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Clinical and Functional Outcomes After 2 Years in the Early Detection and Intervention for the Prevention of Psychosis Multisite Effectiveness Trial

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Objective: **To test effectiveness of the Early Detection, Intervention, and Prevention of Psychosis Program in preventing the onset of severe psychosis and improving functioning in a national sample of at-risk youth.** ***Methods:*** **In a risk-based allocation study design, 337 youth (age 12–25) at risk of psychosis were assigned to treatment groups based on severity of positive symptoms. Those at clinically higher risk (CHR) or having an early first episode of psychosis (EFEP) were assigned to receive Family-aided Assertive Community Treatment (FACT); those at clinically lower risk (CLR) were assigned to receive community care. Between-groups differences on outcome variables were adjusted statistically according to regression-discontinuity procedures and evaluated using the Global Test Procedure that combined all symptom and functional measures.** ***Results:*** **A total of 337 young people (mean age: 16.6) were assigned to the treatment group (CHR + EFEP, $n = 250$) or comparison group (CLR, $n = 87$). On the primary variable, positive symptoms, after 2 years FACT, were superior to community care (2 *df*, $p < .0001$) for both CHR ($p = .0034$) and EFEP ($p < .0001$) subgroups. Rates of conversion (6.3% CHR vs 2.3% CLR) and first negative event (25% CHR vs 22% CLR) were low but did not differ. FACT was superior in the Global Test ($p = .0007$; $p = .024$ for CHR and $p = .0002$ for EFEP, vs CLR) and in improvement in participation in work and school ($p = .025$).** ***Conclusion:*** **FACT is effective in improving positive, negative, disorganized and general symptoms, Global Assessment of Functioning, work and school participation and global outcome in youth at risk for, or experiencing very early, psychosis.**

Key words: schizophrenia/family psychoeducation/multifamily group/supported education/supported employment/assertive community treatment

Introduction

Schizophrenia and the psychotic forms of the major mood disorders are debilitating, exacting a significant toll on patients, families, and society. Psychoses rank in the top 3 most disabling conditions worldwide.[1,2] It is estimated that 2%–3% of the adult population develops a psychosis, constituting a major burden to public health. These are devastating disorders for families, who often assume major caretaking and psychological burdens. It has been estimated that the annual total costs are $61 billion for schizophrenia alone.[3]

Recent evidence suggests that early intervention prior to onset of a psychotic disorder may delay or prevent onset of frank psychosis and the deterioration in functioning so common in the psychoses.[4] A recent comprehensive meta-analysis reported that the overall risk ratio in 9 preventive clinical trials was 0.34.[5] Research to date has built on the observation that duration of untreated psychosis predicts later outcomes.[6] Even when the individual already meets criteria for a current psychotic episode, intervention shortly after onset may improve outcomes by initiating treatment when the individual is more sensitive to treatment.[7,8] Without treatment, many of those found to be at risk function poorly, even in the absence of a

psychotic episode.[9] For those at risk, early intervention has the potential to prevent onset of a full psychotic disorder; treat the impaired cognitive, social, and occupational functioning already present; and alleviate family distress.[10–12]

One example of these indicated prevention approaches, the Portland Identification and Early Referral (PIER) program, is a population-wide system of early detection and preventive intervention in Greater Portland, ME.[13] It includes extensive community education about the early signs of psychosis and the potential benefits of early treatment. Families and young people who meet criteria for high risk of onset of psychosis receive Family-aided Assertive Community Treatment (FACT), a package of interventions consisting of psychoeducational multifamily group (PMFG) therapy, elements of assertive community treatment, supported education and employment, and psychotropic medication.[13–15] Family intervention is the principal treatment component, based on the evidence for its efficacy in schizophrenia and first episode and prodromal psychosis.[16–19]

The Early Detection and Intervention for the Prevention of Psychosis Program (EDIPPP) was undertaken to build on these findings by testing the effectiveness of the PIER approach across the United States in a large, ethnically, and geographically diverse population, in 6 typical mental health agencies and settings. The goal was to evaluate whether early intervention, ie, prior to onset of psychosis, with young people at clinical high risk could delay or prevent the development of frank psychosis and reduce functional impairment, in typical and diverse populations and clinical settings.

Methods

Details of the study design, implementation, assessment, psychosocial and pharmacological treatments, methods, and characteristics of the sample have been reported elsewhere.[20]

Early Identification

A community outreach and education program targeted to teachers, school, and college counselors; nurses and social workers; family and pediatric physicians; and psychiatric practitioners, clinics, and hospitals was undertaken at each site. The objectives were to: (*a*) increase knowledge of early warning signs for psychotic disorders, (*b*) increase appropriate referrals of youth at risk, (*c*) create and educate a system of professional and community member early identifiers, and (*d*) decrease barriers to early identification, including stigma.[13,21–23] The 6 study sites conducted extensive, ongoing community and professional education within their respective catchment areas, beginning in July, 2007. Enrollment began in September, 2007 and continued throughout the study period, ceasing on June 1, 2010.

Setting

In addition to the Greater Portland, ME, the other 5 sites were: Sacramento, CA; Ypsilanti, MI; Glen Oaks, NY; Salem, OR; and Albuquerque, NM.

Inclusion and Exclusion Criteria

Both positive and negative symptoms of psychotic disorders warranted referral for an assessment. All referrals of adolescents and young adults living in a site's catchment area were considered for eligibility. A phone screening interview with a trained referrer assessed whether eligibility was likely. If so, the young person and family were offered a full research and clinical assessment, which included the Structured Interview for Prodromal Syndromes (SIPS),[24] a component of which is the Scale of Prodromal Symptoms (SOPS) scale.[21,22] Inclusion criteria for the full study sample were established to recruit clinically lower risk (CLR), clinically higher risk (CHR), and very early first-episode psychosis (EFEP) participants. Those criteria were: (*a*) age 12–25, (*b*) living in the site's defined catchment area, and (*c*) having at least a 1 on any Positive Symptom Scale or a 3 on any Negative Symptom Scale of the SOPS. For instance, for Unusual Thought Content (the prodromal version of delusional ideas), a "1" would be rated if the person experienced "mind tricks" or a "sense that something is different." At a level "3" on Avolition on the Negative Symptoms Scale, the person would be manifesting "low levels of motivation to participate in goal-directed activities" or "impairment in task initiation and/or persistence." Youth having a current frank psychotic episode (a 6 on any Positive Symptom Scale for longer than 30 consecutive days) were excluded from the study and assisted in finding other treatment. Other exclusion criteria included: (*a*) a prior episode of psychosis or having received antipsychotic medication for 30 days or more at a dosage appropriate to treat a psychotic episode, (*b*) IQ less than 70, (*c*) permanent residence outside the catchment area, (*d*) not an English speaker or neither parent is an English speaker, (*e*) currently a prisoner in the criminal justice system, and (*f*) psychotic symptoms due to an acute toxic or medical etiology.

Intake and Follow-up Assessments

Independent research interviewers conducted all baseline and outcome assessments and were kept blind to treatment assignment. In addition to the SIPS interview, baseline assessment included the Global Assessment of Functioning (GAF)[23] and the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-I/CV).[25] Although onset of psychosis (ie, conversion) has been the focus of previous prevention studies, an additional emphasis of EDIPPP was on role and social functional outcomes.[13,26] Measures

included the Global Functioning: Social and Global Functioning: Role Scales (GF:S, GF:R)[27] and the Heinrichs Quality of Life Scale (QLS).[28] The Premorbid Adjustment Scale[29] and family history of mental disorder (Family History-Epidemiological)[30] were also collected at baseline. SIPS, GAF, GF:R and GF:S, and the Heinrichs QLS assessments were repeated at the 6-, 12-, and 24-month points; the SCID was repeated at the 24-month point.

