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

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ABSTRACT

Objective: The ultra-high risk clinical phenotype is associated with substantial distress and functional impairment and confers a greatly enhanced risk for transition to full-threshold psychosis. A range of interventions aimed at relieving current symptoms and functional impairment and reducing the risk of transition to psychosis has shown promising results, but the optimal type and sequence of intervention remain to be established. The aim of this study was to determine which intervention was most effective at preventing transition to psychosis: cognitive therapy plus low-dose risperidone, cognitive therapy plus placebo, or supportive therapy plus placebo.

Method: A double-blind, randomized, placebo-controlled 12-month trial of low-dose risperidone, cognitive therapy, or supportive therapy was conducted in a cohort of 115 clients of the Personal Assessment and Crisis Evaluation Clinic, a specialized service for young people at ultra-high risk of psychosis located in Melbourne, Australia. Recruitment commenced in August 2000 and ended in May 2006. The primary outcome measure was transition to full-threshold psychosis, defined a priori as frank psychotic symptoms occurring at least daily for 1 week or more and assessed using the Comprehensive Assessment of At-Risk Mental States. Secondary outcome measures were psychiatric symptoms, psychosocial functioning, and quality of life.

Results: The estimated 12-month transition rates were as follows: cognitive therapy + risperidone, 10.7%; cognitive therapy + placebo, 9.6%; and supportive therapy + placebo, 21.8%. While there were no statistically significant differences between the 3 groups in transition rates (log-rank test $P = .60$), all 3 groups improved substantially during the trial, particularly in terms of negative symptoms and overall functioning.

Conclusions: The lower than expected, essentially equivalent transition rates in all 3 groups fail to provide support for the first-line use of antipsychotic medications in patients at ultra-high risk of psychosis, and an initial approach with supportive therapy is likely to be effective and carries fewer risks.

Trial Registration: Australian New Zealand Clinical Trials Registry identifier: ACTRN012605000247673

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The development of operational criteria accurately defining a clinical phenotype with substantial predictive power for transition to first-episode psychosis has created momentum for the conduct of clinical trials examining options for preventive intervention to reduce the risk of full-threshold psychotic disorder.[1,2] Despite the lower transition rates reported in recent studies, the relative risk for transition conferred by this phenotype ranges from approximately 200–400,[3,4] representing an indicator of risk superior to any presently known biomarker or endophenotype. These criteria have significant clinical utility, given that this phenotype captures an already symptomatic, distressing, and disabling syndrome that justifies intervention on the grounds of a need for care alone.

Several randomized clinical trials have been carried out in samples of patients with this clinical phenotype, termed by our group the *ultra-high risk* (UHR) state. The evidence available to date suggests that several different treatment strategies, including low-dose antipsychotic medication, cognitive therapy, and omega-3 fatty acids, either alone or in combination, are able to significantly reduce the risk of transition to psychosis over a 12-month period.[5–10] However, each of these interventions was offered for a brief, time-limited period only and, apart from the trial using omega-3 fatty acids,[5] has not been shown to have an enduring effect. Indeed, for most patients, these interventions have probably only deferred the transition to psychosis, although the studies are too small to be definitive. This initial wave of studies has therefore raised a series of second-order questions: Which is the safest and most effective intervention to reduce the risk of transition to psychosis? How long should an intervention be continued if transition is to be avoided and recovery attained? What is the ideal sequence and combination of preventive strategies? and How are the risks and/or inconveniences of intervention to be balanced against the benefits? We have continued to study these questions within the framework of the clinical staging model, adapted from internal medicine.[11,12] This model proposes that certain lower-risk treatments are more likely to be effective if delivered early in the course of illness, while proving much less effective during the later stages. Conversely, some treatments that are necessary and justified later in the course of illness represent "overkill" if employed earlier on, proving too onerous or producing unacceptable adverse effects. In the context of early psychosis, we need to define the optimal timing for the use of antipsychotic medications, since the alternative options are more generic and involve less risk.

In previous reports, we have described the rationale, design, and baseline characteristics[13] and the 6-month outcomes[14] of a double-blind, placebo-controlled randomized trial designed

Clinical Points

- Watchful monitoring and psychosocial interventions such as supportive therapy and cognitive therapy should be the first-line interventions in this patient group.
- Antipsychotic treatment should typically be reserved for those whose symptoms, distress, and functional impairment have clearly worsened significantly, despite psychosocial intervention, to the point where sustained frank psychosis has developed.

to assess the benefits and potential risks of 3 alternative interventions, cognitive therapy + risperidone, cognitive therapy + placebo, and supportive therapy + placebo, in young people at ultra-high risk of transition to a first episode of psychosis. Here, we report the 12-month outcomes of this trial.

