# A PRELIMINARY TRIAL OF ADHERENCE-COPING-EDUCATION (ACE) THERAPY FOR FIRST-EPISODE SCHIZOPHRENIA

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ABSTRACT

SARAH R. UZENOFF: A Preliminary Trial of Adherence-Coping-Education (ACE) Therapy for First-Episode Schizophrenia
(Under the direction of David Penn, PhD)

A randomized controlled trial was conducted to examine the effectiveness of Adherence-Coping-Education (ACE) Therapy. Twenty-four individuals were randomized to receive 14 sessions of either ACE therapy in addition to treatment as usual (TAU), or Supportive Therapy (ST) in addition to TAU. Participants were assessed on measures of medication attitudes, insight, symptoms, and social functioning. ACE therapy was well tolerated, with comparable attrition rates between the two interventions and high therapy attendance. ACE Therapy was associated with significant improvements in medication attitudes as well as psychotic symptoms, insight and functioning. A greater proportion of individuals in the ACE condition had clinically significant change on positive symptom scores than did those in the ST condition. These results lend initial support for the feasibility of ACE Therapy, and suggest that it may facilitate recovery from an initial psychotic episode. Findings are discussed within the context of the study's limitations.

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# A PRELIMINARY TRIAL OF ADHERENCE-COPING-EDUCATION (ACE) THERAPY FOR FIRST-EPISODE SCHIZOPHRENIA

A central challenge in the treatment of schizophrenia is to prevent relapses, which are both costly (Weiden & Olfson, 1995) and dangerous (Swartz et al., 1998). Relapse prevention is of paramount concern for individuals recovering from their first episode of schizophrenia, as relapse rates of up to 33% are reported within one year of initial hospitalization (Ucok, Polat, Cakir, & Genc, 2006) and to over 90% within 5 years of initial treatment response (Perkins, Gu, Boteva, & Lieberman, 2005). Such relapses may themselves be neurotoxic, as repeated relapse and rehospitalization is associated with progressive loss of brain grey matter and ventricular enlargement, which may lead to long-term functional decline (Perkins et al., 2004; Waddington, Scully, & O'Callaghan, 1997).

Medication nonadherence is among the strongest factors associated with relapse in schizophrenia (Kane, 1999): it is estimated that the risk of relapse for nonadherent individuals is more than three times greater than that for adherent individuals (Fenton, Blyler, & Heinssen, 1997). Medication non-adherence is a particular problem for individuals with first episode psychosis, with rates of nonadherence estimated between 19-40% at one year and as high as 75% at 2 years (Kampman et al., 2002; Perkins, 1999; Robinson et al., 2002). This is significant in that poor medication adherence during the first 6 months after an individual's initial presentation strongly predicts poor adherence throughout the first 2 years of treatment, and is associated with an episodic course of illness and involuntary readmission (Verdoux et al., 2000). Additionally, research suggests that there is a 'critical period' (i.e.

within 2-3 years of initial treatment) when psychosocial influences (such as reducing treatment resistance and influencing how individuals conceptualize their illness) may be most effective (Birchwood, Todd, & Jackson, 1998). For these reasons, it is essential that individuals with schizophrenia remain adherent and engaged with their treatment early in the course of their illnesses.

The importance of medication adherence in the successful treatment of psychotic disorders is typically addressed via psychoeducation. However, findings suggest that psychoeducation has little impact on medication adherence rates in randomized controlled trials (Gray, Wykes, & Gournay, 2002; Mueser et al., 2002; Zygmunt, Olfson, Boyer, & Mechanic, 2002). This may reflect the fact that nearly two-thirds of first-episode patients have significant impairments in insight (Keshavan, Rabinowitz, DeSmedt, Harvey, & Schooler, 2004). Additionally, a majority of individuals recovering from a first episode of psychosis will have no residual positive or negative symptoms after the first year of treatment (Robinson et al., 1999) and therefore underestimate or fail to understand their potential to relapse. The Health Belief Model (HBM) of treatment adherence in preventative healthcare suggests that in order to arrive at an adherence decision, one must first perceive their own vulnerability to relapse, and also believe that medications will be efficacious in preventing relapse (Becker & Maiman, 1975). An important premise of this approach is that an individual's beliefs, attitudes and goals are important determinants of adherence decisions. Thus, a therapeutic intervention that addresses medication adherence must necessarily explore client beliefs and attitudes in a systematic way—an approach typically adopted by cognitive behavioral therapy (CBT).

CBT has consistently shown to be effective at reducing persistent positive and negative symptoms of schizophrenia (Dickerson, 2000; Rector & Beck, 2001; Tarrier, 2005; Zimmermann, Favrod, Trieu, & Pomini, 2005). Additionally, recent trials of CBT for first-episode psychosis have shown benefits in a number of outcome domains (Addington & Gleeson, 2005; Penn, Waldheter, Perkins, Mueser, & Lieberman, 2005), including recovery from acute symptoms (Lewis et al., 2002; Tarrier, Haddock, & Lewis, 2004), improving individuals' adaptation to the illness, quality of life, and attitudes towards treatment (Jackson et al., 1998; Jackson et al., 2001), and reducing suicidal ideation (Power et al., 2003). Though less extensively examined, cognitive behavioral interventions have also shown promise in improving medication adherence, albeit in chronically ill samples (Boczkowski, Zeichner, & DeSanto, 1985; Hayward, Chan, Kemp, & Youle, 1995). In particular, Compliance Therapy (CT) (Kemp, David, & Hayward, 1996a) has been associated with significantly greater improvement in attitudes towards medication, insight, and compliance with treatment as compared to a control group (Kemp, Hayward, Applewhaite, Everitt, & David, 1996b). Furthermore, at 18-months, individuals who received CT also showed greater improvement in global social functioning, as well as longer survival in the community prior to rehospitalization (Kemp, Kirov, Everitt, Hayward, & David, 1998). These outcomes are noteworthy in that they demonstrate the potential for cognitive behavioral therapies to impact both adherence behavior and community functioning, as well essential underlying attitudes surrounding medication adherence (see Byerly, Fisher, Carmody, & Rush, 2005; O'Donnell et al., 2003 for conflicting findings).