Key outcome variables included (*a*) conversion to psychosis, (*b*) positive and negative symptoms, (*c*) first occurrence of a negative event, and (*d*) changes in social and occupational functioning. Conversion to psychosis was defined according to the Presence of Psychosis Scale (POPS) criteria: sustaining any 6 on the Positive Symptom Scale for 4 or more days per week, at least 1 hour per day for at least 30 days, or demonstrating seriously disorganized or dangerous behavior.[21] Negative events included conversion, relapse, psychiatric hospitalization, incarceration, suicide attempt, completed suicide, severe self-harm, rape, or assault.

Design

The effectiveness of EDIPPP's clinical intervention was tested using a Risk-based Allocation Design (also known as Regression-Discontinuity).[31,32] The range of symptoms among study subjects was reflected in 3 clinically meaningful subgroups: CLR, CHR, and EFEP. A person's baseline score on the primary outcome variable, psychotic symptoms, determined his or her treatment group. A participant was assigned to the treatment group if the sum Positive Symptoms score (P-score) was 7 or higher (CHR and EFEP subgroups), while those below that threshold were assigned to the CLR comparison group. The EFEP group was defined as those participants with psychotic symptoms of 30 days or less duration. A P-score of 7 was selected as the threshold to maximize the probability that a participant at high risk for psychosis would be assigned to the treatment group. Among sum scores of 6–11, 7 had a high sensitivity score of 0.91 and acceptable specificity of 0.78, the dependent variable being prodromal vs not prodromal by SOPS criteria. Adjusting statistically for baseline P-score removes the bias of initial differences between the treatment and comparison groups (see McFarlane et al[20] and the supplementary data for fuller explanation of methods and assumptions). Consequently, significant postintervention differences between groups can be attributed to the intervention itself, where the intervention effect is represented by a discontinuity in the regression lines at the cut-point. Compared with randomized assignment, this design has the ethical advantage that those who most need treatment are assigned to the treatment condition, while participants at lower risk may be protected from the adverse effects of unnecessary treatment. Youth who were assigned to the CLR comparison group were considered to be at lower risk for developing psychosis, but *not* risk free.

Treatment

Both the CHR and EFEP subgroups were provided FACT, regardless of level of psychosis (see supplementary data for additional detail on FACT).[14,15,24] Regarding psychotropic medication, if attenuated positive symptoms were present or emerged at or above a level of "4" on the Positive Symptom Scale of the SIPS, aripiprazole was offered within a dosage range of 1–15 mg. If that was not tolerated, another antipsychotic medication was offered; antipsychotic medications were discontinued altogether if severe side effects persisted. Mood-stabilizing, antidepressant, and anxiolytic medications were provided for specific symptoms of major mood or anxiety disorders, using current clinical practice guidelines. The principal modification to FACT to accommodate younger patients was to differentiate multifamily groups by age. Thus, 12- to 15-year olds were assigned to a "younger" multifamily group and those in the 17–25 range to an "older" group, while those in the 15–17 range were assigned on the basis of developmental age and family preferences.

The CLR group received monthly monitoring through a phone assessment conducted by a care manager. They could choose, but were neither encouraged nor assisted, to obtain treatment elsewhere in the community. As a subject protection measure, markedly increasing psychotic symptoms were treated with antipsychotic medication by the EDIPPP team until symptoms resolved.

Reliability Assessment, Blinding, and Treatment Fidelity

Reliability on the SOPS symptom scores, POPS, Heinrichs QLS, GF:S, and GF:R scales was measured among 37 raters' scores, compared with criterion scoring by an experienced psychiatric researcher.[20]

The interviewers were highly reliable: overall intraclass correlation for ratings of positive symptoms was .91, and the cross-site range was from .82 to .94. The reliability of the POPS criterion rating was also good ($\kappa = 0.68$; percent agreement = 93%). Possible bias of interviewers was assessed at each assessment point and analyzed to determine whether raters from a given site evaluated the patient differently than fully blinded raters from other sites. Among 35 pairs of ratings, correlations ranged from .90 for positive symptoms to .71 for disorganized symptoms and GAF; all were significant ($p < .001$). We concluded that the blinding process was adequate to prevent biased ratings.

After initial training and during ongoing supervision, clinicians' fidelity to the PMFG treatment component was assessed using the Competency Checklist.[33] This measure had been validated in a trial of the multifamily psychoeducation modality.[33] Fidelity was high (mean 85.6% of

checklist items, ranging from 82% to 90% across sites and increasing from 80% to 92% during the study) and above the threshold found to predict treatment effects.[33]

Analysis

All statistical tests were conducted on an "as assigned" basis. Two types of outcomes analysis were conducted: the effect of treatment on (*a*) time to first negative event and (*b*) clinical symptoms and psychosocial functioning. A preliminary test showed that the regression-discontinuity model fit significantly better when the CHR and EFEP subgroups were distinguished as 2 groups as opposed to pooled. Therefore, in all subsequent analyses, we used 2 df tests of significance for FACT intervention and included 2 indicator variables for CHR and EFEP subgroups. The effect of treatment on the time to first negative event was analyzed using Cox regression analysis[34] and hazard ratios (HRs) are reported with 95% CIs. The Cox proportional hazards assumption was tested for each model variable (baseline P-score, CHR, and EFEP indicators) and found acceptable (p = .0945, 0.1710, and 0.8816, respectively). The effect of treatment on symptom and functioning outcomes was analyzed using mixed-effects regression analysis as the primary and the Global Test Procedure (GTP) as a secondary analysis.[35,36] In the primary analysis, the main effects for the 2 intervention-group indicators (CHR and EFEP) tested the difference between those groups and the CLR comparison group, with emphasis on the 24-month outcome as the primary endpoint. Indicator variables for time points at which the outcome was observed were included in the model to allow estimation of the trajectory of response at 6, 12, and 24 months and to allow for a nonlinear trajectory; and visit-by-subgroup interaction terms were included in the model to allow for arbitrary changes in the intervention effect over these time points. The random intercept included in the mixed model allows for subject-to-subject variation in the overall level of the outcome variable across the follow-up period, though the trajectories through time were considered nonrandom and estimated through the fixed-effect time-point indicators.

The intervention-group assignment variable (the sum P-score) was entered as a covariate in all analyses, as is necessary in a regression-discontinuity analysis. For analyses of outcome variables other than the positive symptom scale, the baseline value of each of those variables was also entered as a covariate. Study site indicators were included to adjust for variations in outcomes by geographic location. The assumptions of parallel and linear regressions were tested and found acceptable (p = .64 for group-by-P-score interactions and p = .63 for quadratic P-score term). Previous analyses[20] had shown that after adjustment for the baseline value of the positive symptom variable, mean values of the other measures at baseline were essentially equivalent, demonstrating the ability of the regression discontinuity analysis subsequently to furnish unbiased estimates of treatment effects. For descriptive purposes only, we also report unadjusted mean change scores between baseline and 24 months with corresponding t tests.

The proportion of subjects who increased their participation in work or school from baseline to 24 months—(*a*) from participation in neither work nor school to either work or school, or both work and school or (*b*) from either work or school to both work and school—was compared using Fisher's exact test with 95% CIs for the OR comparing the CLR group with the combined CHR + EFEP groups.