METHOD

Setting and Participants

This trial was approved by the North Western Mental Health Research and Ethics Committee and registered with the Australian and New Zealand Clinical Trials Registry (identifier: ACTRN012605000247673). The study was conducted at the Personal Assessment and Crisis Evaluation (PACE) Clinic, in Melbourne, Australia, a clinical service for young people at ultra-high risk of developing a psychotic disorder.[15] The intake criteria for the study were being aged 14–30 years, residing in the Melbourne metropolitan area, and meeting at least 1 of the following criteria for UHR status[16]: (1) the presence of attenuated (subthreshold) psychotic symptoms within the previous 12 months; (2) a history of brief self-limited psychotic symptoms, which spontaneously resolve, within the previous 12 months; and (3) a presumed genetic vulnerability to psychotic disorder plus persistent low functioning for at least 1 month within the previous 12 months. 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 known history of a previous psychotic or manic episode (treated or untreated); known history of a medical condition that may account for symptoms leading to initial referral (eg, epilepsy); clinically relevant neurologic, biochemical, or hematologic abnormalities; serious coexisting illnesses; a lifetime antipsychotic dose of 15 mg of haloperidol (or equivalent) or greater; any previous or current use of mood-stabilizing medication; history of severe drug allergy; intellectual disability (IQ < 70); in females, pregnancy or lactation; and insufficient English language skills to participate in research interviews or psychological treatment without assistance from an interpreter.

Interventions

Trial medication, either risperidone or placebo, was dispensed in plain packaging by an independent 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. Side effects were monitored using the UKU Side Effect Rating Scale.[17] Treatment adherence was monitored by pill count, and psychiatrists and case managers used standard behavioral strategies to enhance adherence, such as encouraging participants to keep their medication in a prominent place (beside the bed, in the kitchen, etc) and using alarm clock or phone reminders, diary systems, and phone calls from research assistants. Definitions of full, partial, and poor adherence were the same as in our previous trial[7]: full adherence, ≥ 90%; partial adherence, 50%–89%; and poor adherence, < 50%.

Cognitive therapy was provided by clinical psychologists using a manualized program consisting of 4 modules: stress management, reducing depression and negative symptoms, coping with positive symptoms, and managing other comorbidities. This cognitive therapy approach is presented in more detail elsewhere.[18,19] Supportive therapy was provided by the same clinical psychologists who provided the cognitive therapy, and the aim of this therapy was to provide the patient with emotional and social support,[20] as well as basic problem solving,[21] stress management, and psychoeducation. This intervention was intended as an active control intervention, akin to the needs-based intervention in our first intervention trial,[7] and was felt to be justified as potentially effective in relation to the immediate need for care, but less likely to be effective in reducing the risk of transition to psychosis. In addition to providing therapy, psychologists also provided practical case management and crisis intervention where necessary.

