Randomized Controlled Trial of Interventions for Young People at Ultra High Risk for Psychosis: 6-Month Analysis

Alison R. Yung, MD, FRANZCP; Lisa J. Phillips, PhD; Barnaby Nelson, PhD; Shona M. Francey, PhD; Hok PanYuen, PhD; Magenta B. Simmons, BA; Margaret L. Ross, DPsych (Clin); Daniel Kelly, Grad Dip (Psych); Kathryn Baker, DPsych (Clin); G. Paul Amminger, MD; Gregor Berger, MD; Andrew D. Thompson, MD; Annette Thampi, MRCPsych; and Patrick D. McGorry, MD, PhD

Objective: Cognitive therapy and/or low-dose antipsychotic administered during the prodromal phase of schizophrenia may prevent or delay the onset of full-blown illness. However, it is unclear which of these treatments are most effective, how long treatment should be given, and whether effects will be sustained over a prolonged period.

Method: In order to examine these issues, we conducted a randomized controlled trial of cognitive therapy + risperidone; cognitive therapy + placebo; and supportive therapy + placebo in young people at ultra high risk for developing a psychotic disorder (that is, putatively prodromal). The main outcome was transition to psychotic disorder, with level of symptoms and functioning the secondary outcomes. This article reports the interim 6-month follow-up results. The study was conducted from August 2000 to May 2007.

Results: Of a possible 464 eligible ultra high risk individuals, 115 were recruited to the randomized controlled trial (cognitive therapy + risperidone, n = 43; cognitive therapy + placebo, n = 44; and supportive therapy + placebo, n = 28). An additional 78 individuals agreed to follow-up assessments but not to randomization ("monitoring group," n = 78). At 6 months, 8 of the 115 participants (7.0%) and 4 of the monitoring group (5.1%) had developed psychotic disorder. There were no significant differences between the 3 randomized groups (log rank test, $P = .92$) or between all 4 groups (log rank test, $P = .93$). There was also no difference between the 4 groups in secondary measures, with all groups showing a reduction in symptoms and increased functioning.

Conclusions: Rates of transition to psychosis were lower than expected, particularly in the control supportive therapy + placebo group. This may have accounted for the negative finding, as the sample was therefore underpowered to find any difference between groups. Alternatively, it may be that all treatments were equally effective or equally ineffective at 6 months.

Trial Registration: http://www.anzctr.org.au Identifier: ACTRN012605000247673

J Clin Psychiatry 2011;72(4):430–440

Submitted: *December 22, 2008; accepted September 25, 2009.*
Online ahead of print: *October 19, 2010 (doi:10.4088/JCP.08m04979ora).*
Corresponding author: *Alison R. Yung, MD, Orygen Research Centre and University of Melbourne, Department of Psychiatry, 35 Poplar Rd, Parkville 3052, Victoria, Australia (aryung@unimelb.edu.au).*

Schizophrenia and other psychotic disorders are known to have a prodromal phase that precedes the onset of full-blown psychotic symptoms.[1–3] Intervening during this prodromal phase may ameliorate, delay, or even prevent onset of fully fledged disorder. However, a major challenge has been to prospectively identify the prodrome, particularly given the nonspecific nature of prodromal symptoms.[4,5] Over the last decade, reliable criteria have been introduced for the prospective identification of individuals at heightened risk for developing a first episode of psychosis within a brief time period—that is, as possibly being in the prodromal phase of illness.[6] These criteria are based on a combination of known trait and state risk factors for psychosis, including attenuated positive psychotic symptoms, brief self-limited psychotic symptoms, and family history of psychotic disorder. They have been termed the "ultra-high-risk" (UHR) criteria.[7] The first published study using the UHR criteria found a transition rate of 40% to threshold psychotic disorder within 1 year,[6] despite the provision of needs-based psychosocial intervention and antidepressant medication where indicated. This finding has subsequently been replicated by several groups internationally. Using a combination of various studies, Ruhrmann et al[8] report an average 1-year transition rate of 36.7% in UHR subjects who did not receive antipsychotic treatment. A recent, large-scale, multisite North American study[9] (North American Prodrome Longitudinal Study [NAPLS]) also validated the UHR or prodromal criteria, with a transition rate of 35% over 2½ years.

Following these advances in identification of the UHR or prodromal group, 3 treatment trials have indicated that specific intervention, both psychological and pharmacologic, may benefit individuals, in terms of reducing the risk of transition from UHR state to full-threshold psychotic disorder or at least delaying or attenuating onset (for detailed description of these studies, see Phillips et al[10]). In brief, the Personal Assessment and Crisis Evaluation (PACE) study, conducted in Melbourne, Australia, compared combined cognitive therapy and low-dose atypical antipsychotic medication with usual case management. The rate of transition to psychosis in the treatment group was significantly lower than in the control group after the 6-month treatment phase. However, at 12-month follow-up, there was no difference in transition unless participants were fully compliant with the antipsychotic medication.[11] Medium-term follow-up

(mean of 3 years) showed no significant difference between treatment groups in terms of transition rate, level of symptomatology, or functioning.[12]

The Prevention Through Risk Identification, Management, and Education (PRIME) study,[13] conducted in New Haven, Connecticut, compared 12 months of low-dose antipsychotic (olanzapine) with placebo. There was a trend toward the treatment group showing a reduction in transition rate, although this did not reach statistical significance. This may have been due to underpowering of the study.

A third trial[14] was conducted in Manchester, United Kingdom, in which subjects were randomly assigned to receive cognitive therapy for 6 months or monitoring of mental state only. The group that received cognitive therapy had a significantly lower rate of transition to full threshold disorder and a significantly greater reduction in psychiatric symptoms at 12 months. However, as in the PACE medium-term follow-up study, these significant differences were not maintained at 3-year follow-up.[15]

Thus, these studies provide preliminary evidence for the short-term efficacy of psychological and pharmacologic treatments for UHR individuals. However, they indicate that the beneficial effects of medication and cognitive therapy tend to decline once treatment has ceased. Extending the duration of specific treatments may be more effective in reducing incidence of psychotic disorders over the longer term. There is also a need to determine if antipsychotic medication provides any advantage over cognitive therapy alone. To investigate these issues, we conducted a second trial in the PACE UHR group. This was a double-blind, placebo-controlled randomized trial comparing 3 different treatment regimens in the UHR group: cognitive therapy + risperidone, cognitive therapy + placebo, and supportive therapy + placebo. There was a 12-month treatment phase and a 12-month follow-up phase. The trial was registered with the Australian Clinical Trials Registry (identifier: ACTRN012605000247673), and was approved by the North Western Mental Health Research and Ethics Committee. This interim article reports baseline and 6-month follow-up findings. More detailed methodology is reported in Phillips et al.[10] It is of relevance to report these 6-month findings to inform researchers, clinicians, and service planners who are developing studies or services for UHR patients. These groups need to be informed about which period they should focus resources on. Clinicians need to know when the highest risk for transition is, and an important question for service planners and researchers is whether a large number of patients should be managed for a brief intervention, such as 6 months, or whether a smaller number of patients should be seen for a longer period of treatment, such as 12 months. Another issue is how long UHR patients generally adhere to trial medication, as this too may impact on study designs. Thus, the attrition rate 6 months into this study was examined. Further, it is of interest to compare the 6-month results in this trial to the 6-month results in the first PACE randomized controlled trial (RCT).[11]

Aims and Hypotheses

The primary aim of the study was to determine if cognitive therapy plus low-dose risperidone was superior to cognitive therapy alone and if either was superior to supportive therapy alone in the treatment of young people at UHR of psychotic disorder.

