** Neurocognitive functioning of youth (ages 8 to 19 years) with schizophrenia or schizoaffective disorder was evaluated in a four-site, randomized, double-blind clinical trial comparing molindone, olanzapine, and risperidone. The primary outcomes were overall group change from baseline in neurocognitive composite and six domain scores after 8 weeks and continued treatment up to 52 weeks. Age and sex were included as covariates in all analyses. **Results:** Of 116 TEOSS participants, 77 (66%) had post-baseline neurocognitive data. No significant differences emerged in the neurocognitive outcomes of the three medication groups. Therefore, the three treatment groups were combined into one group to assess overall neurocognitive outcomes. Significant modest improvements were observed in the composite score and in three of six domain scores in the acute phase, and in four of six domain scores in the combined acute and maintenance phases. Partial correlation analyses revealed very few relationships among Positive and Negative Syndrome Scale (PANSS) baseline or change scores and neurocognition change scores. **Conclusions:** Antipsychotic intervention in youth with early-onset schizophrenia spectrum disorders (EOSS) led to modest improvement in measures of neurocognitive function. The changes in cognition were largely unrelated to baseline symptoms or symptom change. Small treatment effect sizes, easily accounted for by practice effects, highlight the critical need for the development of more efficacious interventions for the enduring neurocognitive deficits seen in EOSS. *J. Am. Acad. Child Adolesc. Psychiatry*, 2012;51(5):496–505. Clinical trial registry information—Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS); <http://www.clinicaltrials.gov>; NCT00053703. **Key Words:** early-onset, schizophrenia, neurocognition, outcomes, antipsychotics

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**E**arly-onset schizophrenia (EOS) is defined by having the onset of symptoms before age 18 years. The lifetime prevalence of schizophrenia is 1%, with a substantial number of individuals diagnosed before age 18.<sup>1,2</sup> EOS is often more severe than adult-onset schizophrenia (AOS), and includes both a higher rate of pre-

morbid abnormalities and worse functional outcome.<sup>3-5</sup> Studies have documented comparable neurocognitive deficits in EOS and AOS,<sup>6,7</sup> including a recent meta-analysis that showed mostly large deficits for EOS compared to controls (effect sizes ranged from  $-1.27$  [processing speed] to  $-0.58$  [motor skills]).<sup>8</sup> Another meta-analysis documented more severe neurocognitive deficits in EOS compared with AOS,<sup>9</sup> suggesting that illness severity may be associated with age of onset.<sup>10</sup> The adult literature demonstrates that neurocognitive deficits are stronger



This article is discussed in an editorial by Dr. Peter Bachman and colleagues on page 464.

predictors of social and role functioning than other illness features.<sup>11,12</sup> Similarly, a recent 13-year follow-up study of EOS found that baseline neurocognitive measures were associated with social and community functioning at follow-up.<sup>13</sup>

Neurocognitive functioning is an important target of treatment.<sup>14</sup> Much of the earlier research on antipsychotics in adults with schizophrenia suggested favorable cognitive enhancing effects of second-generation antipsychotics (SGAs) over first-generation antipsychotics (FGAs).<sup>15</sup> Data from the NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)<sup>16</sup> and the European First Episode Schizophrenia Trial (EUFEST) randomized clinical trials,<sup>17</sup> however, failed to support the early claims of SGA superiority. Both CATIE and EUFEST interpreted their lack of differential medication effects as being due, in part, to the administration of FGAs at lower and more appropriate doses. The effects of antipsychotics in youth with EOS disorders are just beginning to be understood. Controlled efficacy studies<sup>18-23</sup> have documented that antipsychotics are superior to placebo in reducing positive and negative symptoms, but there have been no studies of antipsychotic effects on cognition in youth with EOS.

The NIMH-funded, multisite, randomized, controlled trial "Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS)" provided an opportunity to examine this issue in the largest sample of youths with EOS studied to date.<sup>4,24</sup> The initial purpose of this study was to compare the effects of olanzapine, risperidone, and molindone on neurocognition. However, because of limited power, the main focus of this paper is on whole group analyses to evaluate neurocognitive outcomes following antipsychotic treatment. We expected that the overall group would demonstrate modest improvements in neurocognition with antipsychotic treatment as evidenced by change in a single composite score and, to a lesser degree, change in specific domain scores at 8 weeks and 52 weeks or termination. We also assessed relationships among baseline and changes in clinical symptoms and change in the neurocognitive composite and domain scores.