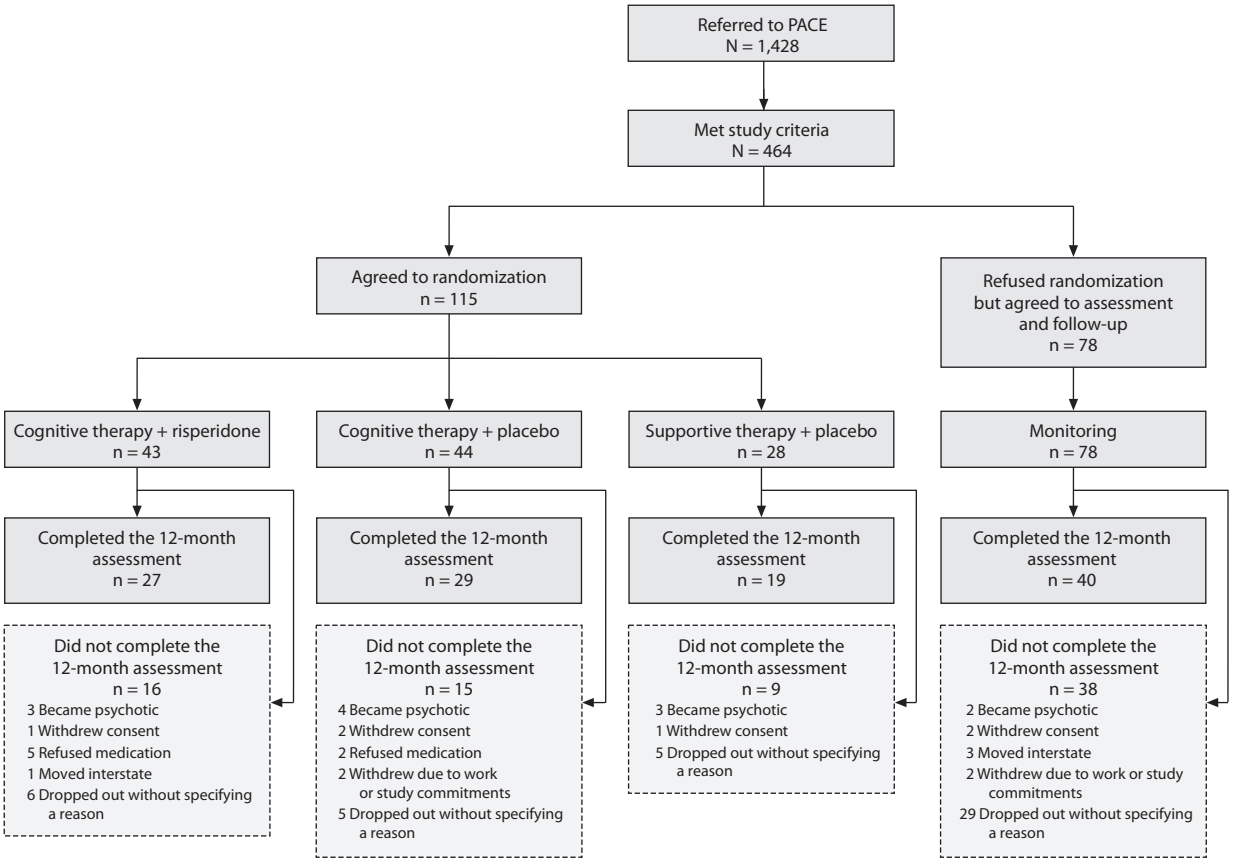
Outcomes

The primary 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 and were assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS).[22] The secondary outcome measures were psychiatric symptoms, psychosocial functioning, and quality of life. These were assessed using the Structured Clinical Interview for *DSM-IV-TR* (SCID-IV),[23] Brief Psychiatric Rating Scale (BPRS),[24] Scale for the Assessment of Negative Symptoms (SANS),[25] Hamilton Depression Rating Scale (HDRS),[26] Substance Use Questionnaire developed at PACE from the *DSM-IV-TR*[27] (available from the authors on request), Global Assessment of Functioning (GAF),[27] and Quality of Life Scale (QLS).[28]

Procedure

The trial procedure has been described in detail elsewhere.[13] Recruitment commenced in August 2000 and ended in May 2006. Briefly, the randomization sequence was created by an independent statistician, who created sealed envelopes containing the medication number and the group assignation code. The participants were not randomized according to any clinically relevant criteria;

Figure 1. Participant Distribution for the Trial



Abbreviation: PACE = Personal Assessment and Crisis Evaluation.

however, randomization was done at a 3:3:2 ratio (cognitive therapy + risperidone:cognitive therapy + placebo:supportive therapy + placebo) due to differences in the predicted rates of transition to psychosis between the groups. Consenting participants were allocated consecutive envelopes by the trial manager, who then informed the therapists of the allocated psychological treatment, but not the medication group. Participants were seen weekly by their treating psychiatrist, who was blind to the form of psychological therapy that each participant received, for 4 weeks and then monthly from months 2–12. They were seen weekly to every 2 weeks by their therapist case manager for 12 months. Demographic information and a lifetime history of hospitalization for mental health difficulties were collected at baseline, and the following measures were also administered: the SCID-IV, CAARMS, GAF, QLS, BPRS, SANS, HDRS, and Substance Use Questionnaire. Research assessments were undertaken monthly and comprised the BPRS, SANS, and HDRS, with the SCID-IV, GAF, and QLS also included at months 6, 12, and 24.

