Early Detection, Intervention, and Prevention of Psychosis Program: Rationale, Design, and Sample Description

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Abstract: *Objective*: To describe the rationale, design, intervention, and sample characteristics of the Early Detection, Intervention, and Prevention of Psychosis Program (EDIPPP), a multi-site study of the effectiveness of Family-Aided Assertive Community Treatment (FACT) in preventing the onset of psychosis in a nationally representative sample of at-risk young people.

Methods: Young people (age 12 - 25) and their families are assigned to a clinical high risk (CHR) group or a low risk group based on severity of positive symptoms of psychosis. Treatment families (CHR group) receive minimally 1 year of FACT and comparison families (low risk group) receive community care and monthly assessments. Initial between-groups differences on key variables are statistically controlled according to procedures of the regression discontinuity design (RDD), so any emerging between-group differences in outcomes can be attributed to treatments.

Results: 337 young people (mean age 16.6) were assigned to the treatment group (n = 250) or comparison group (n = 87). 86% of the CHR sample met DSM-IV criteria for an Axis I disorder. The RDD procedure successfully removed between-group differences in baseline scores on all but one of the key outcome variables.

Conclusion: Six sites located in 4 distinct regions of the U. S. have successfully collaborated in the initial phase of a large-sample test of FACT in preventing the onset of psychosis. Treatment outcome findings and other research initiated at individual sites will significantly increase our knowledge of the early phases of psychotic illness and the factors that may prevent it.

Keywords: Adolescents, psychosis, prevention, early intervention, risk, prodromal psychosis.

In 2006, the Robert Wood Johnson Foundation (RWJF) established the Early Detection and Intervention for the Prevention of Psychosis Program (EDIPPP) to test the effects of a preventive intervention specifically developed for young people at clinical high risk (CHR) of psychosis. The goal was to demonstrate that by intervening early with young people who show signs of a potential psychosis, the development of frank psychosis and functional impairment could be delayed or prevented. The outreach and intervention model selected for this national demonstration project was based on the Portland Identification and Early Referral (PIER) program (McFarlane, Cook, Downing, Verdi, Woodbury, & Ruff, 2010). PIER itself was established in 2000 as a population-wide system of early detection and preventive intervention in Greater Portland, Maine. To obtain referrals of individuals at risk of developing psychosis, the program conducted extensive community education about the early signs of psychosis and the potential benefits of early treatment, as has been done in similar early identification projects (Falloon, 1992; Johannessen, Larsen, McGlashan, & Vaglum, 2000; Phillips, McGorry, & Yung, 1999). Families of CHR young people who met study inclusion criteria, consented to study participation, and were randomly assigned to the treatment condition, received Family-aided Assertive Community Treatment (FACT), a package of interventions consisting of psycho educational multifamily group therapy, elements of assertive community treatment, supported education and employment, and psychotropic medication (Craig *et al*., 2000; Jorgensen *et al*., 2000; McFarlane, Stastny, & Deakins, 1992; McFarlane, 2001; McFarlane *et al*., 2010; O'Connell, Boat, & Warner, 2009). However, the sample on which the PIER Program was being tested was ethnically and racially homogeneous (Caucasian) and, with respect to statistical power, quite small. Thus, the ultimate goal of EDIPPP was to assess the value of wider dissemination of the indicated prevention approach based on a larger sample from cities of different size, greater cultural and ethnic diversity, and from different regions of the country. We report here characteristics of the study methods and design, results of the community identification and enrollment effort, reliability of key assessment measures, and description of the sample. The

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results of the intervention will be presented in a subsequent report after the completion of the trial.

To implement and manage a nationwide demonstration project based on the PIER program, the RWJF created a National Program Office (NPO) under the direction of the PIER Program's principal investigator (WRM). A National Advisory Committee consisting of distinguished scientists in psychiatry and prevention research was convened to guide the NPO in the selection of the study sites. In addition to the PIER Program, the five sites are: Sacramento, California (University of California, Davis); Ypsilanti, Michigan (Washtenaw Community Health Organization and University of Michigan); Glen Oak, New York (Zucker Hillside Hospital and Albert Einstein College of Medicine); Salem, Oregon (Mid-Valley Behavioral Care Network and Oregon Health Sciences University) and Albuquerque, NM (University of New Mexico). Institutional Review Boards for the Protection of Human Subjects approved the study at each site, and the overall (multi-site) study was approved by the IRB for Maine Medical Center. This study has been registered at ClinicalTrials.gov (#NCT00531518).

RATIONALE AND CLINICAL INTERVENTIONS

The PIER intervention is based on the idea that family involvement is a necessary component of psychosis prevention. Family interaction and functioning has been found to predict onset of schizophrenia-spectrum disorders (Goldstein, 1985; Tienari *et al*., 2004) and is a consistent predictor of relapse in schizophrenia, major depressive disorder, and bipolar disorder (Leff & Vaughn, 1985; Miklowitz, Goldstein, Nuechterlein, Snyder, & Mintz, 1988). The stress of family conflict likely functions as a trigger for an underlying vulnerability to psychosis (Neuchterlein & Dawson, 1984), whereas positive family relationships may actually buffer against other, extra-familial stressors (McFarlane & Cook, 2007; O'Brien *et al*., 2006). Consequently, family interventions, if successful in reducing family stress and promoting intra-familial support, can potentially prevent the onset of psychosis (Leff & Vaughn, 1985). The PIER intervention is the early psychosis-specific version of family-aided assertive community treatment (FACT), a key component of which is psycho educational multifamily groups (PMFGs). The efficacy of PMFGs in relapse prevention has been documented in established and first-episode psychotic disorders (Dyck *et al*., 2000; Fjell *et al*., 2007; McFarlane, Link, Dushay, Marchal, & Crilly, 1995; McFarlane *et al*., 1995; Melle *et al*., 2006; Petersen *et al*., 2005). PMFGs led to lower rates of relapse and higher rates of engagement, occupational functioning and retention in treatment (McFarlane *et al*., 1999; McFarlane, Dushay, Stastny, Deakins, & Link, 1996). In a recent randomized controlled trial, FACT led to a significantly lower rate of conversion to psychosis in a sample of people with schizotypal personality disorder, a diagnostic group considered to be at high risk for psychosis (Nordentoft *et al*., 2006).

