ONLINE FIRST

Randomized Trial to Evaluate the Efficacy of Cognitive Therapy for Low-Functioning Patients With Schizophrenia

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Context: Low-functioning patients with chronic schizophrenia have high direct treatment costs and indirect costs incurred due to lost employment and productivity and have a low quality of life; antipsychotic medications and psychosocial interventions have shown limited efficacy to promote improved functional outcomes.

Objective: To determine the efficacy of an 18-month recovery-oriented cognitive therapy program to improve psychosocial functioning and negative symptoms (avolition-apathy, anhedonia-asociality) in low-functioning patients with schizophrenia.

Design, Setting, and Participants: A single-center, 18-month, randomized, single-blind, parallel group trial enrolled 60 low-functioning, neurocognitively impaired patients with schizophrenia (mean age, 38.4 years; 33.3% female; 65.0% African American).

Interventions: Cognitive therapy plus standard treatment vs standard treatment alone.

Main Outcome Measures: The primary outcome measure was the Global Assessment Scale score at 18 months after randomization. The secondary outcomes were scores on the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms at 18 months after randomization.

Results: Patients treated with cognitive therapy showed a clinically significant mean improvement in global functioning from baseline to 18 months that was greater than the improvement seen with standard treatment (within-group Cohen *d*, 1.36 vs 0.06, respectively; adjusted mean [SE], 58.3 [3.30] vs 47.9 [3.60], respectively; $P=.03$; between-group $d=0.56$). Patients receiving cognitive therapy as compared with those receiving standard treatment also showed a greater mean reduction in avolition-apathy (adjusted mean [SE], 1.66 [0.31] vs 2.81 [0.34], respectively; $P=.01$; between-group $d=-0.66$) and positive symptoms (hallucinations, delusions, disorganization) (adjusted mean [SE], 9.4 [3.3] vs 18.2 [3.8], respectively; $P=.04$; between-group $d=-0.46$) at 18 months. Age was controlled in the analyses, and there were no meaningful group differences in baseline antipsychotic medications (class or dosage) or in medication changes during the course of the trial.

Conclusion: Cognitive therapy can be successful in promoting clinically meaningful improvements in functional outcome, motivation, and positive symptoms in low-functioning patients with significant cognitive impairment.

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BETWEEN 2 AND 3 MILLION American adults currently have schizophrenia.[1] The modal onset is in early adulthood,[2] and roughly two-thirds of affected individuals experience a chronic or fluctuating course of illness.[3] Annual overall direct treatment costs and indirect costs incurred due to lost employment and productivity approach $63 billion in the United States or an average of between $26 000 and $31 000 per patient,[4] which is 5 times the per-patient cost of depression.[5] Although antipsychotic medications have been demonstrated to reduce hallucinations and delusions, one-third to one-half of patients with schizophrenia continue to experience residual symptoms or have intolerable adverse effects.[6,7] The disorganized (speech disturbance) and negative (affective flattening, alogia, apathy, anhedonia, and asociality) symptoms of

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schizophrenia are even less responsive to the medications than hallucinations and delusions.[8] Importantly, the effect of medications on functional outcomes has been modest, even when medication regimens have been optimized.[9]

Starting in the 1950s, patients with schizophrenia have been moved from mental hospitals to the community.[10] In Philadelphia, Pennsylvania, for example, patients enrolled in community mental health centers are offered supported housing and a wide range of therapeutic and vocational services; however, a large proportion continue to function at a low level. We sought to determine whether a novel version of cognitive therapy (CT) would lead to an increase in functioning and decreases in negative symptoms and positive symptoms (hallucinations, delusions, and disorganization) in this population. To determine the efficacy of this targeted CT derived from basic research and adapted to this population, we selected a sample of patients who were on the low end of the continuum of psychosocial functioning. This sample was also neurocognitively impaired (difficulties with information processing on tasks of memory, attention, and executive functioning) and experienced residual positive symptoms. Cognitive therapy (often labeled *cognitive behavior therapy*) has an extensive empirical basis in theory[11] and has been successfully applied to a wide range of psychiatric problems.[12] It was initially applied to schizophrenia by investigators in the United Kingdom,[13] and results demonstrated success at reducing positive and negative symptoms.[14-17] Despite these encouraging findings, studies of CT have not focused on those patients with neurocognitive impairment and poor functioning. Similarly, studies of other psychosocial, behavioral, or neurocognitive remediation interventions have been limited by the following: a focus on acute rather than chronic psychosis, inclusion of a heterogeneous sample of patients, or a failure to find that treatment effects generalize adequately to psychosocial functioning.[18-22]