Statistical Methods

Sample size considerations were described previously.[13] SPSS for Windows 15.0 (SPSS Inc; Chicago, Illinois) and S-PLUS for Windows 6.1 (Insightful Corporation; Seattle, Washington) were used for the analysis, and data were analyzed by intention to treat. All statistical tests were interpreted at the 5% significance level (2-tailed). Kaplan-Meier survival analysis and the log-rank test were used to assess whether the 3 groups differed in terms of their transition rates over time. For analysis of adverse events, the UKU Side Effect Rating Scale items were dichotomized into presence or absence of symptoms. Logistic regression was then employed to compare the different groups at the 12-month assessment using the corresponding baseline presence or absence of the symptom as a covariate.

RESULTS

Participant Flow

Of the 1,428 young people referred to the PACE Clinic over the recruitment period (August 2000–May 2006), 464 (32.5%) met study criteria, and 115 agreed to randomization. An additional 78 individuals who met study criteria refused participation but agreed to assessment and follow-up (the "monitoring" group). 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 (Figure 1). The baseline characteristics of all 4 groups are presented in detail elsewhere[13] and are summarized briefly in Table 1.

Table 1. Baseline Characteristics of 193 Young People at Ultra-High Risk of Psychosis[a]

Characteristic	Cognitive Therapy + Risperidone (n = 43)	Cognitive Therapy + Placebo (n = 44)	Supportive Therapy + Placebo (n = 28)	Monitoring (n = 78)	*P* Value[b]
Age, mean ± SD, y	17.6 ± 3.0	18.0 ± 2.7	18.8 ± 3.7	17.8 ± 2.6	.56
Female	28 (65.1)	27 (61.4)	15 (53.6)	47 (60.3)	.93
Education					.19
≤ Year 10	25 (58.1)	22 (50.0)	12 (42.9)	40 (51.3)	
Year 11/12	14 (32.6)	10 (22.7)	6 (21.4)	26 (33.3)	
TAFE/apprenticeship	2 (4.7)	5 (11.4)	5 (17.9)	2 (2.6)	
Tertiary	2 (4.7)	7 (15.9)	5 (17.9)	10 (12.8)	
Employment					.57
Employed	1 (2.3)	6 (13.6)	4 (14.3)	11 (14.1)	
Homemaker	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Unemployed	8 (18.6)	10 (22.7)	8 (28.6)	20 (25.6)	
Student	33 (76.7)	28 (63.6)	16 (57.1)	47 (60.3)	
Duration of symptoms prior to contact with PACE Clinic, mean ± SD, d	359.0 ± 403.7	408.3 ± 485.6	375.5 ± 402.7	358.6 ± 417.6	.72

[a]Data expressed as n (%) unless otherwise noted.
[b]Randomized groups vs monitoring group. Randomized groups combined = (cognitive therapy + risperidone) + (cognitive therapy + placebo) + (supportive therapy + placebo).
Abbreviations: PACE = Personal Assessment and Crisis Evaluation, TAFE = technical and further education.

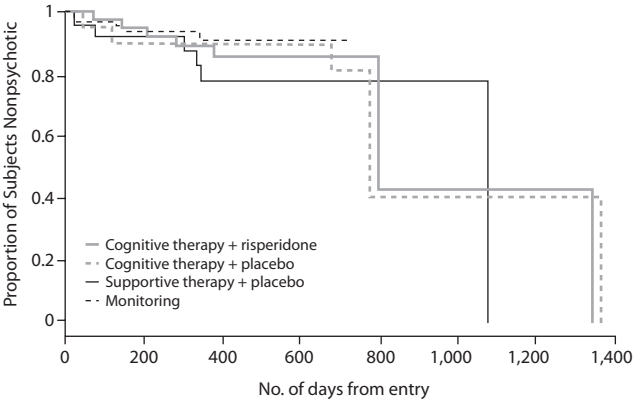
Outcomes

During the course of the study, 25 participants transitioned to psychosis: 7 in the cognitive therapy + risperidone group, 7 in the cognitive therapy + placebo group, 6 in the supportive therapy + placebo group, and 5 in the monitoring group. Figure 2 presents a plot of the survival curves of the 4 groups over the entire study period. Because post–12-month data on transition status could be ascertained from medical records, they were included in this analysis. Interestingly, of the 25 subjects who were known to have made the transition to psychosis, only 7 transitioned at a time later than 12 months. The estimated 12-month transition rates were 10.7% ± 5.0% for the cognitive therapy + risperidone group, 9.6% ± 4.6% for the cognitive therapy + placebo group, 21.8% ± 8.8% for the supportive therapy + placebo group, and 8.7% ± 3.8% for the monitoring group. There were no significant differences in the rate of transition between the randomized groups (log-rank test $P = .60$) or the 4 groups (log-rank test $P = .59$).