The FACT model includes a multidisciplinary team comprised of a psychiatrist or nurse practitioner, nurse, occupational therapist, licensed clinical counselors (LCSW, LMFT, LCPC, or PhD), and an employment specialist. The FACT team provides proactive outreach and *in vivo* treatment that is family-based and client-centered. Each CHR treatment family is assigned a primary clinician and offered the following interventions: case management, supportive counseling, PMFG, supported employment and education, and medication management. The psycho-educational multifamily group attendance is an expectation of all treatment families while the intensity of other treatment interventions is dependent on the client's level of functioning and symptom acuity.

The FACT PMFG intervention includes engagement of the family, key supports, and the at-risk youth, an educational workshop, and ongoing multifamily groups. It reinforces the family's role in alleviating and buffering subjective, functional, and relationship stresses. The group emphasizes skill building and strategies for avoiding psychosis and coping with the vicissitudes of the CHR state, for both family members and the affected youth. The treatment protocol is described in greater detail elsewhere (McFarlane, 2001, 2002). A second component of FACT, supported education, includes collaboration with counselors and selected teachers at schools and colleges, advocacy and facilitation of informal accommodations or Individualized Education Plans (IEPs) when needed, as well as enhancement of individual skills. An educational and employment specialist (ES) provides this support, while an occupational therapist (OT) evaluates the student's functional and cognitive abilities and impairments and uses the information to guide intervention (Downing, 2006). For patients who are out of school and working, supported employment is provided by collaboration between the ES, the OT, the patient and the family (Drake, Becker, Biesanz, Wyzik, & Torrey, 1996; Rudnick & Gover, 2009).

The third component of FACT is to offer psychotropic medication based on individual patient need. If attenuated positive symptoms are present or emerge at a Scale of Prodromal Symptoms (SOPS: Miller *et al*., 2003) score of 4 or higher, aripiprazole is offered at 5-10 mg [or less in those under 70 kg (~.1 mg/kg)]. If akathisia or other extrapyramidal symptoms develop and cannot be managed, the patient is switched to quetiapine (100-600 mg.), ziprasidone (80-120 mg.), risperidone (0.5-4 mg.) olanzapine (2.5-7.5 mg.), or perphenazine (1–4 mg.). Dosages are then decreased to the lowest effective maintenance dose. Antipsychotic medication is discontinued altogether if intolerable side effects persist. The Abnormal and Involuntary Movements Scale (Guy, 1976) and Barnes Scales (Barnes, 2003) are administered every 30 days to all participants who are prescribed anti-psychotic medication; weight and laboratory indicators of metabolic syndrome are assessed at baseline, 2, 6, and 12 and 24 months. Mood-stabilizing, anti-depressant and anxiolytic drugs are used for specific symptoms of major mood or anxiety disorders, using current clinical practice guidelines.

METHODS

Participants

Recruitment

The goal of early intervention is to identify and treat young people at risk before they have received a psychosis-

related diagnosis. Consequently, psychiatric practitioners and clinics are not the best source for referrals. Targeted referrers are those who can identify and refer the young person to the prevention service before more serious symptoms emerge; for example, teachers, school nurses or social workers, and family physicians. Consequently, a community outreach and education program targeting these potential referral sources was undertaken at each site 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 (Johannessen, *et al*., 2000; Kretzmann & McKnight, 1993; McFarlane *et al*., 2010; Ruff, McFarlane, Downing, Cook, & Woodbury, in this issue). To facilitate contact with potential early-referrers, each EDIPPP site convened a steering council of community members representing various disciplines and interests. The purpose was to actively seek advice on the development of outreach messages and materials and to help identify, prioritize, and engage key identifying groups (Fiscus & Flora, 2001). The sites conducted extensive and ongoing community and professional education within their respective catchment areas, beginning in October, 2007 for 4-6 months, prior to enrolling participants early in 2008. Outreach efforts continued throughout the study intake period. Participant enrollment ceased on June 1, 2010.

Inclusion and Exclusion Criteria

Following education on the early warning signs of psychosis, potential referrers were encouraged to refer young people perceived to be at risk. Both positive and negative symptoms of psychotic disorders warranted referral for an assessment. All referrals of adolescents and young adults between the ages of 12 and 25 and living in the site's experimental catchment area were considered for eligibility. A phone screening interview with the referrer was used to assess whether eligibility was likely, in which case the young person and family were scheduled for a full research assessment. This assessment included the Structured Interview for the Prodromal Syndrome (SIPS: McGlashan *et al*., 2003), a component of which is the SOPS (Miller *et al*., 2003). The SOPS measures the severity of psychiatric symptoms as well as other criteria for determining the risk of psychosis. Young people with a current frank psychotic disorder of 30 days duration or longer, or who had a prior episode of psychosis, were excluded from the study and assisted in finding treatment elsewhere. In this category were young people who already had at least one positive symptom at a psychotic level (a 6 on any of the SOPS positive symptom scales) for 30 days or more or who had been receiving antipsychotic medication for 30 days or more at a dosage appropriate to treat psychotic illness. Other exclusion criteria included: (a) IQ less than 70, (b) permanent residence outside the experimental catchment area, (c) not an English speaker, and/or neither parent is an English speaker, (d) prisoner of the criminal justice system, (e) psychotic symptoms due to an acute toxic or medical etiology.