## METHOD

### Study Design

The TEOSS study design, methods, and results have been described previously.<sup>20,22,24</sup> TEOSS participants were randomized to one of three active treatments (risperidone, olanzapine, or molindone). In this report, we focus on treatment-related change in neurocognition from baseline

to weeks 8 and 52/termination, and between weeks 8 and 52/termination. Neurocognitive assessments were administered at baseline and the end of the acute phase (week 8). After acute treatment (week 8), participants who had adequate response (20% decrease in baseline Positive and Negative Syndrome Scale [PANSS]<sup>25</sup> score plus a Clinical Global Impression-Improvement [CGI-I]<sup>26</sup> score of  $\leq 2$ ) and tolerated their randomized treatment, were eligible to begin maintenance phase treatment with the same antipsychotic medication under double-blind conditions. Individuals who did not have adequate response at week 8, or who relapsed or experienced intolerable adverse effects during either the acute or maintenance phase, were offered randomly assigned, double-blind treatment with one of the other study medications for up to 52 weeks of treatment.<sup>20</sup> The data reported here are based on changes observed during treatment with whichever medication was used for the longest period. The maintenance phase was up to a total of 44 weeks, and the TEOSS neurocognitive battery was administered a third time at the end of the maintenance phase or at study termination. Neurocognitive assessments were obtained at week 8 and 52/termination during all subsequent treatments.

### Participants

TEOSS enrolled youths (age 8 to 19 years) meeting *DSM-IV* diagnostic criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder.<sup>27</sup> Diagnoses were confirmed with the Structured Clinical Interview for *DSM-IV* Childhood Diagnoses (KID-SCID).<sup>28</sup> Participants also had to have a score of moderate or greater on at least one PANSS positive symptom item.<sup>29</sup> Additional details regarding methods and baseline sample characteristics are described elsewhere.<sup>4,7,22,24</sup>

### Neurocognitive Measures

The battery of tasks assessed the following neurocognitive domains: General Intellectual Functioning, using the Wechsler Abbreviated Scale of Intelligence (WASI)<sup>30</sup>; Academic Achievement Skills, using the Wide Range Achievement Test (WRAT-3)<sup>31</sup> Reading, Spelling and Arithmetic subtests; Fine-Motor Speed and Coordination, using the Finger Tapping Test (FT)<sup>32</sup> and Grooved Pegboard (GP)<sup>33</sup>; Attention and Inhibitory Control, using the auditory and visual versions of VIGIL Continuous Performance Test (CPT)<sup>34</sup>; Short-Term Memory, using the Hopkins Verbal Learning Test—Revised (HVLTR),<sup>35</sup> Wide Range Assessment of Memory and Learning (WRAML)<sup>36</sup> Visual Learning subtest, Visuospatial Working Memory Test (VSWM),<sup>37</sup> and Woodcock-Johnson-III (WJ-III) Numbers Reversed<sup>38</sup>; Cognitive Efficiency, using the Controlled Oral Word Association Test (COWAT)<sup>39</sup> and Ruff Figural Fluency Test (RFFT)<sup>40</sup>; and Social Cognition, using the Eyes Test.<sup>41</sup> The WASI, WRAT-3, and Wisconsin Card Sorting Test-64-Computer Version (WCST-64-CV)<sup>42</sup> were administered at baseline and

termination only; all other measures were administered at each time point. Cognitive measures were selected based on their established psychometric properties, potential sensitivity to medication treatment, and general alignment with CATIE.<sup>16</sup>

## Data Analysis

**Neurocognitive Dataset Construction.** The baseline neurocognitive data always came from the week a patient entered TEOSS (week 0). That is, baseline data remained constant, regardless of re-randomization ensure a uniform starting point (i.e., study entry) for all subjects. In contrast, post-baseline data points varied to some extent across subjects. To minimize practice effects, all data from a post-baseline (e.g., “week 8”) neurocognitive visit were excluded if the visit occurred less than 6 weeks after the previous visit. Data included for the week 8 and termination assessments came from weeks 6 through 10 and weeks 16 through 52, respectively. Some patients had post-baseline neurocognitive data from more than one medication randomization. To maximize sample size, data from all available randomizations were considered, but each patient only contributed only one set of post-baseline scores to the analyses. For example, if the first randomization included both week 8 and termination data, then the first randomization would be included. In general, the randomization that had the most post-baseline data was selected for inclusion in the post-baseline analysis. A later randomization was included instead of an earlier one if the latter had both week 8 and termination data and the earlier randomization had *only* week 8 data or only termination data. In all cases, regardless of which randomization was chosen for inclusion in the post-baseline data set, the baseline data was always from week 0.