Perkins, Penn and Lieberman (unpublished manual) adapted CT to a first-episode sample by considering specific issues associated with an initial psychotic break (International

Early Psychosis Association Writing Group, 2005; Tarrier, Khan, Cater, & Picken, 2006), such as managing the trauma following an initial hospital admission and dealing with the stigma of mental illness. In addition, this modified intervention increased the number of therapy sessions, since the brevity of CT (4-6 sessions) is likely inadequate for individuals with first-episode psychosis who typically undergo a long recovery process and for whom initial engagement may be difficult. Thus, Adherence-Coping-Education (ACE) Therapy was developed to enhance adherence to treatment, reduce the stigma associated with psychosis, and to improve functional outcomes among individuals with first-episode psychosis.

The purpose of this study was to conduct a preliminary evaluation of the effectiveness of ACE Therapy compared to a control treatment (i.e. supportive therapy; ST). The primary hypotheses were that individuals receiving ACE would; 1) report greater medication adherence (i.e. less deviation from the medication regiment as prescribed), and 2) show a greater increase in positive attitudes toward their medication than individuals receiving Supportive Therapy (ST) at three months (mid-treatment) and six months (end of treatment). A secondary hypothesis was that individuals in the ACE group would show greater improvement in social functioning and insight, and a greater reduction in symptoms (psychotic and depressive) at mid-treatment and post-treatment than individuals in the ST group.

## Methods

### *Research Design and Overview*

We conducted a randomized, single blind, controlled clinical trial of ACE therapy. Participants were randomized to receive either ACE Therapy in addition to treatment as usual or ST in addition to treatment as usual. Both groups received their clinical treatment at the

same outpatient treatment clinic and all decisions about medications and other supportive therapies were made by their treating clinicians independent of study assignment. Both therapy interventions consisted of a total of 14 therapy sessions over the course of 6 months: the first 6 sessions occurred on a weekly basis, followed by 8 biweekly sessions. Assessments were conducted at baseline, 3 months (mid-treatment), and 6 months (end of treatment) by interviewers blind to treatment condition.

*Participants*

The sample comprised 24 participants recovering from a first psychotic episode. Participants were recruited from local inpatient and outpatient clinics, community mental health centers, and through media advertising and referrals from community clinicians. Brochures describing the study were mailed to area psychiatrists, psychologists, pediatricians, and social workers. Study inclusion and exclusion criteria were as follows: 16 years of age or older; meets DSM-IV (APA, 2000) diagnostic criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder; has been in treatment for a first episode of psychosis for less than 12 months, and no known mental retardation.

*Measures*

*Screening*. Eligibility for study participation was determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)(First, 1996).

*Primary Outcomes.* Medication adherence was assessed by patient report using the following prompts: "Over the past month/since your last visit, on how many days did you *not take*/*miss* your medication?" (<7, 7-13, 14-20, >20); "Over the past 4 weeks/ since your last visit, how often did you take *less than the prescribed dose?*" (1=always, 2=usually, 3=sometimes, 4=never, almost never); "In summary, over the past 4 weeks, how often did

you take your medication *as prescribed*?" (1=always, 2=usually, 3=sometimes, 4=never, almost never).

The Rating of Medication Influences (ROMI) scale (Weiden et al., 1994) is a comprehensive measure of attitudes regarding adherence to antipsychotic medications. The measure is divided into two subscales, 'Reasons for Adherence' (9 items) and 'Reasons for Nonadherence' (10 items), each containing attitudinal and behavioral factors thought to influence adherence behavior. Items are rated on a 1 through 3 scale, where 1=no influence, 2=mild influence, 3=strong influence, and 96=not applicable. Weiden et al. (1994) reported moderate internal consistency for both scales; in the current study, these subscales yielded Cronbach's alphas of .53-.61. Higher scores on the 'Reasons for Adherence' subscale correspond to an endorsement of factors influencing the individual to take his/her medication, whereas higher scores on the 'Reasons for Nonadherence' subscale correspond to an endorsement of factors influencing the individual to *stop taking* his/her medication.

In addition, health beliefs were evaluated using two scales developed to map onto the central constructs of the Health Belief Model; 'Need for Treatment,' and 'Benefits of Medication' (Perkins et al., 2006). Each comprises selected items from the ROMI and the ITAQ (discussed below) and was found to have excellent internal reliability; in the current study, these subscales yielded Cronbach's alphas of .81-.93. Perkins et al. (2006) found that both of these scales significantly predicted likelihood of medication nonadherence in a large sample of individuals recovering from a first psychotic episode. The Need for Treatment and Benefits of Medication scales are calculated as the average of the individual item scores and therefore had a range of 1-3 (ITAQ items were rescaled from 0-2 to 1-3). Higher scores indicate positive beliefs.

*Secondary Outcomes.* The Insight and Treatment Attitudes Questionnaire (ITAQ) (McEvoy et al., 1989) is designed to assess an individual's recognition of illness and need for treatment. The ITAQ includes 11 questions. Reponses are rated as follows: 2=good insight, 1=partial insight, and 0=no insight, which are summed to provide a total insight score; higher scores correspond to better insight.