A GTP was used to assess whether information from all 10 variables (SIPS, GAF, etc.) supports a positive intervention effect across the battery of outcome measures. The procedure used a fixed-effects model and estimated a single coefficient representing the treatment effect across the entire battery, while allowing other terms such as intercepts and time-point effects to vary from one outcome measure to another. The baseline assignment variable was included in all outcome measure equations to reflect the regression-discontinuity design. No adjustment for multiple comparisons due to the several measures considered is required because there is only a single intervention effect measured (one for each intervention subgroup); ie, the model assumes a single, constant treatment effect for each measure. The 10 measures were linearly transformed to a scale of 1–10 with reversal of direction for the 4 SIPS variables in order to put each outcome measure on a uniform scale in which the assumption of a constant intervention effect is plausible. The intervention effects for the CHR and EFEP subgroups (each vs the CLR group) were estimated assuming an unstructured covariance matrix in both variable space (10 measures) and time (3 time points). Details of the GTP model are contained in the supplementary data.

Results

Referrals and Participant Sample

Across sites, 520 cases were recommended for orientation, and 392 (75.4%) signed informed consent/assent and were oriented and assessed (figure 1). Of these, 337 (86.0%) met inclusion criteria and were allocated to treatment, 87 (25.8%) to the CLR comparison group, and 250 (74.2%) to the CHR + EFEP treatment group. Within the treatment group, 205 cases (82%) were designated as the CHR subgroup; 45 (18%) were found to have an early psychosis and were designated as the EFEP subgroup.

The study sample as a whole matched national racial, ethnic, and socioeconomic distributions rather closely (table 1).

Fifteen percent of the population was of Hispanic origin (compared with 15.1% nationally), while 9% was African-American (compared with 12.8% nationally):

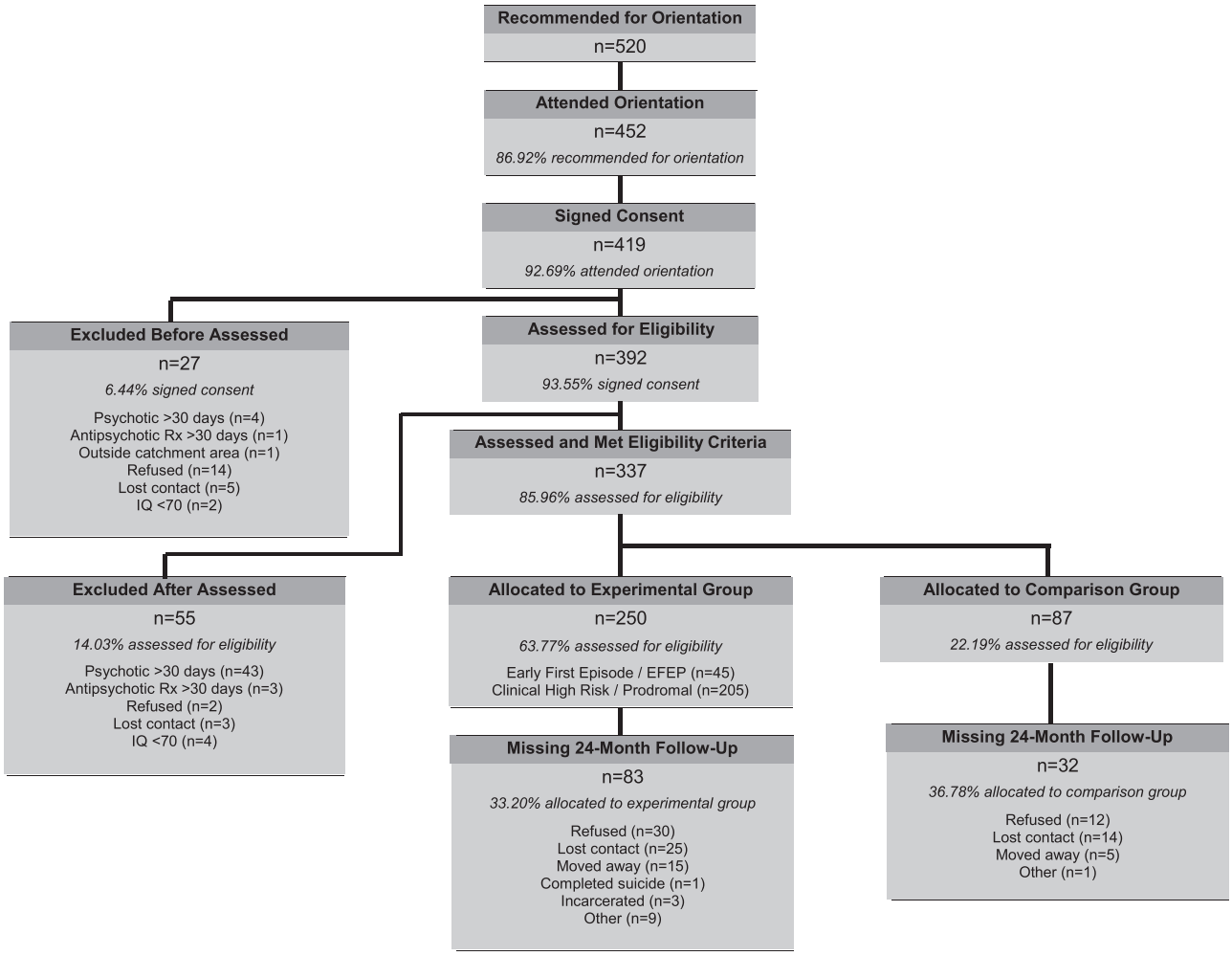

Fig. 1. Flow diagram of participant identification, recruitment, and entry into study.

males predominated, 60%–40%. The mean age for the CHR and EFEP subsamples—16.4 and 17.9 years, respectively—was in mid-adolescence, much younger than the usual age of onset for psychoses, usually found to be in the range of 20–25 years.[37] The between-groups differences in positive symptom scores reflected the expected levels, given that the patients were assigned to groups on the basis of this score. Although mean baseline GAF scores and diagnoses were also distributed across groups as expected, social and role functioning scores (ie, GF:R, GF:S, and QLS) were not, being nearly equal for all 3 conditions (see table 2). Eighty-four percent of the CHR and 78% of the CLR groups had current Axis I disorders; 49% of the CHR group had a major mood disorder, including 6% with bipolar disorder, and 42% had an anxiety disorder. Equal proportions of the CHR and CLR comparison subsamples had been hospitalized (26% vs 24%), received prior outpatient treatment (75% vs 72%), and had prior exposure to antipsychotic drugs (31% vs 27%). Eighty-four percent of the sample was in school or working, and this did not differ across all 3 assigned subgroups.

After treatment assignment at baseline, 76% of the CLR group sought and received a variety of treatments in the community, ie, not provided by the study clinicians. Sixty-three percent received individual therapy, 36% family therapy, 37% supported employment/education, 30% antipsychotic medication, 47% antidepressants, and 4.8% mood stabilizers. However, PMFG treatment was only received by the FACT cohort. Eighty percent of the CHR and 89% of the EFEP subgroups received the PMFG component of the FACT intervention.

Symptom Outcomes

For the primary outcome variable, positive symptoms, FACT was superior, for both CHR and EFEP subgroups, to the CLR comparison group treatment, controlling for baseline P-score and site (CHR + EFEP: $F = 25.32$, $p < .0001$; CHR: $\beta = -2.54$, SE = 0.86, $p = .0034$; EFEP: $\beta = -8.77$, SE = 1.40, $p < .0001$; see figure 2).