In adapting CT for low-functioning patients with schizophrenia, we shifted the emphasis from the predominantly symptom-oriented approach that typifies the UK protocols to a person-oriented therapeutic approach by highlighting the patients' interests, assets, and strengths. The objective was to improve the level of functioning in the form of enhanced productivity, independence, and quantity and quality of social interactions. We developed the framework for our therapy from the finding that dysfunctional beliefs, in conjunction with neurocognitive impairment, impede functioning.[23-26] In addition, our therapy is largely influenced by the principles and spirit of the Recovery Movement.[27,28] We focused our treatment methods on identifying and promoting concrete goals for improving quality of life and reintegration into society. In adapting our treatment protocol to this highly regressed group, we decided to extend the duration of treatment from the originally planned 12 months to 18 months. Further, we decided to focus on global functioning as a more appropriate measure of progress than simply the reduction of negative symptoms. Our protocol, in summary, differs from previous CT protocols for patients with schizophrenia in being explicitly recovery oriented, goal directed, and adapted for neurocognitive and skills impairments; it treats functional outcomes as primary rather than secondary targets of therapy and uses therapeutic conceptualizations based on new research on dysfunctional beliefs.

We conducted a randomized controlled trial to evaluate the efficacy of CT for neurocognitively impaired, poorly functioning patients with chronic schizophrenia.

METHODS

The trial was conducted at a single center. The protocol and consent form were approved by 2 institutional review boards (the University of Pennsylvania and the City of Philadelphia). Each participant gave written informed consent before enrollment. Eligibility criteria included the following: diagnosis of *DSM-IV* schizophrenia or schizoaffective disorder; prominent negative symptoms (at least moderate severity on 2 Scale for the Assessment of Negative Symptoms[29] global subscales, or marked severity on 1 subscale); aged 18 to 65 years; proficient in English; and able to give informed consent. Exclusion criteria included the following: neurologic disease or damage that would compromise cognitive functioning; and physical handicaps that would interfere with assessment procedures or therapy attendance. Diagnosis of schizophrenia or schizoaffective disorder was determined on a consensus best-estimate basis by research personnel (with PhD and MD degrees) using a structured interview conducted by an assessor trained to criterion (intraclass correlation >0.80).[30] **Figure 1** indicates the number of individuals who were screened and reasons for those who were not enrolled. Examples of reasons that patients gave for refusing the initial assessment included having an unstable living situation, having medical problems, or not wanting to receive one of the study conditions.

INTERVENTIONS

Participants were randomly assigned (1:1, stratified by sex because females with schizophrenia have a better course[31] and may respond better to CT[32]) to the study intervention condition, CT plus standard treatment (ST), or to the control condition, ST alone, using an encrypted computer-generated randomization list. Personnel enrolling patients did not have access to this list. A single-blind design was used in which outcome assessors were not aware of assigned study condition. To maintain blinding, the assessment team was managed separately from the therapy team (in terms of personnel, physical location, and file access), and all participants were trained to not reveal their study condition prior to each follow-up assessment. (A total of 3 patients broke this rule at the 18-month assessment, 2 receiving CT and 1 receiving ST. Two of these patients were rated as unchanged on the primary outcome measure; 1 patient receiving CT was rated as improved modestly [6 points]. Even if this latter rating were inflated, it does not alter the pattern or significance of the results.) Furthermore, all available raters (6 of 7) were asked to guess the patient condition for each of their follow-up assessments ($n=103$); assessors made 50 correct guesses and 53 incorrect guesses, a chance level of accuracy. Treatment assignment was known to therapists, patients, and, for legal reasons, the treating psychiatrist. Other members of each patient's nonstudy treatment teams (eg, group therapists, case managers) were not informed of treatment assignment.