The Positive and Negative Syndrome Scale (PANSS) is a structured clinical interview consisting of 30 items designed to assess positive, negative, mood, and behavioral symptoms over the last week (Kay, Fiszbein, & Opler, 1987). Items are scored from 1 (absent) to 7 (severe) and yield three scaled scores: Positive Symptoms, Negative Symptoms, and General Psychopathology. Higher total scores correspond to greater severity of symptoms. The PANSS has demonstrated adequate internal reliability ($\alpha$ = .73-.83) and test-retest reliability ($r$ = .77-.89). Raters were trained to reliability ($\underline{r}$ > .80) by a gold-standard rater prior to the study.

Further information regarding participants' symptom severity was collected using the Calgary Depression Rating Scale (CDRS) (Addington, Addington, & Maticka-Tyndale, 1993), a 9-item structured interview scale developed specifically for assessing depression in individuals with schizophrenia. The CDRS has high internal consistency ($\alpha$ = .79) and assesses depression as separate from overlapping negative or extrapyramidal symptoms**.** Higher scores correspond to greater depression.

The Quality of Life Scale (QLS) (Heinrichs, Hanlon, & Carpenter, 1984) was used to assess social and vocational functioning. This 21-item scale is based on a semi-structured interview providing information on symptoms and functioning during the preceding 4 weeks. Items are rated on a 7-point scale, with the high end of the scales (scores of 5 and 6)

reflecting normal or unimpaired functioning, and the low end of the scales (scores of 0 and 1) reflecting severe impairment of the function in question. Higher total scores indicate better social and vocational functioning.

*Interventions*

Both interventions (ACE and ST) were provided by clinicians with at least a Master's degree and one year experience working with individuals with first-episode psychosis. Therapists were trained by one of the authors of the manual (DLP) via directed readings and role-plays.

ACE Therapy is a manual-based psychotherapy designed around the goals of; 1) enhancing insight into illness, 2) improving medication adherence, and 3) developing adaptive coping strategies. ACE Therapy consists of 14 sessions that are delivered over a 6-month period and are divided into 4 phases: (1) establishing therapeutic alliance; (2) promoting treatment adherence; (3) developing a plan for maintenance treatment; and (4) rehabilitation. In ACE Therapy, the therapist assumes an active role consistent with traditional cognitive-behavioral therapies, and the therapeutic stance emphasizes empathy for the patient's point of view. Key therapeutic techniques utilized include: reflective listening, inductive questioning, evaluating the pros and cons (e.g., of medication use), summarizing, reframing, using normalizing rationales, selective validation of the patient's beliefs and attitudes, and graded analysis of evidence to address beliefs about illness and treatment. Individuals randomized to ACE Therapy attended sessions held at weekly intervals for sessions 1 through 6, then every other week for sessions 7 through 14. Sessions lasted approximately 30-45 minutes.

Supportive Therapy (ST) was intended to control for the non-specific aspects of therapy, such as therapeutic relationship and regular contact with a therapist. The goals of ST are: 1) to provide an environment where the client can discuss her/his feelings and concerns; 2) to validate the client's feelings and concerns, and; 3) to provide support and guidance to the client so that she/he can make progress to solving problems or alleviating concerns and worries. ST has two phases, which are; 1) establishing a therapeutic alliance, and 2) providing emotional support and discussing non-illness issues or topics. Therapists were instructed not to bring up or discuss issues related to medication or medication adherence. If patients brought up these issues in ST, the therapist was to listen with an empathic therapeutic stance, and advise the patient to discuss these issues with his or her treating physician. Similar to subjects randomized to ACE Therapy, subjects randomized to ST received 14 sessions of therapy, each lasting approximately 30-45 minutes, delivered over a 6-month period. Sessions were held at weekly intervals for sessions 1 through 6, then every other week for sessions 7 through 14.

*Quality Assurance*

Each therapy session was audiotaped and reviewed by DLP for fidelity to the treatment and procedures. Performance was discussed in individual supervision with the therapist. An independent assessor blind to all patient data and to the audiotape selection procedure listened to a random sampling of 20 therapy tapes stratified according to therapy. The assessor assigned each tape to either the ACE or ST group.

*Procedure*

Eligibility for study participation was determined during a screening visit, at which time a diagnostic screen was conducted using the *Structured Clinical Interview for DSM-IV*

*Axis I Disorders* (SCID-I)(First, 1996) and informed consent was obtained. Baseline assessments were conducted and participants were then randomized to treatment. At mid-treatment and post-treatment, the following variables were assessed: Medication adherence, attitudes towards medication, insight, symptom severity, and social and vocational outcomes.

*Data Analysis Overview*

Two-tailed *t*-tests and $\chi^2$ analyses were used to compare the ACE and ST groups on demographic characteristics and outcome measures at baseline, as well as to compare dropouts with the participants who were included in final data analyses. Because this is a preliminary feasibility study of ACE, we primarily focused on within-group t-tests and effect sizes to evaluate changes on outcome measures at mid- and post-study. Specifically, the two interventions were compared on primary and secondary outcome measures first by examining within-group *t*-statistics for score changes from baseline to mid-study (i.e. 3 months), as well as from baseline to post-study (i.e. 6 months). Additionally, within-group effect sizes were calculated for these same pre-post periods. Effect size calculations (i.e. Cohen's *d;* Cohen, 1988) were evaluated based on accepted standards for 'small to medium' ($0.2 \leq d < 0.5$), 'medium to large' ($0.5 \leq d < 0.8$), and large ($d \geq 0.8$) effect sizes. In a secondary analysis of clinically significant change, we used Fisher's exact tests to compare the proportion of participants assigned to each intervention who showed at least 25% or 50% reductions in PANSS positive subscale scores at mid-study and end-of-study assessments; these figures are recognized as more lenient or conservative (respectively) guidelines for meaningful psychotic symptom reductions in trials of psychotherapeutic interventions for schizophrenia (Durham et al., 2003; Tarrier et al., 1999). Missing individual data points were replaced with group or scale means, as more sophisticated methods of imputation

require larger sample sizes. Individuals missing an entire scale at baseline (N=3) were excluded from all subsequent analyses *on that particular variable*. Data that were missing scale-wise at mid- and post-study assessments were replaced using a last observation carried forward (LOCF) technique for some analyses, as noted below.