The main outcome measure was transition to full-threshold psychotic disorder. Secondary outcome measures were psychiatric symptoms, psychosocial functioning, and quality of life.

We hypothesized that the cognitive therapy + risperidone group would have a lower transition rate and greater symptomatic and functional improvement compared to the cognitive therapy + placebo group, which would in turn have a lower transition rate and greater symptomatic and functional improvement than the supportive therapy + placebo group.

METHOD

Setting

This outpatient study was conducted at the PACE Clinic, a clinical service for young people at UHR for developing a psychotic disorder such as schizophrenia. Referrals to the PACE Clinic come from general practitioners; teachers and university health services; drug and alcohol services; youth support organizations, such as homeless services; and other mental health services, including the wider Orygen Youth Health service.[10,16]

Participants

Intake criteria for the study were (1) age between 14 and 30 years, (2) residing in the Melbourne, Australia, metropolitan area, and (3) met at least 1 of the following criteria for UHR status: (1) attenuated psychotic symptoms—presence of attenuated (subthreshold) psychotic symptoms within the previous 12 months; (2) brief limited intermittent psychotic symptoms—history of brief self-limited psychotic symptoms that spontaneously resolved within the previous 12 months; or (3) trait group—presumed genetic vulnerability to psychotic disorder (either schizotypal personality disorder or family history of psychotic disorder in a first-degree relative) plus persistent low functioning for at least 1 month within the previous 12 months. These UHR criteria have been published in more detail previously.[6] The UHR intake criteria were assessed by the Comprehensive Assessment of At-Risk Mental States (CAARMS).[17] Informed consent was obtained from all participants, and, for those aged under 18 years, informed consent was also obtained from a parent or guardian.

Exclusion criteria were (1) known history of a previous psychotic or manic episode (treated or untreated); (2) known history of a medical condition that may account for symptoms leading to initial referral (eg, epilepsy); (3) clinically relevant neurologic, biochemical, or hematologic abnormalities; (4) serious coexisting illnesses; (5) lifetime antipsychotic dose of 15 mg of haloperidol (or equivalent) or greater;

© Copyright 2010 Physicians Postgraduate Press, Inc.

(6) any previous or current use of mood stabilizing medication; (7) history of severe drug allergy; (8) intellectual disability (IQ < 70); (9) females who were pregnant or lactating; and (10) insufficient English language skills to participate in research interviews or psychological treatment without assistance from an interpreter.

Interventions

Trial medication. Trial medication, either risperidone or placebo, was dispensed in plain packaging by an independent local pharmacy. Risperidone was started at a dose of 0.5 mg/d and gradually increased over 4 weeks to up to 2 mg/d if tolerated. The placebo tablets appeared identical to risperidone tablets. Side effects were monitored using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale[18] every week for the first 4 weeks and then monthly from months 2 to 12. Trial medication was prescribed for 1 year. Participants were instructed to return all medication packs so that compliance could be monitored. Treatment adherence was monitored by pill count. For each subject, the medication adherence level on any particular day was computed as the amount of pills taken divided by the amount prescribed. The overall adherence level at 6-month assessment was the average adherence from the start of the trial to the 6-month assessment time point. Definitions of full, partial, and poor adherence were made a priori, using the same definitions as in our previous trial[11]: ≥ 90% of doses taken (full adherence), 50%–89% of doses taken (partial adherence), and 50% of doses taken (poor adherence).

Cognitive therapy. Cognitive therapy was provided by trained clinical psychologists using a manualized program, consisting of 4 modules:

1. Stress management: based on the stress-vulnerability model of the onset of psychotic episodes, this module was aimed at assisting clients to recognize and monitor their own stress levels, to consider the relationship between stress and symptoms, to develop an understanding of precipitants to distress, and to develop strategies for coping with stressful events.
2. Depression/negative symptoms: aimed at reducing negative and/or depressive symptoms through cognitive and behavioral strategies.
3. Positive symptoms: aimed at enhancing strategies for coping with positive symptoms, recognizing early warning signs, and preventing their exacerbation.
4. Other comorbidity: addressed other problem areas commonly experienced by UHR clients, such as social anxiety, generalized anxiety, panic attacks, posttraumatic symptoms, and substance use.

The selection of modules was informed by an assessment of the presenting problem(s). Homework exercises were used to practice skills and reinforce gains made through therapy. The cognitive therapy is presented in more detail elsewhere.[19,20] Cognitive therapy sessions were of 50 to 60 minutes' duration and were offered weekly to fortnightly, depending on clinical need, for 12 months.

Supportive therapy. The supportive therapy was provided by the same clinical psychologists who provided the cognitive therapy. The supportive therapy aimed to provide the patient with emotional and social support,[21] as well as basic problem solving,[22] stress management, and psychoeducation about psychosis. Cognitive-behavioral techniques were not incorporated in this treatment. Supportive therapy sessions were of 50 to 60 minutes' duration offered weekly to monthly, depending on clinical need, for 12 months. This intervention was intended to be the control intervention, akin to the needs-based intervention in our first intervention trial.[11]

To attempt to maintain fidelity to the allocated psychological treatment, weekly group supervision meetings were held with psychologists and a senior clinical psychologist supervisor. Treatment sessions were audiotaped and reviewed by an independent psychologist trained in cognitive therapy and blind to group allocation in order to assess treatment fidelity.

In addition to providing either cognitive therapy or supportive therapy, psychologists also provided practical case management and crisis intervention when necessary, for example, assisting clients to find housing and apply for employment.

Outcomes

The main outcome measure was transition to full-threshold psychotic disorder. Criteria for full-threshold psychotic disorder were defined a priori as frank psychotic symptoms occurring at least daily for 1 week or more[17] and were assessed using the CAARMS.

Secondary outcome measures were psychiatric symptoms, psychosocial functioning, and quality of life. These were assessed using the CAARMS,[17] Brief Psychiatric Rating Scale (BPRS),[23] Scale for the Assessment of Negative Symptoms (SANS),[24] the Hamilton Depression Rating Scale (HDRS),[25] the Global Assessment of Functioning (GAF),[26] and the Quality of Life Scale (QLS).[27]

The attrition rate was assessed by determining the number of participants who could not be interviewed for assessment at 6 months' postbaseline.

Sample Size

Sample size considerations were derived from Cohen.[28] The proportions of the 3 treatment groups predicted to develop a psychotic disorder within the first 12 months of this study were estimated from the previous treatment trial conducted with the high-risk population at the PACE Clinic.[11] We estimated that 10% of group A (cognitive therapy + risperidone), 30% of group B (cognitive therapy + placebo), and 50% of group C (supportive therapy + placebo) would develop a psychotic disorder by the end of the treatment period. For a significance level of .05 and a power of 0.7, a sample of 75 was required in each of groups A and B, and 50 in group C (3:3:2 randomization ratio). Therefore, it

© Copyright 2010 Physicians Postgraduate Press, Inc.

was calculated that 200 people would need to be randomly assigned to this study.