Cognitive Therapy

Participants in the CT intervention were scheduled to receive up to 18 months of outpatient CT sessions. The sessions typically lasted 50 minutes and were scheduled on a weekly basis; however, based on the participant's needs and progress, the duration and frequency of sessions as well as duration of treatment were flexible. The central features of this psychotherapy were its goal-directed framework and personalized treatment planning. Early sessions focused on engaging the patient and strengthening the therapeutic relationship. Therapy aimed to stimulate patients' interest and motivation to focus respec-

tively on achievable long-term goals (eg, independent housing, employment, relationships), intermediate goals, and short-term goals. Key impediments to reaching these goals are dysfunctional beliefs (eg, "taking even a small risk is foolish because the loss is likely to be a disaster" and "making new friends isn't worth the energy it takes"). The therapists helped patients to undercut their nihilistic beliefs and concomitantly increase their motivation for constructive activity by using a variety of cognitive and behavioral techniques, including activities during the session (eg, exercises, games, role-playing, community outings) and collaboratively devised action plans for practice outside the session. Other impediments to reaching the goals such as the presence of delusions, hallucinations, and disorganized thinking were also addressed by strategies outlined by Beck et al.[33] Further, specific deficiencies such as deficits in attention, executive function, and social skills were targets for the therapy. Later sessions were devoted to consolidation of functional gains and relapse prevention. The treatment was tailored to the participant's level of functioning, such that special adaptations were made for problems due to poor engagement, neurocognitive impairment, thought disorder, and lack of insight. To accommodate neurocognitive impairments, for example, therapists made extensive use of visual aids, including whiteboards for reinforcing session material, laminated cards to help patients remember key take-home points, and colorful signs that patients posted at home to remind them of daily activities and other therapy assignments. The CT sessions followed a treatment manual and were administered by therapists at the doctoral level (PhD and MD). Sessions were videorecorded, and weekly supervision was provided by one of us (A.T.B.).

Standard Treatment

Participants in both study conditions received ST from clinicians in the community. At minimum, this consisted of antipsychotic pharmacotherapy. However, most participants were also actively engaged in services provided by local community mental health centers, including case management, supportive counseling, day treatment services, housing services, peer support, and vocational rehabilitation.

OUTCOMES

The primary objective of adding CT to ST was to aid the progress of patients with schizophrenia toward recovery by producing a clinically significant change in their functional outcome. The Global Assessment Scale (GAS)[34] score was the primary outcome measure. The GAS is a single-item interviewer-scored instrument that assesses functioning level and symptoms during the previous month. The rating is made on a 100-point scale, with lower scores indicating poorer functioning. Endicott et al[34] demonstrated test-retest reliability and predictive validity (rehospitalization rates) for the GAS in patients with schizophrenia. Secondary measures were the 4 global subscale scores of the Scale for the Assessment of Negative Symptoms (SANS)[29] and the total score of the Scale for the Assessment of Positive Symptoms (SAPS).[35] The reliability and validity of the SANS and SAPS have been demonstrated.[36] A recent consensus statement has proposed the SANS and SAPS as standard measures of negative and positive symptoms.[37]

SAMPLE SIZE

On the basis of a meta-analysis of medical and behavioral outcomes showing that an effect size of $d=0.5$ between conditions has an effect on quality of life,[38] we designated $d=0.5$ as the minimal clinically significant change that the trial would be powered to detect. With a sample size of 60, expected dropout rate of 20%, 2-sided $\alpha=.05$, and within-subject correlation of 0.5, we determined that the study would have 80% power to detect a true treatment difference in the rate of change of functioning of 0.5 SD.