All outcome analyses were completed using a modified intent-to-treat sample consisting of individuals who completed both a baseline assessment and at least one follow-up assessment (i.e. 3 months), and who had attended at least one session of their assigned intervention. Effect size analyses and significance tests were conducted with two different methods; 1) observed cases, and; 2) a last observation carried forward (LOCF) technique to estimate data at 6 months for participants in the modified intent to treat sample who did not complete an end-of-study assessment. The former technique examines what may be considered an "efficacy subset" (Lachin, 2000) of individuals who completed the study (i.e. attended a 6 month evaluation), whereas the LOCF technique is believed to yield a more conservative estimate of the treatment effect compared to that which would have been observed if the individual had remained in the study.

Additionally, an exploratory analysis was conducted using observed data to examine treatment by time interactions on measures of medication attitudes, symptoms, insight, and functioning. Using the PROC MIXED command in SAS, linear mixed-effects regression models were computed using time and treatment group as fixed effects and random intercepts for each participant. The *F* tests for the mixed model were based on Kenward-Roger's adjusted degrees of freedom solution, an approach specifically proposed for small sample settings. While we recognize that the small sample size in this study results in reduced

power, we believe it is useful to explore this model to examine the kind of analysis appropriate for a study with a larger sample.

## Results

### *Demographic and Outcome Variables at Baseline*

Twenty-nine individuals were referred to the study, met eligibility criteria and gave their consent to participate; of these, 24 were randomized. Figure 1 shows the participant flow throughout the study. Of the 24 participants randomized to receive treatment, a total of 5 participants were excluded from outcome data analyses. One participant had missing data at baseline, and was therefore excluded from analyses. An additional 3 participants, representing 15.4% of participants assigned to ACE (N=2) and 9.1% of participants assigned to ST (N=1), did not attend any follow-up assessments (i.e. dropped out before mid-study). Finally, one participant in the ACE group was excluded as an age outlier (i.e. the individual's age was more than three standard deviations above the randomized sample mean). Two participants dropped out before the end of the study; data at 6 months for these patients was estimated using a LOCF technique. There was no significant difference between total proportions of drop-outs in the two groups (Fisher's Exact Test $p$=1.00, *ns*), and there were no significant differences in demographics or symptom measures between drop-outs and individuals included in the outcome analyses (all $p$-values >.05).

Table 1 shows demographic data for the participants included in outcome analyses (N=19). Demographic data at baseline did not differ significantly for individuals randomized to receive ACE as compared to individuals randomized to receive ST, with the exception of participant age; participants in the ACE group were significantly older than those in the ST group ($t(17)$=2.43, $p$=.03). Thus, age was examined as a covariate in the exploratory mixed

effects analysis. There were no significant differences between the two groups on outcome variables at baseline (all *p*-values >.05) including self-reported medication adherence.

*Quality Assurance*

The independent assessor correctly assigned 18 of 20 therapy tapes (90%) to the appropriate treatment group.

*Therapy Attendance*

In this study, a 'minimum dose' of therapy was considered to be 6 sessions, which for the ACE condition includes the first two phases of the therapy (i.e. "Establishing a Therapeutic Alliance" and "Promoting Treatment Adherence"). In the ST condition, this includes the first 2 sessions devoted establishing a therapeutic alliance and an additional 4 sessions spent providing emotional support and discussing non-illness issues and topics.

One hundred percent of participants (N=19) received a minimum dose of therapy. In both groups attendance was high. In the ACE group, 9 out of 10 participants (90%) attended 14 sessions (range=12-14 sessions). In the ST group, 8 out of 9 participants (88.9%) attended 14 sessions (range=9-14 sessions). Between the ACE and ST conditions of the modified intent-to-treat sample, there was no significant difference in therapy session attendance (ACE: $M$=13.80, $SD$=0.63; ST: $M$=13.44, $SD$=1.67) ($t(17)$=0.63, $p$=.54). The 2 participants included in the LOCF analysis, but not the observed cases analysis, both received a minimum dose of therapy.

*Primary Outcome Analyses*

At baseline, 100% of participants in both conditions indicated that they failed to take their medication fewer than 7 days of the previous month. One participant in the ACE condition reported 'always' taking less than the prescribed dose of medication, and 'never'

taking the medication as prescribed. However all other patients reported the highest level of adherence, and there were no significant differences between the groups. At mid-study, 100% of participants in both conditions indicated that they failed to take their medication fewer than 7 days of the previous month, reported "never (or almost never)" taking less than the prescribed dose of medication, and, likewise, that they "always" took medication as prescribed. These results were replicated at 6 months, suggesting no difference between groups on self-reported adherence behaviors. Therefore the remainder of the analyses will focus on medication attitudes as the primary outcome.

*Observed cases analysis.* Means for all analyses are presented in Table 2. Participants in the ACE group showed stronger endorsements of reasons for adherence on the ROMI at both mid-study (i.e. 3 months) and post-test (i.e. 6 months) than at baseline. There were medium within-group effect sizes for the ACE group on the ROMI 'Adherence' subscale (see Table 2), although these changes were not statistically significant. Conversely, the ST group showed stronger endorsements for reasons for *nonadherence* at 3 and 6 months than at baseline on the ROMI 'Nonadherence' subscale. There was a large effect size on this measure at 3 months, and the increase in total 'Reasons for Nonadherence' for the ST group was statistically significant at 6 months ($t(5)=-3.162$, $p<.05$), representing a medium to large effect size.