Procedure

The randomization sequence was determined prior to the commencement of the study by a statistician who was not involved in providing treatment or conducting research interviews. Sealed envelopes containing medication number and either "supportive therapy" or "cognitive therapy" were created. Eligible PACE attendees were given information and consented to the trial by treating psychiatrists. Consenting participants were allocated consecutive envelopes by the trial manager (L.J.P.), who informed therapists of the allocated psychological treatment. Thus, psychiatrists were blind to the treatment allocation, but therapists knew which psychological treatment to provide. Therapists, therefore, also knew that, when participants were allocated to supportive therapy, they were also receiving placebo. However, psychologists were blind to medication allocation for those participants receiving cognitive therapy.

Participants received a baseline assessment consisting of CAARMS to document intake criteria; Structured Clinical Interview for *DSM-IV-TR* (SCID-IV)[29] to assess psychiatric diagnosis at baseline and to ensure that participants did not meet criteria for psychotic disorder; and BPRS, SANS, HDRS, GAF, and QLS as noted above to assess symptoms and functioning.

Participants were given a prescription for "trial medication," which was dispensed by an independent pharmacy. The trial medication was packaged as 12 individual monthly supply boxes, each containing 4 individual blister packs. Each blister pack contained 7 days' supply of tablets plus 3 days' supply of spare medication.

Participants were seen weekly by the treating psychiatrist for 4 weeks and then monthly from months 2 to 12. They were seen weekly to fortnightly by their psychological therapist/case manager for 12 months.

In addition, monthly research assessments were undertaken consisting of the same measures administered at baseline, with the exception of the SCID, GAF, and QLS, which were administered only at months 6, 12, and 24.

Statistical Methods

The statistical software SPSS for Windows 15.0[30] and S-PLUS for Windows 6.1[31] was used to carry out the analysis. Data were analyzed by intention to treat. All statistical tests were interpreted at the 5% significance level (2-tailed).

Kaplan-Meier survival analysis and log-rank test was used to test if the 3 groups differed in terms of proportion of subjects becoming psychotic within 6 months. Paired *t* tests were used to compare the baseline and 6-month values within each group for each measure. Also, effect sizes were computed for each of the 3 trial groups using the monitoring group as the reference group. Multiple imputation was used to deal with missing values in both the *t* test and the computation of the effect sizes. For analysis of adverse events, the UKU items were dichotomized into presence or absence of the symptoms. Logistic regression was then employed to compare the different groups at 6-month follow-up by using the corresponding baseline presence or absence of the symptom as a covariate.

RESULTS

Participant Flow

Of the 1,428 young people referred to PACE over the recruitment period (August 2000 to May 2006), 464 (32.5%) met study criteria, and, of them, 115 agreed to be randomly assigned. An open-label trial of lithium in the UHR group (with the same intake criteria as this study) was being conducted simultaneously with this RCT, and 30 people were entered into that study. An additional 78 individuals who met study criteria refused participation in both this RCT and the lithium study but agreed to research assessment and follow-up (this group is hereafter referred to as the "monitoring" group) (Figure 1). No difference was found in age ($t_{488} = -0.75$, $P = .455$) and gender distribution ($\chi^2_1 = 0.14$, $P = .707$) between young people who met intake criteria and agreed to some research involvement and those who met intake criteria but did not agree to any research involvement. The 115 recruited to this study were fewer than our calculated necessary sample size. Forty-three were randomly assigned to the cognitive therapy + risperidone group; 44, to the cognitive therapy + placebo group; and 28, to the supportive therapy + placebo group.

Baseline Characteristics

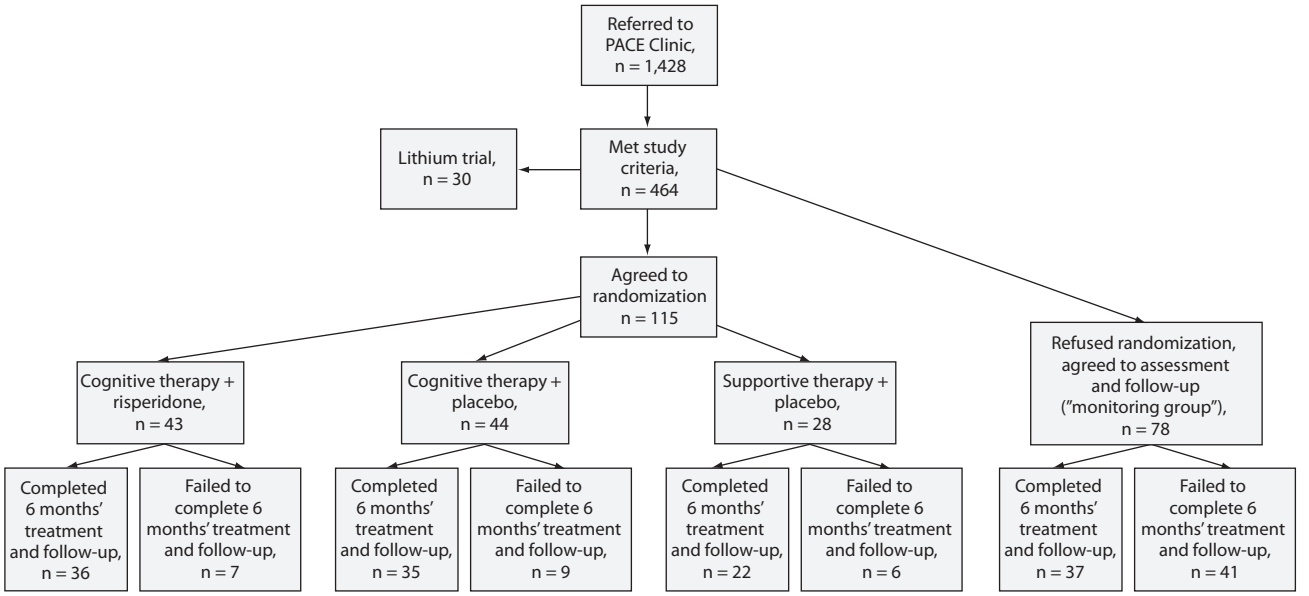
Baseline characteristics are presented in Table 1. Comparison was made between the monitoring group and the 3 randomized groups. Members of the monitoring group had significantly lower levels of global psychopathology (BPRS) ($P = .00$), positive psychotic symptoms (BPRS-psychotic subscale) ($P = .04$), global negative symptoms (SANS total score) ($P = .00$), SANS alogia ($P = .00$), and SANS affective flattening ($P = .00$) than randomly assigned participants.

Outcomes

Transition to psychotic disorder. At the 6-month follow-up point, 8 of the 115 participants (7.0%) had developed psychotic disorder. This included 2 of the 43 subjects (4.7%) in the cognitive therapy + risperidone group, 4 of the 44 subjects (9.1%) in the cognitive therapy + placebo group, and 2 of 28 subjects (7.1%) in the supportive therapy + placebo group. Those who were lost to follow-up before the 6-month assessment were assumed to have not become psychotic. There were no significant differences between the randomized groups in the proportion who became psychotic within 6 months (log-rank test, $P = .92$). In the monitoring group, 4 of 78 (5.1%) became psychotic within 6 months, a proportion not significantly different from the randomized groups (log-rank test, $P = .93$).