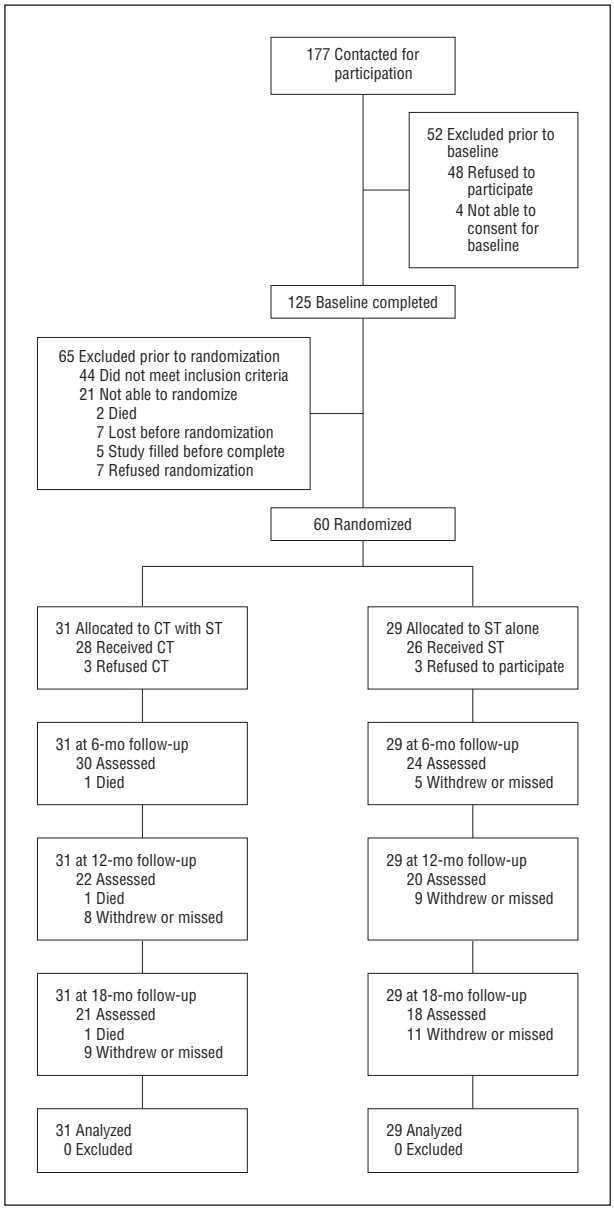

Figure 1. Flowchart of the progress through the phases of the randomized trial for the 2 groups. CT indicates cognitive therapy; ST, standard treatment.

PLANNED ANALYSES

Linear random-effects models (hierarchical regression models) were implemented with random intercepts and slopes. These models estimate main effects for change from baseline to each assessment at 6, 12, and 18 months, main effect for the treatment, and interactions between the visit and treatment indicator variables. For each of the primary (GAS) and secondary (SANS and SAPS) outcomes, separate intent-to-treat tests and estimates (with 95% CIs) of randomized group contrasts at 6, 12, and 18 months were obtained from the estimates of the respective time × treatment interactions.[39] Potential con-

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	CT (n = 31)	ST (n = 29)
Age, mean (SD), y[a]	34.3 (10.9)	42.9 (10.8)
Male, No. (%)	21 (67.8)	19 (65.5)
Race/ethnicity, No. (%)		
African American	20 (64.5)	19 (65.5)
White	10 (32.3)	9 (31.0)
Asian American	1 (3.2)	0
Biracial	0	1 (3.4)
Schizophrenia diagnosis, No. (%)	23 (74.2)	25 (86.2)
Duration of illness, mean (SD), y	13.2 (11.0)	18.0 (12.8)
Age at onset, mean (SD), y	21.3 (7.2)	24.9 (9.4)
Atypical antipsychotic medication, No. (%)[b]	29 (93.5)	26 (89.7)
Chlorpromazine equivalents, mean (SD), mg[b]	415.6 (168.4)	521.1 (271.1)

Abbreviations: CT, cognitive therapy; ST, standard treatment.
[a] $P < .01$.
[b] One person receiving CT was missing data.

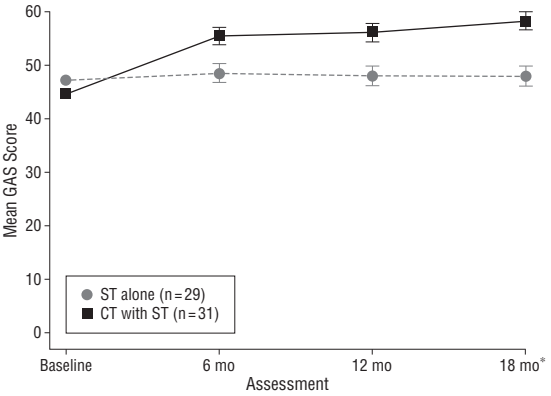

Figure 2. Global functioning. The values at baseline are raw means; the values at 6, 12, and 18 months are adjusted means (SEs) from the intent-to-treat hierarchical linear models. CT indicates cognitive therapy; GAS, Global Assessment Scale; and ST, standard treatment. *P=.03 for the mean difference based on the hierarchical linear modeling interaction of treatment condition × assessment time.

