A Randomized Controlled Trial of Relapse Prevention Therapy for First-Episode Psychosis Patients

John F. M. Gleeson, Ph.D.; Sue M. Cotton, Ph.D.; Mario Alvarez-Jimenez, D.Clin.Psy.; Darryl Wade, Ph.D.; Donna Gee, M.Clin.Psych.; Kingsley Crisp, B.S.W., Dip. (systemic and family therapy); Tracey Pearce, M.Clin.Psych.; Belinda Newman, B.A. (Hons.); Daniela Spiliotacopoulos, B.A., Postgrad. Dip. Psychology; David Castle, M.D.; and Patrick D. McGorry, M.D., Ph.D.

Objective: Patients with first-episode psychosis are responsive to acute-phase treatments, but relapse rates are high. This study aimed to evaluate the effectiveness of a psychosocial treatment designed to prevent the second episode of psychosis compared with standardized early psychosis care.

Method: In a randomized controlled trial, conducted at the Early Psychosis Prevention and Intervention Centre and Barwon Health, Australia, a multimodal individual and family cognitive-behavioral therapy for relapse prevention was compared with standardized case management within a specialist early psychosis service. Patients aged 15 to 25 years with a first episode of a DSM-IV psychotic disorder were recruited between November 2003 and May 2005. The main outcome measures were the number of relapses and time to first relapse.

Results: Forty-one first-episode psychosis patients were randomly assigned to the relapse prevention therapy (RPT) and 40 to standardized case management. At the 7-month follow up, the relapse rate was significantly lower in the therapy condition compared to treatment as usual ($p = .042$) and time to relapse was significantly longer for the RPT condition ($p = .03$). The number needed to treat was 6 over 7 months.

Conclusions: Interim findings suggest that RPT provided within a specialist early psychosis program was effective in reducing relapse in early psychosis when compared with standardized early psychosis case management.

Trial Registration: www.anzctr.org.au Identifier: ACTRN12605000514606

J Clin Psychiatry 2009;70(4):477–486

Received May 22, 2008; accepted July 1, 2008. From the Department of Psychology (Dr. Gleeson), ORYGEN Youth Health Research Centre, Centre for Youth Mental Health (Drs. Cotton, Alvarez-Jimenez, and McGorry and Mss. Newman and Spiliotacopoulos), and Department of Psychiatry (Dr. Castle), University of Melbourne, and Northwestern Mental Health Program, Melbourne Health (Dr. Gleeson), Australia; University Hospital Marqués de Valdecilla, Department of Psychiatry, School of Medicine, University of Cantabria, Santander, Spain (Dr. Alvarez-Jimenez); and ORYGEN Youth Health (Drs. Wade and McGorry and Mss. Gee and Pearce and Mr. Crisp) and St. Vincent's Hospital (Dr. Castle), Melbourne, Australia.

This study was funded by an unrestricted grant from Eli Lilly via the Lilly Melbourne Academic Psychiatry Consortium. Eli Lilly had no involvement in the design or conduct of the study; in the collection, management, or analysis or interpretation of data; or in the preparation of the manuscript. Eli Lilly reviewed the manuscript prior to submission but did not suggest any alterations. In addition, the study was supported by the Colonial Foundation and a Program Grant from the National Health and Medical Research Council of Australia, grant ID 350241; neither body had any involvement in any aspect of the study or manuscript. Furthermore, support was provided by Marqués de Valdecilla Public Foundation–Marqués de Valdecilla Research Institute, Santander, Spain (Dr. Alvarez-Jimenez).

Presented at the World Psychiatric Association International Congress, Dec. 1, 2007, Melbourne, Australia.

Dr. McGorry has received grant/research support from Eli Lilly. Drs. Gleeson, Cotton, Alvarez-Jimenez, Wade, and Castle; Mss. Gee, Pearce, Newman, and Spiliotacopoulos; and Mr. Crisp report no additional financial or other relationships relevant to the subject of this article.

Corresponding author and reprints: John F. M. Gleeson, Ph.D., University of Melbourne Psychology Clinic, 14-20 Blackwood St., The University of Melbourne, Victoria, 3010, Australia (e-mail: jgleeson@unimelb.edu.au).

First-episode psychosis (FEP) can represent a major crisis in the lives of patients and their carers. Fortunately, treatments for acute-phase FEP are efficacious for most patients. Trials of antipsychotic medications for acute FEP have shown a high rate of improvement in positive psychotic symptoms in response to both conventional and atypical antipsychotics.[1–4] For example, Schooler and colleagues[2] reported that three quarters of 555 FEP patients enrolled in a randomized controlled trial comparing risperidone and haloperidol showed initial clinical improvement on treatment with low doses of the respective

medications after 3 months of treatment. Emsley and colleagues[3] recently reported that 70% of 462 FEP patients who participated in their study obtained scores of mild or lower on key items of the Positive and Negative Syndrome Scale during a 2- to 4-year follow-up period.

However, the prognosis for FEP patients is less positive after their response to acute-phase treatments. Naturalistic follow-up studies of FEP patients up to 5 years after treatment commencement have indicated that 70%–82% of FEP patients experience a relapse of positive psychotic symptoms by 5 years.[1] The prevention of the first relapse is a critical goal of treatment because psychotic relapse poses a significant threat to the well-being and psychosocial recovery of the patient and increases the risk of persistent symptoms developing.[5] Positive and negative symptoms of psychosis have also been found to account for a significant proportion of the variance in burden for carers with a relative diagnosed with schizophrenia,[6] so it is likely that the first relapse of positive symptoms increases family burden after FEP. Moreover, relapse is likely to interfere with the social and vocational development of FEP patients, which may affect life-long outcomes.[7] Economic analyses have indicated that the cost of treatment of relapsing psychosis is 4 times that of stable psychosis.[8]

Psychosocial interventions have demonstrated a preventive effect in reducing relapse for patients diagnosed with schizophrenia.[9–11] However, the evidence for effective adjunctive psychosocial interventions specifically for relapse prevention in remitted FEP patients is limited.[12] Given the high rates of relapse in this group, evaluations of novel psychosocial interventions specific for FEP patients are warranted. Recent evidence suggests that specialist FEP programs, which combine early case detection and timely commencement of phase-sensitive biopsychosocial treatments for patients and their families,[13] may significantly reduce the risk of relapse and readmission to psychiatric inpatient units when compared with standard adult mental health services.[14,15] However, there are no published trials that have compared the effectiveness of cognitive-behavioral therapy (CBT) for relapse prevention with treatment in accordance with contemporary treatment guidelines for FEP.[16] The current study—the Episode II trial—is the first to undertake such a comparison. The aim of this article is to evaluate, via a randomized controlled trial, a multimodal individual and family-based psychosocial intervention designed to prevent relapse following remission from FEP in young people aged 15–25 years compared with treatment as usual (TAU) in a specialist FEP service. The primary hypotheses are that a FEP relapse prevention treatment (RPT), including both individual and family-based CBT within a specialist FEP program, will be associated with a significantly lower relapse rate and a significantly longer time to relapse compared to TAU. The secondary hypotheses are that RPT will be associated with improved adherence to medication, improved psychosocial functioning, and improved quality of life, compared to TAU.

