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Three-Year Follow-up of a Randomized Controlled Trial of Cognitive Therapy for the Prevention of Psychosis in People at Ultrahigh Risk

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There have been recent advances in the ability to identify people at high risk of developing psychosis. This has led to interest in the possibility of preventing the development of psychosis. A randomized controlled trial compared cognitive therapy (CT) over 6 months with monthly monitoring in 58 patients meeting criteria for ultrahigh risk of developing a first episode of psychosis. Participants were followed up over a 3-year period. Logistic regression demonstrated that CT significantly reduced likelihood of being prescribed antipsychotic medication over a 3-year period, but it did not affect transition to psychosis defined using the Positive and Negative Syndrome Scale (PANSS) or probable *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis. However, exploratory analyses revealed that CT significantly reduced the likelihood of making progression to psychosis as defined on the PANSS over 3 years after controlling for baseline cognitive factors. Follow-up rate at 3 years was 47%. There appear to be enduring benefits of CT over the long term, suggesting that it is an efficacious intervention for people at high risk of developing psychosis.

Key words: cognitive therapy/psychosis/prevention/early intervention

Introduction

Early intervention in psychotic disorders has recently generated much interest, and a small number of studies have examined the possibility of detecting individuals in the prodromal stage, prior to the development of full psychosis. Yung and colleagues[1] from the personal assessment and crisis evaluation (PACE) clinic in Melbourne developed operational criteria to identify 4 subgroups at ultrahigh risk of incipient psychosis, which they termed at-risk mental state (ARMS); these consisted of attenuated psychotic symptoms (AS), brief limited intermittent psychotic symptoms (BLIPS), a first-degree relative with a psychotic disorder in combination with a deterioration in the patient's functioning, and schizotypal personality disorder in combination with a deterioration in the patient's functioning. They found that 40% of this high-risk sample became psychotic over a 9-month period. The identification of risk factors that yield such a high-risk group suggests the possibility of using preventative interventions. It has been reported that specific pharmacotherapy and psychotherapy reduced the risk of early transition to psychosis in young people at ultrahigh risk, in comparison with supportive therapy and case management, with a reduction in progression to psychosis at end of treatment, but not at 6-month follow-up.[2] This finding was interpreted as a delay in onset, rather than prevention. However, a recent study demonstrated that a psychological intervention alone (cognitive therapy [CT]) appeared to reduce transition to psychosis at 12-month follow-up in a randomized controlled trial of 58 people who met ARMS criteria.[3] This report from the same study aims to determine whether psychological intervention could prevent, in the long term, transition to psychosis in help-seeking individuals at operationally defined high risk. We hypothesized that, at 3-year follow-up, a 6-month course of CT would continue to show significant reductions in the transition rate to psychosis in comparison to a monitoring alone control group. In addition, we hypothesized that taking into account factors that are hypothesized, mechanisms of change in CT would improve prediction.

Materials and Methods

Participants

Recruitment of participants was sought from a variety of sources, including primary care teams (general practitioners, practice nurses, and psychological therapists), student counseling services, accident and emergency departments, specialist services (eg, community drug and

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alcohol teams, child and adolescent psychiatry and adult psychiatry services), and voluntary sector agencies (such as carers' organizations). In order to facilitate the referral process, a series of workshops were held for all these organizations, and regular written reminders were provided. Individuals that met our criteria (based on the PACE criteria) were deemed to be at incipient risk of psychosis (and hence included in the study). In all, 37 patients were randomized to CT and 23 patients to monitoring. The male-to-female ratio was 40:18 (70%:30%) and mean (SD) age at entry was 22 (4.5) years (range 16–36). The routes into the study were as follows: 48 participants were suitable due to AS, 6 were suitable due to BLIPS, and 4 were suitable due to a family history and recent deterioration. Full details of the sample are given elsewhere.[3]