founding variables were evaluated by assessing whether baseline factors imbalanced between the treatment groups were related to outcome. Age was found to be a confounding variable (**Table 1**) and was controlled in all analyses. Although the study was designed to minimize lost observations, the random-effects or hierarchical regression approach is superior to last observation carried forward in minimizing bias and type I error and is inferentially equivalent to multiple imputation.[40]

Intent-to-treat analyses using hierarchical linear modeling were conducted on all outcome measures. The hierarchical linear modeling analysis is able to identify differences between conditions by the presence of a significant month × treatment interaction term. For example, a significant month × treatment interaction in favor of CT on the GAS score at 18 months would support the hypothesis that CT with ST is more efficacious than ST alone at improving functioning. Similar intent-to-treat analyses were run for negative and positive symptoms. Reported variances are standard deviations unless otherwise specified. Analyses were conducted using IBM SPSS version 19.0 statistical software (IBM Corp, Armonk, New York).

Table 2. Intent-to-Treat Hierarchical Linear Modeling Interaction Effects of Condition × 18 Months for Study Measures

Measure	Nonstandardized β	95% CI	*t* Value
Global functioning[a]	9.0	0.98 to 17.11	$t_{145} = 2.20$
Avolition-apathy[b]	–0.9	–1.64 to –0.18	$t_{145} = 2.20$
Positive symptoms[c]	–7.7	–14.97 to –0.50	$t_{129} = -2.11$

[a] Global Assessment Scale score.
[b] Global subscale score on the Scale for the Assessment of Negative Symptoms.
[c] Total score on the Scale for the Assessment of Positive Symptoms.

RESULTS

Between January 2007 and August 2009, 60 individuals were entered into the study, with 31 randomly assigned to CT with ST and 29 to ST alone. The mean (SD) age was 38.4 (11.6) years; 20 (33.3%) were female; and 39 (65.0%) were African American. The mean (SD) age at illness onset was 23.1 (8.5) years, and the mean (SD) duration of illness was 15.5 (12.18) years. The mean (SD) neurocognitive impairment in tasks of memory, attention, and executive functioning as measured by a validated computerized battery[41] was a z score of –1.0 (1.2) relative to a healthy reference group, indicating considerable impairment in the sample. In terms of antipsychotic medication, 55 (91.7%) of the cohort was taking at least 1 atypical (second-generation) agent and 39 (65.0%) of the sample had a chlorpromazine equivalent dosage of 400 mg or greater, indicating a high dosage. There were no meaningful group differences in antipsychotic medications at baseline (Table 1 shows baseline sample characteristics).

As displayed in Figure 1, the 18-month trial was completed by 27 of the 31 participants (87.1%) in the CT group (1 died [hypertension] and 3 withdrew [refused treatment]) and by 24 of the 29 participants (82.8%) in the ST group (5 withdrew [2 moved away, 3 refused to continue participation]).

IMPLEMENTATION OF CT

The mean (SD) number of CT sessions for the 28 patients who engaged in treatment was 50.5 (18.9) (range, 16-81). The 8 therapists (with PhD and MD degrees), each having at least 2 years of experience with CT, treated an average of 3.5 patients (range, 1-7 patients).

TREATMENT WITH MEDICATIONS

There was no difference across the 2 conditions in the number of patients who changed medications or dosages.

OUTCOMES

The CT group improved on global functioning (GAS score) during the course of the trial (within-group Cohen d=1.36), whereas the ST group improved very little (within-group d=0.06) (**Figure 2**). In the intent-to-