METHOD

Design

The Episode II trial comprised a randomized controlled effectiveness trial (Australian Clinical Trials Register Number 12605000514606) and compared a combined family and individual CBT for relapse prevention (RPT) with TAU within 2 specialist FEP services, which included standardized case management for early psychosis. Antipsychotic medication and group-based psychosocial interventions were background treatments in both conditions. The study included a total of 6 assessment time points spanning a 2.5-year follow-up period. This article reports on the end of the experimental treatment, or 7 months' follow-up.

Participants

Patients from the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne and from Barwon Health, Victoria, Australia, were recruited between November 2003 and May 2005. The study inclusion criteria were a diagnosis of a first episode of a DSM-IV[17] psychotic disorder, less than 6 months of prior treatment with antipsychotic medications, age 15 to 25 years inclusive, and remission on positive symptoms of psychosis. Remission was defined as 4 weeks or more of scores of 3 (mild) or below on the subscale items hallucinations, unusual thought disorder, conceptual disorganization, and suspiciousness on the expanded version of the Brief Psychiatric Rating Scale (BPRS).[18,19] Exclusion criteria were ongoing active positive symptoms of psychosis, severe intellectual disability, inability to converse in or read English, and participation in previous CBT trials.

Eligible patients and their families were invited to participate by the project research assistant as soon as possible after they reached remission on positive psychotic symptoms. After informed consent was obtained by the research assistant, baseline measures were completed with the patient and their family before random assignment to TAU or to RPT. Random allocation was managed by the study statistician (S.C.) using computer generated random numbers. The trial coordinator (D.W.), who was informed of the outcome of randomization via e-mail and telephone, informed the treating team and, in relevant cases, the research therapists of the outcome. The statistician was not involved in any way with either the assessments or the treatments. The research assistants (B.N. and D.S.) were kept blind to treatment allocation via the following mechanisms: (1) regular and frequent

reminders were sent to all clinical staff regarding the importance of the blind; (2) the research assistant reminded participants of the importance of the blind at the commencement of each research interview; (3) the research assistant was excluded from all clinical discussions regarding participants; and (4) the research assistant was forbidden from reading participants' medical records.

Patients provided additional optional consent for participation of their family members. The study was approved by the Northwestern Mental Health and the Barwon Health Research and Ethics Committees. All potential participants who met inclusion criteria were given the opportunity to participate. All participants provided informed consent and were assessed as competent to do so. Participants could withdraw consent at any time.

Treatments

Patients randomly assigned to TAU continued with their routine treatment, via the EPPIC program or Barwon Health, which was coordinated via an outpatient case manager and outpatient consultant psychiatrist, with access to home-based treatment and a range of psychosocial interventions.[20] During the course of the trial, the caseload of a full-time case manager was approximately 35. A case management manual provided detailed guidelines for TAU.[20] All case managers were orientated to early psychosis treatment guidelines and were provided with a range of additional therapy manuals and standardized psychoeducation materials. Fidelity was managed via approximately fortnightly one-to-one supervision for all case managers with a senior clinician and via weekly multi-disciplinary case review meetings, which all outpatient staff were required to attend. At entry into the service, all families were routinely offered access to a brief family psychoeducation group, and EPPIC families had access to a family peer support service.

Patients randomly assigned to RPT were introduced to their individual research therapist, who additionally adopted the role of outpatient case manager for the duration of their treatment at EPPIC. All patients randomly assigned to RPT continued their follow-up treatment with their outpatient psychiatrist and had access to home-based treatment and group interventions as indicated. The research therapists functioned as fully integrated members of the EPPIC treatment team and as visiting therapists to Barwon Health, which allowed the effectiveness of RPT to be evaluated within existing "real-world" clinical roles. Key differences between TAU and RPT included (1) the shared, written individualized formulation regarding relapse risk; (2) the systematic and phased approach to relapse prevention via a range of cognitive behavioral interventions; (3) the parallel individual and family sessions focused on relapse prevention; and (4) supervision specifically focused on relapse prevention. The manualized individual therapy intervention comprises 5 phases of therapy underpinned by a CBT framework and informed by previous psychotherapy trials conducted at EPPIC[21,22] and by the collaborative therapy framework developed at the Mental Health Research Institute, Melbourne, Australia.[23]

The aim of the first phase of the individual therapy was to engage the patient and assess their extent of recovery and individual risk for relapse (e.g., substance use, medication noncompliance, stressful life events, and comorbid anxiety and depression). In the second phase, the formulation and agenda for therapy were agreed on with the patient and summarized in a letter, which was read out to the patient—a technique informed by cognitive analytic therapy.[24] The therapeutic agenda was intended to address those risk factors that were identified in the initial assessment. The third phase focused on increasing awareness for the risk of setbacks and how to minimize them, and in the fourth phase, the potential early warning signs of relapse were identified and a relapse plan formulated.[25] The fifth phase included optional modules that addressed issues of nonadherence to treatment, substance abuse, coping with stress, and comorbid anxiety and depression. Selection of the intervention modules to be undertaken during this therapy phase was based on the collaborative formulation and therapy agenda accomplished after initial assessment. The final phase included a review and termination, and a booster session. The individual therapy phases were provided within a 7-month therapy window, approximately fortnightly in order to match the recommended frequency of sessions in TAU.[20]

The family intervention, also manualized and provided by a trained family therapist, was informed by cognitive behavioral family therapy for schizophrenia[26,27] and family interventions for FEP.[28] The phases of family therapy were assessment and engagement, assessment of family communication, burden and coping, psychoeducation regarding relapse risk, and a review of early warning signs and documentation of a relapse prevention plan. Intensive communication skills training and problem solving were undertaken when indicated. Treatment manuals are available on request.