Entry Criteria

Specific state risk factors were operationally defined by the presence of either transient psychotic symptoms (termed BLIPS) or AS (subclinical), both of which were defined using an adaptation of the PACE duration and severity criteria,[1] based on Positive and Negative Syndrome Scale (PANSS)[4] cutoff scores that are described in the original trial.[3] *Trait plus state risk factors* are operationally defined by the presence of an ARMS (defined for the purposes of this study as scoring for caseness on the General Health Questionnaire[5] and/or a recent deterioration in function of 30 points or more on the Global Assessment of Functioning[6]) plus either a family history indicated by a first-degree relative with a history of any psychotic disorder or a diagnosis of schizotypal personality disorder in the participant. Potential participants below the age of 16 or above the age of 36 were considered to be outside the maximum risk period for psychosis and were excluded from the study. Current or past receipt of antipsychotic medication was an exclusion criterion.

Measures

The main measure that was used to assess suitability for inclusion in the study and monitor outcomes was the *PANSS*,[4] a clinician administered 30-item semistructured interview, which was used to assess BLIPS and attenuated symptoms, and is the primary outcome measure used for determining transition to psychosis. Two further scales were used to test explanatory hypotheses about the action of CT. The *Metacognitions Questionnaire*[7] is a measure of beliefs about mental events, which generates scores for subscales including negative beliefs about the controllability of thoughts and corresponding danger (typical items include "Worrying is dangerous for me" and "I cannot ignore my worrying thoughts" and are rated from 1 to 4, whereby 1 = "do not agree," 2 = "agree slightly," 3 = "agree moderately," and 4 = "agree very much"). The *Sociotropy-Autonomy Scale*[8] includes a 10-item abridged subscale that assesses sociotropy (fear of rejection and criticism). Participants choose a percentage (0%–100%) indicating how closely each statement describes them. Mean scores are calculated for each subscale (0–10).

The primary outcome measure was the rate of transition to psychosis, which was operationally defined, based on the PACE criteria, using cutoff points on PANSS subscales (4 or more on hallucinations, and/or 4 or more on delusions, and/or 5 or more on conceptual disorganization), and the frequency of symptoms (at least several times a week) and their duration (more than 1 week). Secondary outcomes assumed to also represent transition to psychosis were the prescription of antipsychotic medication from an independent medical practitioner outside the trial and probable *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis made by a consultant psychiatrist blind to treatment status (Shôn W. Lewis), which was rated using vignettes that were prepared from casenotes and assessment records by the assessors. The rationale for these additional outcome measures was that some patients will not report psychotic experiences in an interview but may be viewed as psychotic by a clinician on the basis of behavioral indices.

Study Design and Intervention

The Early Detection and Intervention Evaluation trial was designed as a pragmatic single-blind (rater-blind), randomized controlled trial. Full details of the trial are provided in the original publication.[3] The randomized participants were monitored at monthly intervals (using PANSS) for a period of 12 months following initial assessment and then at every 6 months for the next 2 years (ie, at 18, 24, 30, and 36 months). Assessments were conducted by research assistants, and good interrater reliability was established using videotaped interviews.

The Local Research Ethics Committees of Salford and Trafford and North, South, and Central Manchester (UK) approved the study. Potential participants who gave informed consent following the receipt of a detailed participant information sheet were assessed using the above measures in relation to the entry criteria. The CT intervention was limited to a maximum of 26 sessions over 6 months and followed the treatment manual.[9] The median inter-quartile range number of sessions received for those participants allocated to CT was 11 (13). If a participant developed a full psychosis, urgent referral to a specialist clinical team outside the trial was effected and a record made of the treatment given. Medication was not prescribed as part of the trial protocol.