**Data Reduction: Neurocognitive Domain and Composite Scores.** Given that most single neuropsychological measures are moderately intercorrelated,<sup>43,44</sup> we chose to reduce the number of variables for analysis by constructing domain and composite score measures, a strategy commonly used in clinical trials.<sup>16</sup> Such summary measures are also often more sensitive to treatment effects than single test scores, and composite measures are often more reliable and sensitive than domain scores.<sup>45</sup> Construction of domain scores was rationally derived and consistent with our earlier work.<sup>7</sup> Each individual test measure was evaluated for normality and outliers to support subsequent data reduction. Single test measures were first converted to standardized z scores by subtracting the baseline mean and dividing by the baseline standard deviation based on the sample contributing to the analysis of each test measure. Such standardization using baseline scores was performed to produce three sets of standardized single test measures, one for each of the groups of subjects contributing to the baseline to 8 weeks, 8 weeks to 52 weeks, and baseline to 52 weeks analyses

of each test measure. Domain summary scores were then constructed by calculating the mean of the z scores for the measures that comprised the domain, and then re-standardizing the domains using baseline data as described previously. This re-standardization was used so that baseline data for each of the three time point analyses of each domain had a mean of 0 and a standard deviation of 1, enabling post-baseline means to be interpreted as effect sizes. This process resulted in six domain scores as follows: Fine Motor Speed/Coordination; Attention; Short-Term Memory; Cognitive Efficiency; Inhibitory Control (auditory and visual Vigil CPT commission errors); and Social Cognition. In addition, composite scores for Academic Achievement and full-scale IQ were constructed in a similar way. Table 1 lists neurocognitive assessments included in each domain and composite.

An overall neurocognitive composite score was calculated as an unweighted average of the six domain summary scores: Fine Motor Speed/Coordination, Attention, Short-Term Memory, Cognitive Efficiency, Inhibitory Control, and Social Cognition. After averaging the six domain summary scores, the composite score was re-standardized using baseline data as described earlier, so that post-baseline means could be interpreted as effect sizes. A composite score was computed only for those subjects with available data on at least four of six of the domains ( $n = 70$ ). Full scale IQ and Academic Achievement summary scores were computed for baseline and week 52/termination and were not available for week 8 per the study design. They did not contribute to the neurocognitive composite score and are treated as composite scores themselves in the analysis. This resulted in a total of six domain and three composite scores for subsequent analyses. Note that data from the WCST-64-CV was not included in these analyses, as data were available only for baseline and 52 week/termination time points per the study design, and the goal of this study was to examine change across three time points (baseline, 8-week/acute phase, and 52-week/termination); as a result, the problem-solving efficiency domain name that we used in our baseline neurocognitive paper<sup>7</sup> was changed to cognitive efficiency here to better reflect the constituent measures of the domain. Four (multi-measure) domain reliability coefficients were acceptable (i.e., Cronbach alpha reliability coefficients ranged between 0.78 and 0.80); however, the internal consistency of the Problem-Solving Efficiency domain was 0.64.

## Statistical Methods

Descriptive statistics for all neurocognitive domain and composite scores were examined for normality and outliers. Change in each standardized neurocognitive domain and composite score from baseline to week 8 or termination/endpoint was compared using