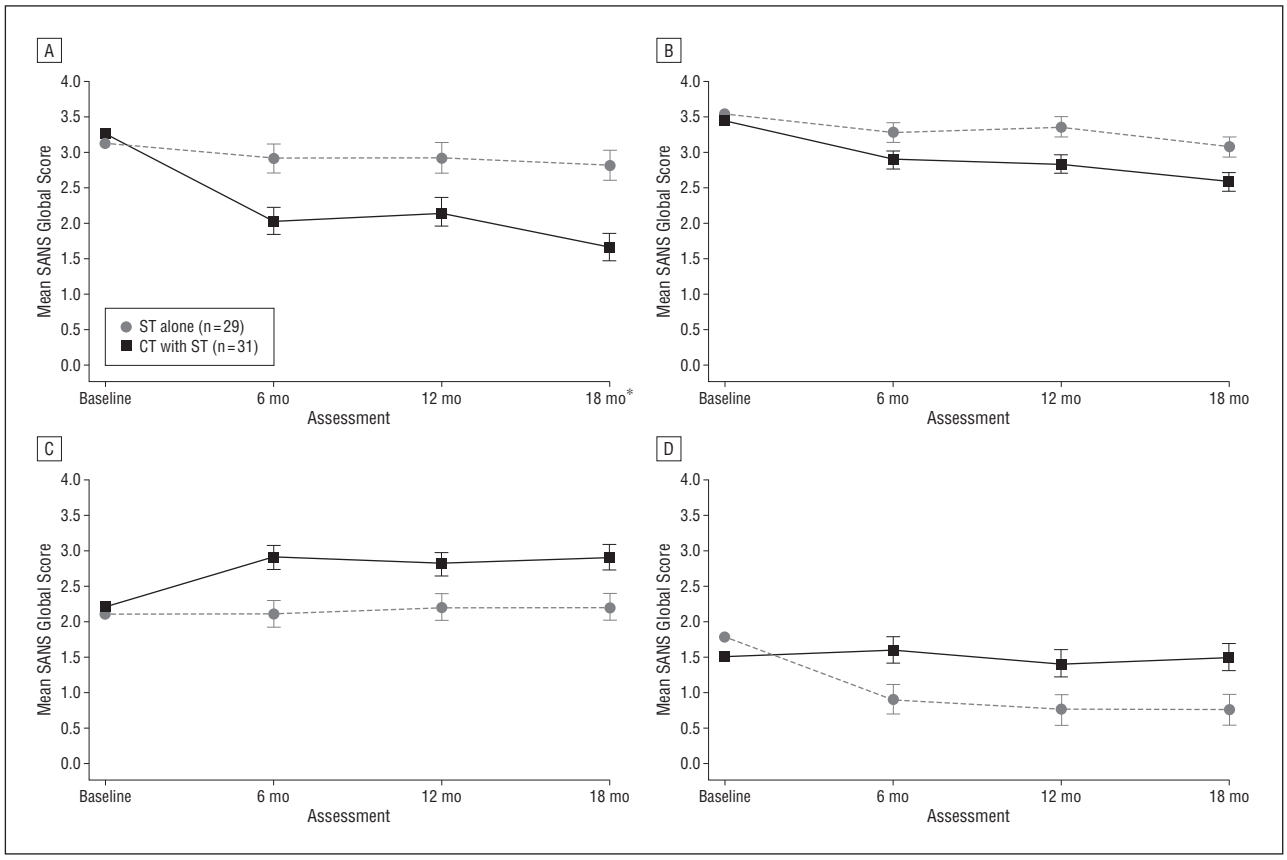

Figure 3. Negative symptoms. The mean global scores for the avolition-apathy (A), anhedonia-asociality (B), affective flattening (C), and alogia (D) subscales of the Scale for the Assessment of Negative Symptoms (SANS) are shown. The values at baseline are raw means; the values at 6, 12, and 18 months are adjusted means (SEs) from the intent-to-treat hierarchical linear models. CT indicates cognitive therapy; ST, standard treatment. *P=.01 for the mean difference based on the hierarchical linear modeling interaction of treatment condition × assessment time.

treat hierarchical linear model (**Table 2**), the interaction term for the condition × GAS score at 18 months was statistically significant (P=.03), indicating that the CT group had functioning superior to that of the ST group at 18 months (adjusted mean [SE], 58.3 [3.30] vs 47.9 [3.60], respectively; between-group d=0.56).

On the 4 SANS negative symptom subscales (**Figure 3**), the CT group showed greater improvement than the ST group across the trial for avolition-apathy (at 18 months: within-group d, –2.16 vs –0.45, respectively; for interaction term of condition × 18 months, P=.01; adjusted mean [SE], 1.66 [0.31] vs 2.81 [0.34], respectively; between-group d=–0.66). There were no significant group differences for the other negative symptoms (affective flattening, alogia, anhedonia-asociality).