Participants in the ACE group showed improvement on the HBM scales at three and six months. There were significant within-group changes at 3 months for ACE participants on both the Need for Treatment scale ($t(7)=-2.55$, $p<.05$) and the Benefits of Medication scale ($t(7)=-2.51$, $p<.05$), with these changes corresponding to large and medium to large effect sizes, respectively. There was also a significant within-group change on the Benefits of

Medication scale for ACE participants at 6 months ($t(7)=-2.55$, $p<.05$) and medium to large effect sizes for both HBM measures at that time point. There were no significant changes on these measures for the ST group, though there were small to medium and medium to large effect sizes for the score increases at six months.

*LOCF analysis.* Using a last observation carried forward (LOCF) technique for primary outcome measures, results differed from those obtained using observed cases in the following ways: the post-test effect size for the ACE group's ROMI Adherence scores falls into the small to medium range, as do the ST group's Need for Treatment and Benefits of Medication effect sizes; and the increase in ROMI Nonadherence scores for the ST group at six months now approaches significance ($t(7)=2.01$, $p=.09$), though the effect size remains in the medium to large range.

*Secondary Outcome Analyses*

*Observed cases.* The ACE group showed significant reductions on the PANSS Positive and General symptom subscales at both three months ($t(9)=4.06$, $p<.01$; $t(9)= 2.84$, $p<.05$) and six months ($t(8)=3.43$, $p<.01$; $t(8)=3.22$, $p<.05$). These reductions correspond to large effect sizes. There was a medium effect size for the decrease in PANSS Negative scores in the ACE group at 6 months and a trend towards statistical significance ($t(8)=2.21$, $p=.058$). The ACE group also improved significantly on the ITAQ, with a significant increase in insight scores at both three months ($t(8)=-3.49$, $p<.01$) and six months ($t(7)=-3.15$, $p<.05$) and large effect sizes at both points. And finally, ACE participants showed a significant increase in QLS (quality of life) total scores from baseline to six months ($t(8)=-2.89$, $p<.05$), which represents a medium effect size. There were no significant changes in CDRS (depression) scores for the ACE group.

For the ST group, there was a significant decrease in PANSS positive symptoms at three months ($t(8)=3.10$, $p<.05$), but not at six months. There were small to medium effect sizes at both time points. The ST group had no significant changes on the other PANSS subscale scores, or on the ITAQ or QLS. Finally, CDRS scores increased for the ST group, with a medium effect size at three months and a large effect size at six months. This change was in the direction of higher depression scores.

*LOCF analysis*. Using a last observation carried forward (LOCF) technique for secondary outcome measures, results differed from those obtained using observed cases in that the increase in QLS total scores for the ACE group now approaches statistical significance ($t(9)=-2.17$, $p=.058$), though the effect size remains in the 'medium' range.

*Supplementary Analysis: Mixed Effects Model*

Mixed effects analyses were also conducted to evaluate differences between participants in the ACE and ST conditions over time. There was a significant time by treatment interaction for symptom reduction on PANSS positive subscale scores ($F(2,31.9)=3.98$, $p<.05$). Contrasts revealed significant between-group differences in change scores from baseline to 3 months ($t(31.7)=2.26$, $p<.05$) and from baseline to 6 months ($t(32)=2.56$, $p<.05$), with greater reductions in symptom scores for the ACE group than for the ST group. There was also a significant time by treatment interaction for symptom reduction on PANSS general subscale scores ($F(2,31.8)=4.44$, $p<.05$). Probing these interactions revealed significant between-group differences in change scores from baseline to 3 months ($t(31.3)=2.50$, $p<.05$) and from baseline to 6 months ($t(32)=2.63$, $p<.05$), with greater reductions for the ACE group than for the ST group. However, the between-group difference in baseline scores for this variable was also significant, which likely accounts for

this significant interaction ($M_{ACE}$=34.00, $M_{ST}$=26.33) ($t$(38.7)=-2.33, $p$<.05)[1]. Results for PANSS positive and general scores remained statistically significant at the $p$<.05 level when age was included as a covariate at baseline.

Time by treatment interactions approached statistical significance for insight (i.e., ITAQ scores) ($F$(2,30.7)=2.33, $p$=0.11) and Need for Treatment ($F$(2,28.5)=2.90, $p$=.07), each with significant between-group differences in change scores from baseline to 3 months [($t$(28.3)=-2.23, $p$<.05) and ($t$(30.4)=-2.10, $p$<.05), respectively]; greater improvements in insight and treatment attitudes were observed in the ACE group than in the ST group. These results generally paralleled the within group analyses.

*Clinically Significant Change*

As summarized in Table 3, a greater proportion of individuals demonstrated clinically significant change in PANSS positive scores (i.e. 25% or 50% reduction) in the ACE group than in the ST group, at both 3 months and 6 months. The difference in proportions approached significance for 25% reductions at 3 months ($p$=.07), as well as for 50% reductions at 6 months ($p$=.09).