**TABLE 1** Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) Neurocognitive Domain and Composite Scores

| Name of Domain/Composite          | Measures   |
|-----------------------------------|--|
| <b>Domain Scores</b>              |  |
| 1. Fine Motor Speed/Coordination  | 1. Finger Tapping, Grooved Pegboard—dominant and non-dominant hand performance   |
| 2. Attention                      | 2. Auditory and visual VIGIL Continuous Performance Test (CPT) omission errors   |
| 3. Short-Term Memory              | 3. Hopkins Verbal Learning Test—Revised (HVLT-R) Total, Wide Range Assessment of Memory and Learning (WRAML VL) Total, Visual Working Memory Test (VSWM) Mean Error 5-second delay, Woodcock Johnson—III (WJ-III) Numbers Reversed Total |
| 4. Cognitive Efficiency           | 4. Controlled Oral Word Association Test (COWAT) Letter and Semantic Fluency Total, Ruff Figural Fluency Test (RFFT) Total Unique Designs  |
| 5. Inhibitory Control             | 5. Auditory and visual VIGIL: CPT commission errors  |
| 6. Social Cognition               | 6. Eyes Test—Total Correct   |
| <b>Composite Scores</b>           |  |
| 1. Academic Achievement           | 1. Wide Range Achievement Test (WRAT-3) Reading, Spelling, Arithmetic Standard Scores  |
| 2. Full Scale IQ                  | 2. Four subtest Wechsler Abbreviated Scale of Intelligence (WASI)  |
| 3. Neurocognitive Composite Score | 3. Unweighted average of Six Domain Scores: Fine Motor Speed/Coordination, Attention, Short-Term Memory, Cognitive Efficiency, Inhibitory Control, and Social Cognition  |

Note: CPT = continuous performance test.

multiple analysis of covariance (ANCOVA), adjusting for baseline score, age, and sex. For clarity and consistency in interpreting the results, age and sex were included as covariates in all models regardless of whether either was a significant predictor in the model. Given multiple comparisons, a Bonferroni correction would establish conservative critical values of  $p < .008$  for the six neurocognitive domain variables (0.05/6) and  $p < .017$  for the neurocognitive composite, IQ, and academic achievement summary scores (0.05/3). Standardized mean change scores provide an effect size estimate that indexes the magnitude of the difference in cognitive domain performance level between time points; positive standardized mean change scores indicate performance improvement, whereas negative values suggest reduced performance. To assess whether there was any greater or lesser cognitive improvement in the younger children versus the older children, we inspected whether age was a significant predictor in the model for each neurocognitive outcome and time point comparison. To correct for the analysis of multiple outcomes, the same Bonferroni  $p$  value corrections were applied to the hypothesis tests determining significance of age in each model. Finally, partial correlation analyses (adjusted for age and sex) were conducted to examine relationships among PANSS (Total, Positive, and Negative scale) baseline and change scores and neurocognitive domain and composite change scores. Significance levels for the correlation analyses were set at  $p < .008$  for the six domain composite scores and  $p < .017$  for the three other composite scores. Analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

## RESULTS

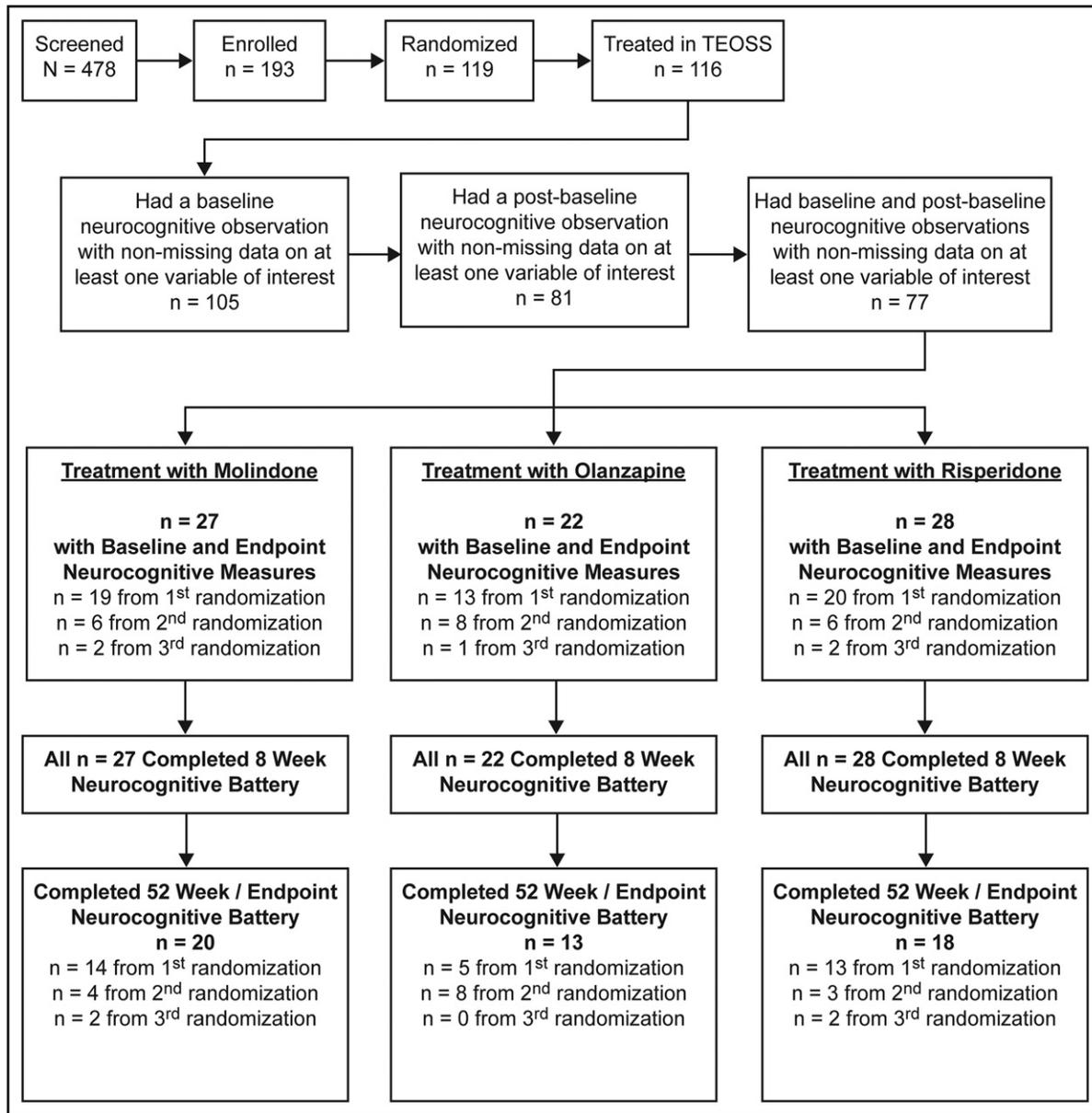
### Subjects and Baseline Characteristics