For negative symptoms, FACT was superior to the CLR comparison group, at the trend level for the CHR subgroup and significantly for the EFEP subgroup,

Table 1. Baseline Demographic and Clinical Characteristics of the Sample

		Comparison (n = 87)	Treatment (n = 250)			
Demographic Characteristics	Total (n = 337)	CLR (n = 87)	CHR (n = 205)	EFEP (n = 45)	Statistic	p
Age (mean, SD)	16.56 (3.28)	16.23 (3.18)	16.40 (3.30)	17.93 (3.10)	$F = 4.72$	.01
Female, n (%)	134 (40)	26 (30)	89 (43)	19 (42)	$\chi^2 = 4.80$	.09
Caucasian, n (%)	208 (62)	62 (71)	125 (61)	21 (47)	$\chi^2 = 7.70$	<.03
African-American, n (%)	31 (9)	5 (6)	16 (8)	10 (22)	$\chi^2 = 10.86$	< .01
Asian-American, n (%)	13 (4)	4 (5)	9 (4)	0 (0)	$\chi^2 = 2.09$	.35
Hispanic, n (%)	47 (15)	8 (9)	33 (17)	6 (16)	$\chi^2 = 2.66$	.27
Married, n (%)	2 (0.6)	1 (0.1)	1 (0.5)	0 (0)	$\chi^2 = 0.77$	.68
In school/working, n (%)	280 (83)	73 (84)	171 (84)	36 (80)	$\chi^2 = 0.40$	.82
Income (dollars)	40K–50K	50K–60K	40K–50K	30K–40K	$F = 3.53$	.03
Mother's age	45.79 (8.11)	46.09 (7.41)	45.96 (8.52)	44.53 (7.45)	$F = 0.54$	.58
Mother's years education	14.13 (2.53)	14.58 (2.32)	13.91 (2.69)	14.32 (2.06)	$F = 1.80$	.17
Father's age	49.20 (8.14)	51.16 (7.17)	48.52 (8.59)	47.81 (7.39)	$F = 1.83$	.17
Father's years education	14.68 (2.10)	14.71 (2.10)	14.76 (2.02)	14.13 (2.41)	$F = 0.65$	.53
SCID-IV diagnoses						
No diagnosis	47 (14%)	19 (22%)	28 (14%)	0 (0%)	$\chi^2 = 11.69$	<.01
Any Axis I, current or lifetime	284 (84%)	67 (78%)	173 (86%)	44 (100%)	$\chi^2 = 11.69$	<.01
Mood disorder	141 (42%)	32 (37%)	101 (50%)	8 (18%)	$\chi^2 = 16.56$	<.01
Bipolar	16 (5%)	2 (2%)	11 (5%)	3 (7%)	$\chi^2 = 1.73$	.42
Major depression	114 (34%)	27 (31%)	83 (41%)	4 (9%)	$\chi^2 = 17.06$	<.01
Anxiety disorder	120 (36%)	26 (30%)	84 (42%)	10 (23%)	$\chi^2 = 7.50$	<.03
PTSD	28 (8%)	1 (1%)	25 (12%)	2 (5%)	$\chi^2 = 10.89$	<.01
Obsessive–Compulsive Disorder	24 (7%)	3 (3%)	20 (10%)	1 (2%)	$\chi^2 = 5.61$	<.07
Generalized anxiety disorder	27 (8%)	5 (6%)	18 (9%)	4 (9%)	$\chi^2 = 0.85$	.65
Substance abuse	28 (8%)	8 (9%)	15 (7%)	5 (11%)	$\chi^2 = 0.82$	.67
Psychosis	44 (13%)	0 (0%)	3 (1%)	41 (93%)	$\chi^2 = 281.2$	<.01
Other	17 (5%)	5 (6%)	10 (5%)	2 (5%)	$\chi^2 = 0.12$	.94
Psychiatric and medical history						
Prior psychiatric hospitalization	103 (31%)	21 (24%)	52 (26%)	30 (68%)	$\chi^2 = 32.97$	< .01
Outpatient counseling	240 (72%)	62 (72%)	152 (75%)	26 (59%)	$\chi^2 = 4.48$	< .11
Prior head injury	44 (13%)	9 (10%)	29 (14%)	6 (13%)	$\chi^2 = 0.78$	.68
Prior antipsychotic medications	112 (34%)	23 (27%)	63 (31%)	26 (59%)	$\chi^2 = 15.32$	< .01

Note: The p values derive from 2 degrees of freedom tests. CHR, clinically higher risk; CLR, clinically lower risk; EFEP, early first-episode psychosis; PTSD, posttraumatic stress disorder; SCID-IV, Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version IV.

controlling for baseline P-score and site (CHR + EFEP: $F = 3.98$, $p = .02$; CHR: $\beta = -1.90$, SE = 1.15, $p = .099$; EFEP: $\beta = -4.61$, SE = 1.83, $p = .012$). For disorganized and general symptoms, the pattern was similar—significant differences for the CHR + EFEP cohort ($F = 12.49$, $p < .0001$ and $F = 6.65$, $p = .0015$, respectively), with significant effects for the EFEP subgroup ($\beta = -3.2345$, SE = 0.8499, $p = .0002$ and $\beta = -3.8298$, SE = 1.1900, $p = .0014$, respectively) and trend or nonsignificant differences for the CHR subgroup ($\beta = -0.6566$, SE = 0.5373, $p = .2226$ and $\beta = -1.4034$, SE = 0.7335, $p = .0567$, respectively; see table 2). Although mean differences in age, gender, race, and family income between treatment groups was in expected directions, further adjustment for these variables did not alter the intervention effects. With respect to improvement over time, the 4 prodromal symptom domains decreased significantly between baseline and 24 months in all 3 groups (see table 2 and figure 3).

Conversion, Relapse, and Negative Events

In the CHR subgroup, 6.3% experienced conversion to psychosis over 24 months, compared with 2.3% in the CLR group. All those in the EFEP subgroup remitted; 11% subsequently relapsed. The number of conversions was too low for a meaningful survival analysis, and a chi-squared test was not significant. Twenty-five percent of the CHR cohort experienced a first negative event, as did 22% in the CLR cohort and 40% in the EFEP group. Adjusting for the allocation variable, there was no difference in the distributions of time to first negative event for the CHR group relative to the CLR control group (HR: 0.94, 95% CI: 0.44–2.04), nor for the EFEP group (HR: 0.90, 95% CI: 0.25–3.20).