## Discussion

The purpose of this study was to conduct a preliminary evaluation of the effectiveness and feasibility of ACE Therapy in a single blind, randomized controlled trial. Participants were randomized to receive either ACE Therapy in addition to treatment as usual (TAU) or supportive therapy (ST) in addition to TAU. Both therapies were well-tolerated, with no significant difference in attrition rates between the two. Individuals receiving ACE therapy

[1] This is in contrast to the statistic obtained using an independent-samples t-test for baseline differences on PANSS general scores ($t$(17)=1.90, $p$=.075), reported earlier, and reflects greater degrees of freedom in the model.

showed significant improvements on attitudes towards medications and treatment, which is consistent with our hypotheses. Also consistent with our hypotheses, ACE participants showed a reduction in symptoms, and improvements in insight and social functioning at post-treatment. There were no significant changes in depression in either treatment group. And, with the exception of a decrease in positive symptoms at mid-study, there were no significant benefits of ST on any of the outcome measures. Analyses utilizing a LOCF technique to replace missing values at 6 months tended to result in reduced effects sizes, but rarely did the statistical significance of the findings change. And finally, there were no differences between groups on self-reported medication adherence behaviors. These findings are discussed in more detail below.

The high rate of retention in ACE therapy (90%) supports the feasibility of this intervention with a first-episode population. This is especially important given that engagement is a significant challenge for this clinical population (Grazebrook et al., 2004). Interestingly, many of the changes on primary and secondary outcome measures for the ACE group were associated with medium to large effect sizes by three months, corresponding to approximately 9 sessions of therapy. Given this finding, it may be that ACE therapy can be successfully implemented in a briefer protocol. This, in turn, may further strengthen therapy engagement if clients know that they need to commit to three, rather than six, months of treatment.

ACE was associated with improvements in attitudes towards medications which were evident at mid-study and endured to post-treatment. These changes were fairly robust, as they were associated with medium to large effect sizes. Improved attitudes towards treatment are consistent with the goals of ACE therapy and are similar to findings from the initial trial of

Compliance Therapy (CT) (Kemp, Hayward, Applewhaite, Everitt, & David, 1996b; Kemp et al., 1998). Changes in treatment attitudes were considerably smaller in the ST group, as manifest in effect sizes. Though these findings are very preliminary, the data suggest that ACE therapy may improve treatment attitudes in individuals recovering from an initial episode of psychosis.

This study did not find any differences between interventions on self-reported medication adherence; there were ceiling effects wherein all patients fell into the highest category of adherence behavior. The rates of adherence reported here are extremely high as compared to the mean rates observed across adherence studies in the field, which have been reported at approximately 33% at baseline and 24% at follow-up (Dolder, Lacro, Leckband, & Jeste, 2003). Thus, it is likely that our measures were not sensitive enough to detect meaningful differences in adherence behaviors. Though common in antipsychotic adherence studies, self-report measures have the potential to exaggerate the degree of adherence (Velligan et al., 2006). Thus, we cannot draw conclusions about the impact of ACE on medication adherence at this time.

Several of the largest effect sizes associated with ACE therapy were for symptom measures. Reduction in symptoms is widely reported in trials of cognitive-behavioral interventions for chronic or treatment-resistant schizophrenia (e.g. Durham et al., 2003; Gumley et al., 2003) as well as for first-episode psychosis (e.g. Tarrier et al., 2004). The large effect size for positive symptom reduction for the ACE group (*ES*=1.19) is similar to the mean within-group effect size for positive symptom reduction in a meta-analysis of studies of cognitive-behavioral interventions for schizophrenia (*ES*=1.31)(Rector & Beck, 2001), though in general, patients in these studies had been ill longer. Additionally,

supplemental mixed effects analyses showed that ACE was associated with a greater decrease in symptoms at both three and six months as compared to ST. However, it is important to exercise caution in interpreting these data for two reasons. First, psychotic symptom scores were higher (albeit non-significantly) for the ACE group at baseline than for the ST group; and second, this study was under-powered to adequately detect such differences between groups over time. Thus, these findings, while promising, clearly need to be replicated in a larger randomized controlled trial before confident conclusions can be drawn.

Among our secondary outcomes, ACE therapy was also associated with significant increases in insight and functioning, which are outcome domains of particular importance in first-episode psychosis treatment. With regard to insight, the gains observed in this study may support the intervention's broader aim of improving medication adherence as a means of relapse prevention. Individuals experiencing their first psychotic episode who show lower insight are at an increased risk of discontinuing their medications (McEvoy et al., 2006). Thus, given the association between insight and treatment adherence, the improvement in insight may have important clinical implications. The findings also suggest that the benefits of cognitive-behavioral interventions for psychosis may extend to social functioning as well (at least as measured by the Quality of Life Scale). Given that individuals with first-episode psychosis who report poorer quality of life tend to be treatment nonadherent (Coldham, Addington, & Addington, 2002), interventions successful at engaging such individuals may impact not only functioning in social domains, but increase the likelihood of future adherence to treatment.

This study suffers from several limitations. First, the sample size was small, therefore resulting in findings that need replication with a larger sample. Second, the ceiling effect on the medication adherence measure underscores the need to supplement client-reported adherence data with direct or objective measures such as pill count or electronic monitoring of pill caps. Third, there was no follow-up data past the 6-month post-treatment assessment. Thus, evidence of the durability of ACE could not be examined.

These limitations notwithstanding, the results of this study support the feasibility of ACE therapy and highlight several potential clinical benefits of the intervention. The current study is one of the first to examine the effectiveness of a CBT intervention for first-episode psychosis that is specifically tailored to addressing treatment adherence and attitudes. Findings suggest that cognitive-behavioral interventions may be effective in improving attitudes towards treatment as well as psychotic symptoms, insight and functioning for individuals recovering from an initial psychotic episode.