Fidelity to therapy was ensured via the following procedures: (1) treatment manuals detailing intervention techniques were used throughout therapy; (2) clinical supervisors (J.F.M.G. and D.W.) provided feedback to research therapists in weekly clinical supervision sessions in which relevant clinical issues were addressed and the implementation of individual and family therapy were coordinated; and (3) audio taping of individual therapy sessions was implemented for all participants who provided additional consent. A representative sample of sessions (N = 46) stratified by therapy phase was rated on a specifically designed fidelity measure (Relapse Prevention Therapy-Fidelity Scale, RPT-FS), which included subscales for each phase of therapy.[29] The RPT-FS was

designed to assess both treatment adherence and therapist competence as defined by the intervention manual.[29] Therapy sessions were randomly ordered and coded by the study statistician (S.C.) and rated by 2 clinical psychologists (M.A.-J. and D.W.), who scored all tapes according to the RPT-FS subscales and made blind judgments of which phase of therapy was being carried out. Sessions were correctly allocated in 43 of the 46 audiotapes rated.[29] Copies of the RPT-FS and rating manual are available on request.

Assessment Procedures

Research assistants (B.N. and D.S.) who were blind to treatment allocation administered all assessment measures. The Structured Clinical Interview for DSM-IV (SCID), including the modules for psychoses, mood disorders, and substance use disorders,[30] and SCID Axis II Personality Disorders[31] were completed at baseline. All diagnostic interviews and available clinical material were reviewed in regular diagnosis consensus meetings attended by 3 of the researchers (J.F.M.G., D.W., B.N.). Symptom measures included the Montgomery-Asberg Depression Rating Scale (MADRS),[32] a measure of the severity of depressive symptoms; the BPRS[19]; and the Scale for the Assessment of Negative Symptoms (SANS).[33] Medication was not controlled for, but was treated as a background factor. Medication adherence was measured via the Medication Adherence Rating Scale (MARS).[34] Premorbid IQ was estimated via the Wechsler Test of Adult Reading.[35] A range of psychosocial functioning measures included the Premorbid Adjustment Scale,[36] the Social and Occupational Functioning Assessment Scale,[37] and the Australian version of the World Health Organization Quality of Life Assessment-abbreviated version (WHOQOL-BREF).[38] Assessment of substance abuse included the WHO Alcohol, Smoking, and Substance Involvement Screening Test, a brief screening instrument for substance abuse,[39] and the Alcohol Use Disorders Identification Test, a more comprehensive measure of patterns of problematic alcohol and substance use.[40] Two single-item, clinician-rated severity scales for alcohol and drug use, respectively, and the Substance Dependence Scale were also included.[41]

Data on hospital readmissions as well as hospital days were obtained from clinical files and hospital records. At time 1 (baseline), hospital days was considered a valid calculation because patients were in remission on entering the study. The research fellow of the study (M.A.-J.) collected all admission data in order to keep assessors blind to treatment assignment.

Face-to-face interviews were completed at 6 time points, including baseline (time 1) and follow-up at months 7 (time 2), 12 (time 3), 18 (time 4), 24 (time 5), and 30 (time 6). At time 2, all efforts were made to recontact study participants by the study research assistants. However, because of the well-known clinical challenges in following up this complex population, there was an allowance made for a maximum of a 3-month window in which assessments were undertaken. Additional interim telephone calls were also undertaken at 6-week intervals in order to complete ratings on the psychosis items of the BPRS to enable prospective assessment of psychotic relapses and psychotic exacerbations.

Relapse definitions were based on criteria utilized in a series of studies at the University of California, Los Angeles.[42] Thus, criteria for relapse include increases from 3 (mild) or below to ratings of 6 or 7 (severe and very severe) on any 1 of the 3 BPRS items: (1) unusual thought content, (2) hallucinations, and (3) conceptual disorganization, with a duration criterion of 1 week. Significant psychotic exacerbations following remission were defined by an increase from 3 or below (for at least 1 month) on all 3 items followed by a score of 5 (moderate) on any of the 3 items plus a 2-point increase on 1 of the other items (again with the addition of a duration criterion of 1 week), or a rating of 5 on any 1 of the 3 items for at least 1 month. Significant psychotic exacerbation following persisting psychotic symptoms (or following a partial remission) was defined as either an increase in 1 item of at least 2 points to a rating of 6 or 7, or a 1-point rise to a rating of 6 or 7 with an accompanying 2-point rise on 1 of the other 2 relapse items, for a period of at least 1 week. Consistent with previous studies of relapse, exacerbations were combined with relapses in the final categorization of patient outcome.[43]

Twenty cases were selected at baseline for the purpose of checking interrater reliability on the total score of the BPRS, with an independent research assistant making simultaneous ratings. The intraclass correlation coefficient for the BPRS total score was 0.93, which indicates good interrater reliability.

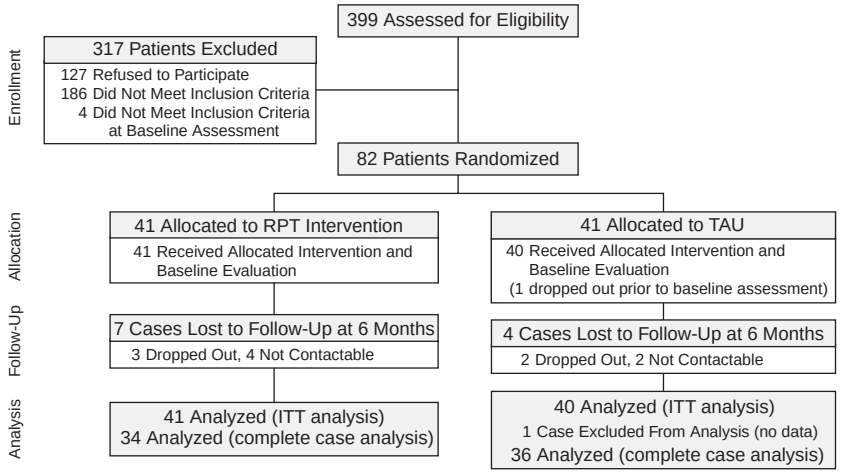
Data verification was conducted on the baseline data of 22 randomly selected cases by having a research fellow (M.A.-J.) reenter the data. The error rate was 0.12% at baseline and 0.08% at time 2, with the a priori acceptable rate set at 0.50%.

Statistical Analyses

Data screening was conducted to determine the presence of outliers, nonnormality, heterogeneity of variance, and heteroscedasticity. In the case that data deviated from the normal Gaussian curve, logarithmic (plus a constant where 0 was valid data value) transformations were conducted. Descriptive statistics are presented for untransformed data.