Symptomatic and functional outcome. The secondary outcome of interest was the comparison between groups in terms of symptomatic and functional outcome. The change in scores between baseline and month 6 on the BPRS, SANS,

Figure 1. Participant Flow Through the Study



Abbreviation: PACE = Personal Assessment and Crisis Evaluation.

HDRS, GAF, and QLS were compared (see Table 1). There was no difference in change score between the groups (see "Trial Groups Only" and "All 4 Groups" columns under "Difference in Change Between Groups"). We also assessed change within each group, and compared the extent of change between groups (see Table 1, "Within-Group Comparison"). We found that all 3 randomized groups and the monitoring group showed significant improvement in BPRS total, BPRS psychotic subscale and HDRS scores. All groups except cognitive therapy + risperidone significantly increased in functioning. In relation to negative symptoms, the supportive therapy + placebo and the monitoring groups showed significant improvement in total negative symptoms (SANS total) and anhedonia/asociality, and the supportive therapy + placebo group showed reduced affective flattening. Only the monitoring group significantly increased QLS score. Effect sizes tended to be small (see Table 1).

Attrition rate. By the 6-month follow-up point, 22 young people (19.1%) had dropped out of the study. The dropout rates in the treatment groups were 16% (7 participants) in the cognitive therapy + risperidone group, 20% (n = 9) in the cognitive therapy + placebo group, and 21% (n = 6) in the supportive therapy + placebo group (see Figure 1). There were no significant differences in the proportion who dropped out from each group ($P = .83$), and young people who dropped out did not differ significantly from those who were retained in the study on any baseline measure. Over half (41 of 78, 52.6%) of the monitoring group dropped out by 6-month assessment, a significantly higher proportion than in the randomized groups (Fisher exact $P = .00$).

Adverse Events

Assessment of potential adverse events was made at baseline and 6-month follow-up. At baseline, participants frequently reported fatigue, depression, concentration difficulties, and orthostatic dizziness (see Table 2). At 6-month follow-up, there were no significant differences between treatment groups in the prevalence of these symptoms or any other adverse events (Table 2).

Adverse events were then grouped into 4 subtypes (predefined in the UKU[18]): psychic (including concentration difficulties, increased fatigability, depression), neurologic (including dystonia, rigidity, tremor), autonomic (including accommodation disturbances, orthostatic dizziness, and constipation), and other (including sexual side effects, such as erectile and orgiastic dysfunction, as well as miscellaneous symptoms, such as rashes, photosensitivity, and headaches). Again, there were no significant differences between treatment groups in terms of prevalence of these subtypes of adverse events (see Table 2). Weight gain was specifically examined as a side effect as it has been a problem in trials of risperidone in first-episode psychosis populations.[32,33] However, many participants were missing UKU data, so only a reduced sample could be examined. Data on weight gain were available for 20 participants in the cognitive therapy + risperidone group, 22 in the cognitive therapy + placebo group, and 15 in the supportive therapy + placebo. The proportion of participants who reported weight gain in each group were 30.0, 9.1, and 6.7, respectively, a nonsignificant difference (Fisher exact test $P = .14$).

Treatment Fidelity

Psychological treatment. An independent rater trained in psychological therapies including cognitive therapy listened to audio-taped psychological sessions of consenting participants in order to assess whether or not they were receiving the allocated psychological treatment. Only a selection of tapes was rated: a tape was randomly selected from each

Table 1. Change in Score Between Baseline and Month 6 in Young People Randomly Assigned to Cognitive Therapy Plus Risperidone, Cognitive Therapy Plus Placebo, and Supportive Therapy Plus Placebo and in Members of the Monitoring Group[a,b]

Group	Baseline, Mean (SD)	Month 6, Mean (SD)	Change (month 6 – baseline), Mean (SD)	Difference in Change Between Groups, *P* Value[c]		Within-Group Comparison *P* Value[d]	Effect Size[e]
				Trial Groups Only	All 4 Groups		
BPRS total							
Cognitive therapy + risperidone	28.1 (9.2)	19.1 (8.2)	−9.0 (8.0)	.279	.471	.000	−0.10
Cognitive therapy + placebo	29.1 (9.0)	16.7 (6.8)	−12.4 (8.8)			.000	0.12
Supportive therapy + placebo	26.8 (9.3)	15.7 (7.4)	−11.1 (7.6)			.000	0.05
Monitoring group	22.4 (9.5)	15.0 (6.9)	−7.4 (8.1)			.000	
BPRS psychotic subscale							
Cognitive therapy + risperidone	7.2 (2.2)	3.7 (2.5)	−3.6 (2.2)	.399	.490	.000	−0.09
Cognitive therapy + placebo	6.6 (3.2)	2.8 (2.3)	−3.8 (2.8)			.000	0.03
Supportive therapy + placebo	5.9 (2.7)	3.3 (2.5)	−2.5 (2.4)			.001	−0.17
Monitoring group	5.8 (3.0)	2.6 (2.0)	−4.0 (2.6)			.000	
SANS total							
Cognitive therapy + risperidone	24.2 (12.6)	23.7 (11.7)	−1.1 (11.0)	.224	.158	.653	−0.34
Cognitive therapy + placebo	23.4 (12.8)	20.3 (11.3)	−3.1 (11.2)			.276	−0.28
Supportive therapy + placebo	24.5 (14.5)	17.1 (13.0)	−7.4 (7.1)			.025	−0.07
Monitoring group	18.0 (13.0)	14.0 (9.3)	−3.9 (9.4)			.108	
SANS affective flattening							
Cognitive therapy + risperidone	6.5 (5.7)	6.0 (5.1)	−0.5 (5.4)	.409	.230	.610	−0.19
Cognitive therapy + placebo	6.8 (5.5)	5.5 (4.2)	−1.3 (4.6)			.412	−0.10
Supportive therapy + placebo	7.0 (6.3)	4.1 (4.6)	−2.9 (4.5)			.445	−0.16
Monitoring group	4.1 (4.9)	2.6 (3.5)	−1.5 (4.7)			.436	
SANS alogia							
Cognitive therapy + risperidone	3.5 (2.6)	3.2 (2.3)	−0.3 (2.3)	.844	.818	.788	−0.26
Cognitive therapy + placebo	3.0 (2.7)	2.5 (2.5)	−0.4 (2.4)			.324	−0.10
Supportive therapy + placebo	3.3 (2.7)	2.9 (2.5)	−0.4 (2.4)			.126	0.07
Monitoring group	1.8 (2.3)	1.6 (1.8)	−0.2 (1.6)			.355	
SANS avolition apathy							
Cognitive therapy + risperidone	4.9 (2.7)	4.9 (2.6)	0.0 (3.2)	.379	.523	.887	−0.51
Cognitive therapy + placebo	5.0 (3.1)	4.4 (2.1)	−0.6 (3.2)			.257	−0.32
Supportive therapy + placebo	4.6 (2.8)	3.6 (2.4)	−1.0 (2.6)			.018	−0.08
Monitoring group	4.1 (3.2)	3.7 (2.4)	−0.4 (2.8)			.003	
SANS anhedonia associality							
Cognitive therapy + risperidone	6.8 (4.3)	7.0 (3.7)	0.2 (4.1)	.130	.014	.326	−0.02
Cognitive therapy + placebo	6.4 (4.4)	5.8 (3.8)	−0.7 (3.9)			.736	−0.01
Supportive therapy + placebo	7.1 (4.5)	5.0 (4.4)	−2.2 (3.3)			.661	−0.06
Monitoring group	6.2 (4.8)	4.0 (2.9)	−2.2 (3.3)			.504	
SANS attention							
Cognitive therapy + risperidone	2.5 (2.1)	2.1 (1.8)	−0.5 (1.9)	.961	.984	.878	−0.39
Cognitive therapy + placebo	2.2 (2.0)	1.9 (1.5)	−0.3 (2.1)			.229	−0.21
Supportive therapy + placebo	2.4 (2.3)	2.1 (2.2)	−0.3 (1.7)			.003	−0.02
Monitoring group	1.8 (2.1)	1.7 (1.5)	−0.1 (1.7)			.030	
HDRS							
Cognitive therapy + risperidone	19.7 (4.7)	11.2 (5.5)	−8.4 (5.4)	.521	.702	.032	−0.10
Cognitive therapy + placebo	20.8 (5.6)	10.4 (4.4)	−10.3 (5.5)			.015	0.13
Supportive therapy + placebo	21.0 (6.2)	7.2 (5.0)	−13.8 (4.2)			.008	0.41
Monitoring group	19.0 (8.2)	9.0 (5.3)	−10.0 (6.5)			.000	
GAF							
Cognitive therapy + risperidone	55.3 (6.9)	57.4 (7.6)	3.5 (8.2)	.113	.092	.226	−0.54
Cognitive therapy + placebo	55.1 (8.3)	60.6 (6.8)	5.5 (5.9)			.001	−0.21
Supportive therapy + placebo	56.0 (9.5)	63.8 (7.4)	7.8 (5.5)			.002	−0.11
Monitoring group	56.9 (9.8)	65.0 (6.5)	8.0 (5.8)			.021	
QLS total							
Cognitive therapy + risperidone	76.6 (16.0)	74.9 (17.3)	−1.7 (10.3)	.282	.091	.955	−0.59
Cognitive therapy + placebo	76.1 (22.1)	79.0 (15.7)	2.9 (14.0)			.526	−0.36
Supportive therapy + placebo	73.4 (21.8)	80.1 (16.4)	6.7 (10.8)			.099	−0.20
Monitoring group	76.7 (22.5)	86.4 (15.8)	9.7 (9.2)			.036	