Given the lower transition rates in the cognitive therapy + risperidone and the cognitive therapy + placebo groups compared to the supportive therapy + placebo group, it is possible that cognitive therapy, as the common element, contributed to their lower transition rates. To examine this issue, transition data from these 2 groups were combined. The 12-month transition rates estimated from survival analysis of the combined data were 10.2% ± 3.4% for the cognitive therapy group, 21.8% ± 8.8% for the supportive therapy + placebo group, and 8.7% ± 3.8% for the monitoring group. Comparison of the 12-month transition rates of the cognitive therapy and supportive therapy + placebo groups yielded a *P* value of .082; that is, a trend level rather than a statistically significant difference.

To determine the symptomatic and functional outcomes, the groups were compared for change in their scores on the BPRS, SANS, HDRS, GAF, and QLS between baseline and month 12 (Table 2). All groups showed improvement for each of these measures. Analysis of covariance was carried out to test for group differences, with the baseline score as a covariate, and revealed no significant differences between the groups. Given the high number of missing values, last-observation-carried-forward, multiple imputation, and linear mixed-effects modeling were also performed. These analyses resulted in similar results to those reported in Table 2.

Figure 2. Survival Curves of the Rates of Transition to Psychosis for All 4 Groups Over the Full Study Period



Attrition Rate

By the 12-month assessment point, 43 participants (37.3%) had dropped out of the study. The dropout rates in the treatment groups were 37.2% (n = 16) in the cognitive therapy + risperidone group, 34.1% (n = 15) in the cognitive therapy + placebo group, and 32.1% (n = 9) in the supportive therapy + placebo group (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. Nearly half of the monitoring group (38/78, 48.7%) had dropped out by the 12-month assessment, which was not significantly different from the randomized groups (Fisher exact $P = .10$).

Table 2. Group Comparison of Change in Psychopathology Scores Between Baseline and Month 12