Baseline characteristics (i.e., demographic, premorbid, diagnostic, symptomatic, and functional) of the RPT and TAU groups were contrasted using χ^2 for categorical dependent variables and the independent samples t test for dependent variables measured on a continuous scale.

Figure 1. Patient Participation Through Various Stages of the Study



Abbreviations: ITT = intent-to-treat, RPT = relapse prevention therapy, TAU = treatment as usual.

All primary and secondary analyses were based on the intent-to-treat paradigm. The main outcome measures were the number of relapses and time to relapse, which was based on the time to the first relapse. Group differences in the proportion of relapses at time 2 were examined using the χ^2 test. Kaplan-Meier analysis was used to estimate survival (i.e., no relapse) in the RPT and TAU groups. The Cox-Mantel log rank test, the Breslow test (generalized Wilcoxon), and the Tarone-Ware test were used to investigate for significant differences between the survival curves of these 2 groups.

For the secondary measures, both last-observation-carried-forward (LOCF) and complete case analyses were conducted. Given that LOCF has its disadvantages, a combined method for data analysis is advantageous.[44] Last-observation-carried-forward analysis was conducted even though some patients did not have posttreatment data and the descriptive statistics for LOCF are presented in the tables. Analysis of covariance (ANCOVA), with time 1 scores as the covariate and group (RPT and TAU) as the independent variable, was used to analyze differences between the groups on secondary outcome measures. Partial η^2 was reported as a measure of effect.

RESULTS

Participant Characteristics

Of 399 patients assessed for eligibility, 213 were initially deemed eligible, and 86 of these patients consented to participate in the study. Of these 86 patients, 4 were found to not meet entry criteria as determined by the presence of the positive symptoms at the baseline assessment. One hundred twenty-seven eligible patients refused to participate. The main reasons for refusal included the following: not interested in the study (N = 80), did not want to change case manager (N = 41), already a participant in another research project (N = 3), and other (N = 3). Thus, 82 patients were randomly assigned to the RPT and TAU groups. Consenters and nonconsenters did not differ significantly with respect to gender and age distributions, marital status, highest level of education, weeks in the service, levels of unemployment, and living arrangements (i.e., percent living with family). Consenters, however, were more likely to have a diagnosis of schizophrenia (consenters, 33.3%, 27/81; nonconsenters, 11.5%, 13/113; χ^2 = 13.74, df = 1, $p < .001$) or psychotic disorder not otherwise specified (consenters, 29.6%, 24/81; nonconsenters, 7.1%, 8/113; χ^2 = 17.42, df = 1, $p < .001$), and less likely to have a diagnosis of schizophreniform disorder (consenters, 11.1%, 9/81; nonconsenters, 38.9%, 44/113; χ^2 = 18.40, df = 1, $p < .001$), than nonconsenters.

Randomization and Attrition

At baseline, 1 participant dropped out after randomization in the TAU group, and no data were available for this patient (thus, n = 41 in RPT and n = 40 in TAU). Of the 81 participants for whom baseline data were available, 77 were recruited from EPPIC and 4 were recruited from Barwon Health. At time 2 (7 months, or end of therapy), there were 7 cases lost to follow-up in the RPT group (3 dropped out; 4 missed assessments) and 4 additional cases lost to follow-up in the TAU group (2 dropped out; 2 missed assessments). The rate of dropout/missing in the 2 groups did not differ significantly (χ^2 = 0.07, df = 1, p = .390), and valid data were available for 36 cases in the RPT group and 34 cases in the TAU group (Figure 1).

Baseline Characteristics

The mean duration of time elapsed from patient entry into the service to entry into the study was 29.96 weeks (SD = 13.32 weeks). Table 1 details the demographic and premorbid characteristics and diagnostic features of the 2 treatment groups. There were no significant differences between the 2 groups with respect to any of the demographics variables. The groups did not differ in terms of the type of psychotic disorder, the prevalence of comorbid depressive disorders and substance use disorders, baseline symptom measures (i.e., BPRS, SANS, and MADRS), rates of medication use, or days of hospitalization prior to entering the study (see Table 2 for descriptive statistics).

Table 1. Premorbid and Baseline Demographic and Diagnostic Characteristics of the Relapse Prevention Therapy (RPT) and Treatment as Usual (TAU) Groups

Variable	Total Cohort (N = 81)	RPT (n = 41)	TAU (n = 40)	p Value[a]
Demographic				
Age, mean (SD), y	20.1 (3.1)	20.1 (2.9)	20.1 (3.2)	.968
Gender, male, % (n)	63.0 (51)	65.9 (27)	60.0 (24)	.585
Marital status, never married, % (n)	95.1 (77)	92.7 (38)	97.5 (39)	.317
Still attending school, % (n)	29.6 (24)	26.8 (11)	32.5 (13)	.576
Total number of years of education completed, mean (SD)				
Still at school	12.0 (2.0)	11.8 (1.6)	12.2 (2.3)	.413
Not at school	12.0 (1.7)	12.0 (1.7)	12.2 (1.7)	.746
Employment, % (n)[b]				
Unemployed	43.2 (35)	51.2 (21)	35.0 (14)	.141
Full-time paid work	12.3 (10)	12.2 (5)	12.5 (5)	.967
Part-time paid work	4.9 (4)	2.4 (1)	7.5 (3)	.293
Casual paid work	14.8 (12)	12.2 (5)	17.5 (7)	.502
Lives with family, % (n)	76.5 (62)	73.2 (30)	80.0 (32)	.468
Premorbid, mean (SD)				
Duration of untreated psychosis, d[c]	384.8 (567.9)	401.1 (529.1)	368.6 (611.9)	.904[d]
Full scale IQ[e]	91.3 (27.8)	90.8 (24.6)	91.8 (30.9)	.875
Premorbid Adjustment Scale[f]				
Childhood	0.2 (0.2)	0.2 (0.1)	0.3 (0.2)	.299
Early adolescence	0.3 (0.2)	0.3 (0.1)	0.3 (0.2)	.594
Late adolescence	0.3 (0.2)	0.4 (0.2)	0.3 (0.2)	.527
General	0.4 (0.2)	0.3 (0.2)	0.3 (0.1)	.785
Average	0.3 (0.1)	0.3 (0.1)	0.3 (0.2)	.658
Psychotic diagnoses, % (n)				
Schizophrenia	33.3 (27)	34.1 (14)	32.5 (13)	.875
Schizophreniform	11.1 (9)	7.3 (3)	15.0 (6)	.271
Schizoaffective disorder	4.9 (4)	7.3 (3)	2.5 (1)	.317
MDE with psychotic features	6.2 (5)	2.4 (1)	10.0 (4)	.157
Bipolar disorder	4.9 (4)	7.3 (3)	2.5 (1)	.317
Delusional disorder	1.2 (1)	0.0 (0)	2.5 (1)	.308
Substance-induced psychotic disorder	3.7 (3)	4.9 (2)	2.5 (1)	.571
Psychotic disorder NOS	29.6 (24)	34.1 (14)	25.0 (10)	.367
Other diagnoses, % (n)				
MDE without psychotic features	23.5 (19)	17.1 (7)	30.0 (12)	.170
Dysthymic disorder	8.6 (7)	9.8 (4)	7.5 (3)	.718
Past history of MDE	22.2 (18)	26.8 (11)	17.5 (7)	.313
Borderline personality disorder[g]	7.6 (6)	10.0 (4)	5.1 (2)	.414
Antisocial personality disorder[h]	10.4 (8)	10.5 (4)	10.3 (4)	.969
Alcohol abuse/dependence	24.7 (20)	24.4 (10)	25.0 (10)	.590
Cannabis abuse/dependence	51.9 (42)	61.0 (25)	42.5 (17)	.096
Opioid abuse/dependence	7.4 (6)	9.8 (4)	5.0 (2)	.414
Cocaine abuse/dependence	3.7 (3)	2.4 (1)	5.0 (2)	.542
Hallucinogen abuse/dependence	14.8 (12)	12.2 (5)	17.5 (7)	.502
Amphetamine abuse/dependence	18.5 (15)	17.1 (7)	20.0 (8)	.735