In terms of positive symptoms (**Figure 4**), the CT group showed greater improvement than the ST group across the trial (at 18 months: within-group d, –0.90 vs 0.37, respectively; for interaction term of condition × 18 months, P=.04; adjusted mean [SE], 9.4 [3.3] vs 18.2 [3.8], respectively; between-group d=–0.46).

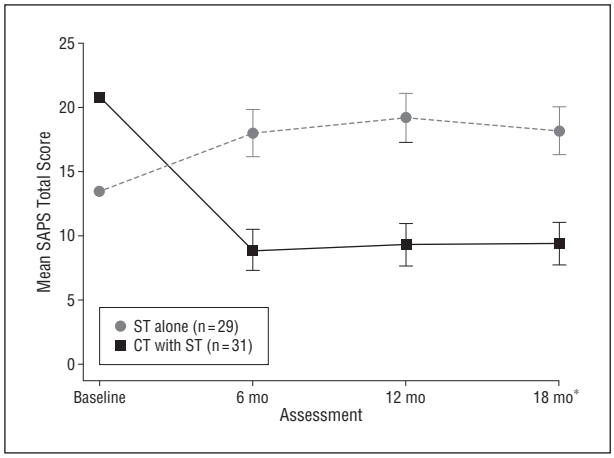

Figure 4. Positive symptoms. The values at baseline are raw means; the values at 6, 12, and 18 months are adjusted means (SEs) from the intent-to-treat hierarchical linear models. CT indicates cognitive therapy; SAPS, Scale for the Assessment of Positive Symptoms; and ST, standard treatment. *P=.04 for the mean difference based on the hierarchical linear modeling interaction of treatment condition × assessment time.

COMMENT

We found that patients assigned to CT had better functioning, reduced avolition-apathy, and improved positive symptoms relative to patients who received ST only. Group differences were statistically significant and clinically meaningful. This is the first time, to our knowledge, that patients with chronic schizophrenia selected from the extreme end of the low-functioning continuum have shown statistically significant and clini-

cally meaningful improvement in psychosocial functioning in response to a psychosocial intervention.

Taking the results of functional outcome, motivation, and positive symptoms together, we propose that the patients who received CT entered into a dynamic cycle of recovery. The treatment encourages the patients to set goals related to their everyday functioning, and they become motivated to engage in tasks (initially simple pleasurable, social, and constructive activities) that move them out of their withdrawn state. This increase in activity and motivation puts the patients more in touch with reality and reduces hallucinations, delusions, and disorganization. Reduced positive symptoms allow for further engagement in activity, leading to better functional outcomes and enhancement of motivation, which in turn facilitate a further amelioration of positive symptoms. Thus, we hypothesize that CT triggers the cycle of recovery by targeting self-defeating and dysfunctional beliefs that inhibit the patients' active engagement in constructive activity. Alternatively, it is possible that improvement in avolition-apathy was largely secondary to improvement in positive symptoms. These are questions that can be addressed by future research.

There are several limitations of this study. First, the measures of functioning and symptoms have been criticized.[8,42] For instance, the GAS includes symptoms in the ratings and, as such, is not a pure measure of functional outcome. Use of the newly developed Schizophrenia Outcomes Functioning Interview[43] and Clinical Assessment Interview for Negative Symptoms[44] is warranted in future clinical trials of CT. More frequent assessment of symptoms and functioning would allow for better tracking of changes over time. Also, the therapy was delivered by doctoral-level therapists; generalization to masters-level community therapists who treat low-functioning patients remains to be demonstrated in future research. The CT condition involved more patient contact than the ST condition, raising the possibility that nonspecific patient contact factors are contributing to the observed group differences. Additionally, both therapists and patients were aware of the condition and participation in an experiment, introducing possible bias in the reported outcomes. Future studies can address nonspecific factors and bias due to single-blind design, as well as other factors, by comparing the CT protocol with active psychotherapy comparison conditions that feature treatments (eg, social skills) that have received empirical support for patients with schizophrenia. Finally, it remains for future studies with revised CT protocols to demonstrate efficacy relative to anhedonia, affective flattening, and alogia.

The major findings of this study—that CT improved functioning and motivation and reduced positive symptoms in low-functioning patients with schizophrenia—suggest that this treatment might have utility to help reduce public health costs for the most expensive per-patient psychiatric population while simultaneously improving patients' quality of life.

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