Statistical Analysis

SPSS for Windows 11.5 was used for all statistical analysis. Comparison of the 2 groups was by intention to treat (with the exception of the 2 individuals who subsequently

Table 1. Transition Rates for Each Group at 3-Year Follow-up

Treatment Group	Follow-up Rate, *N* (%)	PANSS Transition, *N* (%)	Antipsychotic Medication, *N* (%)	*DSM-IV* Psychotic Diagnosis, *N* (%)
Cognitive therapy (*N* = 35)	17 (49)	7 (20)	5 (14)	7 (20)
Monitoring (*N* = 23)	10 (43)	5 (22)	8 (35)	7 (30)

Note: PANSS, Positive and Negative Syndrome Scale; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

reported exclusion criteria, as described in the original study). Missing data were recorded as missing, with the exception of transition status, which was conservatively assumed to be no transition if this data were not obtainable. Attempts were made to contact patients using telephone numbers and addresses, multiple appointments were sent, and general practitioners and other healthcare professionals were also contacted. Follow-up rate at 1 year was 95%, as reported by Morrison and colleagues. However, at 3 years, only 27 patients were successfully followed up (an overall rate of 47% of the original sample). Attrition appeared to be due to a combination of factors, including the mobility of the population, with participants moving home (and, at times, country of residence) without providing new addresses, frequent changes of mobile telephones and, less frequently, withdrawals from the study when contact was made ($n = 2$). The follow-up rates were 49% of the CT group and 43% of the monitoring group. If data were unavailable at a particular assessment occasion, then it was conservatively assumed, for both groups, that PANSS-defined transition had not occurred (medication details were obtained from medical records where possible, and self-report data regarding medication were obtained from all participants who were reassessed at follow-up). All 1-year follow-up data were carried forward (ie, if a participant was coded as having made transition at 1 year, they were automatically coded as having made transition at 3 years, even if no later assessments occurred). Thus, we are assuming no transition by default for 57% of monitoring and 51% of CT, which is clearly conservative in relation to the hypothesis.

The same data analytic strategy that was used in our assessment of outcomes at 12 months was replicated in relation to the 3-year follow-up data. Logistic regression analyses were used to compare occurrence of transition to psychosis between the 2 groups while controlling for the effects of potential confounding variables (age, gender, family history of psychosis, and initial PANSS positive scores), again with primary outcome being PANSS-defined transition and secondary outcomes being antipsychotic medication and vignette-based diagnosis. In addition, a subsidiary exploratory regression analysis was conducted controlling for the variables that are specifically targeted by CT; these were negative beliefs about uncontrollability of unwanted thoughts and fear of rejection and criticism, which are both implicated in the cognitive model of psychosis employed[10,11] and identified as treatment targets within the treatment manual prepared for the trial.[9]

Results

The follow-up rates and the proportion of patients at 3-year follow-up making PANSS-defined transition to psychosis, receiving antipsychotic medication from an independent clinician and being rated as meeting criteria for a *DSM-IV* psychotic disorder are shown in table 1. This means that depending on the method used to determine transition, the number converting in the CT group increased from 2 at 1 year to 5–7 at 3-year follow-up; in the monitoring group, the number making transition at year follow-up either stayed the same (5) or increased by 1 from 7 to 8 or 6 to 7. A chi-squared analysis revealed no significant difference between the follow-up rates for the 2 groups ($\chi^2 = 0.145$, $P = 0.791$).

In order to investigate whether the effects of CT were enduring, a series of logistic regression analyses were conducted with the 3-year follow-up data as the dependent variables. These analyses used gender and family history of psychosis as predictor variables because randomization was stratified using these. They also used baseline PANSS positive subscale scores and age as predictor variables (as continuous variables). Treatment group was represented as a dichotomous variable in these analyses.

Using PANSS-defined transition as the dependent variable, the main effect of CT was not significant (Odds ratio (OR) = 0.38; 95% confidence interval (CI) = 0.08–1.88; $P = 0.236$). Summary statistics for this analysis are shown in table 2.

When a second logistic regression was performed using prescription of antipsychotic medication as the dependent variable, the main effect of CT was significant (OR = 0.13; 95% CI = 0.02–0.76; $P = 0.024$). This means that there is an 87% (CI 24%–98%) reduction in the odds of being in receipt of antipsychotics in the CT group compared with those who received monitoring alone, after adjustment for baseline PANSS score, age, gender, and family history. Summary statistics for this analysis are shown in table 3.