Functional and Global Outcomes

Compared with CLR, FACT had significantly better GAF outcomes for the CHR + EFEP cohort,

Table 2. Symptoms and Functional Scores Across Study Time Points

	CLR			CHR			EFEP		
Adjusted Scores[a]	Baseline	6 mo		Baseline	6 mo		Baseline	6 mo	
	(*n* = 87)	(*n* = 56)		(*n* = 205)	(*n* = 156)		(*n* = 45)	(*n* = 35)	
Outcome Variable	Mean (SD)	Mean (SD)	% Change[b]	Mean (SD)	Mean (SD)	% Change	Mean (SD)	Mean (SD)	% Change
(a) Adjusted clinical and functional outcomes at baseline and 6 mo									
SIPS Positive Symptoms[c]	15.5 (na)	9.74 (1.0)	−37.2	15.5 (na)	9.58 (0.4)	−38.2	15.5 (na)	1.80 (1.0)***	−88.4
SIPS Negative Symptoms[c]	14.5 (1.4)	11.03 (1.2)	−23.9	14.6 (0.6)	10.75 (0.5)	−26.2	13.6 (1.0)	6.14 (1.4)**	−54.8
SIPS Disorganized Symptoms[c]	7.7 (0.6)	4.10 (0.6)	−47.0	6.9 (0.3)	3.87 (0.3)	−43.4	7.6 (0.5)	0.97 (0.6)***	−87.2
SIPS General Symptoms[c]	11.6 (1.0)	7.08 (0.9)	−39.2	11.7 (0.4)	7.14 (1.1)	−38.8	11.2 (0.7)	3.82 (1.0)*	−65.8
Global Assessment of Functioning[c]	36.7 (2.8)	54.78 (3.1)	+49.3	37.9 (1.2)	51.84 (1.4)	+36.7	31.1 (2.1)	63.45 (3.5)	+104.0
GF:Role	4.6 (0.3)	6.21 (0.5)	+35.3	5.3 (0.2)	5.85 (0.2)	+10.2	5.0 (0.4)	5.84 (0.6)	+16.3
GF:Social	5.6 (0.3)	6.87 (0.3)	+23.1	5.9 (0.1)	6.70 (0.1)	+13.5	6.3 (0.2)	6.49 (0.3)	+3.2
QLS Instrumental	2.7 (0.4)	3.70 (0.4)	+38.2	3.1 (0.2)	3.75 (0.2)	+21.4	3.1 (0.3)	3.57 (0.5)	+13.6
QLS Interpersonal	3.3 (0.3)	4.05 (0.2)	+24.4	3.4 (0.1)	3.91 (0.1)	+15.0	3.6 (0.2)	4.14 (0.3)	+14.8
QLS Intrapsychic	3.6 (0.2)	4.04 (0.2)	+12.6	3.6 (0.1)	4.09 (0.1)	+13.7	3.6 (0.2)	4.36 (0.3)	+21.0
Adjusted Scores[a]	Baseline	12 mo		Baseline	12 mo		Baseline	12 mo	
	(*n* = 87)	(*n* = 57)		(*n* = 205)	(*n* = 147)		(*n* = 45)	(*n* = 36)	
Outcome Variable	Mean (SD)	Mean (SD)	% Change[b]	Mean (SD)	Mean (SD)	% Change	Mean (SD)	Mean (SD)	% Change
(b) Adjusted clinical and functional outcomes at baseline and 12 mo									
SIPS Positive Symptoms[c]	15.5 (na)	9.7 (1.0)	−37.6	15.5 (na)	10.24 (1.1)	−33.9	15.5 (na)	2.0 (0.8)***	−87.4
SIPS Negative Symptoms[c]	14.5 (1.4)	11.6 (1.2)	−20.2	14.6 (0.6)	11.46 (1.4)	−21.3	13.6 (1.0)	6.1 (1.0)**	−55.3
SIPS Disorganized Symptoms[c]	7.7 (0.6)	4.0 (0.6)	−48.4	6.9 (0.3)	4.05 (0.7)	−40.9	7.6 (0.5)	1.2 (0.4)***	−84.4
SIPS General Symptoms[c]	11.6 (1.0)	7.1 (0.9)	−39.1	11.7 (0.4)	6.77 (1.5)	−42.0	11.2 (0.7)	3.7 (0.8)*	−67.3
Global Assessment of Functioning[c]	36.7 (2.8)	53.5 (3.2)	+45.8	37.9 (1.2)	54.15 (3.6)	+42.8	31.1 (2.1)	63.8 (2.6)*	+105.0
GF:Role	4.6 (0.3)	6.1 (0.5)	+32.7	5.3 (0.2)	5.66 (0.6)	+6.6	5.0 (0.4)	6.2 (0.4)	+23.2
GF:Social	5.6 (0.3)	7.1 (0.3)	+27.0	5.9 (0.1)	7.25 (0.3)	+22.8	6.3 (0.2)	7.0 (0.2)	+10.7
QLS Instrumental	2.7 (0.4)	3.7 (0.4)	+38.5	3.1 (0.2)	3.87 (0.5)	+25.4	3.1 (0.3)	3.7 (0.3)	+17.4
QLS Interpersonal	3.3 (0.3)	4.0 (0.2)	+24.4	3.4 (0.1)	4.29 (0.3)	+26.4	3.6 (0.2)	4.4 (0.2)	+22.8
QLS Intrapsychic	3.6 (0.2)	4.1 (0.2)	+13.2	3.6 (0.1)	4.20 (0.3)	+16.6	3.6 (0.2)	4.5 (0.2)	+23.7

Table 2. Continued

Adjusted Scores[a]	CLR			CHR			EFEP		
	Baseline	24 mo		Baseline	24 mo		Baseline	24 mo	
	(n = 87)	(n = 55)		(n = 205)	(n = 134)		(n = 45)	(n = 33)	
Outcome Variable	Mean (SD)	Mean (SD)	% Change[b]	Mean (SD)	Mean (SD)	% Change	Mean (SD)	Mean (SD)	% Change
(c) Adjusted clinical and functional outcomes at baseline and 24 mo									
SIPS Positive Symptoms[c]	15.5 (na)	9.2 (1.0)	−40.5	15.5 (na)	6.7 (0.4)**	−56.9	15.5 (na)	0.5 (0.8)***	−97.1
SIPS Negative Symptoms[c]	14.5 (1.4)	10.3 (1.3)	−28.7	14.6 (0.6)	8.4 (0.6)**	−42.1	13.6 (1.0)	5.7 (1.0)***	−57.9
SIPS Disorganized Symptoms[c]	7.7 (0.6)	4.0 (0.6)	−48.2	6.9 (0.3)	3.4 (0.3)**	−51.0	7.6 (0.5)	0.8 (0.5)***	−89.7
SIPS General Symptoms[c]	11.6 (1.0)	5.9 (0.8)	−49.0	11.7 (0.4)	4.5 (0.9)**	−61.1	11.2 (0.7)	2.1 (0.6)***	−81.1
Global Assessment of Functioning[c]	36.7 (2.8)	56.3 (3.2)	+53.5	37.9 (1.2)	58.2 (1.5)**	+53.4	31.1 (2.1)	64.5 (2.6)**	+107.4
GF:Role	4.6 (0.3)	5.6 (5.7)	+21.3	5.3 (0.2)	6.0 (0.3)**	+13.6	5.0 (0.4)	5.9 (0.5)**	+17.4
GF:Social	5.6 (0.3)	6.9 (0.3)	+24.2	5.9 (0.1)	7.2 (0.1)**	+21.4	6.3 (0.2)	7.1 (0.2)**	+12.8
QLS Instrumental	2.7 (0.4)	3.7 (0.4)	+37.7	3.1 (0.2)	4.0 (0.2)**	+28.8	3.1 (0.3)	3.7 (0.4)**	+18.4
QLS Interpersonal	3.3 (0.3)	4.2 (0.2)	+28.9	3.4 (0.1)	4.4 (0.1)**	+28.5	3.6 (0.2)	4.4 (0.2)**	+21.7
QLS Intrapsychic	3.6 (0.2)	4.2 (0.2)	+18.2	3.6 (0.1)	4.4 (0.1)**	+23.3	3.6 (0.2)	4.6 (0.2)**	+28.2