Assessment	Baseline,[a] Mean ± SD	Month 12,[a] Mean ± SD	Change, Mean ± SD	*P* Value[b] (trial groups only)	*P* Value[b] (all 4 groups)	n[c]
BPRS total						
Cognitive therapy + risperidone	27.1 ± 10.8	14.0 ± 9.3	−13.1 ± 10.1	.799	.463	24
Cognitive therapy + placebo	30.3 ± 9.3	16.5 ± 11.1	−13.8 ± 12.6			27
Supportive therapy + placebo	25.2 ± 6.2	15.3 ± 10.1	−9.9 ± 10.7			18
Monitoring	21.8 ± 10.8	10.4 ± 8.0	−11.4 ± 10.4			35
BPRS psychotic subscale						
Cognitive therapy + risperidone	6.6 ± 2.3	2.6 ± 2.5	−4.0 ± 2.9	.637	.223	24
Cognitive therapy + placebo	6.9 ± 3.5	2.8 ± 2.9	−4.1 ± 3.6			27
Supportive therapy + placebo	5.6 ± 2.3	3.1 ± 3.0	−2.6 ± 3.2			18
Monitoring	5.0 ± 3.4	1.5 ± 2.0	−3.6 ± 3.1			35
SANS affective flattening						
Cognitive therapy + risperidone	7.1 ± 6.4	4.5 ± 5.1	−2.6 ± 4.5	.651	.448	24
Cognitive therapy + placebo	6.9 ± 5.4	4.9 ± 5.1	−2.0 ± 6.3			27
Supportive therapy + placebo	6.1 ± 4.8	3.3 ± 4.4	−2.7 ± 5.0			18
Monitoring	4.1 ± 4.1	2.2 ± 3.7	−1.9 ± 5.1			35
SANS alogia						
Cognitive therapy + risperidone	3.3 ± 2.9	2.7 ± 2.8	−0.7 ± 2.3	.491	.446	24
Cognitive therapy + placebo	3.1 ± 3.1	2.6 ± 2.6	−0.6 ± 3.4			27
Supportive therapy + placebo	3.3 ± 2.1	1.8 ± 2.8	−1.4 ± 2.7			18
Monitoring	1.9 ± 2.2	1.4 ± 2.4	−0.6 ± 3.2			35
SANS avolition apathy						
Cognitive therapy + risperidone	4.5 ± 2.6	4.5 ± 3.2	0.1 ± 3.5	.104	.119	24
Cognitive therapy + placebo	5.3 ± 2.9	3.3 ± 2.9	−2.0 ± 3.6			27
Supportive therapy + placebo	4.2 ± 2.2	2.7 ± 3.3	−1.6 ± 2.9			18
Monitoring	3.7 ± 2.7	2.7 ± 2.7	−1.0 ± 3.1			35
SANS anhedonia asociality						
Cognitive therapy + risperidone	6.6 ± 4.6	4.4 ± 4.3	−2.2 ± 3.8	.819	.775	24
Cognitive therapy + placebo	6.3 ± 4.5	3.7 ± 3.5	−2.6 ± 4.8			27
Supportive therapy + placebo	7.1 ± 4.5	4.6 ± 5.0	−2.4 ± 3.5			18
Monitoring	6.1 ± 4.5	3.3 ± 4.0	−2.7 ± 5.1			35
SANS attention						
Cognitive therapy + risperidone	2.3 ± 2.2	1.7 ± 1.6	−0.6 ± 2.6	.805	.828	24
Cognitive therapy + placebo	2.1 ± 2.1	1.8 ± 1.9	−0.3 ± 2.9			27
Supportive therapy + placebo	2.2 ± 2.1	1.4 ± 1.9	−0.8 ± 1.4			18
Monitoring	1.7 ± 2.2	1.8 ± 1.6	0.1 ± 2.2			35
SANS total						
Cognitive therapy + risperidone	23.8 ± 14.8	17.8 ± 13.8	−6.0 ± 11.0	.613	.610	24
Cognitive therapy + placebo	23.7 ± 13.3	16.3 ± 11.6	−7.4 ± 14.6			27
Supportive therapy + placebo	22.8 ± 11.4	13.9 ± 13.9	−8.9 ± 9.5			18
Monitoring	17.5 ± 11.6	11.3 ± 9.8	−6.1 ± 12.2			35
HDRS						
Cognitive therapy + risperidone	20.2 ± 4.3	7.2 ± 6.3	−13.0 ± 5.3	.654	.814	5
Cognitive therapy + placebo	23.2 ± 3.9	10.0 ± 11.1	−13.2 ± 10.4			4
Supportive therapy + placebo	23.8 ± 12.3	5.8 ± 6.0	−18.0 ± 6.4			4
Monitoring	18.7 ± 9.5	6.7 ± 6.6	−12.0 ± 9.2			18
GAF						
Cognitive therapy + risperidone	54.5 ± 7.0	64.8 ± 9.0	10.3 ± 11.5	.499	.248	26
Cognitive therapy + placebo	53.8 ± 9.1	66.8 ± 7.7	13.1 ± 10.5			26
Supportive therapy + placebo	57.6 ± 10.4	64.6 ± 13.6	7.0 ± 12.5			19
Monitoring	58.8 ± 10.7	70.3 ± 11.9	11.4 ± 11.8			39
QLS total						
Cognitive therapy + risperidone	76.1 ± 15.6	86.8 ± 17.7	10.6 ± 18.6	.494	.200	25
Cognitive therapy + placebo	77.8 ± 24.6	81.1 ± 30.3	3.3 ± 26.4			26
Supportive therapy + placebo	78.0 ± 20.3	84.4 ± 22.0	6.4 ± 15.5			18
Monitoring	79.1 ± 20.7	91.5 ± 21.1	12.4 ± 14.5			39

[a]Mean and SD values are based on subjects for whom there were data for that measure at both baseline and month 12.
[b]Group difference using analysis of covariance with baseline score as a covariate.
[c]Number of subjects with valid scores for both baseline and month 12.
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.

Adverse Events

Assessment of adverse events was performed monthly. The most common side effects reported at baseline were fatigue, depression, concentration difficulties, and orthostatic dizziness. A decrease in frequency of side effects was observed in all treatment groups by 12 months, and there was no statistically significant difference between the groups (Table 3).

