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Can We Incorporate Psychosocial Treatment Interventions Into Psychopharmacology Clinical Trials?

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The article by Richard Keefe and colleagues[1] in this month's *Journal* has substantial value to researchers who face an important methodological question in clinical trials of cognitive-enhancing medications in schizophrenia. Do patients in pharmacologic intervention trials need to exercise their cognitive "muscles" for a drug that increases cognitive "muscle mass" to work? This is the analogy offered by these authors. *Exercise* is defined as some form of training in cognitive skills, such as cognitive remediation. Often, discussion of this question is side-tracked by a procedural question, namely, can introducing a cognitive remediation intervention into large, multicenter randomized clinical trials (RCTs) of medication be feasible? First, there is the concern that staff at the clinical sites where trials are conducted will not be able to implement the procedures, and, second, there is concern that patients who enroll in these trials will not actually participate adequately in cognitive remediation activities involving multiple training sessions per week over several months.

The study reported by Keefe et al[1] was formally designed to address these 2 feasibility questions and to provide some information about the efficacy of cognitive remediation training as a stand-alone intervention in this patient population. There was no cognitive-enhancing medication in the trial; therefore, the important substantive question of whether introducing a cognitive remediation or other cognitive-enhancing platform to a study of drug effects would potentiate the drug effect remains an important question to be addressed by future studies.

Keefe and colleagues[1] conducted a small RCT (N = 53) comparing a specific cognitive remediation approach, Posit Science Brain Fitness auditory training[2] and the Neuropsychological and Educational Approach to Remediation (NEAR),[3] to an attention control at 9 sites, 7 of which had no formal prior research experience with cognitive remediation. The cognitive remediation intervention involved individual computer-based auditory training (up to 40 sessions over 12 weeks) and weekly groups designed to provide a link to day-to-day activities and boost self-esteem. The study methods were meticulous, and the authors answer the procedural question of feasibility with a resounding yes. The sites met very rapid enrollment goals: 6 subjects recruited in a 3-month period. Clinicians were centrally trained and monitored, there was no clinician turnover, and subjects participated adequately in the interventions. The majority of subjects completed 40 sessions: 59% in the cognitive remediation group and 57% in the attention control group. The criterion for intervention completion was 24 sessions (60%), which was met by 77% of the study subjects. The investigators provide data to show that acoustic discrimination (a focus of the individual cognitive remediation training) was significantly improved over the full course of treatment. Data also showed that the MATRICS Consensus Cognitive Battery composite score improved more in the cognitive remediation group than in the attention control group after 20 sessions.[1]

Were the methods sound? The answer is yes, but.... The inclusion criteria for subjects in the study yielded a study sample that "looks" much like samples in recent RCTs in schizophrenia, which has clinical implications as noted below. The only novel inclusion criterion compared to criteria in medication trials was that subjects had to be able to "state specific goals relevant to the intervention that they would like to achieve."[1] There is no information on whether this inclusion criterion excluded many subjects. From the CONSORT flowchart, it appears that only 4 subjects were excluded after entering screening for inclusion criteria, suggesting that having goals and other inclusion criteria were assessed informally before potential subjects entered the formal screening process.

Although 7 of the 9 sites had no prior cognitive remediation experience, these were all academic sites with investigators and staff that have vast experience in treating and conducting research with schizophrenia patients. Most had participated in the Clinical Antipsychotic Trials of Intervention Effectiveness,[4] and, because they were among the more successful sites in that study, they were part of the National Institute of Mental Health Schizophrenia Trials Network. So the question remains whether these sites are representative of the clinical trial sites where most studies of cognitive-enhancing medications will be conducted and, by implication, whether the fact that a cognitive remediation intervention can be implemented at these 9 sites provides adequate evidence of feasibility in the hands of less committed investigators and staff.

Second, the study assessment model of Keefe et al[1] followed the usual procedures in cognitive remediation studies: assessments were completed at time points defined by number of completed sessions—in this study, at baseline and after 20 and 40 sessions (or the last session completed). Randomized clinical trials to assess medication effects have assessment schedules tied to study week, eg, at baseline and 6 and 12 weeks. The present study does not allow us to determine how many sessions had been completed at the 6-week time point,

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and there is no assessment tied to that time point or the 12-week time point. If subjects completed all sessions before week 12, they were assessed at the time of completion.

On balance, the Keefe et al study provides evidence that a cognitive remediation intervention package, with a well-matched attention control, can be administered in an RCT model at sites that have experience in providing support that enables schizophrenia subjects to come to the clinic for assessment and medication administration. Typically, this type of intervention would at most require weekly visits, and often less frequent attendance. In the present study, most subjects came in at least 3 times per week over 3 months. In addition, there is a treatment effect consistent with improvement in the auditory discrimination measure that can be taken as evidence that the auditory cognitive remediation training was actually received, with some indication of benefit (at the 20-session assessment) for the MATRICS Consensus Cognitive Battery. The absence of significant effects for other measures is not of concern; the study was small, and these other measures were included only as secondary exploratory measures.

What are the implications of this cognitive remediation feasibility study for clinical practice? Who were the study participants? On average, they were 37 years old. Although there is no information provided on duration of illness or age at first episode, if these participants are like other schizophrenia patients, duration of illness was probably at least 15 years. The Clinical Global Impressions-Severity of illness rating for these patients was between mild (3) and moderate (4), but, in terms of a summary of specific symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS),[5] their overall symptom burden was very low; the mean total PANSS score was 55 (the absence of all symptoms would yield a score of 30), and acutely ill schizophrenia patients would have scores in the range of 100–120. In terms of general life functioning, the majority of patients were living independently, and their scores on the Specific Levels of Functioning scale indicate a high level of functioning; the maximum possible score on this scale is 150, and these subjects had an average score of 127. These findings suggest that a cognitive remediation intervention is possible with people who have been dealing with schizophrenia for a relatively long time, are symptomatically stable, and report relatively high levels of current functioning.

As noted above, there was some improvement in a measure of auditory discrimination and in the cognitive battery that the research field considers the standard outcome measure in this domain. Although these changes are not likely to be detected by clinical observation, they serve to remind us of the possibility of improvement in patients who have been ill for some time, even when they are symptomatically stable.

The clinical caveat may be obvious. Cognitive remediation has shown impressive results in rigorous studies. The present study represents a further step toward general clinical applicability—the transfer from investigators and teams with cognitive remediation expertise to nonexpert settings. As noted above, the investigators and their staff were all highly experienced in research, with enviable skills in engaging, supporting, and retaining patients with schizophrenia in research that translated into an impressive record of assessment and completion of treatment. Whether this intervention model can be transferred to clinical settings that do not have the resources for the kind of intensive effort that was expended by these investigators represents a project for another day.

From the perspective of researchers and pharmaceutical companies eager to advance the development of medications to enhance cognition, this study by Keefe et al is encouraging but does not provide a fully definitive answer to the procedural question of whether clinical trial sites can carry out medication RCTs that require all subjects to engage in a cognitive remediation intervention. Their study sites may not be representative. There may need to be screening of sites to assess readiness and capacity to implement a cognitive remediation intervention in medication RCTs incorporating a cognitive remediation platform. I sense a rating scale on the horizon.

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