Notes: na, not applicable; QLS, Quality of Life Scale; SIPS, Structured Interview for Prodromal Syndromes. Abbreviations are explained in the first footnote to table 1.
[a]Adjusted to baseline Positive Symptoms score of 15.5. Means are averages of site-specific adjusted means weighted by the total number of subjects within sites at baseline. Differences in adjusted means between groups equal the regression-discontinuity intervention coefficients. Outcome variables other than Positive Symptoms additionally adjusted to overall mean of baseline score, as follows: Negative Symptoms = 13.39; Disorganized Symptoms = 5.50; General Symptoms = 10.43; Global Assessment of Functioning = 41.20; GF:Role = 5.41; GF:Social = 6.12; QLS Instrumental = 3.27; QLS Interpersonal = 3.54; QLS Intrapsychic = 3.71.
[b]Percentage changes are calculated on exact means and may not agree with percentage changes in the table due to round-off. Positive Symptoms score is the sum of 5 items; Negative Symptoms score is the sum of 6 items; Disorganized Symptoms score is the sum of 4 items; General Symptoms Score is the sum of 4 items.
[c]Comparisons among 3 groups are jointly significant with 2 degree of freedom tests at p <.05 for all 4 SIPS outcomes and the Global Assessment of Functioning.
*p < .05, **p < .01, ***p < .001, all individual group comparisons are with respect to the CLR group.

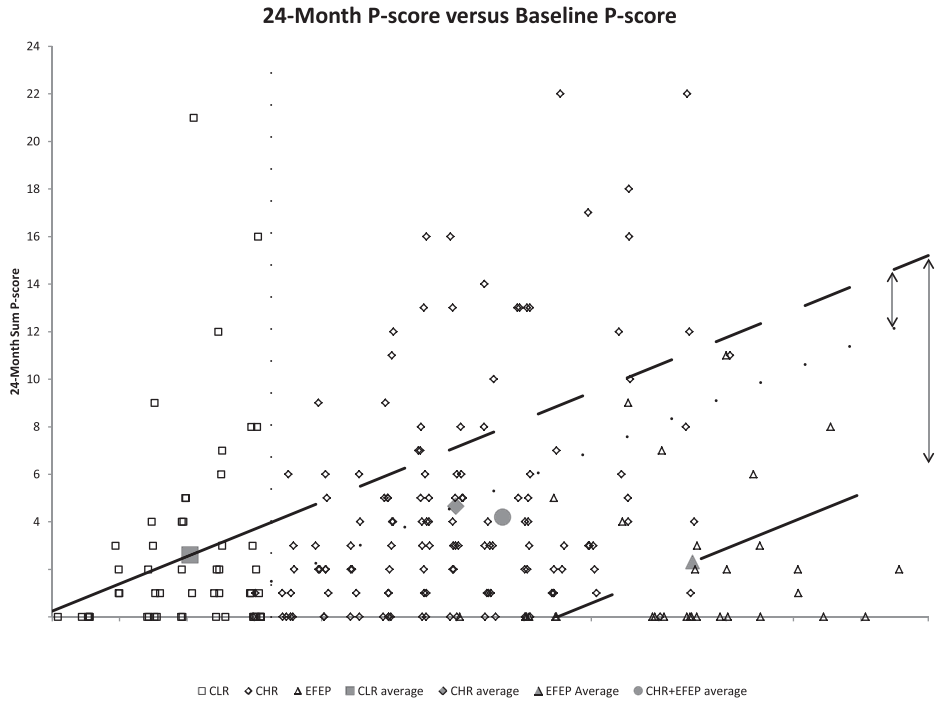

Fig. 2. Regression-discontinuity outcome. CLR vs CHR (small arrow), $p = .0034$. CLR vs EFEP (large arrow), $p < .0001$. Dashed line extending from solid line represents expected regression outcome in the range of CHR and EFEP baseline values, based on CLR values. Regression lines are plotted through group averages with parallel slopes estimated from the primary analysis model. Vertical arrow lengths approximate effect sizes. CHR, clinically higher risk; CLR, clinically lower risk; EFEP, early first-episode psychosis.

though not for the subgroups (CHR + EFEP, $F = 4.79$, $p = .0091$; CHR: $\beta = 1.86$, SE = 2.88, $p = .517$; EFEP: $\beta = 8.19$, SE = 4.64, $p = .079$). Unadjusted change scores at 24 months for GAF increased significantly in all groups, ending at the same level, though change scores over 24 months were larger in the FACT-treated subgroups (CLR: 60.2 [$\Delta = 10.65$; $t = 4.360$, $df = 53$, $p < .001$]; CHR: 59.0 [$\Delta = 17.47$; $t = 10.945$, $df = 131$, $p < .001$]; EFEP: 62.4 [$\Delta = 34.55$; $t = 10.497$, $df = 32$, $p < .001$]). Adjusting for the allocation variable, GF scores for both the EFEP and CHR subgroups did not differ significantly from CLR (see table 2). Both mean GF:Role and GF:Social unadjusted scores increased significantly from baseline to 24 months among CHR (GF:S: $t = 7.143$, $df = 118$, $p < .0001$; GF:R: $t = 2.202$, $df = 118$, $p = .030$) and EFEP (GF:S: $t = 3.832$, $df = 31$, $p = .001$; GF:R: $t = 2.371$, $df = 31$, $p = .024$) groups but not among the CLR group (ns, nonsignificant). The degree of change was greatest for the EFEP subgroup (GF:S: CLR, 5.1% vs CHR, 15.3% and EFEP, 22.3%; GF:R: 0.2% vs 12.1% and 23.6%, respectively; see figure 3).

Likewise, adjusting for the allocation variable, QLS outcomes for both the EFEP and CHR subgroups did not differ significantly from CLR. QLS unadjusted scores improved significantly from baseline in the CHR (QLS sum score: $t = 7.508$, $df = 127$, $p < .0001$) and EFEP ($t = 3.641$, $df = 28$, $p = .001$) groups, but not for the CLR group ($t = 1.402$, $df = 53$, $p = .167$).

Those in school or working at baseline and 24 months were, respectively, 88% and 79% in CLR compared with 84% and 83% in CHR + EFEP (see table 3).

Between baseline and 24 months, the proportion of subjects who increased their level of participation in work or school (from neither to one or both or from either to both) was 20.6% (35/170) in the CHR + EFEP cohort compared with 7.0% (4/57) in the CLR cohort. The OR comparing these 2 proportions was significant (OR: 3.44, 95% CI: 1.16, 11.0, $p = .025$). Those in school and working at baseline and 24 months were, respectively, 11% and 9% in CLR compared with 11% and 18% in CHR + EFEP.

Global Outcome

The GTP, incorporating all 10 clinical and functional variables, demonstrated FACT to be superior to CLR community treatment (CHR + EFEP: $F = 7.50$, $p = .0007$; CHR: $\beta = 0.38$, SE = 0.17, $p = .024$; EFEP: $\beta = 1.0510$, SE = 0.2787, $p = .0002$).