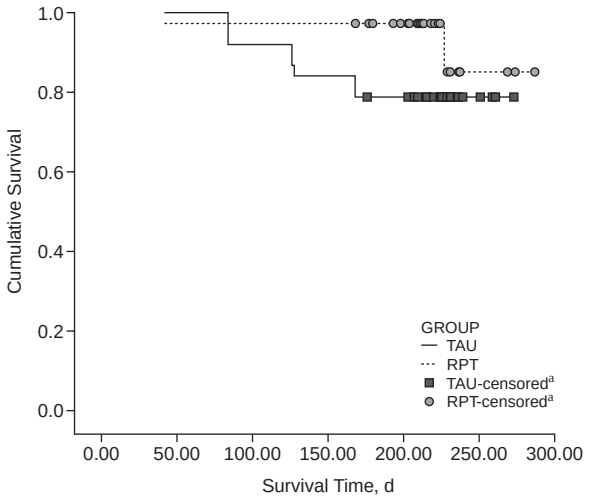
[a]Comparisons of differences between the 2 groups at baseline: t test used for age, years of education, and premorbid variables; for all other variables, χ^2 was used.
[b]Not mutually exclusive categories.
[c]Estimated on the basis of time between onset of symptoms and entry into the service.
[d]Test statistic based on logarithmic transformed data due to the extreme skewness of duration of untreated psychosis.
[e]Estimated on the basis of performance on the Wechsler Test of Adult Reading.
[f]Scores range from 0.0 to 1.0 with higher scores indicative of "healthier" levels of adjustment.
[g]For borderline personality disorder, TAU denominator was 39 and RPT group denominator was 40.
[h]For antisocial personality disorder, TAU denominator was 39 and RPT group denominator was 38.
Abbreviations: MDE = major depressive episode, NOS = not otherwise specified.

Completers at time 2 were contrasted with participants who had dropped out (N = 5) or who had missed their assessment (N = 6) on a range of demographic and baseline clinical variables. One case in the TAU group did not have baseline assessment data and was excluded from these analyses. No differences between the groups were noted with respect to gender, age, marital status, educational background, levels of unemployment, duration of untreated psychosis, premorbid intellectual ability, premorbid adjustment, and Axis I or II diagnoses.

Treatment Outcome

Participants randomly assigned to RPT completed a mean of 8.51 (SD = 4.87) therapy sessions, and 25 (61%) completed a full course of individual RPT, which was defined as the completion of all relevant phases of therapy including the termination phase. Therapy completers received a mean of 11.84 sessions (SD = 1.55). Of 41 families initially allocated to the RPT group, 9 participants refused consent for their family to participate in the family intervention (3 families did not consent and 6 patients

Figure 2. Comparison of the Cumulative Survival of the Relapse Prevention Therapy (RPT) and Treatment As Usual (TAU) Groups Over the Treatment and Immediate Posttreatment (7–10 months) Phases



[a]Censored cases are those cases at follow-up who have not relapsed.

refused for their families to be involved with the study). Those families who participated in therapy (N = 24) received a mean of 10.2 therapy sessions (SD = 4.6), and 15 (62%) completed the family intervention (i.e., they completed all relevant phases of family therapy including termination). Family completers received a mean of 13.1 (SD = 2.2) therapy sessions.

Data on relapse was available at 7 months for 38 patients in the RPT group and 38 patients in the TAU group. Relapse data was obtained for the extra cases from medical file review and from phone contact with patients. Within the 7-month follow-up period, the relapse rates were significantly greater in the TAU group (21.8%, n = 8) as compared to the RPT group (5.3%, n = 2) ($\chi^2 = 4.15$, df = 1, p = .042). Estimates are based on the time to first event. Two cases in the TAU group recorded 2 events, the first of which was a relapse. The relapse was followed by partial and full remission, respectively. The second event in both cases was an exacerbation. Further, relapses occurred earlier on average in the TAU group (mean = 241.00 days, SD = 10.35 days) than for the RPT group (mean = 273.25 days, SD = 9.20 days). Both the Breslow ($\chi^2 = 5.20$, df = 1, p = .023) and the Tarone-Ware ($\chi^2 = 4.75$, df = 1, p = .03), which place greater weight on events early in the survival curve, were significant at $p < .05$ level. The log rank test, which provides an overall difference between the survival curves, was not significant ($\chi^2 = 3.74$, df = 1, p = .053). The number needed to treat (NNT) to prevent 1 relapse during the 7-month period, calculated as the reciprocal of the risk difference in relapse between the 2 groups, was 6 (Figure 2).