Intake and Follow-Up Assessments

Independent research interviewers conduct all baseline and outcome assessments and, to the extent possible, are kept blind to treatment assignment (e.g., patients and family members are asked not to reveal their treatment condition to the interviewers). In addition to the SIPS interview and SOPS symptom ratings, this assessment includes the Positive and Negative Syndrome Scale (PANSS). The PANSS is used to supplement the SOPS positive symptom scores, because the SOPS does not measure the upper range of severity for psychotic symptoms. The Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-I/CV: First, Spitzer, Gibbon, & Williams 1995) is administered to document Axis I schizophrenia spectrum, mood and selected other non-psychotic disorders. Although onset of psychosis has been the focus of previous indicated prevention studies, the emphasis of EDIPPP is on functional outcomes and on the course of cognitive impairments observed prior to onset (Cornblatt *et al*., 2003; Hawkins *et al*., 2004; McFarlane *et al*., 2010). Other variables measured at baseline include the Global Assessment of Functioning (GAF: Jones, Thornicroft, Coffey, & Dunn, 1995); the Global Functioning: Social and Role Scales (GAF: R, GAF: S: Cornblatt *et al*., 2007); the Heinrich Quality of Life Scale (QLS: Heinrichs, Hanlon, & Carpenter, 1984), and neurocognitive functioning as measured by the MATRICS Cognitive Consensus Battery® (Kern *et al*., 2008; Nuechterlein *et al*., 2008) and the AX-CPT (MacDonald, Pogue-Geile, Johnson, & Carter, 2003). Questionnaire measures are obtained to assess aspects of family expressed emotion (Kreisman, Simmens, & Joy, 1979; Kreisman & Blumenthal, 1995; McFarlane & Cook, 2007), family functioning (Cook, 2005, 2007), and family burden (Reinhard, Gubman, Horwitz, & Minsky, 1994). Comprehensive follow-up assessments using most of the intake assessment instruments are conducted when the patient reaches the 6 month, 12 month, and 24 month study points. Follow-ups of the neuropsychological measures and SCID diagnoses are obtained only at the 24 month point. Family assessment follow-up measures are obtained only at the 6 month assessment. Measures of premorbid adjustment were obtained from a modified version of the Premorbid Adjustment Scale (Cannon-Spoor, Potkin, & Wyatt, 1982; Van Mastrigt & Addington, 2002) and family history of mental disorder (Family History-Epidemiological: Lish, Weisman, Adams, Hoven, & Bird, 1995) are collected only at baseline.

Key outcome variables include (a) conversion to psychosis, (b) positive and negative symptoms, and (c) social and occupational functioning. Conversion to psychosis is operationalized in two ways. For patients entering the study with no SOPS positive symptom (P) scores above a 5, conversion is defined as a subsequent score of 6 on any of the P scales for any duration. A 6 on one of the P scales indicates loss of insight into one's psychotic symptoms (e.g., belief that hallucinated voices are real). The second operational definition of conversion includes the first group as well as patients who had level 6 psychotic symptoms at baseline, but where the duration and/or frequency of the symptoms did not meet diagnostic criteria for a psychotic

disorder. These patients are referred to as early first episode patients (EFEP). For this group, conversion is defined according to the Presence of Psychosis Scale (POPS) criteria (Miller *et al*., 2003). Specifically, a person must have a 6 on one of the positive symptom scales for at least an hour a day for four days a week over a period of 30 days or demonstrate seriously disorganized or dangerous behavior to meet this conversion criterion. Conversions are assessed at the earliest possible indication (e.g., a hospitalization) and then repeated at 7, 14 and 30 days or until remission, yielding duration of the conversion episode.

Design

The effectiveness of EDIPPP's clinical intervention is being tested using the Regression Discontinuity Design (Campbell & Stanley, 1966; Cook & Campbell, 1979; Judd & Kenny, 1981; Trochim, 2008). In this quasi-experimental design, a person is assigned to a study condition based on their baseline score on a well-measured quantitative variable, often the primary outcome variable. For EDIPPP this variable is the sum of the five SOPS scales measuring severity of psychotic symptoms (Miller *et al*., 2003). By controlling statistically for the scale score according to which participants are assigned to conditions (e.g., baseline positive symptom scores), initial differences between the treatment and comparison groups are eliminated. Consequently, post-intervention differences between groups can be attributed to the intervention itself. Because symptoms are rated on anchored scales with scores that range from zero to 6, the sum of the 5 positive symptom scales could range from zero to 30. A young person met criteria for assignment to the experimental condition if the sum was 7 or more on this measure. A cut-point score of 7 was selected to maximize the probability that a young person at clinical high risk for psychosis (i.e., a person who met criteria for attenuated psychotic symptoms) would be assigned to the treatment group. Young people below that threshold were assigned to the comparison group. Compared to a random assignment rule, this design has the ethical advantage that those people who need treatment the most are assigned to the treatment condition. Youth who are assigned to the comparison group are considered to be at *low risk* for developing psychosis, but not at *no risk*. They receive monthly monitoring through a phone assessment conducted by a care manager, and they may choose to obtain treatment elsewhere in the community. The amount of external treatment obtained by both treatment and comparison group participants is tracked *via* monthly assessments. By protocol, if a patient in the comparison group reaches the severe and psychotic level on one of the SOPS positive symptom rating scales, they are offered antipsychotic medication by the on-site EDIPPP psychiatrist.

Interviewer Training, Blinding, and Reliability Assessment

Across 6 sites, 37 interviewers were trained on the assessment instruments. At the beginning of the study, interviewers from the initial 5 sites attended a two-day training in Portland, Maine. Additional trainings have subsequently been held in Portland, Maine and Albuquerque, New Mexico. When trained raters left the study, their replacements were individually trained. Reliability on the SOPS symptom scores was measured by computing the intraclass correlation (ICC) of raters' scores with criterion scoring by an experienced psychiatric researcher. The criterion rater was originally trained on the SIPS by Dr. Tandy Miller, one of the developers of the SIPS. This rater had established reliability on the SIPS in prior studies (McFarlane *et al*., 2010; Miller *et al*., 2003). Ratings for the tests of inter-rater reliability were based on video tape and DVD recordings that included patients from both the present and past studies. Patient consent was obtained for the use of all recordings. Because assignment to treatment conditions was based on the sum of the SOPS positive symptom scales, the reliability of this score is of key importance to this study. Inter-rater reliability was also assessed for the Heinrichs Quality of Life scales (HQLS: Heinrichs, Hanlon, & Carpenter, 1984) and the Global Functioning: Social (GF:S) and the Global Functioning: Role (GF:R) scales (Cornblatt *et al*., 2007). The criterion measure for these ratings was a consensus score based on the ratings of three experienced raters, two of whom had major responsibility for the development of the GF:S and GF:R scales. In order to minimize the research time and burden for patients, the GF:S and GF:R ratings were based on information from the HQLS interview rather than the interview developed specifically for these scales. We also assessed the reliability of ratings of whether a patient was psychotic at baseline. This rating was made according to the Presence of Psychosis Scale (POPS: Miller *et al*., 2003). A POPS diagnosis of psychosis obtained after baseline serves as one of the criteria for conversion to psychosis.