Attrition and Site Effects

Though the attrition rate was 34% at 2 years, there were no significant differences in baseline measures between completers and those with missing data at 24 months for any of the 10 outcome measures. The attrition rate was 27% at 6 months, 29% at 12 months, and 34% at 24 months. At each point, the completion

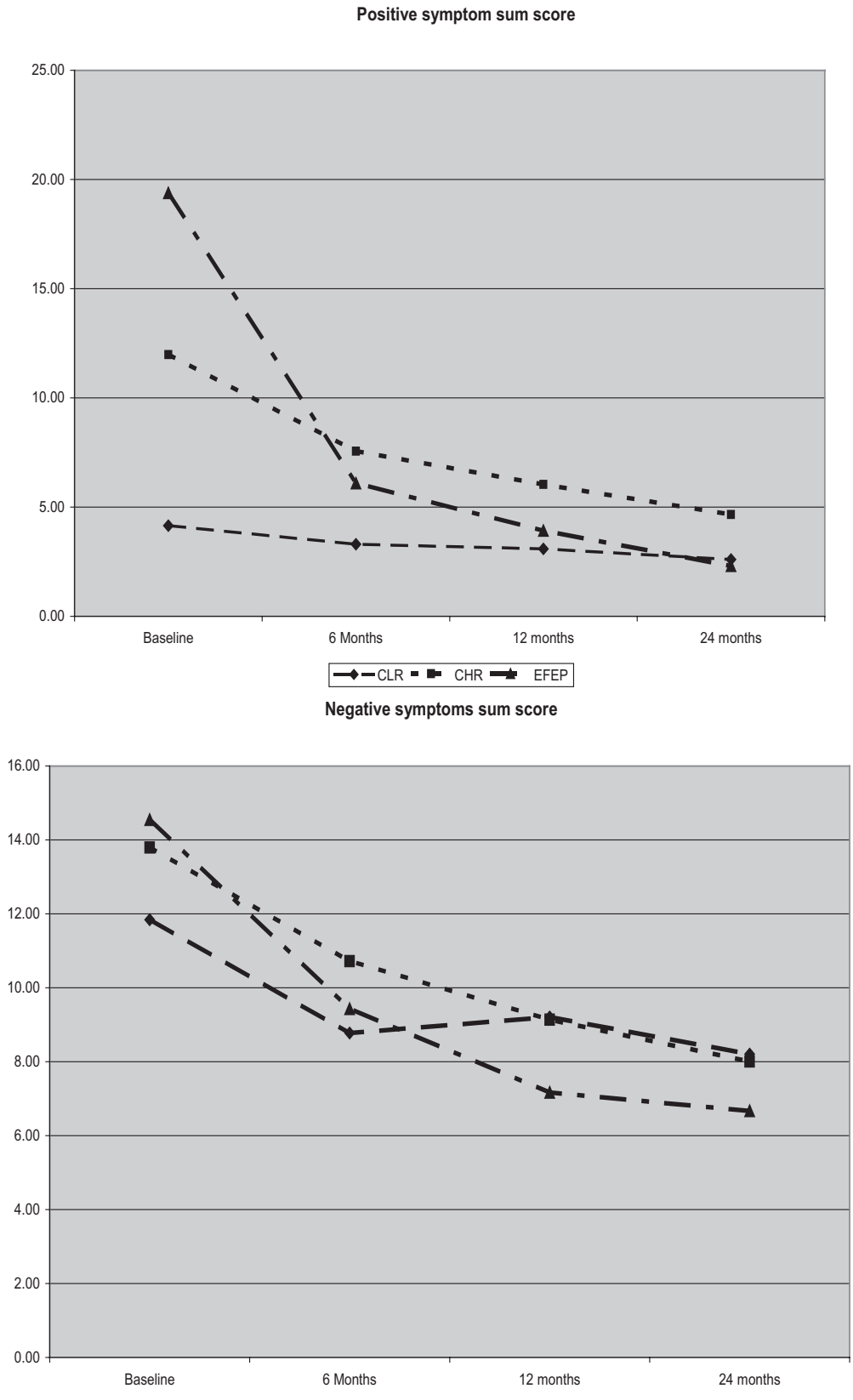

Fig. 3. Symptom and functional levels across study intervals. CLR, clinically lower risk, baseline $n = 87$. CHR, clinically higher risk, baseline $n = 205$. EFEP, early first-episode psychosis, baseline $n = 45$. Data points represent mean raw (unadjusted) scores for each subgroup at the respective assessment date.

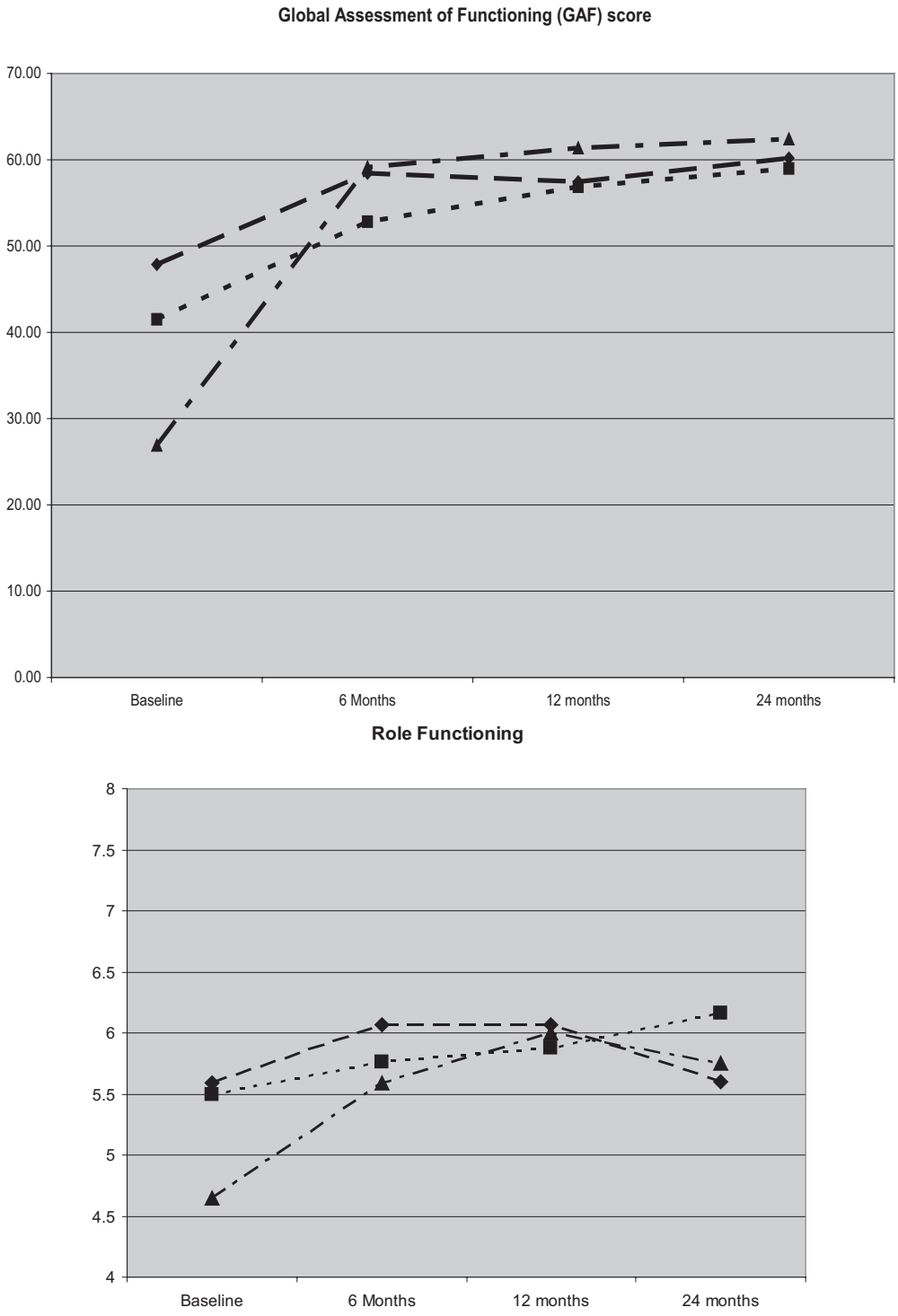

Fig. 3. Continued

rate was lowest for the CLR, higher for the CHR group, and highest for the EFEP group (eg, at 12 months, the respective percentages were 66%, 71%, and 80%). Site was significant as a main effect ($F = 4.29$ on [5,259] *df*, $p = .0009$). However, there was no significant site by group interaction.