When the analysis was repeated using *DSM-IV* diagnosis as the dependent variable, rated on the basis of

Table 2. Logistic Regression Summary Statistics for PANSS-Defined Transition

	Beta	SE	OR (95% CI)	Significance
Family history	0.10	1.19	1.11 (0.11–11.61)	0.932
Age	0.01	0.08	1.01 (0.87–1.18)	0.875
Gender	0.76	0.81	2.14 (0.44–10.44)	0.349
Baseline PANSS positive score	0.23	0.12	1.25 (0.99–1.59)	0.065
Cognitive therapy	−0.97	0.82	0.38 (0.08–1.88)	0.236

Note: OR, odds ratio; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale.

a clinical vignette by a blind consultant psychiatrist, the main effect of CT was not significant (OR = 0.34; 95% CI = 0.08–1.48; $P = 0.152$). Summary statistics for this analysis are shown in table 4.

An exploratory logistic regression analysis was also performed using PANSS-defined transition as the dependent variable, and baseline PANSS positive subscale scores, metacognitive beliefs about uncontrollability, and sociotropy were entered as predictor variables. The latter 2 variables were included because they are potential intervention targets for CT; it was assumed that high scores on these variables would indicate that patients had psychological vulnerabilities that would be amenable to treatment. In this analysis, the main effect of CT was significant (OR = 0.03; 95% CI = 0.01–0.64; $P = 0.026$). This means that there is a 98% reduction (CI 36%–99%) in the odds of making a transition in the CT group compared with those who received monitoring alone, after adjustment for baseline PANSS score, metacognitive beliefs, and sociotropy. Summary statistics for this analysis are shown in table 5.

Discussion

Our results suggest that, over a 3-year period, an initial 6-month package of CT is effective in reducing the likelihood of being prescribed antipsychotic medication in a help-seeking, high-risk group, after controlling for age, gender, baseline PANSS scores, and family history, but is not effective in reducing the likelihood of transition to psychosis defined by the PANSS or by *DSM-IV* diagnosis. However, CT did significantly reduce the likelihood of transition to psychosis defined using the PANSS over the 3-year period, after controlling for beliefs that are targeted during therapy and baseline PANSS scores. The numbers in the analysis are small, however.

This is the first study to suggest that any intervention can prevent progression to psychosis over a long period of time, although with only one of the 3 outcome measures showing a statistically significant difference, there is clearly some ambiguity. The discrepant findings for different methods of operationalizing transition are problematic, and each method has advantages and disadvantages. PANSS-defined transition has the advantage of being based on a clinical interview, but it is possible that people may deny psychotic experiences due to shame, stigma, or suspiciousness. Prescription of antipsychotic medication is probably the most objective measure of transition because PANSS-defined transition involves crossing a somewhat arbitrary threshold, and both

Table 3. Logistic Regression Summary Statistics for Antipsychotic Medication

	Beta	SE	OR (95% CI)	Significance
Family history	1.03	1.05	2.81 (0.36–21.91)	0.323
Age	−0.02	0.08	0.98 (0.83–1.15)	0.809
Gender	−0.58	0.95	0.56 (0.09–3.63)	0.543
Baseline PANSS positive score	0.34	0.15	1.41 (1.06–1.88)	0.019
Cognitive therapy	−2.03	0.90	0.13 (0.02–0.76)	0.024

Note: OR, odds ratio; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale.

Table 4. Logistic Regression Summary Statistics for Diagnosis

	Beta	SE	OR (95% CI)	Significance
Family history	0.83	0.97	2.29 (0.34–15.49)	0.394
Age	−0.07	0.08	0.93 (0.79–1.10)	0.389
Gender	0.15	0.78	1.16 (0.25–5.29)	0.851
Baseline PANSS positive score	0.19	0.11	1.20 (0.96–1.51)	0.106
Cognitive therapy	−1.07	0.74	0.34 (0.08–1.48)	0.152

Note: OR, odds ratio; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale.