In studies of psychosocial interventions, raters cannot be kept completely blind to the treatment condition of a patient or family. During interviews, some patients will inevitably mention factors that imply which group they are in, and patients may be observed in the waiting room prior to clinical appointments. In this study, assignment to treatment conditions was based on severity of positive symptoms. Consequently the treatment group assignment of extremely low scorers and extremely high scorers could be inferred from their SOPS ratings. However, every effort was made to keep interviewers blind to treatment conditions. Patients and family members were asked not to mention to the interviewers whether they were receiving treatment, and in all but one site, research offices were located in buildings other than those where treatment was provided. When all follow-up interviews have been completed, there will be an analysis to determine whether interviewers from the site where the patient was treated evaluated the patient differently than raters from other sites. This analysis should detect whether there was interviewer bias due to failure of the blind or other reasons.

Analysis

Two types of outcomes analysis are planned; the effect of treatment on (1) conversion to psychosis and (2) symptoms and functioning. Because conversion to psychosis is defined in two different ways, testing the effect of treatment on conversion will require two separate analyses. The first analysis will use the criteria that a person who at baseline had SOPS symptom severity scores of 5 or less and is

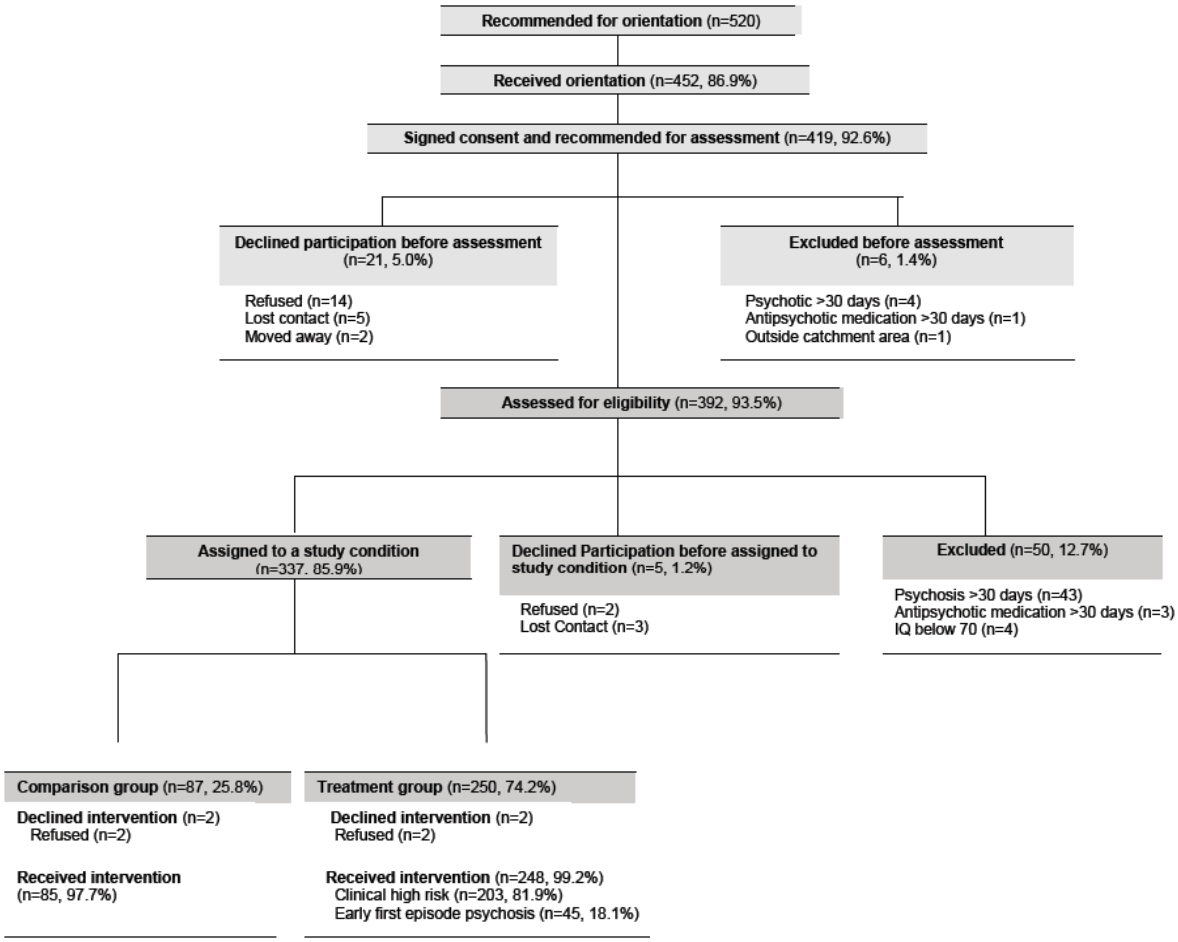

Fig. (1). Subjects identified, entered, assessed and assigned to treatment.

subsequently rated at the 6 level (severe and psychotic) has converted. Because the EFEP group consists of patients who met this criteria at baseline, they will be excluded from this analysis. According to the second definition of conversion, a person must have a 6 on one of the positive symptom scales for at least an hour a day for four days a week for 30 days or more (Miller *et al*., 2003). The EFEP patients do not meet this criteria at baseline, so the entire sample can be used for this analysis. The effect of treatment on the conversion to psychosis will be analyzed using Cox regression analysis (Cox, 1972). This analysis will test whether 'time to conversion' is longer, on average, in the treatment group vs. the comparison group. In other words, it tests whether treatment delays the onset of psychosis.

The effect of treatment on symptom and functioning outcomes will be analyzed using mixed-model regression analysis. The main effect for the experimental treatment will test the difference between groups at 24 months based on the marginal mean (i.e., the predicted mean that has been adjusted for the effects of the independent variables). A variable indicating the time point at which the outcome is observed (baseline, 6 months, 12 months, and 24 months) will be included in the model to estimate the trajectory of change. The statistical interaction of the treatment variable and the time of observation variable will test whether treatment affects the rate at which symptoms and functioning improve. A non-linear trajectory of change is expected due to regression to the mean. This will be modeled by adjusting the time of observation variable by the autocorrelation of the dependent variable (Kenny *et al*., 2004). Both the main effect of treatment and the treatment by time interaction effect test clinical change due to participation in the treatment group.