Of the 116 participants treated in TEOSS, 77 (66%) had post-baseline neurocognitive data suitable for analysis (Figure 1). Table 2 shows baseline demographic and clinical characteristics of the sample with post-baseline neurocognitive data and those without. The sample was two-thirds male and, on average,  $14.3 \pm 2.5$  years of age. Youth included in these analyses did not differ significantly from the non-neurocognitive sample (those without baseline or post-baseline neurocognitive data;  $n = 39$ ) on most variables. However, the neurocognitive sample was more symptomatic at baseline than the non-neurocognitive sample, having higher PANSS-Total, PANSS-Negative, and BPRS-C Total Scores. Because baseline neurocognitive data was often not available for the non-neurocognitive sub-sample, Table 2 does not provide group comparative baseline neurocognitive data.

### Neurocognitive Effects of Treatment

There were no significant differences among the three medication groups on any neurocognitive change variable at any time point. Given limited statistical power, the groups were combined to focus on change in neurocognition for the overall group. Table 3 presents the means and standard deviations for the neurocognitive variables at

**FIGURE 1** Flow diagram of the progress through the Neurocognitive Battery phases of the Treatment of Early-Onset Schizophrenia Spectrum Disorders Study (TEOSS).



each assessment point, and their related mean standardized change score (and standard deviation) around which these results are organized. Note that sample sizes vary across neurocognitive variables based on available data, and are reduced when comparisons are made with the 52-week/termination assessment point. Change in the neurocognitive composite score, the primary outcome measure, showed significant improvement during acute and combined acute and maintenance treatment. Compared to their study

entry baseline performance, participants' neurocognitive composite showed modest improvement by week 8 ( $z = 0.27, p < .0001$ ) and improvement at 52-weeks/termination ( $z = 0.31, p = .0005$ ). Significant differences were not observed on the composite score between the 8-week and 52-week/termination assessments.

Significant change was seen in three of six neurocognitive domains between baseline and week 8 and four of six domains between baseline and week 52/termination (Table 2). Significant