Table 2 includes the descriptive statistics for the symptom measures and treatment characteristics at baseline (time 1) and 7-month follow-up (time 2). The RPT group had a significantly higher mean SANS alogia subscale score than the TAU group at the end of therapy ($F = 15.57$, df = 1,78; $p < .001$, $\eta^2 = 0.17$). The groups did not differ significantly on any other of the symptom measures or on MARS scores. Furthermore, there were no significant differences between groups with respect to prescription of antidepressant and antipsychotic medications at both time points. Both groups had a significant reduction in the rate of prescription of antipsychotic medication over time (McNemar tests, both $p < .05$).

As displayed in Table 3, the 2 groups did not differ with respect to the WHOQOL-BREF ratings (i.e., overall quality of life ratings, health satisfaction, and the 4 domains) or the Social and Occupational Functioning Assessment Scale, or on any of the substance use measures.

The results of the complete case analyses were consistent with the findings of the analyses using LOCF, indicating the robustness of the findings.

DISCUSSION

The Episode II study is the first study to demonstrate the effectiveness of a novel multimodal CBT intervention for relapse prevention early in the course of psychosis, when compared against TAU within high quality, specialist youth FEP programs. Treatment as usual consisted of a full range of integrated biologic and psychosocial interventions including specialist case management, family work, group-based interventions, access to home-based treatment during crises, and follow-up with a treating psychiatrist,[45] which were designed in accordance with specialist treatment guidelines for this phase of the disorder.[16] The primary hypotheses were that the group receiving RPT would show a longer time to relapse and a lower rate of relapse at the 7-month follow-up (which coincided with the end of the experimental treatment). The current results, which allowed for an evaluation of the short-term effectiveness of the intervention, supported the hypotheses, and showed that relapse can be reduced to very low levels (5%) during this initial period of maintenance treatment for patients who have responded to acute phase treatments. Differences between the survival curves of the groups indicated that prevention in relapse was greatest in the early phases of treatment. The effectiveness of the intervention is further highlighted by the NNT (i.e., the number needed to treat in order to prevent 1 patient relapsing over the 7-month period). By way of comparison, a NNT value of 4 has been calculated for response to antipsychotic medication in schizophrenia.[16]

The effectiveness of our comparison intervention is further highlighted by comparisons with naturalistic[1] and

Table 2. Descriptive Statistics for the Symptom and Treatment Characteristics of the Relapse Prevention Therapy (RPT) and Treatment As Usual (TAU) Groups at Time 1 (baseline) and Time 2 (7 months, end of therapy)

	Time 1 (baseline)		Time 2 (7 months)					
Symptomatology	RPT	TAU	RPT	TAU	F[a]	df	p Value	η^2
BPRS score, mean (SD)[b]								
Total	35.4 (6.9)	34.3 (8.0)	34.3 (8.4)	35.0 (9.8)	0.71	1,78	.40	0.01
Psychotic subscale[c]	5.3 (1.6)	5.8 (1.7)	5.7 (2.2)	6.5 (3.3)	0.03	1,78	.86	0.00
SANS score, mean (SD)[b]								
Summary[d]	4.4 (3.4)	4.8 (3.7)	4.2 (3.4)	4.3 (3.7)	0.53	1,78	.47	0.01
Composite[e]	13.4 (11.5)	14.0 (11.6)	14.0 (12.3)	13.8 (12.1)	0.46	1,78	.50	0.01
Affective flattening[f]	5.4 (7.2)	5.2 (7.3)	5.4 (7.3)	6.1 (8.0)	0.01	1,78	.91	0.00
Alogia	2.2 (3.3)	2.5 (2.5)	2.2 (3.2)	0.6 (1.3)	15.57	1,78	< .001	0.17
Avolition	3.6 (4.0)	3.7 (4.8)	3.9 (4.7)	4.2 (5.0)	0.15	1,78	.70	0.00
Anhedonia	5.0 (6.3)	5.0 (5.4)	4.6 (6.6)	5.1 (6.1)	0.18	1,78	.68	0.00
Attention	1.6 (2.5)	2.5 (2.9)	2.1 (2.2)	2.2 (2.8)	0.53	1,77	.47	0.01
MADRS total score, mean (SD)[b]	9.8 (7.7)	11.1 (10.5)	8.3 (9.0)	10.8 (11.5)	1.45	1,78	.23	0.02
Medication								
On medication, % (n)	90.2 (37)	97.5 (39)	91.2 (31)	88.9 (32)	NA	NA	NA	NA
Antipsychotic, % (n)[g]	94.6 (35)	100.0 (39)	77.4 (24)	93.8 (30)	NA	NA	NA	NA
Antidepressant, % (n)[g]	56.8 (21)	46.2 (18)	54.8 (17)	46.9 (15)	NA	NA	NA	NA
MARS score, mean (SD)[h]	6.9 (1.6)	7.5 (1.9)	6.5 (2.0)	7.1 (1.7)	0.55	1,45	.46	0.01
Days in hospital, mean (SD)[i]	7.6 (12.3)	6.9 (11.4)	3.3 (9.8)	1.5 (5.8)	0.41	1,69	.52	0.01

[a]Based on analysis of covariance with group as independent variable, time 1 score as covariate, and time 2 score as dependent variable.
[b]Due to positive skewness, these variables were transformed using logarithmic transformations. Untransformed scores are displayed in the table.
[c]Based on the 4 items: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization.
[d]Based on the scoring recommendations of Andreasen[33] (total of the 5 global items).
[e]Based on the scoring recommendations of Andreasen[33] (total of the 20 individual items).
[f]Based on the scoring recommendations of Andreasen[33] (global item is included in subscale total).
[g]For Time 1, RPT denominator was 37 and TAU denominator was 39; for Time 2, RPT denominator was 31 and TAU denominator was 32.
[h]Only applicable to those patients taking medications. LOCF was not used in reporting of these data.
[i]Only applicable to patients with data pertaining to hospitalizations. LOCF was not used in reporting of these data.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MARS = Medication Adherence Rating Scale, NA = not applicable, SANS = Scale for the Assessment of Negative Symptoms.