Table 5. Logistic Regression Summary Statistics for PANSS-Defined Transition Controlling for Cognitive Factors

	Beta	SE	OR (95% CI)	Significance
Fear of rejection and criticism	−0.81	0.84	0.45 (0.09–2.29)	.335
Negative beliefs about uncontrollability	0.04	0.06	1.04 (0.92–1.17)	.548
Baseline PANSS positive score	0.48	0.27	1.61 (0.94–2.75)	.082
Cognitive therapy	−3.70	1.66	0.03 (0.01–0.64)	.026

Note: OR, odds ratio; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale.

PANSS-defined transition and *DSM-IV* diagnosis relied upon self-report data from interview, whereas data regarding prescription of medication were corroborated from medical records. However, prescription of antipsychotic medication cannot be considered a definitive indicator of transition because it is increasingly used in clinical practice for other disorders. It could also be argued that our CT intervention had somehow deterred patients from seeking treatment as they became unwell, actually leading to an increase in duration of untreated psychosis. (We think this unlikely. The participants did not receive any information that might discourage them from seeking help outside the trial. Indeed, as reports from the participants indicated considerable satisfaction with the treatment, we think this should have led to greater willingness to seek help from other mental health professions.) Finally, *DSM-IV* diagnosis based on clinical vignettes has good clinical validity, as diagnosis is what most clinician's will use to determine clinically significant levels of psychotic experience, and this was done blind to treatment condition; however, this does rely on self-report data, and there are criticisms of reliance upon diagnoses, especially in the early phases of psychosis.[12]

It is interesting that the use of psychological therapy alone appears to have an effect that is at least as efficacious and enduring as that found in the study of combined pharmacological therapy and psychotherapy[2] and that of a double blind placebo-controlled trial of pharmacotherapy alone[13] (it is worth noting that all of these studies had very similar sample sizes). The 2 studies involving medication both found differences at end of treatment (the combined treatment reaching statistical significance, with the pharmacotherapy alone showing a trend approaching significance), but no difference was observed during the follow-up period. Our own study found a significant difference at 6 months after the end of treatment and some indication that there may be a longer term benefit at 3-year follow-up (a statistically significant difference on one of the 3 measures). Given that acceptability rates for CT appear higher than those for pharmacotherapy,[3] that young people meeting ARMS criteria are reluctant to accept antipsychotic medication[14] and that the ethical dilemmas regarding exposure to side effects in false-positives are much less pronounced,[15] these preliminary data at this point in time suggest that CT should, perhaps, be offered to people at high risk of psychosis prior to consideration of the use of antipsychotic medication.

Our study has certain methodological limitations that need to be considered, most of which were documented in relation to the original trial. There were a number of participants lost to follow-up ($n = 33$, 57%), resulting in incomplete data sets, due to the highly mobile nature of this population. However, there were no significant differences between groups in relation to missing data, and the strategy of assuming no transition was made in the absence of follow-up data is conservative. It is possible that participants were also lost to follow-up because of increases in their mental health problems or transition to psychosis; however, as there were more data missing from the monitoring group, this would have made the mistaken acceptance of the null hypothesis more likely (ie, type II error). It would have been useful to collect more data regarding medication, including dosages, duration, and information regarding polypharmacy. In addition, the sample size was small, which will have reduced the statistical power to detect a significant difference between groups, blindness to treatment allocation for assessment of the primary outcome (PANSS) was not maintained, 2 participants were excluded from the original trial due to reporting having been psychotic at baseline at the first postrandomization assessment, and there was no condition that controlled for nonspecific effects of having a therapeutic relationship and regular contact with a mental health professional.

These findings urgently require replication in a larger scale clinical trial. A study of this kind led by the present researchers and funded by the UK Medical Research Council will shortly begin recruiting ARMS participants.

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