Table 1. *Demographic Characteristics of Sample Included in Outcome Analyses*

| Variable | ACE N=10 | ST N=9 | Test statistic (df) | *p*-value |
|---|---|---|---|---|
| Age (years), *M* (S.D.) | 25.30 (5.95) | 19.78 (3.53) | $t(17) = 2.43$ | .03* |
| Gender, *n* (%) | | | | |
| Male | 6 (60.0) | 6 (66.6) | $\chi^2(1) = .090$ | .76 |
| Female | 4 (40.0) | 3 (33.3) | | |
| Marital status, *n* (%) | | | | |
| Never married | 8 (80.0) | 7 (77.7) | $\chi^2(3) = 4.03$ | .26 |
| Married | | 2 (22.2) | | |
| Separated/divorced | 2 (20.0) | | | |
| Ethnicity, *n* (%) | | | | |
| Caucasian | 7 (70.0) | 7 (77.7) | $\chi^2(2) = 1.95$ | .38 |
| African-American | 3 (30.0) | 1 (11.1) | | |
| Other | | 1 (11.1) | | |
| Highest level of education, *n* (%) | | | | |
| Did not complete high school | 2 (20.0) | 3 (33.3) | $\chi^2(5) = 5.85$ | .32 |
| High school/GED | 2 (20.0) | 2 (22.2) | | |
| Some college | 4 (40.0) | 1 (11.1) | | |
| College graduate/Technical degree | 1 (10.0) | 2 (22.2) | | |
| Advanced degree | 1 (10.0) | | | |
| Parent's highest level of education, *n* (%) | | | | |
| Did not complete high school | 1 (10.0) | 1 (11.1) | $\chi^2(5) = 3.75$ | .59 |
| High school/GED | | | | |
| Some college | 2 (20.0) | 1 (11.1) | | |
| College graduate/Technical degree | 2 (20.0) | 4 (44.4) | | |
| Advanced degree | 4 (40.0) | 2 (22.2) | | |

*$p \leq .05$

Table 2. *Means, Within-group Effect Sizes, and Significance Tests for Primary and Secondary Outcome Measures*

| | 0 | 3 | 6 (Observed) | 6 (LOCF) | (0-3) | | (0-6) Observed | | (0-6) LOCF | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *M (SD)* | *M (SD)* | *M (SD)* | *M (SD)* | *ES* | *p* | *ES* | *p* | *ES* | *P* |
| ACE | | | | | | | | | | |
| *Primary Outcomes* | | | | | | | | | | |
| ROMI Adherence | 15.11 (4.49) | 16.89 (6.01) | 17.38 (4.41) | 16.33 (5.17) | 0.40 | .146 | $0.51^{+}$ | .285 | 0.27 | .329 |
| ROMI Nonadherence | 9.44 (4.90) | 8.67 (3.04) | 9.88 (4.12) | 10.38 (2.77) | -0.16 | .713 | 0.09 | .741 | 0.19 | .689 |
| Need for Treatment± | 2.32 (0.41) | 2.74 (0.35) | 2.57 (0.48) | 2.57 (0.48) | $1.03^{++}$ | $.038^{*}$ | $0.60^{+}$ | .065 | $.60^{+}$ | .065 |
| Benefits of Medication± | 2.44 (0.38) | 2.70 (0.27) | 2.67 (0.33) | 2.67 (0.33) | $0.68^{+}$ | $.040^{*}$ | $0.59^{+}$ | $.038^{*}$ | $.59^{+}$ | $.038^{*}$ |
| *Secondary Outcomes* | | | | | | | | | | |
| PANSS Positive | 15.60 (4.97) | 9.80 (3.26) | 9.67 (2.69) | 9.40 (2.68) | $-1.17^{++}$ | $.003^{*}$ | $-1.19^{++}$ | $.009^{*}$ | $-1.25^{++}$ | $.004^{*}$ |
| PANSS Negative | 17.70 (7.06) | 16.60 (7.47) | 14.11 (5.18) | 14.30 (4.92) | -0.16 | .426 | $-0.51^{+}$ | .058 | -0.48 | .069 |
| PANSS General | 34.00 (9.26) | 25.60 (4.27) | 24.56 (3.91) | 24.70 (3.71) | $-0.91^{++}$ | $.020^{*}$ | $-1.02^{++}$ | $.012^{*}$ | $-1.00^{++}$ | $.010^{*}$ |
| CDRS | 10.50 (3.38) | 12.10 (2.81) | 9.67 (0.87) | 10.20 (1.87) | 0.47 | .153 | -0.25 | .512 | -0.09 | .823 |
| ITAQ | 14.33 (4.18) | 19.33 (3.46) | 17.88 (4.67) | 18.33 (4.58) | $1.20^{++}$ | $.008^{*}$ | $0.85^{++}$ | $.016^{*}$ | $0.96^{++}$ | $.009^{*}$ |
| QLS Total[#] | 62.90 (28.40) | 67.11 (19.66) | 76.78 (19.94) | 75.70 (19.10) | 0.15 | .542 | 0.49 | $.020^{*}$ | 0.45 | .058 |
| ST | | | | | | | | | | |
| *Primary Outcomes* | | | | | | | | | | |
| ROMI Adherence | 16.00 (4.06) | 16.89 (2.52) | 16.86 (4.22) | 16.78 (3.73) | 0.22 | .647 | 0.21 | .537 | 0.19 | .729 |
| ROMI Nonadherence | 10.22 (2.73) | 13.00 (3.78) | 12.00 (2.76) | 12.13 (2.48) | $1.02^{++}$ | .088 | $0.65^{+}$ | .025* | $0.70^{+}$ | .085 |
| Need for Treatment± | 2.45 (0.45) | 2.41 (0.55) | 2.61 (0.45) | 2.55 (0.45) | -0.09 | .827 | 0.36 | .180 | 0.23 | .518 |
| Benefits of Medication± | 2.38 (0.39) | 2.45 (0.51) | 2.60 (0.37) | 2.48 (0.47) | 0.18 | .703 | $0.55^{+}$ | .160 | 0.26 | .673 |
| *Secondary Outcomes* | | | | | | | | | | |
| PANSS Positive | 13.78 (5.91) | 11.78 (5.36) | 11.25 (4.03) | 12.11 (4.57) | -0.34 | $.015^{*}$ | -0.43 | .282 | -0.28 | .161 |
| PANSS Negative | 14.33 (5.29) | 13.78 (5.54) | 15.75 (7.85) | 16.00 (7.38) | -0.10 | .805 | 0.27 | .646 | 0.32 | .562 |
| PANSS General | 26.33 (8.23) | 27.22 (7.48) | 26.13 (7.97) | 27.56 (8.60) | 0.11 | .653 | -0.02 | .680 | 0.15 | .646 |
| CDRS | 9.78 (0.97) | 10.33 (2.40) | 11.13 (3.83) | 11.67 (3.94) | $0.57^{+}$ | .479 | $1.39^{++}$ | .379 | $1.94^{++}$ | .211 |
| ITAQ | 15.11 (4.86) | 15.56 (5.81) | 17.50 (4.75) | 16.78 (4.94) | 0.09 | .829 | 0.49 | .074 | 0.34 | .287 |
| QLS Total[a] | 73.38 (33.89) | 81.63 (24.25) | 79.71 (25.91) | 75.63 (26.63) | 0.24 | .245 | 0.19 | .453 | 0.07 | .721 |