Table 3. Descriptive Statistics for the Functioning and Substance Use Measures for the Relapse Prevention Therapy (RPT) and Treatment As Usual (TAU) Groups at Time 1 (baseline) and Time 2 (7 months)

	Time 1 (baseline)		Time 2 (7 months)					
Measure, mean (SD)	RPT	TAU	RPT	TAU	F[a]	df	p Value	η^2
Functioning and quality of life								
WHOQOL-BREF								
Overall QOL[b]	3.6 (0.8)	3.7 (1.0)	3.6 (0.8)	3.6 (1.1)	0.23	1,78	.63	0.00
Satisfaction with health[c]	3.2 (1.0)	3.2 (1.1)	3.2 (0.9)	3.2 (1.1)	0.00	1,77	.95	0.00
Domain scores[d]								
Physical	69.3 (15.4)	65.7 (18.0)	68.6 (15.3)	65.8 (20.4)	0.01	1,78	.92	0.00
Psychological	56.4 (18.5)	54.3 (23.3)	56.4 (20.9)	53.5 (24.0)	0.13	1,78	.72	0.00
Social relationship	63.2 (24.7)	58.5 (25.1)	57.7 (23.7)	56.5 (26.0)	0.37	1,78	.54	0.01
Environment	63.5 (14.0)	62.0 (18.1)	66.1 (14.3)	61.6 (17.9)	1.65	1,78	.20	0.02
SOFAS	61.2 (14.8)	65.2 (16.9)	63.8 (15.7)	64.8 (16.5)	0.21	1,78	.65	0.00
Substance use								
Clinician alcohol use scale	2.0 (0.6)	1.9 (0.5)	2.0 (0.7)	1.8 (0.4)	0.71	1,78	.40	0.01
Clinician drug use scale	2.3 (1.2)	1.9 (1.2)	2.2 (1.2)	1.9 (1.2)	0.01	1,78	.93	0.00
AUDIT	7.8 (7.1)	6.4 (5.3)	6.2 (7.2)	6.3 (5.8)	0.53	1,78	.47	0.01
SDS[e]	2.8 (4.0)	2.3 (3.9)	2.8 (3.9)	2.9 (4.4)	0.22	1,78	.64	0.00
WHO ASSIST[e]								
Tobacco	9.2 (4.1)	6.8 (5.8)	8.8 (4.5)	6.8 (5.3)	0.71	1,77	.40	0.01
Alcohol	3.7 (3.8)	2.7 (2.3)	3.2 (3.9)	3.1 (3.1)	2.29	1,77	.13	0.03
Cannabis	3.8 (4.7)	2.6 (3.9)	3.1 (4.2)	2.8 (4.0)	0.23	1,77	.63	0.00
Amphetamine	0.9 (3.0)	0.8 (1.6)	1.1 (3.1)	0.6 (1.1)	0.48	1,77	.49	0.01

[a]Based on analysis of covariance with group as independent variable, time 1 score as covariate, and time 2 score as dependent variable.
[b]Derived from question 1 of WHOQOL-BREF and on a scale from 1, "very poor," to 5, "very good."
[c]Derived from question 2 of WHOQOL-BREF and on a scale from 1, "very dissatisfied," to 5, "very satisfied."
[d]Domain scores on a scale from 0 to 100, with higher scores denoting higher QOL.
[e]Due to positive skewness, these variables were transformed using logarithmic transformations. Untransformed scores are displayed in the table.
Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, QOL = quality of life, SDS = Substance Dependence Scale, SOFAS = Social and Occupational Functioning Assessment Scale, WHOQOL-BREF = World Health Organization Quality of Life Assessment-abbreviated version, WHO ASSIST = World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test.

treatment outcome studies[12] of FEP, although some caution is warranted due to varying relapse and study inclusion criteria.[1] However, the rate of relapse in the TAU subgroup (22%) and the low number of bed days is consistent with follow-up studies of the early phases of treatment for FEP,[1] which indicates the importance of comparing novel adjunctive treatments for FEP against high quality background and control interventions. In addition, the significant benefits of RPT indicate the importance of engaging patients who have responded to acute phase treatments in specific psychotherapeutic relapse preventive interventions rather than relying solely on the benefits of a specialized program of care. This matching of a specific subgroup of patients to a targeted intervention in accordance with the trajectory of their course of psychosis is illustrative of the potential benefits of the "staging" conceptualization of treatment.[46] Two fundamental assumptions underlie this model. First, patients in the earliest stages of a psychotic disorder have a better response to treatment and a better prognosis than those in later stages. Second, treatments offered in the early stages should be more benign as well as more effective.

The significant effect of the RPT intervention does not appear to be accounted for by adherence to medication or severity of substance abuse. This suggests that RPT may have a unique and specific effect on reducing relapse risk. We hypothesize that attention to individual and family psychoeducation and attention to early warning signs may be the critical components.

Our secondary hypotheses, that the participants randomly assigned to RPT would show improved adherence to medication, improved psychosocial functioning, and improved quality of life, compared to the TAU group, were not supported. This finding suggests that our relapse prevention intervention did not have generalized psychosocial benefits in the short term, and that this subgroup of patients requires additional, specifically targeted interventions for substance abuse, unemployment, and depressive symptoms. Alternatively, it is possible that changes in secondary outcomes may emerge over subsequent time points beyond the 7-month follow-up, or that more frequent measurement of secondary outcomes is required to detect significant differences between the groups. The unexpectedly greater severity of alogia in the RPT group is most likely a chance finding.

The strengths of the study included the successful randomization, the manualized intervention and monitoring of treatment fidelity, the real-world high quality control comparison, and the high frequency of the blind and independent ratings of outcomes. There is no evidence that participant dropouts biased the results. The limitations included the refusal rate, the sample size, and the somewhat higher rates of psychotic disorder not otherwise specified than expected, which might be partly a result of the early detection in EPPIC of a subgroup with relatively short duration of untreated psychosis. The refusal rate was in part attributable to good levels of engagement between patients and their case managers because a significant number of refusers stated that they did not want to change case managers if randomly assigned to RPT. However, the refusal rate does not appear to have greatly affected the representativeness of the sample as refusers and consenters were not statistically different on a range of demographic variables. An additional weakness was that the design did not allow for the analysis of the separate contribution of the individual and family therapy components.

We will analyze the longer term effectiveness of our novel intervention for patients and examine the outcomes in relation to family well-being, as well as the relationship between specific treatment components and participant outcomes via standardized objective ratings of therapy sessions. Future studies should recruit participants from multiple specialist FEP programs internationally in order to provide adequate statistical power to compare the effects of randomization to family RPT alone, individual CBT alone, and combined RPT, compared with TAU. In the meantime, our study highlights the short-term preventive benefits of a brief combined family and individual intervention for the prevention of relapse in patients who have responded to acute phase treatment for FEP.