[a]Multiple imputation was used to impute missing values.
[b]Monitoring group equals individuals who met study criteria but refused participation in both the randomized controlled trial and the lithium study but agreed to research assessment and follow-up.
[c]The *P* values are for testing for group difference using analysis of covariance, with baseline score as a covariate.
[d]The *P* values are for comparing baseline and 6-month values using paired *t* test.
[e]The monitoring group is used as the reference group for the effect sizes.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, GAF = Global Assessment of Functioning, HDRS = Hamilton Depression Rating Scale, QLS = Quality of Life Scale, SANS = Scale for the Assessment of Negative Symptoms.

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 2. Proportion of Participants in Each Group Reporting Adverse Events

Adverse Event	Baseline %[a]	Baseline n[b]	Month 6 %[a]	Month 6 n[b]	Difference Between Groups, *P* Value[c]
Fatigue					
Cognitive therapy + risperidone	55.6	36	52.4	21	.879
Cognitive therapy + placebo	42.9	28	63.6	22	
Supportive therapy + placebo	54.5	22	53.3	15	
Depression					
Cognitive therapy + risperidone	47.2	36	57.1	21	.108
Cognitive therapy + placebo	39.3	28	50.0	22	
Supportive therapy + placebo	50.0	22	33.3	15	
Concentration difficulties					
Cognitive therapy + risperidone	50.0	36	28.6	21	.317
Cognitive therapy + placebo	32.1	28	31.8	22	
Supportive therapy + placebo	45.5	22	13.3	15	
Orthostatic dizziness					
Cognitive therapy + risperidone	33.3	36	23.8	21	.422
Cognitive therapy + placebo	32.1	28	13.6	22	
Supportive therapy + placebo	31.8	22	20.0	15	
UKU Side Effect Rating subscale					
Psychic					
Cognitive therapy + risperidone	80.6	36	81.0	21	.757
Cognitive therapy + placebo	75.0	28	81.8	22	
Supportive therapy + placebo	86.4	22	73.3	15	
Neurologic					
Cognitive therapy + risperidone	27.8	36	23.8	21	.742
Cognitive therapy + placebo	39.3	28	18.2	22	
Supportive therapy + placebo	18.2	22	13.3	15	
Autonomic					
Cognitive therapy + risperidone	47.2	36	57.1	21	.439
Cognitive therapy + placebo	53.6	28	59.1	22	
Supportive therapy + placebo	59.1	22	53.3	15	
Other					
Cognitive therapy + risperidone	66.7	36	57.1	21	.905
Cognitive therapy + placebo	39.3	28	50.0	22	
Supportive therapy + placebo	22.7	22	40.0	15	

[a]Percentage of subjects rated as having the symptom.
[b]Number of subjects with valid ratings.
[c]*P* value from logistic regression comparing the groups in terms of prevalence of symptom.
Abbreviation: UKU = Udvalg for Kliniske Undersogelser.

block of 5 sessions for each participant. Sixty-one therapy tapes were rated: 21 from the cognitive therapy + risperidone group and 20 were from each of the other 2 groups. That is, there were 41 tapes of young people allocated to receive cognitive therapy and 20 tapes of young people allocated to receive supportive therapy. Sixteen of the 20 tapes (80.0%) from the supportive therapy group were classified as supportive therapy. However, only 24 of 41 tapes from the cognitive therapy groups (58.5%) were classified as receiving cognitive therapy. Nine individuals (22.0%) allocated to receive cognitive therapy were judged to be receiving supportive therapy, and, in a further 8 cases (19.5%), the nature of the psychological therapy was rated as not known (Table 3).

Antipsychotic adherence. At 6-month follow-up, in the cognitive therapy + risperidone group (n = 43), 23 subjects (53.5%) had poor adherence (less than 50% of doses taken), 18 (41.9%) had partial adherence (50%–89% of doses taken), and only 2 (4.7%) had full adherence to risperidone (≥ 90% of doses taken). These rates were compared to the other 2 groups (cognitive therapy + placebo and supportive therapy + placebo), which were both prescribed placebo

Table 3. Independent Ratings of Type of Psychological Therapy Received

Rated Therapy	Actual Therapy: Cognitive Therapy, n (%)	Actual Therapy: Supportive Therapy, n (%)
Cognitive therapy	24 (58.5)	2 (10.0)
Supportive therapy	9 (22.0)	16 (80.0)
Don't know	8 (19.5)	2 (10.0)
Total	41	20

Table 4. Average 6-Month Adherence: Comparison Between Risperidone and Placebo[a]

Treatment	Poor Adherence, n (%)	Partial Adherence, n (%)	Full Adherence, n (%)	Total, n
Risperidone	23 (53.5)	18 (41.9)	2 (4.7)	43
Placebo	47 (65.3)	11 (15.3)	14 (19.4)	72

[a]Poor adherence equals < 50% of doses taken, partial adherence equals 50%–89% of doses taken, and full adherence equals ≥ 90% of doses taken; χ^2 test, *P* value = .002.