In the regression discontinuity analysis, for both the Cox regression and the mixed-model regression, the sum of the baseline positive symptom ratings will be a covariate. Inclusion of this variable controls for the between-groups difference at baseline produced by the treatment assignment rule (Campbell & Stanley, 1966; Cook & Campbell, 1979; Judd & Kenny, 1981). Other covariates will include any baseline variables that differ between treatment groups after adjusting for the baseline positive symptom score, study sites, and variables that are associated with missing data. A missing data analysis will use logistic regression analysis to identify possible predictors of missingness (Carpenter & Kenward, 2007). Secondary analyses will assess the influence of baseline symptom severity, neurocognitive impairment, family interaction, family history, and duration of prodromal symptoms on outcomes.

RESULTS

Referrals

Fig. (**1**) illustrates the procedural flow and resulting cases at key points in the enrollment process. Across sites, 520 cases were recommended for orientation after referral and joint screening by the primary identifier and an EDIPPP staff clinician. Of these, 452 (86.9%) were scheduled and met with staff for the orientation meeting. At the beginning of the meeting, patients and their family members were informed about the procedures and risk of the study and at least one family member (i.e. the patient) from 419 families (92.6%) signed informed consent and were recommended for assessment. Information obtained during the orientation meeting identified 6 patients (1.4%) that did not meet inclusion criteria and who were not assessed. An additional 21 patients (5.0%) declined participation before they could be assessed. At least partial baseline assessment information was collected on 392 patients (93.5%). The assessment identified 50 patients (12.7%) who did not meet inclusion criteria. Five patients (1.2%) declined participation before being assigned to a study condition, and 337 (65% of those youth initially recommended) were included in the study. Of these, 250 (74.2%) met criteria for assignment to the experimental treatment and 87 (25.8%), judged to be at lower risk of psychosis, were assigned to the control group. Of the former group, 45 (18.1%) were found to have a psychosis for less than 30 days (the EFEP group).

Inter-Rater Reliability

Intraclass correlations were calculated for the ratings of key outcome variables for each site separately. As can be seen in Table **1**, the interviewers were highly reliable. Of particular importance is the reliability of the SIPS positive symptoms measure, because this measure determined whether patients were assigned to the treatment or comparison condition. It is also a key outcome variable. The overall intraclass correlation for ratings of positive symptoms was .91, and the cross-site range was from .82 to .94. Another variable whose reliability is of key importance is the categorical rating of whether a patient is psychotic or not (POPS criteria). This variable distinguishes the EFEP group from patients who were excluded from the study due to their frequency and duration of psychosis. The reliability of this rating was also good (Kappa = .68; percent agreement = 93%).

Sample Characteristics

Positive symptom scores at baseline allowed separation into three psychosis risk categories: low-risk (less than sum score 7), clinical high risk (CHR; sum score 7 or higher, without a 6 on any of the positive symptoms) and early first episode psychosis (EFEP; any 6 for less than 30 days), as arrayed in Table **2**. The study sample as a whole matches national racial, ethnic and socioeconomic distributions rather closely, confirming a major goal of the study—to test the experimental treatment in a nationally representative CHR and EFEP sample. Using U.S. Census data for 2007, 15% of the sample was of Hispanic origin (compared to 15.1% nationally), while 9% was African-American (compared to 12.8% nationally). As in many samples involving psychotic disorders, males predominate, 60% to 40%. The mean age for the CHR and EFEP subsamples—16.4 and 17.9 years respectively—is in mid-adolescence, much younger than the usual age of onset for psychoses, usually found to be in the range of 20-25 years (Kirkbride *et al*., 2006). The mean family income ($40,000-$50,000 per year) approximates national data, except for the EFEP subsample, for whom this measure was found to be lower.

The between-groups differences in level of positive symptom scores reflects the expected levels given that the

Table 1. Inter-Rater Reliability for Key Measures

		Program						
Measure	**Statistic**	**PIER (ME)**	**RAP (NY)**	**M3P (MI)**	**EDAPT (CA)**	**EAST (OR)**	**EARLY (NM)**	**ALL**
SIPS Positive Symptoms	Intraclass r	.94	.88	.89	.93	.90	.82	.91
SIPS Negative Symptom	Intraclass r	.90	.93	.91	.91	.90	.92	.92
Heinrichs Negative	Intraclass r	.93	.96	.96	.98	.96	.93	.95
Heinrichs Interpersonal	Intraclass r	.91	.93	.96	.98	.96	.93	.95
Heinrichs Role	Intraclass r	.88	.96	.95	.96	.98	.94	.95
Heinrichs Objects	Intraclass r	.96	.97	.98	.99	.99	1.00	.98
GF: Social	Intraclass r	.67	.78	.79	.88	.79	.80	.81
GF: Role	Intraclass r	.88	.98	.86	.97	.95	.94	.94
Clinical High Risk vs. POPS	Percent Agreement	93	87	96	90	92	91	93

Table 2. Comparison of Demographic, Clinical and Psychosocial Characteristics Across Treatment Assignment and Risk Status Groups