±Health Belief Model constructs composed of select ROMI and ITAQ items. See Perkins et al. (2006) for variable construction.

$^{+}$ $0.5 \leq ES < 0.8$, $^{++}$ $ES \geq 0.8$, * $p \leq .05$

[a]The mid-study scores in this table are *observed*—the QLS Total mean obtained at time 3 for the ACE condition using a LOCF technique is *M*=68.30 (18.92)

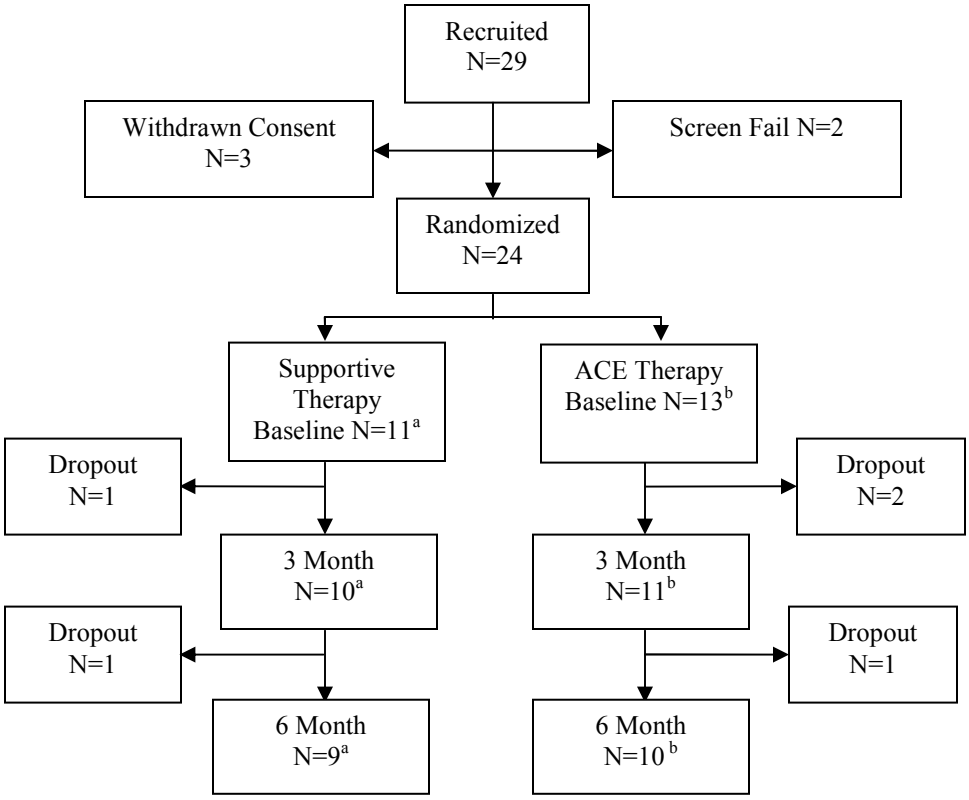
Table 3. *Clinically Significant Change on PANSS Positive Subscale Scores for ACE and ST*

| | Mid-study | | | | Post-test | | | |
|---|---|---|---|---|---|---|---|---|
| | 25% reduction[a] | | 50% reduction | | 25% reduction | | 50% reduction | |
| | Count (%) | Sig.[b] | Count (%) | Sig. | Count (%) | Sig. | Count (%) | Sig. |
| ACE | 8 (80%) | *p*=.07 | 3 (30%) | *p*=.21 | 6 (60%) | *p*=.37 | 4 (40%) | *p*=.09 |
| ST | 3 (33%) | | 0 | | 3 (33%) | | 0 | |

[a] Participants who achieved a 50% reduction are included in both the 25% and 50% columns

[b] Fisher's Exact Test

*Figure1.* Study flow diagram




[a]One participant randomized to ST was missing all baseline data—all scores for this participant were excluded from analyses. Thus, data from 9 participants was available at 3 months, and from 8 participants at 6 months.

[b] One participant assigned to the ACE group was excluded from outcome analyses as an age outlier. Thus, data was available from 10 participants at 3 months, and from 9 participants at 6 months.

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