Antipsychotic Adherence

At 12-month follow-up, in the cognitive therapy + risperidone group (n = 43), 27 subjects (62.8%) showed poor adherence, 16 (37.2%) showed partial adherence, and none showed full adherence to risperidone. Within the cognitive therapy + placebo group (n = 44), 36 participants (81.8%) demonstrated poor adherence, 6 (13.6%) were partially

Table 3. UKU Side Effect Rating Scale Global Ratings at Baseline and Month 12

	Doctor's Rating					Patient's Rating				
	Baseline		Month 12			Baseline		Month 12		
Group	Subjects Rated as Having Side Effects, %	n[a]	Subjects Rated as Having Side Effects, %	n[a]	*P* Value[b]	Subjects Rated as Having Side Effects, %	n[a]	Subjects Rated as Having Side Effects, %	n[a]	*P* Value[b]
Cognitive therapy + risperidone	38.9	36	20.0	10	.593	41.7	36	20.0	10	.906
Cognitive therapy + placebo	37.9	29	23.1	13		20.7	29	15.4	13	
Supportive therapy + placebo	27.3	22	36.4	11		22.7	22	18.2	11	

[a]Number of subjects with valid ratings.
[b]*P* value from logistic regression comparing the groups in terms of prevalence of side effects.

Table 4. Average 12-Month Adherence: Comparison Between Risperidone and Placebo[a,b]

Group	Poor Adherence, n (%)	Partial Adherence, n (%)	Full Adherence, n (%)	n (total)
Cognitive therapy + risperidone	27 (62.8)	16 (37.2)	0 (0)	43
Cognitive therapy + placebo	36 (81.8)	6 (13.6)	2 (4.5)	44
Supportive therapy + placebo	17 (60.7)	8 (28.6)	3 (10.7)	28

[a]Poor: < 50% adherence, partial: 50%–89% adherence, full: ≥ 90% adherence.
[b]χ^2 test, $P = .029$; Fisher exact test, $P = .019$.

adherent, and 2 (4.5%) were fully adherent, while in the supportive therapy + placebo group (n = 28), 17 subjects (60.7%) showed poor adherence, 8 (28.6%) showed partial adherence, and 3 (10.7%) were fully adherent (Table 4). Overall, those prescribed placebo and those prescribed risperidone showed similar rates of poor adherence, with 73.6% of the 2 placebo groups showing poor adherence, although 6.9% of the placebo groups were fully adherent.

DISCUSSION

The main finding in this study was the lack of difference between the 3 randomized groups in terms of the rate of transition to psychotic disorder at the end of the 12-month treatment phase. At approximately 10%, these rates remained low in all groups and were similar to the rates seen at 6 months,[14] although there was a statistically nonsignificant, yet potentially clinically important, increase to 21.8% in the supportive therapy + placebo group. In terms of secondary outcomes, all 3 groups consolidated the symptomatic and functional gains evident at 6 months, representing a clinically important improvement from the substantial symptomatic burden and functional impairment shown at baseline. There was an encouraging trend for additional gains to be made between 6 and 12 months, despite waning adherence to the drug/placebo intervention. These ongoing functional improvements are in contrast with our first randomized trial in UHR young people, in which differences in functional outcome were less marked than differences in symptomatic improvement and transition rates.[7]