(Table 4). Those prescribed placebo and those prescribed risperidone showed similar rates of poor adherence. However, a larger percentage of the subjects in the placebo groups showed full adherence compared to the cognitive therapy + risperidone group.

Post-Hoc Analyses

Given that (1) cognitive therapy seemed to resemble supportive therapy in many cases and (2) adherence to risperidone was poor in over half the sample, additional analyses were carried out. First, an intention-to-treat comparison of those prescribed risperidone versus those prescribed placebo (ie, comparing the cognitive therapy + risperidone group with the combined cognitive therapy + placebo and supportive therapy + placebo groups) was made examining transition to psychosis and level of symptoms and functioning. That is, for the purpose of this analysis, we assumed that cognitive therapy and supportive therapy were equivalent. Second, analyses were performed taking antipsychotic adherence into account, comparing those with full, partial, and poor adherence in terms of transition rate and symptoms and functioning.

Comparison of risperidone versus placebo. Two of 43 subjects in the cognitive therapy + risperidone group (4.7%) made the transition, compared to 6 of 72 in the other 2 groups (8.3%). This difference was not statistically significant (*P* = .77) (log rank test). There were no significant differences in symptoms or level of functioning, although there were trends for those receiving placebo to show greater improvement in functioning (GAF, *P* = .059) and reduction of negative symptoms compared to those receiving risperidone: SANS avolition and apathy (*P* = .092) and SANS anhedonia and asociality (*P* = .073).

Analyses taking antipsychotic adherence into account. Since the number of subjects falling into the full adherence level was low, the "partial" and "full" levels were pooled together, resulting in only 2 levels of medication adherence:

© Copyright 2010 Physicians Postgraduate Press, Inc.

< 50% adherence and ≥ 50% adherence. Of the 2 subjects in the cognitive therapy + risperidone group who were known to have become psychotic by 6-month assessment, both belonged to the < 50% adherence group. However, this was not statistically significant (log-rank test, $P = .57$). There were no significant differences in symptoms or level of functioning between the groups, although there was a trend for those who were poorly adherent to show greater improvement in functioning and quality of life (GAF, $P = .095$; QLS, $P = .089$).

A further analysis comparing those who showed ≥ 50% adherence with a combined group who were either prescribed placebo or had < 50% adherence was also carried out. That is, we compared those with no or low levels of risperidone intake to those with higher intake, testing for the group difference using analysis of covariance (ANCOVA), with baseline score as a covariate. The group that received no or little risperidone showed significantly greater improvement in functioning between baseline and 6-month follow-up compared to those who received higher levels (risperidone-compliant group [n = 14] mean GAF increase = 0.7 [SD = 11.4], risperidone-noncompliant group + placebo groups [n = 39] mean GAF increase = 7.1 [SD = 7.4], $P = .015$). Similarly, the risperidone-noncompliant group + placebo groups (n = 40) had significantly greater improvement in quality of life compared to the risperidone-compliant group (n = 14), with the compliant group actually showing a reduction in QLS score between time points (mean QLS increase in the no or little risperidone group = 3.3 [SD = 15.7], compliant group mean QLS change = −6.0 [SD = 10.9] $P = .015$). There were no significant differences between the groups in positive, negative, or depressive symptoms (data not shown).

Analysis of antidepressant use. Given that antidepressants have been associated with reduced rates of transition to psychosis in other UHR services, albeit in uncontrolled naturalistic trials,[34,35] we examined antidepressant use in this sample. In the cognitive therapy + risperidone group, 26 of 40 people were prescribed antidepressants (65.0%) compared to 20 of 41 (48.8%) in the cognitive therapy + placebo group and 11 of 25 (44.0%) in the supportive therapy + placebo group, a nonsignificant difference (χ^2, $P = .18$).

Next, we employed Cox regression to compare the 3 treatment groups in terms of transition rate, incorporating antidepressant use (dichotomized as present or absent) as a covariate. The resulting P value was .90, indicating no significant difference between the treatment groups.

Finally, the effect of antidepressant use on symptoms and functioning was assessed by using ANCOVA to test for differences between treatment groups, with the baseline score for each variable and antidepressant use (presence or absence) as covariates, and, as in the above analyses, by using multiple imputation to account for missing values. No significant differences between the groups were found.

DISCUSSION

We compared UHR young people randomly allocated to receive cognitive therapy + risperidone, cognitive therapy + placebo, and supportive therapy + placebo. The main finding was the lack of difference between groups in terms of the main outcome measure, transition to psychotic disorder. This finding is in contrast to our previous trial of cognitive therapy + risperidone versus "needs-based intervention" (equivalent to the supportive therapy + placebo group), in which a significant difference in transition rate was found at the end of 6 months of treatment.[11] This difference occurred despite the cognitive therapy + risperidone group and the supportive therapy + placebo group interventions in the current study being essentially the same and their being administered for the same period of time as the treatments tested in the initial study.

It seems that the main reason for the lack of differences between groups in this current study was the low transition rate, in particular, the much lower than expected transition rate in the supportive therapy + placebo group. Prior to the study, we estimated, for our power calculation, that about 50% of this group would develop psychosis by 12 months, with an estimated transition rate of about 35% by 6 months (based on our previous study and data from similar services around the world, eg, Miller et al[36]). However, at the 6-month follow-up point, only 7.1% of the supportive therapy + placebo group (2 of 28) had developed psychosis. This finding is significantly lower than the 6-month rate of 35.7% in the equivalent needs-based intervention group of our initial trial (Fisher exact 2-tailed, $P = .020$). It is also lower than the 13% 6-month transition rate reported in the multisite North American study.[9] Since all 3 treatment groups in our study had quite low transition rates, it was difficult to find a significant difference between them.

Examination of the monitoring group also reveals a low transition rate (4 of 78, 5.1%). This is significantly lower than the transition rate reported in our initial "natural history" study[37] (8 of 20, 40%, Fisher exact, $P = .000$). Thus it seems that, in the PACE Clinic at least, transition rates are decreasing, and not just in those patients who receive treatment via a trial.

We have previously discussed possible reasons why the transition rate may be declining.[38] One reason may be that, unlike our earlier UHR cohorts, this sample includes too many people who are not genuinely at risk of psychotic disorder. That is, they may be experiencing psychotic-like symptoms that are "clinical noise" around a nonpsychotic syndrome and not necessarily associated with risk of schizophrenia or other psychotic disorders. These symptoms might be expected to remit with treatment of the nonpsychotic illness, such as depression.[39,40] We have previously called these "incidental psychotic experiences."[41,42] One reason the PACE Clinic may be seeing more of patients with "incidental psychotic experiences" may be the changes in the service system in which PACE exists. PACE has become increasingly well known among referrers, and it seems that higher numbers of patients are now being referred with, for example, depression being the main problem but with psychotic-like experiences detected upon assessment. Such a person may not have been referred in the early days of PACE when such

a routine inquiry about psychotic experiences may not have occurred.[43] Thus, unlike in our initial study, it is possible that participants did not need any specific treatment to recover from their symptoms and functional impairments and avoid developing a psychotic disorder.