**TABLE 2** Baseline Demographic and Clinical Characteristics

| Variable   | Neurocognitive Sample<br>n = 77 | Non-Neurocognitive Sample<br>n = 39 |
|--|---------------------------------|-------------------------------------|
| Age (y), mean (SD)                                   | 14.3 (2.4)                      | 14.2 (2.3)                          |
| Gender, % male                                       | 66.2                            | 61.5                                |
| Race, % white  | 66.2                            | 59.0                                |
| Family income, <sup>a</sup> mean (SD)                | 2.9 (1.5)                       | 2.6 (1.5)                           |
| Handedness, % right                                  | 86.8                            | 86.7                                |
| Special education, % yes                             | 57.1                            | 51.3                                |
| Diagnosis, % schizophrenia                           | 66.2                            | 64.1                                |
| No. of prior psychiatric hospitalizations, mean (SD) | 0.7 (0.9)                       | 0.9 (1.0)                           |
| Age at first psychosis, mean (SD)                    | 11.0 (3.5)                      | 11.3 (3.4)                          |
| PANSS total, mean (SD)                               | 104.4 (20.0)                    | *94.9 (18.6)                        |
| PANSS positive, mean (SD)                            | 26.7 (5.6)                      | 25.8 (6.1)                          |
| PANSS negative, mean (SD)                            | 26.2 (8.1)                      | *22.6 (7.2)                         |
| CGI severity, mean (SD)                              | 5.7 (0.8)                       | 5.4 (0.9)                           |
| BPRS-C total, mean (SD)                              | 44.5 (11.8)                     | *39.8 (10.2)                        |

Note: BPRS-C = Brief Psychiatric Scale for Children; CGI = Clinical Global Impression scale; PANSS = Positive and Negative Syndrome Scale.  
<sup>a</sup>Family income is described by the following categories: 1 = <\$20K, 2 = \$20K to <\$40K, 3 = \$40K to <\$60K, 4 = \$60K to <\$80K, 5 = \$80K to <100K, and 6 = \$100K+.  
 \*p < 0.05 for test of difference in baseline measures between Treatment of Early-Onset Schizophrenia Spectrum Disorders Study neurocognitive and non-neurocognitive samples.

improvements were shown in Fine motor speed/coordination at 8-weeks ( $z = 0.21, p = .0016$ ) and 52-weeks/termination ( $z = 0.27, p = .006$ ). Inhibitory Control also showed significant improvements at both time points ( $z = 0.25, p < .0001$ ;  $z = 0.25, p = .0007$ , respectively). Significant improvements were documented in Social Cognition between baseline and 8-weeks ( $z = 0.28, p = .0072$ ) only, and in Attention ( $z = 0.16, p =$

$0.0048$ ) and Cognitive Efficiency ( $z = 0.28, p = .0008$ ) between baseline and 52-weeks/termination only. One neurocognitive domain, Cognitive Efficiency, demonstrated improvement over the 8 to 52 weeks maintenance phase ( $z = 0.18, p = .013$ ). Notably, no significant changes were observed in the Short-Term Memory domain at any follow-up assessment point. All effect sizes were small to very small.

**TABLE 3** Change in Neurocognitive Domain Scores During Acute and Maintenance Therapy

| Variable                 | Change from Baseline to 8 Weeks |             |         | Change from Baseline to 52 Weeks |              |         | Change from 8 Weeks to 52 Weeks |              |         |
|--------------------------|---------------------------------|-------------|---------|----------------------------------|--------------|---------|---------------------------------|--------------|---------|
|                          | n                               | Mean (SD)   | p Value | n                                | Mean (SD)    | p Value | n                               | Mean (SD)    | p Value |
| Fine Motor Speed         | 71                              | 0.21 (0.59) | .0016   | 49                               | 0.27 (0.72)  | .0061   | 49                              | 0.13 (0.59)  | .1439   |
| Attention                | 64                              | 0.09 (0.80) | .2489   | 43                               | 0.16 (0.73)  | .0048   | 44                              | 0.12 (0.86)  | .1561   |
| Short-Term Memory        | 73                              | 0.07 (0.68) | .4043   | 51                               | 0.15 (0.81)  | .1899   | 50                              | 0.08 (0.67)  | .3879   |
| Cognitive Efficiency     | 71                              | 0.14 (0.60) | .0444   | 49                               | 0.28 (0.56)  | .0008   | 50                              | 0.18 (0.49)  | 0.0125  |
| Inhibitory Control       | 64                              | 0.25 (0.66) | <.0001  | 43                               | 0.25 (0.86)  | 0.0007  | 44                              | 0.06 (0.66)  | .4928   |
| Social Cognition         | 65                              | 0.28 (0.92) | .0072   | 42                               | 0.23 (1.02)  | .0972   | 44                              | -0.09 (0.93) | 0.5082  |
| Achievement              | N/A                             | N/A         | N/A     | 43                               | -0.04 (0.38) | .5114   | N/A                             | N/A          | N/A     |
| Full Score IQ            | N/A                             | N/A         | N/A     | 45                               | 0.06 (0.41)  | .3263   | N/A                             | N/A          | N/A     |
| Neurocognitive Composite | 70                              | 0.27 (0.52) | <.0001  | 48                               | 0.31 (0.61)  | .0005   | 48                              | 0.12 (0.36)  | .0264   |