One immediate question arising is why the transition rate was so low in all 3 randomized groups, in contrast to the transition rates in the supportive arm of our first study[7] and other recent cohort studies.[3,5,29] One reason may be that we are sampling a less "ill" group or one with a lower vulnerability to psychosis.[4] While this is certainly possible, all cases met the UHR criteria, and their substantial levels of symptomatic and functional impairment at baseline were similar to those seen in our initial study,[7] so, in cross-sectional terms at least, there is no doubt that they were just as "ill." Despite this, it is possible that the current cohort may have been less enriched for risk of transition and hence possessed a lower intrinsic true-positive rate due to sampling differences. Another possibility is that the participants in this trial were detected earlier in the course of their illness and thus were more responsive to simpler and safer interventions. While the mean duration of symptoms prior to treatment was modestly lower than that of our original trial[7] (372.2 ± 425.6 days vs 424.1 ± 714.1 days, respectively), the median duration of untreated symptoms was similar (212.0 days vs 207.5 days, respectively), and these differences were not statistically significant ($P = .300$). We cannot exclude that the participants in this study may be at risk of later transition. Indeed, our longer-term follow-up data (2–9 years after commencement of recruitment) show that the transition rates continue to increase in all groups after the 12-month follow-up point, and, by 3 years after entry, these range between 19%–24% across all groups. This suggests that the low transition rates within the 12-month period of the current study may be partly due to lead-time bias. Crucially, these longer-term follow-up data indicate no differential effect of treatment group on transition rate ($P = .87$ comparing the 3 trial groups, $P = .13$ comparing all 4 groups). Hence, there seems to be no apparent longer-term protective effect of the more specific interventions over the supportive intervention alone. A third possibility is that the interventions provided in the supportive therapy group have become more effective in reducing transition rates and improving functional outcome. There is some support for this argument, in that the functional recovery levels at 12 months in the present study were greater than those seen in our earlier trial. Finally, the high levels of use of antidepressants in this trial—with 62.8% of those in the cognitive therapy + risperidone group, 50.0% of those in the cognitive therapy + placebo group, and 39.3% of those in the supportive therapy + placebo group taking antidepressants during the trial[14]—may have contributed to a lower

transition rate in all groups, since there is some evidence to suggest that these agents may be effective in reducing transition rates, which may also have reduced the power of the study.[30,31]

An important strength of our study is that it represents one of the largest cohorts of UHR cases to have entered a randomized controlled trial. Other strengths included the methodological rigor of the design and conduct of the trial, which was held at a single specialized center over a 5-year period.

The limitations of our study are as follows: despite having a large sample, our study ultimately proved to be underpowered. On the basis of the 12-month transition rates observed in the 3 randomized groups, rather than those used in the a priori calculation, a sample size of 165 participants (ie, 55 subjects per group) would have been required for differences of the magnitude seen here to be statistically significant. Thus, it remains possible that with a larger sample size we would have been able to detect a significant difference, particularly between the supportive therapy + placebo and cognitive therapy + placebo groups. Another contributing factor here was the poor adherence to the trial medication, which undoubtedly reduced its efficacy and thus the power to detect any real effect present, reflecting the all-too-familiar feasibility problem with this aspect of longer-term clinical trials in psychiatry.[32]

Nevertheless, given the lower transition rates even in the placebo groups, it seems reasonable to conclude that antipsychotics are not universally required, at least as a first-line therapy, in this patient group. This is a key point given the potential risks of these agents, notwithstanding the low level of reported adverse events in this study. Recent concern about the potential effects of these medications on physical health and brain structure reinforces this conclusion.[33,34] It remains possible, however, that a subgroup of UHR patients who do not respond to other therapies may benefit from antipsychotic medications despite these risks, but this remains to be established.

What do these results mean for clinical practice? Preti and Cella[2] have argued that while there is clear evidence that treatment at this stage of illness is effective in the short term in reducing risks for full-threshold psychosis in UHR patients, several heterogeneous interventions have been found to have similar effects. This viewpoint is congruent with the findings of our study, in which all 3 intervention groups were associated with transition rates at the level of the experimental conditions in previous trials. Our study aimed to illuminate the optimal sequence of interventions by comparing head-to-head 2 of the strategies found to be effective in earlier studies. While not conclusive, our data fail to support the first-line use of antipsychotic medications in the treatment of young people presenting with the UHR clinical phenotype. The combination of supportive therapy, case management, and the treatment of depression and other syndromes on their merits seems to be an appropriate initial approach. Cognitive therapy techniques, especially for depression and anxiety, may be useful, since a trend was seen for the cognitive therapy–treated groups to have a lower transition rate at 12 months. Watchful monitoring and supportive case management are key elements of the treatment process, particularly during the first 6 to 12 months. These patients still have a 3-year transition risk of around 20% (a relative risk of over 200 compared to their peers) and are also at risk of persistent or recurrent mood and anxiety disorders and probably also secondary substance use disorders.

Finally, our findings are consistent with the predictions of the clinical staging model,[11,12] which suggests that simpler and safer interventions may be efficacious during a defined window early in the course of illness. The findings also highlight the need for larger multicenter trials with sophisticated sequential designs to provide definitive evidence to guide the treatment of this patient group.

Drug names: haloperidol (Haldol and others), risperidone (Risperdal and others).

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