			Treatment (n = 250)				
Demographic Characteristics	**Total (n = 337)**	**Control (n = 87)**	**Clinical High Risk (n = 205)**	**Early First Episode (n = 45)**	**Statistic**	**df**	***p***
Female, n (%)	134 (40%)	26 (30%)	89 (43%)	19 (42%)	$\chi^2 = 4.80$	2	.09
Caucasian, n (%)	208 (62%)	62 (71%)	125 (61%)	21 (47%)	$\chi^2 = 7.70$	2	<.03
African-American, n (%)	31 (9%)	5 (6%)	16 (8%)	10 (22%)	$\chi^2 = 10.86$	2	< .01
Asian-American, n (%)	13 (4%)	4 (5%)	9 (4%)	0 (0%)	$\chi^2 = 2.09$	2	.35
Hispanic	47 (15%)	8 (9%)	33 (17%)	6 (16%)	$\chi^2 = 2.66$	2	.27
Married, n (%)	2 (0.6%)	1 (0.1%)	1 (0.5%)	0 (0%)	$\chi^2 = 0.77$	2	.68
In School/Working, n (%)	279 (83%)	72 (84%)	171 (84%)	36 (80%)	$\chi^2 = 0.40$	2	.82
Age (mean, s.d)	16.56 (3.28)	16.23 (3.18)	16.40 (3.30)	17.93 (3.10)	$F = 4.72$	2, 334	.01
Income (dollars)	40K – 50K	50K – 60K	40K – 50K	30K – 40K	$F = 3.53$	2, 300	.03
Mother's Age	45.79 (8.11)	46.09 (7.41)	45.96 (8.52)	44.53 (7.45)	$F = 0.54$	2, 268	.58
Mother's Years Education	14.13 (2.53)	14.58 (2.32)	13.91 (2.69)	14.32 (2.06)	$F = 1.80$	2, 264	.17
Father's Age	49.20 (8.14)	51.16 (7.17)	48.52 (8.59)	47.81 (7.39)	$F = 1.83$	2, 147	.17
Father's Years Education	14.68 (2.10)	14.71 (2.10)	14.76 (2.02)	14.13 (2.41)	$F = 0.65$	2, 140	.53
SCID-IV Diagnoses							
No Diagnosis	45 (14%)	18 (21%)	27 (13%)	0 (0%)	$\chi^2 = 10.86$	2	<.01
Any Axis I	283 (86%)	67 (78%)	172 (86%)	44 (100%)	$\chi^2 = 11.46$	2	<.01
Mood Disorder	141 (43%)	32 (37%)	101 (50%)	8 (18%)	$\chi^2 = 16.56$	2	<.01
(1) Bipolar	16 (5%)	2 (2%)	11 (6%)	3 (7%)	$\chi^2 = 1.92$	2	.38
(2) Major Depression	114 (34%)	27 (31%)	83 (41%)	4 (9%)	$\chi^2 = 17.06$	2	<.01
Anxiety Disorder	120 (36%)	26 (30%)	84 (42%)	10 (23%)	$\chi^2 = 7.50$	2	<.03
(1) PTSD	28 (9%)	1 (1%)	25 (12%)	2 (5%)	$\chi^2 = 10.89$	2	<.01
(2) OCD	24 (7%)	3 (4%)	20 (10%)	1 (2%)	$\chi^2 = 5.61$	2	<.07
(3) Generalized Anxiety	27 (8%)	5 (6%)	18 (9%)	4 (9%)	$\chi^2 = 0.85$	2	.65
Substance Abuse	29 (9%)	8 (9%)	16 (8%)	5 (11%)	$\chi^2 = 0.57$	2	.75
Psychosis	43 (13%)	0 (0%)	3 (2%)	40 (91%)	$\chi^2 = 281.2$	2	<.01
Other	16 (5%)	4 (5%)	10 (5%)	2 (5%)	$\chi^2 = 0.23$	2	.99
Psychiatric and Medical History							
Prior Psychiatric Hospitalization	103 (31%)	21 (24%)	52 (26%)	30 (68%)	$\chi^2 = 32.97$	2	< .01
Outpatient Counseling	240 (72%)	62 (73%)	152 (75%)	26 (59%)	$\chi^2 = 4.48$	2	< .11
Prior Head Injury	44 (13%)	9 (10%)	29 (14%)	6 (13%)	$\chi^2 = 0.78$	2	.68
Prior Antipsychotic Medications	112 (34%)	23 (27%)	63 (31%)	26 (59%)	$X^2 = 15.32$	2	< .01

(Table 2). Contd…..

			Treatment (n = 250)				
Demographic Characteristics	**Total (n = 337)**	**Control (n = 87)**	**Clinical High Risk (n = 205)**	**Early First Episode (n = 45)**	**Statistic**	**df**	***p***
SOPS Symptoms							
Positive (mean, s.d)	2.19 (1.13)	.83 (.35)	2.40 (.69)	3.88 (.71)	$F = 387.212$	2, 334	< .01
Negative (mean, s.d)	2.23 (1.02)	1.97 (1.11)	2.30 (.95)	2.42 (1.04)	$F = 4.207$	2, 332	< .02
Disorganized (mean, s.d)	1.38 (.84)	.91 (.58)	1.39 (.76)	2.25 (.88)	$F = 48.250$	2, 331	< .01
General (mean, s.d)	2.62 (1.17)	2.24 (1.17)	2.66 (1.07)	3.19 (1.14)	$F = 11.005$	2, 332	< .01
Psychosocial Functioning							
GAF	41.20 (14.10)	47.87 (12.44)	41.50 (12.99)	26.91 (11.67)	$F = 40.668$	2, 333	< .01
Social (n = 319)	6.12 (1.43)	6.22 (1.58)	6.11 (1.33)	5.98 (1.57)	$F = 0.440$	2, 316	<.70
Role (n = 319)	5.41 (2.34)	5.59 (2.26)	5.50 (2.31)	4.65 (2.51)	$F = 2.678$	2, 316	<.08
Heinrichs Interpersonal	3.54 (1.36)	3.65 (1.51)	3.49 (1.29)	3.54 (1.36)	$F = 0.376$	2, 317	< .70

patients were assigned to groups on the basis of this score (see Table **2**); that is, the lowest level of positive symptoms is found in the low-risk group, the CHR group has higher scores, and the EFEP group has the highest scores, on average. Although mean baseline GAF scores were also distributed across groups as expected, social and role functioning scores were not, being nearly equal for all three conditions in both the social and role domains. Diagnostic distributions differed across the three levels of psychosis, reflecting expected differences in the EFEP subgroup. However, the CHR and control groups had high rates of current disorders; 50% of the CHR group had a major mood disorder, including 6% with bipolar disorder and 42% with an anxiety disorder.

A striking finding is that 86% of the CHR cases, and 78% in the lower-risk control condition, met SCID-IV criteria for an Axis-I psychiatric disorder at baseline. Equal proportions of the control and CHR subsamples had been hospitalized (24% vs. 26%), received prior outpatient treatment (73% vs. 75%), and had prior exposure to antipsychotic drugs (27% vs. 31%). It is also noteworthy that 83% of the sample was in school or working at the time of the baseline assessment, and this did not differ across assigned patient subgroups. This indicates a high level of functioning, despite the presence of significant psychological disturbance. Nonetheless, the more sensitive quantitative measures of symptoms and functioning reveal systematic differences across groups. This is expected given that patients were assigned to groups based on the severity of their psychotic symptoms.