Note: All analyses included age and gender as covariates. Because domain and summary scores were calculated via standardization by baseline mean and standard deviation, baseline means, including week 8 in the week 8 to week 52 analysis, are always zero, and the mean change scores presented can be interpreted as effect sizes. Descriptive neurocognitive test data for both the treatment and overall groups is not presented in this paper, but are available upon request to the corresponding author.

In the analysis of age as predictor in the model for each neurocognitive outcome and time point comparison, only the model for change in Attention between weeks 8 and termination was significant, indicating that older children showed greater improvement in attention than younger children (coefficient for the age predictor = 0.132;  $p = .0007$ ). No other significant differential age effects were found.

As expected, there was no significant change observed in the WASI Full Scale IQ ( $z = 0.06$ ,  $p = .33$ ) or in the Academic Achievement composite score based on the WRAT-3 subtests ( $z = -0.04$ ,  $p = .51$ ).

#### Neurocognitive Change and Baseline Symptom Severity and Symptom Change

Partial Pearson correlations (adjusting for age and sex) between change in neurocognitive composite and domain scores from baseline and clinical symptom severity at baseline and change in PANSS total score and symptom factors were calculated to examine their associations. Using criteria for significance of  $p = .008$  for the domains and  $.017$  for the composites, few significant relationships emerged. The correlation between change in PANSS Total and change in Attention from 8 to 52 weeks was significant ( $r = 0.41$ ,  $p = .006$ ) and the correlation between baseline PANSS Negative and change in Fine Motor Speed from week 8 to 52 was significant ( $r = -0.38$ ,  $p = .007$ ). These data suggest little reliable relationship between baseline levels of symptoms or their change over time and change in any neurocognitive index.

## DISCUSSION

This is the first study of EOS to prospectively assess neurocognitive functioning in a large, well-characterized sample of youth over the course of a 52-week double-blind treatment trial with antipsychotic medication. We found that neurocognition, as indexed by a neurocognitive composite score, improved modestly with antipsychotic treatment between study entry and 8 and 52 weeks, with the largest proportion of the small effect emerging in the acute phase of the study. There was no significant change in overall neurocognition between 8 and 52 weeks/termination. At the level of specific neuropsychological domains, very small to small changes in several domain scores achieved statistical significance. These included changes in the Fine

Motor, Inhibitory Control, and Social Cognition domains between baseline and week 8, and Fine Motor, Inhibitory Control, Attention, and Cognitive Efficiency between baseline and week 52/termination. No significant changes were observed in Short-Term Memory (which included measures of new learning) or in Full Scale IQ or the Academic Achievement composite score at any time point. With the exception of greater improvements in attention from week 8 to termination in the older youth, age was not a significant predictor of neurocognitive outcomes. In addition, although sample sizes are small, no differences among medication groups on neurocognitive outcomes were observed. Finally, neurocognitive change at any time point was not reliably associated with baseline or change in diagnostic-clinical symptoms.

Our findings are consistent with recent large studies of adults in documenting minimal cognitive benefits with antipsychotic treatment.<sup>16,17,46</sup> The small magnitude of the performance improvements that emerged in this trial and others have been interpreted as consistent with practice effects.<sup>16,45,47,48</sup> Moreover, given that treatment effects were small and most likely to be observed in the acute phase, it is possible that practice and/or placebo effects were responsible for the changes in neurocognitive performance that emerged.<sup>47,48</sup> Practice effects cannot be ruled out in the present study due to the absence of a control group. Several studies have estimated that practice effects are at least in the small and often in the moderate range, including for tests similar to those used in TEOSS (e.g., MATRICS).<sup>49</sup> Some clinical treatment study researchers have argued that when taking confidence intervals into consideration, effect sizes for conclusively nonrandom changes would have to be substantially higher.<sup>48</sup>