Discussion

Summary of Findings

EDIPPP was established to test the effectiveness of early identification and intervention with FACT for youth at high risk of onset of an initial psychotic episode. Beyond

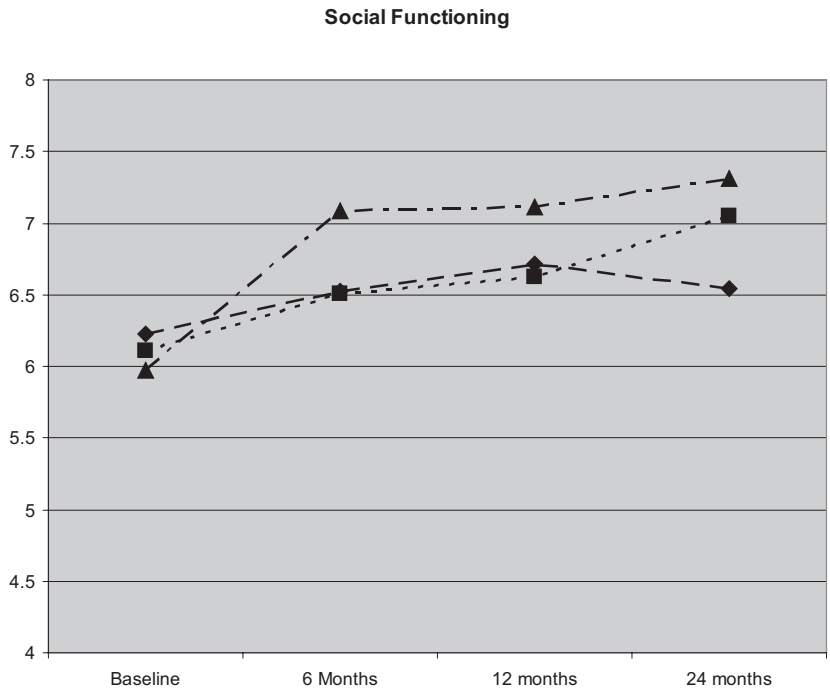

Fig. 3. Continued

Table 3. Participation in School and Work at Baseline and 24 mo

	In School Only		Working Only		Both Work and School[b]		Either or Both	
Group (*N*)[a]	Baseline	24 mo	Baseline	24 mo	Baseline	24 mo	Baseline	24 mo
CLR (57)	40 (70%)	30 (53%)	4 (7%)	10 (18%)	6 (11%)	5 (9%)	50 (88%)	45 (79%)
CHR (136)	96 (71%)	78 (57%)	3 (2%)	15 (11%)	16 (12%)	22 (16%)	115 (85%)	115 (85%)
EFEP (34)	23 (68%)	14 (41%)	2 (6%)	4 (12%)	2 (6%)	8 (24%)	27 (79%)	26 (76%)
CHR + EFEP (170)	119 (70%)	92 (54%)	5 (3%)	19 (11%)	18 (11%)	30 (18%)	142 (84%)	141 (83%)

Notes: Entries are frequencies (percentages). Abbreviations are explained in the first footnote to table 1.
[a]Includes only subjects with nonmissing school and work status.
[b]"Both" includes working and in school simultaneously.

testing clinical and functional outcomes in real-world settings, it also intended to assess feasibility of identification across whole communities and across a wide spectrum of the United States and its diverse populations. The participating sites educated key professionals in identification of early psychosis and provided FACT treatment for 250 youth. Treatment results included significant effects for reduction of positive, negative, disorganized, and general symptoms, increases in GAF, and superior overall improvement for FACT, compared to community care. Over the 24-month period, the FACT group increased their level of participation in work or school by 21% compared to 7% in the CLR group. Unexpectedly, effects for symptoms, GAF, and global outcomes were larger for the group having very early psychosis than in the clinical high-risk group.

Strengths and Threats to Validity

This study's strengths include the large and diverse sample, independent assessment by reliable raters blind to assignment, high fidelity for the key treatment component, successful equalization of lower and higher risk subsamples in the regression-discontinuity analysis, and dissemination of a comprehensive model to 5 other cities, 2 of which sites' staff had no prior experience with early psychosis. Caution is warranted because of the quasi-experimental design. Although it is considered the strongest of the quasi-experimental approaches, other possible interpretations of our findings could hold.[31] The supplementary data contain further discussion of the key assumptions underpinning the regression-discontinuity analysis and evidence in support of their validity. The attrition rate was 27% at 6 months, 29% at 12 months,

and 34% at 24 months. There were no significant differences between completers and noncompleters on any of the baseline demographic variables, and the regression analyses used data for each subject at any point at which they were assessed. Nevertheless, caution is indicated in generalizing the results.

Comparison to Other Studies

These results strengthen the evidence that early intervention to prevent onset or progression of psychosis in youth is effective, warrants expansion of practice, and constitutes an advance for public health. It may alleviate some of the ambiguity of results across studies, which has been cited as contrary evidence for efficacy.[38] More specifically, of the trials included in a recent meta-analysis, 3 had single-trial significant effects, 2 of which applied PMFG treatment of the type used in EDIPPP.[5,17,18] This study also strengthens the evidence for family intervention in early psychosis, continuing a record of efficacy in established schizophrenia and first-episode psychosis.[39–41] The conversion rate, 6.3% over 2 years, compares favorably to the 29% found in the most recent meta-analysis of untreated naturalistic or standard treatment control samples and the 7.6% 1-year rate in treated subsamples in randomized controlled trials to date.[5,22] For studies using the SIPS, the respective rates have been 26.4% and 10.3% at 6 or 12 months in 2 RCTs[12,42] and 35% at 30 months in the North American Prodromal Longitudinal Study naturalistic follow-up study.[43] It suggests that this approach is relevant to the United States, because only one of the treatment studies cited was conducted here.[5,12]

Conclusions

Early identification and intervention with FACT during the period prior to onset of frank and lengthy psychosis was found to be effective in improving symptoms, GAF, and overall outcomes in 6 US cities. The diversity of the sample and sites, the scale of the treatment effects, and the weight of efficacy evidence from the most recent meta-analyses suggests that early intervention, particularly prior to onset of frank psychosis, could lead to reduction in total burden of disease.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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This study was approved by the Maine Medical Center Institutional Review Board and the respective institutional review boards at each study site. After complete description of the study to the subjects, written informed consent was obtained prior to participating in assessment or treatment associated with this study. It was registered at ClinicalTrials.gov (#NCT00531518: http://www.clinicaltrials.gov/ct2/results?term=NCT00531518). This study was reported at the 166th Annual Meeting of the American Psychiatric Association, San Francisco, CA, May 22, 2013. The funders of the study have had no role in the study implementation, data collection, analysis, interpretation, or reporting of the results in this article. The authors are solely responsible for its contents. W.R.M., R.M., and S.L. disclose that they provide onrequest training and consulting to public and not-for-profit agencies implementing the clinical services being tested in EDIPPP. C.S.C. discloses that he has served as a consultant for Merck, Lilly, Pfizer, and Servier. The other authors have declared that there are no conflicts of interest in relation to the subject of this study.

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