The key consideration for the internal validity of this study is whether, after controlling for baseline level of psychotic symptoms, the groups are equated on key outcome variables at baseline. The differences between the treatment group (CHR and EFEP combined) and the lower-risk comparison group—after controlling for level of psychotic symptoms at baseline—are presented in Table **3**. Between-group differences between the *adjusted* (marginal) means for baseline values of 9 key outcome variables were tested. Only one of the 9 variables showed a between-groups difference, the SOPS Disorganized measure. In other words, controlling for baseline level of psychotic symptoms, the treatment and comparison groups were rendered essentially equivalent at baseline. It should be noted that when so many variables are tested, some will be significantly different across groups by chance alone, and this is as true for randomized trials as for this study. To ensure the equality of study conditions at baseline (i.e., internal validity), SIPS Disorganized scores will be included as a covariate in the outcome analyses.

DISCUSSION

This report presents the rationale, design, and patient characteristics for a relatively large clinical trial testing whether Family-aided Assertive Community Treatment (FACT) can delay or prevent the onset of psychosis in a high risk sample. A key goal in this trial is to determine whether the prevention intervention methods developed at the PIER Program can be implemented in other locations across the U.S. and in samples consisting of more diverse populations than those in Portland, Maine. Over 32 months in six sites and from a population of 2,798,000, 337 individuals at varying levels of risk for psychosis were identified, assessed, and assigned to control or treatment conditions.

The demographic and clinical characteristics are similar to those found in the Prevention through Risk Identification, Management, and Education (PRIME) project and the first phase of the North American Prodromal Longitudinal Study (NAPLS) project, and other multi-site North American samples. The mean age of our CHR subsample (16.4 years) is similar to that of patients in the PRIME study (17.7 years) and the NAPLS study (18.2 years). This confirms that early signs of risk of psychosis occur preponderantly in a mid-to-

Table 3. Baseline Differences between Control and Treatment Groups, Controlling for Sum of Positive Prodromal Symptoms

Clinical Variables	Marginal Means Control	Marginal Means Treatment	LSD[a]	*p*
Negative Symptoms	2.067	2.119	-0.052	.770
Disorganized Symptoms	1.195	0.912	0.284	.021
General Symptoms	2.428	2.347	0.081	.674
GAF	44.035	47.338	-3.303	.138
Global Functioning Social	6.104	6.353	-0.249	.341
Global Functioning Role	5.300	5.989	-0.689	.104
Heinrichs Interpersonal	3.568	3.678	-0.111	.653
Heinrichs Instrumental	3.409	3.687	-0.278	.361
Heinrichs Intrapsychic	3.837	3.829	0.007	.969

[a]The least significant difference test (LSD) does not control for multiple tests. Marginal means were estimated assuming a value of 7 (the cutpoint) for the sum of the SOPS positive symptom scales.

late-adolescent population, as opposed to a first-episode young adult population. This is also reflected in our sample by the 1.5 year difference between our CHR and EFEP subsamples. The somewhat younger age of patients in our CHR sample, compared to those in other studies, could reflect our emphasis on outreach to high school counselors and nurses and our encouragement of family involvement. Our EFEP subsample had an average age of 17.9, which further supports the conclusion that psychotic disorders very often originate during adolescence, in many cases during early adolescence. Our identification process produced a racially and ethnically representative sample, supporting the external validity and public health relevance of the outcomes and these methods for community education, identification and treatment.

It is important that equal proportions of the control and CHR subsamples met SCID-IV criteria for an Axis-I psychiatric disorder, had been hospitalized, received prior outpatient treatment, and had prior exposure to antipsychotic drugs. While this equivalence strengthens the study design, it also illustrates the current psychiatric morbidity of the at-risk population, regardless of its true risk for psychosis. We see this finding as strong support for offering treatment for emerging or current psychiatric conditions at this early stage of onset, even if psychosis may not be the eventual or inevitable outcome. It also suggests an explanation for a previous non-experimental study that found a superior effect for antidepressant, compared to antipsychotic, medication (Cornblatt *et al*., 2007). If such a large percentage of a CHR sample is currently affected by a mood or anxiety disorder, SSRI antidepressants and super-nutritional agents like omega-3 fatty acids seem worthy of further clinical testing to reduce the morbidity of the underlying condition, as well as preventing progression of psychosis (Amminger *et al*., 2010).

Consistent with our use of the regression discontinuity design, assignment to treatment vs. comparison conditions was based on the sum of 5 positive symptom scales included in the SOPS (Miller *et al*., 2003). Given that the level of treatment received depended on the rating of positive symptoms, it was of utmost importance that inter-rater reliability on this measure be high. A cross-site ICC of .91 clearly achieves this goal. Inter-rater reliabilities on the other key outcome variables were also in the good to very good range.

Based on the sum of the positive symptom scores, 87 patients were assigned to the comparison condition and 250 were assigned to the experimental treatment condition. Within the experimental group there were 45 patients for whom one of the 5 SOPS positive symptoms scales was rated at the level of 6, severe and psychotic, or who were judged to be seriously disorganized or dangerous. Baseline patient characteristics for this early first episode psychosis group have been broken out so they can be compared to the other groups. There are a number of between-groups differences in demographics, symptoms, diagnostic status, and measures of functioning. Most of these differences, however, can be explained by the method by which individuals were assigned to conditions. It is not surprising that the EFEP group consists of older patients, and because they are older and somewhat less likely to be living with parents, their household income is lower. It is even less surprising that there are between-groups differences on negative, disorganized, and general symptoms, as well as the GAF. All these measures are correlated with scores on the positive symptom scale. It is somewhat surprising that there are not more baseline differences between groups on the other measures of functioning (GF:S, GF:R, and the Heinrichs scales).

Some readers may be perplexed by the use of a comparison group that—by definition—has lower scores on the positive symptom measure (and other measures) than the treatment group. To be sure, an understanding of this feature of the regression discontinuity design requires an understanding of multiple regression analysis and the role of statistical control in producing equivalence between groups.

Nonetheless, as our results demonstrate, controlling for the measure which caused patients to be assigned to particular groups succeeds in producing adjusted baseline means (i.e., baseline marginal means) with non-significant between-group differences on variables that were originally significantly different. Next to the randomized controlled trial, there is no stronger design for inferring treatment effects. Importantly, the RDD can also be used for studies in clinical settings that do not allow the random assignment of patients to groups. If it can be demonstrated through a valid and reliable measurement that some patients are in need of less intensive (or different) services than others, then assignment to groups on the basis of this measure can be both an efficient means of managing limited resources and the basis for evaluations of treatment efficacy.