The absence of a reliable relationship between level of baseline clinical symptoms and neurocognitive change is not surprising, given the ample literature documenting negligible to small relationships between clinical symptoms of schizophrenia and neurocognitive test scores in adults.<sup>7,50</sup> Similar findings are also noted in studies examining the relationship between cognitive change from baseline and changes in symptom measures.<sup>16</sup> Nonetheless, symptom reduction might be associated with better task engagement which may, in turn, significantly change performance on cognitive measures.<sup>50</sup> Despite treatment with antipsychotic medication, which substantially reduced clinical symptoms in approximately half of the TEOSS

youth,<sup>22</sup> cognitive symptoms remain an area of ongoing vulnerability that requires intervention and support across settings. At present, it appears that reducing symptoms of psychosis with medication is not sufficient for remedying cognitive deficits. However, it is reasonable to consider that by improving psychosis, antipsychotics might mitigate some of the psychosis associated cognitive deficits and prevent further decline.

Previous speculation about the benefits of antipsychotic medication on neurocognition has suggested that individuals with schizophrenia who are younger and closer to the onset of their symptoms may be more likely to benefit from the cognitively enhancing effects of treatment.<sup>17,51</sup> Unfortunately, our findings in this younger cohort do not support this hypothesis and are comparable to those from adult studies that included older individuals with chronic illness and more exposures to treatment and/or substances.

Others suggest that the cognitive enhancing effects of antipsychotic medication might be realized in the context of adequate environmental and cognitive stimulation.<sup>52</sup> The premise is that just as muscle enhancing agents have little impact without exercise, so too might antipsychotic medication require routine environmental, cognitive, and/or behavioral stimulation to achieve a procognitive effect. In this vein, the majority of TEOSS subjects were in school, including 45% who were receiving special education at the time of enrollment. Although TEOSS was not designed to track specific educational programming and interventions, the fact that nearly all TEOSS subjects were receiving some form of education-related cognitive stimulation tempers speculation that normative age-related cognitive stimulation might interact with medication treatment to yield procognitive benefits.

In addition to the absence of a control or placebo group, three limitations to the present study also require consideration. First, the majority of TEOSS participants had prior exposure to antipsychotics,<sup>22</sup> thus raising the possibility that any potential cognitively enhancing effects of antipsychotic medication may have already been achieved (e.g., carry-over effects from prior medication treatments) and was represented in their initial, baseline performance. Ethical concerns precluded a medication washout period, and there was no medication-free assessment of neurocognitive function. Secondly, as is common in treatment studies,

fewer patients contributed both baseline and follow-up neurocognitive data leaving a significant minority (34%) who did not contribute data, thus limiting the generalizability of the findings to patients treated with antipsychotics in the community. Thirdly, we were unable to achieve the sample size and statistical power necessary to conduct strong comparative tests of potential differential medication effects on cognition. Low statistical power (which would allow detection of only large effects), however, limits the value of null findings in this regard. At the same time, between group effects sizes were negligible, and our findings complement recent large studies that have found no evidence of differential beneficial effects of second-generation antipsychotics over first-generation antipsychotics.

Youth in TEOSS demonstrated minimal neurocognitive improvement, and the improvements observed were consistent with practice effects as described in adults with chronic schizophrenia treated with first-generation antipsychotics and second-generation antipsychotics. Improvements in cognitive symptoms are much more difficult to achieve with either first- or second-generation antipsychotics than improvements in psychotic symptoms. Moreover, despite earlier and less methodologically rigorous research suggesting that second-generation antipsychotics provide broader clinical and cognitive benefit, TEOSS and related adult studies indicate that antipsychotic treatment selection cannot be based on the presumption of a differential cognitive benefit of one medication over another. Clinicians should not expect that all aspects of schizophrenia can be treated with a single intervention, including antipsychotics. Although it is reasonable to hypothesize that antipsychotics might directly or indirectly mitigate psychosis-associated cognitive deficits, their impact on cognition is not sufficient to remedy functional deficits associated with the illness. Our findings underscore that treatment strategies other than antipsychotic medication are required to improve the cognitive functioning of youth with EOS. Given that cognitive deficits in EOS remain central, enduring, and functionally relevant, there remains a great need for augmentative and multi-modal treatments targeting cognition. These include the discovery of cognitive-enhancing agents and use of currently available psychosocial interventions (e.g., cognitive remediation<sup>53</sup> Cognitive Adaptation Therapy<sup>54</sup> and supported education interventions).

Our data highlight the critical need for the development of effective interventions for the durable cognitive deficits associated with schizophrenia, particularly for youth with EOS given their cognitive and psychosocial at-risk status. &

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