Another cause for the reduction in transition rate may be lead-time bias. That is, transitions may occur later,[38] as has been seen in the Recognition and Prevention (RAP) Clinic.[35] This mechanism may be playing a role, particularly if individuals are seeking help much earlier, as we found in a previous study.[38] This lead-time bias may be important if all treatments are able to delay transition. Thus, we may see a significant difference between groups after a further 6 months of intervention (and note that this article reports only 6-month interim data). Against this possibility is the finding that, in most UHR/prodromal research worldwide, the majority of transitions occur early.[3,6,7,9,13]

A further reason for reduced transition rate may be that as patients are being referred earlier they may be at a stage that is more amenable to nonspecific treatment, such as supportive therapy. This is consistent with the clinical staging model, which states that, in its early phases, a disorder or syndrome will be more responsive to simple and relatively benign treatments than at a more advanced, later stage.[44] Thus, in this study, the lack of difference between the randomized groups may be due to supportive therapy being as effective as cognitive therapy and antipsychotics in these early phase patients. However, this explanation seems to be at odds with the low transition rate and improvement in symptoms in the monitoring group, which did not receive supportive therapy. Hence, it seems that even supportive therapy may not be needed. However, the monitoring group was less symptomatic and less functionally impaired than the randomized groups and so would be expected to have a lower transition rate. Additionally, although they did not receive formalized supportive therapy within the context of a trial, members of the monitoring group did nonetheless receive case management that included elements of supportive therapy and cognitive therapy where indicated.

It is also possible that placebo was an effective treatment in the randomized groups. As Carpenter[45] has argued, effectively all participants in trials of this type receive placebo treatment, including nonspecific psychosocial support, although for some the "placebo" also has an additional active drug effect. The low transition rate and improvement in the monitoring group may contradict this possibility, although these people did also receive psychosocial support.

In post hoc analyses, we examined treatment fidelity and antipsychotic adherence as possible causes for the negative finding in this trial. However, neither poor adherence to antipsychotics nor failure to receive cognitive therapy appeared to be factors in the lack of difference between groups. We also investigated whether antidepressants reduced transition rate, as has been suggested by other UHR researchers[34,35]; however, this did not seem to be the case in this study.

Another finding from this research was the high number of PACE attendees who refused to consent to any form of research. In the current study of 464 eligible individuals, only 115 (24.8%) consented to being randomly assigned and only 225 (48.5%) consented to any form of research. In the previous trial,[11] 59 (43.7%) consented to being randomly assigned and 92 of 135 (68.1%) consented to research, a significantly higher proportion than in the current study (Fisher exact, $P = .00$). Thus one factor to consider is whether there was a selection bias operating, such that patients more likely to contribute to treatment effect may have not participated in this trial. Although refusers were not significantly different from those who consented to any research involvement in terms of age and gender distribution, there is no information about the refusers' level of functioning, symptomatology, or any other potentially relevant variable.

We have considered why research participation, and particularly consent to randomized treatment, was not taken up by our patients. One reason is that treatment at PACE is free for patients as it is funded by the Victorian state government and research grants. Patients were aware that they would still access treatment at the clinic even without participation in any research project. This included case management and treatment by a doctor (either psychiatrist or supervised senior psychiatry trainee). Antipsychotics are not routinely prescribed at PACE unless a patient develops psychosis or deteriorates rapidly in the context of escalating attenuated psychotic symptoms. Thus, a desire to receive antipsychotic medication would not be a factor in PACE attendees' refusing to consent to research. However, a desire not to receive medication may lead to refusal to consent to the trial. Indeed, even among those that did consent to being randomly assigned, medication adherence was not good, with over 50% of the sample taking less than half of the prescribed amount, including those in the placebo groups. It may be that young people (young Australians at least) are reluctant pill takers. Side effects did not seem to differ between the groups receiving active medication and placebo, and so these are unlikely to account for the poor adherence.

Another reason for the low consent rate may be that the 3 different treatment trial options were confusing for the PACE patients. This low proportion of people consenting to being randomly assigned suggests a selection bias, a situation that is true of all RCTs. However, those who agreed to be randomly assigned were actually less well than those who did not consent[10] (possibly related to nonconsenters not wanting the possibility of receiving medication). Thus, the transition rate would be expected to be higher in the participants than nonparticipants, if anything. In fact, the transition rate in the monitoring group was not statistically different from the other groups.

In relation to the secondary outcome measures, there was no significant difference in symptoms and functioning between the treatment groups, although there was a trend for the group that did not receive risperidone to show greater improvement in functioning and reduction of negative symptoms. Similarly, in the within-group analysis, those who were in the supportive therapy + placebo and monitoring groups showed greater improvement in psychosocial functioning

© Copyright 2010 Physicians Postgraduate Press, Inc.

compared to the other groups. These differences did not appear to be due to the medication group having more adverse events.

This study has several limitations. As noted above, participant recruitment was slow and difficult. The poor medication adherence raises a question about whether antipsychotic medication is even feasible at this UHR stage, particularly over a prolonged period. The PRIME olanzapine study similarly found difficulty with recruitment and poor adherence rates with their 12-month medication regimen.[13] Another related problem was the number of people who discontinued the study. We were unable to determine psychosis status for 22 trial participants and 41 in the monitoring group (see Figure 1), so a conservative assumption was made that they were not psychotic. This is a study limitation. The trial dropout rate of 19% by 6-month follow-up was not as high as in the PRIME study, but it nonetheless indicates difficulty maintaining the protocol even at the 6-month point.

We have learned some valuable lessons from this study so far. The difficulties with recruitment suggest a need for multisite studies, as it is difficult to recruit sufficient numbers at a single site. The difficulties maintaining medication adherence, coupled with the evidence of a declining transition rate suggest that we need to investigate more benign and simple options as first-line treatments, perhaps followed by the introduction of antipsychotics if there is evidence of persistent symptoms or deterioration later. The low transition rate also indicates that ongoing research is needed to identify those within the UHR population who are at greatest risk of psychotic disorder. In particular, it would be of benefit to be able to distinguish between those with "incidental psychotic-like experiences" and those whose psychotic-like experiences truly represent an emerging serious psychotic disorder.

CONCLUSION

This article reports the interim 6-month results of a 12-month RCT. The negative finding at 6 months is of note, as it contrasts with the significant treatment effect found in our previous 6-month trial. Although the lower than expected transition rate meant that it was difficult to show an effect, we cannot discount the possibility that all interventions were equally effective. Conversely, all treatments may be equivalently ineffective. It may be that participants would have improved and not developed psychosis without any treatment at all. Twelve-month results may shed more light on the issues.

Drug name: risperidone (Risperdal).