One consequence of using a predetermined cutpoint as the criteria for group assignment is that some patients will be miss-assigned. For example, by the criteria of prodromal syndrome (COPS: Miller *et al*., 2003), a person rated at level 3 on any one of the SOPS positive symptom scales would be categorized as prodromal. In our study, a person rated at level 3 on one of these scales may be rated at level 0 on the other positive symptom scales, for a total score of 3. Given our criteria of assigning patients to the treatment group who have a total score of 7 or more, this person would be in the "wrong" group. It is for this reason that our care managers, who made monthly calls to comparison subjects but who did not provide treatment, are given the responsibility of paying very close attention to these patients. In the event of a symptom exacerbation, such patients are administered an emergency assessment and can be followed by the onsite EDIPPP psychiatrist. Given some doubt in the precision of the prodromal designation (Yung *et al*., 2007), these patients do not appear to be at substantially increased risk of conversion. In a randomized control trial (RCT), half of the patients in the study would be assigned to the control group, but their treatment needs would be the same as for those assigned to the experimental group. Thus, compared to the RCT, the regression discontinuity design has the advantage of insuring that the great majority of patients with the greatest need for treatment are, in fact, assigned to the treatment condition.

When attempting to identify and recruit people at high risk of psychosis, yet prior to the first episode, it is inevitable that a number of cases will be identified who have, at least briefly, experienced psychosis already. In our study this group includes patients who receive a diagnosis of brief intermittent psychotic disorder (BIPS), which is considered part of the prodrome for schizophrenia (Miller *et al*., 2003). Our reasons for placing them in the EFEP group are both clinical and analytical. Clinically, we are trying to prevent young people from ever experiencing even a brief period when they lose insight about the unusual symptoms they are experiencing. Unlike progressions between other levels of ~~the~~ positive symptom, which appear to involve only quantitative differences in symptoms, loss of insight (i.e., transition to level 6) seems like a qualitative difference in the person's psychological state. Consequently, we are particularly interested in whether our treatment is able to delay or prevent this level of illness. For this reason, our analysis of conversion to psychosis will include "transition to a 6" as one outcome. Patients who begin the trial with a 6 on any of the positive symptom scales will necessarily be excluded from this analysis. However, a second analysis will use the POPS (presence of psychosis) criterion as the conversion outcome indicator. As noted previously, the person must have had a 6 on one of the positive symptom scales for an hour a day for 4 days a week for 30 days, or demonstrate seriously disorganized or dangerous behavior, to be counted as a conversion. Using this criterion, all patients included in the trial will be included in the conversion to psychosis outcome analysis.

Having a lower level criteria for conversion to psychosis is also consistent with a second focus of our intervention. This study is as much concerned with preventing loss of social and role functioning as in preventing the onset of psychosis. If the experience of psychosis has a negative effect on social and role functioning, then intervening at lower levels of psychotic symptoms is indicated. Clearly the discussion over whether antipsychotic medications should be used at these lower levels is important, but psychosocial treatments such as multifamily psycho educational group therapy (PMFG), supported education and employment, and cognitive behavioral therapy can be of use to just about anyone facing psychiatric symptoms at just about any level of severity. Each of these interventions can potentially mediate the effect of psychotic symptoms on social and role functioning.

In addition to determining whether FACT is effective in delaying or preventing psychosis, EDIPPP will also determine whether the incidence of first hospitalizations for psychosis was reduced in the six communities where this study is being conducted. The question will be addressed using an interrupted time-series design, another strong quasi-experimental design (Campbell & Stanley, 1966; Cook & Campbell, 1979; McDowall, McCleary, Medinger, & Hay, 1980). A separate paper will present the design, sample, and analysis for this aspect of EDIPPP. There are also planned analyses involving the MATRICS Consensus Cognitive Battery® and the AX Continuous Performance Task (AXCPT). These assessments will be used in analyses of the nature and course of cognitive deficits seen in individuals presenting at risk for psychosis as well as the predictive value of specific measures of cognition that have been linked to the function of the prefrontal cortex in relationship to the transition to psychosis among those who convert. Cognitive deficits will also be related to the course of social and role functioning in at-risk individuals, with particular interest directed at the extent to which problems in cognition account for social and role difficulties. Finally, an assessment of functioning in families of CHR youth will address the question of whether these families differ from non-clinical families in the patterns and dynamics of their relationships.

CONCLUSION

The EDIPPP study has demonstrated that ethnically diverse young people at clinical high risk for psychosis can be identified early, referred to an early intervention program, and accept treatment at clinics in different geographical

regions, and in both urban and rural settings, across the U. S. The characteristics of the sample indicates that the majority of these young people have significant psychiatric illness, even in our lower-risk comparison group. As with most illnesses, earlier treatment for these young people should produce better outcomes, especially given the alternative possibility of a long duration of untreated illness. EDIPPP has also demonstrated that the regression discontinuity design provides effective adjustments for baseline differences between treatment and comparison groups, while insuring that patients with the greatest need for treatment are assigned to the treatment condition. Thus, this design may provide the ethical advantage needed to encourage more clinics to engage in treatment outcome research.

ADDITIONAL CONTRIBUTIONS

The EDIPPP Group includes the authors of this article and the Deputy Directors and Co-Investigators at the sites: Andrea Auther, Ph.D., Bentson McFarland, M.D., Ph.D., Ryan Melton, L.C.P.C., Margaret Migliorati, M.S.W., Daniel Ragland, Ph.D., Tara Niendam, Ph.D., Tamara Sale, Melina Salvador, M. A., and Elizabeth Spring, R.N. The administration, research staff and study clinicians of the respective sites have provided abundant and highly competent effort to the conduct of the study, which has required an unusual amount of effort beyond their roles within their respective institutions. Special thanks to Deanna Williams for management of the multisite data set and Mary Verdi for coordinating cross-site interviewer reliability training.

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FINANCIAL DISCLOSURES

Dr. McFarlane discloses that he provides on-request training and consulting to public and not-for-profit agencies implementing the clinical services being tested in EDIPPP. Dr. Carter discloses that he has served as a consultant for Merck, Lilly, Pfizer and Servier and has received research funding from Glaxo Smith Kline. No other author or EDIPPP Group member has financial disclosures.

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