REFERENCES

1. Robinson DG, Woerner MG, Delman HM, et al. Pharmacological treatments for first-episode schizophrenia. Schizophr Bull 2005;31:705–722
2. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry 2005;162:947–953
3. Emsley R, Rabinowitz J, Medori R. Remission in early psychosis: rates, predictors, and clinical and functional outcome correlates. Schizophr Res 2007;89:129–139
4. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry 2003;160:1396–1404
5. Wiersma D, Nienhuis FJ, Slooff CJ, et al. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. Schizophr Bull 1998;24:75–85
6. Perlick DA, Rosenheck RA, Kaczynski R, et al. Components and correlates of family burden in schizophrenia. Psychiatr Serv 2006;57: 1117–1125
7. Penn DL, Waldheter EJ, Perkins DO, et al. Psychosocial treatment for first-episode psychosis: a research update. Am J Psychiatry 2005; 162:2220–2232
8. Almond S, Knapp M, Francois C, et al. Relapse in schizophrenia: costs, clinical outcomes, and quality of life. Br J Psychiatry 2004;184:346–351
9. Hogarty GE, Greenwald D, Ulrich RF, et al. Three-year trials of personal therapy among schizophrenic patients living with or independent of family, pt 2: effects of adjustment of patients. Am J Psychiatry 1997;154: 1514–1524
10. Pilling S, Bebbington P, Kuipers E, et al. Psychological treatments in schizophrenia, pt 2: meta-analyses of randomized controlled trials of social skills training and cognitive remediation. Psychol Med 2002; 32(5):783–791
11. Gumley A, O'Grady M, McNay L, et al. Early intervention for relapse in schizophrenia: results of a 12-month randomized controlled trial of cognitive behavioural therapy. Psychol Med 2003;33:419–431
12. Linszen DH, Dingemans P, Lenior M. Early intervention and a five year follow-up in young adults with a short duration of untreated psychosis:

ethical implications. Schizophr Res 2001;51(1):55–61
13. International Early Psychosis Association Writing Group. International clinical practice guidelines for early psychosis. Br J Psychiatry Suppl 2005 Aug;48:S120–S124
14. Craig TK, Garety P, Power P, et al. The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. BMJ 2004;329(7474):1067
15. Goldberg K, Norman R, Hoch J, et al. Impact of a specialized early intervention service for psychotic disorders on patient characteristics, service use, and hospital costs in a defined catchment area. Can J Psychiatry 2006;51:895–903
16. McGorry P. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for the Treatment of Schizophrenia and Related Disorders. Aust N Z J Psychiatry 2005;39:1–30
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
18. Lukoff D, Liberman RP, Nuechterlein KH. Symptom monitoring in the rehabilitation of schizophrenic patients. Schizophr Bull 1986;12: 578–593
19. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
20. Early Psychosis Prevention and Intervention Centre. Case Management in Early Psychosis: A Handbook. EPPIC: Parkville, Victoria, Australia: 2001
21. Edwards J, Hinton M, Elkins K, et al. Cannabis abuse and first-episode psychosis. In: Graham HL, Copello A, Birchwood M, et al, eds. Substance Misuse in Psychosis: Approaches to Treatment and Service Delivery. Chichester, England: Wiley; 2003
22. Jackson H, McGorry P, Henry L, et al. Cognitively oriented psychotherapy for early psychosis (COPE): a 1-year follow-up. Br J Clin Psychol 2001;40:57–70
23. Gilbert M, Miller K, Berk L, et al. Scope for psychosocial treatments in psychosis: an overview of collaborative therapy. Australasian Psychiatry 2003;11:220–224
24. Ryle A, Kerr IB. Introducing Cognitive Analytic Therapy: Principles and Practice. Chichester, England: Wiley; 2002
25. Birchwood M, Smith J, Macmillan F, et al. Predicting relapse in schizophrenia: the development of an early signs monitoring system using patients and families as observers, a preliminary investigation. Psychol Med 1989;19:649–656
26. Falloon IR. Handbook of Behavioral Family Therapy. New York, NY: Guilford Press; 1988
27. Mueser KT, Glynn SM. Behavioral Family Therapy for Psychiatric Disorders. 2nd ed. Oakland, Calif: New Harbinger; 1999
28. Linszen DH, Dingemans P, Van Der Does JW, et al. Treatment, expressed emotion, and relapse in recent onset schizophrenic disorders. Psychol Med 1996;26:333–342
29. Alvarez-Jimenez M, Wade D, Cotton S, et al. Enhancing treatment fidelity in psychotherapy research: novel approach to measure the components of cognitive-behavioural therapy for relapse prevention in first-episode psychosis. Aust N Z J Psychiatry 2008;42:1013–1020
30. Ventura J, Liberman RP, Green MF, et al. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). Psychiatry Res 1998;79:163–173
31. First MB, Spitzer RL, Williams JBW, et al. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) User's Guide and Interview. Washington, DC: American Psychiatric Press; 1997
32. Montgomery SM. Depressive symptoms in acute schizophrenia. Prog Neuropsychopharmacol 1979;3:429–433
33. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, Ia: University of Iowa; 1983
34. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res 2000;42:241–247
35. Ginsberg JP. Wechsler Test of Adult Reading [book and test reviews]. Applied Neuropsychol 2003;10:182–184
36. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982;8:470–484
37. Goldman HH, Skodol AE, Lave TR. Revising Axis-V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149: 1148–1156
38. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med 1998;28(3):551–558
39. Ali R, Awwad E, Babor T, et al. The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST): development, reliability, and feasibility. Addiction 2002;97:1183–1194
40. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption, pt 2. Addiction 1993;88:791–804
41. Drake RE, Osher FC, Noordsy DL, et al. Diagnosis of alcohol use disorders in schizophrenia. Schizophr Bull 1990;16:57–67
42. Nuechterlein KH, Dawson ME, Gitlin M, et al. Developmental processes in schizophrenic disorders: longitudinal studies of vulnerability and stress. Schizophr Bull 1992;18:387–425
43. Ventura J, Nuechterlein KH, Hardesty JP, et al. Life events and schizophrenic relapse after withdrawal of medication. Br J Psychiatry 1992; 161:615–620
44. Little R, Rubin DB. Statistical Analysis With Missing Data. New York, NY: John Wiley & Sons; 1987
45. McGorry PD, Edwards J, Mihalopoulos C, et al. EPPIC: an evolving system of early detection and optimal management. Schizophr Bull 1996;22:305–326
46. McGorry PD. Issues for DSM-V: clinical staging: a heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. Am J Psychiatry 2007;164:859–860