Author affiliations: Orygen Youth Health Research Centre (Drs Yung, Nelson, Francey, Yuen, Ross, Baker, Amminger, Berger, Thompson, and McGorry; Ms Simmons; and Mr Kelly); Departments of Psychiatry (Drs Yung, Nelson, Francey, Ross, Amminger, Berger, Thompson, and McGorry and Ms Simmons) and Psychology (Dr Phillips), University of Melbourne; and PACE Clinic, Orygen Youth Health (Drs Yung, Nelson, Francey, Baker, and Thompson), Parkville, Victoria, Australia; and Belfast Trust, Woodstock Lodge, Belfast, United Kingdom (Ms Thampi).

Potential conflicts of interest: **Dr Yung** has received honoraria and grant support from Janssen-Cilag, Eli Lilly, and AstraZeneca. **Dr Berger** has received grant/research support from AstraZeneca; has received honoraria from Janssen-Cilag; and has served on speakers or advisory boards for AstraZeneca and Lundbeck. **Dr McGorry** has received grant/research support and honoraria from Janssen-Cilag, AstraZeneca, and Eli Lilly. **Drs Phillips**, **Nelson**, **Francey**, **Yuen**, **Ross**, **Baker**, **Thompson**, **Thampi**; **Ms Simmons**; and **Mr Kelly** report no financial or other relationships relevant to the subject of this article.

Funding/support: Funding for this study was provided through a major investigator-initiated grant from Janssen-Cilag Pharmaceuticals (RIS-AUS-9).

Role of sponsor: Janssen-Cilag had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of this article; and in the decision to submit this article for publication. Janssen-Cilag did provide assistance with monitoring the trial and assuring quality of data collection and recording over the treatment phase.

Previous presentation: Presented at the first conference of the Schizophrenia International Research Society; June 21–25, 2008; Venice, Italy.

REFERENCES

1. Beiser M, Erickson D, Fleming JA, et al. Establishing the onset of psychotic illness. *Am J Psychiatry*. 1993;150(9):1349–1354.
2. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull*. 1996;22(2):353–370.
3. Olsen KA, Rosenbaum B. Prospective investigations of the prodromal state of schizophrenia: review of studies. *Acta Psychiatr Scand*. 2006; 113(4):247–272.
4. Lieberman JA, Perkins D, Belger A, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biol Psychiatry*. 2001;50(11):884–897.
5. Häfner H, Maurer K, Trendler G, et al. Schizophrenia and depression: challenging the paradigm of two separate diseases—a controlled study of schizophrenia, depression and healthy controls. *Schizophr Res*. 2005; 77(1):11–24.
6. Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr Res*. 2003;60(1): 21–32.
7. Yung AR, Phillips LJ, Yuen HP, et al. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res*. 2004;67(2–3):131–142.
8. Ruhrmann S, Schultze-Lutter F, Klosterkötter J. Early detection and intervention in the initial prodromal phase of schizophrenia. *Pharmacopsychiatry*. 2003;36(suppl 3):162–167.
9. Cannon T, Cadenhead K, Cornblatt B, et al. Prediction of psychosis in ultra high risk youth: a multi-site longitudinal study in North America. *Arch Gen Psychiatry*. 2008;65(1):28–37.
10. Phillips LJ, Nelson B, Yuen HP, et al. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: study design and baseline characteristics. *Aust N Z J Psychiatry*. 2009;43(9): 818–829.
11. McGorry PD, Yung AR, Phillips LJ, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry*. 2002;59(10):921–928.
12. Phillips LJ, McGorry PD, Yuen HP, et al. Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis. *Schizophr Res*. 2007;96(1–3):25–33.
13. McGlashan TH, Zipursky RB, Perkins D, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry*. 2006;163(5):790–799.
14. Morrison AP, French P, Walford L, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. *Br J Psychiatry*. 2004;185(4):291–297.
15. Morrison AP, French P, Parker S, et al. Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophr Bull*. 2007;33(3):682–687.
16. Cosgrave EM, Yung AR, Killackey EJ, et al. Met and unmet need in youth mental health. *J Ment Health*. 2008;17(6):618–628.
17. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry*. 2005;39(11–12):964–971.
18. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand*. 1987;76(s334):1–100.
19. Phillips LJ, Francey SM. Changing PACE: Psychological interventions in the prepsychotic phase. In: Gleeson J, McGorry P, eds.

Psychological Interventions in Early Psychosis: A Treatment Handbook. Chichester, England: John Wiley & Sons; 2004:23–40.
20. Yung AR, Phillips LJ, McGorry PD. *Treating Schizophrenia in the Prodromal Phase*. London, England: Taylor and Francis; 2004.
21. Geldard K, Geldard D. *Counselling Adolescents*. 2nd ed. London, England: Sage Publications; 2004.
22. Malouff JM, Thorsteinsson EB, Schutte NS. The efficacy of problem solving therapy in reducing mental and physical health problems: a meta-analysis. *Clin Psychol Rev*. 2007;27(1):46–57.
23. Overall J, Gorham D. The Brief Psychiatric Rating Scale. *Psychological Reports*. 1962;10:799–812.
24. Andreasen NC. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, IA: The University of Iowa; 1983.
25. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
27. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull*. 1984;10(3):388–398.
28. Cohen J. *Statistical Power Analysis for the Behavioural Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
29. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders–Patient Edition*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 2/2001 revision.
30. SPSS Inc. SPSS for Windows 8.0. Chicago, IL; 1998.
31. Windows S-Pf. *S-PLUS 6 for Windows Guide to Statistics*. Seattle, WA: Insightful Corporation; 2001.
32. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007; 164(7):1050–1060.
33. Strassnig M, Miewald J, Keshavan M, et al. Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one-year analysis. *Schizophr Res*. 2007;93(1–3):90–98.
34. Fusar-Poli P, Valmaggia L, McGuire P. Can antidepressants prevent psychosis? *Lancet*. 2007;370(9601):1746–1748.
35. Cornblatt BA, Lencz T, Smith CW, et al. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. *J Clin Psychiatry*. 2007;68(4):546–557.
36. Miller TJ, McGlashan TH, Rosen JL, et al. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *Am J Psychiatry*. 2002;159(5):863–865.
37. Yung AR, Phillips LJ, McGorry PD, et al. Prediction of psychosis: a step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl*. 1998; 172(33):14–20.
38. Yung AR, Yuen HP, Berger G, et al. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophr Bull*. 2007;33(3):673–681.
39. Krabbendam L, Myin-Germeys I, Hanssen M, et al. Development of depressed mood predicts onset of psychotic disorder in individuals who report hallucinatory experiences. *Br J Clin Psychol*. 2005;44(pt 1):113–125.
40. Yung AR, Buckby JA, Cosgrave EM, et al. Association between psychotic experiences and depression in a clinical sample over 6 months. *Schizophr Res*. 2007;91(1–3):246–253.
41. Yung AR, Stanford C, Cosgrave E, et al. Testing the ultra high risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophr Res*. 2006;84(1):57–66.
42. Yung AR, Nelson B, Baker K, et al. Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia. *Aust N Z J Psychiatry*. 2009; 43(2):118–128.
43. Yung AR, Nelson B, Stanford C, et al. Validation of "prodromal" criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophr Res*. 2008;105(1–3):10–17.
44. McGorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry*. 2006;40(8):616–622.
45. Carpenter WT Jr. Placebo effect in depression. *Am J Psychiatry*. 2009; 166(8):935.